### **APPENDIX 17: GRADE EVIDENCE PROFILES**

1	Clini	cal evidence profiles	3
		sychosocial interventions aimed at core features of autism (overall autistic ours)	3
		sychosocial interventions aimed at the core autism feature of impaired cal social communication and interaction	9
		sychosocial interventions aimed at the core autism feature of restricted and rigid and repetitive behaviours	71
		harmacological interventions aimed at core features of autism (overall autist ours)	
		harmacological Interventions aimed at the core autism feature of impaired cal social communication and interaction	83
		harmacological Interventions aimed at the core autism feature of restricted is and rigid and repetitive behaviours	85
		biomedical Interventions aimed at core features of autism (overall autistic purs)	93
		iomedical interventions aimed at the core autism feature of impaired cal social communication and interaction1	.36
		iomedical interventions aimed at the core autism feature of restricted interes id and repetitive behaviours	
	1.10	Psychosocial interventions aimed at behaviour that challenges 1	.63
	1.11	Pharmacological interventions aimed at behaviour that challenges1	.79
	1.12		
		Biomedical interventions aimed at behaviour that challenges	205
	1.13	Biomedical interventions aimed at behaviour that challenges	
	1.13 1.14	0	230
		Psychosocial interventions aimed at adaptive behaviour	230 242
	1.14	Psychosocial interventions aimed at adaptive behaviour	230 242 258
	1.14 1.15	Psychosocial interventions aimed at adaptive behaviour	230 242 258 282
	1.14 1.15 1.16	Psychosocial interventions aimed at adaptive behaviour	230 242 258 282 299
	1.14 1.15 1.16 1.17	Psychosocial interventions aimed at adaptive behaviour	230 242 258 282 299 804
	1.14 1.15 1.16 1.17 1.18	Psychosocial interventions aimed at adaptive behaviour	230 242 258 282 299 804 805
	1.14 1.15 1.16 1.17 1.18 1.19	Psychosocial interventions aimed at adaptive behaviour	230 242 258 282 299 304 305 310

1	.23	Biomedical interventions aimed at motor skills
1	.24	Psychosocial interventions aimed at coexisting mental health problems 324
1	25	Pharmacological interventions aimed at coexisting mental health problems 330
1	.26	Biomedical interventions aimed at coexisting mental health problems 332
	27 or funct	Psychosocial and pharmacological interventions aimed at coexisting medical tional problems
1	.28	Biomedical interventions aimed at coexisting medical or functional problems 364
	29 amily	Psychosocial interventions aimed at improving the impact of autism on the 368
	30 he fam	Pharmacological interventions aimed at improving the impact of autism on ily
	31 amily	Biomedical interventions aimed at improving the impact of autism on the 379
1	.32	Adverse events associated with pharmacological interventions
1	.33	Adverse events associated with biomedical interventions
2	Econ	omic evidence profiles
		Clinical / economic question: Reciprocal-social communication added to rd care versus standard care alone for preschool children with autism
	nanage	Clinical / economic question: antipsychotics versus placebo for the ement of behaviour that challenges in children and young people with autism 21
		Clinical / economic question: Early Intensive Behavioural Intervention versus rd educational service (special education) for children with autism
		Clinical / economic question: Early Intensive Behavioural Intervention versus evention for preschool children with autism
		Clinical / economic question: Early Intensive Behavioural Intervention versus ent as usual for preschool children with autism
		Clinical / economic question: CBT versus wait list for the management of in children and young people with autism

## **1 CLINICAL EVIDENCE PROFILES**

#### 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

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

		Qu	ality assessm	nent			Summary of Findings				S
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study ev	vent rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Early Start Denver Model versus treatment- as-usual for overall autistic behaviours as indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Early Start Denver Model versus treatment- as-usual for overall autistic behaviours as indirect outcome (95% Cl)
Overall a	autistic	behaviours	(measured with	n: Autism Diag	nostic Observa	ation Schedule (	ADOS/AD	OOS-G): Standardised sev	verity score	; Better ir	ndicated by lower values)
45 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	21	24	-		The mean overall autistic behaviours in the intervention groups was <b>0.16 standard deviations</b> <b>lower</b> (0.75 lower to 0.43 higher)
DSM-IV	Clinical	Diagnosis	(assessed with:	Number of par	ticipants who	showed improve	ment in d	iagnosis from autistic disc	order to PD	D-NOS)	
39 (1 study)	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		17/18 (94.4%)	14/21 (66.7%)	<b>OR 0.12</b> (0.01 to	Study p	opulation
104 weeks						due to risk of bias, imprecision			1.07)	944 per 1000	273 fewer per 1000 (from 799 fewer to 3 more)
									1	Modera	te
										944 per 1000	275 fewer per 1000 (from 800 fewer to 3 more)

<sup>1</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5) <sup>2</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as blinding of outcome assessment is unclear

Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm

#### 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

		Qu	ality assessn	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study eve	nt rates (%)	Relative	Anticipated	l absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Treatment- as-usual	With Teacher consultation and training according to the collaborative model for promoting competence and success (COMPASS)	effect (95% CI)	Risk with Treatment- as-usual	Risk difference with Teacher consultation and training according to the collaborative model for promoting competence and success (COMPASS) (95% CI)
IEP goal a	attainn	nent for targe	eted object	t <b>ives</b> (measu	ured with: Beh	avioural observ	ation; Bette	r indicated by lower value	s)	•	
32 (1 study) 39 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	15	17	N/A	N/A	The mean IEP goal attainment for targeted objectives in the intervention groups was <b>1.42 standard deviations</b> higher (0.63 to 2.2 higher)
with a blinded	l seconda		sor only rating 2	0% of behavio	oural observat			ection bias as the primary only 20% of observations w			he non-blind investigator a standardized observation

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

		Q	uality assessr	nent			Summary of Findings					
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study event	rates (%)	Relative	Anticipated a	bsolute effects	
(studies) Follow up	bias				bias	evidence Intervention- educationa manual-only interventio control (LEAP) trai	With Inclusive educational intervention (LEAP) training	effect (95% CI)	Risk with Intervention- manual-only control	Risk difference with Inclusive educational intervention (LEAP) training (95% Cl)		
Overall a	utistic	behaviours (	measured with: (	Childhood Auti	sm Rating Sca	ale (CARS): Tota	l; Better indica	ted by lower values	)	•		
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	117	177	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.42 standard</b> <b>deviations lower</b> (0.66 to 0.19 lower)	
<sup>1</sup> High risk of outcome asse <sup>2</sup> N<400	•		L bias as interventi	I ion administrat	tors and partic	ipants non-blind	I. In addition, ris	sk of detection bias i	s unclear/ui	l nknown as ident	lity and blinding of	

#### 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

		G	Quality assess	sment				Sui	mmary of	Finding	gs
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Parent training versus treatment-as- usual for overall autistic behaviours as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Parent training versus treatment-as- usual for overall autistic behaviours as an indirect outcome (95% Cl)
Overall a	utistic k	ehaviours (I	PEC+PEBM	combine	<b>d)</b> (measured w	ith: Developmenta	al Behav	iour Checklist (DBC): Au	utism Scree	ning Alg	orithm (ASA); Better indicated
by lower value	es)										
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean overall autistic behaviours (PEC+PEBM combined) in the intervention groups was <b>0.06 standard deviations</b> <b>lower</b> (0.47 lower to 0.34 higher)
Overall a	utistic b	<b>behaviours</b> (m	neasured with: C	hildhood Autis	m Rating Scale	(CARS): Total; Be	tter indic	ated by lower values)		1	
102 (2 studies) 13-46 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊕⊖⊖ LOW <sup>3,4</sup> due to imprecision, publication bias	51	51	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.42 standard deviations</b> <b>lower</b> (0.81 to 0.03 lower)
Overall a	utistic k	ehaviours (l	PEBM grou	<b>p)</b> (measured	with: Childhood	Autism Rating Sc	ale (CAI	RS): Total; Better indicat	ted by lowe	r values)	1
70 (1 study) 46 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to imprecision,	35	35	N/A	N/A	The mean overall autistic behaviours (PEBM group) in the intervention groups was

						publication bias				0.44 standard deviations lower (0.92 lower to 0.03 higher)
Overall	autistic I	behaviours (r	measured with: C	Childhood Autis	sm Rating Scale	(CARS): Total; Be	etter indicated by lov	ver values)		
32 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊝⊖ LOW <sup>3</sup> due to imprecision	16 16	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.38 standard deviations</b> <b>lower</b> (1.08 lower to 0.32 higher)
involved in t <sup>2</sup> N<400 <sup>3</sup> N<400 and <sup>4</sup> Risk of sel	the intervent d 95% CI cro lective repor	ion osses both line of i	no effect and me E2006/2012 as t	asure of appre	ciable benefit or not registered on	harm (SMD -0.5/0 ClinicalTrials.gov	0.5) v or ISRCTN and th			d parents were non-blind and rest as the manuals used in

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

		Qı	uality assessm	ent					Summary	of Findings	;
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study ever	nt rates (%)	Relative	Anticipated	absolute effects
(studies) Follow up	bias				bias	of evidence	With Standard day-care	With Parent and day-care staff training	effect (95% CI)	Risk with Standard day- care	Risk difference with Parent and day-care staff training (95% Cl)
Overall a	utistic be	ehaviour (meas	sured with: Autism	n Behaviour Cł	necklist (ABC):	Total; Better indic	cated by low	er values)	-	•	
35 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	19	16	N/A	N/A	The mean overall autistic behaviour in the intervention groups was <b>0.4 standard deviations</b> <b>lower</b> (1.08 lower to 0.27 higher)
<sup>1</sup> N<400 and 9	95% CI cross	ses both line of no	effect and measu	re of apprecial	ble benefit or h	arm (SMD -0.5/0.	5)		1	1	1

#### 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

		Qı	ality assessn	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study ever	nt rates (%)	Relative	Anticipated	l absolute effects
(studies) Follow up	bias	evidence With Treatme as-usual		With Treatment- as-usual	With Caregiver- mediated social- communication intervention (Child's Talk)	effect (95% CI)	Risk with Treatment- as-usual	Risk difference with Caregiver-mediated social- communication intervention (Child's Talk) (95% Cl)			
Overall a	utistic	behaviours (r	neasured with: A	Autism Diagnos	stic Observatio	on Schedule (Al	DOS/ADOS-	G): Total score; Better i	ndicated by	lower values	3)
28 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	14	14	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.76 standard

### 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

I.		Qı	uality assessr	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study eve	ent rates (%)	Relative	Anticipate	ed absolute effects
(studies) Follow up	bias				bias	quality of evidence	With No treatment	With Picture Exchange Communication System (PECS) training for teachers	effect (95% CI)	Risk with No treatment	Risk difference with Picture Exchange Communication System (PECS) training for teachers (95% CI)
Commun	ication	(assessed with: A	utism Diagnosti	C Observation	Schedule (AD	OS/ADOS-G): C	ommunica	tion (odds of being in a h	igher sever	ity category	on ADOS-G))
84 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		N/A	N/A	<b>OR 0.52</b> (0.24 to	Study pop	pulation
33 weeks						due to risk of bias,			1.12)	N/A	N/A
						imprecision				Moderate	
										0 per 1000	N/A
Social int	teractio	<b>n</b> (assessed with	: Autism Diagno	stic Observatio	on Schedule (A	DOS/ADOS-G)	Social Inte	eraction (odds of being in	a higher se	everity cate	gory on ADOS-G))
84 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		N/A	N/A	<b>OR 0.55</b> (0.25 to	Study pop	pulation
33 weeks						due to risk of bias,			1.2)	N/A	N/A
						imprecision				Moderate	

										0 per 1000	N/A
Social in	nteractio	<b>on</b> (assessed with	n: Autism Diagno	stic Observatio	on Schedule (A	ADOS/ADOS-G)	Social In	teraction (odds of being ir	n a higher s	everity cate	gory on ADOS-G))
53 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected		N/A	N/A	<b>OR 0.28</b> (0.09 to	Study pop	pulation
78 weeks						due to risk of bias,			0.88)	N/A	N/A
						imprecision				Moderate	
										0 per 1000	N/A
	0 and 95%	ice, response and CI crosses both li					d outcome	e assessors were non-blin	d	•	

# **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

l			Quality asse	essment		Summary of Findings				gs	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study ev (%)	ent rates	Relative effect	Anticipate	ed absolute effects
Follow up							With With Waitlist Horseback control riding		(95% CI)	Risk with Waitlist control	Risk difference with Horseback riding (95% CI)
Social im	pairme	nt (measured with	: Social Respons	iveness Scale	(SRS): Total; Bette	r indicated by lower va	alues)				
34 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness		reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision,	15	19	N/A	N/A	The mean social impairment in the intervention groups was <b>0.73 standard</b>

						publication bias					deviations lower (1.43 to 0.03 lower)
Social c	ognitior	(measured with:	Social Responsiv	eness Scale	(SRS): Social Cogn	ition ; Better indicated b	by lower v	alues)			
34 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	15	19	N/A	N/A	The mean social cognition in the intervention groups was <b>0.44 standard</b> <b>deviations lower</b> (1.13 lower to 0.24 higher)
Social a	warenes	SS (measured with	n: Social Respons	iveness Scale	e (SRS): Social Awa	areness ; Better indicate	ed by low	er values)	<b>I</b>	<b>I</b>	
34 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	15	19	N/A	N/A	The mean social awareness in the intervention groups was <b>0.4 standard</b> <b>deviations lower</b> (1.08 lower to 0.28 higher)
Social m	notivatio	<b>)n</b> (measured with	n: Social Respons	iveness Scale	e (SRS): Social Mot	ivation ; Better indicate	d by lowe	er values)			
34 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	15	19	N/A	N/A	The mean social motivation in the intervention groups was <b>0.58 standard</b> <b>deviations lower</b> (1.27 lower to 0.12 higher)
parents non <sup>2</sup> N<400 <sup>3</sup> High risk o	-blind f selective i	reporting bias as d	lata not reported f	or selected su	ubscales: the social						asures are parent-rated and ponsiveness Scale (SRS)

# **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

		Qı	uality assessm	ent		Sumi				lings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study eve (%)	ent rates	Relative effect	Anticipate	d absolute effects
Follow up							With Waitlist control	With Music therapy	(95% CI)	Risk with Waitlist control	Risk difference with Music therapy (95% CI)
		ation (measured v responses and gen					ion (compo	site score fr	om imitatior	ı, verbal and	non-verbal communication,
	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	12	12	N/A	N/A	The mean social communication in the intervention groups was <b>0.23 standard deviations</b> higher (0.58 lower to 1.03 higher)
<sup>1</sup> N<400 and	95% CI cross	es both line of no e	ffect and measure	e of appreciable	e benefit or har	rm (SMD -0.5/0.5)					

## **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

		Qu	ality assessn	nent			Sum	mary of F	inding	\$
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	•	Overall quality of evidence	With	· · ·	effect	Anticip Risk with Control	ated absolute effects Risk difference with Behaviour- focused intervention versus treatment-as-usual for the core

								feature of impaired reciprocal social communication and interaction as direct outcome			autism feature of impaired reciprocal social communication and interaction as direct outcome (95% Cl)
Examine	r-child	joint/shared	attention	(measured witl	h: EScs (Early	Social Commu	inication	Scales): Initiating Joint Attent	tion (IJA);	Better ind	dicated by lower values)
27 (1 study) 10 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	13	14	N/A	N/A	The mean examiner-child joint/shared attention in the intervention groups was <b>0.89 standard deviations</b> higher (0.09 to 1.68 higher)
Examine values)	r-child	joint/shared	attention	<b>(Copy)</b> (me	asured with: E	Scs (Early Soc	ial Com	munication Scales): Initiating	Joint Atten	ition (IJA)	); Better indicated by lower
27 (1 study) 23 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	13	14	N/A	N/A	The mean examiner-child joint/shared attention (copy) in the intervention groups was <b>0.86 standard deviations</b> <b>higher</b> (0.06 to 1.65 higher)
Social ar	nd emo	tional devel	opment (me	asured with: B	ayley Scales o	of Infant Develo	pment:	Social-Emotional ; Better indic	cated by lo	wer value	es)
27 (1 study) 23 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	13	14	N/A	N/A	The mean social and emotional development in the intervention groups was <b>0.41 standard deviations</b> higher (0.36 lower to 1.17 higher)
blinded <sup>2</sup> N<400 <sup>3</sup> High risk of non-blind	performar	·	bias as interve	ntion administi	rators and part	ticipants were r	ion-blind			-	tcome assessors were not

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

		Q	uality assessi	nent				Sı	ummary of	f Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study ever	nt rates (%)	Relative	Anticipated	absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Treatment- as-usual	With Parent- mediated and brief Early Start Denver Model (P-ESDM)	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Parent- mediated and brief Early Start Denver Model (P- ESDM) (95% Cl)
Social af	fect (mea	asured with: Autisn	n Diagnostic Obs	ervation Sche	dule for Toddle	ers (ADOS-T): Se	ocial Affect; I	Better indicated by Ic	wer values)		
98 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	49	49	N/A	N/A	The mean social affect in the intervention groups was <b>0.07 standard</b> <b>deviations lower</b> (0.46 lower to 0.33 higher)
Imitation	(measure	d with: Imitation ta	sks (Rogers et a	I., 2003): Imitat	tive sequences	s; Better indicate	d by lower va	alues)	1	1	1
98 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	49	49	N/A	N/A	The mean imitation in the intervention groups was <b>0.24 standard</b> <b>deviations higher</b> (0.16 lower to 0.63 higher)
Orienting	y to soc	<b>ial stimuli</b> (m	easured with: So	l cial engageme	ent task (Daws	on et al., 2004):	l Mean Social	Orient I; Better indic	ated by low	er values)	-
98 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	49	49	N/A	N/A	The mean orienting to social stimuli in the intervention groups was <b>0.13 standard</b> <b>deviations higher</b> (0.27 lower to 0.52 higher)
Orienting	ı to joir	nt attention (m	neasured with: S	ocial engagem	ent task (Daw	son et al., 2004):	Mean Orien	t to Joint Attention; E	Better indica	ted by lower v	alues)
98 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2,3</sup> due to risk of	49	49	N/A	N/A	The mean orienting to joint attention in the intervention groups was

						bias, imprecision			<b>0 standard deviations</b> <b>higher</b> (0.4 lower to 0.4 higher)
only as 'labor <sup>2</sup> N<400 <sup>3</sup> High risk of outcome ass	atory perso performane essors not	onnel' with no infor	mation about blir ias as interventio bility and validity	nding on administrato of outcome me	ors and particip easure unclear	oants were non-b r	lind, and risk of detection bias is lind, and risk of detection bias is 5/0.5)		

## **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

		C	uality assess	sment				Sum	mary of F	inding	s
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Emotion recognition training versus treatment-as- usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome	effect (95% CI)	Risk with Control	Risk difference with Emotion recognition training versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome (95% Cl)
								Spence, 1995) or Situation-F licated by lower values)	Facial Expr	ession N	latching (SEM): Distant
119 (3 studies) 4-8 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	53	66	N/A	N/A	The mean emotion recognition in the intervention groups was <b>0.65 standard deviations</b> <b>higher</b> (0.27 to 1.03 higher)

49 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,4</sup> due to risk of bias, imprecision	23	26	N/A	N/A	The mean recognising emotion from posture in the intervention groups was <b>0.17 standard deviations</b> higher (0.4 lower to 0.73 higher)
Emotion	unders	standing (mea	asured with: Em	otional vocabu	ılary (study-sp	ecific); Better indic	ated by	y lower values)			
38 (1 study) 4 weeks	serious⁵	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>3,5</sup> due to risk of bias, imprecision	18	20	N/A	N/A	The mean emotion understanding in the intervention groups was <b>1.02 standard deviations</b> higher (0.34 to 1.7 higher)
Emotion	regula	tion and soc	cial skills (m	neasured with:	Emotion Reg	ulation and Social	Skills C	Questionnaire (ERSSO	; study-specific):	Total; Be	etter indicated by lower values)
49 (1 study) 8 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>3,6</sup> due to risk of bias, imprecision	23	26	N/A	N/A	The mean emotion regulation and social skills in the intervention groups was <b>1.39 standard deviations</b> <b>higher</b> (0.76 to 2.02 higher)
Anxiety	coping	skills (measur	ed with: James	and the Maths	Test (Attwood	d, 2004); Better ind	icated	by lower values)			
49 (1 study) 8 weeks	serious <sup>7</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	$\oplus \oplus \ominus \ominus$ LOW <sup>3,7</sup> due to risk of bias, imprecision	23	26	N/A	N/A	The mean anxiety coping skills in the intervention groups was <b>1.23 standard deviations</b> higher (0.62 to 1.85 higher)
Bullying	coping	<b>skills</b> (measu	red with: Dylan	is Being Tease	ed (Attwood, 2	2004); Better indica	ted by	lower values)			
49 (1 study) 8 weeks	serious <sup>7</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	$\oplus \oplus \ominus \ominus$ <b>LOW</b> <sup>3,7</sup> due to risk of bias, imprecision	23	26	N/A	N/A	The mean bullying coping skills in the intervention groups was <b>1.29 standard deviations</b>

											higher (0.67 to 1.91 higher)
Social sk	t <b>ills</b> (mea	sured with: Socia	al Skills Questio	nnaire (Spence	e, 1995): Tota	I; Better indicated	by lowe	er values)			
49 (1 study) 8 weeks	serious <sup>8</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>3,8</sup> due to risk of bias, imprecision	23	26	N/A	N/A	The mean social skills in the intervention groups was 1.42 standard deviations higher (0.79 to 2.05 higher)
is unclear <sup>2</sup> Substantial <sup>3</sup> N<400 <sup>4</sup> N<400 and <sup>5</sup> High risk of and study-spe <sup>6</sup> High risk of study-specific <sup>7</sup> High risk of and blindly co	to conside 95% CI cr performar ecific outc performar outcome performar oded	arable heterogene osses both line o ince and response ome measure with nee and response measure with no nce and response	tity (I-squared v f no effect and r bias as interve h no independe bias as interve independent m bias as interve	alue of 77%, p neasure of app ntion adminsitr nt measures o ntion adminsitr easures of reli ntion adminsitr	= 0.01) preciable bene ators and par f reliability or ators and par ability or valid ators and par	efit or harm (SMD - ticipants were non- validity data ticipants were non- ity data ticipants were non-	0.5/0.5 blind a blind a blind a	) nd high risk of detection bia nd high risk of detection bia	as as outcon as as outcon as as only 33	ne assess ne assess 3% of resp	linding of outcome assessors or was non-blind investigator or was non-blind parent and ponses were independently

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

Quality assessment	Summary of Findings
articipants Risk of bias Inconsistency Indirectness Imprecision Publication bias Overall quality of evidence	Study event rates (%)         Relative effect (95% Cl)         Anticipated absolute effects           With         With Face recognition training control         Risk difference with Face with         Risk difference with Face recognition training versus           Control         the core autism feature of impaired reciprocal social communication and interaction as a direct outcome         Relative effect (95% Cl)         Risk with         Risk difference with Face recognition training versus           Control         treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome (95% Cl)

78 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	37	41	N/A	N/A	The mean face recognition in the intervention groups was <b>0.07 standard deviations</b> <b>lower</b> (0.52 lower to 0.37 higher)
Face rec	ognitio	n (measured with	h: The Let's Fac	e It! Skills Bat	tery: Featural ar	nd configural face	dimen	sions (percent correct); Bette	er indicated	by lowe	r values)
78 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	37	41	N/A	N/A	The mean face recognition in the intervention groups was <b>0.02 standard deviations</b> <b>lower</b> (0.47 lower to 0.42 higher)
Face rec	ognitio	<b>n</b> (measured with	h: The Let's Fac	e It! Skills Bat	tery: Matching id	dentity across exp	pression	n (percent correct); Better in	dicated by lo	ower val	ues)
79 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	37	42	N/A	N/A	The mean face recognition in the intervention groups was <b>0.43 standard deviations</b> <b>lower</b> (0.88 lower to 0.02 higher)
Face rec	ognitio	<b>n</b> (measured with	h: The Let's Fac	e It! Skills Bat	tery: Parts/whole	e identity (percen	t correc	t); Better indicated by lower	values)	1	-
77 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	36	41	N/A	N/A	The mean face recognition in the intervention groups was <b>0.06 standard deviations</b> higher (0.39 lower to 0.51 higher)
Face rec	ognitio	<b>n</b> (measured wit	h: The Let's Fac	e It! Skills Bat	tery: Immediate	memory for faces	s (perce	ent correct); Better indicated	by lower va	lues)	ļ
77 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \bigcirc \bigcirc \bigcirc \\ \hline \textbf{VERY LOW}^{1,2} \\ \text{due to risk of} \\ \text{bias,} \end{array}$	36	41	N/A	N/A	The mean face recognition in the intervention groups was <b>0.26 standard deviations</b>

						imprecision				lower (0.71 lower to 0.19 higher)
assessors not <sup>2</sup> N<400 and 9	t reported 95% CI cro	and no independe	ent reliability or no effect and m	validity data for neasure of app	or outcome mea	asure t or harm (SMD -	and risk of detection bias unclear/unk	nown as id	entity and	d blinding of outcome

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

		Qı	uality assessr	nent				Sum	mary of F	indir	ıgs
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Stuc	ly event rates (%)	Relative	Anti	cipated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With	With Theory of Mind training versus waitlist control for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome	effect (95% CI)	Risk with	Risk difference with Theory of Mind training versus waitlist control for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome (95% CI)
Theory of	fmind	(measured with: T	heory of Mind (	ToM) Test: Tot	al; Better indic	ated by lower	values	;)			
36 (1 study) 16 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	17	19	N/A	N/A	The mean theory of mind in the intervention groups was <b>0.04 standard deviations</b> <b>higher</b> (0.61 lower to 0.7 higher)
Empathy	(measure	d with: Index of E	mpathy for Child	Iren and Adole	scents: Total;	Better indicate	d by lo	ower values)			•
36 (1 study) 16 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	17	19	N/A	N/A	The mean empathy in the intervention groups was <b>0.17 standard deviations lower</b> (0.82 lower to 0.49 higher)
Emotiona	al awar	eness (measur	ed with: Levels	of Emotional A	wareness Sca	le for Children	(LEAS	S-C): Total; Better indicated by l	ower value	s)	
36 (1 study) 16 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	17	19	N/A	N/A	The mean emotional awareness in the intervention groups was <b>0.46 standard deviations</b> <b>higher</b> (0.2 lower to 1.13 higher)
Maladapt	ive soc	ial behaviou	Ur (measured w	ith: Children's	Social Behavi	or Questionnai	re (CS	BQ): Total; Better indicated by	ower value	s)	
36	serious <sup>4</sup>	no serious	no serious	very	undetected	$\oplus \Theta \Theta \Theta$	17	19	N/A	N/A	The mean maladaptive social

(1 study) 16 weeks		inconsistency	indirectness	serious <sup>2</sup>		VERY LOW <sup>2,4</sup> due to risk of bias, imprecision			g 0	nehaviour in the intervention proups was 0.31 standard deviations lower 0.97 lower to 0.35 higher)
outcome asse <sup>2</sup> N<400 and 9 <sup>3</sup> High risk of	essor not i 95% Cl cr performar	reported osses both line of nce and response	no effect and m bias as interven	easure of appl tion administra	reciable benef	it or harm (SMD cipants non-blin	n-blind, and risk of detection bias is u 0 -0.5/0.5) d, and high risk of detection bias as s d, and high risk of detection bias as p	self-complete	ed	

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

		Qı	uality assess	ment				Sumr	nary of F	indings	\$		
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study	event rates (%)		Anticip	ated absolute effects		
(studies) Follow up	bias				bias	of evidence	With Control	With Emotion recognition training (computer-based) versus attention-placebo (computer software training) for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome	(95% CI)	Risk with Control	Risk difference with Emotion recognition training (computer- based) versus attention-placebo (computer software training) for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome (95% CI)		
Emotion	Emotion recognition (IQ <70 and >70 combined) (measured with: Ekman emotion recognition photographs; Better indicated by lower values)												
49 (1 study) 8 weeks	serious <sup>1</sup>		no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	25	24	N/A	N/A	The mean emotion recognition (iq <70 and >70 combined) in the intervention groups was <b>0.96 standard deviations</b> <b>higher</b> (0.37 to 1.56 higher)		
Emotion recognition (IQ <70 and >70 combined) (measured with: Study-specific emotion recognition in drawings test; Better indicated by lower values)													
49	serious <sup>3</sup>	no serious	no serious	serious <sup>2</sup>	undetected	$\oplus \oplus \ominus \ominus$	25	24	N/A	N/A	The mean emotion		

(1 study) 8 weeks		inconsistency	indirectness			LOW <sup>2.3</sup> due to risk of bias, imprecision					recognition (iq <70 and >70 combined) in the intervention groups was <b>1.1 standard deviations</b> higher (0.5 to 1.7 higher)
	•	ition (IQ <70 gs test; Better ind		-	(measured w	ith: Composite s	core fro	om Ekman emotion reco	gnition photograp	ohs and	study-specific emotion
49 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2.3</sup> due to risk of bias, imprecision	25	24	N/A	N/A	The mean emotion recognition (iq <70 and >70 combined) in the intervention groups was <b>1.09 standard deviations</b> higher (0.48 to 1.69 higher)
Face red	cognitio	n (IQ <70 an	d >70 com	<b>bined)</b> (me	asured with: B	enton Facial Rec	cognitio	n Test: Short Form; Bet	er indicated by lo	ower val	ues)
49 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	25	24	N/A	N/A	The mean face recognition (iq <70 and >70 combined) in the intervention groups was <b>0.88 standard deviations</b> <b>higher</b> (0.29 to 1.47 higher)
Face red	cognitio	n (IQ <70 an	d >70 com	bined) (me	asured with: B	enton Facial Red	cognitio	n Test: Long Form; Bett	er indicated by lo	wer valu	les)
49 (1 study) 8 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>2,4</sup> due to risk of bias, imprecision	25	24	N/A	N/A	The mean face recognition (iq <70 and >70 combined) in the intervention groups was 1.13 standard deviations higher (0.53 to 1.74 higher)
Social s	kills (IQ	<70 and >70	0 combined	<b>d)</b> (measured	with: Social S	kills Rating Syste	em (SSI	RS): Social skills (standa	ardized score); B	etter ind	icated by lower values)
49 (1 study) 8 weeks	no serious risk of bias	very serious⁵	no serious indirectness	very serious <sup>6</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>5,6</sup> due to inconsistency,	25	24	N/A	N/A	The mean social skills (iq <70 and >70 combined) in the intervention groups was <b>0.29 standard deviations</b>

						imprecision					higher (0.29 lower to 0.88 higher)
Social s	kills (IQ	<70) (measure	d with: Social S	kills Rating Sy	stem (SSRS):	Social skills (sta	ndardiz	ed score); Better in	dicated by lower valu	ues)	
25 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	14	11	N/A	N/A	The mean social skills (iq <70) in the intervention groups was <b>0.92 standard deviations</b> higher (0.08 to 1.75 higher)
Social s	kills (IQ	>70) (measure	d with: Social S	kills Rating Sy	stem (SSRS):	Social skills (sta	ndardiz	ed score); Better in	dicated by lower value	ues)	
24 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>6</sup>	undetected	⊕⊕⊖⊖ LOW <sup>6</sup> due to imprecision	11	13	N/A	N/A	The mean social skills (iq >70) in the intervention groups was <b>0.29 standard deviations</b> <b>lower</b> (1.09 lower to 0.52 higher)
Positive lower value		nteractions	(IQ <70 an	d >70 con	nbined) (m	easured with: Be	haviour	al observation: Initia	ating or maintaining	social int	eractions; Better indicated by
49 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	24	25	N/A	N/A	The mean positive social interactions (iq <70 and >70 combined) in the intervention groups was <b>0.6 standard deviations</b> <b>higher</b> (0.02 to 1.17 higher)
	e social I ated by lowe		(IQ <70 an	d >70 con	nbined) (m	easured with: Be	haviour	al observation: Soc	ial intention without	nititating	interaction (e.g. proximity);
49 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>6</sup>	undetected	⊕⊕⊝⊝ LOW <sup>6</sup> due to imprecision	25	24	N/A	N/A	The mean positive social interactions (iq <70 and >70 combined) in the interventior groups was <b>0.12 standard deviations</b>

							]				(0.68 lower to 0.45 higher)
Negative lower values		interactions	s (IQ <70 ar	nd >70 cor	<b>nbined)</b> (n	neasured with: B	ehaviou	ral observation: Negative s	ocial interact	ion beha	viours; Better indicated by
49 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	25	24	N/A	N/A	The mean negative social interactions (iq <70 and >70 combined) in the intervention groups was <b>0.88 standard deviations</b> <b>lower</b> (1.47 to 0.29 lower)
<ul> <li><sup>2</sup> N&lt;400</li> <li><sup>3</sup> High risk or</li> <li><sup>4</sup> High risk or</li> <li><sup>4</sup> Validity data</li> <li><sup>5</sup> Substantia</li> </ul>	f performar validity data f performar for the long I to conside	nce bias as intervo a for this outcome nce bias as intervo	ention administr measure ention administr ity with an I-squ	ator non-blind ator non-blind ared value of	and risk of de and risk of de 76% (p = 0.04	tection bias is un tection bias is un	clear/ui clear/ui	nknown as identity of outcor nknown as identity of outcor nknown as identity of outcor 5)	ne assessor	is not rep	ported and no independent

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

Participants (studies) Follow up         Risk of bias         Inconsistency         Indirectness         Imprecision         Publication bias         Overall quality of evidence         Study event rates (%)         Relative effect         Anticipated absolute effects           Follow up         Follow up         Imprecision         bias         Publication bias         Overall quality of evidence         With Enhanced emotion recognition training (DVD-based) for the core autism feature of impaired reciprocal social communication and interaction as a direct autome         Anticipated absolute effects		Qu	ality assessr	nent			Summary of Findings					
a direct ditcome (35% ci)	(studies)	Inconsistency	Indirectness	-	bias	quality of	With	With Enhanced emotion recognition training (DVD-based) versus standard emotion recognition training (DVD-based) for the core autism feature of impaired reciprocal social	effect (95% CI)	Risk with	Risk difference with Enhanced emotion recognition training (DVD- based) versus standard emotion recognition training (DVD-based) for the core autism feature of impaired reciprocal social	

					LOW <sup>1,2</sup> due to risk of bias, imprecision					in the intervention groups was <b>1.2 standard deviations</b> <b>higher</b> (0.34 to 2.07 higher)
recogn	ition (measure	ed with: Develop	mental Neuro	psychological	Assessment (N	NEPSY-	II): Affect Recognition; Better	indicated b	/ lower v	alues)
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	12	13	N/A	N/A	The mean emotion recognition in the intervention groups was <b>1.55 standard deviations</b> higher (0.63 to 2.46 higher)
social l	pehaviours	(measured with:	Social Comm	unication Que	stionnaire (SC	Q): Soc	ial peer interest; Better indicat	ed by lowe	r values)	L.
serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	12	13	N/A	N/A	The mean positive social behaviours in the intervention groups was <b>0.33 standard deviations</b> <b>higher</b> (0.46 lower to 1.12 higher)
social l	pehaviours	(measured with:	Social Comm	unication Que	stionnaire (SC	Q): Eye	contact; Better indicated by lo	ower values	)	
serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	12	13	N/A	N/A	The mean positive social behaviours in the intervention groups was <b>0.04 standard deviations</b> higher (0.74 lower to 0.83 higher)
ersion (r	neasured with: S	ocial Communic	ation Question	nnaire (SCQ):	Gaze aversion	n; Better	indicated by lower values)	•		
serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	12	13	N/A	N/A	The mean gaze aversion in the intervention groups was <b>0.14 standard deviations</b> <b>lower</b> (0.93 lower to 0.64 higher)
	serious <sup>1</sup> social I serious <sup>3</sup> social I serious <sup>3</sup> ersion (r serious <sup>3</sup>	serious <sup>1</sup> no serious         social behaviours         serious <sup>3</sup> no serious         inconsistency         serious <sup>3</sup> no serious         social behaviours         social behaviours         serious <sup>3</sup> no serious         serious <sup>3</sup> no serious         serious <sup>3</sup> no serious         inconsistency       ersion (measured with: S         serious <sup>3</sup> no serious         inconsistency       inconsistency	serious <sup>1</sup> no serious inconsistency       no serious indirectness         social behaviours       (measured with: serious <sup>3</sup> no serious inconsistency       no serious indirectness         social behaviours       (measured with: serious <sup>3</sup> no serious inconsistency       no serious indirectness         serious <sup>3</sup> no serious inconsistency       no serious indirectness         ersion       (measured with: Social Communic serious <sup>3</sup> no serious inconsistency         serious <sup>3</sup> no serious inconsistency       no serious indirectness	serious1no serious inconsistencyno serious indirectnessserious2social behaviours(measured with: Social Comm serious3social Comm inconsistencyno serious indirectnessvery serious4social behaviours(measured with: Social Comm inconsistencyno serious indirectnessvery serious4social behaviours(measured with: Social Comm inconsistencyno serious indirectnessvery serious4serious3no serious inconsistencyno serious indirectnessvery serious4serious3no serious inconsistencyno serious indirectnessvery serious4ersion(measured with: Social Communication Question inconsistencyno serious indirectnessvery serious4	serious1no serious inconsistencyno serious indirectnessserious2undetectedsocial behaviours(measured with: Social Communication Que indirectnessvery serious4undetectedserious3no serious inconsistencyno serious indirectnessvery serious4undetectedsocial behaviours(measured with: Social Communication Que indirectnessvery serious4undetectedsocial behaviours(measured with: Social Communication Que inconsistencyno serious indirectnessvery serious4undetectedserious3no serious inconsistencyno serious indirectnessvery serious4undetectedserious3no serious inconsistencyno serious indirectnessvery serious4undetectedserious3no serious inconsistencyno serious indirectnessvery serious4undetectedserious3no serious inconsistencyno serious indirectnessvery serious4undetected	serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision         SOCial behaviours       (measured with: Social Communication Questionnaire (SC serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision         Social behaviours       (measured with: Social Communication Questionnaire (SC very serious <sup>3</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision         ersion       mo serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊝⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊝⊖	serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision       12         social behaviours       (measured with: Social Communication Questionnaire (SCQ): Social inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊝⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12         social behaviours       (measured with: Social Communication Questionnaire (SCQ): Eye serious <sup>3</sup> 12         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision       12       13         social behaviours (measured with: Social Communication Questionnaire (SCQ): Social peer interest; Better indicat inconsistency       no serious indirectness       no serious very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12       13         social behaviours (measured with: Social Communication Questionnaire (SCQ):       12       13         serious <sup>3</sup> no serious inconsistency       no serious on serious       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12       13         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12       13         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12       13	serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision       12       13       N/A         SOCial behaviours (measured with: Social Communication Questionnaire (SCQ): Social peer interest; Better indicated by lower inconsistency       no serious indirectness       no serious <sup>3</sup> no serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12       13       N/A         social behaviours (measured with: Social Communication Questionnaire (SCQ):       12       13       N/A         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12       13       N/A         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12       13       N/A         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision       12       13       N/A	inconsistency       indirectness       Very         social behaviours       (measured with: Social Communication Questionnaire (SCQ): Social peer interest; Better indicated by lower values)         serious <sup>3</sup> no serious       no serious         inconsistency       indirectness       very         serious <sup>3</sup> no serious       no serious         inconsistency       indirectness       very         serious <sup>3</sup> no serious       no serious         inconsistency       indirectness       very         serious <sup>3</sup> no serious       no serious         inconsistency       indirectness       very         serious <sup>3</sup> no serious       no serious         inconsistency       no serious       very         serious <sup>3</sup> no serious       no serious         inconsistency       no serious       very         serious <sup>3</sup> no serious       no serious         indirectness       very       undetected $\oplus \bigcirc \ominus \ominus$ VERY       LOW <sup>3,4</sup> due to risk of bias, imprecision         very       serious <sup>4</sup> undetected $\oplus \ominus \ominus \ominus$ VERY       LOW <sup>3,4</sup> due to risk of bias, imprecision       N/A         serious <sup>3</sup> </td

outcome assessor unclear and the reliability and validity of this outcome measure is unclear  $^2\,\text{N}{<}400$ 

<sup>3</sup> High risk of performance and detection bias as parents were non-blind and were intervention administrators and outcome assessors <sup>4</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

# **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

		Qı	uality assessn	nent				Sur	nmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study event ra	ates (%)	Relative	Anticipated ab	solute effects
(studies) Follow up	bias				bias	quality of evidence	With Intervention- manual-only control	With Inclusive educational intervention (LEAP) training	effect (95% CI)	Risk with Intervention- manual-only control	Risk difference with Inclusive educational intervention (LEAP) training (95% Cl)
Social sk	<b>ills</b> (mea	sured with: Social	Skills Rating Sys	stem (SSRS):	Positive socia	l skills (percentil	e rank score); B	etter indicated by lo	ower values	)	
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	117	177	N/A	N/A	The mean social skills in the intervention groups was <b>0.76 standard</b> <b>deviations higher</b> (0.52 to 1 higher)
<sup>1</sup> High risk of outcome asse <sup>2</sup> N<400	•		bias as interventi	on administrat	tors and partic	ipants non-blind	. In addition, risk	of detection bias is	s unclear/ur	iknown as identi	ty and blinding of

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

		Q	uality assessi	nent				Sur	nmary of	Findir	ngs
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Stud	y event rates (%)	Relative	Antic	ipated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With IBI- only	With Combined computer- assisted educational intervention and intensive behavioural intervention (IBI) day class program	effect (95% CI)	Risk with IBI- only	Risk difference with Combined computer-assisted educational intervention and intensive behavioural intervention (IBI) day class program (95% CI)
Social sk	<b>ills</b> (mea	sured with: Brigar	nce Inventory of	Child Developr	ment: Social sl	kills; Better indic	ated b	y lower values)			
46 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	24	22	N/A	N/A	The mean social skills in the intervention groups was <b>0.1 standard deviations lowe</b> (0.68 lower to 0.48 higher)
Social sk	ills (pr	eschool sub	group anal	<b>ysis)</b> (measu	red with: Briga	ance Inventory o	f Chilo	Development: Social skills;	Better indic	ated by	v lower values)
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	12	11	N/A	N/A	The mean social skills (preschool subgroup analysis) in the intervention groups was 0.18 standard deviations lower (1 lower to 0.64 higher)
Social sk	ills (K-	1 subgroup	analysis) (m	easured with: I	I Brigance Inver	ntory of Child De	velopi	ment: Social skills; Better indi	cated by lov	wer val	ues)
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	12	11	N/A	N/A	The mean social skills (k-1 subgroup analysis) in the intervention groups was <b>0.03 standard deviations</b> <b>lower</b> (0.85 lower to 0.79 higher)

## **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 or indirect outcome

		Qu	ality assessr	nent				Sun	nmary of I	Finding	S
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Parent training versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction	effect (95% CI)	Risk with Control	Risk difference with Parent training versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction (95% Cl)
Reciproc values)	al soci	al interactio	n (direct ou	<b>itcome)</b> (m	easured with:	Autism Diagno	stic Inter	view-Revised (ADI-R): Recip	orocal Socia	al Interac	tion; Better indicated by lower
24 (1 study) 52 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	<ul> <li>⊕⊖⊖</li> <li>VERY</li> <li>LOW<sup>1,2</sup></li> <li>due to risk of bias,</li> <li>imprecision</li> </ul>	12	12	N/A	N/A	The mean reciprocal social interaction (direct outcome) in the intervention groups was 0.38 standard deviations lower (1.19 lower to 0.43 higher)
Nonverba	al com	nunication (	direct outc	c <b>ome)</b> (meas	sured with: Au	tism Diagnostic	Interviev	w-Revised (ADI-R): Nonverb	al Commur	nication; I	Better indicated by lower
24 (1 study) 52 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	12	12	N/A	N/A	The mean nonverbal communication (direct outcome) in the intervention groups was <b>0.37 standard deviations</b> <b>lower</b> (1.18 lower to 0.44 higher)

Social skills (indirect outcome) (measured with: Social Skills Questionnaire (Spence, 1995): Total or Scales of Independent Behavior-Revised (SIB): Social interaction; Better indicated by lower values)

71 (2 studies)		no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ LOW <sup>3,4</sup>	25	46	N/A	N/A	The mean social skills (indirect outcome) in the intervention
10-12 weeks					due to risk of bias, imprecision					groups was 0.77 standard deviations higher
					Imprecision					(0.25 to 1.28 higher)

### Social skills (indirect outcome; combined workshop + individual sessions) (measured with: Social Skills Questionnaire (Spence, 1995): Total; Better indicated by lower values)

51	serious⁵	no serious	no serious	serious <sup>4</sup>	$\oplus \oplus \ominus \ominus$	15	36	N/A	N/A	The mean social skills (indirect
(1 study)		inconsistency	indirectness		LOW <sup>4,5</sup>					outcome; combined workshop
10 weeks					due to risk of					+ individual sessions) in the
					bias,					intervention groups was
					imprecision					0.98 standard deviations
										higher
										(0.34 to 1.61 higher)

#### Social skills (indirect outcome) (measured with: Scales of Independent Behavior-Revised (SIB-R): Social interaction; Better indicated by lower values)

20	serious <sup>6</sup>	no serious	no serious	very	undetected	$\oplus \Theta \Theta \Theta$	10	10	N/A	N/A	The mean social skills (indirect
(1 study)		inconsistency	indirectness	serious <sup>2</sup>		VERY					outcome) in the intervention
12 weeks						LOW <sup>2,6</sup>					groups was
						due to risk of					0.37 standard deviations
						bias,					higher
						imprecision					(0.52 lower to 1.25 higher)
						-					

<sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome assessors were non-blind <sup>2</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

<sup>3</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias high or unclear as either parent-rated and parents were non-blind and involved in the intervention or the identity and blinding of the outcome assessor was not reported

<sup>4</sup> N<400

<sup>5</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as parent-rated and parents were non-blind and involved in the intervention

<sup>6</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias unclear as the identity and blinding of the outcome assessor was not reported

## **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

		C	Quality asses	sment			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study eve	nt rates (%)	Relative	Anticipate	d absolute effects
(studies) Follow up	bias				bias	of evidence	With Treatment- as-usual	With Caregiver- or preschool-teacher- mediated social- communication interventions	effect (95% CI)	Risk with Treatment- as-usual	Risk difference with Caregiver- or preschool-teacher- mediated social- communication interventions (95% Cl)
		n (Caregive		social co	ommunicat	ion intervent	ion) (mea	sured with: Autism D	agnostic C	bservation	Schedule (ADOS/ADOS-G):
180 (2 studies) 52-56 weeks	no serious risk of bias	serious <sup>1</sup>	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1,2</sup> due to inconsistency, imprecision	89	91	N/A	N/A	The mean social interaction (caregiver- mediated social communication intervention) in the intervention groups was <b>0.29 standard deviations</b> <b>lower</b> (0.59 lower to 0 higher)
		indicated by lowe		social com	imunicatio	on interventio	<b>n)</b> (measu	red with: Autism Diag	nostic Obs	servation Sc	hedule (ADOS/ADOS-G):
152 (1 study) 56 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊕⊖⊖ LOW <sup>2,3</sup> due to imprecision, publication bias	75	77	N/A	N/A	The mean communication (caregiver-mediated social communication intervention) in the intervention groups was <b>0.03 standard deviations</b> <b>lower</b> (0.35 lower to 0.29 higher)

202 (2 studies) 39-56 weeks <b>Parent-ra</b>	no serious risk of bias	serious <sup>1</sup>	no serious indirectness	serious <sup>2</sup>	strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to inconsistency, imprecision, publication bias ocial commutication	nicatio	102	ion) (measure	N/A	The mean social interaction and communication (caregiver mediated social communication intervention) in the intervention groups was <b>0 standard deviations</b> <b>higher</b> (0.28 lower to 0.27 higher)
			•	-		by lower values)	moutio				
152 (1 study) 56 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>2,4</sup> due to risk of bias, imprecision	75	77	N/A	N/A	The mean parent-rated social-communication (caregiver-mediated socia communication intervention) in the intervention groups was <b>0.39 standard deviations</b> higher (0.06 to 0.71 higher)
		• •	-			cation interv	-		: Behavioural c	bservation	Child communication acts or
223 (3 studies) 22-56 weeks	no serious risk of bias	serious <sup>1</sup>	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to inconsistency, imprecision	108	115	N/A	N/A	The mean communication acts (caregiver-mediated social communication intervention) in the intervention groups was 0.37 standard deviations higher (0.1 to 0.64 higher)

111 (2 studies) 8-22 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	50	61	N/A	N/A	The mean examiner-child joint/shared attention (caregiver- or preschool- teacher- mediated social- communication intervention) in the intervention groups was <b>0.06 standard deviations</b> <b>lower</b> (0.43 lower to 0.32 higher)
	-	joint/shared : Initiating Joint A					nunicati	on interventio	<b>n)</b> (measu	red with: ES	cs (Early Social
51 (1 study) 22 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	23	28	N/A	N/A	The mean examiner-child joint/shared attention (caregiver-mediated social communication intervention) in the intervention groups was <b>0.12 standard deviations</b> <b>Iower</b> (0.68 lower to 0.43 higher)
	-	joint/shared : Initiating Joint A		-			ial com	munication int	erventi	<b>on)</b> (measu	red with: EScs (Early Social
60 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	27	33	N/A	N/A	The mean examiner-child joint/shared attention (preschool-teacher- mediated social communication intervention) in the intervention groups was <b>0 standard deviations</b> <b>higher</b> (0.51 lower to 0.51 higher)
	-	<b>t/shared att</b> n: Parent-child join	•	-	-		ediated	social-commu	nicatio	n interve	ntion) (measured with:
302	no	no serious	no serious	serious <sup>2</sup>	undetected	$\oplus \oplus \oplus \ominus$	147	155	N/A	N/A	The mean parent-child

(5 studies) 8-56 weeks	serious risk of bias	inconsistency	indirectness			MODERATE <sup>2</sup> due to imprecision					joint/shared attention (caregiver- or preschool- teacher- mediated social- communication intervention) in the intervention groups was <b>0.30 standard deviations</b> higher (0.07 to 0.53 higher)
	-	<b>t/shared att</b> on; Better indicate	•	-	ediated so	cial commun	ication	intervention) (r	neasured v	vith: Behavio	bural observation: Parent-
241 (4 studies) 8-56 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	120	121	N/A	N/A	The mean parent-child joint/shared attention (caregiver-mediated social communication intervention) in the intervention groups was <b>0.33 standard deviations</b> higher (0.07 to 0.59 higher)
	-	<b>t/shared att</b> d joint/shared atte	•			diated social	commu	inication inter	vention	) (measured	I with: Behavioural
61 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	27	34	N/A	N/A	The mean parent-child joint/shared attention - (preschool-teacher- mediated social communication intervention) in the intervention groups was <b>0.17 standard deviations</b> <b>higher</b> (0.33 lower to 0.68 higher)
	-	tter indicated by l	-	(Caregive	r-mediated	l social comr	nunicat	ion interventio	n) (measu	ured with: Be	havioural observation: Joint
61 (2 studies)	no serious	very serious <sup>6</sup>	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>2,6</sup>	31	30	N/A	N/A	The mean parent-child joint attention responses

						due to inconsistency, imprecision acher- media	ted soc	cial-communic	ation in	terventio	(caregiver-mediated social communication intervention) in the intervention groups was 2.25 standard deviations higher (1.57 to 2.93 higher) <b>DN)</b> (measured with:
99 (2 studies) 8 weeks	no serious risk of bias	n: Joint engagement no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	46 ion inte	53 ervention) (meas	N/A ured with: B	N/A Behavioural	The mean parent-child joint engagement (caregiver- or preschool-teacher- mediated social- communication intervention) in the intervention groups was <b>0.55 standard deviations</b> <b>higher</b> (0.14 to 0.95 higher)
engagement 38 (1 study) 8 weeks	; Better ind no serious risk of bias	icated by lower va	alues) no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	19	19	N/A	N/A	The mean parent-child join engagement (caregiver- mediated social communication intervention) in the intervention groups was <b>0.85 standard deviations</b> higher (0.18 to 1.52 higher)
	-	nt engageme er indicated by lo	•	ool-teach	er-mediate	ed social con	nmunica	ation intervent	: <b>ion)</b> (mea	asured with:	Behavioural observation:
61 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	27	34	N/A	N/A	The mean parent-child join engagement (preschool- teacher-mediated social communication

Teacher	-child jo	int/shared a	ittention (P	reschool-	teacher-m	ediated socia	al comr	nunication inte	rventio	<b>n)</b> (measure	intervention) in the intervention groups was <b>0.37 standard deviations</b> <b>higher</b> (0.14 lower to 0.88 higher) ed with: Behavioural
61 (1 study) 8 weeks	no serious risk of bias	teacher-child play	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	27	34	N/A	N/A	The mean teacher-child joint/shared attention (preschool-teacher- mediated social communication intervention) in the intervention groups was <b>0.57 standard deviations</b> <b>higher</b> (0.05 to 1.08 higher)
		Int engagen d play): Joint enga no serious inconsistency				ted social co ⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	27	34	N/A	N/A	The mean teacher-child joint engagement (preschool-teacher- mediated social communication intervention) in the intervention groups was 0.31 standard deviations lower (0.81 lower to 0.2 higher)
	-	BR); Better indic			communio	cation interve	ention) (	measured with: EScs	(Early Soc	ial Commun	ication Scales): Initiating
51 (1 study) 22 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	23	28	N/A	N/A	The mean behaviour requests (caregiver- mediated social communication intervention) in the

	-	ests (Caregi				cation interve	ntion)	(Copy) (meas	sured with: ESc	s (Early So	intervention groups was <b>0.18 standard deviations</b> <b>higher</b> (0.37 lower to 0.73 higher) cial Communication Scales):
49 (1 study) 39 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	25	24	N/A	N/A	The mean behaviour requests (caregiver- mediated social communication intervention) (copy) in the intervention groups was <b>0.07 standard deviations</b> <b>higher</b> (0.49 lower to 0.63 higher)
		munication mmunication; Bet				mmunication	interv	ention) (meas	sured with: Par	ent Interviev	v for Autism-Clinical Version
47 (1 study) 22 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	20	27	N/A	N/A	The mean non-verbal communication (caregiver- mediated social communication intervention) in the intervention groups was <b>0.09 standard deviations</b> <b>lower</b> (0.67 lower to 0.49 higher)
		munication				mmunication	interv	ention) (meas	sured with: Par	ent Interviev	v for Autism-Clinical Version
47 (1 study) 39 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	24	23	N/A	N/A	The mean non-verbal communication (caregiver- mediated social communication intervention) in the intervention groups was 0.04 standard deviations lower

											(0.62 lower to 0.53 higher)
Focusin indicated by	-	• •	er-mediate	d social o	communica	ation interve	ntion) (m	neasured with: B	ehavioural obs	ervation (P.	AM): Focusing on faces; Bette
23 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	12	11	N/A	N/A	The mean focusing on faces (caregiver-mediated social communication intervention) in the intervention groups was <b>1.87 standard deviations</b> higher (0.86 to 2.88 higher)
Focusin indicated by	-	• •	er-mediate	d social c	communica	ation interve	ntion) (m	neasured with: B	ehavioural obs	ervation (P.	IAM): Focusing on faces; Bette
23 (1 study) 60 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	12	11	N/A	N/A	The mean focusing on faces (caregiver-mediated social communication intervention) in the intervention groups was <b>0.91 standard deviations</b> <b>higher</b> (0.05 to 1.78 higher)
Turn-tak	•••	regiver-med	liated socia	al commu	nication in	tervention) (r	neasured v	with: Behavioural	observation (F	JAM): Turn	-Taking; Better indicated by
23 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	12	11	N/A	N/A	The mean turn-taking (caregiver-mediated socia communication intervention) in the intervention groups was <b>0.73 standard deviations</b> <b>higher</b> (0.12 lower to 1.58 higher)
Turn-tak	-	egiver-medi	ated socia	l commur	nication int	ervention) (m	easured w	ith: Behavioural o	bbservation (P.	JAM): Turn-	Taking; Better indicated by
23	no	no serious	no serious	very	undetected	$\oplus \oplus \ominus \ominus$	12	11	N/A	N/A	The mean turn-taking

(1 study) 60 weeks	serious risk of bias	inconsistency	indirectness	serious⁵	LOW <sup>5</sup> due to imprecision			caregiver-mediated social communication intervention) in the intervention groups was <b>0.14 standard deviations</b> <b>lower</b> (0.96 lower to 0.68 higher)
<sup>2</sup> N<400 <sup>3</sup> High risk of	f selective r					DS communication subdomain ind, and high risk of detection bia	as as outcome measu	re was parent-reported and

High risk or performance and response bias as intervention administrators and participants were non-blind, ar parents were non-blind and involved in the delivery of the intervention <sup>5</sup>N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

<sup>6</sup> Substantial to considerable heterogeneity

### 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

		C	Quality asses	sment				S	Summary	of Finding	gs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study eve	ent rates (%)	Relative effect	Anticipate	ed absolute effects
Follow up							With Treatment- as-usual	With Peer-mediated (and/or therapist- mediated) social- communication interventions	(95% CI)	Risk with Treatment- as-usual	Risk difference with Peer- mediated (and/or therapist- mediated) social-communication interventions (95% CI)
	-		•					rvention) (mea gement in playgrour			al observation: Number of lower values)
114 (2 studies) 6-15 weeks	no serious risk of bias	very serious <sup>1</sup>	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to inconsistency, imprecision, publication bias	51	63	N/A	N/A	The mean peer-child joint engagement (peer-mediated social-communication intervention) in the intervention groups was <b>0.7 standard deviations</b> <b>higher</b> (0.31 to 1.08 higher)
	-	t engagem t in playground ;	•	-		ial-commu	nication	intervention	<b>1)</b> (measu	red with: Be	havioural observations of %
(1 study) 6 weeks	serious risk of bias	inconsistency	indirectness	serious <sup>4</sup>		LOW <sup>4</sup> due to imprecision					engagement (therapist- mediated social- communication intervention in the intervention groups was 0.03 standard deviations higher (0.7 lower to 0.76 higher)

#### Peer-child joint engagement (Peer-mediated social-communication intervention) (measured with: Behavioural observations of % time in joint engagement in playground; Better indicated by lower values) 29 no no serious no serious undetected $\Theta \Theta \Theta \Theta$ 14 15 N/A N/A The mean peer-child joint very LOW<sup>4</sup> (1 study) serious inconsistency indirectness serious<sup>4</sup> engagement (peer-mediated 6 weeks risk of social-communication due to bias imprecision intervention) in the intervention groups was 0.12 standard deviations higher (0.61 lower to 0.84 higher) Peer-child joint engagement (Both therapist- and peer- mediated social-communication intervention) (measured with: Behavioural observations of % time in joint engagement in playground; Better indicated by lower values) 14 29 no no serious no serious undetected $\oplus \oplus \ominus \ominus$ 15 N/A N/A The mean peer-child joint very LOW<sup>4</sup> (1 study) serious inconsistency indirectness serious4 engagement (both therapist-6 weeks risk of due to and peer- mediated socialbias imprecision communication intervention) in the intervention groups was 0 standard deviations higher (0.73 lower to 0.73 higher) Peer-child joint engagement (Therapist-mediated social-communication intervention) (measured with: Behavioural observations of % time in joint engagement in playground; Better indicated by lower values) 30 undetected 15 15 N/A N/A The mean peer-child joint no no serious no serious $\oplus \oplus \ominus \ominus$ verv (1 study) serious inconsistency indirectness serious<sup>4</sup> LOW<sup>4</sup> engagement (therapist-12 weeks risk of due to mediated socialbias imprecision communication intervention) in the intervention groups was 0.13 standard deviations higher (0.59 lower to 0.85 higher)

29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊕⊖⊖ LOW <sup>4</sup> due to imprecision	15	14	N/A	N/A	The mean peer-child joint engagement (peer-mediated social-communication intervention) in the intervention groups was <b>0.75 standard deviations</b> <b>higher</b> (0 to 1.51 higher)
	-		•		•	er - mediated ad by lower values		l-commu	nication i	nterven	tion) (measured with:
30 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	15	15	N/A	N/A	The mean peer-child joint engagement (both therapist- and peer- mediated social- communication intervention) in the intervention groups was <b>0.86 standard deviations</b> higher (0.11 to 1.62 higher)
		<b>social inte</b>	•				nicatio	on interve	ntion) (mea	sured with: I	Behavioural observations of
85 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊕⊖⊖ LOW <sup>2,3</sup> due to imprecision, publication bias	37	48	N/A	N/A	The mean child-initiated social interactions (peer- mediated social- communication intervention) in the intervention groups was 0.65 standard deviations higher

		social inter social interaction	•				nication	n interventio	<b>n)</b> (measu	red with: Be	havioural observations of
85 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊕⊝⊝ LOW <sup>2.3</sup> due to imprecision, publication bias	37	48	N/A	N/A	The mean child-initiated social interactions (peer- mediated social- communication intervention) in the intervention groups was <b>0.68 standard deviations</b> <b>higher</b> (0.24 to 1.12 higher)
		x <b>salience (</b> ; Better indicated	•		d social-c	ommunicat	ion inte	ervention) (me	asured with	n: Social Ne	twork Survey (SNS): Social
30 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean social network salience (therapist-mediated social-communication intervention) in the intervention groups was <b>0.05 standard deviations</b> <b>lower</b> (0.77 lower to 0.66 higher)
		<b>salience (</b>		iated soc	ial-comm	unication ir	nterven	tion) (measured v	with: Socia	Network St	urvey (SNS): Social Network
30 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean social network salience (peer-mediated social-communication intervention) in the intervention groups was <b>0.42 standard deviations</b> <b>higher</b> (0.3 lower to 1.15 higher)
Social n	etwork	salience (	Both thera	apist-me	diated and	d peer-medi	ated so	ocial-commu	nicatio	n interv	rention) (measured with:

Social Netwo	rk Survey	(SNS): Social Net	twork Salience	Ratio; Better i	ndicated by low	er values)					
30 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>2.5</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean social network salience (both therapist- mediated and peer-mediated social-communication intervention) in the intervention groups was <b>1.15 standard deviations</b> higher (0.37 to 1.93 higher)
		; Better indicated	-		u social-c	ommunicat	ion int	ervention) (	measured wit	h: Social N	etwork Survey (SNS): Social
29 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	15	14	N/A	N/A	The mean social network salience (therapist-mediated social-communication intervention) in the intervention groups was <b>0.51 standard deviations</b> <b>lower</b> (1.25 lower to 0.23 higher)
		a salience (		iated soc	ial-comm	unication ir	ntervei	ntion) (measure	ed with: Socia	I Network	Survey (SNS): Social Network
30 (1 study) 12 weeks	serious⁵	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean social network salience (peer-mediated social-communication intervention) in the intervention groups was <b>0.03 standard deviations</b> <b>higher</b> (0.68 lower to 0.75 higher)
Social n	etwork	salience (	Both thera	apist-me	diated and	d peer-medi	ated s	ocial-comm	unicatio	on inter	vention) (measured with:

Social Netwo	rk Survey	(SNS): Social Net	twork Salience	Ratio; Better ir	ndicated by low	er values)					
			-		· ·	⊕⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision st-mediated er indicated by lowe		<sup>15</sup> -communicat	N/A	N/A erventic	The mean social network salience (both therapist- mediated and peer-mediated social-communication intervention) in the intervention groups was <b>0.32 standard deviations</b> higher (0.4 lower to 1.04 higher) <b>ON)</b> (measured with: Social
30 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean number of received friendship nominations (therapist- mediated social- communication intervention) in the intervention groups was <b>0.18 standard deviations</b> <b>lower</b> (0.9 lower to 0.54 higher)
			•		•	diated soci		munication i	nterver	ntion) (m	easured with: Social Network
30 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>2.5</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean number of received friendship nominations (peer-mediated social-communication intervention) in the intervention groups was <b>0.96 standard deviations</b> <b>higher</b> (0.19 to 1.72 higher)

#### Number of received friendship nominations (Both therapist-mediated and peer-mediated social-communication intervention) (measured with: Social Network Survey (SNS): Number of received friendship nominations (Indegrees); Better indicated by lower values) 30 serious55 no serious 15 15 N/A N/A no serious undetected $\oplus \Theta \Theta \Theta$ The mean number of very VERY LOW<sup>4,5</sup> (1 study) inconsistency indirectness serious<sup>4</sup> received friendship 6 weeks due to risk of nominations (both therapistbias, imprecision mediated and peer-mediated social-communication intervention) in the intervention groups was 0.51 standard deviations higher (0.22 lower to 1.24 higher) Number of received friendship nominations (Therapist-mediated social-communication intervention) (measured with: Social Network Survey (SNS): Number of received friendship nominations (Indegrees); Better indicated by lower values) serious⁵ no serious 15 N/A N/A 29 no serious very undetected $\Theta \Theta \Theta \Theta$ 14 The mean number of VERY LOW<sup>4,5</sup> (1 study) inconsistency indirectness serious<sup>4</sup> received friendship 12 weeks due to risk of nominations (therapistbias, imprecision mediated socialcommunication intervention) in the intervention groups was 0.1 standard deviations lower (0.83 lower to 0.63 higher) Number of received friendship nominations (Peer-mediated social-communication intervention) (measured with: Social Network Survey (SNS): Number of received friendship nominations (Indegrees); Better indicated by lower values) 30 serious⁵ $\Theta \Theta \Theta \Theta$ 15 N/A N/A no serious no serious very undetected 15 The mean number of VERY LOW<sup>4,5</sup> (1 study) inconsistency indirectness serious<sup>4</sup> received friendship 12 weeks nominations (peer-mediated due to risk of bias, imprecision social-communication intervention) in the intervention groups was 0.33 standard deviations

											higher (0.39 lower to 1.05 higher)			
-	Number of received friendship nominations (Both therapist-mediated and peer-mediated social-communication intervention) (measured with: Social Network Survey (SNS): Number of received friendship nominations (Indegrees); Better indicated by lower values)													
30 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean number of received friendship nominations (both therapist- mediated and peer-mediated social-communication intervention) in the intervention groups was <b>0.25 standard deviations</b> <b>higher</b> (0.47 lower to 0.97 higher)			
Number of times child identified as someone other children don't like to 'hang out with' (Therapist-mediated social- communication intervention) (measured with: Social Network Survey (SNS): Rejections; Better indicated by lower values)														
27 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	14	13	N/A	N/A	The mean number of times child identified as someone other children don't like to 'hang out with' (therapist- mediated social- communication intervention) in the intervention groups was <b>0.44 standard deviations</b> <b>higher</b> (0.32 lower to 1.21 higher)			
Number of times child identified as someone other children don't like to 'hang out with' (Peer-mediated social- communication intervention) (measured with: Social Network Survey (SNS): Rejections; Better indicated by lower values)														
29 (1 study)	serious⁵	no serious	no serious	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2,5</sup>	14	15	N/A	N/A	The mean number of times child identified as someone			

6 weeks		inconsistency	indirectness			due to risk of bias, imprecision					other children don't like to 'hang out with' (peer- mediated social- communication intervention) in the intervention groups was <b>0.94 standard deviations</b> <b>higher</b> (0.17 to 1.72 higher)
											apist-mediated and
peer-me	diated	social-con	nmunicati	on interv	rention) (me	easured with: Socia	al Network S	Survey (SNS): Rejec	ctions; Bett	er indicated	by lower values)
29 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	14	15	N/A	N/A	The mean number of times child identified as someone other children don't like to 'hang out with' (both therapist-mediated and peer- mediated social- communication intervention) in the intervention groups was <b>0.35 standard deviations</b> <b>higher</b> (0.38 lower to 1.09 higher)
Number	of time	es child ide	entified as	someon	e other cl	hildren don'	t like to	hang out w	vith' (Th	erapist	-mediated social-
								dicated by lower val	•		
26 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	14	12	N/A	N/A	The mean number of times child identified as someone other children don't like to 'hang out with' (therapist- mediated social- communication intervention) in the intervention groups was <b>0.17 standard deviations</b>

											lower (0.94 lower to 0.61 higher)		
Number of times child identified as someone other children don't like to 'hang out with' (Peer-mediated social- communication intervention) (measured with: Social Network Survey (SNS): Rejections; Better indicated by lower values)													
29 (1 study) 12 weeks		no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	e other c	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	14 t liko t	15	N/A	N/A	The mean number of times child identified as someone other children don't like to 'hang out with' (peer- mediated social- communication intervention) in the intervention groups was 0.14 standard deviations higher (0.59 lower to 0.87 higher) 'apist-mediated and		
								Survey (SNS): Reje	-		-		
29 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	14	15	N/A	N/A	The mean number of times child identified as someone other children don't like to 'hang out with' (both therapist-mediated and peer- mediated social- communication intervention) in the intervention groups was <b>0.42 standard deviations</b> <b>higher</b> (0.32 lower to 1.15 higher)		
		social skill	• •	ist-media	ted socia	Il-communio	ation	intervention)	(measured	I with: Teach	ner Perception of Social Skills		

26 (1 study) 6 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>4,6</sup> due to risk of bias, imprecision	13	13	N/A	N/A	The mean teacher-rated social skills (therapist- mediated social- communication intervention) in the intervention groups was <b>0.11 standard deviations</b> <b>Iower</b> (0.88 lower to 0.66 higher)
		social skill y lower values)	s (Peer-m	ediated s	ocial-con	nmunicatior	n interv	ention) (measu	red with: To	eacher Perco	eption of Social Skills (TPSS):
28 (1 study) 6 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,6</sup> due to risk of bias, imprecision	13	15	N/A	N/A	The mean teacher-rated social skills (peer-mediated social-communication intervention) in the intervention groups was <b>0.36 standard deviations</b> higher (0.39 lower to 1.11 higher)
		social skill n of Social Skills					ediated	social-com	nunica	tion inte	ervention) (measured
28 (1 study) 6 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,6</sup> due to risk of bias, imprecision	13	15	N/A	N/A	The mean teacher-rated social skills (both therapist- mediated and peer-mediated social-communication intervention) in the intervention groups was <b>0.32 standard deviations</b> higher (0.43 lower to 1.06 higher)
		social skill	• •	ist-media	ited socia	l-communio	ation i	ntervention)	(measured	l with: Teach	er Perception of Social Skills

25 (1 study) 12 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,6</sup> due to risk of bias, imprecision	14	11	N/A	N/A	The mean teacher-rated social skills (therapist- mediated social- communication intervention) in the intervention groups was <b>0.02 standard deviations</b> <b>Iower</b> (0.81 lower to 0.77 higher)
		social skill	s (Peer-m	ediated s	ocial-con	nmunicatior	n interv	ention) (measur	ed with: Te	eacher Perce	eption of Social Skills (TPSS):
29 (1 study) 12 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>4,6</sup> due to risk of bias, imprecision	14	15	N/A	N/A	The mean teacher-rated social skills (peer-mediated social-communication intervention) in the intervention groups was <b>0.14 standard deviations</b> <b>higher</b> (0.59 lower to 0.87 higher)
		social skills	•			•	ediated	social-comn	nunica	tion inte	ervention) (measured
29 (1 study) 12 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,6</sup> due to risk of bias, imprecision	14	15	N/A	N/A	The mean teacher-rated social skills (both therapist- mediated and peer-mediated social-communication intervention) in the intervention groups was <b>0.48 standard deviations</b> <b>higher</b> (0.26 lower to 1.22 higher)
behaviour to	selective r larger scho	eporting bias for I bol setting				for the Social Beh t or harm (SMD -0	-	Scale which was d	l esigned to	neasure ge	neralization of gains in social

<sup>5</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear as blinding of the typically-developing peer completers was not reported

<sup>6</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear as teacher-rated and blinding of teachers was not reported

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

		C	Quality assess	ment					Summar	y of Find	ings
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e	vent rates (%)	Relative effect	Anticipat	ed absolute effects
Follow up							With EBI/EIBI only	With Combined joint attention training and EBI/EIBI	(95% CI)	Risk with EBI/EIBI only	Risk difference with Combined joint attention training and EBI/EIBI (95% CI)
Examine values)	er-child	joint attent	tion (Child	-initiated	J <b>A)</b> (measur	l ed with: EScs (Ea	l rly Social	Communication S	Scales): Coc	I rdinated JA	A looks; Better indicated by lower
37 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1</sup> due to imprecision	17	20	N/A	N/A	The mean examiner-child joint attention (child-initiated ja) in the intervention groups was <b>0.09 standard deviations</b> <b>lower</b> (0.74 lower to 0.56 higher)
Examine	er-child	joint attent	tion (Child	-initiated	JA) (measur	ed with: EScs (Ea	rly Social	Communication S	Scales): Sho	wing; Bette	er indicated by lower values)
37 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1</sup> due to imprecision	17	20	N/A	N/A	The mean examiner-child joint attention (child-initiated ja) in the intervention groups was <b>0.55 standard deviations</b> <b>higher</b> (0.11 lower to 1.21 higher)
Examine	er-child	joint attent	tion (Child	-initiated	<b>JA)</b> (measur	ed with: EScs (Ea	rly Social	Communication S	Scales): Poir	nting; Bette	r indicated by lower values)
37 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\begin{array}{c} \oplus \oplus \oplus \ominus \\ \textbf{MODERATE}^2 \\ \text{due to} \end{array}$	17	20	N/A	N/A	The mean examiner-child joint attention (child-initiated ja) in the intervention groups was

6 weeks	bias					imprecision					0.69 standard deviations higher (0.02 to 1.36 higher)
Examin	er-chilc	i joint atten	tion (Child	-initiated	JA) (measu	red with: EScs (E	arly Socia	l Communica	tion Scales): G	iving; Bette	r indicated by lower values)
37 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	17	20	N/A	N/A	The mean examiner-child joir attention (child-initiated ja) in the intervention groups was <b>0.48 standard deviations</b> <b>higher</b> (0.18 lower to 1.14 higher)
		I joint atten ter indicated by lov	•	-initiated	<b>JA)</b> (measu	red with: Commu	nication ar	nd Symbolic E	Behavior Scale	s Developm	ental Profile (CSBS DP): Initiatin
48 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to	24	24	N/A	N/A	The mean examiner-child joir attention (child-initiated ja) in the intervention groups was
26 weeks	bias					imprecision					0.31 standard deviations higher (0.26 lower to 0.88 higher)
	bias er-chilo	i joint atten ter indicated by low	•	-initiated	JA) (measu		nication a	nd Symbolic E	Behavior Scale	s Developm	higher

(1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	17	20	N/A	N/A	The mean examiner-child join attention (child responding to ja) in the intervention groups was <b>1.11 standard deviations</b> <b>higher</b> (0.41 to 1.81 higher)
		shared po		•	•	•			shared positive	affect or C	Communication and Symbolic
84 (2 studies) 6-26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	40	44	N/A	N/A	The mean examiner-child shared positive affect in the intervention groups was <b>0.04 standard deviations</b> higher (0.39 lower to 0.47 higher)
		shared po opmental Profile (C				-			shared positive	e affect or C	communication and Symbolic
Behavior Sca 84 (2 studies)		•				-			shared positive	N/A	Communication and Symbolic The mean examiner-child shared positive affect in the intervention groups was 0.43 standard deviations higher (0 to 0.87 higher)
Behavior Sca 84 (2 studies) 26-52 weeks	no serious risk of bias	ppmental Profile (C no serious inconsistency	SBS DP): Share	d positive affe	undetected	r indicated by low ⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	er values) 40	44	N/A	N/A	The mean examiner-child shared positive affect in the intervention groups was 0.43 standard deviations higher

- 16				1	1 · ·		40			<b>N</b> 1/2	
36 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	16	20	N/A	N/A	The mean examiner-child joint attention, shared positive affec & utterance in the intervention groups was 0.04 standard deviations higher (0.62 lower to 0.7 higher)
Examin	er-child	l joint atten	tion, share	d positiv	e affect &	utterance	(measure	d with: EScs (E	Early Social C	ommunicat	tion Scales): JA & shared positive
affect & utte	erance; Bette	er indicated by low	er values)	-							
36 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	16	20	N/A	N/A	The mean examiner-child joint attention, shared positive affect & utterance in the intervention groups was 0.56 standard deviations higher
											(0.12 lower to 1.23 higher)
		<b>joint atten</b> or indicated by low	•	d positiv	e affect &		(measure	d with: EScs (E	Early Social C	ommunicat	(0.12 lower to 1.23 higher) tion Scales): JA & shared positive
		•	•	d positiv	undetected	a utterance ■ ⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	(measure	d with: EScs (E	Early Social C	N/A	
affect & utte 36 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	er values)	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	16	20	N/A	N/A	tion Scales): JA & shared positive The mean examiner-child joint attention, shared positive affec & utterance in the intervention groups was 0.77 standard deviations higher

	bias					imprecision					higher (0.28 lower to 0.86 higher)
Examin	er-child	socially er	ngaged imi	tation (m	easured with: Be	ehavioural observ	ation: So	cially engaged	d imitation (SEI	); Better inc	licated by lower values)
48 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	24	24	N/A	N/A	The mean examiner-child socially engaged imitation in the intervention groups was <b>0.73 standard deviations</b> <b>higher</b> (0.15 to 1.32 higher)
Mother- ower values	-	oint attentio	n (Child-in	itiated J	<b>A)</b> (measured	with: Behavioural	observat	ion: Mother-cl	hild interaction	(Coordinate	ad JA looks); Better indicated by
37 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	17	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) in the intervention groups was <b>0.48 standard deviations</b> <b>higher</b> (0.18 lower to 1.13 higher)
Mother	-child jo	oint attentio	n (Child-in	itiated J	A) (measured	with: Behavioural	observat	ion: Mother-cl	hild interaction	(Showing);	Better indicated by lower values
37 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	17	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) ir the intervention groups was <b>0.51 standard deviations</b> <b>higher</b> (0.15 lower to 1.16 higher)
Mother	-child jo	oint attentio	n (Child-in	itiated J	A) (measured	with: Behavioural	observat	ion: Mother-cl	hild interaction	(Pointing);	Better indicated by lower values
37 (1 study) 6 weeks	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	$ \begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^1 \\ \text{due to} \end{array} $	17	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) ir the intervention groups was

	bias					imprecision					lower (1.04 lower to 0.27 higher)
Mother-	-child jo	oint attentio	n (Child-in	itiated J	A) (measured v	with: Behavioural o	observat	ion: Mother-ch	nild interaction	(Giving); Be	etter indicated by lower values)
37 (1 study) 5 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	17	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) in the intervention groups was <b>0.36 standard deviations</b> <b>higher</b> (0.3 lower to 1.01 higher)
<b>Nother-</b> by lower val		int attentio	n (Child-in	itiated J	A) (measured	with: Behavioural o	observat	ion: Mother-ch	hild interaction	– Duration	of JA (seconds); Better indicated
37 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \oplus \ominus$ <b>MODERATE</b> <sup>2</sup> due to imprecision	17	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) in the intervention groups was <b>0.77 standard deviations</b> <b>higher</b> (0.1 to 1.45 higher)
Mother- by lower val	•	oint attentio	n (Child-in	itiated J	A) (measured v	with: Behavioural o	observat	ion: Mother-ch	ild interaction ·	– Duration	of JA (seconds); Better indicated
37 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	17	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) ir the intervention groups was <b>0.19 standard deviations</b> <b>higher</b> (0.46 lower to 0.83 higher)
<b>Mother-</b> by lower val	-	int attentio	n (Child-in	itiated J	A) (measured v	I with: Behavioural o	observat	ion: Mother-ch	ild interaction	– Duration	of JA (seconds); Better indicated
36 (1 study)	no serious	no serious	no serious	serious <sup>2</sup>	undetected	$\begin{array}{c} \oplus \oplus \oplus \ominus \\ \textbf{MODERATE}^2 \end{array}$	16	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) ir

52 weeks	risk of bias	inconsistency	indirectness			due to imprecision					the intervention groups was <b>0.81 standard deviations</b> <b>higher</b> (0.13 to 1.5 higher)
		ter indicated by lo	-	nt attenti	on (JA ini	tiation com	posit	<b>e)</b> (measured	d with: EScs ar	id mother-c	hild interaction observations: JA
37 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	17	20	N/A	N/A	The mean examiner-child and mother-child joint attention (ja initiation composite) in the intervention groups was <b>0.51 standard deviations</b> <b>higher</b> (0.15 lower to 1.17 higher)
		l and mothe ter indicated by lo	•	nt attenti	on (JA ini	tiation com	posit	<b>e)</b> (measured	d with: EScs ar	id mother-c	hild interaction observations: JA
37 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	17	20	N/A	N/A	The mean examiner-child and mother-child joint attention (ja initiation composite) in the intervention groups was <b>0.53 standard deviations</b> higher (0.13 lower to 1.18 higher)
		and mothe	-	nt attenti	on (JA ini	tiation com	posit	<b>e)</b> (measured	d with: EScs ar	id mother-c	hild interaction observations: JA
36 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	16	20	N/A	N/A	The mean examiner-child and mother-child joint attention (ja initiation composite) in the intervention groups was 0.99 standard deviations higher (0.29 to 1.69 higher)

37 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	17	20	N/A	N/A	The mean examiner-child and mother-child joint attention (ja responses composite) in the intervention groups was <b>1.11 standard deviations</b> <b>higher</b> (0.41 to 1.81 higher)
		and mothe	-	nt attent	ion (JA res	sponses co	mpos	<b>site)</b> (measu	ired with: EScs	and mothe	r-child interaction observations: J
37 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	17	20	N/A	N/A	The mean examiner-child and mother-child joint attention (ja responses composite) in the intervention groups was <b>0.8 standard deviations</b> <b>higher</b> (0.12 to 1.47 higher)
		and mothe Better indicated by	-	nt attent	ion (JA res	sponses co	mpos	<b>site)</b> (measu	Ired with: EScs	and mothe	er-child interaction observations: J
36 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	16	20	N/A	N/A	The mean examiner-child and mother-child joint attention (ja responses composite) in the intervention groups was 0.17 standard deviations higher (0.49 lower to 0.83 higher)

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

		Q	uality assessi	ment					Summa	ary of Findings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rate	es (%)	Relative effect	Anticipated abso	blute effects
Follow up						evidence	With Social Use of Language Programme (SULP)	With LEGO therapy	(95% CI)	Risk with Social Use of Language Programme (SULP)	Risk difference with LEGO therapy (95% Cl)
Social in	Iteract	ion (measured v	l vith: Gilliam Autis	I sm Rating Sca	le (GARS): So	cial interaction; E	Better indicated by	/ lower va	lues)	<u> </u>	
31 (1 study) 18 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	15	16	N/A	N/A	The mean social interaction in the intervention groups was <b>0.73 standard deviations</b> <b>Iower</b> (1.46 lower to 0 higher)
Frequen	cy of c	child-initiate	ed social in	nteraction	ns with T	D peers (me	easured with: Beha	avioural ol	bservation;	Better indicated by	lower values)
21 (1 study) 18 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	10	11	N/A	N/A	The mean frequency of child-initiated social interactions with td peers in the intervention groups was <b>0.23 standard deviations</b> higher (0.63 lower to 1.09 higher)
Duration	n of all	social inter	actions wi	ith TD pe	ers (measure	d with: Behavio	ural observation; E	Better indi	cated by lov	wer values)	
21 (1 study) 18 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias,	10	11	N/A	N/A	The mean duration of all social interactions with td peers in the intervention groups was

						imprecision			<b>0.27 standard deviations</b> <b>higher</b> (0.59 lower to 1.13 higher)
not reported <sup>2</sup> N<400 <sup>3</sup> High risk of which were c	performan arried out l	·	bias as interventi and there was n	on administrat o reliability or	ors and partici validity data re	' pants were non-l ported for obser	olind, and high risk of detectivation measures	·	d and blinding of parents was

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

			Quality asse	ssment			Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect	Anticipated absolute effects		
Follow up							With Treatment- as-usual	With Social skills group	(95% CI)	Risk with Treatment-as- usual	Risk difference with Social skills group (95% Cl)	
		asured with: Socia d ed., parent rated					tem (SSRS):	Social skills	(standardiz	zed score) or I	Behavior Assessment	
137 (3 studies) 6-12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	67	70	N/A	N/A	The mean social skills in the intervention groups was <b>0.6 standard deviations</b> <b>higher</b> (0.26 to 0.95 higher)	

35 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	17	18	N/A	N/A	The mean social impairment in the intervention groups was <b>0.69 standard deviations</b> <b>lower</b> (1.37 lower to 0 higher)
Adaptiv	ve socia	l behaviou	f (measured with	h: Social Corr	npetence Inventory	(SCI): Pro-social inde	ex; Better	indicated by	lower value	es)	
41 (1 study) 16 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	<ul> <li>⊕⊖⊖⊖</li> <li>VERY LOW<sup>4,5</sup></li> <li>due to risk of bias, imprecision</li> </ul>	18	23	N/A	N/A	The mean adaptive social behaviour in the intervention groups was <b>0.11 standard deviations</b> higher (0.51 lower to 0.73 higher)
Capacit	y for so	ocial intera	ctions (meas	ured with: So	cial Competence I	nventory (SCI): Social	l initiation	index; Bette	er indicated b	by lower valu	es)
41 (1 study) 16 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	18	23	N/A	N/A	The mean capacity for social interactions in the intervention groups was 0.03 standard deviations lower (0.65 lower to 0.58 higher)
Study-s	specific	targeted se	ocial skills	(measured v	with: Adapted Skills	streaming Checklist (A	SC): Tota	al; Better ind	icated by lov	wer values)	
36 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	<ul> <li>⊕⊖⊖⊖</li> <li>VERY LOW<sup>1,2,3</sup></li> <li>due to risk of bias, imprecision, publication bias</li> </ul>	18	18	N/A	N/A	The mean study-specific targeted social skills in the intervention groups was 0.9 standard deviations higher (0.21 to 1.59 higher)

Knowledge A	ssessment	: Total; Better inc	licated by lower	values)							
69 (2 studies) 6-12 weeks	serious <sup>6</sup>	very serious <sup>7</sup>	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,6,7</sup> due to risk of bias, inconsistency, imprecision	34	35	N/A	N/A	The mean social skills knowledge (self-rated or researcher-rated) in the intervention groups was <b>1.58 standard deviations</b> higher (1.03 to 2.14 higher)
Social s	kills kn	owledge (	self-rated)	measured wit	h: Test of Adoles	scent Social Skills Know	wledge (T	ASSK): Tota	al; Better ind	licated by low	/er values)
33 (1 study) 12 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>2,6</sup> due to risk of bias, imprecision	16	17	N/A	N/A	The mean social skills knowledge (self-rated) in the intervention groups was 2.17 standard deviations higher (1.29 to 3.06 higher)
Social s	kills kn	owledge (r	esearcher	-rated) (m	easured with: Sk	illstreaming Knowledge	e Assess	ment: Total;	Better indica	ated by lower	values)
36 (1 study) 6 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW <sup>2,6</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean social skills knowledge (researcher- rated) in the intervention groups was <b>1.19 standard deviations</b> higher (0.48 to 1.91 higher)
Feelings	s of lon	eliness (mea	sured with: Lone	liness Scale:	Total; Better indi	cated by lower values)	1				
67 (1 study) 12 weeks	serious <sup>8</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>2,8</sup> due to risk of bias, imprecision	32	35	N/A	N/A	The mean feelings of loneliness in the intervention groups was <b>0.67 standard deviations</b> <b>lower</b>

											(1.16 to 0.18 lower)
Popular	ity (sel	f <b>-rated)</b> (meas	sured with: Piers	-Harris Self-C	Concept Scale (PI	I HS): Popularity; Better	indicated	by lower val	ues)		
68 (1 study) 12 weeks	serious <sup>8</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>2,8</sup> due to risk of bias, imprecision	33	35	N/A	N/A	The mean popularity (self- rated) in the intervention groups was <b>0.56 standard deviations</b> higher (0.07 to 1.04 higher)
Number	r of time	es child inv	ited to a p	lay date	(parent-rat	ed) (measured with:	Quality o	f Play Quest	ionnaire (QF	PQ): Host; Be	etter indicated by lower values)
97 (2 studies) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊖⊖⊖ VERY LOW <sup>1.5</sup> due to risk of bias, imprecision	45	52	N/A	N/A	The mean number of times child invited to a play date (parent-rated) in the intervention groups was <b>0.36 standard deviations</b> <b>higher</b> (0.04 lower to 0.77 higher)
Number	of time	es child inv	ited to a p	lay date	(Self-rated	) (measured with: Qua	lity of Pla	ay Questionn	aire (QPQ):	Host; Better	indicated by lower values)
33 (1 study) 12 weeks	serious <sup>8</sup>	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊖⊖⊖ VERY LOW <sup>5,8</sup> due to risk of bias, imprecision	16	17	N/A	N/A	The mean number of times child invited to a play date (self-rated) in the intervention groups was <b>0.26 standard deviations</b> <b>lower</b> (0.95 lower to 0.42 higher)
Time sp	ent in i	nteractive	activities (n	neasured with	: Quality of Play	Questionnaire (QPQ):	Engage;	Better indica	ted by lower	values)	
62 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,5</sup> due to risk of bias,	27	35	N/A	N/A	The mean time spent in interactive activities in the intervention groups was 0.2 standard deviations

62 (1 study)	serious <sup>1</sup>	no serious	no serious indirectness	activities	6 (measured with undetected	E Quality of Play Quest	tionnaire ( 27	QPQ): Diseng	age; Better i	N/A	The mean time spent in minimally interactive
12 weeks		linconsistency	indirectiless			due to risk of bias, imprecision					activities in the intervention groups was 1.31 standard deviations lower (1.87 to 0.75 lower)
Quality	of frien	dships (se	lf-rated) (me	asured with:	Friendship Qualit	ies Scale (FQS): Total	; Better in	dicated by low	er values)	•	•
33 (1 study) 12 weeks	serious <sup>8</sup>	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊖⊖⊖ VERY LOW <sup>5,8</sup> due to risk of bias, imprecision	16	17	N/A	N/A	The mean quality of friendships (self-rated) in the intervention groups was 0.14 standard deviations higher (0.55 lower to 0.82 higher)
				with Dichotor	nous measure of	number of participants	much im	proved/verv in	nproved' on (	I Clinical Globa	I Impression-Improvement
Positiv (CGI-I))	e treatm	ient respor	ISE (assessed								
(CGI-I)) 41	e treatm	no serious	no serious	serious <sup>10</sup>	undetected	⊕⊕⊝⊝ LOW <sup>9,10</sup>	0/18	16/23	RR 26.12	Study popu	
(CGI-I))		1	no serious			⊕⊕⊝⊝ LOW <sup>9,10</sup> due to risk of bias,			-	1	
(CGI-I)) 41 (1 study)		no serious	no serious			⊕⊕⊝⊝ LOW <sup>9,10</sup>	0/18	16/23	<b>RR 26.12</b> (1.67 to	Study popu	lation

higher (0.22 lower to 1.1 higher)
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<sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measures were parent-rated and parents were non-blind and involved in the intervention

<sup>2</sup> N<400

<sup>3</sup> High risk of selective reporting bias as LOPATA2010 did not report data for the waitlist control group for the staff-rated version of this outcome measure

<sup>4</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measures were parent-rated and parents were non-blind

<sup>5</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

<sup>6</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome assessors (self-completed or researcher) were non-blind

<sup>7</sup> Moderate to substantial heterogeneity

<sup>8</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as self-rated

<sup>9</sup> High risk of performance and response bias as intervention administrator and participants were non-blind, and high risk of detection bias as although the rater of the CGI was blind this measure was based on interview with parents who were non-blind

<sup>10</sup> Events<300

<sup>11</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome assessors (researchers) were nonblind and high levels of variability for this outcome measure were dealt with by administering the test twice at each time point and taking the average score

### 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

		Q	uality assessi	nent			Summary of Findings						
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study ever	nt rates (%)	Relative effect	Anticipated	l absolute effects		
Follow up							With Standard social skills group	With Social skills group specifically modified for individuals with high-functioning autism	(95% CI)	Risk with Standard social skills group	Risk difference with Social skills group specifically modified for individuals with high-functioning autism (95% Cl)		
Social s	kills (me	easured with: Soc	ial Responsiven	ess Scale (SR	I S): Social Awa	reness (standar	l dized change	e score); Better indicate	ed by lower	values)			
50 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	26	24	N/A	N/A	The mean social skills in the intervention groups was 0.68 standard deviations lower (1.26 to 0.11 lower)		
Social s	kills (me	easured with: Soc	ial Responsiven	ess Scale (SR	S): Social Cog	nition (standard	zed change	score); Better indicated	l by lower v	alues)			
50 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	26	24	N/A	N/A	The mean social skills in the intervention groups was 0.33 standard deviations lower (0.89 lower to 0.23 higher)		
Social s	kills (me	easured with: Soc	ial Responsiven	ess Scale (SR	S): Social Com	munication (sta	ndardized ch	ange score); Better inc	licated by le	wer values)			
50 (1 study)	serious <sup>1</sup>	no serious	no serious	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup>	26	24	N/A	N/A	The mean social skills in the intervention groups		

19 weeks		inconsistency	indirectness			due to risk of bias, imprecision					was 0.93 standard deviations lower (1.52 to 0.34 lower)
Social s	skills (me	easured with: Soc	cial Responsiven	ess Scale (SI	RS): Social Moti	ivation (standard	ized cha	nge score); Better	indicated by lowe	er values)	
50 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	26	24	N/A	N/A	The mean social skills in the intervention groups was <b>0.66 standard</b> <b>deviations lower</b> (1.23 to 0.08 lower)
Social s	skills (me	easured with: Soo	cial Responsiven	ess Scale (SI	RS): Autistic Ma	innerisms (stand	ardized o	change score); Be	tter indicated by lo	ower values)	)
50 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \ominus \ominus$ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	26	24	N/A	N/A	The mean social skills in the intervention groups was <b>0.67 standard</b> <b>deviations lower</b> (1.24 to 0.1 lower)
Social s	self-effi	cacy (self-	r <b>ated)</b> (measu	ured with: Soc	ial Self-efficacy	Scale (standarc	lized cha	nge score); Bette	r indicated by lowe	er values)	
52 (1 study) 19 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	28	24	N/A	N/A	The mean social self- efficacy (self-rated) in th intervention groups was <b>0.12 standard</b> <b>deviations lower</b> (0.67 lower to 0.42 higher)
Feeling	s of lor	neliness (me	asured with: Soc	ial Dissatisfac	ction Questionn	aire (standardize	d chang	e score); Better in	dicated by lower v	values)	
	serious <sup>4</sup>	no serious	no serious	very	undetected	<b>000</b>	28	24	N/A	N/A	The mean feelings of

19 weeks		inconsistency	indirectness	serious <sup>3</sup>		due to risk of bias, imprecision				intervention groups was 0.15 standard deviations higher (0.4 lower to 0.69 higher)
and involved <sup>2</sup> N<400 <sup>3</sup> N<400 and	in the inter 95% CI cro	rvention	no effect and me	easure of appre	eciable benefit	or harm (SMD	-blind, and high risk of detection bia -0.5/0.5) -blind, and high risk of detection bia	·	·	

#### 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

		Q	uality assessn	nent		Summary of Findings					
Participants		Inconsistency	Indirectness	Imprecision		• •	Study event	• • •		Anticipated a	absolute effects
(studies) Follow up	bias				bias of evidence With Treatment-a usual		Treatment-as-	With	(95% CI)	Risk with Treatment-as- usual	Risk difference with ESDM or P- ESDM (95% CI)
-		<b>riour (ESDM d</b> ehaviours; Better in	-		h: Repetitive B	ehavior Scale (RB	S): Total or A	utism Diag	nostic Obse	rvation Schedu	lle for Toddlers (ADOS-T):
143 (2 studies) 12-104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	70	73	N/A	N/A	The mean repetitive behaviour (esdm or p-esdm) in the intervention groups was 0.06 standard deviations lower

											(0.39 lower to 0.27 higher)
Repetitiv	ve behav	/iour (ESDM	(measured with:	Repetitive Be	havior Scale (R	BS): Total; Better	indicated b	y lower value	es)		
45 (1 study) 104 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	21	24	N/A	N/A	The mean repetitive behaviour (esdm) in the intervention groups was <b>0.35 standard deviations</b> <b>lower</b> (0.95 lower to 0.24 higher)
Repetitiv	e behav	/iour (P-ESD	(measured w	ith: Autism Dia	agnostic Observ	vation Schedule fo	r Toddlers	(ADOS-T): R	estricted, F	Repetitive Beh	aviours; Better indicated by lowe
98 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	<ul> <li>⊕⊕⊖⊖</li> <li>LOW<sup>2.5</sup></li> <li>due to risk of bias,</li> <li>imprecision</li> </ul>	49	49	N/A	N/A	The mean repetitive behaviour (p-esdm) in the intervention groups was <b>0.07 standard deviations</b> higher (0.32 lower to 0.47 higher)
was either no <sup>2</sup> N<400 <sup>3</sup> High risk of and parents <sup>4</sup> N<400 and <sup>5</sup> High risk of	performan were non-b 95% CI cro performan	or the outcome m ce and response t lind and involved osses both line of	easure was paren bias as interventio in the intervention no effect and mea bias as interventio	nt-completed and n administrato asure of apprecion administrato	nd parents were rs and participa ciable benefit of rs and participa	e non-blind and in ants were non-blin r harm (SMD -0.5/ ants were non-blin	volved in th d, and high 0.5)	e intervention	n tion bias as	s this outcome	blinding ofoutcome assessors e measure was parent-completed as the outcome assessor

# **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

		Qu	ality assessr	ment			Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	event rates (%)	Relative effect	Anticip	ated absolute effects	
Follow up						based) versus standard emotion recognition trainir (DVD-based) for the core autism feature of restricted interests and rigid and	recognition training (DVD- based) versus standard emotion recognition training (DVD-based) for the core autism feature of restricted interests and rigid and repetitive behaviours as an	(95% CI)	Risk with Control	Risk difference with Enhanced emotion recognition training (DVD- based) versus standard emotion recognition training (DVD-based) for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome (95% CI)		
Stereoty	ped b	ehaviour (m	easured with: S	ocial Commun	ication Questi	onnaire (SCQ)	: Stereo	yped behaviour; Better indica	ated by lowe	er values	)	
25 (1 study) 3 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	12	13	N/A	N/A	The mean stereotyped behaviour in the intervention groups was <b>0.31 standard deviations</b> <b>Iower</b> (1.1 lower to 0.48 higher)	

# **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

Quality assessment	Summary of Findings

Participants Risk o (studies) bias		of Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	<b>、</b> <i>、 、</i>	Relative effect			
Follow up							With Control	With Combined antipsychotic and parent training versus antipsychotic only for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome	(95% CI)	Risk with Control	Risk difference with Combined antipsychotic and parent training versus antipsychotic only for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome (95% CI)	
Compuls	sions (	measured with: Cl	hildren's Yale-B	rown Obsessiv	ve Compulsive	e Scales-PDD (	CYBOC	S-PDD): Compulsions; Better	indicated b	by lower	values)	
95 (1 study) 24 weeks	serious <sup>1</sup>		no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	40	55	N/A	N/A	The mean compulsions in the intervention groups was <b>0.42 standard deviations lower</b> (0.83 to 0.01 lower)	
interview, but	unclear w		e is but if parent	tal interview th	en non-blind.	There was also	o a high	I, and risk of detection bias is risk of attrition bias due to hig 18% attrition)				

# **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

		Qu	ality assessm	nent			Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study ever	nt rates (%)	Relative effect	Anticipated absolute effects		
Follow up						evidence	With Treatment- as-usual	With Caregiver- mediated social- communication intervention (PACT)		Risk with Treatment- as-usual	Risk difference with Caregiver-mediated social- communication intervention (PACT) (95% CI)	
Repetitiv	/e beha	<b>aviours</b> (meas	ured with: Autisn	n Diagnostic C	bservation Sc	hedule-Generic	(ADOS-G):	Repetitive Behaviours;	Better indic	ated by lower	values)	
152 (1 study) 56 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	75	77	N/A	N/A	The mean repetitive behaviours in the intervention groups was <b>0.3 standard</b> <b>deviations lower</b> (0.62 lower to 0.02 higher)	
<sup>1</sup> N<400 and 9	95% CI cro	sses both line of n	o effect and mea	asure of appre	ciable benefit	or harm (SMD -	0.5/0.5)			1		

## 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

		Q	uality assessme	ent				S	ummary of	f Findings	3
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study ev	vent rates (%)	Relative	Anticipat	ed absolute effects
(studies) Follow up	bias				bias	of evidence	With Placebo	With Anticonvulsants	effect (95% CI)	Risk with Placebo	Risk difference with Anticonvulsants (95% CI)
		haviours (glo ment [CGI-I]: Autisn	-	nent) (asses	ssed with: Posit	tive treatment respo	onse (num	ber of participant	s 'much impi	oved/very i	mproved' on Clinical
27 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup>	0/11 (0%)	2/16 (12.5%)	<b>RR 3.53</b> (0.19 to	Study po	pulation
12 weeks						due to imprecision	(0.0)	(121210)	67.1)	0 per 1000	NA
										Moderate	ц
										0 per 1000	NA
<sup>1</sup> Events<300	and 95% CI	crosses both line of	no effect and mea	sure of apprec	i iable benefit or	harm (RR 0.75/1.2	25)		1		

### **1.4.2** Antidepressants for overall autistic behaviours as an indirect outcome

#### Fluoxetine versus placebo for overall autistic behaviours as an indirect outcome

utism [CGI-AD] and Chil		-	pulsion Scale [(	bias easured with: G		With Placebo nposite In change	With Antidepressant nprovement (Clir score); Better inc	dicated by lo	Risk with Placebo Improveme ower values	
Pollow up       Dverall autistic be       Autism [CGI-AD] and Chill       9     no serious       1 study)     risk of	ildren's Yale-Browr	Obsessive-Com	pulsion Scale [(	easured with: G CYBOCS] com	Global Autism Cor pulsions subscale	Placebo nposite In e change	Antidepressant nprovement (Clir score); Better inc	(95% CI) nical Global dicated by lo	Placebo Improveme ower values	Antidepressant (95% Cl) ent Scale Adapted to Global s)
utism [CGI-AD] and Chil 9 no serious 1 study) risk of	ildren's Yale-Browr	Obsessive-Com	pulsion Scale [(	CYBOCS] com	pulsions subscale	change	score); Better inc	dicated by lo	wer values	s)
1 study) risk of	no serious	no serious	verv serious <sup>1</sup>	undetected		00				
	inconsistency	indirectness			LOW <sup>1</sup> due to imprecision	20	19	N/A	N/A	The mean overall autistic behaviours (global improvement) in the intervention groups was <b>0.35 standard deviations</b> <b>lower</b> (0.98 lower to 0.28 higher)

### 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

		Q	uality assessi	ment				Findings				
Participants		Inconsistency	Indirectness	Imprecision			Study event rat	tes (%)	Relative	Anticipated abs	solute effects	
(studies) Follow up					bias	of evidence	With Combined antipsychotic and placebo	With Combined antihistamine and antipsychotic	effect (95% CI)	Risk with Combined antipsychotic and placebo	Risk difference with Combined antihistamine and antipsychotic (95% Cl)	
Overall a	utistic k	<b>behaviours</b> (r	measured with: (	Childhood Auti	sm Rating Sca	ale (CARS): Total	[change score]; [	Better indicated by	lower valu	es)		
40 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	20	20	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.96 standard</b> <b>deviations lower</b> (1.62 to 0.3 lower)	
<sup>1</sup> N<400		1	1	1		1	1		1	1	1	

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

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

			Quality asses	sment				Su	mmary of	Finding	S
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study e	event rates (%)	Relative	Anticipa	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Antipsychotics versus placebo for overall autistic behaviours	<b>effect</b> (95% CI)	Risk with Control	Risk difference with Antipsychotics versus placebo for overall autistic behaviours (95% Cl)
Overall a	utistic b	<b>ehaviours</b> (a	ssessed with: Di	chotomous: Po	sitive treatment	response (>20% im	proveme	nt on CARS))			
39 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	reporting bias strongly	⊕⊕⊝⊝ LOW <sup>1,2</sup>	0/20 (0%)	12/19 (63.2%)	<b>RR 26.25</b> (1.66 to	Study p	opulation
26 weeks	bias				suspected <sup>2</sup>	due to imprecision,			414.57)	0 per 1000	N/A
						publication bias				Moderat	te
										0 per 1000	N/A
Overall a	utistic b	ehaviours (a	ssessed with: Di	L chotomous: Pc	ositive treatment	response (>20% im	proveme	nt on Children's Globa	I Assessme	nt Scale))	
39 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	reporting bias strongly		2/20 (10%)	17/19 (89.5%)	<b>RR 8.95</b> (2.38 to	Study p	opulation
26 weeks	bias				suspected <sup>2</sup>	due to imprecision, publication bias	(10,0)		33.62)	100 per 1000	<b>795 more per 1000</b> (from 138 more to 1000 more)
										Modera	te
										100 per 1000	<b>795 more per 1000</b> (from 138 more to 1000 more)

values)											
(2 studies)	risk of	very serious <sup>3</sup>	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to inconsistency, imprecision	64	60	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.87 standard</b> <b>deviations lower</b> (1.25 to 0.5 lower)

#### Overall autistic behaviours (direct outcome) (measured with: Childhood Autism Rating Scale (CARS): Total; Better indicated by lower values)

#### Overall autistic behaviours (indirect outcome) (measured with: Ritvo-Freeman Real-life Rating Scale (RLRS): Total; Better indicated by lower values)

101	no serious	no serious	no serious	serious <sup>4</sup>	undetected	$\oplus \oplus \oplus \ominus$	52	49	N/A	N/A	The mean overall autistic
(1 study)	risk of	inconsistency	indirectness								behaviours (indirect
8 weeks	bias					due to					outcome) in the
						imprecision					intervention groups was
						-					1.19 standard
											deviations lower
											(1.61 to 0.76 lower)
											· ,
<sup>1</sup> Events<30	0										

<sup>2</sup> High risk of selective reporting bias as mean and standard deviation data were not reported for continuous scale outcome measures

<sup>3</sup> Substantial to considerable heterogeneity with an I-squared value of 90%

<sup>4</sup> N<400

<sup>5</sup> High risk of selection bias as the allocation was unconcealed and the groups were not comparable at baseline for this outcome measure (the risperidone group showed significantly greater severity of autism symptoms as measured by the CARS)

<sup>8</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

### Risperidone versus haloperidol for overall autistic behaviours as a direct outcome

		Q	uality assessr	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study	event rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Risperidone versus haloperidol for overall autistic behaviours as a direct outcome	effect (95% CI)	Risk with Control	Risk difference with Risperidone versus haloperidol for overall autistic behaviours as a direct outcome (95% Cl)
Overall a	utistic	behaviours (r	measured with: T	urgay DSM-IV	PDD Rating S	Scale; Better indi	cated by	lower values)			
28 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	15	13	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.35 standard deviations</b> <b>Iower</b> (1.1 lower to 0.4 higher)
Overall a	utistic	behaviours (r	measured with: R	Ritvo-Freeman	Real-life Ratin	ng Scale (RLRS):	Social; I	Better indicated by lower	values)		
28 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1.2</sup> due to risk of bias, imprecision	15	13	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.26 standard deviations</b> <b>Iower</b> (1 lower to 0.49 higher)
Overall a	utistic	behaviours (r	neasured with: F	Ritvo-Freeman	Real-life Ratin	ng Scale (RLRS):	Motor; E	Better indicated by lower v	alues)	<u> </u>	
28 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	15	13	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.34 standard deviations</b> <b>Iower</b> (1.09 lower to 0.41 higher)
Overall a	utistic	behaviours (r	measured with: F	Ritvo-Freeman	Real-life Ratin	ng Scale (RLRS):	Affective	e; Better indicated by lowe	er values)		
28 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		15	13	N/A	N/A	The mean overall autistic behaviours in the

12 weeks		habauiaura				due to risk of bias, imprecision					intervention groups was 0.23 standard deviations lower (0.98 lower to 0.52 higher)
28 (1 study) 12 weeks	serious <sup>1</sup>	behaviours no serious inconsistency	(measured with: I	Ritvo-Freeman	undetected	ng Scale (RLRS): ⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	15	y; Better indicated	d by lower values)	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.17 standard deviations</b> <b>lower</b> (0.92 lower to 0.57 higher)
Overall a	autistic	behaviours	(measured with: I	Ritvo-Freeman	n Real-life Ratir	ng Scale (RLRS):	Langua	ge; Better indicat	ed by lower value	s)	- ł
28 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	15	13	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.22 standard deviations</b> higher (0.53 lower to 0.96 higher)

### **1.4.5** SNRIs for overall autistic behaviours as an indirect outcome

#### Atomoxetine versus placebo for overall autistic behaviours as an indirect outcome

		Qı	ality assessm	ent				Su	immary of	Finding	\$		
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study e	· · ·		Anticipa	ed absolute effects		
(studies) Follow up	bias				bias	of evidence	With Placebo	With Selective noradrenaline reuptake inhibitors	effect (95% CI)	Risk with Placebo	Risk difference with Selective noradrenaline reuptake inhibitors (95% Cl)		
Overall a	Dverall autistic behaviours (measured with: Children's Social Behavior Questionnaire (CSBQ): Total; Better indicated by lower values)												

	no serious risk of bias		no serious indirectness	very serious <sup>1</sup>		⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	46	43	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.27 standard deviations</b> <b>lower</b> (0.68 lower to 0.15 higher)
<sup>1</sup> N<400 and	95% CI cros	ses both line of no	effect and measu	re of apprecia	ble benefit or h	arm (SMD -0.5/0	.5)			

## 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

		Qı	uality assessme	ent					Summa	ry of Finc	lings
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision			Study ev (%)		Relative effect (95% CI)	Anticipat	ed absolute effects
							With Placebo	With Antioxidants		Risk with Placebo	Risk difference with Antioxidants (95% CI)
Social in	npairme	nt (measured with:	Social Responsiv	eness Scale (	SRS): Total; Be	etter indicated by I	ower valu	es)			
29 (1 study)	no serious	no serious	no serious	very	undetected	⊕⊕⊝⊝ LOW <sup>1</sup>	15	14	N/A	N/A	The mean social impairment in the intervention groups

12 weeks	risk of bias	inconsistency	indirectness	serious <sup>1</sup>		due to imprecision					was <b>0.14 standard deviations</b> <b>lower</b> (0.87 lower to 0.59 higher)
Social /	Awarenes	SS (measured wit	h: Social Respons	iveness Scale	e (SRS): Social A	Awareness ; Bette	er indicate	d by lower	values)		
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean social awareness in the intervention groups was <b>0.45 standard deviations</b> <b>lower</b> (1.19 lower to 0.29 higher)
Social (	Cognitior	(measured with:	Social Responsiv	eness Scale (	SRS): Social Co	gnition ; Better in	dicated b	y lower valu	es)		
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean social cognition in the intervention groups was <b>0.02 standard deviations</b> <b>lower</b> (0.74 lower to 0.71 higher)
Social (	Commun	ication (meas	ured with: Social F	Responsivene	ss Scale (SRS):	Social Communio	cation ; Be	etter indicate	ed by lower va	alues)	
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean social communication in the intervention groups was 0.09 standard deviations lower (0.82 lower to 0.64 higher)
Social I	Motivatio	<b>n</b> (measured with	: Social Responsi	veness Scale	(SRS): Social M	otivation ; Better	indicated	by lower va	lues)		
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to	15	14	N/A	N/A	The mean social motivation in the intervention groups was 0.24 standard deviations lower

						imprecision					(0.97 lower to 0.49 higher)
Autistic	Manneri	SMS (measured	I with: Social Resp	onsiveness Sc	cale (SRS): Aut	istic Mannerisms ;	Better in	ndicated by Ic	ower values)		ł
29 (1 study) 12 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean autistic mannerisms in the intervention groups was <b>0.64 standard deviations</b> <b>lower</b> (1.39 lower to 0.11 higher)

## 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

		Q	uality assessm	nent			S	ummary o	of Findings
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	of evidence	Study ev With Placebo			Anticipated absolute effects           Risk with         Risk difference with           Placebo         Antidepressants (95% Cl)

149 1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected		26/76 (34.2%)	24/73 (32.9%)	<b>RR 0.96</b> (0.61 to	Study po	pulation
2 weeks						due to imprecision		()	1.51)	342 per 1000	<b>14 fewer per 1000</b> (from 133 fewer to 174 more)
										Moderate	9
										342 per 1000	<b>14 fewer per 1000</b> (from 133 fewer to 174 more)
mproved' o	n CGI-improve	ement)) no serious	no serious	very	undetected	<b>000</b>	10/76	15/73	RR 1.56	Study po	uch improved/very
1 study) 2 weeks	risk of bias	inconsistency	indirectness	serious <sup>1</sup>		LOW <sup>1</sup> due to imprecision	(13.2%)	(20.5%)	(0.75 to 3.25)	132 per 1000	<b>74 more per 1000</b> (from 33 fewer to 296 more)
										Moderate	9
										132 per 1000	74 more per 1000 (from 33 fewer to 297 more)
					J		PDD): Com	pulsions or Ch	nildren's Yale-E	Brown Obse	ssive Compulsive Scale
		easured with: Child Better indicated b		Obsessive Co	ompuisive Scale	100 (C10003-					

											higher)
Compu	<b>Isive</b> (meas	ured with: Repetit	ive Behavior Scale	e (RBS): Com	pulsive; Better i	ndicated by lower v	alues)				
149 (1 study) 12 days	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	76	73	N/A	N/A	The mean compulsive in the intervention groups was <b>0.09 standard</b> <b>deviations higher</b> (0.23 lower to 0.42 higher)
Restric	t <b>ive</b> (measur	red with: Repetitiv	e Behavior Scale (	(RBS): Restric	tive; Better indi	cated by lower valu	ies)				
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \oplus \ominus$ <b>MODERATE</b> <sup>2</sup> due to imprecision	76	73	N/A	N/A	The mean restrictive in the intervention groups was <b>0.34 standard</b> <b>deviations higher</b> (0.01 to 0.66 higher)
Ritualis	tic (measure	ed with: Repetitive	Behavior Scale (F	RBS): Ritualist	ic; Better indica	ted by lower values	5)				
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	76	73	N/A	N/A	The mean ritualistic in the intervention groups was <b>0 standard deviations</b> <b>higher</b> (0.32 lower to 0.32 higher)
Samene	ess (measure	ed with: Repetitive	e Behavior Scale (I	RBS): Samen	ess; Better indic	cated by lower valu	es)				
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\begin{array}{c} \oplus \oplus \oplus \bigcirc \\ \textbf{MODERATE}^2 \\ \text{due to} \\ \text{imprecision} \end{array}$	76	73	N/A	N/A	The mean sameness in the intervention groups was 0.05 standard deviations higher

											(0.27 lower to 0.37 higher)
Self-injı	u <b>rious</b> (me	easured with: Rep	etitive Behavior So	cale (RBS): Se	elf-injurious; Bet	ter indicated by low	wer values	5)	·		·
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	76	73	N/A	N/A	The mean self-injurious in the intervention groups was <b>0.15 standard</b> <b>deviations higher</b> (0.17 lower to 0.47 higher)
Stereoty	yped (meas	sured with: Repeti	itive Behavior Sca	le (RBS): Ster	eotyped; Better	indicated by lower	values)				
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	76	73	N/A	N/A	The mean stereotyped in the intervention groups was 0.13 standard deviations higher (0.2 lower to 0.45 higher)

## **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

		Qı	ality assessme	ent				Summar	y of Findings
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study event rates	Relative	Anticipated absolute effects

(studies) Follow up	bias				bias	of evidence	(%)		effect (95% CI)		
							With Placebo	With Antioxidants	_	Risk with Placebo	Risk difference with Antioxidants (95% CI)
Compu	Isions (me	asured with: Repe	etitive Behavior Sc	ale (RBS): Co	mpulsions; Bette	er indicated by low	ver values)				-
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean compulsions in the intervention groups was <b>0.68 standard deviations</b> <b>lower</b> (1.43 lower to 0.08 higher)
Restric	ted (measure	ed with: Repetitive	Behavior Scale (F	RBS): Restricte	ed; Better indica	ted by lower valu	es)	·		1	1
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean restricted in the intervention groups was <b>0.42 standard deviations</b> <b>lower</b> (1.15 lower to 0.32 higher)
Rituals	(measured wit	h: Repetitive Beha	avior Scale (RBS):	Rituals; Bette	r indicated by lo	wer values)			1	1	
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean rituals in the intervention groups was 0.3 standard deviations lower (1.03 lower to 0.44 higher)
Samene	<b>ESS</b> (measure	ed with: Repetitive	Behavior Scale (I	RBS): Samene	ess; Better indica	ated by lower valu	ues)				
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean sameness in the intervention groups was 0.46 standard deviations lower (1.2 lower to 0.28 higher)

29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean self-injurious behaviour in the intervention groups was <b>0.26 standard deviations</b> <b>lower</b> (0.99 lower to 0.48 higher)
Stereot	typic beha	<b>aviour</b> (measu	red with: Repetitiv	e Behavior Sc	ale (RBS): Stere	eotypies; Better ir	dicated b	y lower value	es)		
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean stereotypic behaviour in the intervention groups was 0.51 standard deviations

## **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

		Qı	uality assessi	ment			Sum	mary of F	inding	s
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Overall quality of evidence	With	With Antipsychotics versus	effect (95% CI)	Anticip Risk with Control	Risk difference with Antipsychotics versus placebo for the core autism feature of restricted interests and rigid and

							behaviours			repetitive behaviours (95% CI)
•	• •		razole) (n	neasured with:	L Children's Yale-E	I rown Ol	bsessive Compulsiv	ve Scale (CYBOC	S): Compu	lsions (Endpoint or Change
no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	130	255	N/A	N/A	The mean compulsions (risperidone or aripiprazole in the intervention groups was 0.42 standard deviations lower (0.64 to 0.2 lower)
sions (	risperidon	<b>e)</b> (measured w	ith: Children's	S Yale-Brown O	bsessive Compu	lsive Sc	ale (CYBOCS): Co	mpulsions; Better	indicated	by lower values)
no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ MODERATE <sup>1</sup> due to imprecision	86	107	N/A	N/A	The mean compulsions (risperidone) in the intervention groups was <b>0.49 standard deviations</b> <b>lower</b> (0.79 to 0.20 lower)
sions (	aripiprazol	(measured v	vith: Children'	s Yale-Brown C	Dbsessive Compu	Ilsive Sc	cale (CYBOCS): Co	mpulsions (Chang	ge Score);	Better indicated by lower
no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$ \begin{array}{c} \oplus \oplus \bigcirc \bigcirc \\ \textbf{LOW}^2 \\ \text{due to} \end{array} $	44	148	N/A	N/A	The mean compulsions (aripiprazole) in the intervention groups was
	no serious risk of bias sions ( no serious risk of bias sions ( sions (	no       no serious         no       no serious         risk of       inconsistency         sions (risperidon         no       no serious         serious       inconsistency         sions (risperidon         no       no serious         risk of       bias         serious       inconsistency         serious       inconsistency         sions (aripiprazol         no       no serious         no       no serious	no       no serious       no serious         inconsistency       no serious         niconsistency       no serious         sions (risperidone)       (measured w         no       no serious         serious       no serious         no       no serious         no       no serious         inconsistency       (measured w         serious       no serious         inconsistency       no serious         serious       no serious         inconsistency       (measured w         serious       (measured w         inconsistency       (measured w         sions (aripiprazole)       (measured w         no       no serious         no       no serious	no       no serious       no serious       serious       serious       serious <sup>1</sup> inconsistency       indirectness       serious <sup>1</sup> serious <sup>1</sup> sions (risperidone)       (measured with: Children's         no       no serious       no serious <sup>1</sup> inconsistency       no serious       serious <sup>1</sup> sions (risperidone)       (measured with: Children's         no       no serious       no serious         sions (aripiprazole)       (measured with: Children'         no       no serious       very	no       no serious       no serious       serious <sup>1</sup> undetected         inconsistency       indirectness       serious <sup>1</sup> undetected         sions (risperidone)       (measured with: Children's Yale-Brown O         no       no serious       no serious         risk of       bias       no serious         sions (risperidone)       (measured with: Children's Yale-Brown O         no       no serious       no serious         risk of       bias       undetected         sions (aripiprazole)       (measured with: Children's Yale-Brown O         no       no serious       no serious         indirectness       serious <sup>1</sup> undetected         sions (aripiprazole)       (measured with: Children's Yale-Brown O         no       no serious       no serious         no       no serious       very       undetected	no       no serious       no serious       serious'       undetected       ⊕⊕⊕⊖         serious       inconsistency       indirectness       serious'       undetected       ⊕⊕⊕⊖         bias       inconsistency       indirectness       serious'       undetected       @⊕⊕⊖         sions (risperidone)       (measured with: Children's Yale-Brown Obsessive Computing indirectness       serious'       undetected       ⊕⊕⊕⊖         no       no serious       no serious       serious'       undetected       ⊕⊕⊕⊖         serious       inconsistency       indirectness       serious'       undetected       @⊕⊕⊖⊖         serious       inconsistency       indirectness       serious'       undetected       @⊕⊕⊖⊖         sions (aripiprazole)       (measured with: Children's Yale-Brown Obsessive Computing indirectness       inprecision         no       no serious       no serious       very       undetected       ⊕⊕⊖⊖	no       no serious       no serious       serious'       undetected       ⊕⊕⊕⊖       MODERATE1         bias       inconsistency       indirectness       serious'       undetected       ⊕⊕⊕⊖       MODERATE1         sions (risperidone)       (measured with: Children's Yale-Brown Obsessive Compulsive Sc         no       no serious       serious'       undetected       ⊕⊕⊕⊖       MODERATE1         sions (risperidone)       (measured with: Children's Yale-Brown Obsessive Compulsive Sc       MODERATE1       due to       indirectness       serious'       undetected       ⊕⊕⊕⊖       MODERATE1         sions (aripiprazole)       (measured with: Children's Yale-Brown Obsessive Compulsive Sc       mo       no serious       no serious       serious'       44	sions (risperidone or aripiprazole) (measured with: Children's Yale-Brown Obsessive Compulsive reindicated by lower values)         no       no serious         serious       no serious         inconsistency       no serious         indirectness       serious <sup>1</sup> undetected       ⊕⊕⊕⊖         MODERATE <sup>1</sup> 130         due to       imprecision         sions (risperidone) (measured with: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS): Corrections         no       no serious         no serious       no serious         inconsistency       no serious         serious       no serious         serious       no serious         inconsistency       no serious         indirectness       serious <sup>1</sup> undetected       ⊕⊕⊕⊖         MODERATE <sup>1</sup> 86         due to       imprecision         serious       indirectness         serious       indirectness         serious       no serious         indirectness       serious <sup>1</sup> undetected       ⊕⊕⊕⊖⊖         MODERATE <sup>1</sup> due to         inconsistency       indirectness         sions (aripiprazole)       (measured with: Children	sions (risperidone or aripiprazole) (measured with: Children's Yale-Brown Obsessive Compulsive Scale (CYBOC: ar indicated by lower values)         no       no serious inconsistency indirectness       no serious inconsistency indirectness       serious <sup>1</sup> undetected       ⊕⊕⊕⊖       MODERATE <sup>1</sup> due to imprecision       N/A         sions (risperidone) (measured with: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS): Compulsions; Better       no serious inconsistency indirectness       no serious inconsistency indirectness       N/A         sions (risperidone) (measured with: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS): Compulsions; Better       N/A         no       no serious inconsistency indirectness       serious <sup>1</sup> undetected       ⊕⊕⊕⊖       86       107       N/A         sions (risperidone) (measured with: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS): Compulsions; Better       mo serious inconsistency indirectness       serious <sup>1</sup> undetected       ⊕⊕⊕⊖       86       107       N/A         sions (aripiprazole) (measured with: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS): Compulsions (Change)       mo serious inconsistency indirectness       no serious       N/A         no       no serious       no serious       very       undetected       ⊕⊕⊕⊖⊖       44       148       N/A	sions (risperidone or aripiprazole) (measured with: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS): Computer indicated by lower values)         no       no serious       no serious       serious'       undetected       ⊕⊕⊕⊖       130       255       N/A       N/A         sis of bias       no serious       no serious       serious'       undetected       ⊕⊕⊕⊖       MODERATE'       130       255       N/A       N/A         sis of bias       no serious       no serious       serious'       undetected       ⊕⊕⊕⊖       MODERATE'       130       255       N/A       N/A         sions (risperidone)       (measured with: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS): Compulsions; Better indicated I       MODERATE'       86       107       N/A       N/A         serious       no serious       no serious       serious'       undetected       ⊕⊕⊕⊖⊖       86       107       N/A       N/A         sias       inconsistency       no serious       serious'       undetected       ⊕⊕⊕⊖⊖       86       107       N/A       N/A         sias       inconsistency       indirectness       serious'       undetected       ⊕⊕⊕⊖⊖       44       148       N/A       N/A

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

		Qu	ality assessn	nent				Sum	mary of F	inding	s
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	event rates (%)	Relative effect	Anticip	ated absolute effects
Follow up						evidence	With Control	With Low dose antipsychotics versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome	(95% CI)	Risk with Control	Risk difference with Low dose antipsychotics versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome (95% CI)
-		(risperidone d by lower values)		razole) (m	easured with:	L Children's Yale	e-Brown	Obsessive Compulsive Scale	e (CYBOCS	): Compu	ulsions (Endpoint or Change
153 (2 studies) 6-8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	78	75	N/A	N/A	The mean compulsions (risperidone or aripiprazole) i the intervention groups was <b>0.27 standard deviations</b> <b>lower</b> (0.59 lower to 0.04 higher)
				<u> </u>		ļ					
Compuls	sions (	risperidone	e) (measured w	ith: Children's	Yale-Brown O	bsessive Com	pulsive S	Scale (CYBOCS): Compulsion	ns; Better ir	ndicated	by lower values)

90 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>		⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	44	46	N/A	N/A	The mean compulsions (aripiprazole) in the intervention groups was <b>0.27 standard deviations</b> <b>lower</b> (0.68 lower to 0.15 higher)
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## 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

		(	Quality assess	nent					Summa	ry of Fine	dings			
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		Study e (%)	vent rates	Relative effect	Anticipat	ed absolute effects			
Follow up		With With With With With With With With		(95% CI)	Risk with Waitlist	Risk difference with Acupressure (95% Cl)								
Overall a	Dverall autistic behaviours (measured with: Study-specific parent-rated questionnaire: Total score; Better indicated by lower values)													
32 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊖⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	16	16	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.92 standard deviations</b> higher (0.19 to 1.66 higher)			
Overall a	Overall autistic behaviours (measured with: Study-specific parent-rated questionnaire: Language; Better indicated by lower values)													
32 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \ominus \ominus$	16	16	N/A	N/A	The mean overall autistic behaviours in the intervention			

6 weeks						LOW <sup>1,2</sup> due to risk of bias, imprecision					groups was <b>1.33 standard deviations</b> <b>higher</b> (0.55 to 2.1 higher)
Overall a	autistic	behaviours (m	easured with: Stu	dy-specific par	ent-rated quest	ionnaire: Social inte	raction	; Better indic	ated by lower	r values)	
32 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	16	16	N/A	N/A	The mean overall autistic behaviours in the interventior groups was <b>0.98 standard deviations</b> higher (0.24 to 1.72 higher)
Overall a	autistic	behaviours (m	easured with: Stu	dy-specific par	ent-rated quest	ionnaire: Social inte	raction	; Better indic	ated by lower	r values)	
32 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	16	16	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.23 standard deviations</b> higher (0.47 lower to 0.92 higher)
Overall a	autistic	behaviours (m	easured with: tudy	/-specific pare	nt-rated questic	onnaire: Motor functi	oning; I	Better indica	ted by lower	values)	
32 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	16	16	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.45 standard deviations higher

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

		Q	uality assess	sment				Sumr	nary of F	indings	
Participants		Inconsistency	Indirectness	Imprecision			Study event	rates (%)		Anticipated a	absolute effects
(studies) Follow up	bias	tic behaviours (measured with: Autism Evaluation	bias	of evidence	With Conventional educational programme only	With Acupuncture/electro- acupuncture and conventional educational programme	effect (95% CI)	Risk with Conventional educational programme only	Risk difference with Acupuncture/electro- acupuncture and conventional educational programme (95% Cl)		
Overall a	utistic	behaviours	(measured with	n: Autism Eval	uation Treatm	ent Checklist (AT	EC): Total; Be	tter indicated by lower v	alues)		
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.25 standard</b> <b>deviations higher</b> (0.41 lower to 0.9 higher)
Overall a	utistic	behaviours	(measured with	n: Autism Eval	uation Treatm	ent Checklist (AT	EC): Speech/L	.anguage/Communicatio	on; Better ir	ndicated by low	ver values)
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.06 standard</b> <b>deviations lower</b> (0.71 lower to 0.59 higher)
Overall a	utistic	behaviours	(measured with	n: Autism Eval	uation Treatm	ent Checklist (AT	EC): Sociabilit	y; Better indicated by low	wer values)		
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.14 standard</b> <b>deviations higher</b> (0.51 lower to 0.8 higher)

Overall a	autistic	behaviours	(measured wit	h: Autism Eva	luation Treatm	ent Checklist (AT	EC): Sens	ory/Cognitive Awa	reness; Better indic	ated by low	er values)
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.42 standard</b> <b>deviations higher</b> (0.24 lower to 1.08 higher)
Overall a	autistic	behaviours	(measured wit	h: Autism Eva	luation Treatm	ent Checklist (AT	EC): Phys	ical health & beha	viour; Better indicat	ed by lower	values)
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.18 standard</b> <b>deviations higher</b> (0.47 lower to 0.84 higher)
Overall a	autistic	behaviours	(measured wit	h: Ritvo-Freer	nan Real-life F	Rating Scale (RLR	S): Total; I	Better indicated by	/ lower values)		
65 (2 studies) 8 weeks	serious <sup>1</sup>	serious <sup>3</sup>	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	32	33	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.28 standard</b> <b>deviations higher</b> (0.21 lower to 0.77 higher)
Overall a	autistic	behaviours	(measured wit	h: Ritvo-Freer	nan Real-life F	Rating Scale (RLR	S): Motor;	Better indicated b	y lower values)		
66 (2 studies) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	33	33	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.16 standard</b> <b>deviations higher</b> (0.33 lower to 0.64

										]	higher)
Overall a	utistic	behaviours	(measured with	n: Ritvo-Freem	nan Real-life R	ating Scale (RLR	S): Social;	Better indicated b	by lower values)		
66 (2 studies) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	33	33	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.2 standard</b> <b>deviations lower</b> (0.69 lower to 0.28 higher)
Overall a	utistic	behaviours	(measured with	n: Ritvo-Freem	han Real-life R	ating Scale (RLR	S): Affectiv	ve; Better indicate	d by lower values)	4	
66 (2 studies) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	33	33	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.17 standard</b> <b>deviations higher</b> (0.32 lower to 0.66 higher)
Overall a	utistic	behaviours	(measured with	n: Ritvo-Freem	han Real-life R	ating Scale (RLR	S): Senso	ry; Better indicated	d by lower values)		
66 (2 studies) 8 weeks	serious <sup>1</sup>	serious <sup>3</sup>	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	33	33	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.12 standard</b> <b>deviations higher</b> (0.36 lower to 0.61 higher)
Overall a	utistic	behaviours	(measured with	n: Ritvo-Freem	nan Real-life R	ating Scale (RLR	S): Langua	age; Better indicat	ed by lower values)		Ļ
66 (2 studies) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	33	33	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.35 standard</b>

											deviations higher (0.13 lower to 0.84 higher)
Overall	autistic	behaviours	(measured with	h: Clinical Glo	bal Impressior	Scale (CGI): Tot	al; Better inc	licated by lower v	values)		
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,4</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.9 standard</b> <b>deviations lower</b> (1.58 to 0.21 lower)
Overall	autistic	behaviours	(measured with	h: Clinical Glo	bal Impressior	n Scale (CGI): Re	sponse to sc	cial interaction; B	Better indicated by	lower values)	
30 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.2 standard</b> <b>deviations lower</b> (0.91 lower to 0.52 higher)
Overall	autistic	behaviours	(measured with	h: Clinical Glo	bal Impressior	Scale (CGI): So	cial initiation	Better indicated	by lower values)	·	
30 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.1 standard</b> <b>deviations lower</b> (0.81 lower to 0.62 higher)
Overall	autistic	behaviours	(measured with	h: Clinical Glo	bal Impressior	n Scale (CGI): Us	e of speech;	Better indicated b	oy lower values)		ι.
30 (1 study) 8 weeks	N/A	N/A	N/A	N/A	N/A	N/A	15	15	N/A	N/A	Not estimable

Overall	autistic	behaviours	(measured wit	h: Clinical Gl	obal Impressior	n Scale (CGI): Re	epetitive be	naviour; Better ind	icated by lower val	ues)	
30 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1,4</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 1.11 standard deviations lower (1.88 to 0.33 lower)
Overall	autistic	behaviours	(measured wit	h: Clinical Gl	obal Impressior	n Scale (CGI): Be	ehaviour pro	blem; Better indic	ated by lower value	es)	
30 (1 study) 8 weeks	N/A	N/A	N/A	N/A	N/A	N/A	15	15	N/A	N/A	Not estimable
Overall	autistic	behaviours	(measured wit	h: Clinical Gl	obal Impressior	n Scale (CGI): Ad	ctivity level;	Better indicated by	y lower values)		
30 (1 study) 8 weeks	N/A	N/A	N/A	N/A	N/A	N/A	15	15	N/A	N/A	Not estimable
Overall	autistic	behaviours	(measured wit	h: Clinical Gl	obal Impressior	n Scale (CGI): SI	eep probler	n; Better indicated	by lower values)		
30 (1 study) 8 weeks	N/A	N/A	N/A	N/A	N/A	N/A	15	15	N/A	N/A	Not estimable
Overall	autistic	behaviours	(measured wit	h: Clinical Gl	obal Impressior	n Scale (CGI): Di	gestive prol	olem; Better indica	ated by lower value	s)	
30 (1 study) 8 weeks	N/A	N/A	N/A	N/A	N/A	N/A	15	15	N/A	N/A	Not estimable
differed for involved inp measures r <sup>2</sup> N<400 and	each partic out from par elied on no d 95% CI c	pant which may ents who were n n-blind parental r	introduce bias. ot blind to treat eport of no effect and	There was al ment allocation	so an unclear r on or confoundi	isk of detection b	bias as altho systematic	bugh all outcomes	were measured by	blinded ass	al education programme essors, some outcomes report which outcome

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

		Q	uality assess	sment				Summ	nary of Fi	ndings	
Participants		Inconsistency	Indirectness	Imprecision			Study event rates	. (%)		Anticipated absol	ute effects
(studies) Follow up	of bias				bias	quality of evidence	With Sham acupuncture/electro- acupuncture	With Acupuncture/electro- acupuncture	effect (95% CI)	Risk with Sham acupuncture/electro- acupuncture	Risk difference with Acupuncture/electro- acupuncture (95% CI)
Overall a	utistic	behaviours	<b>S</b> (measured w	ith: Ritvo-Free	man Real-life	Rating Scale (R	LRS): Total (change	e scores); Better indi	cated by lo	wer values)	
105 (2 studies) 4-9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	50	55	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.3 standard</b> <b>deviations lower</b> (0.69 lower to 0.09 higher)
Overall a	utistic	behaviours	<b>S</b> (measured w	ith: Ritvo-Free	man Real-life	Rating Scale (R	LRS): Motor (chang	je scores); Better ind	icated by le	ower values)	
105 (2 studies) 4-9 weeks	no serious risk of bias	serious <sup>3</sup>	no serious indirectness	serious <sup>4</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>2,3,4</sup> due to inconsistency, imprecision, publication bias	50	55	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.11 standard</b> <b>deviations lower</b> (0.49 lower to 0.28 higher)
Overall a	utistic	behaviours	S (measured w	ith: Ritvo-Free	eman Real-life	Rating Scale (R	LRS): Social (chang	ge scores); Better inc	licated by I	ower values)	1
105 (2 studies) 4-9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	50	55	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.16 standard</b> <b>deviations lower</b> (0.55 lower to 0.22

											higher)
Overall a	autistic	behaviour:	<b>S</b> (measured w	ith: Ritvo-Free	l eman Real-life	Rating Scale (R	LRS): Affeo	tive (change scores); Bet	tter indicated b	y lower values)	
105 (2 studies) 4-9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	50	55	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.27 standard</b> <b>deviations lower</b> (0.66 lower to 0.11 higher)
Overall a	autistic	behaviour	<b>S</b> (measured w	ith: Ritvo-Free	eman Real-life	Rating Scale (R	LRS): Sens	ory (change scores); Bet	ter indicated b	y lower values)	- <u>-</u>
105 (2 studies) 4-9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊕⊖⊖ LOW <sup>2,4</sup> due to imprecision, publication bias	50	55	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.1 standard</b> <b>deviations lower</b> (0.48 lower to 0.29 higher)
Overall a	autistic	behaviour	<b>S</b> (measured w	ith: Ritvo-Free	eman Real-life	Rating Scale (R	LRS): Lang	uage (change scores); B	etter indicated	by lower values)	
105 (2 studies) 4-9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	50	55	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.32 standard</b> <b>deviations lower</b> (0.7 lower to 0.07 higher)
Positive	treatm	ent respon	SE (assessed	with: Number	of participants	showing much	mproveme	nt on CGI-I for autistic bel	haviours)	<u> </u>	-
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		1/25 (4%)	7/30 (23.3%)	<b>RR 5.83</b> (0.77 to	Study population	
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision, publication	. ,	× ,	44.28)	40 per 1000	<b>193 more per</b> <b>1000</b> (from 9 fewer to

						bias					1000 more)
										Moderate	
										40 per 1000	<b>193 more per</b> <b>1000</b> (from 9 fewer to 1000 more)
55	no	no serious	<b>Se</b> (assessed no serious	very	of participants reporting	<b>000</b>	14/25	nt on CGI-I for autistic	RR 1.19	Study populatio	n
(1 study) 4 weeks	serious risk of bias	inconsistency	indirectness	serious <sup>5</sup>	bias strongly suspected <sup>2</sup>	VERY LOW <sup>2,5</sup> due to imprecision, publication bias	(56%)	(66.7%)	(0.77 to 1.83)	560 per 1000	<b>106 more per</b> <b>1000</b> (from 129 fewer to 465 more)
										Moderate	
										560 per 1000	<b>106 more per</b> <b>1000</b> (from 129 fewer to 465 more)
		ent respon		ial related	Iness (asses	ssed with: Dicho	tomous: Posit	ive treatment response	e for social rela	tedness - Social r	esponse (study-
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		5/25 (20%)	4/30 (13.3%)	<b>RR 0.67</b> (0.2 to	Study populatio	n
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision, publication bias	(2070)	(10.070)	2.22)	200 per 1000	66 fewer per 1000 (from 160 fewer to 244 more)
										Moderate	
										200 per 1000	66 fewer per 1000 (from 160 fewer to 244 more)

parent-report	ed 'better	than before'))									
55 (1 study)			no serious indirectness	very serious⁵	reporting bias		0/25 (0%)	7/30 (23.3%)	RR 12.58	Study population	
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision,		(2010/0)		0 per 1000	-
						publication bias			,	Moderate	1
										0 per 1000	-

**Positive treatment response for social relatedness** (assessed with: Dichotomous: Positive treatment response for social relatedness - Eye contact (study-specific parent-reported 'better than before'))

55 (1 study)		no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		4/25 (16%)	7/30 (23.3%)	<b>RR 1.46</b> (0.48 to	Study populatio	n
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision, publication bias		χ <i>γ</i>		160 per 1000 Moderate	<b>74 more per 1000</b> (from 83 fewer to 547 more)
										160 per 1000	<b>74 more per 1000</b> (from 83 fewer to 547 more)

**Positive treatment response for social relatedness** (assessed with: Dichotomous: Positive treatment response for social relatedness - Share (study-specific parent-reported 'better than before'))

55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵			1/25 (4%)	0/30 (0%)	<b>RR 0.28</b> (0.01 to	Study population	on
4 weeks	risk of bias	inconsistency			strongly	due to imprecision, publication bias	(+70)	(070)		40 per 1000	<b>29 fewer per 1000</b> (from 40 fewer to 223 more)
										Moderate	
										40 per 1000	<b>29 fewer per 1000</b> (from 40 fewer to 223 more)

	1	r than before'))		1							
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias	⊕⊖⊝⊖ VERY LOW <sup>2,5</sup>	1/25 (4%)	0/30 (0%)	<b>RR 0.28</b> (0.01 to	Study population	on
4 weeks	risk of bias	inconsistency	Indirectiness	Senous	strongly suspected <sup>2</sup>	due to imprecision, publication bias	(478)	(070)	6.58)	40 per 1000	<b>29 fewer per 1000</b> (from 40 fewer to 223 more)
						DIAS				Moderate	
										40 per 1000	29 fewer per 1000 (from 40 fewer to 223 more)
		ent respon r than before'))	se for soc	ial related	iness (asses	ssed with: Dicho	tomous: Posit	ive treatment respons	e for social rela	itedness - Patienc	e (study-specific
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		0/25 (0%)	1/30 (3.3%)	<b>RR 2.52</b> (0.11 to	Study population	on
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision,			59.18)	0 per 1000	-
						publication bias				Moderate	
										0 per 1000	-
		ent respon - Expressive lar						sed with: Dichotomou	s: Positive trea	tment response fo	r non-verbal and
54 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias		7/24 (29.2%)	11/30 (36.7%)	<b>RR 1.26</b> (0.58 to	Study population	on
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision, publication bias	(20.270)		2.75)	292 per 1000	<b>76 more per 1000</b> (from 123 fewer to 510 more)
										Moderate	
										292 per 1000	<b>76 more per 1000</b> (from 123 fewer to 511 more)

verbal comm	unication	- Receptive lang	juage (study-sp	pecific parent-	reported 'bette	er than before'))					
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	serious <sup>6</sup>	reporting bias	⊕⊕⊝⊝ LOW <sup>2,6</sup>	5/25 (20%)	17/30 (56.7%)	<b>RR 2.83</b> (1.22 to	Study population	
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision, publication bias			6.59)	200 per 1000	<b>366 more per</b> <b>1000</b> (from 44 more to 1000 more)
										Moderate	
										200 per 1000	<b>366 more per</b> <b>1000</b> (from 44 more to 1000 more)
		ent responst - Pointing (study					ation (assessed	I with: Dichotomous: Po	ositive treat	ment response for	non-verbal and
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		0/25 (0%)	1/30 (3.3%)	<b>RR 2.52</b> (0.11 to	Study population	
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision,			59.18)	0 per 1000	-
						publication bias				Moderate	
										0 per 1000	-
		ent respons					ation (assessed	I with: Dichotomous: Po	ositive treat	ment response for	non-verbal and
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		0/25 (0%)	1/30 (3.3%)	<b>RR 2.52</b> (0.11 to	Study population	
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision,			59.18)	0 per 1000	-
						publication bias				Moderate	1
										0 per 1000	-
		-				l behaviour	(assessed with:	Dichotomous: Positive	treatment	response for stereo	typy interest and
behaviour - T	emper (s	tudy-specific par	ent-reported 'b	etter than befo	ore'))						

55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		5/25 (20%)	8/30 (26.7%)	<b>RR 1.33</b> (0.5 to	Study population	n
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision, publication bias	()	(2007/0)	3.56)	200 per 1000	66 more per 1000 (from 100 fewer to 512 more)
										Moderate	
										200 per 1000	66 more per 1000 (from 100 fewer to 512 more)
		ent respon					(assessed wi	ith: Dichotomous: Positive	e treatment	response for stere	otypy interest and
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		1/25 (4%)	1/30 (3.3%)	<b>RR 0.83</b> (0.05 to	Study population	n
4 weeks	risk of bias	,			strongly suspected <sup>2</sup>	due to imprecision, publication bias		()	12.66)	40 per 1000	<b>7 fewer per 1000</b> (from 38 fewer to 466 more)
										Moderate	
										40 per 1000	<b>7 fewer per 1000</b> (from 38 fewer to 466 more)
behaviour -	Adaptation	n to change (stud	dy-specific pare		etter than befo	ore'))	1	ith: Dichotomous: Positive	- 1	-	
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		1/25 (4%)	0/30 (0%)	<b>RR 0.28</b> (0.01 to	Study population	n
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision, publication bias			6.58)	40 per 1000	<b>29 fewer per 1000</b> (from 40 fewer to 223 more)
						-				Moderate	
										40 per 1000	<b>29 fewer per 1000</b> (from 40 fewer to

							]				223 more)
<b>Positive</b>	e treatm	ient respon	se for cog	nition (ass	essed with: Die	L chotomous: Posi	tive treatmen	t response for cognition	on - Memory (stu	l udy-specific parer	nt-reported 'better thar
55 (1 study)	no	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		2/25 (8%)	1/30 (3.3%)	<b>RR 0.42</b> (0.04 to	Study populati	on
4 weeks	risk of bias	inconsistency	indirectriess	Senous	suspected <sup>2</sup>	due to imprecision, publication bias	(070)	(3.370)	4.33)	80 per 1000	<b>46 fewer per 100</b> (from 77 fewer to 266 more)
						5125				Moderate	
										80 per 1000	<b>46 fewer per 1000</b> (from 77 fewer to 266 more)
'better than 55 (1 study)		no serious	no serious indirectness	very serious <sup>5</sup>	reporting		2/25 (8%)	2/30 (6.7%)	<b>RR 0.83</b> (0.13 to	Study populati	
4 weeks	risk of bias	Inconsistency	Indirectness	senous	strongly suspected <sup>2</sup>	due to imprecision, publication bias	(8%)	(6.7%)	5.5)	80 per 1000	<b>14 fewer per 100</b> (from 70 fewer to 360 more)
						Dias				Moderate	
										80 per 1000	<b>14 fewer per 100</b> (from 70 fewer to 360 more)
		lent respon r than before'))	se for mot	or abnorr	nalities (as	sessed with: Did	hotomous: P	ositive treatment resp	onse for motor a	abnormalities - M	otor skill (study-specifi
55 (1 study)	no	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		0/25 (0%)	5/30 (16.7%)	<b>RR 9.23</b> (0.53 to	Study populati	on
4 weeks	risk of bias	literiolotorioy			strongly suspected <sup>2</sup>	due to imprecision,	(0,0)	(10.170)	159.14)	0 per 1000	N/A
							1				

						bias	]			0 per 1000	N/A
		ent respon		or abnorr	nalities (as	ssessed with: Did	chotomous: F	Positive treatment respo	onse for motor a	abnormalities - Co	pordination (study-
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		2/25 (8%)	8/30 (26.7%)	<b>RR 3.33</b> (0.78 to	Study population	on
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision, publication bias		(2017/0)	14.29)	80 per 1000	<b>186 more per</b> <b>1000</b> (from 18 fewer to 1000 more)
										Moderate	
										80 per 1000	<b>186 more per</b> <b>1000</b> (from 18 fewer to 1000 more)
		r than before')) no serious	no serious	very serious⁵	reporting	essessed with: Did ⊕⊖⊝⊝ VERY LOW <sup>2,5</sup>	2hotomous: F 1/25 (4%)	Positive treatment response	RR 1.67 (0.16 to	abnormalities - Dr	
4 weeks	risk of bias	lineonsistency	munocinoss	301003	strongly suspected <sup>2</sup>	due to imprecision, publication bias	(470)	(0.175)	17.32)	40 per 1000	<b>27 more per 1000</b> (from 34 fewer to 653 more)
						bias				Moderate	
										40 per 1000	<b>27 more per 1000</b> (from 34 fewer to 653 more)
		ient respon		-	reported	changes (ass	sessed with:	Dichotomous: Positive	treatment resp	onse for other par	ent-reported changes
55 (1 study)	no	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		1/25 (4%)	3/30 (10%)	<b>RR 2.5</b> (0.28 to	Study populati	on
i suuv/	Serious	niconsistency	indirectriess	3011003	strongly	due to	("')	(1070)	(0.28 10	40 per 1000	

						publication bias					862 more)
										Moderate	
										40 per 1000	<b>60 more per 1000</b> (from 29 fewer to 862 more)
		ent respon			reported o	changes (ass	sessed with: Dich	otomous: Positive trea	atment respo	onse for other par	ent-reported changes
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias		0/25 (0%)	9/30 (30%)	RR 15.94	Study population	on
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision,	(0,0)		(0.97 to 260.91)	0 per 1000	N/A
						publication bias			,	Moderate	
										0 per 1000	N/A
				-	-	-			•	chee fer ether par	ent-reported changes
55	no	ly-specific parent	t-reported 'bette no serious	er than before'	)) reporting		3/25	7/30	RR 1.94	Study populatio	ent-reported changes -
55 (1 study) 4 weeks	no	1	t-reported 'bette	er than before	))	⊕⊖⊖⊖ VERY LOW <sup>2,5</sup> due to imprecision, publication bias	3/25 (12%)		-	1	
55 (1 study)	no serious risk of	no serious	t-reported 'bette no serious	er than before'	)) reporting bias strongly	VERY LOW <sup>2,5</sup> due to imprecision, publication		7/30	<b>RR 1.94</b> (0.56 to	Study populatio	n 113 more per 1000 (from 53 fewer to
55 (1 study)	no serious risk of	no serious	t-reported 'bette no serious	er than before'	)) reporting bias strongly	VERY LOW <sup>2,5</sup> due to imprecision, publication		7/30	<b>RR 1.94</b> (0.56 to	Study population	n 113 more per 1000 (from 53 fewer to
55 (1 study) 4 weeks Positive	no serious risk of bias	no serious inconsistency	no serious indirectness	er than before very serious⁵	)) reporting bias strongly suspected <sup>2</sup>	VERY LOW <sup>2,5</sup> due to imprecision, publication bias	(12%)	7/30 (23.3%)	<b>RR 1.94</b> (0.56 to 6.75)	Study population	113 more per 1000 (from 53 fewer to 690 more)           113 more per 1000 (from 53 fewer to

(1 study) 4 weeks	serious risk of bias	inconsistency	indirectness	serious <sup>5</sup>	0,	VERY LOW <sup>2,5</sup> due to imprecision, publication bias	(4%)	(6.7%)	(0.16 to 17.32)	(from 34 fewer to		
										40 per 1000	<b>27 more per 1000</b> (from 34 fewer to 653 more)	
<sup>2</sup> High risk of <sup>3</sup> Moderate h <sup>4</sup> N<400	selective eterogen ) and 95%		s trial protocol f	or WONG201	0B states that	follow-up meas	urements will b	e taken but these are 25)	not reported	1	1	

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

			Quality asses	sment					Summa	ry of Fin	dings
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e (%)	event rates	Relative effect	Anticipa	ted absolute effects
Follow up							With Waitlist	With Qigong massage training	(95% CI)	Risk with Waitlist	Risk difference with Qigong massage training (95% Cl)
		<b>behaviours</b> (me site; Better indicate			sm Behaviour (	Checklist (ABC): Total	or Paren	t-rated Pervas	sive Develop	oment Disc	order Behavior Inventory
79 (2 studies) 17-22 weeks	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	39	40	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.85 standard deviations</b> <b>lower</b> (1.32 to 0.39 lower)
Overall at	utistic b	<b>behaviours</b> (me	easured with: Tea	cher-rated Auti	sm Behaviour (	Checklist (ABC): Total	; Better in	dicated by lov	ver values)		
46 (1 study)	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2,3</sup>	21	25	N/A	N/A	The mean overall autistic behaviours in the intervention

22 weeks						due to risk of bias, imprecision					groups was 0.91 standard deviations lower (1.52 to 0.3 lower)
33 (1 study) 17 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2,4</sup> due to risk of bias, imprecision	18	15	N/A	N/A	ter indicated by lower values) The mean overall autistic behaviours in the intervention groups was 0.77 standard deviations lower (1.49 to 0.06 lower) DDBI): Social, language and
		Better indicated by					, velopin				5557. Coolai, languago ana
46 (1 study) 22 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>2,3</sup> due to risk of bias, imprecision	21	25	N/A	N/A	The mean social, language, and communication abilities in the intervention groups was <b>0.82 standard deviations</b> <b>higher</b> (0.22 to 1.43 higher)
		, and commu Better indicated by		<b>lities</b> (measu	red with: Pare	nt-rated Pervasive Dev	relopmer	nt Disorder Be	havior Inver	ntory (PDI	DBI): Social, language and
79 (2 studies) 17-22 weeks	very serious <sup>1</sup>	very serious⁵	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,5</sup> due to risk of bias, inconsistency, imprecision	39	40	N/A	N/A	The mean social, language, and communication abilities in the intervention groups was <b>0.53 standard deviations</b> <b>higher</b> (0.07 to 1 higher)
Maladapti	ive beha	<b>aviour</b> (measure	I ed with: Teacher-r	ated Pervasive	Development	I Disorder Behavior Inve	ntory (P	DDBI): Malad	aptive behav	viour; Bett	er indicated by lower values)
46 (1 study) 22 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>6</sup>	undetected	⊕⊝⊝⊖ VERY LOW <sup>3,6</sup> due to risk of bias, imprecision	21	25	N/A	N/A	The mean maladaptive behaviour in the intervention groups was <b>0.56 standard deviations</b>

											lower (1.16 lower to 0.03 higher)
Maladapti	ve beha	aviour (measure	ed with: Parent-ra	ted Pervasive I	Development Di	sorder Behavior Inven	tory (PD	DBI): Maladap	tive behavi	iour; Bette	er indicated by lower values)
79 (2 studies) 17-22 weeks	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	39	40	N/A	N/A	The mean maladaptive behaviour in the intervention groups was 1.03 standard deviations lower (1.5 to 0.55 lower)
due to parenta comparable at response bias involved in the <sup>2</sup> N<400 <sup>3</sup> High risk of s due to parenta comparable at <sup>4</sup> High risk of p involved in intu <sup>5</sup> Substantial t	al involvem t baseline f as interver intervention selection bi al involvem t baseline f berformance ervention o considera	ent in the treatmen or measures of par ntion administrator on. as in SILVA2009 a ent in the treatmen or measures of par	at and different ge rent rated social of s and participants as groups were as at and different ge rent rated social of as as intervention	ographical area communication s were non-blind signed using a ographical area communication administrators	as were assigne and autism com d, and risk of de random numbe as were assigne and autism com and participant	ad separately to meet the posite and teacher rand teacher rand teacher rand teacher rand teacher rand separately to meet the posite and teacher rand sever non-blind, and	the 'thera ted sens for the p were cav the 'thera ted sens	apist to particip sory problems. parent-rated ou veats to the rar apist to particip sory problems.	oant require There was tcome mea ndomisation oant require	ements'), g also a hig asure as p n (five sets ements'), g	gh risk of performance and arents were non-blind and s of siblings were co-assigned

#### 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

			Quality asses	ssment				Sum	mary of Findings			
· · · · · · · · · · · · · · · · · · ·	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study ev rates (%	)	Relative effect	Anticipated absolute effects		
Follow up							With Placebo	With Secretin		Risk with Risk difference with Secretin (95% CI) Placebo		
Positive t	Positive treatment response (assessed with: Dichotomous: Positive treatment response (decrease of >4.07 points CARS))											
57 (1 study)			no serious indirectness	very serious <sup>2</sup>	reporting bias strongly	⊕⊖⊝⊖ VERY LOW <sup>1,2,3</sup>	7/29 (24.1%)		<b>RR 1.63</b> (0.74 to	Study population		
3 weeks						due to risk of bias,	,	(	3.6)	241 per 152 more per 1000		

						imprecision, publication bias				1000	(from 63 fewer to 628 more)	
										Moderat	e	
										241 per 1000	152 more per 1000 (from 63 fewer to 627 more)	
		nt response ( roved' on CGI-imp		Dichotomous: F	Positive treatment	response (decrease	of >4.07 p	oints CAR	S) or Dicho	otomous: F	Positive treatment response (	
109 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		15/54	19/55 (34.5%)	<b>RR 1.24</b> (0.71 to	Study po	opulation	
4-6 weeks		Inconsistency		Senous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(21.070)	(34.376)	2.19)	278 per 1000	67 more per 1000 (from 81 fewer to 331 more)	
						·				Moderate		
										278 per 1000	<b>67 more per 1000</b> (from 81 fewer to 331 more)	
Overall a	utistic b	<b>ehaviours</b> (m	easured with: Ch	nildhood Autisr	n Rating Scale (C	ARS): Total (endpoint	t or chang	e scores);	Better indi	cated by lo	wer values)	
137 (2 studies) 3-6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>4</sup> due to imprecision	71	66	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.14 standard deviations</b> higher (0.2 lower to 0.48 higher)	
Overall a	utistic b	ehaviours (m	easured with: Au	itism Behaviou	Ir Checklist (ABC)	: Total (change score	); Better in	ndicated b	y lower val	ues)	1	
145 (2 studies) 1-3 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>4</sup> due to imprecision	73	72	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.09 standard deviations lower</b> (0.42 lower to 0.23 higher)	
Overall a	utistic b	ehaviours (m	easured with: Au	itism Behaviou	r Checklist (ABC)	: Total (change score	); Better in	ndicated b	y lower val	ues)		
52 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	25	27	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.46 standard deviations lower</b> (1.01 lower to 0.1 higher)	

140	no serious	no serious	no serious	serious <sup>4</sup>	undetected	$\oplus \oplus \oplus \Theta$	70	70	N/A	N/A	The mean sensory function in the
(2 studies) 1-3 weeks	risk of bias	inconsistency	indirectness	301003	undeteeted	<b>MODERATE</b> <sup>4</sup> due to imprecision	10	10			intervention groups was 0.09 standard deviations lower (0.42 lower to 0.25 higher)
Sensory	function	(measured with:	Autism Behavio	ur Checklist (	ABC): Sensory (c	hange score); Better in	dicated	by lower v	alues)	<b>I</b>	
52 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	25	27	N/A	N/A	The mean sensory function in the intervention groups was <b>0.52 standard deviations lower</b> (1.08 lower to 0.03 higher)
Social re	latednes	<b>S</b> (measured wit	h: Autism Behav	iour Checklis	t (ABC): Social re	latedness (change sco	re); Bett	er indicate	d by lower	values)	
143 (2 studies) 1-3 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>4</sup> due to imprecision	72	71	N/A	N/A	The mean social relatedness in the intervention groups was <b>0.11 standard deviations lower</b> (0.44 lower to 0.22 higher)
Social re	latednes	<b>S</b> (measured wit	h: Autism Behav	iour Checklis	t (ABC): Social re	latedness (change sco	re); Bett	er indicate	d by lower	values)	
52 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	25	27	N/A	N/A	The mean social relatedness in the intervention groups was <b>0.3 standard deviations lower</b> (0.85 lower to 0.25 higher)
Body an	d object	<b>USE</b> (measured	with: Autism Bel	navior Check	ist (ABC): Body a	nd object use (change	score); l	Better indi	cated by lo	wer values	)
145 (2 studies) 1-3 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>4</sup> due to imprecision	73	72	N/A	N/A	The mean body and object use in the intervention groups was <b>0.05 standard deviations lower</b> (0.38 lower to 0.28 higher)
Body an	d object	<b>USE</b> (measured	with: Autism Bel	navior Checkl	ist (ABC): Body a	nd object use (change	score); l	Better indi	cated by lo	wer values	)
52 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	25	27	N/A	N/A	The mean body and object use in the intervention groups was <b>0.11 standard deviations lower</b> (0.66 lower to 0.43 higher)
Languag	e (measured	d with: Autism Be	haviour Checklis	st (ABC): Lan	guage (change so	core); Better indicated b	y lower	values)			
136 (2 studies) 1-3 weeks	no serious risk of bias	serious <sup>6</sup>	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊖ LOW <sup>4,6</sup> due to	67	69	N/A	N/A	The mean language in the intervention groups was 0.01 standard deviations lower

						inconsistency, imprecision					(0.35 lower to 0.33 higher)
Languag	<b>je</b> (measure	d with: Autism Be	haviour Checklis	t (ABC): Lang	juage (change sc	ore); Better indicated b	y lower	values)			
52 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	25	27	N/A	N/A	The mean language in the intervention groups was <b>0.32 standard deviations lower</b> (0.87 lower to 0.23 higher)
Socializa	ation (meas	sured with: Autism	n Behaviour Che	cklist (ABC):	Socialization (cha	nge score); Better indi	cated by	lower valu	ues)	<b>!</b>	
139 (2 studies) 1-3 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>4</sup> due to imprecision	70	69	N/A	N/A	The mean socialization in the intervention groups was <b>0.05 standard deviations lower</b> (0.39 lower to 0.28 higher)
Socializa	ation (meas	sured with: Autism	n Behaviour Che	cklist (ABC):	Socialization (cha	nge score); Better indi	cated by	lower valu	ues)		
52 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	25	27	N/A	N/A	The mean socialization in the intervention groups was <b>0.25 standard deviations lower</b> (0.8 lower to 0.3 higher)
Overall a	autistic b	ehaviours (m	neasured with: G	illiam Autism	Rating Scale (GA	RS): Autism Quotient;	Better in	dicated by	lower valu	ues)	
98 (2 studies) 4-6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	51	47	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.34 standard deviations</b> higher (0.06 lower to 0.74 higher)
Overall a	autistic b	ehaviours (m	l neasured with: G	illiam Autism	Rating Scale (GA	RS): Social Interaction	; Better i	indicated l	by lower va	lues)	
56 (1 study) 4 weeks	1	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊖⊖ LOW <sup>5</sup> due to imprecision	28	28	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.42 standard deviations</b> higher (0.11 lower to 0.95 higher)
Overall a	autistic b	ehaviours (m	neasured with: G	illiam Autism	Rating Scale (GA	RS): Stereotyped beha	aviours; I	Better indi	cated by lo	wer values	s)
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	28	28	N/A	N/A	The mean overall autistic behaviours in the intervention groups was

											<b>0.17 standard deviations</b> <b>higher</b> (0.36 lower to 0.69 higher)
Overall	autistic b	ehaviours (m	easured with: G	illiam Autism	Rating Scale (GA	RS): Communication; I	Better in	dicated by	/ lower valu	ies)	
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	28	28	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.38 standard deviations</b> higher (0.15 lower to 0.9 higher)
Overall	autistic b	ehaviours (m	easured with: C	linical Global	Impression (CGI)	scale; Better indicated	by lowe	r values)			
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	28	28	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.23 standard deviations</b> higher (0.29 lower to 0.76 higher)
Respon	se to soc	ial interactio	n (measured w	ith: Clinical G	lobal Impression	(CGI): Response to so	cial inter	action (ch	ange score	); Better in	dicated by lower values)
52 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	25	27	N/A	N/A	The mean response to social interaction in the intervention groups was <b>0 standard deviations higher</b> (0.54 lower to 0.54 higher)
Respon	se to soc	ial interactio	) <b>n</b> (measured w	ith: Clinical G	lobal Impression	(CGI): Response to so	cial inter	action (ch	ange score	); Better in	dicated by lower values)
49 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	24	25	N/A	N/A	The mean response to social interaction in the intervention groups was <b>0.34 standard deviations lower</b> (0.9 lower to 0.23 higher)
Social in	nitiation (r	neasured with: Cl	inical Global Imp	pression (CGI	): Social initiation	(change score); Better	indicate	d by lowe	r values)		
52 (1 study) 1 weeks		no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW⁵ due to imprecision	25	27	N/A	N/A	The mean social initiation in the intervention groups was <b>0.09 standard deviations lower</b> (0.64 lower to 0.45 higher)
Social in	nitiation (r	I neasured with: CI	I inical Global Imp	I pression (CGI	): Social initiation	(change score); Better	indicate	d by lowe	r values)		_   

49 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	24	25	N/A	N/A	The mean social initiation in the intervention groups was <b>0 standard deviations higher</b> (0.56 lower to 0.56 higher)
Use of s	peech (me	easured with: Clin	ical Global Impre	ssion (CGI): U	lse of speech (cha	ange score); Better ind	dicated by	/ lower val	ues)		
52 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	<pre>⊕⊕⊖⊖ LOW<sup>5</sup> due to imprecision</pre>	25	27	N/A	N/A	The mean use of speech in the intervention groups was <b>0.2 standard deviations lower</b> (0.74 lower to 0.35 higher)
Use of s	peech (me	asured with: Clin	ical Global Impre	ssion (CGI): U	Ise of speech (cha	ange score); Better ind	dicated by	/ lower val	ues)	<u> </u>	ŀ
49 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	24	25	N/A	N/A	The mean use of speech in the intervention groups was <b>0 standard deviations higher</b> (0.56 lower to 0.56 higher)
Types o	f repetitiv	ve behaviou	r (measured with	: Clinical Glob	al Impression (CG	GI): Types of repetitive	behaviou	ur (change	score); Bet	ter indicat	ed by lower values)
52 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	25	27	N/A	N/A	The mean types of repetitive behaviour in the intervention groups was <b>0.18 standard deviations lower</b> (0.72 lower to 0.37 higher)
Types o	f repetitiv	ve behaviou	r (measured with	: Clinical Glob	al Impression (CG	I): Types of repetitive	behaviou	ur (change	score); Bet	ter indicat	ed by lower values)
49 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW <sup>5</sup> due to imprecision	24	25	N/A	N/A	The mean types of repetitive behaviour in the intervention groups was <b>0.26 standard deviations lower</b> (0.82 lower to 0.3 higher)
Behavio	ur proble	<b>ms</b> (measured)	with: Clinical Glo	bal Impression	(CGI): Behaviou	problems (change so	core); Bet	ter indicate	ed by lower	values)	<u>.</u>
52 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	25	27	N/A	N/A	The mean behaviour problems in the intervention groups was <b>0.4 standard deviations higher</b> (0.15 lower to 0.95 higher)
Behavio	ur proble	ms (measured	with: Clinical Glo	bal Impression	(CGI): Behaviou	problems (change so	core); Bet	ter indicate	ed by lower	values)	
49 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	$\oplus \oplus \ominus \ominus$ LOW <sup>5</sup> due to imprecision	24	25	N/A	N/A	The mean behaviour problems in the intervention groups was <b>0.42 standard deviations</b>

											<b>higher</b> (0.14 lower to 0.99 higher)
Activity	level (mea	sured with: Clinica	al Global Impress	sion (CGI): Ac	tivity level (chang	e score); Better indica	ted by lo	ower value	s)		
52 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	25	27	N/A	N/A	The mean activity level in the intervention groups was <b>0.32 standard deviations</b> <b>higher</b> (0.23 lower to 0.87 higher)
Activity	level (meas	sured with: Clinica	al Global Impress	sion (CGI): Ac	tivity level (chang	e score); Better indica	ted by lo	wer value	s)		
49 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	24	25	N/A	N/A	The mean activity level in the intervention groups was <b>0.08 standard deviations</b> <b>higher</b> (0.48 lower to 0.64 higher)
Sleep p	roblems (r	measured with: Cl	inical Global Imp	pression (CGI	): Sleep problems	(change score); Bette	r indicat	ed by lowe	r values)	•	·
49 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	24	25	N/A	N/A	The mean sleep problems in the intervention groups was <b>0.16 standard deviations</b> <b>higher</b> (0.41 lower to 0.72 higher)
Sleep p	roblems (r	measured with: Cl	inical Global Imp	pression (CGI	): Sleep problems	(change score); Bette	r indicat	ed by lowe	r values)		
48 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	24	24	N/A	N/A	The mean sleep problems in the intervention groups was <b>0.23 standard deviations lowe</b> (0.79 lower to 0.34 higher)
Digestiv	e probler	<b>ns</b> (measured w	ith: Clinical Glob	al Impression	(CGI): Digestive	problems (change sco	re); Bett	er indicate	d by lower	values)	
50 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	24	26	N/A	N/A	The mean digestive problems in the intervention groups was <b>0.18 standard deviations lowe</b> (0.74 lower to 0.37 higher)
Digestiv	/e probler	ns (measured w	ith: Clinical Glob	al Impression	(CGI): Digestive	problems (change sco	re); Bett	er indicate	d by lower	values)	
48 (1 study) 4 weeks	-	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	24	24	N/A	N/A	The mean digestive problems in the intervention groups was <b>0 standard deviations higher</b>

											(0.57 lower to 0.57 higher)
		ehaviours ( Better indicated			ic secretin g	roups combine	<b>d)</b> (mea	asured wit	h: Parent-ra	ated Secret	in Outcome Survey-Modified (SC
78 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	31	47	N/A	N/A	The mean overall autistic behaviours (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.1 standard deviations low</b> (0.56 lower to 0.35 higher)
		ehaviours ( score); Better ind			ic secretin g	roups combine	<b>d)</b> (mea	asured wit	h: Teacher	rated Secr	etin Outcome Survey-Modified
56 (1 study) 4 weeks		no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW⁵ due to imprecision	22	34	N/A	N/A	The mean overall autistic behaviours (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.17 standard deviations</b> higher (0.37 lower to 0.71 higher)
Social (	porcine a ated by lower	nd synthetio	c secretin g	roups co	mbined) (mea	asured with: Parent-rate	ed Secre	etin Outco	me Survey	-Modified (	SOS-M): Social (change score);
78 (1 study) 4 weeks	-	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	31	47	N/A	N/A	The mean social (porcine and synthetic secretin groups combined) in the intervention groups was 0.07 standard deviations higher (0.38 lower to 0.53 higher)
	porcine a ated by lower		c secretin g	roups co	mbined) (mea	asured with: Teacher-ra	ated Sec	cretin Outo	come Surve	y-Modified	(SOS-M): Social (change score)
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	22	34	N/A	N/A	The mean social (porcine and synthetic secretin groups combined) in the intervention groups was 0.25 standard deviations higher

Communication	ication ( on (change	porcine and score); Better indic	synthetic s	ecretin gr	oups combi	i <b>ned)</b> (measured wi	th: Parent	t-rated Sec	cretin Outco	me Surve	y-Modified (SOS-M):
78 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊖ LOW <sup>5</sup> due to imprecision	31	47	N/A	N/A	The mean communication (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.25 standard deviations</b> <b>higher</b> (0.2 lower to 0.71 higher)
Communication	ication ( on (change	porcine and score); Better indic	synthetic s	ecretin gr	oups combi	i <b>ned)</b> (measured wi	th: Teach	er-rated S	ecretin Outo	come Surv	/ey-Modified (SOS-M):
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	22	34	N/A	N/A	The mean communication (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.5 standard deviations higher</b> (0.05 lower to 1.04 higher)
		our (porcine			tin groups c	ombined) (meas	ured with:	Parent-ra	ted Secretir	n Outcome	e Survey-Modified (SOS-M):
78 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊖⊖ LOW <sup>5</sup> due to imprecision	31	47	N/A	N/A	The mean repetitive behaviour (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.2 standard deviations lower</b> (0.65 lower to 0.25 higher)
Repetitive be	<b>e behavi</b> haviour (cha	our (porcine	and synthe	etic secret ver values)	tin groups c	ombined) (meas	ured with:	Teacher-	rated Secre	tin Outcor	ne Survey-Modified (SOS-M):
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊖ LOW <sup>5</sup> due to imprecision	22	34	N/A	N/A	The mean repetitive behaviour (porcine and synthetic secretin groups combined) in the intervention groups was 0.18 standard deviations higher (0.36 lower to 0.72 higher)
		e and synthe y lower values)	etic secretir	n groups o	combined) (m	neasured with: Parent	-rated Se	cretin Out	come Surve	y-Modifie	d (SOS-M): Digestive (change
78 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝ LOW⁵	31	47	N/A	N/A	The mean digestive (porcine and synthetic secretin groups

4 weeks	bias					due to imprecision					combined) in the intervention groups was 0.08 standard deviations higher (0.37 lower to 0.54 higher)
		e and synth	etic secreti	n groups	combined)	(measured with: Teach	er-ratec	d Secretin	Outcome S	Survey-Mod	ified (SOS-M): Digestive (change
35 (1 study) 4 weeks		no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	15	20	N/A	N/A	The mean digestive (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.28 standard deviations</b> <b>higher</b> (0.39 lower to 0.96 higher)
	orcine ar		secretin gr	oups cor	nbined) (mea	sured with: Parent-rate	d Secret	tin Outcon	ne Survey-I	Modified (S	OS-M): Mood (change score); Bette
77 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	31	46	N/A	N/A	The mean mood (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.06 standard deviations lowe</b> (0.51 lower to 0.4 higher)
Mood (p Better indica	orcine ar	n <b>d synthetic</b> values)	secretin gr	oups cor	<b>nbined)</b> (mea	sured with: Teacher-rat	ed Secr	etin Outco	ome Survey	-Modified (	SOS-M): Mood (change score);
47 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW⁵ due to imprecision	18	29	N/A	N/A	The mean mood (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.33 standard deviations</b> higher (0.26 lower to 0.93 higher)
	/ (porcine ated by lower		tic secretin	groups	combined) (r	measured with: Parent-	rated Se	ecretin Ou	tcome Surv	/ey-Modifie	d (SOS-M): Sensory (change score)
77 (1 study) 4 weeks	-	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	31	46	N/A	N/A	The mean sensory (porcine and synthetic secretin groups combined) in the intervention groups was 0.39 standard deviations lowe

											(0.85 lower to 0.07 higher)
		e and synthe y lower values)	tic secretin	groups o	combined) (n	neasured with: Teache	r-rated S	ecretin O	utcome Su	rvey-Modifi	ed (SOS-M): Sensory (change
46 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝ LOW <sup>5</sup> due to imprecision	18	28	N/A	N/A	The mean sensory (porcine an synthetic secretin groups combined) in the intervention groups was <b>0 standard deviations higher</b> (0.59 lower to 0.59 higher)
		rcine and sy		retin gro	ups combin	ed) (measured with: I	Parent-ra	ated Secre	etin Outcon	ne Survey-	Modified (SOS-M): Hyperactivity
77 (1 study) 4 weeks	1	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	31	46	N/A	N/A	The mean hyperactivity (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.05 standard deviations lowe</b> (0.51 lower to 0.4 higher)
		rcine and sy		retin gro	ups combin	ed) (measured with: <sup>-</sup>	Teacher-	rated Sec	retin Outco	ome Survey	
43 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	16	27	N/A	N/A	The mean hyperactivity (porcin and synthetic secretin groups combined) in the intervention groups was 0.14 standard deviations higher (0.48 lower to 0.76 higher)
		e and synthe	etic secretir	n groups	combined) (	measured with: Parent	-rated Se	ecretin Ou	Itcome Sur	vey-Modifie	ed (SOS-M): Lethargy (change
76 1 study) 4 weeks	1	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	30	46	N/A	N/A	The mean lethargy (porcine an synthetic secretin groups combined) in the intervention groups was 0.09 standard deviations higher (0.37 lower to 0.55 higher)

41 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊖⊝ LOW <sup>5</sup> due to imprecision	15	26	N/A	N/A	The mean lethargy (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.31 standard deviations</b> higher (0.33 lower to 0.95 higher)
	orcine ar		secretin gr	oups com	<b>bined)</b> (measu	ured with: Parent-rated	d Secretir	Outcome	Survey-Mo	dified (SC	)S-M): Lethargy (change score);
76 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ MODERATE <sup>4</sup> due to imprecision	31	45	N/A	N/A	The mean sleep (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.02 standard deviations</b> higher (0.44 lower to 0.48 higher)
<sup>2</sup> Events<30 <sup>3</sup> High risk o <sup>4</sup> N<400 <sup>5</sup> N<400 and	0 and 95% C f selective re	I crosses both line porting bias in CC sses both line of n	e of no effect and NIGLIO2001 as	I measure of a data could not	ppreciable benefi be extracted for t	vas 'double-blind stud t or harm (RR 0.75/1. he CARS (continuous arm (SMD -0.5/0.5)	25)			come ass	essors were blinded

#### 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

		Qu	ality assess	ment			Summary of Findings					
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	bias	quality of evidence	With Short- term chelation	ζ, γ	effect (95% CI)	Risk with Short-term chelation	d absolute effects Risk difference with Long-term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy) (95% CI)	

							therapy and 6-rounds of placebo)			therapy and 6-rounds of placebo)	
Overall	autisti	c behaviou	JIS (measure	d with: Autism	Evaluation Tre	eatment Check	dist (ATEC):	Total; Better indicate	ed by lowe	r values)	
24 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	10	14	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.25 standard deviations higher</b> (0.57 lower to 1.06 higher)
Speech	/Langu	iage/Comr	nunicatio	<b>n</b> (measured	with: Autism E	valuation Trea	tment Checl	klist (ATEC): Speech	Language	I /Communica	tion; Better indicated by lower
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	15	25	N/A	N/A	The mean speech/language/communication in the intervention groups was <b>0.01 standard deviations higher</b> (0.63 lower to 0.65 higher)
Sociabi	i <b>lity</b> (mea	sured with: Autis	Evaluation T	reatment Che	ecklist (ATEC):	Sociability; Be	etter indicate	d by lower values)			
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	15	25	N/A	N/A	The mean sociability in the intervention groups was <b>0.14 standard deviations higher</b> (0.51 lower to 0.78 higher)

Sensory	/Cogn	itive Awar	<b>eness</b> (mea	sured with: A	utism Evaluatio	on Treatment C	Checklist (A	TEC): Sensory/Cogn	itive Aware	eness; Bette	r indicated by lower values)
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	15	25	N/A	N/A	The mean sensory/cognitive awareness in the intervention groups was <b>0.28 standard deviations higher</b> (0.36 lower to 0.93 higher)
Health/P	hysic	al/Behavio	f (measured w	ith: Autism Ev	aluation Treatr	nent Checklist	(ATEC): H	lealth/Physical/Behav	ior; Better	indicated by	lower values)
24 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	10	14	N/A	N/A	The mean health/physical/behavior in the intervention groups was <b>0.33 standard deviations higher</b> (0.49 lower to 1.14 higher)
Overall a	autisti	c behaviou	JIS (measured	l with: Pervas	ive Developme	nt Disorder Be	havior Inve	entory (PDDBI): Autis	m Compos	ite; Better ir	ndicated by lower values)
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	15	25	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.24 standard deviations higher</b> (0.41 lower to 0.88 higher)
Overall a	autisti	c behaviou	JIS (measured	l with: Severit	y of Autism Sca	ale (SAS): Tota	al; Better ir	dicated by lower valu	ies)	1	
36 (1 study) 17 weeks	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to	14	22	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.13 standard deviations lower

	bias			imprecision, publication bias				(0.8 lower to 0.54 higher)
		osses both line or reporting bias as			MD -0.5/0.5) pressions scale as no measure	of variabili	ty reported	

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

		Q	uality assess	ment					Sum	nmary of F	indings	
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study eve	ent rates (%)	Relative	Anticipate	d absolute effects	
(studies) Follow up	bias				bias	of evidence	With Attention- placebo control	With Hyperbaric oxygen treatment (HBOT)	effect (95% CI)	Risk with Attention- placebo control	Risk difference with Hyperbaric oxygen treatment (HBOT) (95% Cl)	
Positive t	treatme	ent response	e (assessed wit	h: Number of	participants w	no showed improv	vement in A	DOS Total sc	ore)			
34 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup>	4/16 (25%)	5/18 (27.8%)	<b>RR 1.11</b> (0.36 to	Study population		
15 weeks	risk of bias					due to imprecision			3.44)	250 per 1000	<b>28 more per 1000</b> (from 160 fewer to 610 more)	
										Moderate		
										250 per 1000	<b>28 more per 1000</b> (from 160 fewer to 610 more)	
Overall a	utistic	behaviours	(measured with	: Autism Diagr	nostic Observa	ation Schedule (A	DOS): Tota	l score; Better	indicated I	by lower val	ues)	
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^2 \\ \text{due to} \\ \text{imprecision} \end{array}$	26	30	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.16 standard deviations lower</b> (0.69 lower to 0.37 higher)	
Overall a	utistic	behaviours	(parent-rat	ed) (measur	ed with: Autisr	n Evaluation Trea	itment Che	cklist (ATEC):	Total; Bett	er indicated	by lower values)	
114	no	no serious	no serious	serious <sup>3</sup>	undetected	$\oplus \oplus \oplus \ominus$	55	59	N/A	N/A	The mean overall autistic behaviours	

(2 studies) 4 weeks Speech/ indicated by			indirectness	arent-rate	ed) (measured	MODERATE <sup>3</sup> due to imprecision with: Autism Eva	luation T	reatment Cher	cklist (ATE	C): Speech/	(parent-rated) in the intervention groups was <b>0.05 standard deviations lower</b> (0.42 lower to 0.32 higher) Language/Communication; Better
114 (2 studies) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	55	59	N/A	N/A	The mean speech/language/communication (parent-rated) in the intervention groups was <b>0.10 standard deviations higher</b> (0.27 lower to 0.47 higher)
Sociabili	ity (pare	ent-rated) (m	easured with: A	utism Evaluat	tion Treatment	Checklist (ATEC)	: Sociabi	lity; Better indi	cated by lo	wer values)	
114 (2 studies) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	55	59	N/A	N/A	The mean sociability (parent-rated) in the intervention groups was <b>0.02 standard deviations lower</b> (0.39 lower to 0.35 higher)
Sensory	/Cognit	ive Awaren	ess (parent	t <b>-rated)</b> (m	easured with:	Autism Evaluation	Treatme	ent Checklist (	ATEC): Ser	nsory/Cogni	tive Awareness; Better indicated by lower
114 (2 studies) 4 weeks	no serious risk of bias	very serious <sup>4</sup>	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,4</sup> due to inconsistency, imprecision	55	59	N/A	N/A	The mean sensory/cognitive awareness (parent-rated) in the intervention groups was <b>0.25 standard deviations lower</b> (0.62 lower to 0.13 higher)
Health/P	hysical	/Behavior (p	barent-rate	<b>d)</b> (measure	d with: Autism	Evaluation Treatm	nent Che	cklist (ATEC):	Health/Phy	/sical/Behav	vior; Better indicated by lower values)
114 (2 studies) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	55	59	N/A	N/A	The mean health/physical/behavior (parent-rated) in the intervention groups was <b>0.02 standard deviations higher</b> (0.35 lower to 0.39 higher)
Overall a	autistic	behaviours	(clinician-	rated) (mea	asured with: Au	tism Evaluation ⊺	reatmen	t Checklist (AT	EC): Total	; Better indi	cated by lower values)
58	no	no serious	no serious	very	undetected	$\oplus \oplus \ominus \ominus$	29	29	N/A	N/A	The mean overall autistic behaviours

(1 study) 4 weeks	serious risk of bias	inconsistency	indirectness	serious <sup>2</sup>		LOW <sup>2</sup> due to imprecision					(clinician-rated) in the intervention groups was <b>0.03 standard deviations lower</b> (0.54 lower to 0.49 higher)
Speech, indicated by	•	•	nication (cl	inician-ra	t <b>ed)</b> (measu	red with: Autism	Evaluatio	n Treatment (	Checklist (A	TEC): Spee	ch/Language/Communication; Better
58 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>2</sup> due to imprecision	29	29	N/A	N/A	The mean speech/language/communication (clinician-rated) in the intervention groups was <b>0.04 standard deviations lower</b> (0.55 lower to 0.48 higher)
Sociabi	lity (clin	ician-rated)	(measured with	: Autism Eval	uation Treatme	ent Checklist (AT	EC): Soci	iability; Better	indicated b	y lower valu	es)
58 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^2 \\ \text{due to} \\ \text{imprecision} \end{array}$	29	29	N/A	N/A	The mean sociability (clinician-rated) in the intervention groups was <b>0.27 standard deviations higher</b> (0.25 lower to 0.79 higher)
Sensory	-	ive Awaren	ess (clinici	an-rated)	(measured wit	h: Autism Evalua	ation Trea	tment Checkl	ist (ATEC):	Sensory/Co	gnitive Awareness; Better indicated by
58 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	29	29	N/A	N/A	The mean sensory/cognitive awareness (clinician-rated) in the intervention groups was <b>0.07 standard deviations lower</b> (0.59 lower to 0.44 higher)
Health/F	Physical	/Behaviour	(clinician-r	ated) (meas	sured with: Aut	tism Evaluation <sup>-</sup>	Freatment	Checklist (A	TEC): Healt	n/Physical/E	Sehavior; Better indicated by lower values
58 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>2</sup> due to imprecision	29	29	N/A	N/A	The mean health/physical/behaviour (clinician-rated) in the intervention groups was <b>0.2 standard deviations lower</b> (0.72 lower to 0.31 higher)
Global s	severity	(parent-rate	ed) (measured	with: Clinical (	Global Impress	sion Scale (CGI-	S): Severi	ty; Better indi	cated by lov	ver values)	- I
58	no	no serious	no serious	very	undetected	$\oplus \oplus \ominus \ominus$	29	29	N/A	N/A	The mean global severity (parent-

(1 study) 4 weeks	serious risk of bias	inconsistency	indirectness	serious <sup>2</sup>		LOW <sup>2</sup> due to imprecision					rated) in the intervention groups was <b>0.03 standard deviations higher</b> (0.48 lower to 0.55 higher)
Global s	everity	(clinician-ra	<b>ated)</b> (measur	ed with: Clinica	al Global Impre	ession Scale (CG	I-S): Sev	erity; Better ind	cated by	lower value	s)
58 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^2 \\ \text{due to} \\ \text{imprecision} \end{array}$	29	29	N/A	N/A	The mean global severity (clinician- rated) in the intervention groups was <b>0.34 standard deviations lower</b> (0.86 lower to 0.18 higher)
Global ir	mprove	ment (parer	nt-rated) (me	asured with: C	Clinical Global	Impression Scale	(CGI-I):	Improvement; E	Better indi	cated by low	ver values)
58 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	29	29	N/A	N/A	The mean global improvement (parent-rated) in the intervention groups was <b>0.28 standard deviations lower</b> (0.8 lower to 0.23 higher)
Global ir	mprove	ment (cinici	an-rated) (r	neasured with	: Clinical Globa	al Impression Sca	ale (CGI-I	): Improvement	; Better ir	idicated by I	ower values)
58 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	29	29	N/A	N/A	The mean global improvement (cinician-rated) in the intervention groups was <b>0.57 standard deviations lower</b> (1.1 to 0.05 lower)

#### 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

	Quality assessment	Summary of Findings
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Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e	vent rates (%)	Relative effect	Anticipat	ed absolute effects
Follow up							With Placebo	With Multivitamin and mineral supplement	(95% CI)	Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% Cl)
Average	improv	ement (measu	Ired with: Parent 0	Global Impressi	ions-Revised (	I PGI-R): Average ir	nproveme	nt (average of all s	ubscales); E	l Setter indica	ated by lower values)
104 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	51	53	N/A	N/A	The mean average improvement in the intervention groups was <b>0.55 standard deviations</b> higher (0.16 to 0.94 higher)
Overall i	mprove	ment (measure	ed with: Parent Glo	obal Impressio	ns-Revised (P	GI-R): Overall impr	ovement;	Better indicated by	lower value	s)	
104 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	51	53	N/A	N/A	The mean overall improvement in the intervention groups was <b>0.49 standard deviations</b> <b>higher</b> (0.1 to 0.88 higher)
Overall a	autistic	behaviours	(measured with: A	Autism Evaluat	ion Treatment	Checklist (ATEC):	Total; Be	tter indicated by lov	ver values)		
104 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	51	53	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.04 standard deviations</b> higher (0.34 lower to 0.43 higher
Overall a	autistic	behaviours	(measured with:	Severity of Auti	ism Scale (SA	S): Total; Better inc	licated by	lower values)	I	ł	
104 (1 study)	no serious	no serious	no serious	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup>	51	53	N/A	N/A	The mean overall autistic behaviours in the

13 weeks	risk of bias	inconsistency	indirectness			due to imprecision					intervention groups was 0.04 standard deviations lower (0.43 lower to 0.34 higher)
Overall	autistic	behaviours	(measured with: I	Pervasive Dev	elopment Diso	rder Behavior Inver	ntory (PE	DDBI): Total; Better i	ndicated by	lower value	es)
104 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	51	53	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.02 standard deviations</b> higher (0.37 lower to 0.4 higher)
<sup>1</sup> N<400											

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

		(	Quality assess	ment				S	Summary o	of Finding	gs
Participants		Inconsistency	Indirectness	Imprecision		Overall quality of	Study e	vent rates (%)	Relative	Anticipat	ed absolute effects
(studies) Follow up	bias				bias	evidence	With Placebo	With L- carnosine/L- carnitine supplement	effect (95% CI)	Risk with Placebo	Risk difference with L- carnosine/L-carnitine supplement (95% CI)
Global im	provem	ent (measured w	ith: Parent Global	Impressions-I	mprovement (F	PGI-I): Overall impro	vement a	cross subscales; E	Better indicat	ed by lowe	er values)
31 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	17	14	N/A	N/A	The mean global improvement in the intervention groups was <b>0.47 standard deviations</b> higher (0.25 lower to 1.19 higher)
Overall a	utistic b	ehaviours (me	easured with: Chile	dhood Autism	Rating Scale (	CARS): Total; Better	indicated	by lower values)	•	•	•
56 (2 studies)	no serious risk of bias	very serious <sup>2</sup>	no serious indirectness	very serious <sup>1</sup>	undetected		28	28	N/A	N/A	The mean overall autistic behaviours in the

8-26 weeks						due to inconsistency, imprecision					intervention groups was 0.12 standard deviations lower (0.65 lower to 0.42 higher)
Overall a	autistic b	ehaviours (m	easured with: Gill	iam Autism Ra	ting Scale (GA	RS): Total; Better inc	licated b	y lower values)			
31 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	17	14	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.34 standard deviations</b> <b>lower</b> (1.05 lower to 0.38 higher)
		ses both line of n s substantial hete		ure of apprecia	able benefit or l	harm (SMD -0.5/0.5)					(1.05 lower to 0.3

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

		Q	luality assessn	nent					Sumr	nary of Fin	dings
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	•	Publication bias	Overall quality of evidence	Study eve (%)	ent rates	Relative effect (95% Cl)	Anticipated	d absolute effects
							With Healthy diet control	With Omega-3 fatty acids		Risk with Healthy diet control	Risk difference with Omega-3 fatty acids (95% Cl)
Pervasiv	ve Deve	elopmental	Disorder (P	PDD) sym	ptoms (me	easured with: Child	d Behavior	Checklist 1.8	5 - 5 (CBCL	1 (1.5-5): PDD;	Better indicated by lower values)
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean pervasive developmental disorder (pdd) symptoms in the intervention groups was <b>0.98 standard deviations lower</b>

								(1.86 to 0.1 lower)
<sup>1</sup> High risk of performar measure was not blinde <sup>2</sup> N<400	ias as intervention	n administrato	rs and participa	ants were non-blin	id, and high risk of dete	ction bias a	s the outcom	e assessor for this outcome

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

		Q	uality assessn	nent					Summary 	of Findings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event	rates (%)	Relative effect	Anticipated	absolute effects
Follow up							With Treatment-as- usual	With Gluten- free and casein-free diet	(95% CI)	Risk with Treatment-as- usual	Risk difference with Gluten- free and casein-free diet (95% Cl)
Overall a values)	utistic	behaviours	(measured with:	Diagnose of P	sykotisk Adferd	hos Børn (Diagno	osis of Psycho	tic Behaviour	in Children;	DIPAB): Total;	Better indicated by lower
20 (1 study) 52 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	10	10	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>1.37 standard</b> <b>deviations lower</b> (2.36 to 0.37 lower)
	nvestigator	Lee and response bia was blinded to gro									for the DIPAB as nt and other potentially

### 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

			Quality asse	ssment				ŝ	Summary	of Findings	i.
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study ever	nt rates (%)	Relative effect	Anticipated	absolute effects
Follow up							With Treatment- as-usual	With Neurofeedback	(95% CI)	Risk with Treatment-as- usual	Risk difference with Neurofeedback (95% CI)
Parent-r	ated o	verall autis	tic behavio	DUIS (measu	red with: Social (	Communication Que	l stionnaire (S	CQ): Total; Bett	l er indicated	l d by lower valu	ues)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated overall autistic behaviours in the intervention groups was <b>1.85 standard</b> <b>deviations lower</b> (2.94 to 0.77 lower)
Teacher	-rated	overall auti	istic behav	viours (mea	sured with: Socia	al Communication Q	uestionnaire	(SCQ): Total; B	etter indica	ted by lower v	alues)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated overall autistic behaviours in the intervention groups was <b>0.29 standard</b> <b>deviations lower</b> (1.18 lower to 0.59 higher)
interest is als <sup>2</sup> N<400 <sup>3</sup> High risk of	selective	neurofeedback eq	uipment provide data cannot be e:	d by manufact	urer for trial.	articipants and outco		ors were non-blir	I nd. The risk	I of other bias	due to potential conflict o

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

	Qı	uality assessn	nent				S	ummary o	of Findings	
Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rat	es (%)	Relative effect	Anticipated abs	olute effects
					evidence	With Attention- placebo (structured listening) control	With Auditory integration training	(95% CI)	Risk with Attention-placebo (structured listening) control	Risk difference with Auditory integration training (95% CI)
autistic	behaviours	<b>S</b> (measured with	l n: Autism Beha	l aviour Checklis	t (ABC): Total;	Better indicated b	y lower values)		1	·
no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.1 standard</b> <b>deviations higher</b> (0.34 lower to 0.54 higher)
autistic	behaviours	<b>S</b> (measured with	n: Autism Beha	aviour Checklis	t (ABC): Total;	Better indicated b	y lower values)	I	1	
no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.22 standard</b> <b>deviations higher</b> (0.22 lower to 0.66 higher)
	bias nutistic no serious risk of bias nutistic	Risk of biasInconsistencyRisk of biasInconsistencyno serious risk of biasno serious inconsistencyno serious risk of biasno serious inconsistencyno serious risk of biasno serious inconsistencyno serious risk ofno serious inconsistency	Risk of biasInconsistencyIndirectnessRutisticbehaviours(measured with no serious inconsistencyno serious risk of biasno serious inconsistencyno serious indirectnessnutisticbehaviours (measured with no serious) inconsistencyno serious indirectnessno serious serious risk ofno serious inconsistencyno serious indirectnessno serious risk ofno serious inconsistencyno serious indirectness	bias       Image: Second	Risk of biasInconsistencyIndirectnessImprecisionPublication biasRutisticbehaviours(measured with: Autism Behaviour Checklisno serious risk of biasno serious inconsistencyno serious indirectnessvery serious^1undetectedno serious risk of biasno serious inconsistencyno serious indirectnessvery serious^1undetectedno serious risk of biasno serious inconsistencyno serious indirectnessvery serious^1undetectedno serious risk of inconsistencyno serious indirectnessvery serious^1undetected	Risk of biasInconsistency biasIndirectnessImprecision publication biasPublication biasOverall quality of evidenceAutisticbehaviours(measured with: Autism Behaviour Checklist (ABC): Total;no serious risk of biasno serious inconsistencyno serious indirectnessvery serious^1undetected undetected#################################	Risk of biasInconsistency biasIndirectnessImprecision placebo (structured listening) controlPublication biasOverall quality of evidenceStudy event rat With Attention- placebo (structured listening) controlRUTISTICbehaviours(measured with: Autism Behaviour Checklist (ABC): Total; Better indicated by inconsistency inconsistencyno serious indirectnessvery serious1undetected undetectedImprecision40No biasno serious indirectness(measured with: Autism Behaviour Checklist (ABC): Total; Better indicated by serious1Indirectneed imprecision40RUTISTICbehaviours (measured with: Autism Behaviour Checklist (ABC): Total; Better indicated by serious1Indirectneed imprecision40RUTISTICbehaviours (measured with: Autism Behaviour Checklist (ABC): Total; Better indicated by imprecision40No serious risk of inconsistency inconsistency iseriousno serious indirectnessvery serious1undetected bias0	Risk of biasInconsistency biasIndirectnessImprecision pacePublication biasOverall quality of evidenceStudy event rates (%)With Attention- placebo (structured istening) controlWith Attention- placebo (structured istening) controlWith Attention- placebo (structured istening) controlWith Attention- placebo (structured istening) controlnutisticbehaviours (measured with: Autism Behaviour Checklist (ABC): Total; Better indicated by lower values)no serious risk of biasno serious indirectnessvery serious^1undetected ultistic behaviours40tutisticbehaviours (measured with: Autism Behaviour Checklist (ABC): Total; Better indicated by lower values)40no serious risk of biasno serious indirectnessvery serious^1undetected ultister checklist (ABC): Total; Better indicated by lower values)no serious risk of biasno serious indirectnessvery serious^1undetected ultister checklist (ABC): Total; Better indicated by lower values)no serious risk of inconsistency inconsistencyno serious indirectnessvery serious^1undetected ultister checklist (ABC): Total; Better indicated by lower values)	Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias       Overall quality of evidence       Study event rates (%)       Relative effect (95% Cl)         Nutification bias       with Attention-placebo (structured training) integration training)       with Attention-placebo (structured training)       With Attention-placebo (structured training)       Mith Attention-placebo (structured training)       <	Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias       Overall quality of evidence       Study event rates (%)       Relative effect (%)       Anticipated abs effect (%)         Nith Attention-placebo (structured listening) control       With Attention-placebo (structured listening) control       With Attention-placebo (structured listening) control       Relative effect (%)       Anticipated abs effect (%)         Nutlistic       behaviours       (measured with: Autism Behaviour Checklist (ABC): Total; Better indicated by lower values)       N/A       N/A         no serious serious inconsistency       no serious indirectness       very serious <sup>1</sup> undetected       ⊕⊕⊙⊙ LOW <sup>1</sup> due to imprecision       40       N/A       N/A         no serious serious ink of bias       no serious indirectness       very serious <sup>1</sup> undetected       ⊕⊕⊙⊙ LOW <sup>1</sup> due to imprecision       40       N/A       N/A         Nutlistic       behaviours       (measured with: Autism Behaviour Checklist (ABC): Total; Better indicated by lower values)       N/A       N/A       N/A         No       no serious indirectness       no serious indirectness       very serious <sup>1</sup> undetected       ⊕⊕⊙ ⊕ ⊡       40       N/A       N/A         no       no serious indirectness       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊙ ⊕

80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.25 standard</b> <b>deviations higher</b> (0.19 lower to 0.69 higher)
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	S (measured with no serious indirectness	n: Autism Beha	aviour Checklis	t (ABC): Total; ⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	Better indicatec	l by lower values) 40	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.27 standard deviations higher

### 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

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

		Qu	ality assessr	nent			Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	event rates (%)	Relative effect			
Follow up						evidence	With Control	With Acupuncture/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	(95% CI)	Risk with Control	Risk difference with Acupuncture/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 (95% CI)	
Commur 36 (1 study) 8 weeks	no serious risk of bias	DN (measured wi	no serious	very serious <sup>1</sup>	ation Schedul	e (ADOS/ADO DOM <sup>1</sup> due to imprecision	DS-G): C	Communication (change score); I	Better indic	N/A	Iower values) The mean communication in the intervention groups was 0.19 standard deviations Iower (0.85 lower to 0.46 higher)	
36 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	18		N/A	N/A	The mean communication in the intervention groups was <b>0.19 standard deviations</b> <b>lower</b> (0.85 lower to 0.46 higher)	

# **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

		Q	uality assess	ment			Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect	Anticipated absolute effects		
Follow up							With Control	With Secretin versus placebo for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome	(95% CI)	Risk with Control	Risk difference with Secretin versus placebo for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome (95% CI)	
Commur	nicatio	n (measured wit	h: Autism Diagn	ostic Observat	ion Schedule	(ADOS/ADOS-G)	: Commi	unication (endpoint and cha	nge scores	s); Better	indicated by lower values)	
141 (2 studies)	no serious	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \oplus \ominus$ <b>MODERATE</b> <sup>1</sup>	61	80	N/A	N/A	The mean communication in the intervention groups was	
4 weeks	risk of bias					due to imprecision					0.1 standard deviations lower (0.44 lower to 0.24 higher)	
4 weeks	bias	n (measured wit	h: Gilliam Autisr	n Rating Scale	(GARS): Con	imprecision	er indicat	ed by lower values)			lower	

141 (2 studies) 4 weeks	no serious risk of bias	very serious <sup>3</sup>	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to inconsistency, imprecision	61	80	N/A	N/A	The mean social interaction in the intervention groups was <b>0.46 standard deviations</b> higher (0.12 to 0.8 higher)
Social i	nteract	ion (measured	with: Gilliam Au	tism Rating So	cale (GARS): S	Social Interaction;	Better i	ndicated by lower	values)		
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>2</sup> due to imprecision	28	28	N/A	N/A	The mean social interaction in the intervention groups was <b>0.42 standard deviations</b> higher (0.11 lower to 0.95 higher)
		on and Soc I by lower values)		<b>tion</b> (measu	red with: Autis	m Diagnostic Obs	ervatio	n Schedule (ADO	S/ADOS-G): Commu	inication	& Social Interaction (change
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	28	28	N/A	N/A	The mean communication and social interaction in the intervention groups was 0.55 standard deviations higher

# **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

		Q	uality assessn	nent					Summary	of Finding	5	
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study ever	nt rates (%)	Relative	Anticipate	d absolute effects	
(studies) Follow up	bias				bias	quality of evidence	With Attention- placebo control	With Hyperbaric oxygen treatment (HBOT)	effect (95% CI)	Risk with Attention- placebo control	Risk difference with Hyperbaric oxygen treatmen (HBOT) (95% Cl)	
Positive t	treatme	nt response (	(assessed with: N	Number of part	icipants who s	howed improver	nent in ADOS	S Communication)		•		
34 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected		2/16 (12.5%)	3/18 (16.7%)	<b>RR 1.33</b> (0.25 to	Study pop	ulation	
15 weeks	risk of bias					due to imprecision	()	(,	7)	125 per 1000	<b>41 more per 1000</b> (from 94 fewer to 750 more)	
										Moderate		
										125 per 1000	<b>41 more per 1000</b> (from 94 fewer to 750 more)	
Positive t	treatme	nt response (	(assessed with: N	Number of part	icipants who s	howed improver	nent in ADOS	S Socialization)	1			
34 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected		2/16 (12.5%)	3/18 (16.7%)	<b>OR 1.4</b> (0.2 to	Study pop	ulation	
15 weeks	risk of bias	inconcisionery				due to imprecision	(12:070)	(10.170)	9.66)	125 per 1000	<b>42 more per 1000</b> (from 97 fewer to 455 more)	
										Moderate		
										125 per 1000	<b>42 more per 1000</b> (from 97 fewer to 455 more)	
Social Av	varenes	S (measured with	: Social Respons	iveness Scale	(SRS): Social	Awareness (cha	ange score); l	Better indicated by	lower value	es)		
29 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \oplus \oplus \ominus \ominus \\ \textbf{LOW}^2 \\ \text{due to} \\ \text{imprecision} \end{array}$	15	14	N/A	N/A	The mean social awareness in the intervention groups was <b>0.11 standard</b>	

											deviations lower (0.84 lower to 0.62 higher)
Social C	ognition	(measured with: S	Social Responsiv	eness Scale (	SRS): Social C	ognition (change	e score); Be	etter indicated by	y lower values	)	
29 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	15	14	N/A	N/A	The mean social cognition in the intervention groups was <b>0.53 standard</b> <b>deviations higher</b> (0.21 lower to 1.27 higher)
Social C	ommuni	cation (measur	ed with: Social R	esponsivenes	s Scale (SRS):	Social Commur	ication (ch	ange score); Be	tter indicated l	by lower valu	es)
29 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	15	14	N/A	N/A	The mean social communication in the intervention groups was <b>0.32 standard</b> <b>deviations lower</b> (1.05 lower to 0.41 higher)
Social N	lotivatio	<b>n</b> (measured with:	Social Responsi	veness Scale	(SRS): Social I	Notivation (chan	ge score); l	Better indicated	by lower value	es)	
29 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	15	14	N/A	N/A	The mean social motivation in the intervention groups was <b>0.06 standard</b> <b>deviations higher</b> (0.67 lower to 0.79 higher)
Autistic	Manneri	SMS (measured	with: Social Resp	Donsiveness S	Scale (SRS): Au	I Itistic Mannerism	is (change	score); Better in	idicated by lov	ver values)	<b>I</b>
29 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\oplus \oplus \ominus \ominus$ LOW <sup>2</sup> due to imprecision	15	14	N/A	N/A	The mean autistic mannerisms in the intervention groups was <b>0.36 standard</b> <b>deviations higher</b> (0.38 lower to 1.09

							]			]	higher)
Appropr	iate voc	alization (mea	sured with: Beha	vioural observa	ation: Appropri	ate vocalization (	change sco	ore); Better indica	ted by lower	/alues)	
34 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	16	18	N/A	N/A	The mean appropriate vocalization in the intervention groups was <b>0.17 standard</b> <b>deviations higher</b> (0.51 lower to 0.84 higher)
		CI crosses both lin osses both line of r							·	·	

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

		Q	uality assess	ment			Summary of Findings					
-		Inconsistency	Indirectness	Imprecision		Overall	Study event	rates (%)	Relative	Anticipated a	bsolute effects	
(studies) Follow up	bias					quality of evidence	With Short- term chelation (1-round of DMSA therapy and 6-rounds of placebo)	With Long-term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy)	effect (95% CI)	Risk with Short-term chelation (1- round of DMSA therapy and 6- rounds of placebo)	Risk difference with Long- term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy) (95% CI)	
Social Pr	agmati	c Problems	(measured with	: Pervasive D	evelopment Dis	order Behavior	Inventory (PD	DBI): Social Pragmatic;	Better indi	cated by lower	values)	
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	15	25	N/A	N/A	The mean social pragmatic problems in the intervention groups was <b>0.52 standard</b> <b>deviations higher</b> (0.13 lower to 1.17	

										]	higher)
Social A	pproac	h Behaviou	<b>rs</b> (measured w	ith: Pervasive	Development [	Disorder Behav	ior Inventory	(PDDBI): Social Approac	h; Better in	dicated by low	er values)
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	15	25	N/A	N/A	The mean social approach behaviours in the intervention groups was <b>0.08 standard</b> <b>deviations lower</b> (0.72 lower to 0.56 higher)
<sup>2</sup> High risk c	of selective	osses both line c reporting bias as bility reported	of no effect and r efficacy data ca	neasure of ap nnot be extrac	preciable benef cted for the ADC	it or harm (SMI DS Communica	D -0.5/0.5) tion, Sociabi	lity, and Communication+	Sociability	or the Parent (	Blobal Impressions scale

# **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

		Q	uality assessn	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision			Study event rates (%)		Relative	Anticipated	absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Treatment- as-usual	With Gluten- free and casein-free diet	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Gluten-free and casein-free diet (95% Cl)
Commun	ication	(measured with: Au	utism Diagnostic	Observation So	chedule (ADOS	S): Communicatio	n (change sc	ore); Better ir	dicated by	ower values)	
55 (1 study) 35 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean communication in the intervention groups was <b>0.42 standard deviations</b> <b>lower</b> (0.95 lower to 0.12 higher)

Commur	nication	(measured with: G	Silliam Autism Rat	ing Scale (GAF	RS): Communi	cation (change so	ore); Bett	er indicated b	y lower valu	es)	
55 (1 study) 35 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean communication ir the intervention groups was 0.34 standard deviations lower (0.87 lower to 0.19 higher)
Social In	teractio	<b>n</b> (measured with	: Autism Diagnosi	tic Observation	Schedule (AD	OS): Social Intera	action (ch	ange score); E	Better indica	ted by lower	values)
55 (1 study) 35 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean social interaction in the intervention groups was <b>0.01 standard deviations</b> <b>lower</b> (0.54 lower to 0.52 higher)
Social In	teractio	<b>n</b> (measured with	: Gilliam Autism F	Rating Scale (G	ARS): Social I	nteraction (chang	e score);	Better indicate	ed by lower	values)	
55 (1 study) 35 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ LOW <sup>3,4</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean social interaction in the intervention groups was 0.67 standard deviations lower (1.22 to 0.13 lower)
		and interact Better indicated by	`	with: Diagnose	of Psykotisk A	dferd hos Børn (E	Diagnosis	of Psychotic E	Behaviour in	Children; DI	PAB): Communication and
20 (1 study) 52 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ LOW <sup>4,5</sup> due to risk of bias, imprecision	10	10	N/A	N/A	The mean communication and interaction in the intervention groups was <b>1.19 standard deviations</b> higher (0.22 to 2.15 higher)
		Communicatio					k Adferd I	nos Børn (Dia	gnosis of Ps	ychotic Beha	viour in Children; DIPAB):
20 (1 study) 52 weeks	serious⁵	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ LOW <sup>4,5</sup> due to risk of	10	10	N/A	N/A	The mean resistance to communication and interaction in the interventio

			bias, imprecision		groups was <b>1.58 standard deviations</b> <b>Iower</b> (2.61 to 0.55 lower)	
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**Social isolation** (measured with: Diagnose of Psykotisk Adferd hos Børn (Diagnosis of Psychotic Behaviour in Children; DIPAB): Social interaction or isolation (I-scores); Better indicated by lower values)

20	serious⁵		no serious	serious4	undetected	$\oplus \oplus \ominus \ominus$	10	10	N/A	N/A	The mean social isolation in
(1 study)		inconsistency	indirectness			LOW <sup>4,5</sup>					the intervention groups was
52 weeks						due to risk of					1.35 standard deviations
						bias,					lower
						imprecision					(2.34 to 0.35 lower)

<sup>1</sup> High risk of attrition bias as over twice as many dropouts in the experimental group relative to the controls (32% in experimental group and 15% in the control group) <sup>2</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

<sup>3</sup> High risk of performance and response bias as intervention administrators (parents) and participants were non-blind, and unclear/unknown risk of detection bias as the identity and blinding of outcome assessors not reported. Also high risk of attrition bias as over twice as many dropouts in the experimental group relative to the controls (32% in experimental group and 15% in the control group)

<sup>4</sup> N<400

<sup>5</sup> High risk of performance and response bias as intervention administrators (parents) and participants were non-blind. There was also a high risk of detection bias for the DIPAB as although the investigator was blinded to group assignment, this outcome measure was based on parental interview and parents were non-blind to group assignment and other potentially confounding factors

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

		Q	uality assessme	ent					Summary	/ of Findir	ngs
Participants (studies)	Risk of bias	Inconsistency	Indirectness		Study ev (%)	vent rates	Relative effect	Anticipate	ed absolute effects		
Follow up							With Placebo	With Omega- 3 fatty acids		Risk with Placebo	Risk difference with Omega-3 fatty acids (95% CI)
Social sk	ills (measure	ed with: Social Resp	onsiveness Scale	(SRS): Total;	Better indicated	by lower values)					
22 (1 study) 12 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	11	11	N/A	N/A	The mean social skills in the intervention groups was 0.06 standard deviations higher

								(0.77 lower to 0.9 higher)
<sup>1</sup> N<400 and	95% CI crosse	es both line of no eff	ect and measure of	of appreciable	benefit or harm	(SMD -0.5/0.5)		

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

	Q	uality assessm	ent					Summa	ary of Findi	ngs
Risk of	Inconsistency	Indirectness			Overall quality	Study ever	nt rates (%)		Anticipated	l absolute effects
bias				bias	of evidence	With Healthy diet control	With Omega-3 fatty acids		Risk with Healthy diet control	Risk difference with Omega-3 fatty acids (95% CI)
y of pos	itive vocaliza	ations (measure	ed with: Behav	ioural observa	tion; Better indica	ted by lower	values)		1	•
		no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	13	10	N/A	N/A	The mean frequency of positive vocalizations in the intervention groups was <b>0.21 standard deviations</b> <b>higher</b> (0.62 lower to 1.03 higher)
y of soc	ial initiations	(measured with:	Behavioural ol	bservation; Bet	ter indicated by lo	ower values)				1
		no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	13	10	N/A	N/A	The mean frequency of social initiations in the intervention groups was <b>0.44 standard deviations higher</b> (0.4 lower to 1.27 higher)
	bias y of pos no serious risk of bias y of soc no serious	Risk of biasInconsistencycy of positive vocalizationno serious risk of biasno serious risk of biassy of social initiations	Risk of biasInconsistency Indirectnessay of positive vocalizations (measure no serious risk of biasno serious inconsistencyno serious risk of biasno serious inconsistencysy of social initiations no serious no serious(measured with: no serious	bias       Image: sy of positive vocalizations (measured with: Behave no serious risk of bias inconsistency       no serious indirectness       very serious <sup>1</sup> risk of bias       no serious inconsistency       no serious indirectness       very serious <sup>1</sup> ry of social initiations (measured with: Behavioural o no serious no serious no serious       no serious no serious       very serious <sup>1</sup>	Risk of biasInconsistencyIndirectnessImprecisionPublication biasry of positive vocalizations (measured with: Behavioural observations risk of biasno serious inconsistencyno serious indirectnessvery serious1undetectedry of social initiations no serious(measured with: Behavioural observation; Bet no serious1no serious serious1undetected	Risk of biasInconsistencyIndirectnessImprecisionPublication biasOverall quality of evidencecy of positive vocalizations (measured with: Behavioural observation; Better indicat no serious risk of biasno serious inconsistencyno serious indirectnessundetected serious1 $\oplus \oplus \bigcirc \bigcirc$ LOW1 due to imprecisioncy of social initiations risk of biasno serious inconsistencyno serious indirectnessvery serious1undetected 	Risk of biasInconsistency biasIndirectnessImprecision Publication biasOverall quality of evidenceStudy ever With Healthy diet controlcy of positive vocalizations (measured with: Behavioural observation; Better indicated by lower indirectnessno serious indirectnessno serious very serious <sup>1</sup> undetected undetected $\bigoplus \bigoplus \bigcirc \bigcirc \\ LOW^1$ due to imprecision13cy of social initiations risk of bias(measured with: Behavioural observation; Better indicated by lower very serious <sup>1</sup> undetected undetected $\bigoplus \bigoplus \bigcirc \bigcirc \\ LOW^1$ due to imprecision13cy of social initiations risk of bias risk of biasno serious indirectnessvery serious <sup>1</sup> undetected undetected $\bigoplus \bigoplus \bigcirc \bigcirc \\ LOW^1$ due to imprecision13no serious risk of biasno serious inconsistencyno serious indirectnessvery serious <sup>1</sup> undetected undetected $\bigoplus \bigoplus \bigcirc \bigcirc \\ LOW^1$ due to13	Risk of biasInconsistencyIndirectnessImprecisionPublication biasOverall quality of evidenceStudy event rates (%)With Healthy diet controlWith Omega-3 fatty acidsWith Omega-3 fatty acidsWith Omega-3 fatty acidsry of positive vocalizations (measured with: Behavioural observation; Better indicated by lower values)No serious indirectnessNo serious1Undetected wery serious1ImprecisionImprecisionImprecisionno serious risk of biasno serious inconsistencyNo serious indirectnessvery serious1Undetected wery serious1ImprecisionImprecisionvg of social initiations risk of biasno serious inconsistencyNo serious indirectnessvery serious1Undetected wery serious1ImprecisionImprecisionno serious risk of biasNo serious inconsistencyNo serious indirectnessvery serious1Undetected wery serious1ImprecisionImprecisionno serious risk of biasNo serious inconsistencyNo serious indirectnessvery serious1Undetected wery serious1ImprecisionImprecisionno serious risk of biasNo serious inconsistencyNo serious indirectnessVery serious1ImprecisionImprecisionno serious risk of biasNo serious indirectnessVery serious1ImprecisionImprecisionImprecisionno serious inconsistencyNo serious indirectnessVery serious1Imprecision <t< td=""><td>Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias       Overall quality of evidence       Study event rates (%)       Relative effect (95% CI)         vy of positive vocalizations (measured with: Behavioural observation; Better indicated by lower values)       No serious       no serious       no serious       no serious       no serious       10       N/A         vg of social initiations       (measured with: Behavioural observation; Better indicated by lower values)       10       N/A</td><td>Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias       Overall quality of evidence       Study event rates (%)       Relative effect (95% CI)       Anticipate (Risk with Healthy diet control         ry of positive vocalizations (measured with: Behavioural observation; Better indicated by lower values)       no serious indirectness       no serious indirectness       very serious<sup>1</sup>       undetected       <math>\oplus \oplus \bigcirc \bigcirc</math>       13       10       N/A       N/A         vy of social initiations (measured with: Behavioural observation; Better indicated by lower values)       no serious indirectness       no serious<sup>1</sup>       undetected       <math>\oplus \oplus \bigcirc \bigcirc</math>       13       10       N/A       N/A         vy of social initiations (measured with: Behavioural observation; Better indicated by lower values)       no serious indirectness       no serious<sup>1</sup>       undetected       <math>\oplus \oplus \bigcirc \bigcirc</math>       13       10       N/A       N/A         vy of social initiations (measured with: Behavioural observation; Better indicated by lower values)       no serious indirectness       no serious<sup>1</sup>       undetected       <math>\oplus \oplus \bigcirc \bigcirc</math>       13       10       N/A       N/A</td></t<>	Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias       Overall quality of evidence       Study event rates (%)       Relative effect (95% CI)         vy of positive vocalizations (measured with: Behavioural observation; Better indicated by lower values)       No serious       no serious       no serious       no serious       no serious       10       N/A         vg of social initiations       (measured with: Behavioural observation; Better indicated by lower values)       10       N/A	Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias       Overall quality of evidence       Study event rates (%)       Relative effect (95% CI)       Anticipate (Risk with Healthy diet control         ry of positive vocalizations (measured with: Behavioural observation; Better indicated by lower values)       no serious indirectness       no serious indirectness       very serious <sup>1</sup> undetected $\oplus \oplus \bigcirc \bigcirc$ 13       10       N/A       N/A         vy of social initiations (measured with: Behavioural observation; Better indicated by lower values)       no serious indirectness       no serious <sup>1</sup> undetected $\oplus \oplus \bigcirc \bigcirc$ 13       10       N/A       N/A         vy of social initiations (measured with: Behavioural observation; Better indicated by lower values)       no serious indirectness       no serious <sup>1</sup> undetected $\oplus \oplus \bigcirc \bigcirc$ 13       10       N/A       N/A         vy of social initiations (measured with: Behavioural observation; Better indicated by lower values)       no serious indirectness       no serious <sup>1</sup> undetected $\oplus \oplus \bigcirc \bigcirc$ 13       10       N/A       N/A

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

		Q	uality assessm	nent					Summary	of Finding	gs
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study e	vent rates (%)	Relative	Anticipat	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Placebo	With Multivitamin and mineral supplement	effect (95% CI)	Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% Cl)
Sociabili	ty improv	vement (measu	ired with: Parent 0	Global Impressi	ions-Revised (	PGI-R): Sociability	/ improve	ment; Better indica	ted by lower	values)	
104 (1 study) 13 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	51	53	N/A	N/A	The mean sociability improvement in the intervention groups was <b>0.14 standard deviations</b> higher (0.24 lower to 0.53 higher)
Eye cont	act impro	<b>ovement</b> (mea	sured with: Paren	t Global Impres	sions-Revised	I (PGI-R): Eye cor	tact impr	ovement; Better inc	licated by lo	wer values	)
104 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	51	53	N/A	N/A	The mean eye contact improvement in the intervention groups was <b>0.28 standard deviations</b> higher (0.11 lower to 0.67 higher)

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

		Qı	uality assessme	ent					Summary	of Findir	ngs
Participants		Inconsistency	Indirectness	Study ev	( ,		Anticipat	ed absolute effects			
(studies) Follow up	bias					bias of evidence		With L-carnosine supplement	effect (95% CI)	Risk with Placebo	Risk difference with L- carnosine supplement (95% Cl)
Commun	ication (m	easured with: Gillia	m Autism Rating	Scale (GARS)	: Communication	on; Better indicate	d by lowe	r values)			
										The mean communication in the intervention groups	

8 weeks						due to imprecision					was 0.19 standard deviations higher (0.52 lower to 0.9 higher)
Social in 31 (1 study) 8 weeks	no serious	(measured with: 0 no serious inconsistency	Gilliam Autism Ra	ting Scale (GA very serious <sup>1</sup>	RS): Social Inte	eraction; Better inc ⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	licated b	y lower values) 14	N/A	N/A	The mean social interaction in the intervention groups was 0.51 standard deviations lower
<sup>1</sup> N<400 an	d 95% CI cross	ses both line of no	effect and measu	Ire of apprecial	ble benefit or ha	arm (SMD -0.5/0.5	5)				(1.23 lower to 0.21 higher)

# **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

			Quality asses	sment				Ś	Summary	of Findings	;
Participants		Inconsistency	Indirectness	Imprecision	Study even			Anticipated	absolute effects		
(studies) Follow up	bias				bias		With Treatment- as-usual	With Neurofeedback	effect (95% CI)		Risk difference with Neurofeedback (95% CI)
Parent-ra	Parent-rated reciprocal social interaction (measured with: Social Communication Questionnaire (SCQ): Reciprocal social interactions; Better indicated by lower values)										
00	. 1				and a set of the set of the set		10	40	N1/A	N1/A	The second second sector d

20	serious <sup>1</sup>	no serious	no serious	serious <sup>2</sup>	reporting bias	0000	10	10	N/A	N/A	The mean parent-rated
(1 study)		inconsistency	indirectness		strongly	VERY LOW <sup>1,2,3</sup>					reciprocal social
20 weeks					suspected <sup>3</sup>	due to risk of					interaction in the
						bias, imprecision,					intervention groups was
						publication bias					1.54 standard
											deviations lower
											(2.57 to 0.52 lower)

Teacher- values)	rated re	eciprocal so	cial interac	<b>tion</b> (measur	ed with: Social C	ommunication Ques	stionnaire (S	SCQ): Reciprocal	social inter	ractions; Bette	er indicated by lower
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	0,	⊕⊖⊝⊖ VERY LOW <sup>1,3,4</sup> due to risk of	10	10	N/A	N/A	The mean teacher-rated reciprocal social interaction in the
						bias, imprecision, publication bias					intervention groups was 0.39 standard

Parent-rated communication (measured with: Social Communication Questionnaire (SCQ): Communication; Better indicated by lower values)

20	serious <sup>1</sup>	no serious	no serious	serious <sup>2</sup>	reporting bias	$\oplus \Theta \Theta \Theta$	10	10	N/A	N/A	The mean parent-rated
(1 study)		inconsistency	indirectness		strongly	VERY LOW <sup>1,2,3</sup>					communication in the
20 weeks					suspected <sup>3</sup>	due to risk of					intervention groups was
						bias, imprecision,					1.14 standard
						publication bias					deviations lower
											(2.1 to 0.18 lower)

Teacher-rated communication (measured with: Social Communication Questionnaire (SCQ): Communication; Better indicated by lower values)

20 (1 study) 20 weeks	 no serious inconsistency	serious4	suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	The mean teacher-rated communication in the intervention groups was <b>0.19 standard</b> <b>deviations lower</b> (1.07 lower to 0.69
								higher)

Parent-rated communication (measured with: Children's Communication Checklist (CCC-2): Total; Better indicated by lower values)

20	serious <sup>1</sup>	no serious	no serious	very	reporting bias	$\oplus \Theta \Theta \Theta$	10	10	N/A	N/A	The mean parent-rated
(1 study)		inconsistency	indirectness	serious4	strongly	VERY LOW <sup>1,3,4</sup>					communication in the
20 weeks					suspected <sup>3</sup>	due to risk of					intervention groups was
						bias, imprecision,					0.88 standard
						publication bias					deviations lower
											(1.81 lower to 0.04
											higher)

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

deviations lower (1.28 lower to 0.49

higher)

20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated communication in the intervention groups was <b>0.05 standard</b> <b>deviations lower</b> (0.93 lower to 0.83 higher)
Parent-r	ated so	cial impairm	nent (measured	with: Social	Responsiveness S	icale (SRS): Total; E	etter ind	icated by lower	values)		
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁴	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated social impairment in the intervention groups was <b>0.92 standard</b> <b>deviations lower</b> (1.85 lower to 0.02 higher)
Teacher	-rated s	ocial impair	r <b>ment</b> (measu	ed with: Soci	al Responsiveness	Scale (SRS): Total	; Better i	ndicated by low	ver values)		
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated social impairment in the intervention groups was <b>0.01 standard</b> <b>deviations higher</b> (0.87 lower to 0.88 higher)
Parent-r	ated so	cial awaren	<b>ESS</b> (measured	with: Social F	Responsiveness So	ale (SRS): Social A	warenes	s; Better indica	ated by lower	values)	
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated social awareness in the intervention groups was <b>0.64 standard</b> <b>deviations lower</b> (1.55 lower to 0.26 higher)

20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated social awareness in the intervention groups was <b>0.22 standard</b> <b>deviations higher</b> (0.66 lower to 1.1 higher)
Parent-r	ated so	cial cognitio	<b>n</b> (measured wi	th: Social Res	ponsiveness Sca	e (SRS): Social Co	gnition ; B	etter indicated l	by lower value	es)	
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated social cognition in the intervention groups was <b>1.38 standard</b> <b>deviations lower</b> (2.38 to 0.38 lower)
Teacher	-rated s	ocial cognit	ion (measured	with: Social Re	esponsiveness So	cale (SRS): Social C	ognition ;	; Better indicate	d by lower val	ues)	
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated social cognition in the intervention groups was <b>0.35 standard</b> <b>deviations higher</b> (0.53 lower to 1.24 higher)
Parent-r	ated so	cial commu	nication (mea	asured with: So	ocial Responsiver	ness Scale (SRS): S	ocial Con	nmunication ; B	etter indicated	l by lower va	lues)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated social communication in the intervention groups was 0.78 standard deviations lower (1.7 lower to 0.14 higher)
Teacher	-rated s	ocial comm	unication (m	easured with:	Social Responsiv	I veness Scale (SRS)	Social C	ommunication;	Better indicat	ed by lower	values)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	10	10	N/A	N/A	The mean teacher-rated social communication in the intervention groups was

						publication bias					0.49 standard deviations higher (0.4 lower to 1.38 higher)
Parent-r	ated so	cial motivati	on (measured	with: Social R	esponsiveness So	cale (SRS): Social N	lotivation;	Better indicate	d by lower v	alues)	
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated social motivation in the intervention groups was <b>0.54 standard</b> <b>deviations lower</b> (1.43 lower to 0.36 higher)
Teacher	-rated s	ocial motiva	tion (measure	d with: Social	Responsiveness	Scale (SRS): Social	Motivatio	on; Better indica	ated by lower	values)	<b>I</b>
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated social motivation in the intervention groups was <b>0.45 standard</b> <b>deviations higher</b> (0.44 lower to 1.34 higher)
Parent-r	ated aut	tistic manne	risms (measu	red with: Soc	ial Responsivenes	ss Scale (SRS): Auti	stic Manr	nerisms ; Better	indicated by	lower values	3)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated autistic mannerisms in the intervention groups was <b>0.98 standard</b> <b>deviations lower</b> (1.92 to 0.04 lower)
Teacher	-rated a	tistic manne	erisms (measu	ured with: Soc	ial Responsivene	ss Scale (SRS): Aut	istic Man	nerisms ; Bette	r indicated by	lower values	5)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated atistic mannerisms in the intervention groups was <b>0.41 standard</b> <b>deviations lower</b> (1.3 lower to 0.48 higher)

20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of	10	10	N/A	N/A	The mean parent-rated social relations in the intervention groups was
						bias, imprecision, publication bias					0.37 standard deviations lower (1.26 lower to 0.51 higher)
Teacher	-rated s	ocial relatio	ns (measured v	vith: Children	s Communication	Checklist (CCC-2):	Social re	lations; Better i	ndicated by lo	ower values)	·
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated social relations in the intervention groups was <b>0 standard deviations</b> <b>higher</b> (0.88 lower to 0.88 higher)
Parent-r	ated int	<b>erests</b> (measu	red with: Childre	n's Communie	cation Checklist (C	CC-2): Interests; Be	etter indic	ated by lower	/alues)		
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated interests in the intervention groups was <b>1.18 standard</b> <b>deviations lower</b> (2.15 to 0.21 lower)
Teacher	-rated in	nterests (mea	sured with: Child	ren's Commu	nication Checklist	(CCC-2): Interests;	Better in	dicated by lowe	er values)		
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated interests in the intervention groups was <b>0 standard deviations</b> <b>higher</b> (0.88 lower to 0.88 higher)
Parent-r	ated ina	ppropriate i	nitializatio	<b>)</b> (measured	with: Children's Co	mmunication Check	dist (CCC	C-2): Inappropri	ate initializati	on; Better ind	dicated by lower values)
20	serious <sup>1</sup>	no serious	no serious	serious <sup>2</sup>	reporting bias	<b>000</b>	10	10	N/A	N/A	The mean parent-rated

	inconsistency	indirectness		strongly suspected <sup>3</sup>	VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias					inappropriate initialization in the intervention groups was <b>1.08 standard</b> <b>deviations lower</b> (2.03 to 0.13 lower)
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	<b>on</b> (measure very serious <sup>4</sup>	d with: Children's reporting bias strongly suspected <sup>3</sup>	Communication Che Communication Che VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	CC-2): Inappro	priate initializ	N/A	indicated by lower values) The mean teacher-rated inappropriate initialization in the intervention groups was 0.15 standard deviations lower (1.03 lower to 0.73 higher)
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	vith: Children's Co reporting bias strongly suspected <sup>3</sup>	mmunication Check	list (CCC-	-2): Stereotype	d conversatic	n; Better ind	The mean parent-rated stereotyped conversation in the intervention groups was 0.56 standard deviations lower (1.45 lower to 0.34 higher)
-rated s	tereotyped	conversatio	<b>)n</b> (measured	d with: Children's C	Communication Che	l cklist (CC	C-2): Stereoty	ped conversa	tion; Better i	ndicated by lower values)
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated stereotyped conversation in the intervention groups was 0.31 standard deviations higher (0.58 lower to 1.19 higher)
	serious <sup>1</sup>	rated inappropriate serious <sup>1</sup> no serious inconsistency ated stereotyped co serious <sup>1</sup> no serious inconsistency	rated inappropriate initialization         serious <sup>1</sup> no serious inconsistency         no serious <sup>1</sup> no serious indirectness         ated stereotyped conversation         serious <sup>1</sup> no serious inconsistency         serious <sup>1</sup> no serious inconsistency         rated stereotyped conversation         serious <sup>1</sup> no serious inconsistency         serious <sup>1</sup> no serious inconsistency         serious <sup>1</sup> no serious inconsistency         rated stereotyped conversation         serious <sup>1</sup> no serious         no serious       no serious	rated inappropriate initialization (measured indirectness)       no serious indirectness       very serious <sup>4</sup> serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> ated stereotyped conversation (measured very serious <sup>1</sup> )       no serious indirectness       very serious <sup>4</sup> serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> rated stereotyped conversation (measured very serious <sup>4</sup> )       no serious indirectness       very serious <sup>4</sup> serious <sup>1</sup> no serious indirectness       very serious <sup>4</sup> rated stereotyped conversation (measured very serious <sup>4</sup> )       very serious <sup>4</sup> serious <sup>1</sup> no serious       no serious very serious <sup>4</sup>	rated inappropriate initialization (measured with: Children's inconsistency indirectness indirectness is strongly suspected 3         serious <sup>1</sup> no serious indirectness is reporting bias strongly suspected 3         ated stereotyped conversation (measured with: Children's Co inconsistency indirectness indirectness indirectness indirectness is strongly suspected 3         serious <sup>1</sup> no serious indirectness indirectness is strongly suspected 3         ated stereotyped conversation (measured with: Children's Co inconsistency indirectness indirectness is strongly suspected 3         serious <sup>1</sup> no serious indirectness indirectness is strongly suspected 3         reporting bias strongly       strongly suspected 3         serious <sup>1</sup> no serious indirectness indirectness is strongly suspected 3         reporting bias strongly       strongly suspected 3         serious <sup>1</sup> no serious indirectness indirectness is rongly         serious <sup>1</sup> no serious indirectness indirectness is strongly         serious <sup>1</sup> no serious indirectness indirectness is strongly	rated inappropriate initialization (measured with: Children's Communication Chemister indirectness indirectness indirectness indirectness indirectness indirectness inconsistency       no serious indirectness indirectness indirectness indirectness indirectness inconsistency       reporting bias strongly suspected 3       ⊕⊖⊖⊖         ated stereotyped conversation (measured with: Children's Communication Check inconsistency indirectness indirectness inconsistency indirectness indirectness inconsistency indirectness inconsistency indirectness indirectness inconsistency indirectness indirectness inconsistency indirectness indirectness inconsistency indirectness indirectness indirectness inconsistency indirectness indirectness indirectness indirectness indirectnes indirectness indirectnes inditent inditent indirectnes indirectnes indirectnes indir	rated inappropriate initialization (measured with: Children's Communication Checklist (Cd         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       10         ated stereotyped conversation inconsistency       no serious indirectness       very very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       10         ated stereotyped conversation inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       10         rated stereotyped conversation inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       10         rated stereotyped conversation inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	rated inappropriate initialization (measured with: Children's Communication Checklist (CCC-2): Inappro         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       10       10         ated stereotyped conversation inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       10       10         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       10       10         reacted stereotyped conversation (measured with: Children's Communication Checklist (CCC-2): Stereotype very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       10       10	rated inappropriate initialization (measured with: Children's Communication Checklist (CCC-2): Inappropriate initialization in o serious indirectness very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> the orisk of bias, imprecision, publication bias         serious <sup>1</sup> no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> the orisk of bias, imprecision, publication bias         ated stereotyped conversation (measured with: Children's Communication Checklist (CCC-2): Stereotyped conversation indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> the orisk of bias, imprecision, publication bias         serious <sup>1</sup> no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> the orisk of bias, imprecision, publication bias       10       N/A         serious <sup>1</sup> no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> the orisk of bias, imprecision, publication bias       10       N/A         serious <sup>1</sup> no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> the orisk of bias, imprecision, publication bias       10       10       N/A         rated stereotyped conversation (measured with: Children's Communication Checklist (CCC-2): Stereotyped conversation publication bias       10       10       N/A         rated stereotyped conversation (measured with: Children's communication Checklist (CCC-2): Stereotyped conve	rated inappropriate initialization (measured with: Children's Communication Checklist (CCC-2): Inappropriate initialization; Better inconsistency indirectness very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup>

20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated context use in the intervention groups was <b>1 standard deviations</b> <b>lower</b> (1.94 to 0.06 lower)
Teacer-r	rated co	ntext use (m	easured with: Ch	ildren's Comm	nunication Checkli	ist (CCC-2): Context	t use; Be	tter indicated by	y lower values		
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacer-rated context use in the intervention groups was <b>0.29 standard</b> <b>deviations higher</b> (0.6 lower to 1.17 higher)
Parent-r	ated no	n-verbal coi	nmunicatio	<b>n</b> (measured	with: Children's C	communication Cheo	klist (CC	C-2): Non-verb	al communica	tion; Better i	ndicated by lower values)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated non-verbal communication in the intervention groups was <b>1.05 standard</b> <b>deviations lower</b> (2 to 0.1 lower)
Teacher	-rated n	on-verbal c	ommunicat	i <b>on</b> (measure	ed with: Children's	Communication Ch	ecklist (C	CCC-2): Non-ve	rbal communi	cation; Bette	er indicated by lower values)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated non-verbal communication in the intervention groups was <b>0.33 standard</b> <b>deviations higher</b> (0.55 lower to 1.22 higher)
Parent-r	ated pra	agmatics (me	asured with: Chil	dren's Commu	I unication Checklis	I st (CCC-2): Pragmat	ics; Bette	er indicated by	ower values)	1	
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of	10	10	N/A	N/A	The mean parent-rated pragmatics in the intervention groups was

						bias, imprecision, publication bias					0.98 standard deviations lower (1.92 to 0.04 lower)
Teacher	-rated p	ragmatics (m	neasured with: C	hildren's Com	munication Check	klist (CCC-2): Pragm	atics; Bet	ter indicated by lo	wer values)	)	
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated pragmatics in the intervention groups was <b>0.24 standard</b> <b>deviations higher</b> (0.64 lower to 1.13 higher)
interest is al <sup>2</sup> N<400 <sup>3</sup> High risk o	so high as i f selective i	neurofeedback eq	luipment provide data cannot be e	d by manufact	turer for trial.	articipants and outc		ssors were non-b	lind. The ris	k of other bia	s due to potential conflict of

### 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

		Qu	ality assessn	nent		Summary of Findings				
Participant (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	quality of	With	With Secretin versus	offect	Risk	Risk difference with Secretin versus placebo for the core autism feature of

								autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome		Control	restricted interests and rigid and repetitive behaviours as an indirect outcome (95% Cl)
Stereoty values)	yped bel	naviour/inter	rests (measure	ed with: Autisn	n Diagnostic C	bservation Sch	nedule (	ADOS/ADOS-G): Stereot	yped behav	viour/inter	rests; Better indicated by lower
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	28	28	N/A	N/A	The mean stereotyped behaviour/interests in the intervention groups was <b>0.36 standard deviations higher</b> (0.17 lower to 0.89 higher)
Stereoty	yped bel	naviours (mea	asured with: Gilli	am Autism Ra	ting Scale (GA	RS): Stereotyp	ed beh	aviours; Better indicated b	y lower val	ues)	
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	28	28	N/A	N/A	The mean stereotyped behaviours in the intervention groups was <b>0.17 standard deviations higher</b> (0.36 lower to 0.69 higher)
<sup>1</sup> N<400 an	d 95% CI cr	osses both line of	no effect and m	easure of app	reciable benef	it or harm (SMI	D -0.5/0	.5)	<u>I</u>		1

## **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

		Qu	ality assessn	nent				Sum	nmary of	Findings	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	•	bias	quality of evidence	Study event With Short- term chelation (1-round of	With Long torm	effect	Anticipated a Risk with Short-term chelation (1-	Absolute effects Risk difference with Long- term chelation (7-rounds of Dimercaptosuccinic Acid

17 weeks       risk of bias       approach beha the intervention was 0.29 standard higher (0.35 lower to 0         Ritualisms/Resistance to Change (measured with: Pervasive Development Disorder Behavior Inventory (PDDBI): Ritualisms/Resistance to Change; Better indicate lower values)         40       no       no serious inconsistency isk of bias       no serious indirectness verious <sup>1</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision       15       25       N/A       N/A       The mean ritualisms/resist change in the ingroups was 0.18 standard								DMSA therapy and 6-rounds of placebo)	Acid [DMSA] therapy)		round of DMSA therapy and 6- rounds of placebo)	[DMSA] therapy) (95% CI)
(1 study)       serious       inconsistency       indirectness       serious <sup>1</sup> LOW <sup>1</sup> due to       imprecision       sensory/perception approach behat the intervention was       0.29 standard higher         (1 study)       17 weeks       risk of bias       indirectness       serious <sup>1</sup> LOW <sup>1</sup> due to       imprecision       sensory/perception approach behat the intervention was       0.29 standard higher       (0.35 lower to C         Ritualisms/Resistance to Change (measured with: Pervasive Development Disorder Behavior Inventory (PDDBI): Ritualisms/Resistance to Change; Better indicate lower values)       no       no serious       no serious       no serious       no serious       no serious       no serious       no serious <sup>1</sup> undetected       ⊕⊕⊖⊖       15       25       N/A       N/A       The mean ritualisms/resistic change in the ir groups was       0.18 standard         17 weeks       risk of bias       inconsistency       indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖       15       25       N/A       N/A       ritualisms/resistic change in the ir groups was         0.18 standard       bias       indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖       15       25       N/A       N/A       ritualisms/resistic change in the ir groups was       0.18 standard	-			ach Behavi	OUIS (measu	ured with: Per	vasive Develo	pment Disorde	r Behavior Inventory (P	DDBI): Ser	nsory/Perceptua	al Approach Behaviours;
lower values)40 (1 study) 17 weeksno serious inconsistency biasno serious indirectnessno serious very serious1undetected bias⊕⊕⊖⊖ LOW1 due to imprecision1525N/AN/AThe mean ritualisms/resist change in the in groups was 0.18 standard	(1 study)	serious risk of				undetected	LOW <sup>1</sup> due to	15	25	N/A		sensory/perceptual approach behaviours in the intervention groups was 0.29 standard deviations
(1 study)       serious       inconsistency       indirectness       serious <sup>1</sup> LOW <sup>1</sup> due to       ritualisms/resist         17 weeks       bias       bias       low <sup>1</sup> low <sup>1</sup> low <sup>1</sup> low <sup>1</sup> low <sup>1</sup> low <sup>1</sup> 17 weeks       risk of       bias       low <sup>1</sup> low <sup>1</sup> low <sup>1</sup> low <sup>1</sup> low <sup>1</sup> low <sup>1</sup> 17 weeks       loss			stance to C	hange (meas	sured with: Per	vasive Develo	opment Disord	er Behavior In	ventory (PDDBI): Ritual	isms/Resis	tance to Chang	e; Better indicated by
Iower (0.83 lower to 0	(1 study)	serious risk of				undetected	LOW <sup>1</sup> due to	15	25	N/A	N/A	ritualisms/resistance to change in the intervention groups was <b>0.18 standard deviations</b>

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

l		(	Quality assess	sment				Su	mmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study even			Anticipated	absolute effects
(studies) Follow up	bias				bias	of evidence	With Attention- placebo control	With Hyperbaric oxygen treatment (HBOT)	(95% CI)	Risk with Attention- placebo control	Risk difference with Hyperbaric oxygen treatment (HBOT) (95% CI)

34 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	16	18	N/A	N/A	The mean vocal stereotypy in the intervention groups was <b>0.29 standard</b> <b>deviations lower</b> (0.97 lower to 0.39 higher)
Physica 34 (1 study)	no serious risk of	no serious inconsistency	with: Behavioural no serious indirectness	observation: F very serious <sup>1</sup>	Physical stereotypy reporting bias strongly suspected <sup>2</sup>	y (change score); E ⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to	Better indic	ated by lower va	alues)	N/A	The mean physical stereotypy in the intervention groups

# **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

		Q	uality assess	nent					Summary	/ of Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study event	rates (%)		Anticipated a	bsolute effects
(studies) Follow up	bias				bias	of evidence	With Treatment-as- usual	With Kata exercise training	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Kata exercise training (95% CI)

Stereoty	/ped beł	naviour (measu	red with: Gilliam	Autism Rating	Scale (GARS):	Stereotyped beha	aviour; Bet	ter indicated by	lower value	s)	
30 (1 study) 15 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean stereotyped behaviour in the intervention groups was <b>0.9 standard deviations</b> <b>lower</b> (1.66 to 0.15 lower)
Stereoty	/ped beh	naviour (measu	red with: Gilliam	Autism Rating	Scale (GARS):	Stereotyped beha	aviour; Bet	ter indicated by	lower value	s)	
30 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean stereotyped behaviour in the intervention groups was <b>0.76 standard</b> <b>deviations lower</b> (1.51 to 0.02 lower)
		ce and response b d teachers who we					I nd. The risk	c of detection b	as was also	high as the c	putcome measure was based or

# **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

	Quality assessment								Summary of Findings					
•	rticipants Risk of Inconsistency		Indirectness	•	•	Overall quality	Study event	rates (%)	Relative	Anticipated a	absolute effects			
(studies) Follow up	bias				bias		With Treatment-as- usual	With Gluten- free and casein-free diet	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Gluten- free and casein-free diet (95% Cl)			
		re behaviour red by lower values)		Diagnose of Ps	ykotisk Adferd	hos Børn (Diagno	sis of Psychot	ic Behaviour	in Children;	DIPAB): Unusu	al or bizarre behaviour			

20 (1 study) 52 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	10	10	N/A	N/A	The mean unusual or bizarre behaviour in the intervention groups was <b>0.96 standard</b> <b>deviations lower</b> (1.9 to 0.02 lower)
Repetitiv	ve behav	viours (measure	d with: Autism Dia	gnostic Observ	ation Schedule	e (ADOS): Repetiti	ve Behaviou	urs (change sco	re); Better ir	dicated by low	er values)
55 (1 study) 35 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean repetitive behaviours in the intervention groups was <b>0.33 standard</b> <b>deviations lower</b> (0.86 lower to 0.2 higher)
Stereoty	ped beh	aviour (measur	ed with: Gilliam Au	utism Rating Sc	ale (GARS): S	tereotyped behav	iour (change	e score); Better i	ndicated by	lower values)	1
55 (1 study) 35 weeks	serious⁵	no serious inconsistency	no serious indirectness	very serious⁴	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean stereotyped behaviour in the intervention groups was <b>0.08 standard</b> <b>deviations lower</b> (0.61 lower to 0.45 higher)
although the confounding <sup>2</sup> N<400 <sup>3</sup> High risk of <sup>4</sup> N<400 and <sup>5</sup> High risk of	investigator factors attrition bia 95% CI cro performanc utcome asse	s as over twice as sses both line of no ce and response bi essors not reported	many dropouts in o effect and meas as as intervention	the experiment ure of apprecia administrators	al group relative ble benefit or h (parents) and	ve to the controls ( parm (SMD -0.5/0. participants were	terview and (32% in expe 5) non-blind, au	parents were no erimental group nd unclear/unkn	on-blind to g and 15% in lown risk of	roup assignme the control gro detection bias a	nt and other potentially up)

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

		હા	uality assessm	ent					Summary	of Findir	igs
Participants Ri	-		Indirectness	•	•	• •	Study ev		Relative	Anticipat	ed absolute effects
studies) bi Follow up	bias				bias		With Placebo	With L-carnosing	effect (95% CI)	Risk with Placebo	Risk difference with L- carnosine supplement (95% Cl)
Stereotype	ed behav	viours (measure	d with: Gilliam Au	tism Rating Sc	ale (GARS): S	tereotyped behavio	our; Bette	r indicated by low	ver values)		
		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	17	14	N/A	N/A	The mean stereotyped behaviours in the intervention groups was <b>0.41 standard deviations</b> <b>lower</b> (1.13 lower to 0.3 higher)

# **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

			Quality asses	ssment				S	ummary	of Findings	
	cipants Risk of Inconsistenc		Indirectness	Imprecision		• •	Study even	• •		Anticipated	absolute effects
(studies) Follow up	bias				bias	of evidence	With Treatment- as-usual	W/ith	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Neurofeedback (95% CI)
Parent-ra	ted ste	reotyped be	haviour (mea	asured with: So	ocial Communicat	ion Questionnaire (S	SCQ): Stereo	typed behaviou	r; Better ind	licated by lowe	er values)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	5,	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated stereotyped behaviour in the intervention groups was 1.41 standard deviations lower

											(2.41 to 0.4 lower)
Teacher-	rated s	tereotyped b	<b>behaviour</b> (n	neasured with:	Social Communi	cation Questionnaire	e (SCQ): S	Stereotyped be	haviour; Bette	er indicated b	by lower values)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated stereotyped behaviour in the intervention groups was <b>0.56 standard</b> <b>deviations higher</b> (0.33 lower to 1.46 higher)
interest is als 2 N<400	so high as	nce, response and neurofeedback ec reporting bias as c	luipment provide	d by manufact	urer for trial.	articipants and outco	me asses	sors were nor	h-blind. The ris	k of other bi	as due to potential conflict of

### 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

			Quality asses	ssment				Summ	ary of Fi	ndings
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e (%) With Waitlist control	effect (95% CI)	Anticipat Risk with Waitlist control	Risk difference with Horseback riding (95% Cl)

			publication bias					<b>1.2 standard deviations</b> <b>higher</b> (0.46 to 1.94 higher)
ory Profile: Seden	tary; Better in	dicated by lower va reporting bias strongly suspected <sup>3</sup>	alues) ⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	15	19	N/A	N/A	The mean sedentary in the intervention groups was 1.14 standard deviations higher (0.4 to 1.88 higher)
,	no serious indirectness	no serious serious <sup>2</sup>	no serious indirectness serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup>	indirectness strongly VERY LOW <sup>1,2,3</sup> suspected <sup>3</sup> due to risk of bias, imprecision, publication bias	no serious indirectness serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> $\bigoplus \bigcirc \bigcirc$ <b>VERY LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	no serious indirectnessserious <sup>2</sup> reporting bias strongly suspected $^3$ $\bigoplus \bigcirc \bigcirc \bigcirc$ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias1519	no serious indirectnessserious <sup>2</sup> reporting bias strongly suspected $^3$ $\bigoplus \bigcirc \bigcirc \bigcirc$ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias1519N/A	no serious indirectnessserious <sup>2</sup> reporting bias strongly suspected $^3$ $\bigoplus \bigcirc \bigcirc \bigcirc$ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision,1519N/AN/A

#### 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

								Summary of Findings					
Participants (studies) Follow up		Inconsistency	Indirectness	•	bias	quality of	Study of With Control	With Behaviour-focused intervention versus treatment-as-usual for behaviour that challenges	effect (95% CI)	Anticip Risk with Control	Ated absolute effects Risk difference with Behaviour- focused intervention versus treatment-as-usual for behaviour that challenges as a direct		

								as a direct outcome			outcome (95% CI)
Illness-r	related	problem be	haviour (m	easured with:	Study-specific	questionnaire; l	Better in	dicated by lower values)	I	1	
21 (1 study) 43 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \ominus \ominus$ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	11	10	N/A	N/A	The mean illness-related problem behaviour in the intervention groups was <b>1.65 standard deviations</b> <b>lower</b> (2.64 to 0.66 lower)
								and high risk of detection bia and formal assessments of i			

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

u L		Q	uality assessr	nent			Summary of Findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of	Study e	· · ·	Relative effect	Anticipa	ated absolute effects
Follow up				evidence With With EIBI versus parent Control training for behaviour t	With EIBI versus parent training for behaviour that challenges as an indirect outcome	(95% CI)	Risk with Control	Risk difference with EIBI versus parent training for behaviour that challenges as an indirect outcome (95% CI)			
Aggress	ion (pa	arent-rated)	(measured with:	Achenbach C	hild Behavior (	Checklist (Parent	report):	Aggression; Better indica	ted by lowe	er values)	
28 (1 study) 260 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1.2</sup> due to risk of bias, imprecision	13	15	N/A	N/A	The mean aggression (parent-rated) in the intervention groups was <b>0.36 standard deviations</b> <b>Iower</b> (1.1 lower to 0.39 higher)

28 (1 study) 260 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	15	N/A	N/A	The mean aggression (teacher-rated) in the intervention groups was <b>0.47 standard deviations</b> <b>higher</b> (0.28 lower to 1.23 higher)
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#### 1.10.3 Cognitive-behavioural interventions for behaviour that challenges as a direct or indirect outcome

u			Quality asses	ssment			Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study	event rates (%)	Relative effect	Anticipa	ated absolute effects	
Follow up							With Control	With CBT for anger management versus waiting-list control for behaviour that challenges	(95% CI)	Risk with Control	Risk difference with CBT for anger management versus waiting-list control for behaviour that challenges (95% Cl)	
Parent-re indicated by I			s of child a	i <b>nger</b> (meas	sured with: Study	specific parent mor	nitoring o	of anger: Parent-reported	linstances	of child a	nger over a week; Better	
45 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	<b>VERY LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	21	24	N/A	N/A	The mean parent- reported instances of child anger in the intervention groups was <b>0.92 standard</b> deviations lower	

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

											(1.54 to 0.3 lower)
	reporte		s of child a	anger (mea	asured with: Study	-specific parent mor	nitoring	of anger: Parent-re	ported instance	es of child	anger over a week; Better
45 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	21	24	N/A	N/A	The mean parent- reported instances of child anger in the intervention groups was <b>1.03 standard</b> <b>deviations lower</b> (1.65 to 0.4 lower)
		ence in chil	•	ig own ai	nger (measured	I with: Study-specific	c parent	monitoring of ange	er: Parent-repo	rted confid	ence in their child managi
45 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	21	24	N/A	N/A	The mean parent confidence in child managing own anger ir the intervention groups was <b>0.61 standard</b> <b>deviations higher</b> (0 to 1.21 higher)
		ence in chil		ig own ai	nger (measured	I with: Study-specific	c parent	monitoring of ange	er: Parent-repo	rted confid	ence in their child manag
45 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	21	24	N/A	N/A	The mean parent confidence in child managing own anger ir the intervention groups was 1.1 standard deviation higher

<sup>2</sup> N<400</li>
 <sup>3</sup> High risk of selective reporting bias as data cannot be extracted for the Children's Inventory of Anger (ChIA-P) as no measure of variability is reported

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

		G	Quality assessr	nent					Sum	mary of Fi	ndings
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study eve (%)	ent rates	Relative effect (95% CI)	Anticipate	d absolute effects
							With Waitilist control	With CBT for anxiety		Risk with Waitilist control	Risk difference with CBT for anxiety (95% Cl)
Hyperac	tivity a	nd conduct	problems	(parent-ra	ated) (meas	ured with: Strengt	hs and Diffi	culties Que	stionnaire: I	Externalising	; Better indicated by lower values)
47 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	19	28	N/A	N/A	The mean hyperactivity and conduct problems (parent-rated) in the intervention groups was <b>0.62 standard deviations lower</b> (1.22 to 0.03 lower)
Hyperac values)	tivity a	nd conduct	problems	(teacher-	rated) (mea	asured with: Streng	gths and Di	fficulties Qu	lestionnaire	: Externalisir	ng; Better indicated by lower
47 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^{2,3} \\ \text{due to risk of} \\ \text{bias,} \\ \text{imprecision} \end{array}$	19	28	N/A	N/A	The mean hyperactivity and conduct problems (teacher-rated) in the intervention groups was <b>0.62 standard deviations lower</b> (1.21 to 0.02 lower)
non-blind <sup>2</sup> N<400	performan	ce and response bi					-				neausre parent- rated and parents

### 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

		Q	uality assessr	nent					Summary	of Findiı	ngs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study e	event rates (%)	Relative effect	Anticipa	ted absolute effects
Follow up						evidence	With Control	With Parent training versus treatment-as- usual for behaviour that challenges	(95% CI)	Risk with Control	Risk difference with Parent training versus treatment-as-usual for behaviour that challenges (95% CI)
	-	blem behav	•		orkshop ·	+ individua	al ses	sions) (measured	with: Eyberg	l g Child Be	haviour Inventory (ECBI):
51 (1 study) 4-10 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	15	36	N/A	N/A	The mean number of problem behaviours (combined workshop + individual sessions) in the intervention groups was <b>1.26 standard deviations</b> <b>lower</b> (1.91 to 0.61 lower)
	•	blem behav	•		orkshop ·	+ individua	al ses	sions) (measured	with: Eyberg	g Child Be	haviour Inventory (ECBI):
51 (1 study) 13-19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	15	36	N/A	N/A	The mean number of problem behaviours (combined workshop + individual sessions) in the intervention groups was <b>1.23 standard deviations</b> <b>Iower</b> (1.88 to 0.58 lower)

Intensity indicated by I	-		viours (ind	lividual s	essions)	(measured with:	Eyberg	Child Behaviour Invent	ory (ECBI):	Intensity	of problem behaviours; Better
33 (1 study) 10 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	15	18	N/A	N/A	The mean intensity of problem behaviours (individual sessions) in the intervention groups was 1.41 standard deviations lower (2.18 to 0.63 lower)
Intensity indicated by I	-		viours (ind	lividual s	essions)	(measured with:	Eyberg	Child Behaviour Invent	ory (ECBI):	Intensity	of problem behaviours; Better
33 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	15	18	N/A	N/A	The mean intensity of problem behaviours (individual sessions) in the intervention groups was <b>1.35 standard deviations</b> <b>lower</b> (2.12 to 0.59 lower)
Intensity values)	of pro	blem beha	viours (wo	rkshop) (	measured with	: Eyberg Child B	ehaviou	r Inventory (ECBI): Inte	ensity of pro	blem beha	aviours; Better indicated by lower
33 (1 study) 4 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision	15	18	N/A	N/A	The mean intensity of problem behaviours (workshop) in the intervention groups was <b>0.60 standard deviations</b> <b>lower</b> (1.30 lower to 0.10 higher)
Intensity values)	of pro	blem beha	viours (wo	rkshop) (	measured with	: Eyberg Child B	ehaviou	r Inventory (ECBI): Inte	nsity of pro	blem beha	aviours; Better indicated by lower
33 (1 study)	serious <sup>1</sup>	no serious	no serious	very serious <sup>3</sup>	undetected		15	18	N/A	N/A	The mean intensity of problem behaviours (workshop) in the

13 weeks		inconsistency	indirectness			due to risk of bias, imprecision					intervention groups was 0.59 standard deviations lower (1.30 lower to 0.11 higher)
Problem		viour (PEC+	PEBM con	n <b>bined)</b> (m	easured with:	Developmental I	Behaviou	ur Checklist (DBC): To	tal Behaviou	Ir Problem	n Score (TBPS); Better indicated
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean problem behaviour (pec+pebm combined) in the intervention groups was <b>0.35 standard deviations</b> <b>lower</b> (0.76 lower to 0.06 higher)
intervention <sup>2</sup> N<400		ce bias as interve						outcome assessors we	ere non-blind	d parents	who were involved in the

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

								Sur	nmary of	Finding	IS
Participants (studies) Follow up		Inconsistency	Indirectness	Imprecision	bias	Overall quality of evidence	Study of With Control	With Combined	Relative effect (95% CI)	Anticip Risk with Control	Ated absolute effects Risk difference with Combined antipsychotic and parent training versus antipsychotic only for behaviour that challenges as a direct outcome (95% Cl)
Noncom	pliant b	ehaviour in	everyday c	ircumstar	<b>ICES</b> (measu	red with: Home	Situatio	ns Questionnaire (HSQ): Se	everity; Bett	er indica	ted by lower values)
95 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias,	40	55	N/A	N/A	The mean noncompliant behaviour in everyday circumstances in the intervention groups was

						imprecision					<b>0.33 standard deviations</b> <b>lower</b> (0.74 lower to 0.08 higher)
Noncom	pliant b	ehaviour in	everyday c	ircumstar	ICES (measu	red with: Home	Situatio	ons Questionnaire (HSQ):	Severity; Be	tter indic	ated by lower values)
87 (1 study) 80 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	36	51	N/A	N/A	The mean noncompliant behaviour in everyday circumstances in the intervention groups was 0.17 standard deviations lower (0.6 lower to 0.26 higher)
		ehaviour in ale; Better indicat			<b>ICES</b> (measu	ired with: Study	-specific	c noncompliance index ba	sed on the V	ineland A	Adaptive Behaviour Scale (VABS)
124 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	49	75	N/A	N/A	The mean noncompliant behaviour in everyday circumstances in the intervention groups was <b>0.46 standard deviations</b> <b>lower</b> (0.83 to 0.1 lower)
Irritabilit	<b>y</b> (measur	ed with: Aberrant	Behaviour Chec	klist (ABC): Irr	itability & Agita	ation; Better ind	icated b	y lower values)			
95 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	40	55	N/A	N/A	The mean irritability in the intervention groups was <b>0.43 standard deviations</b> <b>lower</b> (0.85 to 0.02 lower)
Irritabilit	<b>y</b> (measur	ed with: Aberrant	Behaviour Chec	klist (ABC): Irr	itability & Agita	ation; Better ind	icated b	y lower values)			
87 (1 study) 80 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	36	51	N/A	N/A	The mean irritability in the intervention groups was <b>0.33 standard deviations</b> <b>lower</b> (0.75 lower to 0.1 higher)

Lethargy	/Social	withdrawal	(measured with:	Aberrant Beh	aviour Checkli	st (ABC): Letha	rgy & S	Social Withdrawal; E	Better indicated by	ower valu	ies)
95 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	40	55	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was <b>0.36 standard deviations</b> <b>lower</b> (0.77 lower to 0.06 higher)
Lethargy	/Social	withdrawal	(measured with:	Aberrant Beh	aviour Checkli	st (ABC): Letha	rgy & S	Social Withdrawal; E	Better indicated by I	ower valu	ies)
87 (1 study) 80 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1,3</sup> due to risk of bias, imprecision	36	51	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was <b>0.46 standard deviations</b> <b>lower</b> (0.89 to 0.03 lower)
Stereoty	pic beh	aviour (measu	red with: Aberra	nt Behaviour (	Checklist (ABC	): Stereotypic E	Behavio	our; Better indicated	by lower values)		
95 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,3</sup> due to risk of bias, imprecision	40	55	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0.63 standard deviations</b> <b>lower</b> (1.04 to 0.21 lower)
Stereoty	pic beh	<b>aviour</b> (measu	red with: Aberra	nt Behaviour (	Checklist (ABC	): Stereotypic E	Behavio	our; Better indicated	by lower values)		
87 (1 study) 80 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	36	51	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0.35 standard deviations</b> <b>lower</b> (0.78 lower to 0.08 higher)
Hyperac	tivity (m	easured with: Abe	rrant Behaviour	Checklist (AB	C): Hyperactiv	ity & Noncompl	iance; l	Better indicated by I	ower values)	1	
95 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,3</sup> due to risk of bias,	40	55	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.48 standard deviations</b> lower

imprecision (0.89 to 0.07 lower)	imprecision					
Checklist (ABC): Hyperactivity & Noncompliance; Better indicated by lower values)	peractivity & Noncom	Checklist (ABC): Hyperacti	rrant Behaviour C	easured with: Abe	<b>tivity</b> (me	Hyperac
very serious2undetected $\bigoplus \bigcirc \bigcirc \bigcirc$ VERY LOW1.2 due to risk of bias, imprecision3651N/AN/AThe mean hyperactivity i intervention groups was 0.13 standard deviation lower (0.56 lower to 0.29 higher)	VERY LOW due to risk o bias,			no serious inconsistency	serious <sup>1</sup>	87 (1 study) 80 weeks
Behaviour Checklist (ABC): Inappropriate Speech; Better indicated by lower values)	t (ABC): Inappropriat	Behaviour Checklist (ABC	ed with: Aberrant	<b>Deech</b> (measure	oriate sp	Inapprop
very serious2undetected $\bigoplus \bigcirc \bigcirc \bigcirc$ VERY LOW12 due to risk of bias, imprecision4055N/AN/AThe mean inappropriate speech in the interventio groups was 0.23 standard deviation lower (0.63 lower to 0.18 higher)	VERY LOW due to risk o bias,	- ,		no serious inconsistency		95 (1 study) 24 weeks
Behaviour Checklist (ABC): Inappropriate Speech; Better indicated by lower values)	t (ABC): Inappropriat	Behaviour Checklist (ABC	ed with: Aberrant	<b>Deech</b> (measure	oriate sp	Inapprop
serious <sup>3</sup> undetected $\bigoplus \bigoplus \bigoplus$	LOW <sup>1,3</sup> due to risk o bias,	serious <sup>3</sup> undetected	no serious s indirectness	no serious inconsistency	serious <sup>1</sup>	
LOW <sup>1,3</sup> speech in th         due to risk of       groups was         bias,       0.02 standa         imprecision       higher	LOW <sup>1,3</sup> due to risk o bias, imprecision nd participants were not rates in the experi	tion administrators and part s due to higher dropout rate	bias as interventionsk of attrition bias 9% attrition)	ce and response Jlind. Also high ris /) group (N=9; 18'	f performan were non-b eridone only	parents who control (rispe

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

Quality assessment	Summary of Findings

		Inconsistency	Indirectness	Imprecision		Overall quality	Study	event rates (%)	Relative	Anticip	ated absolute effects
Follow up	bias	behaviour	that challe	inges (mix	bias	of evidence		With Combined parent training and early intervention centre programme versus early intervention centre programme only for behaviour that challenges as an indirect outcome sured with: Behavior Screeni	effect (95% CI)	Risk with Control	Risk difference with Combined parent training and early intervention centre programme versus early intervention centre programme only for behaviour that challenges as an indirect outcome (95% Cl) 3SQ): Total; Better indicated by
lower values)	•						-, (				
58 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, indirectness, imprecision	28	30	N/A	N/A	The mean parent-reported behaviour that challenges (mixed asd & dd sample) in the intervention groups was <b>0.02 standard deviations</b> <b>Iower</b> (0.54 lower to 0.49 higher)
Parent-re lower values)	-	l behaviour		nges (mix	ced ASD &	& DD sample	<b>e)</b> (mea	sured with: Behavior Screeni	ng Questio	nnaire (I	BSQ): Total; Better indicated by
50 (1 study) 108 weeks	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, indirectness, imprecision	23	27	N/A	N/A	The mean parent-reported behaviour that challenges (mixed asd & dd sample) in the intervention groups was <b>0.16 standard deviations</b> <b>Iower</b> (0.71 lower to 0.4 higher)
	rated k	ehaviour th	at challen	ges (mixe	d ASD & I	DD sample)	(measu	ed with: Preschool Behavior	Checklist (	PBCL): <sup>-</sup>	
Teacher- values)											Total; Better indicated by lower

34 (1 study) 40 weeks Teacher-	serious <sup>4</sup>	no serious inconsistency pehaviour th	no serious indirectness at challeng			⊕⊕⊖⊖ LOW <sup>4,5</sup> due to risk of bias, imprecision DD sample)	18 (measu	16 rred with: Preschool Behavior		N/A	The mean teacher-rated behaviour that challenges (asd-only sample) in the intervention groups was <b>0.98 standard deviations</b> <b>lower</b> (1.69 to 0.26 lower) Total; Better indicated by lower
values)	-								-	-	
46 (1 study) 108 weeks	serious <sup>4</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>		⊕⊖⊖⊖ VERY LOW <sup>2,3,4</sup> due to risk of bias, indirectness, imprecision	23	23	N/A	N/A	The mean teacher-rated behaviour that challenges (mixed asd & dd sample) in the intervention groups was <b>0.11 standard deviations</b> <b>Iower</b> (0.68 lower to 0.47 higher)
psychologist <sup>2</sup> Population <sup>3</sup> N<400 and	outcome was indire 95% CI c	assessor this out ect (as the sample rosses both line c	come measure e included partic of no effect and	relied on non- ipants with de measure of ap	blind parental evelopmental oppreciable ber	report delay or language nefit or harm (SMI	delay 0 -0.5/0	without autism) 9.5)			s although there was a blinded

#### 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

		C	Quality asses	sment				:	Summary	of Find	lings
•	Risk of bias	Inconsistency	Indirectness	-		Overall quality of evidence	With	With Social skills	effect (95% CI)	Risk	Ated absolute effects Risk difference with Social skills groups versus treatment-as-usual for behaviour that challenges as an indirect outcome (95% Cl)
Conflict (	parent	-rated) (measu	red with: Qualit	y of Play Que	stionnaire (QF	Q): Conflict; Better	indicate	d by lower values)			

95 (2 studies) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \ominus \ominus$ LOW <sup>1,2</sup> due to risk of bias, imprecision	43	52	N/A	N/A	The mean conflict (parent-rated) in the intervention groups was <b>0.6 standard deviations lower</b> (1.01 to 0.18 lower)
Conflict	(self-ra	ted) (measured	d with: Quality of	Play Question	nnaire (QPQ):	Conflict; Better indi	cated b	y lower values)			
33 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	16	17	N/A	N/A	The mean conflict (self-rated) in the intervention groups was <b>0.09 standard deviations lower</b> (0.77 lower to 0.59 higher)
		ssive behav	••	nt-rated) (n	neasured with	: Social Skills Rating	g Syste	m (SSRS): Exter	nalizing or Socia	l Skills R	ating System (SSRS): Problem
101 (2 studies) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	49	52	N/A	N/A	The mean intrusive/aggressive behaviour (parent-rated) in the intervention groups was <b>0.78 standard deviations lower</b> (1.19 to 0.37 lower)
Intrusive	e/aggres	ssive behav	viour (teach	ner-rated)	(measured wit	h: Pupil Evaluation	Invento	ry (PEI): Aggres	sion; Better indic	ated by lo	ower values)
59 (1 study) 12 weeks	serious⁵	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	28	31	N/A	N/A	The mean intrusive/aggressive behaviour (teacher-rated) in the intervention groups was <b>0.24 standard deviations lower</b> (0.75 lower to 0.28 higher)
		/al (parent-r awal; Better indic			al Skills Rating	g System (SSRS): Ir	Internaliz	zing or Behavior	Assessment Sys	stem for C	Children, 2nd ed., parent rated
104 (2 studies) 6-12 weeks	serious <sup>1</sup>	very serious <sup>6</sup>	no serious indirectness	serious <sup>2</sup>	undetected	<b>VERY LOW</b> <sup>1,2,6</sup> due to risk of bias, inconsistency, imprecision	51	53	N/A	N/A	The mean social withdrawal (parent-rated) in the intervention groups was <b>0.68 standard deviations lower</b> (1.08 to 0.28 lower)
Social w	ithdraw	al (teacher	-rated) (meas	sured with: Pu	oil Evaluation	Inventory (PEI): With	ndrawa	l; Better indicate	d by lower value	s)	
59 (1 study) 12 weeks	serious⁵	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	$\bigcirc \bigcirc \bigcirc \bigcirc$ <b>VERY LOW</b> <sup>4,5</sup> due to risk of bias,	28	31	N/A	N/A	The mean social withdrawal (teacher-rated) in the intervention groups was

			imprecision		<b>0.04 standard deviations lower</b> (0.55 lower to 0.47 higher)
performance and re the intervention.	sponse bias as inte	rvention adminis	rators and participants were non-	blind, and high risk of detection bi	as as parent-rated and parents were non-blind and
				blind, and high risk of detection bi	as as self-rated
			preciable benefit or harm (SMD - trators and participants were non-		as as teacher-rated and teachers were non-blind
to considerable hete				,	

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

		Qı	ality assess	nent				Sur	nmary of	Finding	<u>js</u>
Participants	Risk of	Inconsistency	Indirectness	Imprecision			Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias					ovidonoo	With Control	With LEGO therapy versus Social Use of Language Programme (SULP) for behaviour that challenges as an indirect outcome		Risk with Control	Risk difference with LEGO therapy versus Social Use of Language Programme (SULP) for behaviour that challenges as an indirect outcome (95% Cl)
Maladapt	ive bel	naviour (meas	ured with: Vinela	and Adaptive I	Behaviour Sca	le (VABS): Mala	adaptive	Behaviour Index; Better inc	licated by lo	ower valu	ies)
31 (1 study) 18 weeks	serious <sup>1</sup>			very serious <sup>1</sup>		⊕⊖⊖⊖ VERY LOW <sup>1</sup> due to risk of bias, imprecision	15	16	N/A	N/A	The mean maladaptive behaviour in the intervention groups was <b>0.51 standard deviations</b> <b>lower</b> (1.23 lower to 0.21 higher)
<sup>1</sup> N<400 and 9	95% CI cr	osses both line of	no effect and m	easure of app	preciable bene	l fit or harm (SMI	D -0.5/0	.5)		I	

### 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

l		(	Quality asses	sment				Sum	mary of F	Findings	3
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Anticonvulsants versus placebo for behaviour that challenges as a direct outcome	effect (95% CI)	Risk with Control	Risk difference with Anticonvulsants versus placebo for behaviour that challenges as a direct outcome (95% Cl)
Irritability	<b>y</b> (measure	d with: Aberrant E	Behaviour Check	list (ABC): Irrit	ability & Agitation	n; Better indicated	by lower	values)			
57 (2 studies) 8-12 weeks	no serious risk of bias	serious <sup>1</sup>	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to inconsistency, imprecision	25	32	N/A	N/A	The mean irritability in the intervention groups was <b>0.05 standard deviations</b> <b>lower</b> (0.58 lower to 0.48 higher)
Irritability	<b>y</b> (measure	d with: Overt Agg	ression Scale (C	AS): Irritability	; Better indicated	d by lower values)	<b></b>				
27 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency <sup>1</sup>	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to imprecision	11	16	N/A	N/A	The mean irritability in the intervention groups was <b>0.43 standard deviations</b> <b>lower</b> (1.21 lower to 0.35 higher)
Aggressi	<b>on</b> (meas	ured with: Overt A	ggression Scale	e (OAS): Total;	Better indicated	by lower values)			ł		
30 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>2.3</sup> due to imprecision, publication bias	14	16	N/A	N/A	The mean aggression in the intervention groups was 0.03 standard deviations higher

91 per 1000	
91 per	intervention groups wa 0.43 standard deviation (1.16 lower to 0.29 high Study population 91 per 1000 (from 2 more to 1000
	intervention groups wa <b>0.43 standard deviati</b> <b>lower</b> (1.16 lower to 0.29 high
	intervention groups wa 0.43 standard deviation lower
N/A	N/A The mean global
	was 0 standard deviations higher (0.72 lower to 0.72 high
N/A	N/A The mean global sever in the intervention grou

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

		Q	uality assess	ment				Sum	mary of F	inding	5
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Combined anticonvulsants and antipsychotics versus combined placebo and antipsychotics for behaviour that challenges as a direct outcome	effect (95% CI)	Risk with Control	Risk difference with Combined anticonvulsants and antipsychotics versus combined placebo and antipsychotics for behaviour that challenges as a direct outcome (95% Cl)
Irritability	(measure	ed with: Aberrant	Behaviour Chec	klist (ABC): Irr	itability & Agit	ation; Better indi	cated by	lower values)			
40 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	20	20	N/A	N/A	The mean irritability in the intervention groups was <b>1.88 standard deviations</b> <b>Iower</b> (2.63 to 1.12 lower)
Lethargy/	/Social	withdrawal	(measured with:	Aberrant Beh	aviour Checkl	ist (ABC): Lethar	gy & So	cial Withdrawal; Better indica	ted by lowe	er values	)
40 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	20	20	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was <b>0.25 standard deviations</b> <b>lower</b> (0.88 lower to 0.37 higher)
Stereotyp	oic beh	aviour (measu	red with: Aberra	nt Behaviour (	Checklist (ABC	C): Stereotypic Be	ehaviour	; Better indicated by lower va	alues)	•	
40 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	20	20	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>2.02 standard deviations</b> <b>lower</b> (2.8 to 1.25 lower)
Hyperact	<b>ivity</b> (me	easured with: Abe	rrant Behaviour	Checklist (AB	C): Hyperactiv	ity & Noncomplia	ance; Be	tter indicated by lower value	s)		
40 (1 study) 8 weeks	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to	20	20	N/A	N/A	The mean hyperactivity in the intervention groups was <b>1.87 standard deviations</b>

	bias					imprecision					lower (2.63 to 1.12 lower)
Inappro	priate s	<b>Deech</b> (measur	ed with: Aberran	t Behaviour C	hecklist (ABC)	): Inappropriate S	Speech;	Better indicated by	v lower values)		
40 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>2</sup> due to imprecision	20	20	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>0.16 standard deviations</b> <b>lower</b> (0.78 lower to 0.46 higher)
<sup>1</sup> N<400 <sup>2</sup> N<400 and	d 95% CI cr	osses both line of	f no effect and m	easure of app	preciable bene	fit or harm (SMD	-0.5/0.	5)			

## **1.11.2** Antidepressants for behaviour that challenges as an indirect outcome

#### Citalopram versus placebo for behaviour that challenges as an indirect outcome

		Q	uality assessr	nent				Sum	mary of F	Finding	5		
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study	event rates (%)	Relative	Anticip	ated absolute effects		
(studies) Follow up	bias of evidence With Contr		With Control	With Antidepressants versus placebo for behaviour that challenges as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Antidepressants versus placebo for behaviour that challenges as an indirect outcome (95% Cl)						
Irritability	rritability (measured with: Aberrant Behaviour Checklist (ABC): Irritability & Agitation; Better indicated by lower values)												
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	76	73	N/A	N/A	The mean irritability in the intervention groups was <b>0.01 standard deviations</b> <b>lower</b> (0.33 lower to 0.31 higher)		
Lethargy	/Social	withdrawal	measured with:	Aberrant Beha	aviour Checklis	t (ABC): Lethargy	& Socia	al Withdrawal; Better indica	ted by lowe	er values)			
149	no	no serious	no serious	serious <sup>1</sup>	undetected	$\oplus \oplus \oplus \ominus$	76	73	N/A	N/A	The mean lethargy /social		

(1 study) 12 weeks	serious risk of bias	inconsistency	indirectness			MODERATE <sup>1</sup> due to imprecision				withdrawal in the intervention groups was <b>0.01 standard deviations</b> <b>Iower</b> (0.33 lower to 0.31 higher)
Stereoty	pic beh	aviour (measur	ed with: Aberran	t Behaviour C	hecklist (ABC)	Stereotypic Beha	aviour; Better indicate	ed by lower values)		
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	76 73	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0.05 standard deviations</b> higher (0.27 lower to 0.37 higher)
Hyperac	<b>tivity</b> (me	easured with: Aber	rant Behaviour (	Checklist (ABC	): Hyperactivity	y & Noncompliand	e; Better indicated b	y lower values)		
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	76 73	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.09 standard deviations</b> <b>higher</b> (0.23 lower to 0.41 higher)
Inapprop	oriate sp	<b>eech</b> (measure	d with: Aberrant	Behaviour Ch	ecklist (ABC):	Inappropriate Spe	ech; Better indicated	by lower values)		
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	76 73	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>0.06 standard deviations</b> higher (0.26 lower to 0.38 higher)
<sup>1</sup> N<400	1			<u>I</u>		1	<u> </u>			

## 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

		Qı	uality assess	ment				Sum	mary of <b>F</b>	inding	s
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	lies) bias w up				bias of evidenc		With With Combined antihistamine Control and antipsychotic versus combined antipsychotic and placebo for behaviour that challenges as a direct outcome		(95% CI)	Risk with Control	Risk difference with Combined antihistamine and antipsychotic versus combined antipsychotic and placebo for behaviour that challenges as a direct outcome (95% Cl)
Behaviou	ir that o	challenges (r	measured with:	Aberrant Beha	aviour Checkli	st (ABC): Total (0	Change	Score); Better indicated by lo	wer values	)	
(1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>		⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	20	20	N/A	N/A	The mean behaviour that challenges in the intervention groups was <b>0.98 standard deviations</b> <b>lower</b> (1.64 to 0.32 lower)
<sup>1</sup> N<400		1	I	I	I	I	·		I	1	

## 1.11.4 Antioxidants for behaviour that challenges as a direct outcome

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

		Qı	uality assessm	ent				Summa	ry of Find	dings	
· /	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e (%)	vent rates	Relative effect	Anticipat	ed absolute effects
Follow up							With Placebo	With Antioxidants	(95% CI)	Risk with Placebo	Risk difference with Antioxidants (95% CI)
Irritability	(measured	with: Aberrant Beha	aviour Checklist (A	BC): Irritability	/ & Agitation; B	etter indicated by	lower valu	ues)			
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean irritability in the intervention groups was <b>0.7 standard deviations</b> <b>lower</b> (1.46 lower to 0.05 higher)

Letharg	y/Social W	/ithdrawal (m	easured with: Abe	errant Behavio	ur Checklist (AE	BC): Lethargy & S	Social Witl	hdrawal; Be	tter indicated	by lower val	ues)
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was <b>0.31 standard deviations</b> higher (0.43 lower to 1.04 higher)
Stereoty	pic behav	iour (measure	d with: Aberrant B	ehaviour Cheo	cklist (ABC): Ste	reotypic Behavio	ur; Better	indicated by	/ lower values	5)	
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0.36 standard deviations</b> <b>lower</b> (1.1 lower to 0.37 higher)
Hyperac	tivity (meas	sured with: Aberra	Int Behaviour Che	cklist (ABC): H	lyperactivity & N	Ioncompliance; E	Better indi	cated by low	ver values)		
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.73 standard deviations</b> <b>lower</b> (1.49 lower to 0.03 higher)
Inappro	priate spe	ech (measured	with: Aberrant Bel	haviour Check	list (ABC): Inapp	propriate Speech	; Better in	ndicated by I	ower values)		
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>0.34 standard deviations</b> <b>lower</b> (1.07 lower to 0.4 higher)
Global s	severity (m	easured with: Clir	ical Global Impres	ssion Scale (C	GI-S): Severity;	Better indicated	by lower v	values)			1
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean global severity in the intervention groups was <b>0.46 standard deviations</b> <b>Iower</b>

											(1.19 lower to 0.28 higher)
Global in	nproveme	ent (measured wit	h: Clinical Global I	Impression Sc	ale (CGI-I): Imp	provement; Better	indicated	d by lower val	ues)		
29 (1 study) 12 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	15	14	N/A	N/A	The mean global improvement in the intervention groups was <b>0.29 standard deviations</b> <b>lower</b> (1.02 lower to 0.44 higher)

## 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

		(	Quality assess	sment				Sui	nmary of	Finding	gs
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality of	Study e	vent rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	evidence	With Control	With Antipsychotics versus placebo for behaviour that challenges	effect (95% CI)	Risk with Control	Risk difference with Antipsychotics versus placebo for behaviour that challenges (95% Cl)
		<b>it response (</b> d/very improved' c			azole) (ass	essed with: Positive	treatmen	t response (clinician-ra	ated: >25%	improve	ment on ABC-Irritability with
501 r	no serious risk of bias	,	ry serious <sup>1</sup> no serious indirectness		undetected	⊕⊕⊝⊝ LOW <sup>1</sup>	44/184 (23.9%)	183/317 (57.7%)	<b>RR 2.27</b> (1.75 to	Study p	oopulation
						due to inconsistency			2.94)	239 per 1000	<b>304 more per 1000</b> (from 179 more to 464 more)
										Modera	ite
										245 per 1000	<b>311 more per 1000</b> (from 184 more to 475 more)

		nt response ( on CGI-improvem	• •	<b>e)</b> (assessed w	vith: Positive tr	eatment response (c	linician-ra	ted: >25% improve	ment on ABC	C-Irritabilit	y with or without 'much
193 (2 studies)	no serious risk of bias	very serious <sup>1</sup>	no serious indirectness	serious <sup>2</sup>	undetected		20/86 (23.3%)	73/107 (68.2%)	<b>RR 2.72</b> (1.85 to	Study p	population
6-8 weeks						due to inconsistency, imprecision	()	()	3.99)	233 per 1000	<b>400 more per 1000</b> (from 198 more to 695 more)
										Moderate         245       421 more per 1000         per       (from 208 more to 733         1000       more)         3C-Irritability with or without 'much	ate
Positivo t										per	(from 208 more to 733
		<b>It response</b> ( on CGI-improvem		le) (assessed v	vith: Positive tr	reatment response (d	clinician-ra	ated: >25% improve	ment on AB	C-Irritabili	ty with or without 'much
308 (2 studies)	no serious risk of bias	very serious <sup>1</sup>	ious <sup>1</sup> no serious serio indirectness			24/98 (24,5%)	110/210 (52.4%)	<b>RR 1.95</b> (1.37 to	Study p	oopulation	
8 weeks						due to inconsistency, imprecision		(021.776)	2.78)	245 per 1000	<b>233 more per 1000</b> (from 91 more to 436 more)
										Modera	ate
										245 per 1000	<b>233 more per 1000</b> (from 91 more to 436 more)
Positive symptom sca		t response	(risperidon	e) (assessed w	ith: Dichotomo	ous: Positive treatme	nt respon	se (<3 "definitely im	proved" or b	etter on S	-point parent-defined target
87 (1 study)	no serious risk of bias		no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \oplus \ominus$ <b>MODERATE</b> <sup>2</sup>	9/43 (20.9%)	31/44 (70.5%)	<b>RR 3.37</b> (1.83 to	Study p	population
8 weeks		inconsistency indirectness		385		due to imprecision		()	6.21)	209 per 1000	<b>496 more per 1000</b> (from 174 more to 1000 more)
										Modera	ate

										209 per 1000	<b>495 more per 1000</b> (from 173 more to 1000 more)
Maladapt	ive beha	<b>viour</b> (measure	ed with: Vineland	d Adaptive Beha	aviour Scale (V	ABS): Maladaptive E	Behaviou	r Index; Better indicate	ed by lower	values)	1
101 (1 study) 8 weeks		no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>3</sup> due to imprecision	52	49	N/A	N/A	The mean maladaptive behaviour in the intervention groups was <b>1.17 standard deviations</b> <b>Iower</b> (1.59 to 0.75 lower)
Irritability values)	y (risperi	done or arip	oiprazole) (m	neasured with: A	Aberrant Behav	viour Checklist (ABC	): Irritabil	ity & Agitation (Endpo	nt or Chan	ge score)	; Better indicated by lower
363 (4 studies) 6-8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>3</sup> due to imprecision	173	190	N/A	N/A	The mean irritability (risperidone or aripiprazole) in the intervention groups was <b>0.92 standard deviations</b> <b>lower</b> (1.14 to 0.7 lower)
Irritability	y (risperi	<b>done)</b> (measur	ed with: Aberran	t Behaviour Ch	ecklist (ABC):	Irritability & Agitation	(Endpoi	nt or Change score); E	Better indica	ated by Ic	wer values)
268 (3 studies) 6-8 weeks		no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	124	144	N/A	N/A	The mean irritability (risperidone) in the intervention groups was <b>0.96 standard deviations</b> <b>Iower</b> (1.22 to 0.71 lower)
Irritability	y (aripipr	azole) (measu	red with: Aberra	nt Behaviour Ch	ecklist (ABC):	Irritability & Agitation	n (Endpo	int or Change score);	Better indic	ated by lo	ower values)
95 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>3</sup> due to imprecision	49	46	N/A	N/A	The mean irritability (aripiprazole) in the intervention groups was <b>0.81 standard deviations</b> <b>Iower</b> (1.23 to 0.39 lower)

486	serious <sup>4</sup>	no serious	no serious	no serious	undetected	$\oplus \oplus \oplus \ominus$	188	298	N/A	N/A	The mean lethargy/social
(4 studies) 8 weeks	senous	inconsistency	indirectness	imprecision	undelected	₩₩₩₩ MODERATE <sup>4</sup> due to risk of bias	100	290	N/A	N/A	withdrawal (risperidone or aripiprazole) in the intervention groups was 0.28 standard deviations lower (0.47 to 0.08 lower)
•••	/Social v	•	risperidone	(measured w	ith: Aberrant Be	ehaviour Checklist (A	ABC): Le	ethargy & Social \	Withdrawal (End	dpoint and	d Change scores); Better
178 (2 studies) 8 weeks	risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	90	88	N/A	N/A	The mean lethargy/social withdrawal (risperidone) in the intervention groups was <b>0.45 standard deviations</b> <b>lower</b> (0.75 to 0.15 lower)
	/Social V lower values		aripiprazol	e) (measured v	with: Aberrant E	Behaviour Checklist (	ABC): L	ethargy & Social.	Withdrawal (Er	idpoint an	d Change scores); Better
308 (2 studies) 8 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>3,4</sup> due to risk of bias, imprecision	98	210	N/A	N/A	The mean lethargy/social withdrawal (aripiprazole) in the intervention groups was 0.15 standard deviations lower (0.40 lower to 0.10 higher)
•	pic beha	•••	ridone or a	ripiprazole	) (measured w	ith: Aberrant Behavio	our Che	cklist (ABC): Ster	eotypic Behavio	our (Endp	oint and Change scores);
485 (4 studies) 8 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	$\begin{array}{c} \oplus \oplus \oplus \ominus \\ \textbf{MODERATE}^4 \\ \text{due to risk of bias} \end{array}$	188	297	N/A	N/A	The mean stereotypic behaviour (risperidone or aripiprazole) in the intervention groups was

										]	(0.68 to 0.29 lower)
Stereoty values)	pic beha	viour (rispe	r <b>idone)</b> (meas	sured with: Aber	rant Behaviou	I r Checklist (ABC): Sf	ereotyp	ic Behaviour (Endpoin	t and Chang	ge scores	); Better indicated by lower
177 (2 studies) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	90	87	N/A	N/A	The mean stereotypic behaviour (risperidone) in the intervention groups was <b>0.34 standard deviations</b> <b>lower</b> (0.64 to 0.05 lower)
Stereoty values)	pic beha	viour (aripip	<b>orazole)</b> (mea	sured with: Abe	rrant Behaviou	ır Checklist (ABC): S	tereotyp	ic Behaviour (Endpoir	it and Chan	ge scores	;); Better indicated by lower
308 (2 studies) 8 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>3,4</sup> due to risk of bias, imprecision	98	210	N/A	N/A	The mean stereotypic behaviour (aripiprazole) in the intervention groups was 0.59 standard deviations lower (0.84 to 0.33 lower)
••	tivity (ris lower values	-	aripiprazol	<b>e)</b> (measured v	with: Aberrant	I Behaviour Checklist	(ABC): I	Hyperactivity & Noncor	npliance (E	ndpoint o	r Change score); Better
484 (4 studies) 8 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊝ MODERATE <sup>4</sup> due to risk of bias	187	297	N/A	N/A	The mean hyperactivity (risperidone or aripiprazole) in the intervention groups was <b>0.84 standard deviations</b> <b>lower</b> (1.04 to 0.64 lower)
Hyperac	tivity (ris	<b>peridone)</b> (m	easured with: At	Derrant Behavior	ur Checklist (A	BC): Hyperactivity &	Noncor	npliance (Endpoint or	Change sco	ore); Bette	⊥ r indicated by lower values)
176 (2 studies) 8 weeks		no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>3</sup> due to imprecision	89	87	N/A	N/A	The mean hyperactivity (risperidone) in the intervention groups was 1.03 standard deviations lower

											(1.34 to 0.71 lower)
Hyperact	ivity (ari	piprazole) (m	easured with: A	berrant Behavio	ur Checklist (/	ABC): Hyperactivity &	Noncor	mpliance (Endpoint or	Change sco	ore); Bette	er indicated by lower values
308 (2 studies) 8 weeks	serious <sup>4</sup>	serious <sup>5</sup>	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4,5</sup> due to risk of bias, inconsistency, imprecision	98	210	N/A	N/A	The mean hyperactivity (aripiprazole) in the intervention groups was <b>0.72 standard deviations</b> <b>lower</b> (0.97 to 0.46 lower)
Inapprop Better indicat	-	• •	done or ari	piprazole)	(measured wit	h: Aberrant Behaviou	ır Check	list (ABC): Inappropria	te Speech	(Endpoint	and Change scores);
485 (4 studies) 8 weeks	serious <sup>4</sup>	serious <sup>5</sup>	no serious indirectness	no serious imprecision	undetected	⊕⊕⊝⊖ LOW <sup>4,5</sup> due to risk of bias, inconsistency	187	298	N/A	N/A	The mean inappropriate speech (risperidone or aripiprazole) in the intervention groups was <b>0.54 standard deviations</b> <b>lower</b> (0.74 to 0.35 lower)
Inapprop values)	riate Spe	ech (risperi	done) (meas	ured with: Aberr	ant Behaviour	Checklist (ABC): Ina	ppropria	ate Speech (Endpoint a	and Change	scores);	Better indicated by lower
178 (2 studies) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	90	88	N/A	N/A	The mean inappropriate speech (risperidone) in the intervention groups was <b>0.66 standard deviations</b> <b>lower</b> (0.96 to 0.36 lower)
Inapprop values)	riate Spe	ech (aripipr	azole) (meas	ured with: Aber	rant Behaviou	r Checklist (ABC): In	appropria	ate Speech (Endpoint	and Change	e scores);	Better indicated by lower
307 (2 studies) 8 weeks	serious <sup>4</sup>	very serious <sup>6</sup>	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4,6</sup> due to risk of bias, inconsistency, imprecision	97	210	N/A	N/A	The mean inappropriate speech (aripiprazole) in the intervention groups was 0.46 standard deviations lower

											(0.72 to 0.20 lower)
Parent-de			DMS (measured	d with: Parent-d	lefined target s	J ymptom scale (9-poir	nt) or Visu	ial Analog Scale f	for the most tro	ublesom	e symptom (VAS-MS); Bett
163 (2 studies) 8 weeks	serious <sup>7</sup>	very serious <sup>8</sup>	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,7,8</sup> due to risk of bias, inconsistency, imprecision	80	83	N/A	N/A	The mean parent-defined target symptoms in the intervention groups was <b>0.96 standard deviation</b> <b>lower</b> (1.29 to 0.63 lower)
Global st improvement		sitive treatm	ent respons	se (risperio	done) (asses	sed with: Dichotomo	us: Positiv	ve treatment resp	onse ( 'much in	nproved	very improved' on CGI-
171 (2 studies) 6-8 weeks	serious <sup>9</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>2,9</sup>	12/72 (16.7%)	45/99 (45.5%)	<b>RR 2.83</b> (1.61 to	Study	population
						due to risk of bias, imprecision		<b>`</b>	4.95)	167 per 1000	<b>305 more per 1000</b> (from 102 more to 658 more)
										Moder	ate
										166 per 1000	<b>304 more per 1000</b> (from 101 more to 656 more)
Global st Better indicat	•	-	rity (risperio	done or ari	ipiprazole)	(measured with: Cli	l nical Glob	al Impression Sc	ale (CGI-S): Se	verity (E	ndpoint or Change Scores);
273 (2 studies) 6-8 weeks	serious <sup>10</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>3,10</sup> due to risk of bias, imprecision	75	198	N/A	N/A	The mean global state: symptom severity (risperidone or aripiprazole) in the intervention groups was 0.32 standard deviation lower (0.59 to 0.05 lower)

92 (1 study) 6 weeks	no serious risk of bias			very serious <sup>3,11</sup>		⊕⊕⊖⊖ LOW <sup>3,11</sup> due to imprecision	34	58	N/A		The mean global state: symptom severity (risperdione) in the intervention groups was <b>0.28 standard deviations</b> <b>lower</b> (0.71 lower to 0.14 higher)
----------------------------	----------------------------	--	--	---------------------------------	--	---	----	----	-----	--	---

#### Global state: Symptom severity (aripiprazole) (measured with: Clinical Global Impression Scale (CGI-S): Severity; Better indicated by lower values)

							1				
181	serious <sup>10</sup>	no serious	no serious	very serious <sup>11</sup>	undetected	$\oplus \Theta \Theta \Theta$	41	140	N/A	N/A	The mean global state:
(1 study)		inconsistency	indirectness			VERY LOW <sup>10,11</sup>					symptom severity
8 weeks						due to risk of bias,					(aripiprazole) in the
						imprecision					intervention groups was
											0.34 standard deviations
											lower
											(0.69 lower to 0.01 higher)
1	1	1	1		1				1		

#### Global state: Improvement (risperidone) (measured with: Clinical Global Impression Scale (CGI-I): Improvement; Better indicated by lower values)

77	serious <sup>9</sup>	no serious	no serious	serious <sup>3</sup>	undetected	$\oplus \oplus \Theta \Theta$	38	39	N/A	N/A	The mean global state:
(1 study)		inconsistency	indirectness			LOW <sup>3,9</sup>					improvement (risperidone)
8 weeks						due to risk of bias,					in the intervention groups
						imprecision					was
											0.98 standard deviations
											lower
											(1.45 to 0.51 lower)

<sup>1</sup> Substantial to considerable heterogeneity

<sup>2</sup> Events<300

<sup>3</sup> N<400

<sup>4</sup> With the exception of RUPPRISPERIDONE2001, the blinding is unclear for the trials as the papers state 'double-blind' but give no further detail with regards to who is blinded, i.e. participant, parent, investigator, intervention administrator, outcome assessor.

<sup>5</sup> Moderate heterogeneity

<sup>6</sup> Substantial heterogeneity

<sup>7</sup> In RUPPRISPERIDONE<sup>2</sup>001 a study-specific outcome measure without indpendent reliability and validity data was used and in SHEA2004/PANDINA2007 the blinding is unclear as the paper states 'double-blind' but gives no further detail with regards to who is blinded, i.e. participant, parent, investigator, intervention administrator, outcome assessor

<sup>8</sup> Substantial to considerable heterogeneity

<sup>9</sup> Blinding is unclear in SHEA2004/PANDINA2007 as paper states 'double-blind' but gives no further detail with regards to who is blinded, i.e. participant, parent, investigator, intervention administrator, outcome assessor

<sup>10</sup> Blinding is unclear in MARCUS2009 as paper states 'double-blind' but gives no further detail with regards to who is blinded, i.e. participant, parent, investigator, intervention administrator, outcome assessor

<sup>11</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

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

l.		Q	uality assessr	nent				Sun	nmary of	Finding	s
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study e	vent rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Low dose antipsychotics versus placebo for behaviour that challenges	effect (95% CI)	Risk with Control	Risk difference with Low dose antipsychotics versus placebo for behaviour that challenges (95% Cl)
		-	• •		•			: Positive treatment resp d' on CGI-improvement))		6 improve	ement on ABC-Irritability) or
164 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup>	31/83 (37.3%)	44/81 (54.3%)	<b>RR 1.46</b> (1.03 to	Study p	opulation
6-8 weeks						due to risk of bias, imprecision			2.06)	373 per 1000	<b>172 more per 1000</b> (from 11 more to 396 more)
										Modera	te
										379 per 1000	<b>174 more per 1000</b> (from 11 more to 402 more)
Positive t	treatmer	nt response	(risperidon	<b>e)</b> (assessed	with: Dichotor	nous: Positive trea	atment re	sponse (>25% improvem	ent on ABC	C-Irritabili	ty))
63 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2,3</sup>	14/34 (41,2%)	15/29 (51.7%)	<b>RR 1.26</b> (0.74 to	Study p	opulation
6 weeks	bias					due to imprecision	(,)	(070)	2.14)	412 per 1000	<b>107 more per 1000</b> (from 107 fewer to 469 more)
										Modera	te
										379 per 1000	99 more per 1000 (from 99 fewer to 432 more)
Positive 1		-	(aripiprazo	<b>e)</b> (assessed	with: Dichoto	mous: Positive tre	atment re	sponse (>25% improven	nent on AB	C-Irritabil	ity & 'much improved/very

(1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected		17/49 (34 7%)	29/52 (55.8%)	<b>RR 1.61</b> (1.02 to	Study p	oopulation
8 weeks		lineeneisteney				due to risk of bias, imprecision	(0 /0)	(00.070)	2.53)	347 per 1000	<b>212 more per 1000</b> (from 7 more to 531 more)
										Modera	ite
										379 per 1000	231 more per 1000 (from 8 more to 580 more)
Irritabili	ty (risper	idone) (measu	red with: Aberra	nt Behaviour (	Checklist (ABC	): Irritability & Agita	ation; Be	tter indicated by lower va	alues)		
63 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>4</sup> due to imprecision	34	29	N/A	N/A	The mean irritability (risperidone) in the intervention groups was <b>0.52 standard deviations</b> <b>lower</b> (1.02 to 0.01 lower)
Letharg	y/Social v	withdrawal (	aripiprazol	e) (measured	with: Aberrant	Behaviour Check	ist (ABC)	): Lethargy (Change Sco	re); Better i	ndicated	by lower values)
101 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,4</sup> due to risk of bias, imprecision	49	52	N/A	N/A	The mean lethargy/social withdrawal (aripiprazole) in the intervention groups was <b>0.07 standard deviations</b> <b>lower</b> (0.46 lower to 0.32 higher)
Stereoty	ypic beha	viour (aripij	orazole) (mea	asured with: Al	perrant Behavi	iour Checklist (AB	C): Stered	otypic behaviour (Chang	e Score); B	etter indic	cated by lower values)
101 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1,4</sup> due to risk of bias, imprecision	49	52	N/A	N/A	The mean stereotypic behaviour (aripiprazole) in the intervention groups was <b>0.55 standard deviations</b> <b>lower</b> (0.95 to 0.15 lower)
Hyperac	ctivity (ar	ipiprazole) (r	neasured with: A	Aberrant Behav	l /iour Checklist	(ABC): Hyperactiv	l /ity (Char	nge Score); Better indica	ted by lowe	er values)	<u> </u>
101 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	$\oplus \oplus \ominus \ominus$ <b>LOW</b> <sup>1,4</sup> due to risk of bias, imprecision	49	52	N/A	N/A	The mean hyperactivity (aripiprazole) in the intervention groups was <b>0.53 standard deviations</b>

											<b>lower</b> (0.93 to 0.14 lower)
Inapprop	riate Sp	eech (aripip	razole) (meas	sured with: Abe	errant Behavio	our Checklist (ABC	): Inappro	opriate Speech (C	Change Score); Be	tter indic	ated by lower values)
100 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,5</sup> due to risk of bias, imprecision	48	52	N/A	N/A	The mean inappropriate speech (aripiprazole) in the intervention groups was <b>0.25 standard deviations</b> <b>lower</b> (0.65 lower to 0.14 higher)
Global st	ate: Pos	itive treatmo	ent respons	Se (assessed	with: Dichotor	nous: Positive trea	tment re	sponse ( 'much in	nproved/very impro	oved' on	CGI-improvement))
64 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		5/34 (14.7%)	5/30 (16.7%)	<b>RR 1.13</b> (0.36 to	Study	population
6 weeks	bias					due to imprecision	(1.11.70)	(,)	3.54)	147 pe 1000	r 19 more per 1000 (from 94 fewer to 374 more)
										Modera	ate
										147 pe 1000	r 19 more per 1000 (from 94 fewer to 373 more)
Global so values)	everity (r	isperidone	or aripipraz	<b>:ole)</b> (measu	red with: Clini	cal Global Impress	ion Scale	e (CGI-S): Severi	ty (Endpoint or Cha	ange Sco	ores); Better indicated by lower
148 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,5</sup> due to risk of bias, imprecision	75	73	N/A	N/A	The mean global severity (risperidone or aripiprazole) in the intervention groups was <b>0.09 standard deviations</b> <b>lower</b> (0.41 lower to 0.24 higher)
Global s	everity (r	isperidone)	(measured with	Clinical Globa	al Impression	Scale (CGI-S): Sev	/erity; Be	tter indicated by	lower values)	1	
63 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW <sup>5</sup> due to imprecision	34	29	N/A	N/A	The mean global severity (risperidone) in the intervention groups was <b>0.1 standard deviations</b> <b>higher</b> (0.39 lower to 0.6 higher)

Global s	everity (	aripiprazole	) (measured with	n: Clinical Glob	al Impression	Scale (CGI-S): Se	verity (	(Change Scores	s); Better indic	ated by I	ower val	ues)
85 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,5</sup> due to risk of bias, imprecision	41	44	Ν	J/A	N/A	The mean global severity (aripiprazole) in the intervention groups was <b>0.23 standard deviations</b> <b>lower</b> (0.65 lower to 0.2 higher)
outcome as <sup>2</sup> Events<30 <sup>3</sup> Events<30 <sup>4</sup> N<400	sessor. 10 10 and 95% (	CI crosses both lir	ne of no effect ar	d measure of a	appreciable b	er detail with regard enefit or harm (RR or harm (SMD -0.1	0.75/1		e. participant,	parent, ir	nvestigat	tor, intervention administrator,

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

Li construction de la construction		Q	uality assessr	nent					Summai	y of Findi	ngs
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study eve	ent rates (%)		Anticipate	ed absolute effects
(studies) Follow up	bias				bias	of evidence	With Switch to placebo	With Continued antipscyhotic		Risk with Switch to placebo	Risk difference with Continued antipscyhotic (95% CI)
Relapse	rate afte	r discontinu	ation (assesse	ed with: Numb	er of participa	nts showing >25%	worsening	in ABC-Irritabilit	y and rated	as 'worse/v	ery much worse' on CGI-I)
56 (2 studies)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup>	18/28 (64.3%)	5/28 (17.9%)	<b>RR 0.28</b> (0.12 to	Study pop	pulation
32-33 weeks						due to imprecision	(=,	(	0.64)	643 per 1000	<b>463 fewer per 1000</b> (from 231 fewer to 566 fewer)
										Moderate	
										646 per 1000	<b>465 fewer per 1000</b> (from 233 fewer to 568 fewer)
Time to r	elapse a	after discont	inuation (in	weeks) (n	neasured with:	Time to relapse (i	n weeks); E	Better indicated b	y lower val	ues)	
24 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	12	12	N/A	N/A	The mean time to relapse after discontinuation (in weeks) in the intervention groups was <b>0.97 standard deviations</b>

											higher (0.11 to 1.82 higher)
Irritabilit	<b>ty</b> (measure	d with: Aberrant E	Behaviour Checkl	ist (ABC): Irrita	ability & Agitat	ion; Better indicat	ed by lowe	r values)	<b>!</b>		
24 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>3</sup> due to imprecision	12	12	N/A	N/A	The mean irritability in the intervention groups was <b>0.74 standard deviations</b> <b>Iower</b> (1.58 lower to 0.09 higher)
Letharg	y/Social v	withdrawal (	measured with: A	berrant Behav	/iour Checklist	(ABC): Lethargy	& Social W	/ithdrawal; Be	ter indicated	by lower va	ilues)
24 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊝⊖ LOW <sup>3</sup> due to imprecision	12	12	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was <b>0.58 standard deviations</b> lower (1.4 lower to 0.24 higher)
Stereoty	pic beha	<b>viour</b> (measur	ed with: Aberrant	Behaviour Ch	necklist (ABC):	Stereotypic Beha	aviour; Bett	er indicated b	/ lower value	s)	
24 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>3</sup> due to imprecision	12	12	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0.02 standard deviations</b> <b>lower</b> (0.82 lower to 0.78 higher)
Hyperac	tivity (mea	asured with: Aber	rant Behaviour C	hecklist (ABC)	): Hyperactivity	<ul> <li>&amp; Noncompliand</li> </ul>	e; Better ir	ndicated by low	ver values)		
24 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>3</sup> due to imprecision	12	12	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.23 standard deviations</b> <b>lower</b> (1.03 lower to 0.58 higher)
Inappro	priate sp	eech (measure	d with: Aberrant I	Behaviour Che	ecklist (ABC): I	nappropriate Spe	ech; Bette	r indicated by	ower values)		
24 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊝⊝ LOW <sup>3</sup> due to imprecision	12	12	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>0 standard deviations highe</b>

								(0.8 lower to 0.8 higher)
<sup>1</sup> Events<300 <sup>2</sup> N<400								
	95% CI cros	sses both line of n	o effect and mea	sure of appre	ciable benefit	or harm (SMD -0.5	5/0.5)	

#### Risperidone versus haloperidol for behaviour that challenges as an indirect outcome

		Q	uality assess	nent				Su	mmary of	Finding	s
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall	Study	event rates (%)	Relative	Anticipa	ited absolute effects
studies) <sup>S</sup> ollow up	bias				bias	ovidonco	With Control	With Risperidone versus haloperidol for behaviour that challenges as an indirect outcome	effect (95% CI)	Control	Risk difference with Risperidone versus haloperidol for behaviour that challenges as an indirect outcome (95% Cl)
Behaviou	ur that o	<b>challenges</b> (r	neasured with: A	berrant Behav	viour Checklist	: (ABC): Total; Be	etter indi	cated by lower values)			
8 1 study) 2 weeks		no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	<b>VERY LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	15	13	N/A	N/A	The mean behaviour that challenges in the intervention groups was <b>0.5 standard deviations</b> <b>Iower</b> (1.25 lower to 0.26 higher)

### 1.11.6 Antivirals for behaviour that challenges as a direct outcome

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

		Q	uality assessme	ent			S	Summary o	f Findings	;
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	 	Study eve (%)		effect	Anticipate	d absolute effects
Follow up						With Placebo	With Antivirals		Risk with Placebo	Risk difference with Antivirals (95% CI)

38 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	$\oplus \oplus \ominus \ominus$ LOW <sup>1</sup>	7/19 (36.8%)	9/19 (47.4%)	<b>RR 1.29</b> (0.6 to	Study po	oulation
5 weeks						due to imprecision	(001070)	(,0)	2.74)	368 per 1000	<b>107 more per 1000</b> (from 147 fewer to 641 more)
										Moderate	
										368 per 1000	<b>107 more per 1000</b> (from 147 fewer to 640 more)
Positive	e investigat	or-rated treat	ment respon	Se (assessed	with: 'much impr	oved/very improved' o	n CGI-impi	rovement)			
39 (1 study)	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected		5/20 (25%)	10/19 (52.6%)	<b>RR 2.11</b> (0.88 to	Study po	oulation
5 weeks				Sonedo		due to risk of bias, imprecision	(2070)	(02.070)	5.03)	250 per 1000	<b>277 more per 1000</b> (from 30 fewer to 1000 more)
										Moderate	
										250 per 1000	277 more per 1000 (from 30 fewer to 1000 more)

## 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

		Qı	uality assessi	nent				Sun	nmary of I	Finding	js
Participants		Inconsistency	Indirectness	•		Overall quality	Study	· · ·		Anticip	pated absolute effects
(studies)	bias				bias	of evidence	With	With Combined piracetam	effect	Risk	Risk difference with Combined

Follow up							Control	and risperidone versus combined placebo and risperidone for behaviour that challenges as a direct outcome	(95% CI)	with Control	piracetam and risperidone versus combined placebo and risperidone for behaviour that challenges as a direct outcome (95% Cl)
Behavio	our that	challenges (n	neasured with: A	berrant Behav	viour Checklist	(ABC): Total (Ch	ange Sc	ore); Better indicated by lo	wer values)		
40 (1 study) 10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	20	20	N/A	N/A	The mean behaviour that challenges in the intervention groups was <b>1.93 standard deviations</b> <b>Iower</b> (2.69 to 1.16 lower)
<sup>1</sup> N<400											

## 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

		Qı	uality assessi	ment				Sum	mary of F	inding	\$
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias					quality of evidence	With Control	With Combined	effect (95% CI)	Risk with Control	Risk difference with Combined methylxanthine and antipsychotic versus combined antipsychotic and placebo for behaviour that challenges as a direct outcome (95% Cl)
Irritability	(measure	ed with: Aberrant I	Behaviour Chec	klist (ABC): Irr	itability & Agita	ation; Better indic	ated by	lower values)			
40 (1 study) 10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>		⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	20	20	N/A	N/A	The mean irritability in the intervention groups was <b>1.71 standard deviations</b> lower

							]				(2.44 to 0.97 lower)
Letharg	y & Soci	al Withdraw	<b>val</b> (measured v	with: Aberrant	Behaviour Che	ecklist (ABC): Let	hargy a	& Social Withdrawal;	Better indicated b	y lower va	alues)
40 (1 study) 10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	20	20	N/A	N/A	The mean lethargy & social withdrawal in the intervention groups was <b>1.69 standard deviations</b> <b>lower</b> (2.42 to 0.96 lower)
Stereoty	/pic Beh	aviour (meas	ured with: Aberra	ant Behaviour	Checklist (AB	C): Stereotypic B	ehavio	ur; Better indicated b	y lower values)		
40 (1 study) 10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	20	20	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>1.55 standard deviations</b> lower (2.27 to 0.83 lower)
Hyperac	<b>tivity</b> (me	easured with: Abe	errant Behaviour	Checklist (AE	BC): Hyperactiv	ity & Noncomplia	ince; B	etter indicated by low	wer values)		
40 (1 study) 10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	20	20	N/A	N/A	The mean hyperactivity in the intervention groups was <b>1.14 standard deviations</b> <b>lower</b> (1.81 to 0.47 lower)
Inappro	priate S	<b>peech</b> (measu	red with: Aberra	nt Behaviour C	Checklist (ABC	): Inappropriate S	Speech	; Better indicated by	lower values)		
40 (1 study) 10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	20	20	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>2.1 standard deviations</b> <b>lower</b> (2.89 to 1.31 lower)
<sup>1</sup> N<400		1	1	1	1	1	<u> </u>				

## 1.11.9Opioid antagonists for behaviour that challenges as a direct outcome

Naltrexone versus placebo for behaviour that challenges as a direct outcome

	C	Quality assessm	ient				S	Summary o	f Findings	5
Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality	Study ev	ent rates (%)	Relative	Anticipat	ed absolute effects
				bias	of evidence	With Placebo	With Opioid antagonists	effect (95% CI)	Risk with Placebo	Risk difference with Opioid antagonists (95% CI)
	-	onse for beha	viour that	challenge	S (assessed with:	Dichotomo	us measure of 'r	nuch improv	ed/very imp	roved' on Clinical Globa
	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup>	7/18 (38.9%)	13/23 (56.5%)	<b>RR 1.45</b> (0.74 to	Study po	pulation
					due to imprecision		<b>、</b> ,	2.87)	389 per 1000	<b>175 more per 1000</b> (from 101 fewer to 727 more)
									Moderate	•
									389 per 1000	<b>175 more per 1000</b> (from 101 fewer to 727 more)
r	<b>psitive tre</b> aprovement [C no serious	Risk of bias       Inconsistency         Distive treatment response         Inprovement [CGI-I])         no serious	Risk of bias       Inconsistency       Indirectness         Distive treatment response for behat       Indirectness         Improvement [CGI-I])       Improvement [CGI-I])         no serious       no serious	positive treatment response for behaviour that         nprovement [CGI-I])         no serious       no serious         very	Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias         Desitive treatment response for behaviour that provement [CGI-I])       Response for behaviour that challenge       Construction         no serious       no serious       no serious       very       undetected	Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias       Overall quality of evidence         Desitive treatment response for behaviour that challenges       (assessed with: nprovement [CGI-I])       Imprecision       Imprecision	Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias       Overall quality of evidence       Study evidence         Positive treatment response for behaviour that challenges (assessed with: Dichotomon provement [CGI-I])       no serious inconsistency       no serious indirectness       very serious <sup>1</sup> undetected	Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias       Overall quality of evidence       Study event rates (%)         With       With Opioid antagonists         Positive treatment response for behaviour that challenges (assessed with: Dichotomous measure of 'r provement [CGI-I])       no serious inconsistency       no serious indirectness       very serious <sup>1</sup> undetected       \$	Risk of bias       Inconsistency       Indirectness       Imprecision       Publication bias       Overall quality of evidence       Study event rates (%)       Relative effect (95% Cl)         Desitive treatment response for behaviour that challenges       (assessed with: Dichotomous measure of 'much improvement [CGI-I])       no serious inconsistency       no serious indirectness       very serious <sup>1</sup> undetected	Risk of biasInconsistencyIndirectnessImprecisionPublication biasOverall quality of evidenceStudy event rates (%) With PlaceboRelative effect (95% Cl)Anticipat Risk with Placebopositive treatment response for behaviour that provement [CGI-I])challenges inconsistency(assessed with: Dichotomous measure of 'much improved/very imp serious1moderate undetected7/18 (18.9%)13/23 (56.5%)RR 1.45 (0.74 to 2.87)Study po (0.74 to 2.87)no serious risk of biasno serious inconsistencyno serious indirectnessvery serious1undetected imprecision $\mathcal{P} \oplus \bigcirc \bigcirc$ LOW1 due to imprecision7/18 (18.9%)13/23 (56.5%)RR 1.45 (0.74 to 2.87)Study po 389 per 1000Moderate 389 per

# 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

		Q	uality assessi	ment		Sun	nmary of I	Findings
Participan (studies) Follow up	bias	Inconsistency	Indirectness		 of evidence	With With Selective	effect	Anticipated absolute effects           Risk         Risk difference with Selective           with         noradrenaline reuptake inhibitors

								inhibitors versus placebo for behaviour that challenges as an indirect outcome		Control	versus placebo for behaviour that challenges as an indirect outcome (95% CI)
Irritabili	<b>ty</b> (measure	ed with: Aberrant	Behaviour Chec	klist (ABC): Irr	itability & Agita	ation; Better indic	ated by	v lower values)			
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	46	43	N/A	N/A	The mean irritability in the intervention groups was <b>0.09 standard deviations</b> <b>Iower</b> (0.51 lower to 0.32 higher)
Letharg	y/Social	withdrawal	(measured with:	Aberrant Beh	aviour Checklis	st (ABC): Letharg	y & So	cial Withdrawal; Better indic	ated by lowe	er values	)
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	46	43	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was <b>0.05 standard deviations</b> <b>lower</b> (0.46 lower to 0.37 higher)
Stereoty	pic beh	<b>aviour</b> (measu	red with: Aberra	nt Behaviour (	Checklist (ABC	): Stereotypic Be	haviour	; Better indicated by lower v	values)		•
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	46	43	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0 standard deviations</b> higher (0.42 lower to 0.42 higher)
Hyperac	ctivity (me	easured with: Abe	rrant Behaviour	Checklist (AB	C): Hyperactivi	ty & Noncomplia	nce; Be	tter indicated by lower value	es)		
88 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	45	43	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.19 standard deviations</b> <b>lower</b> (0.61 lower to 0.22 higher)
Inappro	priate sp	<b>Deech</b> (measure	ed with: Aberran	t Behaviour Cl	hecklist (ABC):	Inappropriate Sp	eech;	Better indicated by lower va	lues)		1
89	no	no serious	no serious	very	undetected	$\oplus \oplus \ominus \ominus$	46	43	N/A	N/A	The mean inappropriate

(1 study) 8 weeks	serious risk of bias	inconsistency	indirectness	serious <sup>1</sup>		LOW <sup>1</sup> due to imprecision		speech in the intervention groups was <b>0.22 standard deviations</b> <b>lower</b> (0.64 lower to 0.19 higher)
<sup>1</sup> N<400 and <sup>2</sup> N<400	95% CI cro	osses both line of	no effect and me	easure of appr	eciable benefit	t or harm (SMD -(	0.5/0.5)	

## **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

		Qı	uality assessr	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With         With Thai massage and sensory integration therapy versus sensory integration therapy only for behaviour that challenges as a direct outcome           cales (CTRS): Conduct problem; E	effect (95% CI)	Risk with Control	Risk difference with Thai massage and sensory integration therapy versus sensory integration therapy only for behaviour that challenges as a direct outcome (95% CI)	
Teacher-I	rated be	haviour that	t challenge	S (measured	with: Conners	Teacher Rating S	cales (C	CTRS): Conduct problem; E	Better indica	ated by l	ower values)
60 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	30	30	N/A	N/A	The mean teacher-rated behaviour that challenges in the intervention groups was <b>0.22 standard deviations</b> <b>lower</b> (0.73 lower to 0.28 higher)
Teacher-I	rated be	haviour that	t challenge	S (measured	with: Conners	Teacher Rating S	Scales (C	CTRS): Hyperactivity; Bette	r indicated	by lower	values)
60	no	no serious	no serious	serious <sup>2</sup>	undetected	$\oplus \oplus \oplus \ominus$	30	30	N/A	N/A	The mean teacher-rated

(1 study) 8 weeks	serious risk of bias	inconsistency	indirectness			MODERATE <sup>2</sup> due to imprecision					behaviour that challenges in the intervention groups was <b>0.56 standard deviations</b> <b>lower</b> (1.08 to 0.04 lower)
Teacher	r-rated be	ehaviour tha	t challenge	S (measured	with: Conners	Teacher Rating S	Scales	(CTRS): Inattenti	on-passivity; Better	ndicated	by lower values)
60 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	30	30	N/A	N/A	The mean teacher-rated behaviour that challenges in the intervention groups was <b>0.36 standard deviations</b> <b>lower</b> (0.87 lower to 0.15 higher)
Teacher	-rated b	ehaviour tha	t challenge	S (measured	with: Conners	Teacher Rating	Scales	(CTRS): Hyperac	ctivity index; Better in	dicated b	y lower values)
60 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	30	30	N/A	N/A	The mean teacher-rated behaviour that challenges in the intervention groups was <b>0.4 standard deviations</b> <b>lower</b> (0.91 lower to 0.11 higher)
Parent-r	rated beh	naviour that	challenges	(measured wi	th: Conners P	arent Rating Scal	es (CP	RS): Conduct pro	oblem; Better indicate	ed by low	er values)
60 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	30	30	N/A	N/A	The mean parent-rated behaviour that challenges in the intervention groups was <b>0.1 standard deviations</b> <b>lower</b> (0.61 lower to 0.41 higher)
Parent-r	rated beh	aviour that	challenges	(measured wi	th: Conners P	arent Rating Scal	es (CP	RS): Learning Pr	oblem; Better indicat	ed by lov	ver values)
60 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	30	30	N/A	N/A	The mean parent-rated behaviour that challenges in the intervention groups was <b>0.21 standard deviations</b> <b>lower</b> (0.72 lower to 0.29 higher)

Parent-r	ated beh	aviour that	challenges	(measured w	ith: Conners P	arent Rating Scal	es (CP	RS): Psychosoma	atic; Better indicated	by lower	values)
60 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	30	30	N/A	N/A	The mean parent-rated behaviour that challenges in the intervention groups was <b>0.07 standard deviations</b> <b>higher</b> (0.44 lower to 0.57 higher)
Parent-r	ated beh	aviour that	challenges	(measured w	ith: Conners P	arent Rating Scal	es (CP	PRS): Impulsivity-h	yperactivity; Better	indicated	by lower values)
60 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	30	30	N/A	N/A	The mean parent-rated behaviour that challenges in the intervention groups was <b>0.5 standard deviations</b> <b>lower</b> (1.02 lower to 0.01 higher)
Parent-r	ated beh	aviour that	challenges	(measured w	ith: Conners P	arent Rating Scal	es (CP	PRS): Anxiety; Bet	ter indicated by lowe	er values)	
60 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	30	30	N/A	N/A	The mean parent-rated behaviour that challenges in the intervention groups was <b>0.2 standard deviations</b> <b>lower</b> (0.71 lower to 0.3 higher)
Parent-r	ated beh	aviour that	challenges	(measured w	ith: Conners P	arent Rating Scal	es (CF	RS): Hyperactivity	y; Better indicated b	y lower va	alues)
60 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	30	30	N/A	N/A	The mean parent-rated behaviour that challenges in the intervention groups was <b>0.24 standard deviations</b> <b>lower</b> (0.75 lower to 0.27 higher)
Parent-r	ated slee	ep-related p	roblems (me	easured with: S	Sleep Diary (SI	D): Sleep behavio	ur; Bet	ter indicated by lo	ower values)		
60 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>2,3</sup> due to risk of bias,	30	30	N/A	N/A	The mean parent-rated sleep-related problems in the intervention groups was <b>0.53 standard deviations</b>

				imprecision				lower (1.04 to 0.01 lower)
<sup>2</sup> N<400	performanc	sses both line of n		, ,	.5/0.5) lind, and high risk of detection bias	as outcome	measu	re parent-rated and parents

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

		Q	uality assess	sment				Sumi	mary of F	inding	S
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias					quality of evidence	With Control	With Acupuncture/Electro- acupuncture versus sham acupuncture/electro- acupuncture for behaviour that challenges as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Acupuncture/Electro-acupuncture versus sham acupuncture/electro- acupuncture for behaviour that challenges as an indirect outcome (95% Cl)
Irritability	<b>y</b> (measu	red with: Aberran	t Behaviour Ch	ecklist (ABC):	Irritability & Agi	tation; Better in	dicated	by lower values)			
55 (1 study) 4 weeks	no serious risk of bias		no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	<b>VERY LOW</b> <sup>1,2</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean irritability in the intervention groups was <b>0.18 standard deviations</b> <b>higher</b> (0.36 lower to 0.71 higher)
Lethargy	/Social	l withdrawa	(measured wit	h: Aberrant Be	ehaviour Check	list (ABC): Leth	argy & S	Social Withdrawal; Better indica	ated by lov	ver value	es)
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>		⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was <b>0.02 standard deviations</b> <b>Iower</b> (0.56 lower to 0.51 higher)
Stereoty	pic beh	naviour (meas	ured with: Aber	rant Behaviou	r Checklist (AB	C): Stereotypic	Behavio	our; Better indicated by lower v	alues)		
55 (1 study)		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly	⊕⊖⊝⊖ VERY LOW <sup>1,2</sup>	25	30	N/A	N/A	The mean stereotypic behaviour in the intervention

4 weeks	risk of bias				suspected <sup>2</sup>	due to imprecision, publication bias					groups was <b>0.05 standard deviations higher</b> (0.48 lower to 0.58 higher)
Hyperac	<b>tivity</b> (m	easured with: At	errant Behavio	ur Checklist (/	ABC): Hyperacti	vity & Noncomp	liance;	Better indicated by	lower values)		
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.01 standard deviations</b> <b>Iower</b> (0.54 lower to 0.52 higher)
Inappro	priate s	<b>peech</b> (measu	red with: Aberr	ant Behaviou	Checklist (ABC	): Inappropriate	Speed	h; Better indicated	by lower values)		-
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>0.14 standard deviations</b> <b>lower</b> (0.68 lower to 0.39 higher)

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

		Qua	ality assessr	nent				Sumn	nary of F	inding	s
(studies) Follow up	bias	Inconsistency			bias	With Control	With Acupuncture/electro- acupuncture and conventional educational programme versus conventional educational programme only for behaviour that challenges as an indirect outcome	effect (95% CI)	Risk with	Risk difference with Acupuncture/electro-acupuncture and conventional educational programme versus conventional educational programme only for behaviour that challenges as an indirect outcome (95% Cl)	
Behaviou	Ir that	challenges	measured with	: Aberrant Be	haviour Chec	klist (ABC): To	otal; Bet	ter indicated by lower values)			

36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean behaviour that challenges in the intervention groups was <b>0.3 standard deviations higher</b> (0.36 lower to 0.95 higher)
Irritabilit	<b>ty</b> (measu	red with: Aberrar	it Behaviour Ch	necklist (ABC):	Irritability (Cl	nange Score);	Better in	ndicated by lower values)			
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean irritability in the intervention groups was <b>0.42 standard deviations</b> <b>higher</b> (0.24 lower to 1.08 higher)
Lethargy	y/Socia	l withdrawa	(measured wi	th: Aberrant B	ehaviour Che	cklist (ABC): L	ethargy	(Change Score); Better indicat	ed by lowe	values	
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was <b>0.23 standard deviations</b> higher (0.42 lower to 0.89 higher)
Stereoty	vpic beł	naviour (meas	sured with: Abe	rrant Behaviou	ur Checklist (A	ABC): Stereoty	py (Cha	nge Score); Better indicated by	lower valu	es)	
36 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY	18	18	N/A	N/A	The mean stereotypic behaviour in the intervention groups was
8 weeks						LOW <sup>1,2</sup> due to risk of bias, imprecision					0.29 standard deviations higher (0.37 lower to 0.94 higher)
8 weeks	tivity (m		perrant Behavio	ur Checklist (/	ABC): Hypera	LOW <sup>1,2</sup> due to risk of bias, imprecision	e Score)	; Better indicated by lower valu	les)		0.29 standard deviations higher
8 weeks	serious <sup>1</sup>		perrant Behavio no serious indirectness	very serious <sup>2</sup>	ABC): Hypera	LOW <sup>1,2</sup> due to risk of bias, imprecision	e Score)	; Better indicated by lower valu	nes) N/A	N/A	0.29 standard deviations higher
8 weeks Hyperac 36 (1 study) 8 weeks	serious <sup>1</sup>	neasured with: At no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	LOW <sup>1,2</sup> due to risk of bias, imprecision ctivity (Change <b>VERY</b> LOW <sup>1,2</sup> due to risk of bias, imprecision	18		N/A		0.29 standard deviations higher         (0.37 lower to 0.94 higher)         The mean hyperactivity in the intervention groups was         0.06 standard deviations lower         (0.72 lower to 0.59 higher)

(1 study) 8 weeks		inconsistency	indirectness	serious <sup>2</sup>	bias,	<sup>1,2</sup> o risk of			in the intervention groups was <b>0.58 standard deviations</b> <b>higher</b> (0.09 lower to 1.25 higher)
differed for ea involved inpu measures rel	ach partic it from pa ied on no	ipant which may rents who were n n-blind parental r	introduce bias. ot blind to treat eport	There was als ment allocation	o an unclear risk of	f detectio ariables a	e non-blind and potential for care confound n bias as although all outcomes were m and systematic review from which data w SMD -0.5/0.5)	easured by blir	nded assessors, some outcomes

## **1.12.2**Hormones for behaviour that challenges as an indirect outcome

#### Secretin versus placebo for behaviour that challenges as an indirect outcome

		Q	uality assessr	nent				Su	immary of	Finding	gs
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study e	event rates (%)	Relative	Anticipa	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Secretin versus placebo for behaviour that challenges as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Secretin versus placebo for behaviour that challenges as an indirect outcome (95% Cl)
Behaviou	ir that c	hallenges (P	arent-rated)	(measured w	ith: Aberrant E	Sehaviour Checklis	t (ABC):	Total (change score); E	Better indica	ted by lov	wer values)
77 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	29	48	N/A	N/A	The mean behaviour that challenges (parent-rated) in the intervention groups was <b>0.13 standard deviations</b> <b>lower</b> (0.59 lower to 0.33 higher)
Behaviou	ir that c	hallenges (To	eacher-rate	<b>d)</b> (measured	with: Aberran	t Behaviour Check	dist (ABC	): Total (change score)	; Better ind	cated by	lower values)
65 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	26	39	N/A	N/A	The mean behaviour that challenges (teacher-rated) in the intervention groups was <b>0.51 standard deviations</b> higher

											(0 to 1.01 higher)
Irritabilit	y (Parer	nt-rated) (meas	sured with: Aberr	ant Behaviour	Checklist (ABC	C): Irritability & Ag	itation (e	endpoint and cha	ange scores); Bett	er indicate	ed by lower values)
133 (2 studies) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	57	76	N/A	N/A	The mean irritability (parent rated) in the intervention groups was <b>0.11 standard deviations</b> <b>lower</b> (0.45 lower to 0.24 higher)
Irritabilit	y (Teacl	her-rated) (me	easured with: Abe	errant Behavio	our Checklist (A	BC): Irritability & A	Agitation	(change scores	;); Better indicated	by lower	values)
65 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	26	39	N/A	N/A	The mean irritability (teacher-rated) in the intervention groups was <b>0.2 standard deviations</b> higher (0.3 lower to 0.69 higher)
Lethargy	/ (Paren	<b>t-rated)</b> (meas	ured with: Aberra	Int Behaviour (	Checklist (ABC)	): Lethargy & Soci	al Witho	drawal (endpoint	and change score	es); Better	indicated by lower values)
133 (2 studies) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigoplus \bigoplus \\ \textbf{MODERATE}^2 \\ \text{due to} \\ \text{imprecision} \end{array}$	57	76	N/A	N/A	The mean lethargy (parent- rated) in the intervention groups was 0.11 standard deviations higher (0.24 lower to 0.46 higher)
Lethargy lower values	-	er-rated por	cine secreti	i <b>n)</b> (measured	d with: Aberrant	Behaviour Check	dist (AB	C): Lethargy & S	Social Withdrawal	(change s	cores); Better indicated by
48 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	26	22	N/A	N/A	The mean lethargy (teacher rated porcine secretin) in the intervention groups was <b>0.74 standard deviations</b> higher (0.15 to 1.33 higher)

43 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	26	17	N/A	N/A	The mean lethargy (teacher- rated synthetic porcine secretin) in the intervention groups was <b>0.05 standard deviations</b> higher (0.56 lower to 0.67 higher)
Stereoty values)	pic beh	aviour (Pare	nt-rated) (me	asured with:	Aberrant Behav	iour Checklist (AB	C): Ster	eotypic Behavic	our (endpoint and c	hange sco	Dres); Better indicated by lower
133 (2 studies) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	57	76	N/A	N/A	The mean stereotypic behaviour (parent-rated) in the intervention groups was <b>0.1 standard deviations</b> <b>higher</b> (0.25 lower to 0.45 higher)
Stereoty	pic beh	aviour (Teac	<b>her-rated)</b> (r	neasured with	h: Aberrant Beh	aviour Checklist (A	ABC): St	ereotypic Beha	viour (change scor	es); Bette	r indicated by lower values)
65 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	26	39	N/A	N/A	The mean stereotypic behaviour (teacher-rated) in the intervention groups was <b>0.33 standard deviations</b> higher (0.17 lower to 0.82 higher)
Hyperac values)	tivity (P	arent-rated)	(measured with:	Aberrant Beh	aviour Checklis	t (ABC): Hyperacti	vity & N	oncompliance (	endpoint and chan	ge scores	); Better indicated by lower
133 (2 studies) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	57	76	N/A	N/A	The mean hyperactivity (parent-rated) in the intervention groups was <b>0.01 standard deviations</b> <b>lower</b> (0.36 lower to 0.34 higher)
Hyperac	tivity (T	eacher-rated	) (measured with	n: Aberrant B	ehaviour Check	list (ABC): Hypera	ctivity &	Noncompliance	e (change scores);	Better ind	licated by lower values)
65 (1 study) 4 weeks	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to	26	39	N/A	N/A	The mean hyperactivity (teacher-rated) in the intervention groups was

	bias					imprecision					<b>0.53 standard deviations</b> <b>higher</b> (0.03 to 1.04 higher)
Inapprop values)	priate sp	beech (Paren	<b>it-rated)</b> (mea	asured with: A	berrant Behavio	our Checklist (ABC	c): Inapp	propriate Speec	h (endpoint and ch	ange scor	es); Better indicated by lower
131 (2 studies) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	55	76	N/A	N/A	The mean inappropriate speech (parent-rated) in the intervention groups was <b>0.39 standard deviations</b> <b>lower</b> (0.75 to 0.04 lower)
Inapprop 65 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	ner-rated) (m no serious indirectness	very serious <sup>1</sup>	Aberrant Beha	viour Checklist (A ⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	BC): Ina	appropriate Spe	ech (change scores	s); Better i	ndicated by lower values) The mean inappropriate speech (teacher-rated) in the intervention groups was 0.28 standard deviations higher (0.22 lower to 0.78 higher)

## 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

			Quality assessment				Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness		Overall quality of evidence	Study event rates (%)		Relative effect	Anticipated	absolute effects		
Follow up							With Attention- placebo	With Hyperbaric oxygen treatment	- (95% CI)	Risk with Attention- placebo	Risk difference with Hyperbaric oxygen treatment (HBOT) (95% CI)	

							control	(HBOT)		control	
Behavic by lower val		challenges	(measured with	n: Aberrant Be	haviour Checklis	t (ABC): Total or Beha	avioural obs	servation: Chal	lenging beha	viours (chang	ge score); Better indicated
90 (2 studies) 4-15 weeks	no serious risk of bias	serious <sup>1</sup>	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to inconsistency, imprecision, publication bias	42	48	N/A	N/A	The mean behaviour that challenges in the intervention groups was <b>0.17 standard</b> <b>deviations lower</b> (0.59 lower to 0.24 higher)
Behavio	our that	challenges	s (direct ou	utcome) (r	measured with: A	berrant Behaviour Ch	necklist (AB	C): Total; Bette	er indicated b	y lower value	s)
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	26	30	N/A	N/A	The mean behaviour that challenges (direct outcome) in the intervention groups was <b>0.04 standard</b> <b>deviations higher</b> (0.48 lower to 0.57 higher)
Behavic values)	our that	challenges	(indirect	outcome	) (measured with	n: Behavioural observ	ation: Chall	enging behavio	ours (change	score); Bette	r indicated by lower
34 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to imprecision, publication bias	16	18	N/A	N/A	The mean behaviour that challenges (indirect outcome) in the intervention groups was <b>0.54 standard</b> <b>deviations lower</b> (1.23 lower to 0.15 higher)

Irritabili	<b>ty</b> (measu	red with: Aberran	t Behaviour Che	cklist (ABC):	Irritability; Better	indicated by lower valu	ues)				
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	26	30	N/A	N/A	The mean irritability in the intervention groups was <b>0.11 standard</b> <b>deviations lower</b> (0.64 lower to 0.41 higher)
Letharg	y/Socia	al withdraw	al (measured w	vith: Aberrant	Behaviour Check	list (ABC): Lethargy; E	Better ind	licated by lowe	r values)		
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	26	30	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was <b>0.06 standard</b> <b>deviations higher</b> (0.46 lower to 0.59 higher)
Stereoty	<b>ypy</b> (mea	sured with: Aberra	ant Behaviour C	hecklist (ABC	:): Stereotypy; Be	tter indicated by lower	values)				
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	26	30	N/A	N/A	The mean stereotypy in the intervention groups was <b>0.17 standard</b> <b>deviations higher</b> (0.36 lower to 0.7 higher
Hyperac	ctivity (n	neasured with: Al	Derrant Behaviou	ır Checklist (A	ABC): Hyperactivi	ty or Behavioural obse	ervation: I	Hyperactivity (	change score)	; Better indi	cated by lower values)
90 (2 studies) 4-15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊕⊖⊖ LOW <sup>3,4</sup> due to imprecision, publication bias	42	48	N/A	N/A	The mean hyperactivity in the intervention groups was 0.06 standard deviations higher

										(0.36 lower to 0.47 higher)
ctivity (	direct outc	ome) (measu	red with: Abe	rrant Behaviour C	hecklist (ABC): Hyper	activity; E	Better indicate	d by lower valu	ies)	
no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	26	30	N/A	N/A	The mean hyperactivity (direct outcome) in the intervention groups was <b>0.12 standard</b> <b>deviations higher</b> (0.41 lower to 0.64 higher)
ctivity (	indirect ou	tcome) (mea	asured with: E	Behavioural obser	vation: Hyperactivity (	change s	core); Better ir	dicated by lov	ver values)	
no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to imprecision, publication bias	16	18	N/A	N/A	The mean hyperactivity (indirect outcome) in the intervention groups was <b>0.04 standard</b> <b>deviations lower</b> (0.72 lower to 0.63 higher)
opriate s	speech (meas	sured with: Aber	rant Behaviou	r Checklist (ABC)	I Inappropriate Speec	h; Better	indicated by lo	ower values)		
no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	26	30	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>0.24 standard</b> <b>deviations lower</b> (0.77 lower to 0.28 higher)
	no serious risk of bias ctivity ( no serious risk of bias priate s no serious risk of	no serious risk of bias       no serious inconsistency         ctivity (indirect ou         no serious risk of bias         no serious risk of bias         no serious risk of bias         no serious risk of bias         no serious risk of bias         no serious risk of bias         no serious risk of         no serious risk of         no serious risk of	no serious risk of biasno serious inconsistencyno serious indirectnessctivity (indirect outcome) (mean serious risk of biasno serious inconsistencyno serious indirectnessno serious risk of biasno serious inconsistencyno serious indirectnessno serious risk of biasno serious inconsistencyno serious indirectnessno serious risk of biasno serious inconsistencyno serious indirectnessno serious risk ofno serious inconsistencyno serious indirectness	no serious risk of biasno serious inconsistencyno serious indirectnessvery serious²ctivity (indirect outcome) serious risk of biasno serious inconsistencyno serious indirectnessvery serious²no serious risk of biasno serious inconsistencyno serious indirectnessvery serious²no serious risk of biasno serious inconsistencyno serious indirectnessvery serious²opriate speech serious risk of inconsistencyno serious indirectnessvery serious²no serious risk ofno serious inconsistencyno serious indirectnessvery serious²	no serious risk of biasno serious inconsistencyno serious indirectnessvery serious²undetectedctivity (indirect outcome) (indirect outcome) (measured with: Behavioural obsending inconsistencyno serious indirectnessvery serious²reporting bias strongly suspected 3no serious risk of biasno serious inconsistencyno serious indirectnessvery serious²reporting bias strongly suspected 3priate speech (measured with: Aberrant Behaviour Checklist (ABC)no serious inconsistencyno serious indirectnessvery serious²undetected	no serious risk of bias       no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision         ctivity (indirect outcome) (measured with: Behavioural observation: Hyperactivity (measured with: Aberrant Behaviour Checklist (ABC): Inappropriate Speece         no serious risk of       no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊕⊝⊖ LOW <sup>2</sup> due to imprecision	no serious risk of bias       no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊕⊖⊖ LOW <sup>2</sup> due to imprecision       26         ctivity (indirect outcome) (measured with: Behavioural observation: Hyperactivity (change s inconsistency       no serious indirectness       reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to imprecision, publication bias       16         priate speech (measured with: Aberrant Behaviour Checklist (ABC): Inappropriate Speech; Better inconsistency serious       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊕⊖⊖ UOW <sup>2,3</sup> due to imprecision, publication bias       26	no serious risk of bias       no serious inconsistency bias       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊕⊖⊖ LOW <sup>2</sup> due to imprecision       26       30         ctivity (indirect outcome) (measured with: Behavioural observation: Hyperactivity (change score); Better in serious risk of bias       no serious inconsistency       no serious indirectness       very serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to imprecision, publication bias       16       18         opriate speech (measured with: Aberrant Behaviour Checklist (ABC): Inappropriate Speech; Better indicated by low serious risk of inconsistency risk of       no serious indirectness       very very serious <sup>2</sup> undetected       ⊕⊕⊖⊖ LOW <sup>2</sup> due to imprecision       26       30	no serious risk of bias       no serious inconsistency indirectness       no serious very serious <sup>2</sup> undetected undetected       ⊕⊕⊖⊖ LOW <sup>2</sup> due to imprecision       26       30       N/A         ctivity (indirect outcome) (measured with: Behavioural observation: Hyperactivity (change score); Better indicated by low serious risk of bias       no serious inconsistency       no serious indirectness       very serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>2.3</sup> due to imprecision, publication bias       16       18       N/A         opriate speech (measured with: Aberrant Behaviour Checklist (ABC): Inappropriate Speech; Better indicated by lower values)       no serious inconsistency indirectness       no serious very serious <sup>2</sup> Undetected ⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision       26       30       N/A	serious risk of bias       inconsistency       indirectness       serious <sup>2</sup> LOW <sup>2</sup> due to imprecision       LOW <sup>2</sup> due to imprecision         ctivity (indirect outcome) (measured with: Behavioural observation: Hyperactivity (change score); Better indicated by lower values)         no serious risk of bias       no serious inconsistency       no serious indirectness       very serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to imprecision, publication bias       16       18       N/A       N/A         priate speech (measured with: Aberrant Behaviour Checklist (ABC):       Inappropriate Speech; Better indicated by lower values)         no serious risk of       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊕⊙⊝ LOW <sup>2</sup> due to imprecision, publication bias       26       30       N/A       N/A

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

		Qu	ality assessn	nent				Sumr	nary of F	indings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event	rates (%)	Relative effect	Anticipated a	bsolute effects
Follow up						evidence	With Short- term chelation (1-round of DMSA therapy and 6-rounds of placebo)	With Long-term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy)	(95% CI)	Risk with Short-term chelation (1- round of DMSA therapy and 6- rounds of placebo)	Risk difference with Long- term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy) (95% CI)
Maladap			Composite	e (measured v	with: Pervasive	e Developmen	t Disorder Beh	avior Inventory (PDDBI):	Maladapti	ve Behaviours (	Composite; Better
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	25	N/A	N/A	The mean maladaptive behaviours composite in the intervention groups was <b>0.17 standard</b> <b>deviations higher</b> (0.47 lower to 0.81 higher)
Arousal values)	Regul	ation Probl	ems (measu	red with: Perva	asive Develop	nent Disorder	Behavior Inve	ntory (PDDBI): Arousal F	Regulation	Problems; Bette	er indicated by lower
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	15	25	N/A	N/A	The mean arousal regulation problems in the intervention groups was <b>0.2 standard</b> <b>deviations higher</b> (0.44 lower to 0.85

											higher)
Aggress	sivenes	SS (measured w	ith: Pervasive D	evelopment D	isorder Behavi	ior Inventory (F	PDDBI): Ag	gressiveness; Be	tter indicated by lo	wer values)	
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>		⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	15	25	N/A	N/A	The mean aggressiveness in the intervention groups was <b>0.2 standard</b> <b>deviations higher</b> (0.44 lower to 0.84 higher)

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

		Q	uality assessm	ent					Summa	ary of Fin	dings
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e <sup>v</sup> (%)	vent rates	Relative effect	Anticipat	ed absolute effects
Follow up							With Placebo	With Omega- 3 fatty acids	(95% CI)	Risk with Placebo	Risk difference with Omega-3 fatty acids (95% Cl)
Irritability	(measured	with: Aberrant Beha	aviour Checklist (A	BC): Irritability	& Agitation; B	etter indicated by I	ower valu	ies)			
24 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	12	12	N/A	N/A	The mean irritability in the intervention groups was <b>0.09 standard deviations</b> <b>lower</b> (0.89 lower to 0.71 higher)
Lethargy	/Social w	ithdrawal (mea	sured with: Aberra	ant Behaviour	Checklist (ABC	c): Lethargy & Soci	al Withdra	awal; Better ir	ndicated by I	ower value	s)
24 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to	12	12	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was

						imprecision					<b>0.28 standard deviations</b> <b>lower</b> (1.09 lower to 0.52 higher)
Stereoty	pic behav	iour (measured	with: Aberrant Be	haviour Chec	klist (ABC): Ster	eotypic Behaviou	r; Better i	ndicated by	lower values	5)	
24 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	12	12	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0.81 standard deviations</b> <b>lower</b> (1.65 lower to 0.03 higher)
Hyperac	tivity (meas	sured with: Aberran	nt Behaviour Chec	klist (ABC): H	yperactivity & N	oncompliance; Be	etter indic	ated by low	ver values)		
24 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1</sup> due to imprecision	12	12	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.42 standard deviations</b> <b>lower</b> (1.23 lower to 0.39 higher)
Inappro	priate spe	<b>ech</b> (measured v	with: Aberrant Beh	aviour Check	list (ABC): Inapp	ropriate Speech;	Better inc	licated by l	ower values)	<b>I</b>	
24 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	12	12	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>0.68 standard deviations</b> <b>lower</b> (1.51 lower to 0.14 higher)
External	lizing (meas	ured with: Behavio	or Assessment Sy	stem for Child	Iren (BASC): Ext	ternalizing; Better	indicated	l by lower v	alues)		
24 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	12	12	N/A	N/A	The mean externalizing in the intervention groups was <b>0.44 standard deviations</b> <b>lower</b> (1.25 lower to 0.37 higher)
Behavio	oural symp	toms (measure	d with: Behavior A	ssessment S	ystem for Childr	en (BASC): Beha	vioral syn	nptoms; Be	tter indicated	by lower va	lues)
23 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup>	11	12	N/A	N/A	The mean behavioural symptoms in the intervention

12 weeks						due to imprecision					groups was 0.24 standard deviations lower (1.06 lower to 0.58 higher)
Hyperac 24 (1 study) 12 weeks	no serious	no serious inconsistency	or Assessment Sy no serious indirectness	vstem for Child very serious <sup>1</sup>	ren (BASC): Hy	eractivity; Better ⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	r indicate	d by lower v 12	values)	N/A	The mean hyperactivity in the intervention groups was 0.19 standard deviations lower

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

		Q	uality assessr	nent					Summ	ary of Find	lings
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study ever (%)	nt rates	Relative effect	Anticipated	absolute effects
Follow up							With Healthy diet control	With Omega-3 fatty acids	(95% CI)	Risk with Healthy diet control	Risk difference with Omega-3 fatty acids (95% CI)
Total pro	blem se	CORE (measured v	vith: Child Behavi	or Checklist 1.	5 - 5 (CBCL/1.	5-5): Total probler	n score; Bet	ter indicated	l by lower va	alues)	
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean total problem score in the intervention groups was <b>0.17 standard deviations</b> <b>Iower</b> (0.99 lower to 0.66 higher)
Externali	<b>zing</b> (me	asured with: Child	Behavior Checklis	st 1.5 - 5 (CBC	L/1.5-5): Exter	nalizing; Better ind	dicated by lo	ower values)			
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean externalizing in the intervention groups was <b>0.1 standard deviations lower</b> (0.92 lower to 0.73 higher)

23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean emotional regulation in the intervention groups was <b>0.09 standard deviations</b> <b>lower</b> (0.92 lower to 0.73 higher)
Withdra	<b>wn</b> (measu	ured with: Child Be	ehavior Checklist	1.5 - 5 (CBCL	(1.5-5): Withdra	wn; Better indicate	ed by low	er values)			
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean withdrawn in the intervention groups was <b>0.81 standard deviations</b> <b>lower</b> (1.67 lower to 0.05 higher)
Attentio	n proble	ms (measured v	with: Child Behavi	or Checklist 1	5 - 5 (CBCL/1.	5-5): Attention prol	blems; Be	etter indicate	d by lower v	alues)	
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean attention problems in the intervention groups was <b>0.53 standard deviations</b> <b>lower</b> (1.37 lower to 0.31 higher)
Aggress	sive beh	aviours (meas	ured with: Child E	ehavior Checl	klist 1.5 - 5 (CB	L CL/1.5-5): Aggress	sive beha	viours; Bette	er indicated I	by lower valu	es)
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean aggressive behaviours in the intervention groups was <b>0 standard deviations higher</b> (0.83 lower to 0.82 higher)
Opposit	ional De	fiant Disord	er (ODD) sy	mptoms (r	neasured with:	Child Behavior Ch	ecklist 1.	5 - 5 (CBCL	/1.5-5): ODD	; Better indic	ated by lower values)
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean oppositional defiant disorder (odd) symptoms in the intervention groups was <b>0.04 standard deviations</b> <b>lower</b> (0.87 lower to 0.78 higher)

measure was not blinded.  $^{2}$  N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

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

		Qı	ality assessn	nent				S	ummary o	of Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study event r	ates (%)	Relative	Anticipated a	absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Combined placebo and risperidone	With Combined ginkgo biloba and risperidone	effect (95% CI)	Risk with Combined placebo and risperidone	Risk difference with Combined ginkgo biloba and risperidone (95% Cl)
Irritability	(measure	d with: Aberrant B	ehaviour Checkl	ist (ABC): Irrita	ability & Agitati	on; Better indica	ated by lower va	lues)			
47 (1 study) 10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	24	23	N/A	N/A	The mean irritability in the intervention groups was <b>0.1 standard</b> <b>deviations higher</b> (0.47 lower to 0.67 higher)
Lethargy/	/Social	Withdrawal (	measured with: A	Aberrant Behav	viour Checklist	(ABC): Letharg	y & Social With	drawal; Better inc	licated by lo	ower values)	
47 (1 study) 10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	24	23	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was <b>0.08 standard</b> <b>deviations lower</b> (0.65 lower to 0.49 higher)
Stereotyp	oic Beha	<b>aviour</b> (measure	ed with: Aberran	t Behaviour Ch	necklist (ABC):	Stereotypic Bel	haviour; Better i	ndicated by lowe	r values)	J	-
47 (1 study) 10 weeks	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to	24	23	N/A	N/A	The mean stereotypic behaviour in the intervention groups

	bias					imprecision					was 0.02 standard deviations lower (0.59 lower to 0.55 higher)
Hyperact	<b>tivity</b> (me	asured with: Aberr	ant Behaviour C	hecklist (ABC	): Hyperactivity	& Noncompliar	nce; Better in	dicated by lower val	ues)		
47 (1 study) 10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	24	23	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.22 standard</b> <b>deviations higher</b> (0.35 lower to 0.8 higher)
Inapprop	oriate Sp	eech (measure	d with: Aberrant	Behaviour Ch	ecklist (ABC): I	Inappropriate Sp	eech; Better	indicated by lower	values)		
47 (1 study) 10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	24	23	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>0.21 standard</b> <b>deviations lower</b> (0.79 lower to 0.36 higher)

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

			Quality assess	sment			Su	mmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision	Overall quality of	Study ev	vent rates (%)	Relative	Anticipat	ted absolute effects
(studies) Follow up	bias					With Placebo	With Dimethylglycine	effect (95% CI)	Risk with Placebo	Risk difference with Dimethylglycine (95% Cl)
Positive t	reatmen	t response (as	sessed with: Pare	ental report)				-		

38 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	-	reporting bias strongly		10/19 (52.6%)	11/19 (57.9%)	<b>RR 1.1</b> (0.62 to	Study po	pulation
4 weeks					suspected <sup>2</sup>	due to imprecision, publication bias	(02.070)	(01.070)	1.95)	526 per 1000 Moderate	53 more per 1000 (from 200 fewer to 500 more)
										526 per 1000	<b>53 more per 1000</b> (from 200 fewer to 500 more)
<sup>2</sup> High risk of	selective rep	orting bias as data	could not be extra	icted for the Ab	errant Behavior C	arm (RR 0.75/1.25) hecklist (Irritability, L Behavior Scale and					

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

l.		Q	uality assessn	nent				S	Summary	of Findin	igs
Participants	Risk of	Inconsistency	Indirectness	hiss of ovidence	vent rates (%)	Relative	Anticipa	ted absolute effects			
(studies) Follow up	bias				bias	of evidence	With Placebo	With Multivitamin and mineral supplement	effect (95% CI)	Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% Cl)
Hyperact	ivity imp	provement (me	easured with: Pare	ent Global Imp	pressions-Revi	sed (PGI-R): Hype	ractivity ir	nprovement; Better	indicated b	y lower va	lues)
104 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	51	53	N/A	N/A	The mean hyperactivity improvement in the intervention groups was <b>0.6 standard deviations</b> higher (0.2 to 0.99 higher)
Tantrum	ming imp	provement (me	easured with: Par	ent Global Im	oressions-Rev	ised (PGI-R): Tantr	umming i	mprovement; Bette	r indicated b	by lower va	alues)
104 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	51	53	N/A	N/A	The mean tantrumming improvement in the intervention groups was 0.52 standard deviations higher

					(0.13 to 0.91 higher)
<sup>1</sup> N<400					

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

			Quality asses	sment				Sun	nmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study ev	vent rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Placebo	With Immunoglobulin (dosages combined)	effect (95% CI)	Risk with Placebo	Risk difference with Immunoglobulin (dosages combined) (95% Cl)
Positive of	clinician	-rated treatn	nent respon	Se (assessed	with: Dichtomous	measure of 'much	n improved	d/very improved' on C	linical Glob	al Impress	ion-Improvement (CGI-I))
111 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	reporting bias strongly	⊕⊕⊝⊖ LOW <sup>1,2</sup>	11/28 (39.3%)	17/83 (20.5%)	<b>RR 0.52</b> (0.28 to	Study po	opulation
12 weeks	bias				suspected <sup>2</sup>	due to imprecision, publication bias		、 <i>,</i>	0.97)	393 per 1000	<b>189 fewer per 1000</b> (from 12 fewer to 283 fewer)
										Moderat	e
										393 per 1000	<b>189 fewer per 1000</b> (from 12 fewer to 283 fewer)
Positive p	parent-ra	ated treatme	nt response	e (assessed wi	th: Dichotomous r	l neasure of 'much i	mproved/\	very improved' on Pa	rent Global	Impression	-Improvement (PGI-I))
112 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	reporting bias strongly		16/29 (55.2%)	25/83 (30.1%)	<b>RR 0.55</b> (0.34 to	Study po	opulation
12 weeks	bias	meensisteney			suspected <sup>2</sup>	due to imprecision, publication bias	(00.270)	(00.176)	0.87)	552 per 1000	248 fewer per 1000 (from 72 fewer to 364 fewer)
										Moderat	e
									-	552 per 1000	<b>248 fewer per 1000</b> (from 72 fewer to 364

							fewer)
<sup>1</sup> Events<300 <sup>2</sup> High risk of s	porting bias as con	tinuous data cou	ld not be extra	cted for the CGI-I	or PGI-I scale		

### **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

		Q	uality assessr	nent				S	ummary	of Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study event ra	tes (%)	Relative	Anticipated abs	solute effects
(studies) Follow up	bias				bias	of evidence	With Attention- placebo (structured listening) control	With Auditory integration training	effect (95% CI)	Risk with Attention-placebo (structured listening) control	Risk difference with Auditory integration training (95% Cl)
Parent-ra	ted beh	aviour that o	challenges	(measured wit	h: Developmer	ntal Behaviour Ch	ecklist (DBC): To	otal; Better indi	cated by lo	wer values)	
80 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean parent- rated behaviour that challenges in the intervention groups was <b>0.06 standard</b> <b>deviations higher</b> (0.38 lower to 0.5 higher)
Parent-ra	ted beh	aviour that o	challenges	(measured wit	h: Developmer	ntal Behaviour Ch	ecklist (DBC): To	otal; Better indi	cated by lo	wer values)	
80 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean parent- rated behaviour that challenges in the intervention groups was 0.2 standard deviations higher

											(0.24 lower to 0.64 higher)
Parent-r	ated bel	naviour that	challenges	(measured wi	th: Developme	ntal Behaviour C	Checklist (DB	C): Total; Better	indicated by	lower values)	
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean parent- rated behaviour that challenges in the intervention groups was <b>0.26 standard</b> <b>deviations higher</b> (0.18 lower to 0.7 higher)
Parent-r	ated bel	naviour that	challenges	(measured wi	th: Developme	ntal Behaviour C	Checklist (DB	C): Total; Better	indicated by	lower values)	
80 (1 study) 56 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean parent- rated behaviour that challenges in the intervention groups was <b>0.24 standard</b> <b>deviations higher</b> (0.2 lower to 0.68 higher)
Teacher	-rated b	ehaviour tha	t challenge	S (measured	with: Developr	mental Behaviou	r Checklist (D	BC): Total; Bett	er indicated b	y lower values	)
80 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean teacher- rated behaviour that challenges in the intervention groups was <b>0.16 standard</b> <b>deviations lower</b> (0.6 lower to 0.28 higher)
Teacher	-rated b	ehaviour tha	t challenge	S (measured	with: Developr	nental Behaviou	r Checklist (D	BC): Total; Bett	er indicated b	y lower values	)
80	no	no serious	no serious	very	undetected	$\oplus \oplus \ominus \ominus$	40	40	N/A	N/A	The mean teacher-

(1 study) 13 weeks Teacher	serious risk of bias	ehaviour tha	indirectness at challenge	serious <sup>1</sup>	with: Developn	LOW <sup>1</sup> due to imprecision nental Behaviour	Checklist (DB	SC): Total; Bett	er indicated b	y lower value	rated behaviour that challenges in the intervention groups was <b>0.15 standard</b> <b>deviations lower</b> (0.59 lower to 0.29 higher) s)
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	40	40	N/A	N/A	The mean teacher- rated behaviour that challenges in the intervention groups was <b>0.04 standard</b> <b>deviations lower</b> (0.48 lower to 0.39 higher)
Teacher	-rated b	ehaviour that	at challenge	S (measured	with: Developn	nental Behaviour	Checklist (DB	BC): Total; Bett	er indicated b	y lower value	s)
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean teacher- rated behaviour that challenges in the intervention groups was <b>0.09 standard</b> <b>deviations higher</b> (0.35 lower to 0.53 higher)

## **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

			Quality asses	sment				Sı	ummary of	Findin	gs
Participants	Risk of	Inconsistency	Indirectness	Imprecision		Overall quality	Study e	event rates (%)	Relative	Anticipa	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With ESDM or P-ESDM versus treatment-as- usual for adaptive behaviour as a direct or indirect outcome	effect (95% CI)	Risk with Control	Risk difference with ESDM or P- ESDM versus treatment-as- usual for adaptive behaviour as a direct or indirect outcome (95% CI)
Adaptive	behavi	OUI (measured	with: Vineland A	daptive Behavi	our Scale (VAE	3S/VABS II): Adaptiv	e behavi	our composite score; I	Better indica	ited by lo	wer values)
143 (2 studies) 12-104 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	70	73	N/A	N/A	The mean adaptive behaviour in the intervention groups was <b>0.03 standard deviations</b> higher (0.31 lower to 0.36 higher)
Daily livin	ng skills	(measured with	: Vineland Adapt	ive Behaviour	Scale (VABS/\	ABS II): Daily living	skills; Be	tter indicated by lower	values)		
143 (2 studies) 12-104 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	70	73	N/A	N/A	The mean daily living skills in the intervention groups was <b>0.1 standard deviations</b> higher (0.23 lower to 0.43 higher)
Socializat	tion (mea	asured with: Vinel	and Adaptive Be	haviour Scale	(VABS/VABS	I): Socialization; Bet	ter indica	ted by lower values)	•	•	·
143	serious <sup>1</sup>	very serious <sup>2</sup>	no serious	serious <sup>3</sup>	undetected	$\oplus \Theta \Theta \Theta$	70	73	N/A	N/A	The mean socialization in

(2 studies) 12-104 weeks			indirectness			VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision					the intervention groups was 0.08 standard deviations higher (0.25 lower to 0.41 higher)
Commun	nication	(measured with:	Vineland Adaptiv	e Behaviour S	cale (VABS/VA	BS II): Communicat	ion; Bett	er indicated by lower va	alues)		
143 (2 studies) 12-104 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	70	73	N/A	N/A	The mean communication in the intervention groups was 0.11 standard deviations higher (0.23 lower to 0.44 higher)
with (non-blin	nd) parent r	ce and response ather than direct es substantial to	observation		ors and particip	pants were non-blind	l and hig	gh risk of detection bias	as the outo	ome mea	asure was based on interview

### EIBI versus parent training for adaptive behaviour as a direct outcome

		Q	uality assessn	nent				S	ummary o	of Findin	gs
Participants		Inconsistency	Indirectness	Imprecision			Study e	· · ·	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias					evidence	With Control	With EIBI versus parent training for adaptive behaviour as a direct outcome	effect (95% CI)	Risk with Control	Risk difference with EIBI versus parent training for adaptive behaviour as a direct outcome (95% Cl)
Adaptive	behavi	OUI (measured w	vith: Vineland Ada	aptive Behavic	our Scale (VAB	S): Total; Better i	ndicated	by lower values)			
28 (1 study) 260 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>		⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	15	N/A	N/A	The mean adaptive behaviour in the intervention groups was <b>0.11 standard deviations</b> <b>higher</b> (0.64 lower to 0.85 higher)

28 (1 study) 260 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	15	N/A	N/A	The mean daily living skills in the intervention groups was <b>0.03 standard deviations</b> <b>lower</b> (0.77 lower to 0.71 higher)
Socializa	ation (me	easured with: Vine	eland Adaptive Be	haviour Scale	(VABS): Socia	lization; Better inc	dicated	by lower values	5)		
28 (1 study) 260 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	15	N/A	N/A	The mean socialization in the intervention groups was <b>0.12 standard deviations</b> <b>Iower</b> (0.86 lower to 0.63 higher)
Commu	nication	(measured with:	Vineland Adaptiv	ve Behaviour S	cale (VABS): C	Communication; B	etter in	dicated by lowe	r values)		- +
28 (1 study) 260 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	15	N/A	N/A	The mean communication in the intervention groups was <b>0.28 standard deviations</b> <b>higher</b> (0.47 lower to 1.02 higher)

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

		Qı	uality assessn	nent				S	Summary	of Finding	gs	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study of With Control	With Home-based	offect	Risk with Control	Risk difference with Home-based versus Centre-based EBI for adaptive behaviour as a direct outcome (95% CI)	
Socializat	Socialization (measured with: Vineland Adaptive Behaviour Scale (VABS): Socialization; Better indicated by lower values)											

56 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	29	27	N/A	N/A	The mean socialization in the intervention groups was <b>0.63 standard deviations</b> <b>lower</b> (1.17 to 0.09 lower)
Commu	nication	(measured with: \	/ineland Adaptive	e Behaviour So	ale (VABS): C	ommunication; E	Better ind	dicated by lower values)	)	1	
55 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean communication in the intervention groups was <b>0.46 standard deviations</b> <b>lower</b> (1 lower to 0.07 higher)
Adaptive	e functio	oning and ps	ychopathol	<b>ogy</b> (measur	ed with: Devel	opmental Behavi	iour Che	ecklist (DBC): Total; Bet	ter indicate	d by lowe	r values)
44 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	22	22	N/A	N/A	The mean adaptive functioning and psychopathology in the intervention groups was <b>0.11 standard deviations</b> <b>lower</b> (0.7 lower to 0.48 higher)
outcome me problems wi <sup>2</sup> N<400	easure relies th self-asse	s on interview with	parent and pare	nts were non-b	lind to group a	ssignment and c	other pot				ling outcome assessors, the part of the intervention so

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

### CBT versus waitlist for adaptive behaviour as an indirect outcome

		Q	uality assessn	nent				Su	mmary of	Findings	5
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	14/:41-		effect	Risk with Control	ed absolute effects Risk difference with CBT for anxiety versus waitlist control for adaptive behaviour as an indirect

								indirect outcome			outcome (95% CI)	
Adaptive behaviour (self-care) (measured with: Vineland Adaptive Behaviour Scale (VABS): Daily Living Skills; Better indicated by lower values)												
40 (1 study) 16 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	20	20	N/A	N/A	The mean adaptive behaviour (slef-care) in the intervention groups was <b>0.63 standard deviations</b> higher (0.01 lower to 1.26 higher)	
interview wit	<sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as outcome measure based on interview with non-blind parent rather than direct behavioural observation <sup>2</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)											

## **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

		Qu	ality assessm	ent				S	ummary c	of Findir	igs
Participants		Inconsistency	Indirectness	-			Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Parent training versus treatment as usual for adaptive behaviour as a direct or indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Parent training versus treatment as usual for adaptive behaviour as a direct or indirect outcome (95% Cl)
Function	al emoti	onal develop	oment (clini	cian-rated	<b>d)</b> (measured	with: Functional	Emotior	al Assessment Scale (F	EAS): Tota	l; Better i	ndicated by lower values)
32 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	16	16	N/A	N/A	The mean functional emotional development (clinician-rated) in the intervention groups was <b>0.25 standard deviations</b> <b>lower</b> (0.95 lower to 0.45 higher)
Function values)	al emoti	onal develop	oment (pare	ent-rated)	(measured wit	h: Functional En	notional	Developmental Question	nnaires (FE	DQ): Tota	al; Better indicated by lower

32 (1 study) 13 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	16	16	N/A	N/A	The mean functional emotional development (parent-rated) in the intervention groups was <b>0.2 standard deviations</b> <b>lower</b> (0.9 lower to 0.49 higher)
Daily livi	ing skills	<b>(PEBM)</b> (mea	asured with: Vine	land Adaptive	Behaviour Sca	ale (VABS): Daily	/ Living	Skills; Better indicated	by lower val	ues)	
70 (1 study) 46 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	35	N/A	N/A	The mean daily living skills (pebm) in the intervention groups was <b>0.46 standard deviations</b> higher (0.01 lower to 0.94 higher)
Daily livi	ing skills	(PEC) (measu	red with: Vinelar	nd Adaptive Be	haviour Scale	(VABS): Daily L	iving Sk	ills; Better indicated by	lower value	s)	
68 (1 study) 46 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	33	N/A	N/A	The mean daily living skills (pec) in the intervention groups was <b>0.14 standard deviations</b> <b>lower</b> (0.61 lower to 0.34 higher)
Socializa	ation (PE	<b>BM)</b> (measured	with: Vineland A	daptive Behav	viour Scale (VA	ABS): Socializati	on; Bett	er indicated by lower va	alues)		
70 (1 study) 46 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	35	N/A	N/A	The mean socialization (pebm) in the intervention groups was <b>0.35 standard deviations</b> <b>higher</b> (0.12 lower to 0.83 higher)
Socializa	ation (PE	C) (measured w	th: Vineland Ada	ptive Behavio	ur Scale (VAB	S): Socialization;	Better	indicated by lower value	es)	•	
68 (1 study) 46 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	33	N/A	N/A	The mean socialization (pec) in the intervention groups was <b>0.26 standard deviations</b> <b>lower</b> (0.74 lower to 0.21 higher)

Commu	inication	(PEBM) (meas	ured with: Vinela	and Adaptive E	Behaviour Scal	e (VABS): Comr	nunicat	ion; Better indica	ted by lower value	es)	
70 (1 study) 46 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	35	N/A	N/A	The mean communication (pebm) in the intervention groups was <b>0.1 standard deviations</b> higher (0.37 lower to 0.57 higher)
68 (1 study) 46 weeks	serious <sup>3</sup>	(PEC) (measure no serious inconsistency	ed with: Vineland	Adaptive Beh	naviour Scale (	VABS): Commun ⊕⊕⊖⊝ LOW <sup>3,4</sup> due to risk of bias, imprecision	35	; Better indicated	I by lower values)	N/A	The mean communication (pec) in the intervention groups was 0.56 standard deviations lower (1.04 to 0.07 lower)
<ul> <li><sup>2</sup> High risk of involved in the study.</li> <li><sup>3</sup> High risk of</li> </ul>	of performand the intervent	ion so problems w	ias as intervention ith self-assessmo ias as intervention	on administrate ent. There was	ors and particip s also no indep ors and particip	pants were non-leadent reliability	olind, and va	nd high risk of de alidity data for the nd risk of detectio	e Thai-version of the transformed terms of t	nis outcon unknown a	and parents were non-blind and ne measure which was used in as although the outcome

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

l		Qu	ality assess	ment			Sum	mary of F	inding	s
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	-	of evidence	With		<b>effect</b> (95% CI)	Anticip Risk with Control	ated absolute effects Risk difference with Combined parent training and early intervention centre programme versus early intervention centre programme only for adaptive behaviour as a direct outcome (95% CI)

## Parent-reported adaptive behaviour (mixed ASD & DD sample) (measured with: Vineland Adaptive Behaviour Scale (VABS): Total; Better indicated by lower values)

,								
58 (1 study)	 no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>		28	30	N/A	The mean parent-reported adaptive behaviour (mixed
40 weeks				due to risk of				asd & dd sample) in the
				bias,				intervention groups was
				indirectness,				0.25 standard deviations
				imprecision				higher
								(0.27 lower to 0.77 higher)

Parent-reported adaptive behaviour (mixed ASD & DD sample) (measured with: Vineland Adaptive Behaviour Scale (VABS): Total; Better indicated by lower values)

51	serious <sup>1</sup>	no serious	serious <sup>2</sup>	very	0000	23	28	N/A	N/A	The mean parent-reported
(1 study)		inconsistency		serious <sup>3</sup>	VERY LOW <sup>1,2,3</sup>					adaptive behaviour (mixed
108 weeks					due to risk of					asd & dd sample) in the
					bias,					intervention groups was
					indirectness,					0.31 standard deviations
					imprecision					higher
										(0.24 lower to 0.87 higher)

#### Clinician-rated adaptive behaviour (mixed ASD & DD sample) (measured with: Bayley Behavior Rating Scale (BRS): Total; Better indicated by lower values)

57 (1 study) 40 weeks	no serious risk of bias	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>		⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to indirectness, imprecision	28	29	N/A	N/A	The mean clinician-rated adaptive behaviour (mixed asd & dd sample) in the intervention groups was <b>0.4 standard deviations</b> <b>higher</b> (0.12 lower to 0.93 higher)
Clinician-rated adaptive behaviour (mixed ASD & DD sample) (measured with: Bayley Behavior Rating Scale (BRS): Total; Better indicated by lower values)											
47				4	and a factor of a st	<b>~~~~~</b>	00	0.1	N1/A	N1/A	The second all all all and second

47	no	no serious	serious <sup>2</sup>	serious <sup>4</sup>	<b>~~</b> ~	23	24	N/A	N/A	The mean clinician-rated
(1 study)	serious	inconsistency			LOW <sup>2,4</sup>					adaptive behaviour (mixed
108 weeks	risk of				due to					asd & dd sample) in the
	bias				indirectness,					intervention groups was
					imprecision					0.62 standard deviations
										higher
										(0.04 to 1.21 higher)

<sup>1</sup> High risk of performance and response bias as intervention administrator and participants were non-blind, and risk of detection bias was unclear/unknown as, although the interviewer was a blinded research assistant, the outcome measure was based on non-blind parent report and parents were involved in the intervention
 <sup>2</sup> Population was indirect (as the sample included participants with developmental delay or language delay without autism)
 <sup>3</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)</li>
 <sup>4</sup> N<400</li>

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

		Qı	uality assessn	nent				Su	mmary of	Finding	gs
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Parent and day-care staff training versus standard day-care for adaptive behaviour as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Parent and day-care staff training versus standard day-care for adaptive behaviour as an indirect outcome (95% Cl)
Self-care	(measured	d with: Early Interv	ention Developm	nental Profile (I	EIDP)/Prescho	ol Developmer	tal Profile	e (PSDP): Self-Care; Bett	er indicated	by lower	r values)
35 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	19	16	N/A	N/A	The mean self-care in the intervention groups was <b>0.04 standard deviations</b> <b>lower</b> (0.7 lower to 0.63 higher)

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

		Qı	ality assessn	nent			Summary of Findings				
		Inconsistency	Indirectness	Imprecision	Publication		Study			Anticip	ated absolute effects
(studies) Follow up	bias					quality of evidence	With Control	With Combined antipsychotic and parent training versus antipsychotic only for adaptive behaviour as an	effect (95% CI)	Risk with Control	Risk difference with Combined antipsychotic and parent training versus antipsychotic only for adaptive behaviour as an indirect outcome (95% Cl)

								indirect outcome			
Adaptive	e behav	iour (measured	with: Vineland	Adaptive Beha	viour Scale (VA	ABS): Adaptive	Compo	site; Better indicated by	lower values	)	
124 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	49	75	N/A	N/A	The mean adaptive behaviou in the intervention groups was <b>0.56 standard deviations</b> <b>higher</b> (0.19 to 0.93 higher)
Daily livi	ing skill	S (measured wit	h: Vineland Ada	otive Behaviou	Ir Scale (VABS	): Daily Living S	kills; Be	etter indicated by lower	values)		
124 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	49	75	N/A	N/A	The mean daily living skills in the intervention groups was <b>0.48 standard deviations</b> <b>higher</b> (0.12 to 0.85 higher)
Socializa	ation (me	easured with: Vine	eland Adaptive E	Behaviour Scal	e (VABS): Soc	ialization; Better	indica	ted by lower values)	<b>I</b>	Į	
124 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	49	75	N/A	N/A	The mean socialization in the intervention groups was <b>0.6 standard deviations</b> <b>higher</b> (0.23 to 0.96 higher)
Commu	nication	(measured with:	Vineland Adapt	ive Behaviour	Scale (VABS):	Communication	i; Bette	r indicated by lower value	ues)		
124 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	49	75	N/A	N/A	The mean communication in the intervention groups was <b>0.47 standard deviations</b> <b>higher</b> (0.11 to 0.84 higher)

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

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

		Qı	ality assessn	nent				Sun	nmary of I	Finding	S
•		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Caregiver-mediated social-communication interventions versus treatment-as-usual for adaptive behaviour as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Caregiver- mediated social-communication interventions versus treatment- as-usual for adaptive behaviour as an indirect outcome (95% CI)
Adaptive	behavi	iour (measured	with: Vineland A	daptive Behav	viour Scale (VA	ABS): Total; Bet	tter indic	ated by lower values)			
152 (1 study) 56 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	75	77	N/A	N/A	The mean adaptive behaviour in the intervention groups was <b>0.17 standard deviations</b> <b>lower</b> (0.48 lower to 0.15 higher)
Daily Livi	ing Skil	IIS (measured wit	h: Vineland Ada	ptive Behavio	ur Scale (VAB	S): Daily Living	Skills; B	etter indicated by lower valu	es)	•	
39 (1 study) 39 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	20	19	N/A	N/A	The mean daily living skills in the intervention groups was <b>0.55 standard deviations</b> <b>higher</b> (0.09 lower to 1.19 higher)
Socializa	tion (me	asured with: Vine	and Adaptive B	ehaviour Scale	e (VABS): Soci	alization; Bette	r indicate	ed by lower values)			
39 (1 study) 39 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision	20	19	N/A	N/A	The mean socialization in the intervention groups was <b>0.1 standard deviations</b> <b>higher</b> (0.53 lower to 0.73 higher)

245 (4 studies) 39-56 weeks	serious⁵	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>2,5</sup> due to risk of bias, imprecision	122	123	N/A	N/A	The mean communication in the intervention groups was <b>0.04 standard deviations</b> <b>lower</b> (0.29 lower to 0.22 higher)
teacher not re <sup>2</sup> N<400 <sup>3</sup> High risk of interview with <sup>4</sup> N<400 and	ported performan non-blind 95% CI cro	ce and response parent rather the	e bias as interver an direct behavio f no effect and n	ntion administra oural observati neasure of app	ators and partion on preciable benef	cipants were nc it or harm (SME	on-blind, 0 -0.5/0.	and risk of detectio 5)	on bias was unclea	ar/unknowr	eacher-rated and blinding of n as outcome measure based or blinding of outcome assessment

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

			Quality assess	ment					Summary	of Findings	
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study event	rates (%)	Relative	Anticipated a	absolute effects
(studies) Follow up	bias				bias		With Treatment-as- usual	With Social skills group	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Social skills group (95% CI)
Self-contr	r <b>ol</b> (meas	ured with: Social Sl	kills Rating System	(SSRS): Self-c	control; Better ir	ndicated by lower va	alues)				
68 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \ominus \ominus$ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	33	35	N/A	N/A	The mean self-control in the intervention groups was <b>0.63 standard</b> <b>deviations higher</b> (0.14 to 1.11 higher)

	ies) wup bias qualievide ialization (measured with: Vineland Adaptive Behaviour Scale (VABS): Socializati							Su	mmary o	f Findin	gs
-		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With LEGO therapy versus Social Use of Language Programme (SULP) for adaptive behaviour as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with LEGO therapy versus Social Use of Language Programme (SULP) for adaptive behaviour as an indirect outcome (95% Cl)
Socializa	tion (me	easured with: Vine	land Adaptive B	ehaviour Scale	e (VABS): Soci	alization; Better	indicate	d by lower values)			
31 (1 study) 18 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	15	16	N/A	N/A	The mean socialization in the intervention groups was 0.32 standard deviations higher (0.39 lower to 1.03 higher)
Commun	ication	(measured with:	Vineland Adaptiv	ve Behaviour S	Scale (VABS):	Communication	; Better	indicated by lower values)			1
31 (1 study) 18 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	15	16	N/A	N/A	The mean communication in the intervention groups was <b>0.48 standard deviations</b> <b>higher</b> (0.23 lower to 1.2 higher)

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

## **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

**Quality assessment** 

Summary of Findings

Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall quality of	Study e	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	evidence	With Control	With Antipsychotics versus placebo for adaptive behaviour as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Antipsychotics versus placebo for adaptive behaviour as an indirect outcome (95% Cl)
Adaptive	behav	iour (aripipr	azole) (measu	red with: Peds	QL: Total (cha	inge score); Better in	dicated b	oy lower values)		-	
243 (2 studies) 8 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	76	167	N/A	N/A	The mean adaptive behaviour (aripiprazole) in the intervention groups was <b>0.51 standard deviations</b> higher (0.21 to 0.8 higher)
Emotiona	al funct	tioning (arip	iorazole) (me	easured with: F	edsQL: Emoti	onal functioning (cha	nge scor	e); Better indicated by lo	wer values)		
243 (2 studies) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	76	167	N/A	N/A	The mean emotional functioning (aripiorazole) in the intervention groups was <b>0.41 standard deviations</b> higher (0.12 to 0.7 higher)
Social fu	nctioni	ng (aripiora	zole) (measure	d with: PedsQ	L: Social funct	ioning (change score	e); Better	indicated by lower value	s)		
243 (2 studies) 8 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,4</sup> due to risk of bias, inconsistency, imprecision	76	167	N/A	N/A	The mean social functioning (aripiorazole) in the intervention groups was 0.27 standard deviations higher (0.02 lower to 0.56 higher)
Cognitive	e functi	ioning (aripi	prazole) (mea	asured with: Pe	ı edsQL: Cognit	ive functioning (chan	ge score	); Better indicated by low	ver values)		
242 (2 studies) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	$\begin{array}{c} \oplus \oplus \ominus \ominus \\ \textbf{LOW}^{1,3} \\ \text{due to risk of bias,} \end{array}$	75	167	N/A	N/A	The mean cognitive functioning (aripiprazole) in the intervention groups

						imprecision			was <b>0.4 standard deviations</b> <b>higher</b> (0.11 to 0.69 higher)
<sup>2</sup> I-squared va <sup>3</sup> N<400	alue indica	is unclear as blind tes substantial to o osses both line of	considerable het	erogeneity	eciable benefit	or harm (SMD -0.5/0	0.5)		

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

		Qı	uality assessr	nent				Sun	nmary of I	Finding	S
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Low dose antipsychotics versus placebo for adaptive behaviour as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Low dose antipsychotics versus placebo for adaptive behaviour as an indirect outcome (95% CI)
Adaptive	behavi	our (low dos	se aripipraz	ole 5mg/d	<b>ay)</b> (measure	ed with: PedsQL	: Total (o	hange score); Better indica	ated by low	er values)	)
80 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	37	43	N/A	N/A	The mean adaptive behaviour (low dose aripiprazole 5mg/day) in the intervention groups was <b>0.21 standard deviations</b> <b>higher</b> (0.23 lower to 0.65 higher)
Emotiona	al funct	ioning (low o	dose aripipi	razole 5m	<b>g/day)</b> (mea	asured with: Ped	sQL: Em	otional functioning (change	e score); Be	tter indica	ated by lower values)
80 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	37	43	N/A	N/A	The mean emotional functioning (low dose aripiprazole 5mg/day) in the intervention groups was 0.19 standard deviations higher

											(0.25 lower to 0.63 higher)
Social fu	unctioni	ng (low dos	e aripiprazo	ole 5mg/da	<b>ay)</b> (measured	d with: PedsQL: \$	Social f	unctioning (change	e score); Better inc	licated by I	ower values)
80 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	37	43	N/A	N/A	The mean social functioning (low dose aripiprazole 5mg/day) in the intervention groups was <b>0 standard deviations</b> higher (0.43 lower to 0.44 higher)
Cognitiv	/e functi	ioning (low o	dose aripipi	azole 5mg	<b>g/day)</b> (mea	sured with: Peds	QL: Co	ognitive functioning	(change score); E	Better indic	ated by lower values)
80 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	37	43	N/A	N/A	The mean cognitive functioning (low dose aripiprazole 5mg/day) in the intervention groups was <b>0.32 standard deviations</b> higher (0.12 lower to 0.76 higher)

## **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

		C	Quality asses	sment		Summ	nary of Fi	ndings
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	•	of evidence	With With Acupuncture/Electro-	effect	Anticipated absolute effects           Risk         Risk difference with           with         Acupuncture/Electro-

							acupuncture/electro- acupuncture for adaptive behaviour as an indirect outcome		Control	acupuncture versus sham acupuncture/electro- acupuncture for adaptive behaviour as an indirect outcome (95% Cl)
behav	<b>iour</b> (measured	d with: Functiona	al Independen	ce Measure for	Children (WeeFIM	): Total	(change score); Better indica	ated by lowe	er values	:)
no serious risk of bias	very serious <sup>1</sup>	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to inconsistency, imprecision, publication bias	50	55	N/A	N/A	The mean adaptive behaviour in the intervention groups was <b>0.59 standard deviations</b> higher (0.19 to 0.98 higher)
(measure	ed with: Functiona	al Independence	Measure for	L Children (WeeF	IM): Self-care (cha	inge sco	ore); Better indicated by lowe	er values)	J	ł
no serious risk of bias	very serious <sup>1</sup>	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	<b>WERY LOW</b> <sup>1,2,3</sup> due to inconsistency, imprecision, publication bias	50	55	N/A	N/A	The mean self-care in the intervention groups was <b>0.56 standard deviations</b> <b>higher</b> (0.17 to 0.96 higher)
(measured	with: Functional	Independence	Measure for C	hildren (WeeFI	I): Mobility (chang	e score	); Better indicated by lower v	alues)		
no serious risk of bias	serious <sup>4</sup>	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>2,3,4</sup> due to inconsistency, imprecision, publication bias	50	55	N/A	N/A	The mean mobility in the intervention groups was <b>0.08 standard deviations lower</b> (0.46 lower to 0.31 higher)
<b>n</b> (measu	red with: Function	nal Independen	ce Measure fo	r Children (Wee	FIM): Cognition (c	hange s	core); Better indicated by low	wer values)	•	
no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊕⊖⊖ LOW <sup>2,3</sup> due to imprecision, publication bias	50	55	N/A	N/A	The mean cognition in the intervention groups was <b>0.48 standard deviations</b> <b>higher</b> (0.09 to 0.87 higher)
	no serious risk of bias (measured no serious risk of bias (measured no serious risk of bias no serious risk of bias	no       very serious <sup>1</sup> serious       risk of         bias       very serious <sup>1</sup> (measured with: Functional         no       very serious <sup>1</sup> risk of       very serious <sup>1</sup> p (measured with: Functional         no       serious         risk of       serious         p (measured with: Functional         no       serious         risk of       serious         p (measured with: Functional         no       serious         risk of       serious         p (measured with: Functional         no       serious         risk of       bias	no serious risk of biasvery serious1 no serious indirectness(measured with: Functional Independence serious risk of biasno serious1 no serious1 no serious indirectnessno serious risk of biasvery serious1 no serious indirectnessno serious risk of biasvery serious1 no serious indirectnessno serious risk of 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  no serious risk of bias       serious <sup>4</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>2,3,4</sup> due to inconsistency, imprecision, publication bias         no serious risk of bias       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>2,3,4</sup> due to inconsistency, imprecision, publication bias         no serious risk of bias       no serious inconsistency inconsistency indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to imprecision,	no serious risk of bias       very serious <sup>1</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to inconsistency, imprecision, publication bias       50         e (measured with: Functional Independence Measure for Children (WeeFIM): Self-care (change scot serious risk of bias       no serious indirectness       reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to inconsistency, imprecision, publication bias       50         (measured with: Functional Independence Measure for Children (WeeFIM): Mobility (change score indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to inconsistency, imprecision, publication bias       50         (measured with: Functional Independence Measure for Children (WeeFIM): Mobility (change score indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>2,3,4</sup> due to inconsistency, imprecision, publication bias       50         no serious risk of bias       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ LOW <sup>2,3</sup> due to imprecision,       50	Image: serious risk of bias       no serious indirectness       serious <sup>2</sup> serious <sup>3</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       VERV LOW <sup>1,2,3</sup> or LOW <sup>1,2,3</sup> 50       55         e (measured with: Functional Independence Measure for Children (WeeFIM): Total (change score); Better indicated by lower visits of bias       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       VERV LOW <sup>1,2,3</sup> or LOW <sup>1,2,3</sup> 50       55         e (measured with: Functional Independence Measure for Children (WeeFIM): Self-care (change score); Better indicated by lower visks of bias       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       50       55         e (measured with: Functional Independence Measure for Children (WeeFIM): Self-care (change score); Better indicated by lower visks of bias       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       50       55         emeasured with: Functional Independence Measure for Children (WeeFIM): Mobility (change score); Better indicated by lower viscons indirectness       serious <sup>3</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       50       55         no       serious indirectness       serious <sup>2</sup> reporting bias suspected <sup>3</sup> ⊕⊖⊖⊖⊖       50       55         no       serious indirectness       serious <sup></sup>	Image: Serious risk of bias       very serious <sup>1</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       50       55       N/A         no       very serious <sup>1</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       50       55       N/A         no       very serious <sup>1</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       50       55       N/A         no       wery serious <sup>1</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       50       55       N/A         no       serious <sup>1</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       50       55       N/A         no       serious <sup>1</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       50       55       N/A         no       serious <sup>4</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       50       55       N/A         no       serious <sup>4</sup> no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> 55       S5 <td>Image: Serious is serio</td>	Image: Serious is serio

55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean comprehension in the intervention groups was <b>0.51 standard deviations</b> <b>higher</b> (0.03 lower to 1.05 higher)
Express	ion (meas	sured with: Functi	onal Independe	nce Measure	for Children (W	eeFIM): Expressio	n (chan	ge score); Better indicated by	/ lower valu	ues)	
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean expression in the intervention groups was <b>0.17 standard deviations</b> <b>higher</b> (0.36 lower to 0.7 higher)
Social in	nteractio	<b>on</b> (measured wi	th: Functional Ir	ndependence l	Measure for Ch	ildren (WeeFIM): S	Social in	teraction (change score); Be	tter indicate	ed by low	ver values)
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean social interaction in the intervention groups was <b>0.23 standard deviations</b> <b>Iower</b> (0.77 lower to 0.3 higher)
Problem	solving	(measured with	: Functional Ind	ependence M	easure for Child	Iren (WeeFIM): Pro	oblem s	olving (change score); Better	indicated	by lower	values)
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean problem solving in the intervention groups was <b>0.24 standard deviations</b> <b>lower</b> (0.77 lower to 0.3 higher)
Memory	(measured	with: Functional	Independence	Measure for C	hildren (WeeFII	M): Memory (chang	ge score	e); Better indicated by lower	alues)		,
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean memory in the intervention groups was <b>0.13 standard deviations</b> <b>higher</b> (0.4 lower to 0.67 higher)

55	no	no serious	no serious	very	reporting bias	$\oplus \Theta \Theta \Theta$	25	30	N/A	N/A	The mean self-care
(1 study) 4 weeks	serious risk of bias	inconsistency	indirectness	serious <sup>5</sup>	strongly suspected <sup>3</sup>	VERY LOW <sup>3.5</sup> due to imprecision, publication bias	20	30	NA	N/A	(functional skill) in the intervention groups was <b>0.22 standard deviations</b> <b>lower</b> (0.75 lower to 0.31 higher)
Self-car	e (indep	<b>bendence)</b> (m	l leasured with: F	Pediatric Eval	Luation of Disabili	l ty Inventory (PEDI	): Self-	care (caregiver assi	stant); Better indica	ated by Ic	wer values)
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean self-care (independence) in the intervention groups was <b>0.44 standard deviations</b> <b>lower</b> (0.97 lower to 0.1 higher)
Mobility	(functio	onal skill) (m	easured with: P	ediatric Evalu	ation of Disabilit	y Inventory (PEDI)	: Mobil	lity; Better indicated	by lower values)		
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean mobility (functional skill) in the intervention groups was <b>0.11 standard deviations</b> <b>lower</b> (0.64 lower to 0.42 higher)
Mobility	(indepe	endence) (me	asured with: Pe	ediatric Evalua	ation of Disability	Inventory (PEDI):	Mobili	ty (caregiver assista	nt); Better indicate	d by lowe	r values)
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean mobility (independence) in the intervention groups was <b>0.19 standard deviations</b> <b>lower</b> (0.72 lower to 0.35 higher)
Social f	unction	(functional	<b>skill)</b> (measu	red with: Ped	iatric Evaluation	of Disability Inven	ory (Pl	EDI): Social function	; Better indicated b	y lower v	alues)
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly suspected <sup>3</sup>	$\bigcirc \bigcirc \bigcirc$ <b>VERY LOW</b> <sup>3,5</sup> due to imprecision,	25	30	N/A	N/A	The mean social function (functional skill) in the intervention groups was 0.04 standard deviations

						publication bias					higher (0.49 lower to 0.57 higher)
Social f	unction	(independe	ence) (measur	ed with: Pedia	tric Evaluation of	of Disability Invento	ory (PEDI	I): Social function (caregiver	assistant);	Better i	ndicated by lower values)
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean social function (independence) in the intervention groups was <b>0.14 standard deviations</b> <b>lower</b> (0.67 lower to 0.39 higher)
<sup>2</sup> N<400 <sup>3</sup> High risk <sup>4</sup> I-squared	of selective I value indica	ates moderate he	trial protocol fo	r WONG2010E		ow-up measureme íit or harm (SMD -0		e taken but these are not re	ported		

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

		Q	uality assess	sment				Sumr	nary of Fi	indings	\$
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study	event rates (%)		Anticip	pated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Acupuncture/electro- acupuncture and conventional educational programme versus conventional educational programme only for adaptive behaviour as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Acupuncture/electro- acupuncture and conventional educational programme versus conventional educational programme only for adaptive behaviour as an indirect outcome (95% Cl)
Adaptive	behav	iour (measured	with: Functiona	al Independen	ce Measure fo	r Children (WeeF	IM): Tot	al (change score); Better indic	ated by lov	ver value	es)
64 (2 studies) 8 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	31	33	N/A	N/A	The mean adaptive behaviour in the intervention groups was <b>0.41 standard deviations</b> higher (0.11 lower to 0.93 higher)

Self-care	(measure	d with: Functiona	al Independence	e Measure for	Children (Wee	eFIM): Self-care (	change	score); Better indicate	d by lower values	;)	
64 (2 studies) 8 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	31	33	N/A	N/A	The mean self-care in the intervention groups was <b>0.16 standard deviations</b> <b>higher</b> (0.35 lower to 0.67 higher)
Mobility	(measured	with: Functional	Independence	Measure for C	hildren (Weef	TM): Mobility (cha	ange sc	ore); Better indicated b	y lower values)		
64 (2 studies) 8 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	31	33	N/A	N/A	The mean mobility in the intervention groups was <b>0.52 standard deviations</b> <b>higher</b> (0 to 1.05 higher)
Cognitio	<b>n</b> (measu	red with: Function	nal Independen	ce Measure fo	r Children (We	eeFIM): Cognition	(chang	je score); Better indica	ted by lower valu	es)	
64 (2 studies) 8 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,4</sup> due to risk of bias, inconsistency, imprecision	31	33	N/A	N/A	The mean cognition in the intervention groups was <b>0.62 standard deviations</b> <b>higher</b> (0.1 to 1.14 higher)
Comprei	hensior	(measured with	: Functional Ind	ependence M	easure for Chi	ildren (WeeFIM):	Compe	hension (change score	); Better indicate	d by lowe	r values)
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean comprehension in the intervention groups was <b>0.47 standard deviations</b> <b>lower</b> (1.13 lower to 0.19 higher)
Expressi	i <b>on</b> (meas	sured with: Funct	ional Independe	ence Measure	for Children (	WeeFIM): Expres	sion (cł	nange score); Better in	dicated by lower	/alues)	
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean expression in the intervention groups was <b>0.4 standard deviations</b> <b>higher</b> (0.26 lower to 1.06 higher)

36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean social interaction in the intervention groups was <b>0.4 standard deviations</b> higher (0.26 lower to 1.06 higher)
Problem	n solving	g (measured with	n: Functional Ind	dependence N	leasure for Ch	ildren (WeeFIM):	Probler	m solving (change	score); Better indicate	ed by low	ver values)
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean problem solving in the intervention groups was <b>0.33 standard deviations</b> <b>higher</b> (0.32 lower to 0.99 higher)
Memory	(measured	with: Functional	Independence	Measure for C	Children (Weel	- FIM): Memory (ch	ange so	core); Better indicat	ed by lower values)	_	
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	18	18	N/A	N/A	The mean memory in the intervention groups was 0.15 standard deviations lower (0.81 lower to 0.5 higher)
may introdu parents who blind parent <sup>2</sup> I-squared	ice bias. Th o were not t tal report value indica	e risk of detection blind to treatment ates considerable	n bias was also allocation or co heterogeneity	unclear/unkno onfounding va	own as all outo riables and sys	come measures w	ere rate om whic	ed by blinded asses ch data was extract	ssors, but some outco	ome mea	ered for each participant which sures involved input from come measures relied on non-

## **1.15.2Hormones for adaptive behaviour as an indirect outcome**

Secretin versus placebo for adaptive behaviour as an indirect outcome

	ality assessm	ient	Summary of Findings					
Participants Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall	Study event rates (%)	Relative	Anticipated absolute effects

(studies) Follow up	bias				bias	quality of evidence	With Control	With Secretin versus placebo for adaptive behaviour as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Secretin versus placebo for adaptive behaviour as an indirect outcome (95% Cl)
Adaptive	e behavi	OUI (measured w	vith: Vineland Ada	aptive Behavio	ur Scale (VAB	S): Adaptive Com	posite; E	Better indicated by low	ver values)		
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	28	28	N/A	N/A	The mean adaptive behaviour in the intervention groups was <b>0.08 standard deviations</b> <b>Iower</b> (0.61 lower to 0.44 higher)
Daily liv	ing skill	S (measured with:	Vineland Adaptiv	e Behaviour S	Scale (VABS): [	Daily Living Skills;	; Better i	ndicated by lower valu	ues)	1	I
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	28	28	N/A	N/A	The mean daily living skills in the intervention groups was <b>0.11 standard deviations</b> <b>higher</b> (0.42 lower to 0.63 higher)
Socializa	ation (me	asured with: Vinela	and Adaptive Beh	aviour Scale (	VABS): Sociali	zation; Better indi	icated by	/ lower values)		<u> </u>	
56 (4. attualu)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	$\oplus \oplus \ominus \ominus$ LOW <sup>1</sup>	28	28	N/A	N/A	The mean socialization in the intervention groups was
(1 study) 4 weeks	risk of bias					due to imprecision					0.26 standard deviations lower (0.78 lower to 0.27 higher)
4 weeks	bias	(measured with: V	/ineland Adaptive	Behaviour Sc	ale (VABS): Co	imprecision	etter indic	cated by lower values	)		lower

## 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

		Qu	ality assessn	nent				Sumi	mary of F	indings	
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study event	rates (%)	Relative	Anticipated a	bsolute effects
(studies) Follow up	bias				bias	quality of evidence	With Short- term chelation (1-round of DMSA therapy and 6-rounds of placebo)	With Long-term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy)	(95% CI)	Risk with Short-term chelation (1- round of DMSA therapy and 6- rounds of placebo)	Risk difference with Long- term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy) (95% CI)
Adaptive	behav	iour (measured	with: Pervasive	Development	Disorder Beh	avior Inventor	y (PDDBI): Ada	aptive Behaviours Compo	osite; Bette	r indicated by lo	ower values)
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	25	N/A	N/A	The mean adaptive behaviour in the intervention groups was <b>0.2 standard</b> <b>deviations lower</b> (0.84 lower to 0.44

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

		Qu	ality assessm	ent				S	ummary c	f Findings		
Participants		Inconsistency	Indirectness	Imprecision			Study event			Anticipated a	absolute effects	
(studies) Follow up	bias					quality of evidence	With Attention- placebo control	With Hyperbaric	effect (95% CI)	Risk with Attention- placebo control	Risk difference with Hyperbaric oxygen treatment (HBOT) (95% CI)	
Adaptive	Adaptive behaviour (measured with: Vineland Adaptive Behaviour Scale (VABS): Adaptive Composite (change score); Better indicated by lower values)											

34 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	16	18	N/A	N/A	The mean adaptive behaviour in the intervention groups was <b>0.18 standard</b> <b>deviations lower</b> (0.85 lower to 0.5 higher)
Daily liv	ing skills	(measured with:	Vineland Adaptiv	ve Behaviour	Scale (VABS): [	Daily Living Skills	s (change s	score); Better in	dicated by lowe	er values)	
34 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	16	18	N/A	N/A	The mean daily living skills in the intervention groups was <b>0.11 standard</b> <b>deviations higher</b> (0.56 lower to 0.78 higher)
Socializa	ation (mea	asured with: Vinela	and Adaptive Beh	aviour Scale	(VABS): Sociali	zation (change s	score); Bett	ter indicated by	lower values)	<b>I</b>	1
34 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	16	18	N/A	N/A	The mean socialization in the intervention groups was <b>0.38 standard</b> <b>deviations lower</b> (1.06 lower to 0.3 higher)
Commu	nication	(measured with: V	ineland Adaptive	Behaviour So	cale (VABS): Co	ommunication (c	hange sco	re); Better indica	ated by lower v	alues)	
34 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	16	18	N/A	N/A	The mean communication in the intervention groups was <b>0.23 standard</b> <b>deviations higher</b> (0.45 lower to 0.9 higher)

56 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/26 (7.7%)	9/30 (30%)	<b>RR 3.9</b> (0.92 to	Study popula	tion
4 weeks	risk of bias					due to imprecision		()	16.45)	77 per 1000	223 more per 1000 (from 6 fewer to 1000 more)
										Moderate	L
										77 per 1000	223 more per 1000 (from 6 fewer to 1000 more)
Parent-r	ated pos	itive treatme	ent response	e (assessed w	ith: Number of	participants 'mu	ch improved	/very improved	on Parental G	lobal Impressior	(PGI)-improvement for
overall funct 56	ioning) no	no serious	no serious	very	undetected	000	4/26	9/30	RR 1.95	Study popula	tion
	3,	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW <sup>2</sup> due to imprecision	4/26 (15.4%)	9/30 (30%)	<b>RR 1.95</b> (0.68 to 5.6)		tion 146 more per 1000 (from 49 fewer to 708 more)
56 (1 study)	no serious risk of				undetected	LOW <sup>2</sup> due to			(0.68 to		<b>146 more per 1000</b> (from 49 fewer to 708

# 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

		Qı	uality assessme	Summary of Findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness			· · · · · · · · · · · · · · · · · · ·	Relative effect	Anticipated absolute effects

Follow up							With Placebo	With Omega- 3 fatty acids	(95% CI)	Risk with Placebo	Risk difference with Omega-3 fatty acids (95% Cl)
Adaptive	skill (meas	ured with: Behavior	Assessment Syst	em for Childre	n (BASC): Adap	otive skill; Better in	dicated by	lower values)			
	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	12	12	N/A	N/A	The mean adaptive skill in the intervention groups was <b>0.2 standard deviations</b> lower (1 lower to 0.6 higher)

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

		Qı	uality assessm	ent					Summa	ary of Findi	ngs
Participants		Inconsistency	Indirectness	Imprecision		• •	Study ever	nt rates (%)		Anticipated	l absolute effects
(studies) Follow up	bias				bias		With Healthy diet control	With Omega-3 fatty acids	effect (95% CI)	Risk with Healthy diet control	Risk difference with Omega-3 fatty acids (95% CI)
Frequenc	y of atte	nding to task	<b>dactivity</b> (mea	asured with: Be	ehavioural obse	ervation; Better in	dicated by lo	ower values)			
23 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	13	10	N/A	N/A	The mean frequency of attending to task/activity in the intervention groups was <b>0.65 standard deviations</b> <b>higher</b> (0.2 lower to 1.5 higher)
<sup>1</sup> N<400 and 9	95% CI cross	ses both line of no	effect and measu	re of appreciat	ble benefit or h	arm (SMD -0.5/0.5	5)			1	1

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

		Q	uality assessm	nent		Summary of Findings			
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Overall quality	Study event rates (%)	Relative	Anticipated absolute effects	

studies) Follow up	bias				bias	of evidence	With Treatment-as- usual	With Gluten- free and casein-free diet	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Gluten-free and casein-free diet (95% CI)
Daily Livi	ing Skill	S (measured with:	Vineland Adaptiv	e Behaviour Sc	ale (VABS): Da	aily Living Skills (c	hange score);	Better indica	ted by lower	values)	
55 1 study) 35 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean daily living skills in the intervention groups was <b>0.32 standard</b> <b>deviations higher</b> (0.21 lower to 0.85 higher)
Socializa	tion (mea	asured with: Vinela	nd Adaptive Beha	viour Scale (VA	BS): Socializat	ion (change score	e); Better indica	ated by lower	values)	4	
55 1 study) 35 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean socialization in the intervention groups was <b>0.05 standard</b> <b>deviations higher</b> (0.48 lower to 0.58 higher)
Commun	ication	(measured with: Vi	neland Adaptive E	Behaviour Scale	(VABS): Com	munication (chang	je score); Bette	er indicated b	y lower valu	es)	
55 1 study) 35 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean communication in the intervention groups was <b>0.12 standard</b> <b>deviations lower</b> (0.65 lower to 0.41 higher)

# 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

		Q	uality assessi	ment				Sun	nmary of I	indings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study eve	ent rates (%)	Relative effect	Anticipate	ed absolute effects
Follow up						evidence	With No treatment	With Picture Exchange Communication System (PECS) training for teachers	(95% CI)	Risk with No treatment	Risk difference with Picture Exchange Communication System (PECS) training for teachers (95% CI)
Spontan	eous	child comm	unicative	initiations	S (assessed w	ith: Behavioural	observatio	n (odds of being in a hig	her initiatior	l n category))	
0 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup>	N/A	N/A	<b>OR 2.73</b> (1.22 to	Study po	pulation
33 weeks						due to risk of bias,			6.09)	N/A	N/A
						imprecision				Moderate	
										0 per 1000	N/A
Spontan	eous o	child comm	unicative	initiations	<b>S</b> (assessed w	l /ith: Behavioural	observatio	n (odds of being in a hig	her initiatior	category))	1
0 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	undetected		N/A	N/A	<b>OR 1.08</b> (0.3 to	Study po	oulation
78 weeks						LOW <sup>1,2,3</sup> due to risk of			3.89)	N/A	N/A
						bias, imprecision				Moderate	
										0 per	N/A

										1000		
PECS u	ISE (asses	sed with: Behavio	oural observation	(odds of beir	ig in a higher ca	ategory for rate o	f PECS u	ise))				
) 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup>	N/A	N/A	<b>OR 3.90</b> (1.75 to	Study po	opulation	
33 weeks						due to risk of			8.69)	N/A	N/A	
						bias, imprecision				Moderate		
										0 per 1000	N/A	
PECS u	I <b>SE</b> (asses	sed with: Behavio	oural observation	(odds of beir	ng in a higher ca	ategory for rate o	f PECS u	ise))	I	1	-1	
0 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		N/A	N/A	<b>OR 1.56</b> (0.46 to	Study po	opulation	
78 weeks		inconcionary		Conouc		due to risk of			5.3)	N/A N/A		
						bias, imprecision				Moderate		
										0 per 1000	N/A	
Speech	/vocalis	sation use	(assessed with: E	Behavioural ol	oservation (odd	s of being in a hi	gher cate	egory for rate of sp	l beech/vocalisation u	se))		
0 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		N/A	N/A	<b>OR 1.10</b> (0.46 to	Study po	opulation	
33 weeks		moonsisterioy		5011045		due to risk of			2.63)	N/A	N/A	
						bias, imprecision				Moderat	e	
										0 per 1000	N/A	
Recepti	ive lang	juage (assess	ed with: British P	icture Vocabu	lary test (BPVS	s): Receptive lan	guage (oo	dds of being in a h	higher category on B	PVS))	1	
	serious <sup>1</sup>	no serious	no serious	very	undetected	<b>000</b>	N/A	N/A	OR 1.54		opulation	

(1 study)		inconsistency	indirectness	serious <sup>3</sup>		VERY LOW <sup>1,3</sup>			(0.52 to	N/A	N/A
33 weeks						due to risk of bias,			4.55)	Moderate	
						imprecision				0 per 1000	N/A
Express	sive lan	iguage (asse	ssed with: Expres		rd Picture Voca	bulary Test (EO	WPVT) Expressive	e language (odds o	of being in	a higher ca	tegory on EOWPVT))
0 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup>	N/A N/A		<b>OR 1.01</b> (0.89 to	Study po	
33 weeks						due to risk of			1.15)	N/A	N/A
						bias, imprecision				Moderate	
										0 per 1000	N/A
<sup>2</sup> Events<30	0	CI crosses both I					d outcome assess	ors were non-blind	ł	1	1

## PECS versus RPMT for speech and language as a direct outcome

		Q	uality assess	ment				Sum	mary of F	indings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rat	tes (%)	Relative effect	Anticipated ab	solute effects
Follow up						evidence	With Responsive Education and Prelinguistic Milieu Teaching (RPMT)	With Picture Exchange Communication System (PECS)		Risk with Responsive Education and Prelinguistic Milieu Teaching (RPMT)	Risk difference with Picture Exchange Communication System (PECS) (95% CI)
Frequen	cy of r	onimitative	e spoken a	acts (measu	red with: Behav	<i>i</i> oural observat	on; Better indicat	ed by lower values)	)		

36 (1 study) 26 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	17	19	N/A	N/A	The mean frequency of nonimitative spoken acts in the intervention groups was <b>0.61 standard</b> <b>deviations higher</b> (0.06 lower to 1.28 higher)
Frequer	ncy of n	onimitativ	e spoken a	acts (meas	ured with: Beha	vioural observation	on; Better i	ndicated by lower	values)		
36 (1 study) 52 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	17	19	N/A	N/A	The mean frequency of nonimitative spoken acts in the intervention groups was <b>0.03 standard</b> <b>deviations higher</b> (0.62 lower to 0.68 higher)
Number	r of diffe	erent nonir	nitative w	ords (meas	sured with: Beha	vioural observati	on; Better	indicated by lower	values)		
36 (1 study) 26 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	17	19	N/A	N/A	The mean number of different nonimitative words in the intervention groups was 0.49 standard deviations higher (0.18 lower to 1.15 higher)

36 (1 study) 52 weeks Number values)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup> ed with: EScs-	undetected	♥⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	17 nication Scale	19 s-Abridged): Number	N/A of picture e	N/A	The mean number of different nonimitative words in the intervention groups was <b>0.08 standard</b> <b>deviations higher</b> (0.57 lower to 0.74 higher)
36 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊕⊖⊝ LOW <sup>3,4</sup> due to imprecision, publication bias	17	19	N/A	N/A	The mean number of picture exchanges in the intervention groups was <b>0.8 standard</b> <b>deviations higher</b> (0.12 to 1.48 higher)
group chose between the as participar <sup>2</sup> N<400 and <sup>3</sup> N<400 <sup>4</sup> High risk or	to receive in treatment a nts were nor 1 95% CI cro f selective re	more hours of tra and follow-up peri h-blind and detect bases both line of	ining [mean: 10. lods, and this ind tion bias as iden no effect and m only post-interve	6 hours] than crease was gre tity and blindir easure of app ntion (and not	parents in the P eater for the PE ng of outcome a reciable benefit	ECS group [mea CS group [4 hou ssessors is not or harm (SMD -	an 7.9 hours]. rs] than for th reported 0.5/0.5)	In addition, the numb	er of hours ours]). The	of 'other interven re was also a hig	h risk of response bias

## 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

	Quality assessment	Summary of Findings
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Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event r	ates (%)	Relative effect	Anticipated ab	solute effects
Follow up							With Waitlist or treatment-as- usual control	With Music therapy	(95% CI)	Risk with Waitlist or treatment-as- usual control	Risk difference with Music therapy (95% CI)
Verbal c	ommu	nication (mea	sured with: Child	I hood Autism R	L Rating Scale (C	I CARS): Verbal com	I nmunication; Be	tter indicat	ed by lower	values)	·
24 (1 study) 30 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	12	12	N/A	N/A	The mean verbal communication in the intervention groups was <b>0.09 standard deviations</b> <b>lower</b> (0.89 lower to 0.71 higher
Non-ver	bal cor	nmunicatio	<b>n</b> (measured wit	h: Childhood A	utism Rating S	Scale (CARS): Nor	n-verbal commu	nication; E	letter indica	ted by lower valu	es)
24 (1 study) 30 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	12	12	N/A	N/A	The mean non-verbal communication in the intervention groups was <b>0.35 standard deviations</b> higher (0.45 lower to 1.16 higher
Express values)	ive lan	guage (mus	sic therapy	) (measured w	l <i>i</i> ith: Verbal Pro	duction Evaluatio	n Scale (VPES;	study-spe	cific): Expre	l essive language;	Better indicated by lower
32	no serious	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$ \bigoplus \bigoplus \bigoplus \bigoplus \bigoplus $ <b>MODERATE</b> <sup>2</sup>	14	18	N/A	N/A	The mean expressive language (music therapy)

values) 32 (1 study) 4 days	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	14	18	N/A	N/A	The mean expressive language (speech therapy) in the intervention groups was <b>1.09 standard deviations</b> higher (0.33 to 1.84 higher)
<sup>1</sup> N<400 and <sup>2</sup> N<400	I 95% CI cro	sses both line of n	o effect and mea	asure of appre	ciable benefit c	or harm (SMD -0.5	/0.5)		1	1	

# 1.16.3 Behavioural interventions for speech and language as an indirect outcome

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

		Qı	ality assessm	ent					Summa	ry of Finding	js
(studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		Study even (%)	t rates	Relative effect	Anticipated a	absolute effects
Follow up						evidence	With Treatment- as-usual	With ESDM or P-ESDM	(95% CI)	Risk with Treatment-as- usual	Risk difference with ESDM or P-ESDM (95% Cl)
Receptive	e languag	<b>ge (ESDM)</b> (me	easured with: Mull	en Scales of E	arly Learning (I	MSEL): Receptive	e Language; E	Better indica	ated by lowe	r values)	
45 (1 study) 104 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	21	24	N/A	N/A	The mean receptive language (esdm) in the intervention groups was <b>0.6 standard deviations</b> <b>higher</b> (0 to 1.2 higher)
Expressiv	ve langua	age (ESDM) (n	neasured with: Mu	ullen Scales of	Early Learning	(MSEL): Express	ive Language	e; Better ind	dicated by lo	wer values)	
45 (1 study)		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	$\oplus \oplus \ominus \ominus$	21	24	N/A	N/A	The mean expressive language (esdm) in the

104 weeks						LOW <sup>1</sup> due to imprecision					intervention groups was 0.55 standard deviations higher (0.05 lower to 1.15 higher)
Phrases	understo	od (measured wit	h: MacArthur Cor	nmunication De	evelopmental Ir	ventories (CDI):	Phrases unde	erstood; Be	tter indicated	d by lower valu	es)
98 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	49	49	N/A	N/A	The mean phrases understood in the intervention groups was <b>0.23 standard deviations</b> <b>lower</b> (0.63 lower to 0.16 higher)
Vocabula	ary comp	rehension (me	easured with: Mac	Arthur Commu	inication Develo	opmental Inventor	ies (CDI): Vo	cabulary c	omprehensio	on; Better indic	ated by lower values)
98 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	49	49	N/A	N/A	The mean vocabulary comprehension in the intervention groups was <b>0.19 standard deviations</b> <b>lower</b> (0.58 lower to 0.21 higher)
Vocabula	ary produ	ction (measured	d with: MacArthur	Communicatio	n Development	al Inventories (CI	DI): Vocabula	ry production	on; Better ind	dicated by lowe	er values)
98 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>2,3</sup> due to risk of bias, imprecision	49	49	N/A	N/A	The mean vocabulary production in the intervention groups was <b>0.05 standard deviations</b> <b>higher</b> (0.35 lower to 0.45 higher)
Total ges	stures pro	oduced (measu	red with: MacArth	ur Communica	tion Developme	ental Inventories (	CDI): Total g	estures pro	oduced; Bette	er indicated by	lower values)
98 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	49	49	N/A	N/A	The mean total gestures produced in the intervention groups was 0.13 standard deviations lower

								(0.53 lower to 0.26 higher)
<sup>2</sup> High risk of	performance	es both line of no e and response bias ad in the interventio	as intervention a			bias as com	e measure was	s parent-rated and parents

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

		Qı	uality assessn	nent				Si	ummary o	f Finding	js
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study e	event rates (%)	Relative effect	Anticipa	ited absolute effects
Follow up						evidence	With Control	With EIBI versus parent training for speech and language as an indirect outcome	(95% CI)	Risk with Control	Risk difference with EIBI versus parent training for speech and language as an indirect outcome (95% CI)
Receptiv	ve lang	uage (measured	I with: Reynell De	evelopmental L	anguage Scal	e: Comprehensio	n; Better	indicated by lower value	ues)		
28 (1 study) 260 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	13	15	N/A	N/A	The mean receptive language in the intervention groups was <b>0.48 standard deviations</b> higher (0.28 lower to 1.23 higher)
Express	ive lang	guage (measur	ed with: Reynell I	Developmental	l Language Sc	ale: Expressive L	anguage	e; Better indicated by lo	wer values)	<u> </u>	
28 (1 study) 260 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	13	15	N/A	N/A	The mean expressive language in the intervention groups was 0.36 standard deviations higher

												(0.39 lower to 1.11 higher)
Receptiv	/e + Ex	pressive la	nguage (mea	asured with: R	eynell Developr	mental Language	e Scale:	Total; Better in	dicated by lowe	er values	5)	
1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	13	15	N/A	N	N/A	The mean receptive + expressive language in the intervention groups was <b>0.63 standard deviations</b> higher (0.13 lower to 1.39 higher)

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

		Q	uality assessm	nent				Su	mmary of	Finding	gs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	event rates (%)	Relative effect	Anticipa	ated absolute effects
Follow up						evidence	With Control	With Home-based versus Centre-based EBI for speech and language as an indirect outcome	(95% CI)	Risk with Control	Risk difference with Home-based versus Centre-based EBI for speech and language as an indirect outcome (95% CI)
53 (1 study)	-	no serious	with: Reynell De	velopmental L	anguage Scal	e: Comprehens	on; Bette	r indicated by lower valu	N/A	N/A	The mean receptive
40 weeks	bias	inconsistency	indirectricss	3011003		due to					language in the intervention

53 (1 study) 40 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	26	27	N/A	N/A	The mean expressive language in the intervention groups was <b>0.26 standard deviations</b> <b>lower</b> (0.8 lower to 0.28 higher)
56 (1 study) 40 weeks	serious <sup>2</sup>	age functio	no serious indirectness	ed with: Pragm very serious <sup>1</sup>	undetected		etter indi	icated by lower values) 27	N/A	N/A	The mean everyday language functioning in the intervention groups was 0.52 standard deviations lower
<sup>2</sup> High risk of	f performance		as as intervention	n administrator	s and participa	r harm (SMD -0.5 ants were non-bli	nd, and	risk of detection bias in and were part of the inter		nown as	(1.06 lower to 0.01 higher)

# **1.16.4** Educational 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

		Qı	uality assessn	nent				Sun	nmary of I	Findir	ngs
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study With IBI- only	, , ,	Relative effect (95% CI)	Antic Risk with IBI- only	ipated absolute effects Risk difference with Combined computer-assisted educational intervention and intensive behavioural intervention (IBI) day class program (95% CI)
Receptiv	e lang	uage (measure	ed with: Peabody	Picture Vocal	oulary Test, 3r	d Ed. (PPVT-III)	: Total	; Better indicated by lower va	lues)	1	

46 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	24	22	N/A	N/A	The mean receptive language in the intervention groups was <b>0.33 standard deviations</b> <b>higher</b> (0.25 lower to 0.92 higher)
Recepti values)	ive lang	juage (pres	school sub	group ar	nalysis) (m	easured with: Pe	abody	y Picture Vocabula	ry Test, 3rd Ed. (PP)	/T-III): T	otal; Better indicated by lower
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \ominus \ominus \ominus \\ \textbf{VERY LOW}^{1,2} \\ \text{due to risk of} \\ \text{bias,} \\ \text{imprecision} \end{array}$	12	11	N/A	N/A	The mean receptive language (preschool subgroup analysis) in the intervention groups was <b>0.4 standard deviations</b> <b>higher</b> (0.43 lower to 1.22 higher)
Recept	ive lang	juage (K-1	subgroup	analysis	(measured wi	th: Peabody Pict	ure V	ocabulary Test, 3rd	d Ed. (PPVT-III): Tota	al; Bette	r indicated by lower values)
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	12	11	N/A	N/A	The mean receptive language (k-1 subgroup analysis) in the intervention groups was <b>0.27 standard deviations</b> <b>higher</b> (0.55 lower to 1.09 higher)
Recepti	ive lang	<b>Juage</b> (measu	red with: Briganc	e Inventory of	Child Develop	ment: Receptive	langu	age; Better indicat	ed by lower values)		
46 (1 study) 13 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	24	22	N/A	N/A	The mean receptive language in the intervention groups was 0.09 standard deviations higher (0.49 lower to 0.67 higher)
Recept values)	ive lang	juage (pres	school sub	group ar	nalysis) (m	easured with: Br	gance	e Inventory of Child	I Development: Rece	eptive la	nguage; Better indicated by lower

23 (1 study) 13 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	12	11	N/A	N/A	The mean receptive language (preschool subgroup analysis) in the intervention groups was <b>0.02 standard deviations</b> <b>lower</b> (0.84 lower to 0.8 higher)
Recepti	ive lang	juage (K-1	subgroup	analysis)	(measured wi	th: Brigance Inve	entory	of Child Developmer	nt: Receptive lang	uage; Be	etter indicated by lower values)
23 (1 study) 13 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	12	11	N/A	N/A	The mean receptive language (k-1 subgroup analysis) in the intervention groups was <b>0.2 standard deviations</b> higher (0.62 lower to 1.02 higher)
Expres	sive lan	<b>guage</b> (meas	sured with: Expre	ssive Vocabul	ary Test (EVT)	: Total; Better inc	licate	d by lower values)		<b>F</b>	
46 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	24	22	N/A	N/A	The mean expressive language in the intervention groups was <b>0.27 standard deviations</b> higher (0.31 lower to 0.85 higher)
Expres	sive lan	iguage (pre	eschool su	bgroup a	inalysis) (	I measured with: E	Expres	ssive Vocabulary Tes	t (EVT): Total; Be	tter indic	ated by lower values)
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	12	11	N/A	N/A	The mean expressive language (preschool subgroup analysis) in the intervention groups was 0.33 standard deviations higher (0.5 lower to 1.15 higher)
Expres	sive lan	guage (K-1	l subgroup	o analysi:	S) (measured	I with: Expressive	Voca	bulary Test (EVT): To	I otal; Better indicate	ed by low	ver values)
23 (1 study)	serious <sup>1</sup>	no serious	no serious	very	undetected		12	11	N/A	N/A	The mean expressive language (k-1 subgroup analysis) in the

13 weeks		inconsistency	indirectness	serious <sup>2</sup>		due to risk of bias, imprecision					intervention groups was 0.22 standard deviations higher (0.6 lower to 1.04 higher)
Express	ive lan	<b>guage</b> (measu	ured with: Brigan	ce Inventory o	of Child Develo	pment: Expressi	ve lar	nguage; Better indicated by I	ower values)	)	•
46 (1 study) 13 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	24	22	N/A	N/A	The mean expressive language in the intervention groups was <b>0.01 standard deviations</b> <b>higher</b> (0.57 lower to 0.59 higher)
Express lower values)		iguage (pre	school sul	bgroup a	nalysis) (	measured with: I	Brigar	nce Inventory of Child Develo	opment: Exp	ressive	language; Better indicated by
23 (1 study) 13 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	12	11	N/A	N/A	The mean expressive language (preschool subgroup analysis) in the intervention groups was <b>0.07 standard deviations</b> <b>higher</b> (0.75 lower to 0.89 higher)
Express	ive lan	guage (K-1	subgroup	analysis	<b>5)</b> (measured	with: Brigance In	vento	bry of Child Development: Ex	pressive lan	guage;	Better indicated by lower values)
23 (1 study) 13 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	12	11	N/A	N/A	The mean expressive language (k-1 subgroup analysis) in the intervention groups was 0.05 standard deviations lower (0.87 lower to 0.77 higher)
assessors no <sup>2</sup> N<400 and <sup>3</sup> High risk of	t reported. 95% CI cr performan	osses both line of ace and response	no effect and me bias as intervent	easure of appr ion administra	reciable benefit	t or harm (SMD ipants non-blind	0.5/0 . Risk	.5)	unknown as	the ide	ntity and blinding of outcome

		Q	uality assessi	nent				Su	mmary of	Findings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event	rates (%)	Relative effect	Anticipated a	bsolute effects
Follow up						evidence	With Intervention- manual-only control	With Inclusive educational intervention (LEAP) training	(95% CI)	Risk with Intervention- manual-only control	Risk difference with Inclusive educational intervention (LEAP) training (95% CI)
Languag	<b>je</b> (measu	ured with: Prescho	l pol Language Sc	ale-4 (PLS-4):	Total; Better i	I ndicated by lowe	er values)			<u> </u>	
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	117	177	N/A	N/A	The mean language in the intervention groups was <b>0.94 standard</b> <b>deviations higher</b> (0.7 to 1.19 higher)
Receptiv	ve lang	<b>Juage</b> (measure	ed with: Mullen S	Scales of Early	Learning (MS	EL): Receptive L	anguage Age	(months); Better inc	dicated by lo	wer values)	
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	117	177	N/A	N/A	The mean receptive language in the intervention groups was 1.1 standard deviations higher (0.85 to 1.35 higher)
Express	ive lan	guage (measi	ured with: Muller	Scales of Ear	ly Learning (M	ISEL): Expressiv	l ve Language Ag	ge (months); Better	indicated by	v lower values)	
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \ominus \ominus$ <b>LOW</b> <sup>1,2</sup> due to risk of bias,	117	177	N/A	N/A	The mean expressive language in the intervention groups was <b>0.49 standard</b>

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

					imprecision				deviations higher (0.25 to 0.73 higher)
<sup>1</sup> High risk o outcome ass <sup>2</sup> N<400	•	oias as interventi	on administrat	ors and partici	pants non-blind.	In addition, risk of detection bias is	unclear/ur	known as identity	y and blinding of

# **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

			Quality asses	sment		Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study	event rates (%)	Relative effect	Anticipa	ated absolute effects
Follow up							With Control	With Parent training versus treatment-as- usual for speech and language	(95% CI)	Risk with Control	Risk difference with Parent training versus treatment-as- usual for speech and language (95% CI)
						EL): Receptive Langua dicated by lower value		lacArthur Communica	ation Develo	pmental I	nventories (CDI): Vocabulary
147 (3 studies) 12-52 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	57	90	N/A	N/A	The mean receptive language in the intervention groups was <b>0.2 standard deviations</b> <b>lower</b> (0.54 lower to 0.14 higher)
Receptiv	ve lang	uage (direc	t outcome	) (measured v	vith: Mullen Sc	ales of Early Learning	(MSEL)	): Receptive Languag	le; Better in	dicated by	/ lower values)
20 (1 study) 12 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias,	10	10	N/A	N/A	The mean receptive language (direct outcome) in the intervention groups was <b>0.09 standard deviations</b>

					imprecision					higher (0.78 lower to 0.97 higher)
ve lang	juage (indi	rect outcor	<b>ne)</b> (measur	ed with: MacAr	rthur Communication I	Develop	mental Invento	ries (CDI): Voca	bulary Co	mprehension; Better indicated
serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to risk of bias, imprecision	12	12	N/A	N/A	The mean receptive language (indirect outcome in the intervention groups was 0.71 standard deviations higher (0.12 lower to 1.54 higher)
_		rect outcor	ne; PEC-	PEBM co	ombined) (measu	ured with	h: Reynell Deve	elopmental Lang	uage Scal	e: Comprehension; Better
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>6</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,6</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean receptive language (indirect outcome pec+pebm combined) in th intervention groups was <b>0.5 standard deviations</b> <b>lower</b> (0.91 to 0.08 lower)
								ommunication D	evelopme	ntal Inventories (CDI):
serious <sup>1</sup>	serious <sup>7</sup>	no serious indirectness	serious <sup>6</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,6,7</sup> due to risk of bias, inconsistency, imprecision	57	90	N/A	N/A	The mean expressive language in the interventio groups was 0.14 standard deviations lower (0.48 lower to 0.2 higher)
	es) serious <sup>5</sup> /e lang ower value serious <sup>1</sup> ive lan	es)          serious <sup>5</sup> no serious inconsistency         /e language (indional ower values)         serious <sup>1</sup> no serious inconsistency         serious <sup>1</sup> no serious inconsistency         ive language (meas broduction or Reynell Develow         serious <sup>1</sup> serious <sup>7</sup>	es)          serious <sup>5</sup> no serious inconsistency       no serious indirectness         /e language (indirect outcor ower values)         serious <sup>1</sup> no serious inconsistency       no serious indirectness         serious <sup>1</sup> no serious inconsistency       no serious indirectness         ive language (measured with: Muller roduction or Reynell Developmental Langua         serious <sup>1</sup> serious <sup>7</sup> no serious indirectness	es)          serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>3</sup> /e language (indirect outcome; PEC- ower values)       very serious       serious; pec- serious         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>6</sup> ive language (measured with: Mullen Scales of Ea production or Reynell Developmental Language Scale: Exp         serious <sup>1</sup> serious <sup>7</sup> no serious indirectness	es) serious <sup>5</sup> no serious no serious very serious <sup>3</sup> undetected /e language (indirect outcome; PEC+PEBM co ower values) serious <sup>1</sup> no serious no serious serious <sup>6</sup> undetected inconsistency no serious serious <sup>6</sup> undetected ive language (measured with: Mullen Scales of Early Learning (M roduction or Reynell Developmental Language Scale: Expressive Language serious <sup>1</sup> serious <sup>7</sup> no serious serious <sup>6</sup> undetected	ve language (indirect outcome) (measured with: MacArthur Communication les)         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>3</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to risk of bias, imprecision         /e language (indirect outcome; PEC+PEBM combined) (measured ower values)       no serious inconsistency       no serious indirectness       serious <sup>6</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,6</sup> due to risk of bias, imprecision         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>6</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,6</sup> due to risk of bias, imprecision         ive language (measured with: Mullen Scales of Early Learning (MSEL): Expressive Lar roduction or Reynell Developmental Language Scale: Expressive Language; Better indicated to serious <sup>1</sup> serious <sup>7</sup> no serious indirectness       serious <sup>6</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>1,6,7</sup> due to risk of bias, inconsistency,	/e language (indirect outcome) (measured with: MacArthur Communication Developes)         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>3</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3.5</sup> due to risk of bias, imprecision       12         /e language (indirect outcome; PEC+PEBM combined) (measured with ower values)       no serious indirectness       serious <sup>6</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1.6</sup> due to risk of bias, imprecision       35         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>6</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1.6</sup> due to risk of bias, imprecision       35         ive language (measured with: Mullen Scales of Early Learning (MSEL): Expressive Language ( troduction or Reynell Developmental Language Scale: Expressive Language; Better indicated by lower       ⊕⊖⊖⊖ VERY LOW <sup>1.6.7</sup> due to risk of bias, inconsistency,       57	re language (indirect outcome)       (measured with: MacArthur Communication Developmental Invento         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>3</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3.5</sup> due to risk of bias, imprecision       12       12         /e language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental ower values)       no serious indirectness       serious <sup>6</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1.6</sup> due to risk of bias, imprecision       35       68         iserious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>6</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1.6</sup> due to risk of bias, imprecision       35       68         ive language (measured with: Mullen Scales of Early Learning (MSEL): Expressive Language or MacArthur C troduction or Reynell Developmental Language Scale: Expressive Language; Better indicated by lower values)       57       90         serious <sup>1</sup> serious <sup>7</sup> no serious indirectness       serious <sup>6</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>1.6,7</sup> due to risk of bias, inconsistency,       57       90	/e language (indirect outcome) (measured with: MacArthur Communication Developmental Inventories (CDI): Voca es)         serious <sup>6</sup> no serious inconsistency       no serious indirectness       very serious <sup>3</sup> undetected       ⊕⊙⊙⊙ VERY LOW <sup>3.5</sup> due to risk of bias, imprecision       12       12       N/A         //e language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Lang ower values)       no serious indirectness       serious <sup>6</sup> undetected       ⊕⊕⊙⊙ LOW <sup>1.6</sup> due to risk of bias, imprecision       35       68       N/A         ive language (measured with: Mullen Scales of Early Learning (MSEL): Expressive Language or MacArthur Communication D roduction or Reynell Developmental Language Scale: Expressive Language; Better indicated by lower values)       90       90       N/A         serious <sup>1</sup> serious <sup>7</sup> no serious indirectness       serious <sup>9</sup> undetected       ⊕⊙⊙⊙ LOW <sup>1.6</sup> due to risk of bias, imprecision       57       90       N/A	ve language (indirect outcome) (measured with: MacArthur Communication Developmental Inventories (CDI): Vocabulary Cores)         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>3</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>3.6</sup> due to risk of bias, imprecision       12       12       N/A       N/A         ver language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Language Scal over values)       no serious indirectness       serious <sup>6</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,6</sup> due to risk of bias, imprecision       35       68       N/A       N/A         ive language (measured with: Mullen Scales of Early Learning (MSEL): Expressive Language or MacArthur Communication Development roductor or Reynell Developmental Language Scale: Expressive Language; Better indicated by lower values)       \$7       90       N/A       N/A

20 (1 study)	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>3,4</sup>	10	10	N/A	N/A	The mean expressive language (direct outcome) in
12 weeks						due to risk of bias, imprecision					the intervention groups was 0.15 standard deviations lower
•		iguage (ind	lirect outco	ome) (meas	ured with: Mac	Arthur Communication	n Develo	opmental Inventor	ies (CDI): Voca	bulary Pro	(1.03 lower to 0.73 higher)
lower values	.)										
24 (1 study) 52 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,5</sup> due to risk of bias, imprecision	12	12	N/A	N/A	The mean expressive language (indirect outcome) in the intervention groups was <b>0.56 standard deviations</b> higher (0.26 lower to 1.38 higher)
Express Better indica			lirect outco	ome; PEC	C+PEBM c	combined) (mea	asured w	vith: Reynell Deve	lopmental Lang	juage Sca	le: Expressive Language;
			Iirect outco	ome; PEC	C+PEBM c	Combined) (mean ⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	ith: Reynell Deve	N/A	Juage Sca	Ide: Expressive Language; The mean expressive language (indirect outcome; pec+pebm combined) in the intervention groups was <b>0.31 standard deviations</b> <b>lower</b> (0.72 lower to 0.1 higher)
Better indica 103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean expressive language (indirect outcome; pec+pebm combined) in the intervention groups was 0.31 standard deviations lower
Better indica 103 (1 study) 46 weeks <b>Overall</b> non-verbal (- 24	serious <sup>1</sup>	no serious inconsistency ge rating o	no serious indirectness f non-verb	very serious <sup>3</sup> al (<5 wo	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision irect outcome ⊕⊖⊖⊖	35 ) (asses 9/12	68 ssed with: Dichoto 4/12	omous: Overall I	N/A danguage	The mean expressive language (indirect outcome; pec+pebm combined) in the intervention groups was <b>0.31 standard deviations</b> <b>lower</b> (0.72 lower to 0.1 higher)
Better indica 103 (1 study) 46 weeks <b>Overall</b> non-verbal (-	serious <sup>1</sup> serious <sup>1</sup> langua <5 words))	no serious inconsistency ge rating o	no serious indirectness f non-verb	very serious <sup>3</sup> al (<5 wo	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35 ) (asses	68 ssed with: Dichoto	N/A pmous: Overall I	N/A danguage	The mean expressive language (indirect outcome; pec+pebm combined) in the intervention groups was <b>0.31 standard deviations</b> <b>lower</b> (0.72 lower to 0.1 higher) rating (based on ADI-R) of <b>population</b>

										750 per 1000	<b>420 fewer per 1000</b> (from 608 fewer to 37 more)
Overall words)	langua	ge rating o	f single wo	ord speed	ch (indire	ct outcome) (a	ssessed	with: Dichotomo	ous: Overall lang	uage ratin	g (based on ADI-R) of single
24 (1 study)	serious⁵	no serious inconsistency	no serious indirectness	very serious <sup>8</sup>	undetected		3/12 (25%)	5/12 (41.7%)	<b>RR 1.67</b> (0.51 to	Study p	opulation
52 weeks						due to risk of bias, imprecision		(1117,0)	5.46)	250 per 1000	<b>167 more per 1000</b> (from 123 fewer to 1000 more)
										Modera	te
										250 per 1000	<b>167 more per 1000</b> (from 123 fewer to 1000 more)
24 (1 study)	serious <sup>5</sup>	no serious	no serious indirectness	very serious <sup>8</sup>	undetected		0/12 (0%)	3/12 (25%)	RR 7 (0.4 to		d on ADI-R) of phrase opulation
52 weeks		lineeneisteney		5011005		due to risk of bias, imprecision	(0,0)	(2070)	122.44)	0 per 1000	N/A
										Moderate	
										0 per 1000	N/A
Total ge indicated by		•	(indirect o	utcome) (	(measured with	i: MacArthur Commun	ication E	Developmental Ir	nventories (CDI):	Total ges	tures produced; Better
24	serious⁵	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		12	12	N/A	N/A	The mean total gestures produced (indirect outcome

					imprecision		<b>0.58 standard deviations</b> <b>higher</b> (0.24 lower to 1.4 higher)
<ul> <li><sup>2</sup> I-squared value in</li> <li><sup>3</sup> N&lt;400 and 95% (I</li> <li><sup>4</sup> High risk of perfor outcome assessor/</li> <li><sup>5</sup> High risk of perfor parents were non-b</li> <li><sup>6</sup> N&lt;400</li> <li><sup>7</sup> I-squared value in</li> </ul>	licates considerable h I crosses both line of nance and response l are not reported nance and response l ind and involved in th dicates moderate hete	neterogeneity no effect and mea bias as intervention bias as intervention e intervention erogeneity	asure of appre on administrate	ciable benefit ors and partici	•	5) and risk of detection bias is and high risk of detection bia	wn as the identity and blinding of measure was parent-rated and

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

		Qı	uality assessn	nent				Su	mmary of	Findin	gs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	event rates (%)	Relative effect	Anticip	ated absolute effects
Follow up						evidence	With Control	With Parent and day-care staff training versus standard day-care for speech and language as an indirect outcome	(95% CI)	Risk with Control	Risk difference with Parent and day-care staff training versus standard day-care for speech and language as an indirect outcome (95% Cl)
Langua	<b>ge</b> (measi	ured with: Early Int	ervention Develo	opmental Profil	e (EIDP)/Pres	chool Developr	nental Pr	ofile (PSDP): Language; I	Better indica	ated by Ic	ower values)
35 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to	19	16	N/A	N/A	The mean language in the intervention groups was <b>0.66 standard deviations</b>

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

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

		Qı	uality assessi	nent				Sum	mary of F	indings	5
•		Inconsistency	Indirectness	Imprecision			Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Caregiver-mediated social-communication interventions versus treatment-as-usual for speech and language as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Caregiver- mediated social-communication interventions versus treatment- as-usual for speech and language as an indirect outcome (95% Cl)
Receptive	e langu	age (clinicia	n-rated) (me	asured with: N	Iullen Scales	of Early Learning	(MSEL)	: Receptive Language Age (	months) or	Prescho	ol Language Scale-3 (PLS-3):
Auditory Com	prehensior	n; Better indicated	by lower values	5)							
```	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	112	113	N/A	N/A	The mean receptive language (clinician-rated) in the intervention groups was <b>0.04 standard deviations</b> <b>higher</b> (0.23 lower to 0.30 higher)
Receptive	e langua	age (parent-	rated) (measu	ured with: Mac	Arthur Comm	unication Develop	omental	Inventories (CDI): Vocabula	ry Compret	nension;	Better indicated by lower
180 (2 studies) 52-56 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \ominus \ominus$ LOW <sup>1,2</sup> due to risk of bias, imprecision	89	91	N/A	N/A	The mean receptive language (parent-rated) in the intervention groups was <b>0.16 standard deviations</b> <b>higher</b> (0.13 lower to 0.45 higher)
-	-	uage (clinician munication; Bett	• •		Mullen Scale	s of Early Learnin	g (MSE	L): Expressive Language Ag	e (months)	or Preso	chool Language Scale-3
225 (3 studies) 39-56 weeks	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\begin{array}{c} \oplus \oplus \bigoplus \bigcirc \\ \textbf{MODERATE}^1 \\ \text{due to} \end{array}$	112	113	N/A	N/A	The mean expressive language (clinician-rated) in the intervention groups was

	bias					imprecision					<b>0.03 standard deviations</b> <b>higher</b> (0.23 lower to 0.29 higher)
Expressi	ve lang	uage (parent	t <b>-rated)</b> (mea	sured with: Ma	acArthur Com	munication Deve	lopmer	ntal Inventories (CD	0I): Vocabulary Pro	duction; B	etter indicated by lower values)
180 (2 studies) 52-56 weeks		no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	89	91	N/A	N/A	The mean expressive language (parent-rated) in the intervention groups was <b>0.05 standard deviations</b> higher (0.24 lower to 0.34 higher)
<sup>1</sup> N<400 <sup>2</sup> High risk of parents were		ce and response b	bias as intervent	ion administrat	tors and partic	cipants were non-	-blind,	and high risk of det	ection bias as this	outcome	measure was parent-rated and

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

		C	uality assessr	ment		Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event	• • •	Relative effect	Anticipated a	bsolute effects
Follow up									(95% CI)	Risk with Treatment-as- usual	Risk difference with Social skills group (95% Cl)
Idiomatio	c langı	Iage (measured v	with: Comprehens	i sive Assessme	nt of Spoken L	I anguage (CASL): I	l diomatic Lang	uage; Bette	r indicated b	l by lower values)	
34 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	16	18	N/A	N/A	The mean idiomatic language in the intervention groups was <b>0.05 standard</b> <b>deviations higher</b> (0.62 lower to 0.73

										higher)
blind and no	reliability or	e and response bia validity data for the sses both line of no	e use of this scale	in this age gro	oup (only for >1	1 years)	0	n bias as res	earcher-rated ar	nd researchers were non-

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

		Qı	ality assessn	nent				Sı	ımmary of	Finding	gs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	event rates (%)	Relative effect	Anticip	ated absolute effects
Follow up						evidence	With Control	With Combined joint attention training and EBI/EIBI versus EBI/EIBI only for speech and language as an indirect outcome	— (95% CI)	Risk with Control	Risk difference with Combined joint attention training and EBI/EIBI versus EBI/EIBI only for speech and language as an indirect outcome (95% CI)
Receptive by lower value		uage (measure	d with: Reynell I	Developmental	Language Sc	ale: Comprehe	nsion or	Mullen Scales of Early Le	arning (MSE	EL): Rece	ptive language; Better indicated
85 (2 studies) 6-26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	41	44	N/A	N/A	The mean receptive language in the intervention groups was <b>0.27 standard deviations</b> <b>higher</b> (0.16 lower to 0.69 higher)
Receptive by lower value		luage (measure	l d with: Reynell I	Developmental	Language Sc	ale: Comprehe	nsion or	Mullen Scales of Early Le	arning (MSE	L): Rece	ptive language; Better indicate
85 (2 studies) 26-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	41	44	N/A	N/A	The mean receptive language in the intervention groups was <b>0.23 standard deviations</b> <b>higher</b> (0.2 lower to 0.65 higher)

36 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	16	20	N/A	N/A	The mean receptive language in the intervention groups was 0.36 standard deviations higher (0.31 lower to 1.02 higher)
Express indicated by			ured with: Reyne	ell Developme	ntal Language	Scale: Express	ve Lang	guage or Mullen S	cales of Early Lear	ning (MSE	EL): Expressive Language; Better
85 (2 studies) 6-26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	41	44	N/A	N/A	The mean expressive language in the intervention groups was <b>0.19 standard deviations</b> higher (0.23 lower to 0.62 higher)
-			ured with: Reyne	ell Developme	ntal Language	Scale: Express	ve Lang	guage or Mullen S	cales of Early Lear	ning (MSE	L): Expressive Language; Better
Express indicated by 85 (2 studies) 26-52 weeks	lower value no serious		no serious indirectness	very serious <sup>1</sup>	undetected	Scale: Expressi ⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	ve Lang	guage or Mullen S	cales of Early Lear	ning (MSE	EL): Expressive Language; Better The mean expressive language in the intervention groups was 0.29 standard deviations higher (0.14 lower to 0.72 higher)
indicated by 85 (2 studies) 26-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	41	44		N/A	The mean expressive language in the intervention groups was 0.29 standard deviations higher

# **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

		Qua	ality assessn	nent				Summ	ary of Fi	ndings	
		Inconsistency	Indirectness	Imprecision		Overall	Study e	vent rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Acupuncture/Acupressure and language therapy versus language therapy only for the coexisting problem of speech and language as a direct outcome	effect (95% CI)	Risk with Control	Risk difference with Acupuncture/Acupressure and language therapy versus language therapy only for the coexisting problem of speech and language as a direct outcome (95% Cl)
Receptive	e sema	ntics (measure	ed with: Arabic	Language Tes	st: Receptive S	Semantics; Be	tter indica	ated by lower values)			
20 (1 study) 39 weeks			no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	10	10	N/A	N/A	The mean receptive semantics in the intervention groups was <b>0.66 standard deviations</b> <b>higher</b> (0.24 lower to 1.57 higher)
Expressiv	ve sem	antics (measu	ured with: Arabi	c Language T	est: Expressiv	e Semantics;	Better ind	dicated by lower values)			
20 (1 study) 39 weeks		no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	10	10	N/A	N/A	The mean expressive semantics in the intervention groups was <b>0.08 standard deviations</b> <b>lower</b> (0.96 lower to 0.79 higher)
Attention	level (	measured with: A	rabic Language	e Test: Attentio	on Level; Bette	er indicated by	lower va	ilues)	•	•	•
20	serious <sup>1</sup>	no serious	no serious	very	undetected	$\oplus \Theta \Theta \Theta$	10	10	N/A	N/A	The mean attention level in the

(1 study) 39 weeks		inconsistency	indirectness	serious <sup>2</sup>		VERY LOW <sup>1,2</sup> due to risk of bias, imprecision					intervention groups was <b>0.36 standard deviations</b> <b>higher</b> (0.53 lower to 1.24 higher)
Positive	treatme	ent respons	e for voca	lization (as	sessed with: I undetected	Dichotomous: ⊕⊝⊝⊝		y of improvement in basic deve 1/16	elopmental RR 0.44	1	nent) population
(1 study) 39 weeks	Concus	inconsistency	indirectness	serious <sup>3</sup>		VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	(14.3%)		(0.04 to 4.32)	143 per 1000	80 fewer per 1000 (from 137 fewer to 474 more)
										Moder	ate
										143 per 1000	<b>80 fewer per 1000</b> (from 137 fewer to 475 more)
Positive	treatme	ent respons	e for babb	ling (assess	ed with: Dicho	tomous: Freq	uency of ir	nprovement in basic developm	nental asse	ssment)	
30 (1 study)	serious <sup>1</sup>	no serious	no serious indirectness	very serious <sup>3</sup>	undetected		4/14 (28.6%)	2/16	<b>RR 0.44</b> (0.09 to	Study	population
39 weeks		inconsistency	Indirectiless	senous		LOW <sup>1,3</sup> due to risk of bias,	(20.0%)	(12.5%)	2.04)	286 per 1000	<b>160 fewer per 1000</b> (from 260 fewer to 297 more)
						imprecision				Moder	ate
										286 per 1000	<b>160 fewer per 1000</b> (from 260 fewer to 297 more)
Positive	treatme	ent respons	e for spee	<b>ch</b> (assessed	I with: Dichoto	mous: Freque	ency of imp	provement in basic development	ntal assess	ment)	<u> </u>
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		2/14 (14.3%)	8/16 (50%)	<b>RR 3.5</b> (0.89 to	Study	population
39 weeks						LOW <sup>1,3</sup> due to risk of bias,	(		13.82)	143 per 1000	<b>357 more per 1000</b> (from 16 fewer to 1000 more)

						imprecision				Moder	ate
										143 per 1000	<b>358 more per 1000</b> (from 16 fewer to 1000 more)
		ent respons	-	ch compr	ehension	(assessed wit	th: Dichoto	omous: Frequency of	f improvement in Chir	a Reha	bilitation Research Council
30 (1 study)	serious <sup>1</sup>	no serious	no serious indirectness	very serious <sup>3</sup>	undetected		5/14	5/16 (31.3%)	<b>RR 0.88</b> (0.32 to	Study	population
39 weeks		inconsistency	Indirectiless	senous		<b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	(35.7%)	(31.3%)	(0.32 10	357 per 1000	<b>43 fewer per 1000</b> (from 243 fewer to 500 more)
						Imprecision				Moder	ate
										357 per 1000	43 fewer per 1000 (from 243 fewer to 500 more)
Positive sign-significa		-	e for spee	ch expres	sion (asses	sed with: Dich ⊕⊝⊝⊝	notomous:	Frequency of improv	vement in China Reha	1	n Research Council (CRRC)
(1 study) 39 weeks	301003	inconsistency	indirectness	serious <sup>3</sup>		VERY LOW <sup>1,3</sup> due to risk of bias,	(21.4%)		(0.31 to 4.34)	214 per 1000	36 more per 1000 (from 148 fewer to 716 more)
						imprecision				Moder	ate
										214 per 1000	<b>36 more per 1000</b> (from 148 fewer to 715 more)
	treatmore relations s	-	e for spee	ch imitatio	ON (assessed	with: Dichoto	mous: Fre	equency of improvem	nent in China Rehabili	tation R	esearch Council (CRRC) sign-
significance											

(1 study) 39 weeks		inconsistency	indirectness	serious <sup>3</sup>		VERY LOW <sup>1,3</sup> due to risk of bias,	(14.3%)	(6.3%)	(0.04 to 4.32)	143 per 1000	80 fewer per 1000 (from 137 fewer to 474 more)
						imprecision				Mode	rate
										143 per 1000	80 fewer per 1000 (from 137 fewer to 475 more)
		ent respons		bulary coi	mprehens	sion (assess	ed with: I	Dichotomous: Frequency of imp	rovement i	n China	Rehabilitation Research Council
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		0/14 (0%)	5/16 (31.3%)	<b>RR 9.71</b> (0.58 to	Study	population
39 weeks		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,				LOW <sup>1,3</sup> due to risk of bias,	()	()	161.31)	0 per 1000	N/A
						imprecision				Moderate	
										0 per 1000	N/A
		ent respons		bulary exp	pression (	assessed with	n: Dichoto	mous: Frequency of improveme	ent in China	a Rehab	bilitation Research Council
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		0/14 (0%)	5/16 (31.3%)	<b>RR 9.71</b> (0.58 to	Study	population
39 weeks						LOW <sup>1,3</sup> due to risk of bias,	(	()	161.31)	0 per 1000	N/A
						imprecision				Mode	rate
										0 per 1000	N/A
		ent respons	-	se compre	hension	(assessed with	h: Dichoto	omous: Frequency of improvem	ent in Chin	a Rehal	bilitation Research Council
30	serious <sup>1</sup>	no serious	no serious	very	undetected	$\oplus \Theta \Theta \Theta$	0/14	1/16	RR 2.65	Study	population

(1 study) 39 weeks		inconsistency	indirectness	serious <sup>3</sup>		VERY LOW <sup>1,3</sup> due to risk of bias,	(0%)	(6.3%)	(0.12 to 60.21)	0 per 1000 Modera	N/A ate
						imprecision				0 per 1000	N/A
Positive t sign-significar		-	e for phras	se expres	sion (assess	sed with: Dich	otomous:	Frequency of improvement in	China Reha	abilitatior	Research Council (CRRC)
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY	0/14 (0%)	1/16 (6.3%)	<b>RR 2.65</b> (0.12 to	Study	population
39 weeks		Inconsistency	indirectriess	Senous		LOW <sup>1,3</sup> due to risk of bias,	(078)	(0.5%)	60.21)	0 per 1000	N/A
						imprecision				Modera	ate
										0 per 1000	N/A
		ent respons ce relations scale		nunicatio	n attitude	(assessed wi	th: Dichot	tomous: Frequency of improve	ment in Chi	na Reha	bilitation Research Council
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected		8/14 (57.1%)	15/16 (93.8%)	<b>RR 1.64</b> (1.02 to	Study	population
39 weeks		inconsistency	mancetricss			due to risk of bias, imprecision	(37.170)		2.63)	571 per 1000	<b>366 more per 1000</b> (from 11 more to 931 more)
										Moder	ate
										571 per 1000	365 more per 1000 (from 11 more to 931 more)
outcome asse <sup>2</sup> N<400 and 9	essors not 95% CI cr and 95%	nce and response reported and no osses both line o CI crosses both	independent re f no effect and	liability or vali measure of ap	dity data for the preciable ben	nis outcome m efit or harm (S	easure SMD -0.5		unclear/unl	known as	s identity and blinding of

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

Quality assessment								Summary of Findings					
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study	event rates (%)	Relative effect (95% CI)	Anticipated absolute effects			
							With Control	With Acupuncture/Electro- acupuncture versus sham acupuncture/electro- acupuncture for speech and language as an indirect outcome		Risk with Control	Risk difference with Acupuncture/Electro- acupuncture versus sham acupuncture/electro-acupuncture for speech and language as an indirect outcome (95% CI)		
Receptive language (measured with: Reynell Developmental Language Scale (change score): Comprehension score; Better indicated by lower values)													
	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	25	25	N/A	N/A	The mean receptive language in the intervention groups was <b>0.18 standard deviations</b> <b>lower</b> (0.73 lower to 0.38 higher)		
105 (2 studies) 4-9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	$\oplus \oplus \ominus \ominus$ LOW <sup>2,3</sup> due to imprecision, publication bias	50	orehension age (years); Bette	N/A	N/A	The mean receptive language in the intervention groups was 0.39 standard deviations higher (0 to 0.78 higher)		
Expressiv	ve lang	<b>Juage</b> (measure	ed with: Reynell	Development	al Language Sc	ale (change sc	ore): Exp	oression score; Better indicate	ed by lower	values)			
(	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	25	25	N/A	N/A	The mean expressive language in the intervention groups was <b>0.42 standard deviations</b> higher (0.14 lower to 0.98 higher)		

Expressive language (measured with: Reynell Developmental Language Scale (change score): Expression age (years); Better indicated by lower values)												
105 (2 studies) 4-9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊕⊖⊖ LOW <sup>2,3</sup> due to imprecision, publication bias	50	55		N/A	N/A	The mean expressive language in the intervention groups was <b>0.11 standard deviations</b> higher (0.28 lower to 0.49 higher)
<ul> <li><sup>1</sup> N&lt;400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)</li> <li><sup>2</sup> N&lt;400</li> <li><sup>3</sup> High risk of selective reporting bias in WONG2010B as trial protocol includes a follow-up but no follow-up data reported</li> </ul>												

# 1.17.2Hormones for speech and language as an indirect outcome

#### Secretin versus placebo for speech and language as an indirect outcome

Quality assessment								Summary of Findings					
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative	Anticipated absolute effects			
							With Control	With Secretin versus placebo for speech and language as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Secretin versus placebo for speech and language as an indirect outcome (95% Cl)		
Receptive language (measured with: Preschool Language Scale-3 (PLS-3): Auditory Comprehension (change score) or Mullen Scales of Early Learning (MSEL): Receptive Language or MSEL/PPVT-III: Receptive Language (months; change score); Better indicated by lower values)													
187 (3 studies) 3-6 weeks	no serious risk of bias		no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to inconsistency, imprecision	96	91	N/A	N/A	The mean receptive language in the intervention groups was <b>0.02 standard deviations</b> <b>lower</b> (0.31 lower to 0.27 higher)		
Expressive language (measured with: Preschool Language Scale-3 (PLS-3): Expressive Communication (change score) or Behavioural observation: Mean length of utterance (MLU) or Expressive One Word Picture Vocabulary Test-Revised (EOWPVT-R) Expressive language (change score); Better indicated by lower values)													
212 (3 studies)	no serious		no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \oplus \ominus$ <b>MODERATE</b> <sup>2</sup>	100	112	N/A	N/A	The mean expressive language in the		

3-6 weeks	risk of bias					due to imprecision					intervention groups was 0.16 standard deviations lower (0.43 lower to 0.11 higher)
Receptiv	ve and e	xpressive la	nguage (meas	ured with: Pre	school Langua	u age Scale-3 (PLS-3)	): Total (cl	hange score); Better ir	dicated by	lower valu	les)
85 (1 study) 3 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>3</sup> due to imprecision	44	41	N/A	N/A	The mean receptive and expressive language in the intervention groups was <b>0.28 standard deviations</b> higher (0.15 lower to 0.71 higher)
Vocabula lower values		ured with: Behavio	ural observation:	Type token ra	tio or MacArth	ur Communication I	Developm	ental Inventories (CDI	): Vocabula	ary (change	e score); Better indicated by
115 (2 studies) 4-6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	53	62	N/A	N/A	The mean vocabulary in the intervention groups was <b>0.06 standard deviations</b> <b>lower</b> (0.43 lower to 0.31 higher)
Positive	treatme	nt response	(assessed with: [	Dichotomous: I	Positive treatm	ent response (impre	ovement :	>=4 points on PLS-3))		1	
95 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊕⊝⊝ LOW⁴	10/48 (20.8%)	16/47 (34%)	<b>RR 1.63</b> (0.83 to	Study p	opulation
3 weeks	risk of bias	meenelectricy				due to imprecision	(20.070)		3.23)	208 per 1000	<b>131 more per 1000</b> (from 35 fewer to 465 more)
										Moderat	e
										208 per 1000	<b>131 more per 1000</b> (from 35 fewer to 464 more)
<sup>2</sup> N<400 <sup>3</sup> N<400 and	95% CI cro	tes moderate heter osses both line of r CI crosses both lin	o effect and mea	sure of appred measure of a	ciable benefit o ppreciable ber	n harm (SMD -0.5/0 hefit or harm (RR 0.	).5) 75/1.25)		1	1	1

# 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

		Qu	ality assessn	nent				Sumi	mary of F	indings	
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study event	rates (%)	Relative	Anticipated a	bsolute effects
(studies) Follow up	bias				bias	quality of evidence	With Short- term chelation (1-round of DMSA therapy and 6-rounds of placebo)	With Long-term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy)	effect (95% CI)	Risk with Short-term chelation (1- round of DMSA therapy and 6- rounds of placebo)	Risk difference with Long- term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy) (95% Cl)
Semantic values)	: Pragn	natic Proble	<b>MS</b> (measured	with: Pervasiv	ve Developme	ent Disorder Be	ehavior Invento	ory (PDDBI): Semantic P	ragmatic P	roblems; Better	indicated by lower
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	15	25	N/A	N/A	The mean semantic pragmatic problems in the intervention groups was <b>0.44 standard</b> <b>deviations higher</b> (0.2 lower to 1.09 higher)
Expressiv	ve Lan	<b>guage</b> (measu	red with: Pervas	sive Developm	ent Disorder E	Behavior Inven	tory (PDDBI): I	Expressive Language; B	etter indica	ted by lower va	lues)
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	15	25	N/A	N/A	The mean expressive language in the intervention groups was <b>0.26 standard</b> <b>deviations lower</b> (0.91 lower to 0.38 higher)

•		ory, and Rec ated by lower value	-	i <b>guage</b> (me	easured with: F	Pervasive Deve	elopment [	Disorder Behavior Ir	nventory (PDDBI):	Learning, Me	mory, and Receptive
(1 study) 17 weeks	-	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	15	25	N/A	N/A	The mean learning, memory, and receptive language in the intervention groups was <b>0.12 standard</b> <b>deviations lower</b> (0.76 lower to 0.52 higher)

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

		Qı	uality assessm	nent				Su	immary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study ever	nt rates (%)	Relative	Anticipated a	bsolute effects
(studies) Follow up	bias				bias	quality of evidence	With Attention- placebo control	With Hyperbaric oxygen treatment (HBOT)	effect (95% CI)	Risk with Attention- placebo control	Risk difference with Hyperbaric oxygen treatment (HBOT) (95% Cl)
Receptive	e langua	I <b>ge</b> (measured wi	th: Peabody Pictu	ure Vocabulary	/ Test, 3rd Ed.	(PPVT-III): Tota	(change sco	ore); Better indicated	d by lower v	alues)	
27 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	13	14	N/A	N/A	The mean receptive language in the intervention groups was <b>0.45 standard</b> <b>deviations lower</b> (1.22 lower to 0.31 higher)

# 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

		C	Quality assessn	nent					Summa	ry of Find	lings
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e (%)	vent rates	Relative effect	Anticipat	ed absolute effects
Follow up							With Placebo	With Omega- 3 fatty acids	(95% CI)	Risk with Placebo	Risk difference with Omega-3 fatty acids (95% Cl)
Receptive	e languag	e (measured with	: Peabody Picture	Vocabulary Te	st, 3rd Ed. (PP	VT-III): Total; Bette	er indicate	d by lower val	ues)	-	
25 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	12	13	N/A	N/A	The mean receptive language in the intervention groups was <b>0.52 standard deviations</b> <b>lower</b> (1.32 lower to 0.28 higher)
Expressiv	ve langua	<b>ige</b> (measured wi	th: Expressive Vo	cabulary Test (I	EVT): Total; Be	tter indicated by lo	wer value	s)			
25 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	12	13	N/A	N/A	The mean expressive language in the intervention groups was <b>0.69 standard deviations</b> <b>lower</b> (1.51 lower to 0.12 higher)

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

		C	uality assessn	nent				Summar	y of Finding	S
Participants		Inconsistency	Indirectness	Imprecision			Study event rates (%)		Anticipated a	absolute effects
(studies) Follow up	bias				bias	of evidence	With Healthy With Omega- diet control 3 fatty acids	effect (95% CI)		Risk difference with Omega-3 fatty acids (95% Cl)

23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean receptive language in the intervention groups was <b>0.21 standard deviations</b> <b>higher</b> (0.61 lower to 1.04 higher)
Express 23 (1 study) 13 weeks	ive lang	uage (measured	with: Mullen Sca	les of Early Le	arning (MSEL):	Expressive Langua	ge; Bette	er indicated by	N/A	s) N/A	The mean expressive language in the intervention groups was 0.36 standard deviations higher (0.47 lower to 1.19 higher)
<sup>1</sup> High risk o measure wa			ias as interventio	n administrato	rs and participa	nts were non-blind,	and high	risk of detect	on bias as th	ne outcome a	•

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

		Q	uality assess	nent		Summary of Findings					
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study e	vent rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Placebo	With Multivitamin and mineral supplement	effect (95% CI)	Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% Cl)
104	no serious	[	no serious indirectness	with: Parent C	Global Impressi	ons-Revised (PGI- DOBERATE <sup>1</sup> due to imprecision	R): Rece	ptive language imp 53	N/A	Better indic	The mean receptive language improvement in the intervention groups was 0.43 standard deviations higher (0.04 to 0.82 higher)

Express	Expressive language improvement (measured with: Parent Global Impressions-Revised (PGI-R): Expressive language improvement; Better indicated by lower values)												
104 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	51	53	N/A	N/A	The mean expressive language improvement in the intervention groups was <b>0.37 standard deviations</b> <b>higher</b> (0.02 lower to 0.76 higher)		
<sup>1</sup> N<400 <sup>2</sup> N<400 and	N<400 N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)												

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

		G	Quality assess	nent					Summary	of Findir	ngs
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study e	vent rates (%)	Relative	Anticipat	ed absolute effects
(studies) Follow up	bias				bias	of evidence	With Placebo	With L-carnosine supplement	effect (95% CI)	Risk with Placebo	Risk difference with L- carnosine supplement (95% Cl)
Receptive	e langua	<b>ge</b> (measured with	h: Receptive One-	-Word Picture V	ocabulary Tes	t (ROWPVT) Rece	eptive lang	uage (raw score)	; Better indi	cated by lo	wer values)
31 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	17	14	N/A	N/A	The mean receptive language in the intervention groups was <b>0.25 standard deviations</b> higher (0.46 lower to 0.96 higher)
Receptive	e langua	<b>ge</b> (measured with	h: Receptive One-	-Word Picture V	ocabulary Tes	t (ROWPVT) Rece	eptive lang	juage (age adjust	ed score); E	Better indica	ated by lower values)
31 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	17	14	N/A	N/A	The mean receptive language in the intervention groups was <b>0.2 standard deviations</b> higher (0.5 lower to 0.91 higher)

imprecision 0.21 standard deviation	31 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	17	14	N/A	N/A	The mean expressive language in the intervention groups was <b>0.2 standard deviations</b> higher (0.51 lower to 0.91 higher)
	31 (1 study)	no serious	no serious	no serious	very	1	⊕⊕⊝⊝ LOW <sup>1</sup> due to	-			1	The mean expressive

# 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

		Q	uality assessr			Summary of Findings					
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study event rat	es (%)	Relative	Anticipated abso	olute effects
(studies) Follow up	bias				bias	of evidence	With Attention- placebo (structured listening) control	With Auditory integration training		Risk with Attention-placebo (structured listening) control	Risk difference with Auditory integration training (95% Cl)
Receptive	e langua	age (measured w	ith: Peabody Pic	ture Vocabula	ry Test (PPVT	): Total; Better inc	licated by lower v	alues)		•	
80 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean receptive language in the intervention groups was <b>0.24 standard</b> <b>deviations lower</b>

										(0.68 lower to 0.2 higher)
/e langu	age (measured	with: Peabody Pi	icture Vocabul	ary Test (PPV)	Γ): Total; Better in	dicated by lo	ower values)	1	1	
no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean receptive language in the intervention groups was <b>0.32 standard</b> <b>deviations lower</b> (0.76 lower to 0.12 higher)
/e langu	age (measured	with: Peabody Pi		ary Test (PPV1	F): Total; Better in	dicated by lo	ower values)			
no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	40	40	N/A	N/A	The mean receptive language in the intervention groups was <b>0.5 standard</b> deviations lower (0.94 to 0.05 lower)
	no serious risk of bias /e langu no serious risk of	no       serious         serious       inconsistency         risk of       bias         bias       ////////////////////////////////////	no       serious       no serious       no serious         risk of       inconsistency       indirectness         bias       ////////////////////////////////////	no       serious       no serious       no serious       very         risk of       inconsistency       indirectness       very         bias       very       serious <sup>1</sup> /e       language (measured with: Peabody Picture Vocabul         no       no serious       no serious         serious       inconsistency       indirectness         serious       no serious       serious <sup>2</sup> risk of       inconsistency       indirectness	no       serious       no serious       no serious       very       undetected         risk of       bias       inconsistency       indirectness       very       serious <sup>1</sup> undetected         /e       language       (measured with: Peabody Picture Vocabulary Test (PPVT)         no       no serious       no serious       serious <sup>2</sup> undetected         inconsistency       indirectness       serious <sup>2</sup> undetected	no       serious       no serious       no serious       undetected       ⊕⊕⊝⊖         serious       inconsistency       indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖         bias       undetected       undetected       undetected       undetected       undetected         re       language (measured with: Peabody Picture Vocabulary Test (PPVT): Total; Better in       no serious       no serious       no serious       indirectness         serious       no serious       no serious       no serious       serious <sup>2</sup> undetected       ⊕⊕⊕⊝         MODERATE <sup>2</sup> due to       undetected       undetected       undetected	no serious risk of biasno serious inconsistencyno serious indirectnessvery serious1undetected $\bigoplus \bigoplus \bigoplus \bigoplus \bigcup LOW1$ due to imprecision40 <i>Very</i> serious1very serious1undetected $\bigoplus \bigoplus \bigoplus \bigoplus \bigcup LOW1$ due to imprecision <i>Very</i> serious1 <i>Very</i> serious1undetected $\bigoplus \bigoplus \bigoplus \bigoplus \bigoplus \bigcup LOW1$ due to imprecision <i>Very</i> serious1 <i>very</i> serious1undetected $\bigoplus \bigoplus \bigcup LOW1$ due to imprecision <i>No</i> serious inconsistencyno serious indirectnessserious2undetected $\bigoplus \bigoplus $	serious risk of bias       inconsistency       indirectness       serious <sup>1</sup> LOW <sup>1</sup> due to imprecision         /e language (measured with: Peabody Picture Vocabulary Test (PPVT): Total; Better indicated by lower values)         no serious risk of       no serious inconsistency       no serious indirectness       serious <sup>2</sup> undetected	no serious risk of biasno serious inconsistencyno serious indirectnessvery serious1undetected undetected $\oplus \oplus \ominus \ominus$ LOW1 due to imprecision4040N/AVery LOW1 due to imprecisionvery biasno serious indirectnessvery serious1undetected undetected $\oplus \oplus \ominus \ominus$ LOW1 due to imprecision40N/Avery biasvery biasno serious indirectnessvery serious1undetected undetected $\oplus \oplus \ominus \ominus$ MODERATE24040N/A	$\begin{array}{ c c c c c }\hline no & serious \\ serious \\ risk of \\ bias \\ \hline no serious \\ inconsistency \\ indirectness \\ risk of \\ bias \\ \hline no & serious \\ risk of \\ bias \\ \hline no & serious \\ risk of \\ \hline no & serious \\ \hline no & serious \\ risk of \\ \hline no & serious \\ risk of \\ \hline no & serious \\ \hline no & serious \\ risk of \\ \hline no & serious \\ \hline no & seri$

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

			Quality asses	ssment		Summary of Findings						
Participants		Inconsistency	Indirectness	Imprecision		Overall quality of	Study even	• • •	Relative	Anticipated	absolute effects	
(studies) Follow up	bias				bias		With With I		effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Neurofeedback (95% CI)	
Parent-ra	Parent-rated speech production (measured with: Children's Communication Checklist (CCC-2): Speech production; Better indicated by lower values)											
20 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly	⊕⊖⊝ VERY LOW <sup>1,2,3</sup>	10	10	N/A	N/A	The mean parent-rated speech production in	

20 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias					the intervention groups was <b>0.38 standard</b> <b>deviations lower</b> (1.26 lower to 0.51 higher)
Teacher	-rated s	peech produ	<b>iction</b> (measu	red with: Child	ren's Communica	tion Checklist (CCC-	-2): Speech	n production; Be	etter indicate	d by lower val	ues)
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated speech production in the intervention groups was <b>0.75 standard</b> <b>deviations higher</b> (0.16 lower to 1.67 higher)
Parent-r	ated sy	ntax (measured	with: Children's	Communicatio	n Checklist (CCC	-2): Syntax; Better in	dicated by	lower values)			-1
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated syntax in the intervention groups was <b>0.54 standard</b> <b>deviations lower</b> (1.44 lower to 0.35 higher)
Teacher	-rated s	yntax (measure	ed with: Children'	s Communicat	tion Checklist (CC	C-2): Syntax; Better	indicated I	by lower values)	)		
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated syntax in the intervention groups was <b>0.2 standard</b> <b>deviations higher</b> (0.68 lower to 1.08 higher)
Parent-r	ated se	mantics (meas	sured with: Childr	en's Commun	ication Checklist (	CCC-2): Semantics;	Better indi	icated by lower	values)	-	-
20 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		10	10	N/A	N/A	The mean parent-rated semantics in the

20 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias					intervention groups was 0.89 standard deviations lower (1.82 lower to 0.04 higher)
Teacher	-rated s	emantics (me	easured with: Chi	Idren's Comm	unication Checklis	st (CCC-2): Semantic	s; Better	indicated by lo	ower values)		
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated semantics in the intervention groups was <b>1.12 standard</b> <b>deviations higher</b> (0.17 to 2.08 higher)
Parent-r	ated co	herence (mea	sured with: Child	ren's Commur	nication Checklist	(CCC-2): Coherence	; Better i	ndicated by lov	ver values)	1	
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated coherence in the intervention groups was <b>0.68 standard</b> <b>deviations lower</b> (1.59 lower to 0.23 higher)
Teacher	-rated c	oherence (me	easured with: Ch	ildren's Comm	nunication Checkli	st (CCC-2): Coheren	ce; Bette	r indicated by I	ower values)		
20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated coherence in the intervention groups was <b>0.89 standard</b> <b>deviations higher</b> (0.04 lower to 1.82 higher)
interest is al	so high as I 95% CI cr	neurofeedback ec	uipment provide no effect and me	d by manufact easure of appr	turer for trial. reciable benefit or	articipants and outcom harm (SMD -0.5/0.5		ssors were non	-blind. The ris	k of other bi	as due to potential conflict of

# 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

			Quality assess	sment					Summa	ry of Findin	gs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study even (%)	t rates	Relative effect	Anticipated	absolute effects
Follow up							With Treatment- as-usual	With ESDM or P-ESDM	(95% CI)	Risk with Treatment-as- usual	Risk difference with ESDM or P-ESDM (95% CI)
IQ (ESDM	or P-E	SDM) (measured	with: Mullen Sca	ales of Early Le	earning (MSEL)	Early learning comp	osite score o	r developn	nental quotie	ent; Better indi	cated by lower values)
143 (2 studies) 12-104 weeks	serious <sup>1</sup>	serious <sup>2</sup>	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency, imprecision	70	73	N/A	N/A	The mean iq (esdm or p- esdm) in the intervention groups was <b>0.25 standard deviations</b> higher (0.08 lower to 0.58 higher)
Verbal de	velopm	ental quotier	nt (P-ESDM)	(measured wi	th: Mullen Scal	es of Early Learning (	MSEL): Verb	al develop	mental quot	ient; Better ind	licated by lower values)
98 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,4</sup> due to risk of bias, imprecision	49	49	N/A	N/A	The mean verbal developmental quotient (p- esdm) in the intervention groups was <b>0.1 standard deviations</b> higher (0.3 lower to 0.5 higher)
Non-verba values)	al deve	lopmental qu	otient (P-E	SDM) (measu	ured with: Mulle	en Scales of Early Lea	arning (MSEL	): Non-ver	bal developi	mental quotien	t; Better indicated by lower
98 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^{1,4} \\ \text{due to risk of bias,} \end{array}$	49	49	N/A	N/A	The mean non-verbal developmental quotient (p- esdm) in the intervention

					imprecision				groups was 0.08 standard deviations higher (0.31 lower to 0.48 higher)
outcome asse	ssors not r lue indicate	eported es moderate hetero	ogeneity		nts were nonblind, and harm (SMD -0.5/0.5)	d risk of detection bias i	s unclear/un	known as ider	ntity and blinding of

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

		Q	uality assessr	nent				S	ummary o	f Finding	js
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study e	event rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With EIBI versus parent training for IQ as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with EIBI versus parent training for IQ as an indirect outcome (95% CI)
IQ (measure	ed with: Bayle	ey Scales of Infant	Development: M	ental Developr	nent Index; Be	tter indicated by lo	wer value	es)			
28 (1 study) 260 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	13	15	N/A	N/A	The mean iq in the intervention groups was <b>0.74 standard deviations</b> higher (0.04 lower to 1.51 higher)
Academi	c skills (r	neasured with: We	echsler Individuali	zed Achievem	ent Test (WIAT	): Total; Better ind	icated by	lower values)		•	
28 (1 study) 260 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	13	15	N/A	N/A	The mean academic skills in the intervention groups was <b>0.84 standard deviations</b> higher (0.06 to 1.62 higher)
<sup>1</sup> N<400 and	95% CI cros	ses both line of no	effect and meas	ure of apprecia	ble benefit or	harm (SMD -0.5/0.	5)		1	1	1

#### <sup>2</sup> N<400

### 1.18.2 Educational interventions for IQ as an indirect outcome

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

		Qı	uality assessr	nent				Sur	nmary of	Findings				
Participants		Inconsistency	Indirectness	•	Publication	Overall	Study event r	rates (%)	Relative	Anticipated at	osolute effects			
(studies) Follow up	bias				bias	evidence	With Intervention- manual-only control	With Inclusive educational intervention (LEAP) training	effect (95% CI)	Risk with Intervention- manual-only control	Risk difference with Inclusive educational intervention (LEAP) training (95% Cl)			
IQ (measure	Q (measured with: Mullen Scales of Early Learning (MSEL): Early-learning composite score; Better indicated by lower values)													
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	117	177	N/A	N/A	The mean iq in the intervention groups was <b>0.87 standard</b> <b>deviations higher</b> (0.63 to 1.12 higher)			
<sup>1</sup> High risk of outcome asse <sup>2</sup> N<400	•	•	l bias as interventi	I ion administrat	tors and partic	I ipants non-blind	I . In addition, ris	k of detection bias i	ı s unclear/u	I nknown as identi	ty and blinding of			

# 1.18.3Parent training for IQ as an indirect outcome

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

			Quality assess	sment				Su	ummary of	f Finding	IS
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	•	Publication bias	Overall quality of evidence	Study e With Control	With Paront training	effect	Risk with	ted absolute effects Risk difference with Parent training versus treatment-as- usual for IQ (95% CI)

			ntal Development omental quotient;				lucationa	I Profile-Revise	ed (PEP-R): Dev	elopmental	Quotient (DQ) or Mullen		
147 (3 studies) 12-52 weeks	no serious risk of bias		no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to inconsistency, imprecision	57	90	N/A	N/A	The mean iq in the intervention groups was <b>0.04 standard deviations</b> <b>higher</b> (0.3 lower to 0.38 higher)		
<sup>1</sup> I-squared va <sup>2</sup> N<400	I-squared value indicates moderate heterogeneity N<400												

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

		Qı	uality assessr	nent			Sum	mary of F	indings	
Participants		Inconsistency	Indirectness	Imprecision		Study event ra	( )		Anticipated ab	solute effects
(studies) Follow up	bias				quality of evidence	With Early intervention centre programme only	With Combined parent training and early intervention centre programme	(95% CI)	Risk with Early intervention centre programme only	Risk difference with Combined parent training and early intervention centre programme (95% CI)

IQ (mixed ASD & DD sample) (measured with: Bayley Scales of Infant Development-Second Edition or Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R); Better indicated by lower values)

59 (1 study) 40 weeks	no serious risk of bias	no serious inconsistency	 very serious <sup>2</sup>		⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to indirectness, imprecision	29	30	N/A	N/A	The mean iq (mixed asd & dd sample) in the intervention groups was <b>0.35 standard</b> <b>deviations higher</b> (0.17 lower to 0.86 higher)
indicated by lo		s)	cales of Infant	t Development		or Wechsler Pr	reschool and Primary		ntelligence-Revis	ed (WPPSI-R); Better The mean iq (asd-

	serious risk of bias	inconsistency	indirectness	serious <sup>2</sup>		LOW <sup>2</sup> due to imprecision					only sample) in the intervention groups was <b>0.43 standard</b> <b>deviations higher</b> (0.21 lower to 1.07 higher)
WPPSI-R); Be 54 1 study) 108 weeks		& DD sample ated by lower value no serious inconsistency	•	th: Bayley Sca	undetected	evelopment-Seco Decision WERY LOW <sup>1,2</sup> due to indirectness, imprecision	26	r Wechsler Pres	chool and Prima	N/A	telligence-Revised The mean iq (mixed asd & dd sample) in the intervention groups was

# 1.18.4 Social-communication interventions for IQ as an indirect outcome

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

		Qı	ality assessn	nent			Summary of Findings					
-		Inconsistency	Indirectness	Imprecision	Study		Relative	Anticip	ated absolute effects			
(studies) Follow up	bias					quality of evidence	With Control	With Reciprocal social- communication interventions versus treatment-as-usual for IQ as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Reciprocal social-communication interventions versus treatment- as-usual for IQ as an indirect outcome (95% Cl)	
IQ (measure	Q (measured with: Mullen Scales of Early Learning (MSEL): Early-learning composite score; Better indicated by lower values)											

49 (1 study) 39 weeks	serious <sup>1</sup>		no serious indirectness	very serious <sup>2</sup>		⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	25	24	N/A		The mean iq in the intervention groups was <b>0.06 standard deviations</b> <b>lower</b> (0.62 lower to 0.5 higher)	
outcome asse	<sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as identity and blinding of outcome assessors is not reported <sup>2</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)											

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

Image: Note of the series			Qu	ality assessm	nent				Su	mmary of	Finding	S
Follow up       With combined joint       With Combined joint       (95% Cl)       Risk difference with Control joint attention training and EIBI versus EIBI only for IQ as an indirect outcome         Follow up       IQ (measured with: Mullen Scales of Early Learning (MSEL): Developmental quotient; Better indicated by lower values)       with Combined joint       (95% Cl)       Risk difference with Control joint attention training and up to the provide the provided indirect outcome         36       no       no serious inconsistency       no serious indirectness       very serious <sup>1</sup> undetected $\oplus \oplus \ominus \ominus$ 16       20       N/A       N/A       The mean iq in the intervention groups wa 0.54 standard deviation imprecision	-		Inconsistency	Indirectness	Imprecision			Study e	• •		Anticipa	ated absolute effects
36 (1 study)       no       serious       no serious       no serious       very indirectness       undetected       ⊕⊕⊝⊝       16       20       N/A       N/A       The mean iq in the intervention groups wa 0.54 standard deviation higher	` '	bias				bias	• •	-	attention training and EIBI versus EIBI only for IQ as			Risk difference with Combined joint attention training and EIBI versus EIBI only for IQ as an indirect outcome (95% CI)
(1 study)       serious       inconsistency       indirectness       serious <sup>1</sup> LOW <sup>1</sup> intervention groups wa         52 weeks       risk of bias       bias       bias       bias       LOW <sup>1</sup> due to imprecision       bias       <	IQ (measure	d with: Mul	len Scales of Early	Learning (MSEL	_): Developme	ntal quotient; I	Better indicated b	by lower	values)			
	(1 study) 52 weeks	serious risk of				undetected	LOW <sup>1</sup> due to	16	20	N/A	N/A	intervention groups was 0.54 standard deviations

# **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

Image: standard deviation			Qı	uality assessm	ient				Su	mmary of	Findings	3
Follow upWith SolutionWith ControlWith With Antipsychotics versus placebo for academic skillsRisk with ControlRisk with Antipsychotics versus placebo for academic skillsMaths problem-solving (measured with: Classroom Analogue Task: Total number of maths problems correctly calculated; Better indicated by lower values)N/AN/AThe mean maths problems correctly calculated; Better indicated by lower values)38 (1 study) 8 weeksno serious biasno serious inconsistencyvery serious <sup>1</sup> undetected Very serious <sup>1</sup> $\bigcirc \bigcirc \bigcirc \bigcirc \\ LOW^1 \\ due toimprecision1820N/AN/AThe mean maths problems correctly calculated; Better indicated by lower values)$	-		Inconsistency	Indirectness	Imprecision			Study e	event rates (%)		Anticipa	ted absolute effects
38 no serious no serious inconsistency bias no serious indirectness very serious <sup>1</sup> undetected LOW <sup>1</sup> due to imprecision imprecision induced imprecision 0.45 standard deviation lower	<b>、</b> ,	bias				bias	of evidence	-	versus placebo for			Antipsychotics versus placebo for academic skills
(1 study) 8 weeks bias inconsistency indirectness serious <sup>1</sup> LOW <sup>1</sup> due to imprecision intervention of the	Maths pro	oblem-se	olving (measure	ed with: Classroo	m Analogue Ta	ask: Total numl	ber of maths prob	lems coi	rrectly calculated; Bette	r indicated b	y lower va	lues)
	(1 study)	risk of				undetected	LOW <sup>1</sup> due to	18	20	N/A	N/A	0.45 standard deviations

# **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

		Q	uality assess	ment			Summary of Findings					
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	bias	Overall quality of evidence	With	With Acupuncture/Electro	effect (95% CI)	Anticip Risk with Control	Risk difference with Acupuncture/Electro- acupuncture versus sham acupuncture/electro- acupuncture for IQ as a direct outcome (95% CI)	
General quotient/FIQ (measured with: Griffiths Mental Development Scale (change score): General Quotient or Leiter International Performance Scale-Revised: Visualization and Reasoning: Battery (IQ/Composite Score) (change score); Better indicated by lower values)												
105	no	no serious	no serious	very	reporting bias	$\oplus \Theta \Theta \Theta$	50	55	N/A	N/A	The mean general	

(2 studies) 4-9 weeks Mental a	serious risk of bias	inconsistency	indirectness	serious <sup>1</sup>	strongly suspected <sup>2</sup>	VERY LOW <sup>1,2</sup> due to imprecision, publication bias	Mental	age (months); Bette	prindicated by lowe		quotient/fiq in the intervention groups was <b>0.23 standard deviations</b> <b>higher</b> (0.15 lower to 0.62 higher)
50 (1 study) 9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	$\begin{array}{c} \oplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^1 \\ \text{due to} \\ \text{imprecision} \end{array}$	25	25	N/A	N/A	The mean mental age in months in the intervention groups was <b>0.43 standard deviations</b> higher (0.13 lower to 0.99 higher)
Locomo	tor (meas	ured with: Griffith	ns Mental Develo	opmental Sca	le: Locomotor (c	hange score); B	etter in	dicated by lower valu	ues)		
50 (1 study) 9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1</sup> due to imprecision	25	25	N/A	N/A	The mean locomotor in the intervention groups was <b>0.2 standard deviations</b> <b>lower</b> (0.76 lower to 0.35 higher)
Persona	I-Social	(measured with:	Griffiths Menta	l Developmen	tal Scale: Perso	nal-Social (chan	ge scol	re); Better indicated	by lower values)		
50 (1 study) 9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	25	25	N/A	N/A	The mean personal-social in the intervention groups was <b>0.53 standard deviations</b> <b>higher</b> (0.03 lower to 1.1 higher)
Hearing	and spe	eech (measure	d with: Griffiths	Mental Develo	opmental Scale:	Hearing & Spee	ch (cha	ange score); Better ir	ndicated by lower v	alues)	
50 (1 study) 9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	25	25	N/A	N/A	The mean hearing and speech in the intervention groups was <b>0.15 standard deviations</b> higher (0.4 lower to 0.71 higher)

50 (1 study) 9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	25	25	N/A	N/A	The mean eye and hand coordination in the intervention groups was <b>0.12 standard deviations</b> <b>higher</b> (0.44 lower to 0.67 higher)
50 (1 study) 9 weeks	no serious risk of bias	easured with: Grif	ffiths Mental Dev no serious indirectness	velopmental S very serious <sup>1</sup>	undetected	€ (change score ⊕⊕⊖⊝ LOW <sup>1</sup> due to imprecision	e); Bett	ter indicated by low	er values)	N/A	The mean performance in the intervention groups was <b>0.41 standard deviations</b> <b>higher</b> (0.15 lower to 0.97 higher)
50 (1 study) 9 weeks	no serious risk of bias	no serious inconsistency	with: Griffiths M no serious indirectness	Mental Develo very serious <sup>1</sup>	pmental Scale: P undetected	ractical Reasoni ⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	ing (ch	ange score); Better 25	indicated by lower v	N/A	The mean practical reasoning in the intervention groups was <b>0.32 standard deviations</b> higher (0.23 lower to 0.88 higher)
Attentio	on and m	<b>iemory</b> (meas	ured with: Leiter	r International	Performance Sc	ale-Revised: Att	ention	and Memory: Batte	ry (Composite Score	e); Better	indicated by lower values)
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly suspected <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean attention and memory in the intervention groups was <b>0.04 standard deviations</b> <b>lower</b> (0.57 lower to 0.49 higher)

# 1.20.2 Hormones for IQ as an indirect outcome

#### Secretin versus placebo for IQ as an indirect outcome

		Q	uality assessm	ent		Summary of Findings					
Participants		Inconsistency	Indirectness	Imprecision	Publication		Study e	event rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Secretin versus placebo for IQ as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Secretin versus placebo for IQ as an indirect outcome (95% Cl)
IQ (measure	ed with: Merri	II-Palmer Scale; B	etter indicated by	lower values)							
42 (1 study)		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected		23	19	N/A	N/A	The mean iq in the intervention groups was

# 1.20.3 Nutritional intervention for IQ as an indirect outcome

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

		Q	uality assessm	ent			S	ummary c	of Finding	ıs			
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study e	vent rates (%)	Relative	Anticipat	ed absolute effects		
(studies) Follow up	bias				bias	of evidence	With Placebo	With Multivitamin and mineral supplement	(95% CI)	Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% Cl)		
Cognition improvement (measured with: Parent Global Impressions-Revised (PGI-R): Cognition improvement; Better indicated by lower values)													
-	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1</sup> due to imprecision	51	53	N/A	N/A	The mean cognition improvement in the intervention groups was <b>0.32 standard deviations</b> higher (0.06 lower to 0.71 higher)		
<sup>1</sup> N<400 and 9	95% CI cross	ses both line of no	effect and measu	re of appreciat	ble benefit or ha	arm (SMD -0.5/0.5	5)				1		

# **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

	0		0		,			0, 1			
		Qı	uality assessn	nent				Su	mmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study event rate	es (%)	Relative	Anticipated abso	lute effects
(studies) Follow up	bias				bias	quality of evidence	With Attention- placebo (structured listening) control	With Auditory integration training	effect (95% CI)	Risk with Attention- placebo (structured listening) control	Risk difference with Auditory integration training (95% Cl)
PIQ (measu	ured with: L	eiter International I	Performance Sca	le (LIPS): Tota	al; Better indica	ated by lower val	ues)			•	
80 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean piq in the intervention groups was <b>0.16 standard</b> <b>deviations lower</b> (0.6 lower to 0.28 higher)
PIQ (measu	ured with: L	eiter International F	Performance Sca	le (LIPS): Tota	al; Better indica	ated by lower val	ues)	-		1	1
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean piq in the intervention groups was <b>0.17 standard</b> <b>deviations lower</b> (0.61 lower to 0.26 higher)
PIQ (measu	ured with: L	eiter International F	Performance Sca	le (LIPS): Tota	al; Better indica	ated by lower val	ues)		<u>I</u>	Į	Į
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean piq in the intervention groups was <b>0.22 standard</b> <b>deviations lower</b> (0.66 lower to 0.22 higher)

<sup>1</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

# **1.21**PYCHOSOCIAL 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

			Quality ass	essment					Summary	of Findin	gs
Participants (studies)	s Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e (%)	vent rates	Relative effect	Anticipat	ed absolute effects
Follow up							With Waitlist control	With Horseback riding	(95% CI)	Risk with Waitlist control	Risk difference with Horseback riding (95% CI)
Sensory	probler	<b>NS</b> (measured with	th: Sensory Profil	e: Total; Better	indicated by lower	values)					
34 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	15	19	N/A	N/A	The mean sensory problems in the intervention groups was <b>0.45 standard</b> <b>deviations higher</b> (0.23 lower to 1.14 higher)
Sensory	seeking	g (measured with:	Sensory Profile:	Sensory seekir	ng; Better indicated	by lower values)	1				
34 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	15	19	N/A	N/A	The mean sensory seeking in the intervention groups was <b>0.89 standard</b> <b>deviations higher</b> (0.17 to 1.6 higher)
Sensory	sensiti	vity (measured w	vith: Sensory Prof	ile: Sensory se	nsitivity; Better indi	cated by lower values)	)				
34	serious <sup>1</sup>	no serious	no serious	very	reporting bias	<b>000</b>	15	19	N/A	N/A	The mean sensory

(1 study) 12 weeks		inconsistency	indirectness	serious <sup>2</sup>	suspected <sup>3</sup>	VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias			sensitivity in the intervention groups was <b>0.39 standard</b> <b>deviations higher</b> (0.29 lower to 1.08 higher)
parents non-t	olind 95% CI cro	osses both line of n	o effect and meas	sure of apprec	iable benefit or harr	m (SMD -0.5/0.5)	a high risk of detection sensitivity, and poor regi		ires are parent-rated and e Sensory Profile scale

# **1.21.2** Educational interventions for sensory sensitivities as an indirect outcome

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

l		Qı	uality assessn	nent				Sun	nmary of	Findin	igs			
Participants		Inconsistency	Indirectness	Imprecision		Overall	Stud	y event rates (%)	Relative	Antic	ipated absolute effects			
(studies) Follow up	bias				bias	quality of evidence	With With Combined computer- IBI- assisted educational only intervention and intensive behavioural intervention (IBI) day class program		effect (95% CI)	Risk with IBI- only	Risk difference with Combined computer-assisted educational intervention and intensive behavioural intervention (IBI) day class program (95% CI)			
Auditory	uditory processing (measured with: Brigance Inventory of Child Development: Auditory processing; Better indicated by lower values)													
46 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision			N/A	N/A	The mean auditory processing in the intervention groups was <b>0.21 standard deviations</b> <b>higher</b> (0.37 lower to 0.79 higher)			
Auditory values)	Auditory processing (preschool subgroup analysis) (measured with: Brigance Inventory of Child Development: Auditory processing; Better indicated by lower values)													
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of	12	11	N/A	N/A	The mean auditory processing (preschool subgroup analysis) in the intervention groups was			

						bias, imprecision				0.13 standard deviations higher (0.69 lower to 0.95 higher)			
Auditory	Auditory processing (K-1 subgroup analysis) (measured with: Brigance Inventory of Child Development: Auditory processing; Better indicated by lower values)												
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	12 11	N/A	N/A	The mean auditory processing (k-1 subgroup analysis) in the intervention groups was <b>0.29 standard deviations</b> higher (0.54 lower to 1.11 higher)			
<sup>1</sup> High risk of performance and response bias as intervention administrators and participants non-blind. Risk of detection bias is unclear/unknown as the identity and blinding of outcome assessors not reported. In addition, for the Brigance Inventory of Child Development scale there are no independent reliability and/or validity data reported <sup>2</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)													

# **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

		Qı	ality assessn	nent			Summary of Findings				
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall	Study e	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias					quality of evidence	With Control	Nith With Qigong massage		Risk with Control	Risk difference with Qigong massage versus waitlist for the coexisting problem or disorder of sensory sensitivities as a direct outcome (95% Cl)
Sensory i	impairr	nent (measured	with: Pervasive	Development	Disorder Beha	vior Inventory (I	PDDBI):	Sensory; Better indicated b	by lower val	ues)	
79 (2 studies) 17-22 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,2</sup> due to risk of bias,	39	40	N/A	N/A	The mean sensory impairment in the intervention groups was <b>0.8 standard deviations</b>

						imprecision						lower (1.27 to 0.34 lower)
Sensory	impairr	nent (measured	with: Sense and	d Self-Regulati	on Checklist (	SSC): Sense ch	ecklist;	Better indicated by lo	wer value	es)		
87 (2 studies) 17-22 weeks		no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	39	48	N	I/A	N/A	The mean sensory impairment in the intervention groups was 1.11 standard deviations lower (1.56 to 0.65 lower)
<sup>1</sup> High risk of selection bias in SILVA2009 as although groups were assigned using a random number generator, there were caveats to the randomisation (five sets of siblings were co- assigned due to parental involvement in the treatment and different geographical areas were assigned separately to meet the 'therapist to participant requirements'). Groups were also not comparable at baseline for measures of parent rated social communication and autism composite and teacher rated sensory problems. There was also a high risk of performance and response bias as intervention administrators and participants were non-blind, and an unclear or high risk of detection bias due to unclear blinding or non-blind outcome assessment <sup>2</sup> N<400												

### **1.22.2**Sensory interventions for sensory sensitivities as a direct outcome

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

		Q	uality assessr	nent			Summary of Findings						
Participants (studies)		Inconsistency	Indirectness	Imprecision			Study event rat	es (%)	Relative	Anticipated abs	olute effects		
(studies) Follow up	bias				bias	of evidence	With Attention- placebo (structured listening) control	With Auditory integration training	effect (95% CI)	Risk with Attention-placebo (structured listening) control	Risk difference with Auditory integration training (95% Cl)		
Sound se	ound sensitivity (measured with: Sound Sensitivity Questionnaire (SSQ): Total; Better indicated by lower values)												
80 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean sound sensitivity in the intervention groups was 0.27 standard deviations lower		

											(0.71 lower to 0.17 higher)
Sound s	ensitivit	<b>y</b> (measured with	: Sound Sensitiv	ity Questionna	ire (SSQ): Tota	al; Better indicated	d by lower va	lues)	1	- 1	
80 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean sound sensitivity in the intervention groups was <b>0.13 standard</b> <b>deviations lower</b> (0.57 lower to 0.31 higher)
Sound s	ensitivit	<b>y</b> (measured with	: Sound Sensitiv	ity Questionna	ire (SSQ): Tota	al; Better indicate	d by lower va	lues)	·		•
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean sound sensitivity in the intervention groups was <b>0.12 standard</b> <b>deviations higher</b> (0.32 lower to 0.56 higher)
Sound s	ensitivit	<b>y</b> (measured with	: Sound Sensitiv	ity Questionna	ire (SSQ): Tota	al; Better indicated	d by lower va	lues)	1	1	
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean sound sensitivity in the intervention groups was <b>0.2 standard</b> <b>deviations higher</b> (0.24 lower to 0.64 higher)
Sound d	listress (	I measured with: So	ound Sensitivity	Questionnaire	l (SSQ): Sound	distress; Better in	l dicated by lo	wer values)	<b> </b>		
80 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigoplus \bigoplus \\ \textbf{MODERATE}^2 \\ \text{due to} \\ \text{imprecision} \end{array}$	40	40	N/A	N/A	The mean sound distress in the intervention groups was

											<b>0.02 standard</b> <b>deviations lower</b> (0.46 lower to 0.41 higher)
Sound c	distress (	measured with: So	ound Sensitivity	Questionnaire	(SSQ): Sound	distress; Better ir	dicated by l	ower values)	<b>I</b>		1
80 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	40	40	N/A	N/A	The mean sound distress in the intervention groups was <b>0 standard</b> <b>deviations higher</b> (0.44 lower to 0.44 higher)
Sound c	distress (	measured with: Se	ound Sensitivity	Questionnaire	(SSQ): Sound	distress; Better ir	dicated by l	ower values)			
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean sound distress in the intervention groups was <b>0.43 standard</b> <b>deviations higher</b> (0.01 lower to 0.87 higher)
Sound c	distress (	measured with: So	ound Sensitivity (	Questionnaire	(SSQ): Sound	distress; Better ir	dicated by l	ower values)		I	
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean sound distress in the intervention groups was <b>0.2 standard</b> <b>deviations higher</b> (0.24 lower to 0.63 higher)
Sensory	/ self-sti	nulation (mea	sured with: Sens	ory Problems	I Checklist (SP)	: Total; Better ind	icated by lo	wer values)			
80 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup>	40	40	N/A	N/A	The mean sensory self-stimulation in

4 weeks	risk of bias					due to imprecision					the intervention groups was <b>0.07 standard</b> <b>deviations higher</b> (0.36 lower to 0.51 higher)
Sensory	self-sti	mulation (mea	asured with: Sens	sory Problems	Checklist (SP)	: Total; Better ind	icated by lo	wer values)	•	•	
80 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean sensory self-stimulation in the intervention groups was <b>0.1 standard</b> <b>deviations higher</b> (0.34 lower to 0.54 higher)
Sensory	self-sti	mulation (mea	asured with: Sens	sory Problems	Checklist (SP)	: Total; Better ind	icated by lo	wer values)	<b>I</b>		
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>2</sup> due to imprecision	40	40	N/A	N/A	The mean sensory self-stimulation in the intervention groups was <b>0.05 standard</b> <b>deviations higher</b> (0.39 lower to 0.49 higher)
Sensory	v self-sti	mulation (mea	asured with: Sens	sory Problems	Checklist (SP)	: Total; Better ind	icated by lo	wer values)			
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean sensory self-stimulation in the intervention groups was <b>0.22 standard</b> deviations higher (0.22 lower to 0.66 higher)

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

li internet interne		Q	uality assessr	nent				S	Summary o	of Findings				
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study event	rates (%)	Relative	Anticipated a	absolute effects			
(studies) Follow up	bias				bias	of evidence	With Treatment-as- usual	With Sensory integration therapy	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Sensory integration therapy (95% CI)			
Sensory	Sensory problems (measured with: Sensory Evaluation Form for Children with Autism: Total; Better indicated by lower values)													
30 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean sensory problems in the intervention groups was 2 standard deviations lower (2.9 to 1.11 lower)			
<sup>1</sup> High risk of assessor is no <sup>2</sup> N<400	•		as as interventior	n administrator	s and participa	ants non-blind, and	d risk of detec	tion bias is uncle	ear/unknown	as the identity	and blinding of 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

		C	uality assess	nent					Summa	ry of Findi	ings	
Participants		Inconsistency	Indirectness	Imprecision		• •	Study ev	ent rates (%)		Anticipate	d absolute effects	
(studies) Follow up	bias				bias		With Waitlist control	With Horseback riding	(95% CI)	Risk with Waitlist control	Risk difference with Horseback riding (95% CI)	
Fine mote	Fine motor/perception (measured with: Sensory Profile: Fine motor/perception; Better indicated by lower values)											

34 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	15	19	N/A		The mean fine motor/perception in the intervention groups was <b>0.22 standard deviations</b> <b>higher</b> (0.45 lower to 0.9 higher)
parents non-l	blind	ce and response bi					a high risk of de	tection bias	as outcome	measures are parent-rated and

# 1.23.2Behavioural interventions for motor skills as an indirect outcome

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

		Qu	ality assessm	nent			Summary of Findings				S
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Behaviour-focused intervention versus treatment-as-usual for fine and gross motor skills as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Behaviour- focused intervention versus treatment-as-usual for fine and gross motor skills as an indirect outcome (95% Cl)
Fine mot	or skills	(measured with: I	Nullen Scales of	Early Learning	g (MSEL): Fin	e Motor; Better i	ndicated	l by lower values)			
45 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	21	24	N/A	N/A	The mean fine motor skills in the intervention groups was <b>0.45 standard deviations</b> <b>higher</b> (0.15 lower to 1.04 higher)
Motor sk	<b>ills</b> (meas	ured with: Vineland	d Adaptive Beha	viour Scale (V	ABS): Motor S	kills; Better indi	cated by	lower values)	<u> </u>	<u> </u>	1
45 (1 study) 104 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW <sup>2,3</sup> due to risk of bias, imprecision	21	24	N/A	N/A	The mean motor skills in the intervention groups was <b>0.78 standard deviations</b> higher (0.17 to 1.39 higher)

N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)
<sup>2</sup> High risk of performance and response bias as intervention administrators and participants were non-blind and risk of detection bias is unclear/unknown as although outcome assessors
were blinded the outcome measure was based on interview with (non-blind) parent rather than direct observation
<sup>3</sup> N<400

#### 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

		Q	uality assessr	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study event	rates (%)	Relative	Anticipated absolute effects	
(studies) Follow up	bias				bias	quality of evidence	With Intervention- manual-only control	With Inclusive educational intervention (LEAP) training	effect (95% CI)	Risk with Intervention- manual-only control	Risk difference with Inclusive educational intervention (LEAP) training (95% Cl)
Fine mot	or skill	S (measured with:	Mullen Scales c	of Early Learnin	ng (MSEL): Fir	ne Motor Age (m	onths); Better i	ndicated by lower va	alues)		
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	117	177	N/A	N/A	The mean fine motor skills in the intervention groups was <b>0.69 standard</b> <b>deviations higher</b> (0.45 to 0.93 higher)
<sup>1</sup> High risk of outcome asse <sup>2</sup> N<400	•		l bias as interventi	ion administrat	tors and partic	l ipants non-blind	I. In addition, ris	sk of detection bias i	l s unclear/ui	l nknown as identi	ty and blinding of

#### **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

	Q	uality assessn	nent	Summary of Findings						
Participants Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall	Study event rates (%) Relative Anticipated absolute effects				

(studies) Follow up	bias				bias	quality of evidence	With Control	With Parent training versus treatment-as- usual for motor skills as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Parent training versus treatment-as- usual for motor skills as an indirect outcome (95% CI)
Motor sk	kills (PE	C+PEBM cor	<b>nbined)</b> (mea	sured with: Vi	neland Adaptiv	e Behaviour Sca	le (VABS	6): Motor Skills; Better ind	dicated by l	ower value	es)
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean motor skills (pec+pebm combined) in the intervention groups was <b>0.11 standard deviations</b> <b>higher</b> (0.3 lower to 0.52 higher)
blinded clinic	cian outcom		Itcome measure	was based on	parental interv	view and simultan	eous ch	risk of detection bias is Id observation and parer			although the study included a

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

		Qı	uality assessn	nent	Summary of Findings						
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias			bias quality of evidence With With Parent and day Control staff training versus standard day-care for and gross motor ski an indirect outcome					effect (95% CI)	Risk with Control	Risk difference with Parent and day-care staff training versus standard day-care for fine and gross motor skills as an indirect outcome (95% Cl)
Fine mot	or skills	S (measured with:	Early Intervention	on Developmer	ntal Profile (EI	DP)/Preschool E	Developm	nental Profile (PSDP): Per	rceptual/Fir	e Motor;	Better indicated by lower
values)											
values) 35 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	19	16	N/A	N/A	The mean fine motor skills in the intervention groups was <b>0.01 standard deviations</b> <b>higher</b> (0.66 lower to 0.67 higher)
35 (1 study) 12 weeks	serious risk of bias	inconsistency	indirectness	serious <sup>1</sup>		LOW <sup>1</sup> due to imprecision					the intervention groups was 0.01 standard deviations higher

(1 study) 12 weeks	serious risk of bias	inconsistency	indirectness	serious <sup>1</sup>		LOW <sup>1</sup> due to imprecision		in the intervention groups was 0.18 standard deviations lower (0.85 lower to 0.48 higher)
<sup>1</sup> N<400 and	95% CI cro	sses both line of n	o effect and mea	asure of appred	ciable benefit c	or harm (SMD -	0.5/0.5)	

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

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

		Qı	uality assessn	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias					quality of evidence	With Control	With Reciprocal social- communication interventions versus treatment-as-usual for fine and gross motor skills as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Reciprocal social-communication interventions versus treatment- as-usual for fine and gross motor skills as an indirect outcome (95% Cl)
Fine mot	or skill	S (measured with	: Mullen Scales	of Early Learn	ing (MSEL): F	ine Motor Age (	(months)	; Better indicated by lower va	alues)		
50 (1 study) 39 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>		⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	25	25	N/A	N/A	The mean fine motor skills in the intervention groups was <b>0.02 standard deviations</b> <b>higher</b> (0.53 lower to 0.58 higher)
Motor sk	ills (mea	sured with: Vinela	nd Adaptive Bel	naviour Scale	(VABS): Motor	Skills; Better in	ndicated	by lower values)			
39 (1 study) 39 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	20	19	N/A	N/A	The mean motor skills in the intervention groups was <b>0.19 standard deviations</b> <b>higher</b> (0.44 lower to 0.82 higher)

<sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias unclear/unknown as identity and blinding of outcome assessors not reported

 $^{2}$  N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

<sup>3</sup> High risk of performance and response bias as intervention administrators and participants non-blind, and risk of detection bias unclear/unknown as outcome measure based on parent interview rather than direct behaviour observation and parents non-blind and involved in the intervention

# **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

		Qı	uality assessm	nent		Summary of Findings					
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study e	event rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	/ith With Secretin versus		Risk with Control	Risk difference with Secretin versus placebo for fine and gross motor skills as an indirect outcome (95% Cl)
Fine mote	or skills	(measured with: N	/ullen/DTVP-2: F	ine motor (mo	nths); Better ir	dicated by lower	values)		•	-	
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	28	28	N/A	N/A	The mean fine motor skills in the intervention groups was <b>0.04 standard deviations</b> <b>lower</b> (0.57 lower to 0.48 higher)

#### **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

		C	auality assess	Summary of Findings					
Participants F	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study event rates (%)	Relative	Anticipated absolute effects

(studies) Follow up	bias				bias	of evidence	-	With Omega- 3 fatty acids		Risk with Healthy diet control	Risk difference with Omega-3 fatty acids (95% Cl)
Fine mot	t <b>or</b> (measu	red with: Mullen Sca	ales of Early Learr	ning (MSEL): F	ine Motor; Bett	er indicated by low	er values)				
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean fine motor in the intervention groups was <b>0.03 standard</b> <b>deviations lower</b> (0.86 lower to 0.79 higher)
measure was	s not blinde	ce and response bia d. sses both line of no					0	of detection b	ias as the ou	utcome assess	or for this outcome

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

li internet interne		(	Quality assessi	nent			Summary of Findings					
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study event	rates (%)	Relative	Anticipated a	absolute effects	
(studies) Follow up	bias				bias	of evidence	With Treatment-as- usual	With Gluten- free and casein-free diet	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Gluten-free and casein-free diet (95% Cl)	
Motor im	pairme	<b>nt</b> (measured with	: Movement Asse	ssment Battery	y for Children:	Test of Motor Impa	airment (TOM	); Better indica	ted by lower	values)		
20 (1 study) 52 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\bigcirc \bigcirc \bigcirc$ <b>VERY LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	10	10	N/A	N/A	The mean motor impairment in the intervention groups was <b>0.12 standard</b> <b>deviations lower</b> (1 lower to 0.76 higher)	
outcome asse	essors not				u /			d unclear/unkn	own risk of c	letection bias a	s identity and blinding of	

# 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

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Waitlist or treatment- as-usual	With CBT		Risk with Waitlist or treatment-as- usual	Risk difference with CBT (95% Cl)
No longer meet anxiety disorder diagnosis (assessed with: Number of participants who no longer met DSM-IV criteria for anxiety disorder)											
87 (2 studies) 16-24 weeks		no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	2/42 (4.8%)	29/45 (64.4%)	(3.14 to 44.5)	Study population	
										48 per 1000	<b>515 more per 1000</b> (from 102 more to 1000 more)
										Moderate	
										44 per 1000	<b>476 more per 1000</b> (from 94 more to 1000 more)
Improvement in anxiety symptoms (assessed with: Clinical global impressions scale: Improvement ratings)											
83	no serious	no serious	no serious	serious <sup>1</sup>	undetected	$\oplus \oplus \oplus \ominus$	4/46	23/37	RR 7.2	Study population	

(2 studies) ri 16-24 weeks	risk of bias	inconsistency	indirectness			MODERATE <sup>1</sup> (8 due to imprecision	(8.7%)	(62.2%)	(2.74 to 18.91)	87 per 1000	<b>539 more per 1000</b> (from 151 more to 1000 more)
										Moderate	
										87 per 1000	<b>539 more per 1000</b> (from 151 more to 1000 more)
Self-repo values)	orted an	<b>xiety</b> (measur	ed with: Spence (	L Childrens Anx	iety Scale (SCA	S) or Multidimension	al Anxiety Sc	ale for Child	ren (MASC	): Child version;	Better indicated by lower
83 (2 studies) 16-24 weeks	serious <sup>2</sup>	very serious <sup>3</sup>	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3,4</sup> due to risk of bias, inconsistency, imprecision	41	42	N/A	N/A	The mean self-reported anxiety in the intervention groups was <b>1.06 standard</b> <b>deviations lower</b> (1.58 to 0.55 lower)
Parent-re Better indicate			asured with: Spe	nce Childrens	Anxiety Scale:	Parent Version (SCA	S-P) or Multi	dimensional	Anxiety Sc	ale for Children	(MASC): Parent version;
149 (3 studies) 6-24 weeks	serious⁵	very serious <sup>3</sup>	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>3,4,5</sup> due to risk of bias, inconsistency, imprecision	61	88	N/A	N/A	The mean parent- reported anxiety in the intervention groups was <b>0.99 standard</b> <b>deviations lower</b> (1.39 to 0.6 lower)
						le for Children - Clinic ated by lower values)	cal Severity F	Rating Scale	(ADIS-CSI	R) or Anxiety Dis	sorders Interview
79 (2 studies) 16-24 weeks	no serious risk of bias	very serious <sup>6</sup>	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,6</sup> due to inconsistency,	45	34	N/A	N/A	The mean clinician-rated anxiety in the intervention groups was 1.19 standard deviations lower

						imprecision					(1.7 to 0.68 lower)
Chronic	anxiety	(measured with:	Revised Childrer	n's Manifest A	nxiety Scale (R	CMAS); Better indicate	ed by lowe	r values)			
47 (1 study) 24 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>2,4</sup> due to risk of bias, imprecision	19	28	N/A	N/A	The mean chronic anxiety in the intervention groups was <b>3.29 standard</b> <b>deviations lower</b> (4.19 to 2.38 lower)
Social a			bence Child Anxie	ety Scale-Pare	ent (SCAS-P): S	ocial phobia or Anxiet	y Disorder	s Interview S	Schedule fo	r Children - P	arent Version (ADIS-P): Socia
109 (2 studies) 6-24 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision	43	66	N/A	N/A	The mean social anxiety in the intervention groups was <b>0.2 standard</b> <b>deviations lower</b> (0.59 lower to 0.2 higher)
•		iety (measured vited by lower value		d Anxiety Sca	le-Parent (SCA	S-P): Separation or A	nxiety Disc	rders Interv	iew Schedu	lle for Childrei	n - Parent Version (ADIS-P):
109 (2 studies) 6-24 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision	43	66	N/A	N/A	The mean separation anxiety in the intervention groups was 0.39 standard deviations lower (0.78 lower to 0.01 higher)

87 (2 studies) 6-24 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊝ LOW <sup>4,5</sup> due to risk of bias, imprecision	43	44	N/A	N/A	The mean generalised anxiety disorder in the intervention groups was <b>0.66 standard</b> <b>deviations lower</b> (1.1 to 0.22 lower)
Anxiety by lower valu	-	l to a specif	f <b>ic phobia</b> (r	measured with	: Anxiety Disor	ders Interview Schedu	Ile for Childre	n - Parent '	Version (AD	NS-P): Specific	phobia; Better indicated
43 (1 study) 24 weeks	serious <sup>8</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ LOW <sup>4,8</sup> due to risk of bias, imprecision	23	20	N/A	N/A	The mean anxiety relating to a specific phobia in the intervention groups was <b>0.99 standard</b> <b>deviations lower</b> (1.63 to 0.36 lower)
Panic (me	easured with	: Spence Child Ar	nxiety Scale-Pare	nt (SCAS-P): F	Panic; Better in	dicated by lower value	es)		1	4	1
66 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision	20	46	N/A	N/A	The mean panic in the intervention groups was <b>0.15 standard</b> <b>deviations higher</b> (0.37 lower to 0.68 higher)
Panic (m	easured with	n: Spence Child Ar	nxiety Scale-Pare	nt (SCAS-P): I	Panic; Better in	I dicated by lower value	es)				
66 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision	20	46	N/A	N/A	The mean panic in the intervention groups was 0.13 standard deviations lower (0.65 lower to 0.4 higher)
Fear of	persona	I injury (mea	sured with: Spend	ce Child Anxie	ty Scale-Paren	t (SCAS-P): Personal	Injury; Better	indicated b	y lower valu	ues)	(0.65 lower to 0.4

serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision	20	46	N/A	N/A	The mean fear of personal injury in the intervention groups was <b>0.2 standard</b> <b>deviations higher</b> (0.32 lower to 0.73 higher)
persona	<b>al injury</b> (mea	sured with: Spen	ce Child Anxie	ty Scale-Paren	t (SCAS-P): Personal	Injury; Bett	er indicated b	oy lower va	lues)	
serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊝⊝⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision	20	46	N/A	N/A	The mean fear of personal injury in the intervention groups was <b>0.31 standard</b> <b>deviations lower</b> (0.84 lower to 0.22 higher)
asured with:	Spence Child Anx	iety Scale-Parent	t (SCAS-P): O	CD; Better indic	cated by lower values)	)				
serious⁵	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision	20	46	N/A	N/A	The mean ocd in the intervention groups was <b>0.33 standard</b> <b>deviations lower</b> (0.86 lower to 0.19 higher)
asured with:	Spence Child Any	kiety Scale-Paren	t (SCAS-P): O	CD; Better indi	cated by lower values	)				
serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ LOW <sup>4,5</sup> due to risk of bias, imprecision	20	46	N/A	N/A	The mean ocd in the intervention groups was <b>1 standard deviations</b> <b>lower</b> (1.55 to 0.45 lower)
	persona serious <sup>5</sup> asured with: serious <sup>5</sup>	inconsistency         inconsistency         personal injury (mean inconsistency)         serious <sup>5</sup> no serious inconsistency         asured with:       Spence Child Anxiet         serious <sup>5</sup> no serious inconsistency         asured with:       Spence Child Anxiet         asured with:       Spence Child Anxiet	inconsistency       indirectness         personal injury (measured with: Spen         serious <sup>5</sup> no serious inconsistency       no serious indirectness         asured with: Spence Child Anxiety Scale-Parent inconsistency       no serious indirectness         serious <sup>5</sup> no serious inconsistency       no serious indirectness         serious <sup>5</sup> no serious inconsistency       no serious indirectness         serious <sup>5</sup> no serious inconsistency       no serious indirectness         asured with: Spence Child Anxiety Scale-Parent serious <sup>5</sup> no serious	inconsistency       indirectness       serious <sup>7</sup> personal injury (measured with: Spence Child Anxie         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> asured with: Spence Child Anxiety Scale-Parent (SCAS-P): O         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> asured with: Spence Child Anxiety Scale-Parent (SCAS-P): O         serious <sup>5</sup> no serious       no serious         asured with: Spence Child Anxiety Scale-Parent (SCAS-P): O         serious <sup>5</sup> no serious       no serious	inconsistency       indirectness       serious <sup>7</sup> personal injury (measured with: Spence Child Anxiety Scale-Paren serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected         asured with: Spence Child Anxiety Scale-Parent (SCAS-P): OCD; Better indir serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected         asured with: Spence Child Anxiety Scale-Parent (SCAS-P): OCD; Better indir inconsistency       no serious indirectness       very serious <sup>7</sup> undetected         asured with: Spence Child Anxiety Scale-Parent (SCAS-P): OCD; Better indir indirectness       serious <sup>7</sup> undetected         asured with: Spence Child Anxiety Scale-Parent (SCAS-P): OCD; Better indir       serious <sup>7</sup> undetected	inconsistency       indirectness       serious <sup>7</sup> VERY LOW <sup>6,7</sup> due to risk of bias, imprecision         personal injury (measured with: Spence Child Anxiety Scale-Parent (SCAS-P): Personal inconsistency       no serious indirectness       undetected       ⊕⊖⊖⊖ VERY LOW <sup>6,7</sup> due to risk of bias, imprecision         serious <sup>6</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>6,7</sup> due to risk of bias, imprecision         asured with: Spence Child Anxiety Scale-Parent (SCAS-P): OCD; Better indicated by lower values) inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>6,7</sup> due to risk of bias, imprecision         serious <sup>6</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊖⊖⊖ UENY LOW <sup>6,7</sup> due to risk of bias, imprecision         asured with: Spence Child Anxiety Scale-Parent (SCAS-P): OCD; Better indicated by lower values         serious <sup>6</sup> no serious inconsistency       no serious indirectness       serious <sup>4</sup> undetected       ⊕⊕⊖⊖ LOW <sup>4,5</sup> due to risk of bias, due to risk of bias,	inconsistency       indirectness       serious <sup>7</sup> VERY LOW <sup>5,7</sup> due to risk of bias, imprecision         perSonal injury (measured with: Spence Child Anxiety Scale-Parent (SCAS-P): Personal Injury; Bett inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊝⊖⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision       20         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊝⊖⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision       20         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision       20         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊖⊖⊖ LOW <sup>4,5</sup> due to risk of bias, inconsistency       20	inconsistency       indirectness       serious <sup>7</sup> VERY LOW <sup>6,7</sup> due to risk of bias, imprecision         personal injury       (measured with: Spence Child Anxiety Scale-Parent (SCAS-P): Personal Injury; Better indicated by serious <sup>6</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>6,7</sup> due to risk of bias, imprecision       20       46         serious <sup>6</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>6,7</sup> due to risk of bias, imprecision       20       46         serious <sup>6</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>6,7</sup> due to risk of bias, imprecision       20       46         serious <sup>6</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊖⊖⊖ LOW <sup>4,6</sup> 20       46         serious <sup>6</sup> no serious inconsistency       no serious indirectness       serious <sup>4</sup> undetected       ⊕⊖⊖⊖ LOW <sup>4,6</sup> 20       46	inconsistency       indirectness       serious <sup>7</sup> VERY LOW <sup>6,7</sup> due to risk of bias, imprecision         personal injury       (measured with: Spence Child Anxiety Scale-Parent (SCAS-P): Personal Injury; Better indicated by lower values inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       DO OO VERY LOW <sup>6,7</sup> due to risk of bias, imprecision       20       46       N/A         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       DO OO VERY LOW <sup>6,7</sup> due to risk of bias, imprecision       20       46       N/A         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       DO OO VERY LOW <sup>6,7</sup> due to risk of bias, imprecision       20       46       N/A         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       DO OO VERY LOW <sup>6,7</sup> due to risk of bias, imprecision       20       46       N/A         serious <sup>6</sup> no serious indirectness       serious <sup>4</sup> undetected       DO OO LOW <sup>4,5</sup> due to risk of bias, indirectness       20       46       N/A	Inconsistency       Indirectness       serious <sup>7</sup> VERY LOW <sup>6,7</sup> due to risk of bias, imprecision         perSonal injury (measured with: Spence Child Anxiety Scale-Parent (SCAS-P): Personal Injury; Better indicated by lower values)         serious <sup>5</sup> no serious inconsistency       no serious indirectness       very very serious <sup>7</sup> undetected undetected       ⊕⊖⊖⊖ VERY LOW <sup>6,7</sup> due to risk of bias, imprecision       20       46       N/A       N/A         seured with: Spence Child Anxiety Scale-Parent (SCAS-P): OCD; Better indicated by lower values)       20       46       N/A       N/A         seured with: Spence Child Anxiety Scale-Parent (SCAS-P): OCD; Better indicated by lower values)       20       46       N/A       N/A         serious <sup>6</sup> no serious inconsistency       no serious indirectness       very serious <sup>7</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>5,7</sup> due to risk of bias, imprecision       20       46       N/A       N/A         seured with: Spence Child Anxiety Scale-Parent (SCAS-P): OCD; Better indicated by lower values)       20       46       N/A       N/A         setious <sup>6</sup> no serious inconsistency       no serious       serious <sup>4</sup> undetected       ⊕⊕⊖⊖ LOW <sup>4,6</sup> due to risk of bias, inconsistency       N/A       N/A

47 (1 study) 24 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ LOW <sup>4,5</sup> due to risk of bias, imprecision	19	28	N/A	N/A	The mean emotional symptoms in the intervention groups was <b>4.29 standard</b> <b>deviations lower</b> (5.37 to 3.21 lower)
Emotio	nal symp	otoms (measur	ed with: Strength	s and Difficulti	es Questionna	ire: Teacher Version:	Emotional;	Better indica	ted by lowe	r values)	
47 (1 study) 24 weeks	serious <sup>9</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊝ LOW <sup>4,9</sup> due to risk of bias, imprecision	19	28	N/A	N/A	The mean emotional symptoms in the intervention groups was 2.75 standard deviations lower (3.57 to 1.93 lower)
Self-dire	ected ne	gative thou	ights (measure	ed with: Childr	en's Automatic	Thoughts Scale (CA	ΓS): Interna	lising; Better	indicated b	y lower values	)
47 (1 study) 24 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2,4</sup> due to risk of bias, imprecision	19	28	N/A	N/A	The mean self-directed negative thoughts in the intervention groups was 4.61 standard deviations lower (5.75 to 3.48 lower)
Outwar	d-directe	ed negative	thoughts (r	neasured with	: Children's Au	I Itomatic Thoughts Sca	le (CATS):	Hostile Inten	t; Better inc	licated by lowe	r values)
47 (1 study) 24 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,7</sup> due to risk of bias, imprecision	19	28	N/A	N/A	The mean outward- directed negative thoughts in the intervention groups was <b>0.33 standard</b> <b>deviations lower</b> (0.91 lower to 0.26 higher)
<sup>2</sup> High risk o	ts less than 3 f performanc value is consi		etection bias. Selt =0.00001)	f-report and cl	nildren were no	t blind to treatment all	ocation or o	confounding	factors.		

<sup>1</sup> Total N less than 400

<sup>5</sup> High risk of performance, response and detection bias. Parent-rated and parents were not blind to treatment allocation or confounding factors.

<sup>6</sup> I squared value is considerable at 91% (p=0.00001)

Total N is less than 400. 95% confidence interval crosses both line of no effect and measure of appreciable benefit/harm (SMD -0.5/0.5)

<sup>8</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias was unclear/unknown as although outcome assessors were blind to treatment allocation the outcome measure was based on interview with parents who were involved in the intervention and not blind to treatment allocation <sup>9</sup> High risk of performance, response and detection bias. Teacher-rated and unclear if teachers were blind to treatment allocation. Teachers are not blind to confounding factors.

# 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

		Q	uality assess	ment			Summary of Findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	event rates (%)	Relative effect	Anticip	ated absolute effects
Follow up						evidence	With Control	With Selective noradrenaline reuptake inhibitors versus placebo for hyperactivity/ADHD symptoms as a direct outcome	(95% CI)	Risk with Control	Risk difference with Selective noradrenaline reuptake inhibitors versus placebo for hyperactivity/ADHD symptoms as a direct outcome (95% CI)
Hyperac	tivity (	parent-rate	<b>d)</b> (measured	with: Aberrant	Behaviour Ch	ecklist (ABC): Hy	peractiv	ity & Noncompliance; Better	indicated b	y lower v	values)
88 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	45	43	N/A	N/A	The mean hyperactivity (parent-rated) in the intervention groups was <b>0.19 standard deviations</b> <b>lower</b> (0.61 lower to 0.22 higher)

(1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	36	36	N/A	N/A	The mean hyperactivity (teacher-rated) in the intervention groups was <b>0.12 standard deviations</b> <b>lower</b> (0.59 lower to 0.34 higher)
ADHD	sympto	ms (parent	<b>-rated)</b> (mea	asured with: [	DSM-IV ADHD I	Rating Scale (AD	HD-RS	3): Total; Better ind	icated by lower value	es)	
90 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup> due to imprecision	47	43	N/A	N/A	The mean adhd symptoms (parent-rated) in the intervention groups was <b>0.48 standard deviations</b> <b>lower</b> (0.9 to 0.06 lower)
ADHD	sympto	ms (teache	er-rated) (m	easured with	Conners' Teac	her Rating Scale	- Revi	sed: Short Form (C	CTRS-R:S): ADHD; B	Setter indi	cated by lower values)
	no	no serious	no serious	very serious <sup>1</sup>	undetected		36	36	N/A	N/A	The mean adhd symptoms
72 (1 study) 8 weeks	serious risk of bias	inconsistency	indirectness	Senous		due to imprecision					lower
(1 study) 8 weeks	serious risk of bias				Teacher Rating	imprecision	: Short	Form (CTRS-R:S)	: Cognitive/Attention	; Better in	intervention groups was 0.15 standard deviations

(1 study) s 8 weeks ri	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	36	36	N/A	N/A	The mean oppositional (teacher-rated) in the intervention groups was <b>0.1 standard deviations</b> <b>higher</b> (0.36 lower to 0.56 higher
ower values) 89 n (1 study) s 8 weeks ri	no serious risk of bias	n ADHD sy	no serious indirectness	Clinician very serious <sup>1</sup>	undetected	easured with: C ⊕⊕⊝⊝ LOW <sup>1</sup> due to	linical G	lobal Impression S	Scale-ADHD-Improve	ment (CG	I-ADHD-I); Better indicated to The mean improvement in adhd symptoms (clinician- rated) in the intervention

# 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

	Quality assessment							Summary of Findings				
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study event rates (%)	Relative	Anticipated absolute effects			

(studies) Follow up	bias				bias		With Healthy diet control	With Omega- 3 fatty acids	effect (95% CI)	Risk with Healthy diet control	Risk difference with Omega-3 fatty acids (95% CI)
ADHD s	ymptor	<b>NS</b> (measured with	n: Child Behavior (	Checklist 1.5 -	5 (CBCL/1.5-5)	): ADHD; Better ind	icated by low	ver values)			
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean adhd symptoms in the intervention groups was <b>0.3 standard deviations</b> <b>lower</b> (1.13 lower to 0.53 higher)
measure wa	s not blinde	•					0	of detection b	i bias as the c	utcome asses	ssor for this outcome

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

		C	Quality assess	nent			Summary of Findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event	rates (%)	Relative effect	Anticipated	absolute effects
Follow up							With Treatment-as- usual	With Gluten- free and casein-free diet	(95% CI)	Risk with Treatment-as- usual	Risk difference with Gluten-free and casein- free diet (95% Cl)
Inattentio	<b>DN</b> (measu	ured with: Attention	Deficit Hyperactiv	ity Disorder-IV	rating scale bas	sed on DSM-IV cri	iteria (ADHD-I	V): Inattention	(change sc	ore); Better ind	icated by lower values)
55 (1 study) 35 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^{1,2} \\ \text{due to risk of } \\ \text{bias,} \end{array}$	29	26	N/A	N/A	The mean inattention in the intervention groups was 0.59 standard deviations lower

						imprecision					(1.13 to 0.05 lower)
Hyperac <sup>®</sup> values)	tivity (m	easured with: Atter	I ntion-Deficit Hypera	activity Disorder	I -IV rating scale	e based on DSM-I'	V criteria (A	ADHD-IV): Hyper	activity (cha	nge score);	Better indicated by lower
55 1 study) 35 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.5 standard</b> <b>deviations lower</b> (1.04 lower to 0.04 higher)
treatment allo (32% in expendence N<400	cation and imental gro	other potentially co oup and 15% in the	onfounding factors.	There was also	a high risk of	attrition bias as ov	er twice as				ported and non-blind to p relative to the controls

# **1.27.2**Nutritional interventions for anxiety as an indirect outcome

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

		Qı	uality assessme	ent					Summary	/ of Findi	ngs
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision		of evidence	(%)	went rates With Omega- 3 fatty acids	Relative effect (95% CI)	Anticipat Risk with Placebo	ed absolute effects Risk difference with Omega-3 fatty acids (95% Cl)
Internali	<b>zing</b> (meas	ured with: Behavior	Assessment Syste	em for Childrer	n (BASC): Intern	nalizing; Better indi	cated by I	ower values)		•	

			no serious indirectness	very serious <sup>1</sup>		⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	12	12	N/A	The mean internalizing in the intervention groups was <b>0.48 standard deviations</b> <b>lower</b> (1.3 lower to 0.33 higher)
<sup>1</sup> N<400 and 9	95% CI crosse	es both line of no eff	ect and measure of	of appreciable	benefit or harm	(SMD -0.5/0.5)				

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

		C	Quality assessi	nent					Summa	ary of Findi	ings
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study ever	nt rates (%)	Relative effect	Anticipated	l absolute effects
Follow up			With Healthy diet control	With Omega-3 fatty acids	(95% CI)	Risk with Healthy diet control	Risk difference with Omega-3 fatty acids (95% Cl)				
Internali	zing (me	easured with: Child	Behavior Checkli	st 1.5 - 5 (CBC	L/1.5-5): Inter	nalizing; Better ind	licated by lov	wer values)		1	
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \ominus \ominus \ominus \\ \textbf{VERY LOW}^{1,2} \\ \text{due to risk of} \\ \text{bias,} \\ \text{imprecision} \end{array}$	13	10	N/A	N/A	The mean internalizing in the intervention groups was <b>0.17 standard deviations</b> <b>lower</b> (0.99 lower to 0.66 higher)
Anxious	/Depre	<b>SSEC</b> (measured	l with: Child Beha	vior Checklist	1.5 - 5 (CBCL/	1.5-5): Anxious/De	pressed; Be	tter indicated	d by lower v	alues)	
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \ominus \ominus \ominus \\ \textbf{VERY LOW}^{1,2} \\ \text{due to risk of} \\ \text{bias,} \\ \text{imprecision} \end{array}$	13	10	N/A	N/A	The mean anxious/depressed in the intervention groups was <b>0.23 standard deviations</b> <b>lower</b> (1.05 lower to 0.6 higher)

23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	13	10	N/A	N/A	The mean affective in the intervention groups was <b>0.07 standard deviations</b> higher (0.76 lower to 0.89 higher)
Anxiety	(measured	with: Child Behav	vior Checklist 1.5	- 5 (CBCL/1.5-	5): Anxiety; Bet	ter indicated by lov	wer values	5)			
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>1,2</sup> due to risk of	13	10	N/A	N/A	The mean anxiety in the intervention groups was 0.16 standard deviations

# **1.27.3Medical 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

		Qu	ality assessn	nent				Sumr	nary of F	indings	
(studies)	Risk of bias	Inconsistency	Indirectness	•	Publication bias	quality of	Study event		effect	Anticipated a	bsolute effects
Follow up							With Short- term chelation (1-round of DMSA therapy and 6-rounds	(7-rounds of Dimercaptosuccinic Acid		Risk with Short-term chelation (1- round of DMSA therapy and 6- rounds of	Risk difference with Long- term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy) (95% CI)

							of placebo)			placebo)	
Specific	Fears	(measured with:	Pervasive Deve	lopment Diso	rder Behavior	Inventory (PDI	DBI): Specific	Fears; Better indicated by	y lower valu	ues)	-
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	15	25	N/A	N/A	The mean specific fears in the intervention groups was <b>0.11 standard</b> <b>deviations lower</b> (0.75 lower to 0.53 higher)

# 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

		Q	uality assessm	nent					Summa	ry of Fin	dings
` '	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study e (%)		Relative effect	Anticipat	ed absolute effects
Follow up			With Control	With CBT versus placebo	(95% CI)	Risk with Control	Risk difference with CBT versus placebo (95% Cl)				
Sleep on	set latenc	<b>y</b> (measured with:	Actigraph; Better	indicated by lo	ower values)						
65 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	32	33	N/A	N/A	The mean sleep onset latency in the intervention groups was 0.68 standard deviations lower

											(1.18 to 0.18 lower)
Wake af	ter sleep o	<b>DINSET</b> (measured	I with: Actigraph; E	Better indicate	d by lower value	es)					
65 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	32	33	N/A	N/A	The mean wake after sleep onset in the intervention groups was <b>0.24 standard deviations</b> <b>lower</b> (0.73 lower to 0.24 higher)
Nap time	e (measured w	vith: Actigraph; Bet	ter indicated by lo	wer values)	·						·
65 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	33	N/A	N/A	The mean nap time in the intervention groups was <b>0.81 standard deviations</b> <b>lower</b> (1.32 to 0.3 lower)
Bedtime	(measured wi	th: Actigraph; Bett	er indicated by low	ver values)							·
65 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	33	N/A	N/A	The mean bedtime in the intervention groups was <b>0.89 standard deviations</b> <b>lower</b> (1.4 to 0.38 lower)
Total sle	eep time (m	easured with: Acti	graph; Better indic	ated by lower	values)		J				
65 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	33	N/A	N/A	The mean total sleep time in the intervention groups was <b>0.62 standard deviations</b> <b>higher</b> (0.12 to 1.12 higher)
Sleep ef	ficiency (m	easured with: Acti	graph; Better indic	ated by lower	values)	1	I		<u>_</u>		-
65 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	32	33	N/A	N/A	The mean sleep efficiency in the intervention groups was 1.98 standard deviations higher

											(1.38 to 2.58 higher)
	rebleme (										
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	al score; Better indic	32	33	N/A	N/A	The mean sleep problems in the intervention groups was <b>1.01 standard deviations</b> <b>lower</b> (1.53 to 0.5 lower)
Bed res	istance (m	easured with: Child	Iren's Sleep Habits	s Questionnair	e (CSHQ): Bed	resistance; Better ind	dicated	by lower va	lues)		
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1,3</sup> due to risk of bias, imprecision	32	33	N/A	N/A	The mean bed resistance in the intervention groups was <b>1.18 standard deviations</b> <b>Iower</b> (1.71 to 0.65 lower)
Sleep or	nset delay	(measured with: 0	Children's Sleep H	abits Questior	nnaire (CSHQ):	I Sleep onset delay; B	etter ind	licated by lo	ower values)		
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	32	33	N/A	N/A	The mean sleep onset delay in the intervention groups was 0.94 standard deviations lower (1.45 to 0.42 lower)
Sleep ar	n <b>xiety</b> (mea	sured with: Childre	n's Sleep Habits C	Questionnaire	(CSHQ): Sleep	anxiety; Better indica	ted by lo	ower values	5)		
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	32	33	N/A	N/A	The mean sleep anxiety in the intervention groups was <b>0.43 standard deviations</b> <b>Iower</b> (0.92 lower to 0.06 higher)
Night-wa	<b>akings</b> (me	asured with: Child	ren's Sleep Habits	Questionnaire	e (CSHQ): Night	-wakings; Better indi	cated by	/ lower valu	ies)		1
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,3</sup> due to risk of bias, imprecision	32	33	N/A	N/A	The mean night-wakings in the intervention groups was 0.84 standard deviations lower

										(1.34 to 0.33 lower)
ration (mea	asured with: Childr	en's Sleep Habits	Questionnaire	(CSHQ): Sleep	duration; Better ind	icated b	y lower value	s)		
serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	32	33	N/A	N/A	The mean sleep duration in the intervention groups was <b>0.23 standard deviations</b> <b>higher</b> (0.26 lower to 0.71 higher)
nias (meas	ured with: Children	's Sleep Habits Qu	uestionnaire (C	SHQ): Paraso	mnias; Better indicat	ed by lo	wer values)			
serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	32	33	N/A	N/A	The mean parasomnias in the intervention groups was <b>0.34 standard deviations</b> <b>higher</b> (0.15 lower to 0.83 higher)
ordered	breathing (me	asured with: Child	en's Sleep Ha	bits Questionn	aire (CSHQ): Sleep o	disorder	ed breathing;	Better indica	ited by lov	wer values)
serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	32	33	N/A	N/A	The mean sleep disordered breathing in the intervention groups was <b>0 standard deviations</b> <b>higher</b> (0.49 lower to 0.49 higher)
sleepines	S (measured with	: Children's Sleep	Habits Question	Donnaire (CSHQ	): Daytime sleepines	s; Bette	r indicated by	lower values	5)	
serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	32	33	N/A	N/A	The mean daytime sleepiness in the intervention groups was <b>0.5 standard deviations</b> <b>lower</b> (1 to 0.01 lower)
		Sleep onset	atency (as	sessed with: N	umber of participants	s who sh	lowed sleep c	onset latency	<30 min	or reduction of sleep onset
r		no serious	verv	undetected		0/32	3/33	RR 6 79	Study	opulation
	serious <sup>3</sup> nias (measu serious <sup>3</sup> sordered l serious <sup>3</sup> sleepines serious <sup>3</sup>	serious <sup>3</sup> no serious         nias (measured with: Children serious <sup>3</sup> no serious inconsistency         sordered breathing (me serious <sup>3</sup> no serious inconsistency         serious <sup>3</sup> no serious inconsistency         sleepiness (measured with serious <sup>3</sup> no serious inconsistency         steepiness (measured with serious <sup>3</sup> no serious inconsistency         streatment response - 3 % based on actigraph data)       1	serious3no serious inconsistencyno serious indirectnessnias (measured with: Children's Sleep Habits Que serious3no serious inconsistencyno serious indirectnessserious3no serious inconsistencyno serious indirectnesssordered breathing (measured with: Children's serious3no serious inconsistencyno serious indirectnessserious3no serious inconsistencyno serious indirectnessserious3no serious inconsistencyno serious indirectnesssleepiness serious3(measured with: Children's Sleep inconsistencyno serious indirectnessserious3no serious inconsistencyno serious indirectnessstreatment response - Sleep onset % based on actigraph data)tereatment response	serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> nias (measured with: Children's Sleep Habits Questionnaire (C serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> sordered breathing (measured with: Children's Sleep Habits serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> sleepiness (measured with: Children's Sleep Habits Question inconsistency       no serious indirectness       serious <sup>1</sup> serious <sup>3</sup> no serious inconsistency       serious indirectness       serious <sup>1</sup> serious <sup>3</sup> no serious inconsistency <t< td=""><td>serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected         nias (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parason serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected         sordered breathing (measured with: Children's Sleep Habits Questionnaire inconsistency       no serious indirectness       serious<sup>1</sup>       undetected         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected         sleepiness (measured with: Children's Sleep Habits Questionnaire (CSHQ inconsistency       no serious indirectness       serious<sup>1</sup>       undetected         serious<sup>3</sup>       no serious inconsistency       serious       serious<sup>1</sup>&lt;</td><td>serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊙⊖⊖ VERY LOW<sup>2.3</sup> due to risk of bias, imprecision         <b>nias</b> (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicat inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊙⊖ VERY LOW<sup>2.3</sup> due to risk of bias, imprecision         <b>sordered breathing</b> (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicat inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊙⊖ VERY LOW<sup>2.3</sup> due to risk of bias, imprecision         <b>sordered breathing</b> (measured with: Children's Sleep Habits Questionnaire (CSHQ): Sleep of inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊖ LOW<sup>1.3</sup> due to risk of bias, imprecision         <b>sleepiness</b> (measured with: Children's Sleep Habits Questionnaire (CSHQ): Daytime sleepines serious<sup>3</sup>       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊖ LOW<sup>1.3</sup> due to risk of bias, imprecision         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊖ LOW<sup>1.3</sup> due to risk of bias, imprecision         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊖ LOW<sup>1.3</sup> due to risk of bias, imprecision         serious<sup>3</sup>       no serious inconsistency       no serious i</td><td>serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊖⊖⊖ VERY LOW<sup>2,3</sup> due to risk of bias, imprecision       32         nias (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicated by lo serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊖⊖⊖ VERY LOW<sup>2,3</sup> due to risk of bias, imprecision       32         sordered breathing (measured with: Children's Sleep Habits Questionnaire (CSHQ): Sleep disorder inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32         sleepiness (measured with: Children's Sleep Habits Questionnaire (CSHQ): Daytime sleepiness; Bette indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32         serious<sup>3</sup>       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32         serious<sup>3</sup>       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32         sterious<sup>3</sup>       no serious indirectness       serious<sup>1</sup>       undetec</td><td>serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊖⊖⊖ VERY LOW<sup>2.3</sup> due to risk of bias, imprecision       32       33         nias (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicated by lower values)       32       33         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊖⊙⊖ VERY LOW<sup>2.3</sup> due to risk of bias, imprecision       32       33         sordered breathing (measured with: Children's Sleep Habits Questionnaire (CSHQ): Sleep disordered breathing;       32       33         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊙ LOW<sup>1.3</sup> due to risk of bias, imprecision       32       33         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊙ LOW<sup>1.3</sup> due to risk of bias, imprecision       32       33         sleepiness inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊙ LOW<sup>1.3</sup> due to risk of bias, imprecision       32       33         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊙ LOW<sup>1.3</sup> due to risk of bias, imprecision       32       33         serious<sup>3</sup></td></t<> <td>inconsistency       indirectness       serious<sup>2</sup>       VERY LOW<sup>2,3</sup> due to risk of bias, imprecision         niaS (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicated by lower values)         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊖⊖⊖ VERY LOW<sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A         cordered breathing (measured with: Children's Sleep Habits Questionnaire (CSHQ): Sleep disordered breathing; Better indicates inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊖⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊖⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A         sleepiness       (measured with: Children's Sleep Habits Questionnaire (CSHQ): Daytime sleepiness; Better indicated by lower values inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected UOW<sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A         serious<sup>3</sup>       no serious inconsistency<td>serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊖⊖⊖ VERY LOW<sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         nias (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicated by lower values)       inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊝⊖⊖ VERY LOW<sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊝⊖⊖ VERY LOW<sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious<sup>3</sup>       &lt;</td></td>	serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected         nias (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parason serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected         sordered breathing (measured with: Children's Sleep Habits Questionnaire inconsistency       no serious indirectness       serious <sup>1</sup> undetected         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected         sleepiness (measured with: Children's Sleep Habits Questionnaire (CSHQ inconsistency       no serious indirectness       serious <sup>1</sup> undetected         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected         serious <sup>3</sup> no serious inconsistency       serious       serious <sup>1</sup> <	serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊙⊖⊖ VERY LOW <sup>2.3</sup> due to risk of bias, imprecision <b>nias</b> (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicat inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊙⊖ VERY LOW <sup>2.3</sup> due to risk of bias, imprecision <b>sordered breathing</b> (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicat inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊙⊖ VERY LOW <sup>2.3</sup> due to risk of bias, imprecision <b>sordered breathing</b> (measured with: Children's Sleep Habits Questionnaire (CSHQ): Sleep of inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1.3</sup> due to risk of bias, imprecision <b>sleepiness</b> (measured with: Children's Sleep Habits Questionnaire (CSHQ): Daytime sleepines serious <sup>3</sup> no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1.3</sup> due to risk of bias, imprecision         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1.3</sup> due to risk of bias, imprecision         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1.3</sup> due to risk of bias, imprecision         serious <sup>3</sup> no serious inconsistency       no serious i	serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision       32         nias (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicated by lo serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision       32         sordered breathing (measured with: Children's Sleep Habits Questionnaire (CSHQ): Sleep disorder inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32         sleepiness (measured with: Children's Sleep Habits Questionnaire (CSHQ): Daytime sleepiness; Bette indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32         serious <sup>3</sup> no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32         serious <sup>3</sup> no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32         sterious <sup>3</sup> no serious indirectness       serious <sup>1</sup> undetec	serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>2.3</sup> due to risk of bias, imprecision       32       33         nias (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicated by lower values)       32       33         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊖⊙⊖ VERY LOW <sup>2.3</sup> due to risk of bias, imprecision       32       33         sordered breathing (measured with: Children's Sleep Habits Questionnaire (CSHQ): Sleep disordered breathing;       32       33         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊙ LOW <sup>1.3</sup> due to risk of bias, imprecision       32       33         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊙ LOW <sup>1.3</sup> due to risk of bias, imprecision       32       33         sleepiness inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊙ LOW <sup>1.3</sup> due to risk of bias, imprecision       32       33         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊙ LOW <sup>1.3</sup> due to risk of bias, imprecision       32       33         serious <sup>3</sup>	inconsistency       indirectness       serious <sup>2</sup> VERY LOW <sup>2,3</sup> due to risk of bias, imprecision         niaS (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicated by lower values)         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A         cordered breathing (measured with: Children's Sleep Habits Questionnaire (CSHQ): Sleep disordered breathing; Better indicates inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊖⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊖⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A         sleepiness       (measured with: Children's Sleep Habits Questionnaire (CSHQ): Daytime sleepiness; Better indicated by lower values inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected UOW <sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A         serious <sup>3</sup> no serious inconsistency <td>serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊖⊖⊖ VERY LOW<sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         nias (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicated by lower values)       inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊝⊖⊖ VERY LOW<sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       very serious<sup>2</sup>       undetected       ⊕⊝⊖⊖ VERY LOW<sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious<sup>3</sup>       no serious inconsistency       no serious indirectness       serious<sup>1</sup>       undetected       ⊕⊖⊖ LOW<sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious<sup>3</sup>       &lt;</td>	serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         nias (measured with: Children's Sleep Habits Questionnaire (CSHQ): Parasomnias; Better indicated by lower values)       inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊝⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious <sup>3</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       ⊕⊝⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious <sup>3</sup> no serious inconsistency       no serious indirectness       serious <sup>1</sup> undetected       ⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision       32       33       N/A       N/A         serious <sup>3</sup> <

(1 study) 12 weeks	risk of bias	inconsistency	indirectness	serious <sup>4</sup>		<b>LOW</b> <sup>4</sup> due to imprecision	(0%)	(9.1%)	(0.36 to 126.5)	0 per 1000	N/A
										Moderat	e
										0 per 1000	N/A
Positive	treatment	response - S	Sleep efficier	ICY (assesse	d with: Number	of participants who	showed	=>85% for sl	eep efficiend	cy based o	n actigraph data)
65 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊕⊝⊝ LOW⁴	0/32 (0%)	3/33 (9.1%)	<b>RR 6.79</b> (0.36 to	Study p	opulation
12 weeks						due to imprecision		、 <i>,</i>	126.5)	0 per 1000	N/A
										Moderat	ie
										0 per 1000	N/A
<sup>3</sup> High risk of involved in the	f performance ne intervention		as intervention ad	ministrators a	nd participants			etection bias a	as parent-co	mpleted a	nd parents non-blind and

# **1.28.2 Melatonin for sleep problems as a direct outcome**

## Melatonin versus placebo for sleep problems as a direct outcome

		Q	uality assessn	nent				Su	ummary o	f Finding	IS	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study of With Control	With Melatonin versus	effect (95% CI)	-	ted absolute effects Risk difference with Melatonin versus placebo for the coexisting problem of sleep (95% Cl)	
Sleep on	leep onset latency (measured with: Actigraph; Better indicated by lower values)											

66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean sleep onset latency in the intervention groups was <b>1.23 standard deviations</b> lower (1.75 to 0.7 lower)
Wake af	ter sleep	onset (measur	ed with: Actigraph	; Better indica	ated by lower v	alues)					
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean wake after sleep onset in the intervention groups was <b>0.82 standard deviations</b> <b>lower</b> (1.32 to 0.31 lower)
Nap time	e (measured	with: Actigraph; B	etter indicated by	lower values)			1			-	
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean nap time in the intervention groups was <b>0.57 standard deviations</b> <b>lower</b> (1.06 to 0.08 lower)
Bed time	e (measured	with: Actigraph; B	etter indicated by	lower values)			1				
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean bed time in the intervention groups was <b>1.08 standard deviations</b> <b>lower</b> (1.6 to 0.56 lower)
Total sle	ep time (	measured with: Ad	tigraph; Better in	dicated by low	ver values)		1				
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean total sleep time in the intervention groups was <b>1.45 standard deviations</b> higher (0.9 to 1.99 higher)

Sleep ef	<b>ficiency</b> (	measured with: A	ctigraph; Better in	ndicated by lov	wer values)						
66 (1 study) 12 weeks	-	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean sleep efficiency in the intervention groups was 2.47 standard deviations higher (1.82 to 3.12 higher)
Sleep pr	roblems (r	measured with: C	hildren's Sleep H	abits Question	naire (CSHQ):	Total score; Better	r indicate	ed by lower v	alues)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean sleep problems in the intervention groups was <b>1.81 standard deviations</b> <b>lower</b> (2.39 to 1.23 lower)
Bed res	istance (m	easured with: Ch	nildren's Sleep Ha	bits Questionr	naire (CSHQ): E	Bed resistance; Be	tter indic	ated by lowe	r values)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean bed resistance ir the intervention groups was <b>1.72 standard deviations</b> <b>lower</b> (2.29 to 1.15 lower)
Sleep or	nset delay	(measured with	n: Children's Sleep	o Habits Ques	tionnaire (CSH	Q): Sleep onset de	lay; Bett	ter indicated	by lower values)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean sleep onset delay in the intervention groups was <b>1.58 standard deviations</b> <b>lower</b> (2.14 to 1.03 lower)
Sleep ar	<b>1xiety</b> (mea	asured with: Child	Iren's Sleep Habit	s Questionnai	re (CSHQ): Sle	ep anxiety; Better	indicate	d by lower va	llues)	1	
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	32	34	N/A	N/A	The mean sleep anxiety in the intervention groups was 0.37 standard deviations lower

											(0.86 lower to 0.12 higher)
Night-wa	akings (me	easured with: Chile	dren's Sleep Hab	its Questionna	aire (CSHQ): N	ight-wakings; Bette	er indica	ted by lower	values)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean night-wakings in the intervention groups was 2.88 standard deviations lower (3.58 to 2.18 lower)
Sleep du	uration (m	easured with: Chil	dren's Sleep Hab	its Questionna	aire (CSHQ): S	leep duration; Bett	er indica	ated by lower	values)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean sleep duration in the intervention groups was <b>1.39 standard deviations</b> <b>lower</b> (1.93 to 0.85 lower)
Parason	nnias (mea	sured with: Childr	en's Sleep Habits	Questionnair	e (CSHQ): Par	asomnias; Better ir	ndicated	by lower val	ues)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^2 \\ \text{due to} \\ \text{imprecision} \end{array}$	32	34	N/A	N/A	The mean parasomnias in the intervention groups was <b>0.11 standard deviations</b> <b>higher</b> (0.37 lower to 0.6 higher)
Sleep di	sordered	breathing (n	neasured with: Ch	nildren's Sleep	Habits Questi	onnaire (CSHQ): S	leep dis	ordered brea	thing; Better indicate	d by lowe	er values)
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>2</sup> due to imprecision	32	34	N/A	N/A	The mean sleep disordered breathing in the intervention groups was <b>0.11 standard deviations</b> <b>lower</b> (0.59 lower to 0.38 higher)
Daytime	sleepine	<b>SS</b> (measured wi	ith: Children's Sle	ep Habits Que	estionnaire (CS	HQ): Daytime slee	piness;	Better indica	ted by lower values)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	34	N/A	N/A	The mean daytime sleepiness in the intervention groups was 0.72 standard deviations lower

											(1.21 to 0.22 lower)
Sleep o	nset later	ICY (measured w	ith: Sleep diary (	study-specific)	; Better indicate	ed by lower values	5)				
49 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	24	25	N/A	N/A	The mean sleep onset latency in the intervention groups was <b>0.76 standard deviations</b> lower (1.35 to 0.18 lower)
Total slo	eep time (	measured with: S	leep diary (study-	specific); Bett	er indicated by	lower values)					
47 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	24	23	N/A	N/A	The mean total sleep time in the intervention groups was 0.15 standard deviations higher (0.43 lower to 0.72 higher)
latency =>5 66	0% based on no serious	actigraph data) no serious	no serious	et latency	/ (assessed with undetected	•	0/32	13/34	RR 25.46		reduction of sleep onset
	0% based on	actigraph data)	-								
latency =>5 66 (1 study)	0% based on no serious risk of	actigraph data) no serious	no serious			⊕⊕⊕⊝ MODERATE <sup>3</sup> due to	0/32	13/34	<b>RR 25.46</b> (1.58 to	Study 0 per	population
latency =>5 66 (1 study)	0% based on no serious risk of	actigraph data) no serious	no serious			⊕⊕⊕⊝ MODERATE <sup>3</sup> due to	0/32	13/34	<b>RR 25.46</b> (1.58 to	Study   0 per 1000	population
latency =>5 66 (1 study) 12 weeks	0% based on no serious risk of bias	actigraph data) no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>3</sup> due to	0/32 (0%)	13/34 (38.2%)	<b>RR 25.46</b> (1.58 to 411.3)	Study per 1000 Modera 0 per 1000	population N/A ate N/A
latency =>5 66 (1 study) 12 weeks <b>Positive</b> 66	0% based on no serious risk of bias	actigraph data) no serious inconsistency <b>ht response</b> no serious	no serious indirectness - Sleep effic no serious	serious <sup>3</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision nber of participant ⊕⊕⊕⊖	0/32 (0%)	13/34 (38.2%) nowed =>85% fo 16/34	RR 25.46 (1.58 to 411.3) r sleep efficiency to RR 31.11	Study p 0 per 1000 Modera 0 per 1000 pased on	population N/A ate N/A
latency =>5 66 (1 study) 12 weeks	0% based on no serious risk of bias	actigraph data) no serious inconsistency nt response	no serious indirectness - Sleep effic	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>3</sup> due to imprecision	0/32 (0%)	13/34 (38.2%) owed =>85% fo	RR 25.46 (1.58 to 411.3)	Study p 0 per 1000 Modera 0 per 1000 pased on	population         N/A         ate         N/A         actigraph data)

							0 per 1000	N/A
<sup>1</sup> N<400 <sup>2</sup> N<400 and <sup>3</sup> Events<300	ses both line of no	effect and meas	ure of appreci	able benefit or	harm (SMD -0.5/0	5)		

## Melatonin versus CBT for sleep problems as a direct outcome

		Q	uality assessr	nent				S	ummary o	f Finding	gs
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study e	event rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Melatonin versus CBT for coexisting problem of sleep	effect (95% CI)	Risk with Control	Risk difference with Melatonin versus CBT for coexisting problem of sleep (95% Cl)
Sleep on	set laten	CY (measured with	h: Actigraph; Bett	er indicated by	/ lower values)						
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	33	34	N/A	N/A	The mean sleep onset latency in the intervention groups was <b>0.54 standard deviations</b> lower (1.03 to 0.05 lower)
Wake afte	er sleep (	onset (measure	d with: Actigraph;	Better indicate	ed by lower va	lues)				•	
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	33	34	N/A	N/A	The mean wake after sleep onset in the intervention groups was <b>0.73 standard deviations</b> <b>Iower</b> (1.22 to 0.23 lower)
Nap time	(measured v	with: Actigraph; Be	tter indicated by I	ower values)	•		1				
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to	33	34	N/A	N/A	The mean nap time in the intervention groups was <b>0.16 standard deviations</b>

						imprecision					higher (0.32 lower to 0.64 higher)
Bed time	e (measured v	with: Actigraph; Be	etter indicated by	lower values)	1						I
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW <sup>2</sup> due to imprecision	33	34	N/A	N/A	The mean bed time in the intervention groups was <b>0.23 standard deviations</b> <b>lower</b> (0.71 lower to 0.25 higher)
Total sle	eep time (r	neasured with: Ac	tigraph; Better ind	dicated by lowe	er values)				1		
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	33	34	N/A	N/A	The mean total sleep time in the intervention groups was <b>0.76 standard deviations</b> higher (0.26 to 1.26 higher)
Sleep ef	ficiency (r	neasured with: Ac	tigraph; Better inc	dicated by lowe	er values)		1				
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	33	34	N/A	N/A	The mean sleep efficiency in the intervention groups was <b>0.89 standard deviations</b> higher (0.39 to 1.4 higher)
Sleep pr	roblems (n	neasured with: Ch	ildren's Sleep Ha	bits Questionn	aire (CSHQ): T	otal score; Better ir	ndicated	d by lower values)	1		
67 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \ominus \ominus$ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	33	34	N/A	N/A	The mean sleep problems in the intervention groups was <b>0.94 standard deviations</b> <b>lower</b> (1.45 to 0.44 lower)
Bed resi	istance (m	easured with: Chil	dren's Sleep Hab	its Questionna	ire (CSHQ): Be	ed resistance; Bette	r indica	ted by lower values)			1
67 (1 study)	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,3</sup>	33	34	N/A	N/A	The mean bed resistance in the intervention groups

12 weeks						due to risk of bias, imprecision					was <b>0.5 standard deviations</b> <b>Iower</b> (0.99 to 0.01 lower)
Sleep or	nset delay	(measured with:	Children's Sleep I	Habits Questic	onnaire (CSHQ	): Sleep onset delay	/; Better	indicated by lower v	alues)		
67 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	33	34	N/A	N/A	The mean sleep onset delay in the intervention groups was <b>0.65 standard deviations</b> <b>lower</b> (1.14 to 0.15 lower)
Sleep ar	<b>xiety</b> (mea	sured with: Childre	en's Sleep Habits	Questionnaire	(CSHQ): Slee	p anxiety; Better inc	dicated b	by lower values)	<b>I</b>		-
67 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	33	34	N/A	N/A	The mean sleep anxiety in the intervention groups was <b>0.02 standard deviations</b> higher (0.46 lower to 0.5 higher)
Night-wa	akings (me	easured with: Child	ren's Sleep Habit	s Questionnair	re (CSHQ): Nig	ht-wakings; Better i	indicate	d by lower values)			
67 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \ominus \ominus$ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	33	34	N/A	N/A	The mean night-wakings in the intervention groups was <b>1.86 standard deviations</b> <b>lower</b> (2.44 to 1.28 lower)
Sleep du	uration (me	easured with: Child	I Iren's Sleep Habit	s Questionnai	re (CSHQ): Sle	ep duration; Better	indicate	ed by lower values)			
67 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	33	34	N/A	N/A	The mean sleep duration in the intervention groups was 1.74 standard deviations lower (2.31 to 1.18 lower)

	1	1				1	r				T
67 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	33	34	N/A	N/A	The mean parasomnias in the intervention groups was <b>0.23 standard deviations</b> <b>lower</b> (0.71 lower to 0.25 higher)
Sleep di	sordered	breathing (m	neasured with: Ch	nildren's Sleep	Habits Questio	nnaire (CSHQ): Sle	ep disor	dered breathing;	Better indicated	l by lower	values)
67 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	33	34	N/A	N/A	The mean sleep disordered breathing in the intervention groups was 0.11 standard deviations lower (0.59 lower to 0.37 higher)
Daytime	sleepine	SS (measured wi	th: Children's Sle	ep Habits Que	estionnaire (CSI	HQ): Daytime sleepi	ness; B	etter indicated by	lower values)		
67 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	33	34	N/A	N/A	The mean daytime sleepiness in the intervention groups was <b>0.26 standard deviations</b> <b>lower</b> (0.74 lower to 0.22 higher)
		<b>it response</b> - actigraph data)	- Sleep onse	et latency	(assessed with	Number of particip	ants who	o showed sleep o	nset latency <3	0 min or re	eduction of sleep onset
67 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	$\oplus \oplus \oplus \ominus$ <b>MODERATE</b> <sup>4</sup>	3/33 (9.1%)	13/34 (38.2%)	<b>RR 4.21</b> (1.32 to	Study p	opulation
12 weeks		inconsistency				due to imprecision	(3.170)	(30.278)	13.42)	91 per 1000	<b>292 more per 1000</b> (from 29 more to 1000 more)
										Modera	te
										91 per 1000	<b>292 more per 1000</b> (from 29 more to 1000 more)

67 (1 study)	 no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	$\oplus \oplus \oplus \ominus$ <b>MODERATE</b> <sup>4</sup>	3/33 (9.1%)	16/34 (47.1%)	<b>RR 5.18</b> (1.66 to	Study p	opulation
12 weeks					due to imprecision		、 <i>,</i>	16.13)	91 per 1000	<b>380 more per 1000</b> (from 60 more to 1000 more)
									Moderate	e
									91 per 1000	<b>380 more per 1000</b> (from 60 more to 1000 more)

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

## COMB versus placebo for sleep problems as a direct outcome

		Q	uality assessn	nent			S	ummary o	f Finding	gs		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	•	Publication bias	Overall quality of evidence	Study e With Control	event rates (%) With Combined melatonin and CBT	Relative effect (95% CI)	•	ted absolute effects Risk difference with Combined melatonin and CBT	
Sleep on:	Control melatonin and CB1 versus placebo Control Combined r versus placebo Control Combined r versus placebo											
67	no serious risk of bias	no serious inconsistency	no serious indirectness	1	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	35	N/A	N/A	The mean sleep onset latency in the intervention groups was 1.86 standard deviations lower	

											(2.44 to 1.29 lower)
Nake af	ter sleep o	<b>onset</b> (measure	d with: Actigraph;	Better indicate	l ed by lower val	ues)					
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	35	N/A	N/A	The mean wake after sleep onset in the intervention groups was <b>1.29 standard deviations</b> lower (1.82 to 0.76 lower)
Nap time	e (measured v	with: Actigraph; Be	tter indicated by I	ower values)							
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	35	N/A	N/A	The mean nap time in the intervention groups was <b>0.95 standard deviations</b> <b>lower</b> (1.45 to 0.44 lower)
Bedtime	(measured w	ith: Actigraph; Bet	ter indicated by lo	ower values)	1	1					
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	32	35	N/A	N/A	The mean bedtime in the intervention groups was <b>1.32 standard deviations</b> <b>lower</b> (1.85 to 0.79 lower)
Total sle	ep time (n	neasured with: Act	igraph; Better ind	icated by lowe	r values)	I				<b>I</b>	
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	32	35	N/A	N/A	The mean total sleep time in the intervention groups was 2.33 standard deviations higher (1.7 to 2.96 higher)
Sleep ef	ficiency (n	neasured with: Act	igraph; Better ind	icated by lowe	r values)	1			I		1
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigoplus \bigcirc \\ \textbf{MODERATE}^1 \\ \text{due to} \\ \text{imprecision} \end{array}$	32	35	N/A	N/A	The mean sleep efficiency in the intervention groups was 2.8 standard deviations

											higher (2.12 to 3.49 higher)
Sleep p	roblems (i	measured with: Chi	Idren's Sleep Hat	oits Questionna	aire (CSHQ): T	otal score; Better inc	dicated	by lower values	)	<b>I</b>	
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	32	35	N/A	N/A	The mean sleep problems in the intervention groups was 4.44 standard deviations lower (5.35 to 3.53 lower)
Bed res	istance (m	neasured with: Child	dren's Sleep Habi	ts Questionna	ire (CSHQ): Be	d resistance; Better	indicat	ed by lower valu	es)	<b>!</b>	
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	32	35	N/A	N/A	The mean bed resistance in the intervention groups was <b>3.34 standard deviations</b> <b>lower</b> (4.09 to 2.58 lower)
Sleep or	nset dela	<b>y</b> (measured with:	Children's Sleep I	Habits Questio	onnaire (CSHQ)	: Sleep onset delay;	Better	indicated by low	ver values)	<b>I</b>	1
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \ominus \ominus$ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	32	35	N/A	N/A	The mean sleep onset delay in the intervention groups was 2.21 standard deviations lower (2.82 to 1.59 lower)
Sleep ar	nxiety (mea	asured with: Childre	en's Sleep Habits	Questionnaire	(CSHQ): Slee	o anxiety; Better indi	icated I	by lower values)	<b>I</b>		
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	32	35	N/A	N/A	The mean sleep anxiety in the intervention groups was <b>1.74 standard deviations</b> <b>lower</b> (2.3 to 1.17 lower)
Night-wa	akings (me	easured with: Child	ren's Sleep Habit	s Questionnair	re (CSHQ): Nig	ht-wakings; Better ir	ndicate	d by lower value	s)		, , , , , , , , , , , , , , , , , , ,

(1 study) 12 weeks		inconsistency	indirectness			LOW <sup>1,2</sup> due to risk of bias, imprecision					in the intervention groups was <b>3.96 standard deviations</b> <b>lower</b> (4.8 to 3.12 lower)
Sleep du	iration (me	easured with: Child	ren's Sleep Habits	s Questionnair	e (CSHQ): Sle	ep duration; Better i	ndicate	d by lower values)		•	
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	32	35	N/A	N/A	The mean sleep duration in the intervention groups was 1.73 standard deviations lower (2.29 to 1.16 lower)
Parasom	nnias (mea	sured with: Children	n's Sleep Habits (	Questionnaire	(CSHQ): Paras	omnias; Better indic	cated by	y lower values)	-		
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2.3</sup> due to risk of bias, imprecision	32	35	N/A	N/A	The mean parasomnias in the intervention groups was <b>0.16 standard deviations</b> <b>lower</b> (0.64 lower to 0.32 higher)
Sleep di	sordered	breathing (me	asured with: Chil	I dren's Sleep ⊦	labits Question	naire (CSHQ): Slee	p disor	dered breathing; Be	tter indicated	by lower	values)
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	32	35	N/A	N/A	The mean sleep disordered breathing in the intervention groups was <b>0.03 standard deviations</b> <b>higher</b> (0.45 lower to 0.51 higher)
Daytime	sleepine	SS (measured with	n: Children's Slee	p Habits Ques	tionnaire (CSH	Q): Daytime sleepir	ness; Be	etter indicated by low	ver values)		
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	32	35	N/A	N/A	The mean daytime sleepiness in the intervention groups was 1.15 standard deviations lower (1.67 to 0.63 lower)

# **Positive treatment response - Sleep onset latency** (assessed with: Number of participants who showed sleep onset latency <30 min or reduction of sleep onset latency =>50% based on actigraph data)

67 (1 study)	no serious	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected		0/32 (0%)	30/35 (85.7%)	<b>RR 55.92</b> (3.56 to	Study population
12 weeks		inconsistency	maneotricoo			due to	(070)	(00.170)	·	0 per N/A
						imprecision				1000
										Moderate
										0 per N/A
										1000

Positive treatment response - Sleep efficiency (assessed with: Number of participants who showed =>85% for sleep efficiency based on actigraph data)

67 (1 study)	no serious risk of bias	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>4</sup>	0/32 (0%)	22/35 (62.9%)	<b>RR 41.25</b> (2.6 to	Study po	pulation
12 weeks					due to imprecision			653.27)	0 per 1000	N/A
									Moderate	e
									0 per 1000	N/A

<sup>1</sup> N<400

<sup>2</sup> High risk of performance and response bias as intervention administrators and participants non-blind, and high risk of detection bias as parent-completed and parents non-blind and involved in the intervention

<sup>3</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)</p>
<sup>4</sup> Events<300</p>

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

		Q	uality assessn	nent				Su	mmary of	Finding	ls
Participants		Inconsistency	Indirectness	Imprecision			Study	event rates (%)		Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Combined	(95% CI)		Risk difference with Combined melatonin and CBT versus CBT- only for coexisting problem of sleep (95% CI)

								sleep			
								Sieep			
-	nset laten	CY (measured w	vith: Actigraph; Be	-	by lower value	es)	-		I		
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	33	35	N/A	N/A	The mean sleep onset latency in the intervention groups was <b>1.15 standard deviations</b> <b>lower</b> (1.67 to 0.64 lower)
Wake af	ter sleep	onset (measu	red with: Actigrap	h; Better indic	ated by lower	/alues)					
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	33	35	N/A	N/A	The mean wake after sleep onset in the intervention groups was <b>1.4 standard deviations</b> <b>lower</b> (1.94 to 0.87 lower)
Nap time	e (measured	with: Actigraph; E	Better indicated by	y lower values	)	1			I		
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	33	35	N/A	N/A	The mean nap time in the intervention groups was <b>0.13 standard deviations lower</b> (0.61 lower to 0.35 higher)
Bed time	<b>e</b> (measured	with: Actigraph; E	Better indicated by	y lower values	)						
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	33	35	N/A	N/A	The mean bed time in the intervention groups was <b>0.47 standard deviations</b> <b>lower</b> (0.95 lower to 0.01 higher)
Total sle	eep time (r	measured with: A	ctigraph; Better i	ndicated by lov	wer values)	1			1	1	
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	33	35	N/A	N/A	The mean total sleep time ir the intervention groups was 1.46 standard deviations higher

											(0.93 to 2 higher)
Sleep ef	ficiency (r	neasured with: Ad	tigraph; Better in	ndicated by low	ver values)		I				
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	33	35	N/A	N/A	The mean sleep efficiency in the intervention groups was <b>1.33 standard deviations</b> higher (0.81 to 1.86 higher)
Sleep pr	roblems (r	neasured with: Ch	nildren's Sleep H	abits Question	naire (CSHQ):	Total score; Better	r indicat	ed by lower va	lues)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	33	35	N/A	N/A	The mean sleep problems in the intervention groups was <b>3.1 standard deviations</b> <b>lower</b> (3.81 to 2.38 lower)
Bed resi	stance (m	easured with: Chi	Idren's Sleep Ha	bits Questionn	aire (CSHQ): I	Bed resistance; Be	tter indi	cated by lower	values)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	33	35	N/A	N/A	The mean bed resistance in the intervention groups was <b>1.7 standard deviations</b> <b>lower</b> (2.26 to 1.14 lower)
Sleep or	nset delay	(measured with:	Children's Sleep	Habits Quest	ionnaire (CSH	Q): Sleep onset de	lay; Bet	ter indicated by	y lower values)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	33	35	N/A	N/A	The mean sleep onset delay in the intervention groups was <b>1.23 standard deviations</b> <b>lower</b> (1.75 to 0.71 lower)
Sleep ar	<b>nxiety</b> (mea	sured with: Childr	en's Sleep Habit	s Questionnai	re (CSHQ): Sle	ep anxiety; Better	indicate	ed by lower valu	Jes)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,3</sup> due to risk of	33	35	N/A	N/A	The mean sleep anxiety in the intervention groups was <b>1.55 standard deviations</b>

						bias, imprecision					lower (2.1 to 1.01 lower)
Night-wa	<b>kings</b> (m	easured with: Child	dren's Sleep Hab	its Questionna	aire (CSHQ): N	light-wakings; Bette	er indica	ated by lower v	values)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	33	35	N/A	N/A	The mean night-wakings in the intervention groups was <b>2.66 standard deviations</b> <b>lower</b> (3.32 to 2 lower)
Sleep du	iration (m	easured with: Chil	dren's Sleep Hat	oits Questionn	aire (CSHQ): S	Sleep duration; Bet	ter indic	ated by lower	values)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	33	35	N/A	N/A	The mean sleep duration in the intervention groups was <b>2.09 standard deviations</b> <b>lower</b> (2.68 to 1.49 lower)
Parasom	inias (mea	sured with: Childre	en's Sleep Habits	s Questionnair	e (CSHQ): Pa	asomnias; Better i	ndicate	d by lower valu	ies)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	33	35	N/A	N/A	The mean parasomnias in the intervention groups was <b>0.48 standard deviations</b> <b>lower</b> (0.96 lower to 0 higher)
Sleep di	sordered	breathing (m	neasured with: C	hildren's Sleep	Habits Quest	ionnaire (CSHQ): S	Sleep di	sordered breat	thing; Better indicate	ed by low	er values)
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	33	35	N/A	N/A	The mean sleep disordered breathing in the intervention groups was <b>0.03 standard deviations</b> <b>higher</b> (0.45 lower to 0.5 higher)
Daytime	sleepine	SS (measured wi	ith: Children's Sle	ep Habits Qu	estionnaire (CS	SHQ): Daytime slee	epiness	; Better indicat	ed by lower values)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	33	35	N/A	N/A	The mean daytime sleepiness in the intervention groups was <b>0.61 standard deviations</b>

										<b>lower</b> (1.09 to 0.12 lower)
		actigraph data)	- Sleep ons	et latency	(assessed wit	h: Number of part	ticipants who showed	sleep onset latency <	30 min or	reduction of sleep onset
68 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	$\oplus \oplus \oplus \ominus$ <b>MODERATE</b> <sup>4</sup>	3/33 30/35 (9.1%) (85.7%)	<b>RR 9.43</b> (3.18 to	Study p	oopulation
12 weeks	bias	,				due to imprecision		27.97)	91 per 1000	766 more per 1000 (from 198 more to 1000 more)
									Moderate	
									91 per 1000	767 more per 1000 (from 198 more to 1000 more)
efficiency ba	and on action	_								owed =>85% for sleep
68 (1 study)		aph data) no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>4</sup>	3/33 22/35 (9.1%) (62.9%)	<b>RR 6.91</b> (2.28 to	Study p	population
68	no serious	no serious		serious <sup>4</sup>	undetected				Study p 91 per 1000	· ·
68 (1 study)	no serious risk of	no serious		serious <sup>4</sup>	undetected	<b>MODERATE</b> <sup>4</sup> due to		(2.28 to	91 per	<b>537 more per 1000</b> (from 116 more to 1000 more)

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

		Q	uality assessi	ment				Su	mmary of	Finding	js
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study e	vent rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Combined melatonin and CBT versus melatonin-only for coexisting problem of sleep	effect (95% CI)	Risk with Control	Risk difference with Combined melatonin and CBT versus melatonin-only for coexisting problem of sleep (95% Cl)
Sleep on	set laten	CY (measured w	ith: Actigraph; Be	etter indicated	by lower value	es)			•		
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	34	35	N/A	N/A	The mean sleep onset latency in the intervention groups was <b>0.59 standard deviations</b> lower (1.07 to 0.11 lower)
Wake afte	er sleep	onset (measur	ed with: Actigrap	h; Better indic	ated by lower	values)	,	-	1	1	
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	34	35	N/A	N/A	The mean wake after sleep onset in the intervention groups was 0.68 standard deviations lower (1.17 to 0.19 lower)
Nap time	(measured	with: Actigraph; B	etter indicated by	y lower values	)	Į	1		1	1	
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	34	35	N/A	N/A	The mean nap time in the intervention groups was <b>0.27 standard deviations</b> <b>lower</b> (0.75 lower to 0.2 higher)
Bed time	(measured	with: Actigraph; B	etter indicated by	y lower values	)	ł	<b>,</b>		1	Į	4
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>2</sup> due to imprecision	34	35	N/A	N/A	The mean bed time in the intervention groups was <b>0.22 standard deviations</b> <b>lower</b> (0.69 lower to 0.25 higher)

Total sle	ep time (	measured with: A	ctigraph; Better	ndicated by lo	ower values)						
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>1</sup> due to imprecision	34	35	N/A	N/A	The mean total sleep time in the intervention groups was <b>0.61 standard deviations</b> higher (0.13 to 1.1 higher)
Sleep ef	ficiency (	measured with: A	ctigraph; Better	ndicated by lo	wer values)						
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>2</sup> due to imprecision	34	35	N/A	N/A	The mean sleep efficiency in the intervention groups was <b>0.42 standard deviations</b> higher (0.06 lower to 0.9 higher)
Sleep pr	oblems (r	measured with: C	hildren's Sleep H	labits Questio	nnaire (CSHQ)	: Total score; Bett	er indica	ated by lower va	alues)		
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to risk of bias, imprecision	34	35	N/A	N/A	The mean sleep problems in the intervention groups was 1.42 standard deviations lower (1.95 to 0.89 lower)
Bed resi	i <b>stance</b> (m	neasured with: Ch	ildren's Sleep Ha	abits Question	naire (CSHQ):	Bed resistance; E	etter inc	licated by lowe	r values)		
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	34	35	N/A	N/A	The mean bed resistance in the intervention groups was <b>1.1 standard deviations</b> <b>lower</b> (1.61 to 0.59 lower)
Sleep or	nset dela	y (measured with	: Children's Slee	p Habits Ques	stionnaire (CSF	IQ): Sleep onset o	lelay; Be	etter indicated b	by lower values)		I
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	34	35	N/A	N/A	The mean sleep onset delay in the intervention groups was 0.57 standard deviations lower

											(1.06 to 0.09 lower)
Sleep ar	<b>nxiety</b> (me	asured with: Child	lren's Sleep Habi	ts Questionna	ire (CSHQ): SI	eep anxiety; Bette	r indicate	ed by lower va	lues)		
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,3</sup> due to risk of bias, imprecision	34	35	N/A	N/A	The mean sleep anxiety in the intervention groups was <b>1.33 standard deviations</b> <b>lower</b> (1.85 to 0.8 lower)
Night-wa	<b>akings</b> (m	easured with: Chi	ldren's Sleep Ha	bits Questionn	naire (CSHQ): I	Night-wakings; Bet	ter indica	ated by lower	values)		
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	$\begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^{1,3} \\ \text{due to risk of} \\ \text{bias,} \\ \text{imprecision} \end{array}$	34	35	N/A	N/A	The mean night-wakings in the intervention groups was <b>0.6 standard deviations</b> <b>lower</b> (1.08 to 0.12 lower)
Sleep d	uration (m	neasured with: Ch	ildren's Sleep Ha	bits Questionr	naire (CSHQ):	Sleep duration; Be	tter indic	ated by lower	values)	-	·
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2.3</sup> due to risk of bias, imprecision	34	35	N/A	N/A	The mean sleep duration in the intervention groups was <b>0.44 standard deviations</b> <b>lower</b> (0.92 lower to 0.03 higher)
Parason	nnias (mea	asured with: Child	ren's Sleep Habit	s Questionnai	ire (CSHQ): Pa	rasomnias; Better	indicate	d by lower valu	ues)		
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \ominus \ominus \ominus \\ \textbf{VERY LOW}^{2,3} \\ \text{due to risk of} \\ \text{bias}, \\ \text{imprecision} \end{array}$	34	35	N/A	N/A	The mean parasomnias in the intervention groups was 0.27 standard deviations lower (0.74 lower to 0.21 higher)
Sleep di	isordered	d breathing (	measured with: C	hildren's Slee	p Habits Ques	tionnaire (CSHQ):	Sleep di	sordered brea	thing; Better indicate	d by low	er values)
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	<ul> <li>⊕⊖⊖</li> <li>VERY LOW<sup>2,3</sup></li> <li>due to risk of</li> <li>bias,</li> <li>imprecision</li> </ul>	34	35	N/A	N/A	The mean sleep disordered breathing in the interventior groups was 0.09 standard deviations higher

											(0.38 lower to 0.56 higher)
Daytime	sleepine	SS (measured w	ith: Children's S	leep Habits Qu	uestionnaire (C	I SHQ): Daytime sl	eepiness;	Better indicated b	by lower values)		
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	34	35	N/A	N/A	The mean daytime sleepiness in the intervention groups was <b>0.27 standard deviations</b> <b>lower</b> (0.74 lower to 0.21 higher)
		nt response actigraph data)	- Sleep ons	et latency	(assessed wit	th: Number of par	ticipants w	ho showed sleep	onset latency <3	0 min or	reduction of sleep onset
69 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	$\oplus \oplus \oplus \ominus$ <b>MODERATE</b> <sup>4</sup>	13/34	30/35 (85.7%)	<b>RR 2.24</b> (1.43 to	Study p	oopulation
12 weeks	bias					due to imprecision	(00.270)		3.51)	382 per 1000	<b>474 more per 1000</b> (from 164 more to 960 more)
										Modera	ite
										382 per 1000	• <b>474 more per 1000</b> (from 164 more to 959 more)
Positive	treatmer	nt response	- Sleep effi	<b>ciency</b> (ass	essed with: Nu	I Imber of participa	nts who sh	nowed =>85% for	sleep efficiency b	ased on	actigraph data)
69 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊝⊝ L <b>OW</b> ⁵	16/34 (47.1%)	22/35 (62.9%)	<b>RR 1.34</b> (0.86 to	Study p	oopulation
12 weeks	bias					due to imprecision	,	· · · ·	2.07)	471 per 1000	<b>160 more per 1000</b> (from 66 fewer to 504 more
										Modera	ite
										471 per 1000	160 more per 1000 (from 66 fewer to 504 more)
<sup>3</sup> High risk of								k of detection bia	s as parent-comp	leted and	l parents non-blind and

## **1.28.4SNRIs for sleep problems as an indirect outcome**

Atomoxetine versus placebo for sleep problems as an indirect outcome

		Qu	ality assessn	nent				Sum	mary of I	Finding	S
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Selective noradrenaline reuptake inhibitors versus placebo for sleep problems as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Selective noradrenaline reuptake inhibitors versus placebo for sleep problems as an indirect outcome (95% Cl)
Time to f	all aslee	<b>ep</b> (measured with	h: Sleep Measur	e Scale: Time	to fall asleep;	Better indicated	l by lowe	r values)			
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	46	43	N/A	N/A	The mean time to fall asleep in the intervention groups was 0.29 standard deviations lower (0.7 lower to 0.13 higher)
Total hou	urs of sl	eep (measured v	with: Sleep Meas	sure Scale: To	tal hours of sle	eep; Better indic	ı ated by l	ower values)	<u> </u>	. <b>.</b>	
88 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	46	42	N/A	N/A	The mean total hours of sleep in the intervention groups was <b>0.13 standard deviations</b> lower (0.55 lower to 0.29 higher)
Difficulty	falling	<b>asleep</b> (measu	red with: Sleep I	Measure Scale	: Difficulty falli	ing asleep; Bett	er indicat	ed by lower values)	I		
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	$\oplus \oplus \ominus \ominus$ LOW <sup>1</sup> due to imprecision	46	43	N/A	N/A	The mean difficulty falling asleep in the intervention groups was 0.17 standard deviations higher

											(0.24 lower to 0.59 higher)
Quality	of sleep	(measured with: S	Sleep Measure S	cale: Quality c	of sleep; Better	indicated by lo	wer valu	Jes)			
89 (1 study) 8 weeks Functio	no serious risk of bias	no serious inconsistency ome during	no serious indirectness day (measured	very serious <sup>1</sup> with: Sleep M	undetected easure Scale:	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	46 ome du	43	N/A	N/A N/A	The mean quality of sleep in the intervention groups was <b>0.23 standard deviations</b> <b>lower</b> (0.65 lower to 0.18 higher)
			-		-					-	

# 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

		Qı	uality assessm	ent	Summary of Findings						
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision			Study e With Placebo	vent rates (%) With Multivitamin and mineral supplement		Anticipat Risk with Placebo	ed absolute effects Risk difference with Multivitamin and mineral supplement (95% CI)

Sleep im	provem	ent (measured	with: Parent Glob	al Impression	s-Revised (PGI-	R): Sleep improv	ement; B	Better indicated	l by lower values)	)	
-	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW <sup>1</sup> due to imprecision	51	53	N/A	N/A	The mean sleep improvement in the intervention groups was <b>0.18 standard deviations</b> <b>higher</b> (0.2 lower to 0.57 higher)

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

			Quality assess	ment		Summary of Findings					
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study ever	nt rates (%)	Relative effect	Anticipated	l absolute effects
							With Healthy diet control	With Omega- 3 fatty acids	(95% CI)	Risk with Healthy diet control	Risk difference with Omega- fatty acids (95% CI)
Sleep pr	oblem	S (measured with:	Child Behavior Cl		(CBCL/1.5-5): \$	Sleep problems; Be	tter indicated	l by lower val	ues)		
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of	13	10	N/A	N/A	The mean sleep problems in the intervention groups was

## **1.29.2**Hormones for gastrointestinal symptoms as an indirect outcome

#### Secretin versus placebo for gastrointestinal symptoms as an indirect outcome

		Qu	ality assessm	nent			Summary of Findings					
	Risk of bias	Inconsistency	Indirectness	Imprecision	bias	Overall quality of	Study e	event rates (%)	Relative effect	Anticipa	ated absolute effects	
ollow up						evidence	With Control	With Secretin versus placebo for gastrointestinal symptoms as an indirect outcome	(95% CI)	Risk with Control	Risk difference with Secretin versus placebo for gastrointestinal symptoms as an indirect outcome (95% Cl)	
lumber	of gast	trointestina	l problems	(measured w	ith: GI sympto	ms questionnair	e: Total	(change score); Better indi	cated by lo	wer value	es)	
l study) weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	48	47	N/A	N/A	The mean number of gastrointestinal problems in the intervention groups was 0.18 standard deviations lower (0.59 lower to 0.22 higher)	

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

#### Immunoglobulin versus placebo for gastrointestinal symptoms as a direct outcome

		1	Quality assess	sment	Summary of Findings						
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision		of evidence		vent rates (%) With Immunoglobulin (dosages combined)	<b>effect</b> (95% CI)		Risk difference with Immunoglobulin (dosages

											combined) (95% CI)
		-			us measure of 'mo /GIS] for GI sympt		ntially impr	oved' on at least	two of last 4 as	sessments	or 'somewhat improve
125 (1 study)		no serious	no serious	very	reporting bias	$\oplus \Theta \Theta \Theta$	14/31	31/94	RR 0.73	Study po	opulation
(1 study) 12 weeks	risk of bias	inconsistency	indirectness	serious'	strongly suspected <sup>2</sup>	VERY LOW <sup>1,2</sup> due to imprecision, publication bias	(45.2%)	(33%)	(0.45 to 1.18)	452 per 1000	<b>122 fewer per 1000</b> (from 248 fewer to 81 more)
										Moderate	e
										452 per 1000	<b>122 fewer per 1000</b> (from 249 fewer to 81 more)

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

		Q	uality assessn	nent		Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study e	event rates (%)	Relative effect	Anticipa	ted absolute effects
Follow up						evidence	With Placebo	With With Multivitamin		Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% CI)
Gastroin	testinal	l symptom i	mproveme	ent (measured	d with: Parent	Global Impression	ons-Revise	ed (PGI-R): GI impr	ovement; B	etter indica	ated by lower values)
104 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	$ \begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \textbf{LOW}^1 \\ \text{due to} \end{array} $	51	53	N/A	N/A	The mean gastrointestinal symptom improvement in the intervention groups was <b>0.3 standard deviations</b>

						imprecision			higher (0.09 lower to 0.68 higher)
<sup>1</sup> N<400 and 9	95% CI cros	ses both line of no	effect and measu	ure of apprecia	able benefit or l	narm (SMD -0.5/0	).5)		

## 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

		Qı	ality assessn	nent				Si	ummary c	of Findin	igs
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study e	event rates (%)	Relative effect	Anticipa	ated absolute effects
(studies) Follow up	bias					quality of evidence	With Control	With With Home-based versus Control Centre-based EBI for improving the impact on the family as an indirect outcome		Risk with Control	Risk difference with Home-based versus Centre-based EBI for improving the impact on the family as an indirect outcome (95% CI)
Family qu	uality o	f life (measured	with: Beach Fan	nily Quality of	Life Questionn	aire: Total; Bett	er indica	ted by lower values)			
44 (1 study) 40 weeks	serious <sup>1</sup>		no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	23	21	N/A	N/A	The mean family quality of life in the intervention groups was <b>0.16 standard deviations</b> <b>higher</b> (0.43 lower to 0.76 higher)
Family qu	uality o	f life (family	interaction	(measured w	vith: Beach Fai	mily Quality of L	ife Ques	tionnaire: Family interact	ion; Better i	ndicated	by lower values)
44 (1 study) 40 weeks	serious <sup>1</sup>		no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>1,2</sup> due to risk of bias,	23	21	N/A	N/A	The mean family quality of life (family interaction) in the intervention groups was <b>0.14 standard deviations</b>

						imprecision					higher (0.45 lower to 0.73 higher)
Family q	uality o	f life (paren	ting) (measure	d with: Beach	Family Quality	of Life Question	naire:	Parenting; Better ir	dicated by lowe	r values)	
44 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	23	21	N/A	N/A	The mean family quality of life (parenting) in the intervention groups was <b>0 standard deviations higher</b> (0.59 lower to 0.59 higher)
Family q	uality o	f life (emoti	onal wellbe	<b>ing)</b> (measur	ed with: Beach	n Family Quality	of Life	Questionnaire: Em	otional wellbeing	; Better ir	ndicated by lower values)
44 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	23	21	N/A	N/A	The mean family quality of life (emotional wellbeing) in the intervention groups was <b>0.22 standard deviations</b> <b>higher</b> (0.38 lower to 0.81 higher)
Family q	uality o	f life (physic	cal wellbein	<b>g)</b> (measured	I with: Beach F	amily Quality of	Life Q	uestionnaire: Physi	cal wellbeing; Be	etter indica	ated by lower values)
44 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	23	21	N/A	N/A	The mean family quality of life (physical wellbeing) in the intervention groups was <b>0 standard deviations higher</b> (0.59 lower to 0.59 higher)
Family q	uality o	f life (disabi	lity suppor	<b>t)</b> (measured v	with: Beach Fa	I mily Quality of L	ife Qu	estionnaire: Disabil	ty support; Bette	er indicate	d by lower values)
44 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	23	21	N/A	N/A	The mean family quality of life (disability support) in the intervention groups was <b>0.1 standard deviations</b> <b>higher</b> (0.49 lower to 0.69 higher)
Parental	coping	<b>skills</b> (measu	red with: Parent I	Perception Que	estionnaire: To	tal; Better indica	ated by	v lower values)		-	ļ.
46 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of	23	23	N/A	N/A	The mean parental coping skills in the intervention groups was 0.15 standard deviations

						bias, imprecision					lower (0.73 lower to 0.43 higher)
Parental	coping	skills (confi	<b>dence)</b> (mea	sured with: Pa	rent Perceptio	n Questionnaire	Confid	lence; Better indicated by	/ lower valu	es)	·
46 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	23	23	N/A	N/A	The mean parental coping skills (confidence) in the intervention groups was <b>0 standard deviations higher</b> (0.58 lower to 0.58 higher)
Parental	coping	skills (copii	ng) (measured	with: Parent P	erception Que	stionnaire: Copir	ng; Bet	er indicated by lower val	ues)		
46 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	23	23	N/A	N/A	The mean parental coping skills (coping) in the intervention groups was <b>0.33 standard deviations</b> higher (0.25 lower to 0.91 higher)
Parental	coping	skills (know	<b>/ledge)</b> (meas	sured with: Pa	ent Perception	n Questionnaire:	Knowl	edge; Better indicated by	lower value	s)	
46 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	23	23	N/A	N/A	The mean parental coping skills (knowledge) in the intervention groups was <b>0.52 standard deviations</b> <b>Iower</b> (1.11 lower to 0.07 higher)
Parental	coping	skills (unde	erstanding)	(measured wit	h: Parent Perc	ception Question	naire: l	Inderstanding; Better ind	icated by lo	wer value	es)
46 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	23	23	N/A	N/A	The mean parental coping skills (understanding) in the intervention groups was <b>0.26 standard deviations</b> <b>lower</b> (0.84 lower to 0.32 higher)
Parental	coping	skills (famil	<b>y issues)</b> (m	l leasured with:	Parent Percer	ption Questionna	iire: Fa	mily issues; Better indica	ted by lower	values)	
46 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		23	23	N/A	N/A	The mean parental coping skills (family issues) in the

40 weeks						due to risk of bias, imprecision					intervention groups was 0.23 standard deviations higher (0.35 lower to 0.81 higher)
Parental	coping	skills (plan	ning) (measure	ed with: Paren	t Perception Q	uestionnaire: Pl	anning	; Better indicated b	y lower values)		
46 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	23	23	N/A	N/A	The mean parental coping skills (planning) in the intervention groups was <b>0.09 standard deviations</b> <b>lower</b> (0.67 lower to 0.49 higher)
Parental	stress	(measured with: F	Parenting Stress	Index-3rd Edit	tion (PSI): Tota	I; Better indicate	ed by lo	ower values)			- <b>I</b>
40 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	20	20	N/A	N/A	The mean parental stress in the intervention groups was <b>0.26 standard deviations</b> <b>lower</b> (0.89 lower to 0.36 higher)
Parental	stress	(defensive r	esponding)	(measured w	ith: Parenting \$	Stress Index (PS	I): De	fensive responding	; Better indicated	by lower	values)
40 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	20	20	N/A	N/A	The mean parental stress (defensive responding) in the intervention groups was <b>0.21 standard deviations</b> <b>lower</b> (0.83 lower to 0.42 higher)
Parental	stress	(parental di	<b>stress)</b> (meas	ured with: Par	enting Stress I	ndex (PSI): Pare	ental d	istress; Better indic	ated by lower val	ues)	
40 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	$\begin{array}{c} \bigoplus \ominus \ominus \ominus \\ \textbf{VERY LOW}^{1,2} \\ \text{due to risk of} \\ \text{bias,} \\ \text{imprecision} \end{array}$	20	20	N/A	N/A	The mean parental stress (parental distress) in the intervention groups was <b>0.22 standard deviations</b> <b>lower</b> (0.84 lower to 0.4 higher)
Parental	stress	(parent-chil	d dysfunctie	onal inter	action) (me	asured with: Par	renting	Stress Index (PSI)	: Parent-child dy	sfunctiona	(0.84 lower to 0.4 higher)

lower values	)										
40 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	20	20	N/A	N/A	The mean parental stress (parent-child dysfunctional interaction) in the intervention groups was <b>0.15 standard deviations</b> <b>lower</b> (0.77 lower to 0.47 higher)
40 (1 study) 40 weeks	serious <sup>1</sup>	no serious	( <b>d</b> ) (measured v no serious indirectness	vith: Parenting very serious <sup>2</sup>	Stress Index (	PSI): Difficult ch ⊕⊖⊝⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	20	tter indicated by lower va	N/A	N/A	The mean parental stress (difficult child) in the intervention groups was 0.35 standard deviations lower (0.98 lower to 0.27 higher)
were blinded	, this outco		based on intervi	ew with paren	t and parents v	were non-blind a	nd wer	e part of the interventior		on bias a	s although the outcome assessors

# 1.30.2Cognitive-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

		Qu	ality assessn	nent				S	ummary	of Findi	ngs	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With	With Behaviour-focused intervention versus treatment-as-usual for improving the impact on the family as an indirect outcome	Relative effect (95% CI)	Risk	Ated absolute effects Risk difference with Behaviour- focused intervention versus treatment-as-usual for improving the impact on the family as an indirect outcome (95% CI)	
Parent in	arent intrusiveness/child independence (measured with: Parent-Child Interaction Questionnaire (PCIQ): Parent Intrusiveness ; Better indicated by lower values)											

40 (1 study) 16 weeks			no serious indirectness	serious <sup>2</sup>		⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	20	20	N/A		The mean parent intrusiveness/child independence in the intervention groups was <b>0.68 standard deviations lower</b> (1.32 to 0.04 lower)
<sup>1</sup> High risk of <sup>2</sup> N<400	performan	ce and response	bias as interven	tion administra	ators and partion	cipants were no	n-blind,	and high risk of detection	n bias as ou	tcome as	sessors were non-blind parents

## 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

		Q	uality assessr	nent				Su	ummary o	f Finding	gs
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Parent training versus treatment-as- usual for improving the impact of autism on the family	effect (95% CI)	Risk with Control	Risk difference with Parent training versus treatment-as-usual for improving the impact of autism on the family (95% CI)
		(direct or inc		<b>me)</b> (measu	red with: Parer	nting Stress The	rmomete	r or Parental Stress Inve	ntory: Total	or Parent	ing Stress Index-3rd Edition
143 (3 studies) 12-52 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	55	88	N/A	N/A	The mean parental stress (direct or indirect outcome) in the intervention groups was <b>0.39 standard deviations</b> <b>lower</b> (0.73 to 0.04 lower)
Parental s	stress	(direct outco	me; combi	ned PEBN	I+PEC pos	st-intervent	t <b>ion)</b> (m	neasured with: Parenting	Stress The	rmometer	; Better indicated by lower
103 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \bigcirc \bigcirc$ <b>LOW</b> <sup>1,2</sup> due to risk of bias,	35	68	N/A	N/A	The mean parental stress (direct outcome; combined pebm+pec post-intervention) in the intervention groups was

						imprecision					0.42 standard deviations lower (0.84 to 0.01 lower)
Parental	stress	(indirect out	come) (measu	ured with: Pare	ental Stress Inv	entory: Total or	Parenting	g Stress Index-3rd Editic	n (PSI): To	tal; Bette	r indicated by lower values)
40 (2 studies) 12-52 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1.3</sup> due to risk of bias, imprecision	20	20	N/A	N/A	The mean parental stress (indirect outcome) in the intervention groups was <b>0.30 standard deviations</b> <b>lower</b> (0.93 lower to 0.32 higher)
Parental	mental	health (com	bined PEB	M+PEC gr	oups) (meas	sured with: Gene	ral Healt	h Questionnaire (GHQ-2	28): Total; B	etter indi	cated by lower values)
103 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1.3</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean parental mental health (combined pebm+pec groups) in the intervention groups was <b>0.26 standard deviations</b> <b>lower</b> (0.67 lower to 0.15 higher)
Parental	mental	health (com	bined PEB	M+PEC gr	oups) (meas	sured with: Gene	ral Healt	h Questionnaire (GHQ-2	28): Total; B	etter indi	cated by lower values)
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean parental mental health (combined pebm+pec groups) in the intervention groups was <b>0.45 standard deviations</b> <b>lower</b> (0.86 to 0.03 lower)
Parental : lower values)		c symptoms	(combined	PEBM+P	EC groups	<b>5)</b> (measured wit	h: Genei	ral Health Questionnaire	(GHQ-28):	Somatic	symptoms; Better indicated by
103 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1.3</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean parental somatic symptoms (combined pebm+pec groups) in the intervention groups was 0.19 standard deviations lower

											(0.6 lower to 0.22 higher)
Parental		c symptoms	(combined	I PEBM+P	EC group	<b>S)</b> (measured wi	th: Gen	eral Health Quest	onnaire (GHQ-2	3): Somati	c symptoms; Better indicated
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean parental somatic symptoms (combined pebm+pec groups) in the intervention groups was <b>0.22 standard deviations</b> <b>lower</b> (0.63 lower to 0.19 higher)
Parental ndicated by	-		nia (combin	ed PEBM	+PEC grou	<b>ups)</b> (measure	d with: (	General Health Qu	estionnaire (GH0	Q-28): Anx	iety and insomnia; Better
103 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean parental anxiety and insomnia (combined pebm+pec groups) in the intervention groups was <b>0.16 standard deviations</b> <b>lower</b> (0.57 lower to 0.25 higher)
Parental indicated by	•		nia (combin	ed PEBM	+PEC grou	ups) (measure	d with: (	General Health Qu	estionnaire (GH0	Q-28): Anx	iety and insomnia; Better
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	$\oplus \oplus \ominus \ominus$ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean parental anxiety and insomnia (combined pebm+pec groups) in the intervention groups was <b>0.54 standard deviations</b> <b>lower</b> (0.95 to 0.12 lower)
Parental lower values		dysfunction	(combined	PEBM+P	EC groups	) (measured wit	h: Gene	eral Health Question	onnaire (GHQ-28	): Social d	ysfunction; Better indicated by
103 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup> due to risk of bias,	35	68	N/A	N/A	The mean parental social dysfunction (combined pebm+pec groups) in the intervention groups was

						imprecision					0.65 standard deviations lower (1.07 to 0.23 lower)
Parental lower values)		dysfunction	(combined	PEBM+PE	EC groups	) (measured with	n: Gene	al Health Questionnaire	(GHQ-28):	Social d	vsfunction; Better indicated by
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1.3</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean parental social dysfunction (combined pebm+pec groups) in the intervention groups was <b>0.37 standard deviations</b> <b>lower</b> (0.78 lower to 0.04 higher)
Parental		depression	(combined	PEBM+PE	EC groups	(measured with	n: Gene	al Health Questionnaire	(GHQ-28):	Severe o	depression; Better indicated by
103 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean parental severe depression (combined pebm+pec groups) in the intervention groups was <b>0.09 standard deviations</b> <b>higher</b> (0.32 lower to 0.49 higher)
Parental		depression	(combined	PEBM+PE	EC groups	<b>)</b> (measured with	n: Gene	al Health Questionnaire	(GHQ-28):	Severe o	lepression; Better indicated by
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	68	N/A	N/A	The mean parental severe depression (combined pebm+pec groups) in the intervention groups was 0.14 standard deviations lower (0.55 lower to 0.27 higher)
General	family f	unction (con	nbined PEB	M+PEC g	roups) (me	asured with: McN	/laster F	amily Assessment Devic	e (FAD); B	etter indi	cated by lower values)
103 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,3</sup> due to risk of	35	68	N/A	N/A	The mean general family function (combined pebm+pe groups) in the intervention

General	family f	unction (cor	nbined PEB	M+PEC g	roups) (me	bias, imprecision asured with: McI	Master Family Asse	ssment Device (FAD); E	Setter indi	groups was <b>0.31 standard deviations</b> <b>lower</b> (0.72 lower to 0.1 higher) cated by lower values)
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	1	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35 68	N/A	N/A	The mean general family function (combined pebm+pec groups) in the intervention groups was <b>0.14 standard deviations</b> <b>lower</b> (0.55 lower to 0.27 higher)
intervention <sup>2</sup> N<400	and not bli				·		Ū	ection bias as parent-co	mpleted a	and parents involved in

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

		Qı	uality assessn	nent				Sui	mmary of	Finding	js
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Parent and day-care staff training versus standard day-care for improving the impact of autism on the family as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Parent and day-care staff training versus standard day-care for improving the impact of autism on the family as an indirect outcome (95% CI)
Maternal	stress	(measured with: S	Stress-Arousal C	hecklist: Moth	ers' Stress; Be	etter indicated by	y lower v	values)			
35 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	19	16	N/A	N/A	The mean maternal stress in the intervention groups was 0.06 standard deviations lower

											(0.73 lower to 0.61 higher)
Maternal	arousa	(measured with	h: Stress-Arousa	I Checklist: Mo	others' Arousal	; Better indicated	d by lov	wer values)			
35 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	19	16	N/A	N/A	The mean maternal arousal in the intervention groups was 0.18 standard deviations higher (0.48 lower to 0.85 higher)
Paternal	stress	(measured with: \$	Stress-Arousal C	hecklist: Fathe	ers' Stress; Be	tter indicated by	lower	values)			
35 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	19	16	N/A	N/A	The mean paternal stress in the intervention groups was <b>0.14 standard deviations</b> <b>higher</b> (0.53 lower to 0.8 higher)
Paternal	arousa	(measured with	: Stress-Arousa	Checklist: Fat	hers' Arousal;	Better indicated	by low	ver values)	I	<b>I</b>	-
35 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	19	16	N/A	N/A	The mean paternal arousal in the intervention groups was <b>0.51 standard deviations</b> <b>higher</b> (0.16 lower to 1.19 higher)

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

## **1.31.1 SNRIs 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

		Qu	ality assessn	nent				Sum	mary of F	inding	S
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Selective noradrenaline reuptake inhibitors versus placebo for improving the impact of autism on the family as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Selective noradrenaline reuptake inhibitors versus placebo for improving the impact of autism on the family as an indirect outcome (95% CI)
Parental	mental	health (measu	red with: Genera	al Health Ques	tionnaire (GH	Q-28): Total; B	etter indi	cated by lower values)	•		
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	46	43	N/A	N/A	The mean parental mental health in the intervention groups was <b>0.24 standard deviations</b> lower (0.66 lower to 0.18 higher)
Parental	stress (	measured with: Ni	jmeegse Ouder	lijke Stress Inc	lex (NOSI): To	tal; Better indic	cated by	lower values)	Į	Į	<u> </u>
77 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	39	38	N/A	N/A	The mean parental stress in the intervention groups was <b>0.24 standard deviations</b> <b>lower</b> (0.69 lower to 0.21 higher)
N<400 and	95% CI cro	osses both line of	no effect and me	easure of appr	eciable benefi	L t or harm (SMD	0 -0.5/0.5	i)		<u> </u>	

## 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

Quality assessment	Summary of Findings

Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study e	event rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Qigong massage versus waitlist for impact on family as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Qigong massage versus waitlist for impact on family as an indirect outcome (95% Cl)
Parental	stress (	measured with: Au	itism Parenting S	tress Index (A	SPI); Better ind	dicated by lower v	alues)			•	
41 (1 study) 17 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	18	23	N/A	N/A	The mean parental stress in the intervention groups was <b>0.78 standard deviations</b> <b>lower</b> (1.42 to 0.14 lower)
		ce and response b on and the outcom							as as outco	ne asses:	sors were parents who were

# 1.33ADVERSE EVENTS ASSOCIATED WITH PHARMACOLOGICAL INTERVENTIONS

### 1.33.1 Adverse events associated with anticonvulsants

Adverse events associated with divalproex versus placebo

			Quality asse	ssment				Sum	nmary of F	indings	
Participants		Inconsistency	Indirectness	Imprecision		Overall quality of	Study e	vent rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	evidence	With Control	With Adverse events associated with anticonvulsants	effect (95% CI)	Control	Risk difference with Adverse events associated with anticonvulsants (95% Cl)
Any adve	erse eve	ent (assessed wit	h: Number of pa	rticipants expe	riencing any side	effect during the trial	l (measur	ed using checklist der	ved from P	hysicians'	Desk Reference, 1997))
30 (1 study)	serious <sup>1</sup>		no serious indirectness	· .	reporting bias strongly		11/14 (78.6%)		<b>RR 1.19</b> (0.88 to	Study po	opulation
8 weeks		•			suspected <sup>3</sup>	due to risk of bias,	. ,	. ,	1.61)	786 per	149 more per 1000

						imprecision, publication bias				1000	(from 94 fewer to 479 more)
										Moderat	te
										786 per 1000	<b>149 more per 1000</b> (from 94 fewer to 479 more)
27	serious <sup>1</sup>	no serious	no serious	very	reporting bias	000	2/11	event during the trial	RR 1.72		sical examination)) opulation
(1 study) 12 weeks		inconsistency	indirectness	serious <sup>2</sup>	strongly suspected <sup>3</sup>	VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	(18.2%)	(31.3%)	(0.4 to 7.32)	182 per 1000	<b>131 more per 1000</b> (from 109 fewer to 1000 more)
										Moderat	te
										182 per 1000	<b>131 more per 1000</b> (from 109 fewer to 1000 more)
Disconti	nuation	due to adve	e <b>rse event</b> (a	ssessed with:	Number of partici	pants who discontinu	l ied due to	adverse event)			
57 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		0/25 (0%)	2/32 (6.3%)	<b>RR 2.37</b> (0.26 to	Study p	opulation
8-12 weeks		inconsistency	mancomess	301003	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(070)	(0.076)	21.43)	0 per 1000	N/A
						publication bias				Moderat	te
										0 per 1000	N/A
Weight g	<b>jain</b> (mea	sured with: Numb	er of kilograms o	r pounds that	participants gaine	d during the trial; Bet	ter indicat	ted by lower values)	<u> </u>	<u> </u>	
57 (2 studies) 8-12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	$\bigcirc \bigcirc \bigcirc$ <b>VERY LOW</b> <sup>1.2.3</sup> due to risk of bias, imprecision,	25	32	N/A	N/A	The mean weight gain in the intervention groups was <b>0.29 standard</b>

						publication bias				deviations higher (0.24 lower to 0.82 higher)
<sup>2</sup> Events<300	and 95%	CI crosses both lin	e of no effect an	d measure of a	appreciable benefi	it or harm (RR 0.75/	er term adverse events 1.25) or authors are consultants to ph	armaceutic	al compar	nies

## **1.33.2**Adverse events associated with antidepressants

#### Adverse events associated with citalopram versus placebo

			Quality asse	ssment				Sun	nmary of F	indings	
Participants		Inconsistency	Indirectness	Imprecision		Overall quality of	Study e	vent rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	evidence	With Control	With Adverse events associated with antidepressants	effect (95% CI)	Risk with Control	Risk difference with Adverse events associated with antidepressants (95% Cl)
Any adve	erse ev	<b>ent</b> (assessed wi	th: Safety Monito	oring Uniform F	Report Form)						
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly		66/76 (86.8%)	71/73 (97.3%)	<b>RR 1.12</b> (1.02 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		(* ***)	1.23)	868 per 1000	<b>104 more per 1000</b> (from 17 more to 200 more)
										Modera	te
										868 per 1000	<b>104 more per 1000</b> (from 17 more to 200 more)
Nightmar	' <b>es</b> (asse	ssed with: Safety	I Monitoring Unifo	I rm Report Forr	n )	_	1	·			Į
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		0/76 (0%)	5/73 (6.8%)	<b>RR 11.45</b> (0.64 to	Study p	opulation
12 weeks		lineerioieterioy			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0,0)	(0.070)	203.38)	0 per 1000	N/A
										Modera	te
										0 per 1000	N/A
Increased	d enerc	<b>jy level</b> (assess	sed with: Safety I	I Monitoring Unit	orm Report Form	ַן ו			I	ļ	

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly		15/76 (19.7%)	28/73 (38.4%)	<b>RR 1.94</b> (1.13 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(	()	3.33)	197 per 1000	<b>186 more per 1000</b> (from 26 more to 460 more)
										Moderat	e
										197 per 1000	<b>185 more per 1000</b> (from 26 more to 459 more)
Anger or	<sup>r</sup> irritabi	lity (assessed w	vith: Safety Monit	oring Uniform	Report Form )		<u> </u>	•		1	Į
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		13/76	18/73 (24.7%)	<b>RR 1.44</b> (0.76 to	Study p	opulation
12 weeks		inconsistency	maneetness	301003	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(17.170)	(24.170)	2.73)	171 per 1000	75 more per 1000 (from 41 fewer to 296 more)
										Moderat	e
										171 per 1000	75 more per 1000 (from 41 fewer to 296 more)
Aggress	ion or h	ostility (asses	sed with: Safety	Monitoring Ur	niform Report Form	n )					
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		13/76	17/73 (23.3%)	<b>RR 1.36</b> (0.71 to	Study p	opulation
12 weeks		inconsistency	maneetness	301003	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(17.170)	(20.070)	2.6)	171 per 1000	62 more per 1000 (from 50 fewer to 274 more)
										Moderat	e
										171 per 1000	<b>62 more per 1000</b> (from 50 fewer to 274 more)
Headach	e or mi	graine (assess	ed with: Safety N	Ionitoring Unit	form Report Form	)	<u> </u>				

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁴	reporting bias strongly		10/76 (13.2%)	15/73 (20.5%)	<b>RR 1.56</b> (0.75 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		( )	3.25)	132 per 1000	74 more per 1000 (from 33 fewer to 296 more)
										Modera	te
										132 per 1000	74 more per 1000 (from 33 fewer to 297 more)
Restless	ness or	difficulty s	ettling down	l (assessed w	vith: Safety Monito	ring Uniform Report	Form)		<b>I</b>		1
149 (1 study)	serious1	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		7/76 (9.2%)	13/73 (17.8%)	<b>RR 1.93</b> (0.82 to	Study p	opulation
12 weeks		inconcisionaly		Schous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.270)	(11.070)	4.57)	92 per 1000	86 more per 1000 (from 17 fewer to 329 more)
										Modera	te
										92 per 1000	86 more per 1000 (from 17 fewer to 328 more)
Disinhibi	ited, im	pulsive, or i	ntrusive be	haviour (as	ssessed with: Safe	ety Monitoring Uniform	n Report	Form)		1	
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly		5/76 (6.6%)	14/73 (19.2%)	<b>RR 2.92</b> (1.11 to	Study p	opulation
12 weeks		Inconsistency	Indirectiless		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.0 %)	(19.276)	7.68)	66 per 1000	<b>126 more per 1000</b> (from 7 more to 439 more)
										Modera	te
										66 per 1000	<b>127 more per 1000</b> (from 7 more to 441 more)
Silliness	(assessed	I with: Safety Mor	itoring Uniform R	eport Form )	ļ	ļ	I	•		<u> </u>	1

serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		10/76 (13.2%)	9/73 (12.3%)	<b>RR 0.94</b> (0.4 to	Study p	opulation
				suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		(,	2.17)	132 per 1000	8 fewer per 1000 (from 79 fewer to 154 more)
									Moderat	e
									132 per 1000	8 fewer per 1000 (from 79 fewer to 154 more)
assessed v	with: Safety Monit	oring Uniform Re	port Form)		1	1		I	_	1
serious <sup>1</sup>	no serious	no serious	very	reporting bias		9/76	8/73	<b>RR 0.93</b>	Study p	opulation
	inconsistency	indirectriess	361003	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(11.076)	(1170)	2.27)	118 per 1000	8 fewer per 1000 (from 73 fewer to 150 more)
									Moderate	
									118 per 1000	8 fewer per 1000 (from 73 fewer to 150 more)
<b>bility</b> (ass	sessed with: Safe	ty Monitoring Uni	form Report F	Form )						
serious <sup>1</sup>	no serious	no serious	very	reporting bias		9/76	7/73	RR 0.81	Study p	opulation
	inconsistency	indirectriess	361003	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(11.076)	(3.076)	2.06)	118 per 1000	22 fewer per 1000 (from 81 fewer to 126 more)
									Moderate	
									118 per 1000	22 fewer per 1000 (from 80 fewer to 125 more)
	assessed v serious <sup>1</sup>	assessed with: Safety Monit serious <sup>1</sup> no serious inconsistency bility (assessed with: Safe	inconsistency indirectness indirectness assessed with: Safety Monitoring Uniform Re serious <sup>1</sup> no serious inconsistency indirectness indirectness pility (assessed with: Safety Monitoring Uni serious <sup>1</sup> no serious no serious	inconsistency       indirectness       serious <sup>4</sup> assessed with: Safety Monitoring Uniform Report Form )         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> bility (assessed with: Safety Monitoring Uniform Report F serious <sup>1</sup> no serious       very serious <sup>4</sup>	inconsistency       indirectness       serious <sup>4</sup> strongly         suspected <sup>3</sup> assessed with: Safety Monitoring Uniform Report Form )         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> pility (assessed with: Safety Monitoring Uniform Report Form )       no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> pility (assessed with: Safety Monitoring Uniform Report Form )       no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly	inconsistency       indirectness       serious <sup>4</sup> strongly suspected <sup>3</sup> VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias         assessed with: Safety Monitoring Uniform Report Form )       serious <sup>1</sup> no serious inconsistency       no serious indirectness       reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias         bility (assessed with: Safety Monitoring Uniform Report Form )       no serious inconsistency       no serious indirectness       reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias         serious <sup>1</sup> no serious inconsistency       no serious indirectness       reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	inconsistency       indirectness       serious <sup>4</sup> strongly suspected <sup>3</sup> VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       (13.2%)         assessed with: Safety Monitoring Uniform Report Form )       serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       9/76 (11.8%)         bility (assessed with: Safety Monitoring Uniform Report Form )       serious <sup>1</sup> no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       9/76 (11.8%)         bility (assessed with: Safety Monitoring Uniform Report Form )       mo serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊝⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,       9/76 (11.8%)	inconsistency       indirectness       serious <sup>4</sup> strongly       VERY LOW <sup>1,3,4</sup> (13.2%)       (12.3%)         assessed with:       Safety Monitoring Uniform Report Form )       publication bias       (11.8%)       (11.8%)       (11.8%)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       9/76       8/73 (11.8%)         bility (assessed with: Safety Monitoring Uniform Report Form )       serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       9/76       8/73 (11.8%)         bility (assessed with: Safety Monitoring Uniform Report Form )       mo serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,       9/76 (11.8%)       7/73 (11.8%)	inconsistency       indirectness       serious <sup>4</sup> strongly       VERY LOW <sup>1,3,4</sup> (13.2%)       (12.3%)       (0.4 to         assessed with:       Safety Monitoring Uniform Report Form )       serious <sup>1</sup> no serious       no serious       very       reporting bias       9/76       8/73       RR 0.93         serious <sup>1</sup> no serious       no serious       very       serious <sup>4</sup> strongly       Strongly       9/76       8/73       (11%)       (0.38 to         supprecision, publication bias       inconsistency       no serious       very       reporting bias       Strongly       9/76       8/73       (11%)       (1.3%)       (11%)       (0.38 to         supprecision, publication bias       inconsistency       indirectness       very       reporting bias       9/76       8/73       (11%)       (2.27)         sitility (assessed with: Safety Monitoring Uniform Report Form )       serious <sup>1</sup> no serious       no serious       very       reporting bias       9/76       7/73       RR 0.81       (0.32 to         serious <sup>1</sup> inconsistency       indirectness       very       serious <sup>4</sup> strongly       VERY LOW <sup>1.3.4</sup> 9/76       9/76       7/73       R0.81       (0.32 to       2.06)         <	inconsistency       indirectness       serious <sup>4</sup> strongly suspected <sup>3</sup> VERY LOW <sup>13.4</sup> due to risk of bias, imprecision, publication bias       (13.2%)       (12.3%)       (0.4 to 2.17)       132 per 1000         assessed with: Safety Monitoring Uniform Report Form )       serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> $\Theta \ominus \ominus$ VERY LOW <sup>13.4</sup> due to risk of bias, imprecision, publication bias       9/76       8/73       RR 0.93 (0.38 to 2.27)       Study p 118 per 1000         inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> $\Theta \ominus \ominus \ominus$ VERY LOW <sup>13.4</sup> due to risk of bias, imprecision, publication bias       9/76       8/73 (11.8%)       (11%)       RR 0.93 (0.38 to 2.27)       Study p 18 per 1000         serious <sup>4</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> 9/76       7/73 (11.8%)       RR 0.81 (0.32 to 2.06)       Study p 18 per 1000

	inconsistency			strongly suspected <sup>3</sup>	VERY LOW <sup>1,3,4</sup>	(5.3%)	(11%)	(0.66 to		
				im	due to risk of bias, imprecision, publication bias		< <i>/</i>	6.62)	53 per 1000	57 more per 1000 (from 18 fewer to 296 more)
									Modera	te
									53 per 1000	<b>57 more per 1000</b> (from 18 fewer to 298 more)
d atten	tion and co	ncentration	(assessed wit	th: Safety Monitori	ing Uniform Report F	orm)		<b>I</b>		1
serious <sup>1</sup>	no serious inconsistency	no serious	serious <sup>2</sup>	reporting bias		2/76 (2.6%)	9/73 (12.3%)	<b>RR 4.68</b> (1.05 to	Study p	opulation
	inconciency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2.070)	(12.070)	20.96)	26 per 1000	97 more per 1000 (from 1 more to 525 more)
									Modera	te
									26 per 1000	<b>96 more per 1000</b> (from 1 more to 519 more)
vity (ass	sessed with: Safe	ty Monitoring Uni	iform Report F	Form )		I			1	
serious <sup>1</sup>	no serious	no serious	serious <sup>2</sup>	reporting bias		2/76	9/73	<b>RR 4.68</b>	Study p	opulation
	inconsistency	Indirectriess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2.078)	(12.376)	20.96)	26 per 1000	<b>97 more per 1000</b> (from 1 more to 525 more)
									Modera	te
									26 per 1000	<b>96 more per 1000</b> (from 1 more to 519 more)
566 V	erious <sup>1</sup>	inconsistency inconsistency ity (assessed with: Safe perious <sup>1</sup> no serious inconsistency inconsistency	erious <sup>1</sup> no serious inconsistency       no serious indirectness         ity (assessed with: Safety Monitoring Uni erious <sup>1</sup> no serious inconsistency       no serious indirectness	erious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> ity (assessed with: Safety Monitoring Uniform Report F erious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup>	erious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ity (assessed with: Safety Monitoring Uniform Report Form )       no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup>	erious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias         ity (assessed with: Safety Monitoring Uniform Report Form )        ●⊖⊖⊖         erious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖         verious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	inconsistency       indirectness       strongly       VERY LOW <sup>1,2,3</sup> (2.6%)         imprecision, publication bias       imprecision, publication bias       (2.6%)       (2.6%)         ity (assessed with: Safety Monitoring Uniform Report Form )       inconsistency       no serious       serious <sup>2</sup> reporting bias       (2.6%)         erious <sup>1</sup> no serious       no serious       indirectness       serious <sup>2</sup> reporting bias       (2.6%)         inconsistency       no serious       indirectness       serious <sup>2</sup> reporting bias       (2.6%)       (2.6%)         ue to risk of bias, imprecision, publication bias       indirectness       serious <sup>2</sup> reporting bias       (2.6%)       (2.6%)	erious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> Image: Comparison of the text of	erious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> POOO VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias       2/76 (12.3%)       9/73 (12.3%)       RR 4.68 (1.05 to 20.96)         ity (assessed with: Safety Monitoring Uniform Report Form )       mo serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> 2/76 VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias       9/73 (12.3%)       RR 4.68 (1.05 to 20.96)         erious <sup>1</sup> no serious inconsistency       no serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> POOO VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias       9/73 (2.6%)       RR 4.68 (1.05 to 20.96)	arious <sup>1</sup> inconsistency       no serious indirectness       serious <sup>2</sup> strongly suspected <sup>3</sup> reporting bias strongly suspected <sup>3</sup> 2/76 VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias       9/73 (12.3%)       RR 4.68 (1.05 to 20.96)       Study p         ity (assessed with: Safety Monitoring Uniform Report Form )       mo serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> 0 VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency       2/76 (12.3%)       9/73 (12.3%)       RR 4.68 (1.05 to 20.96)       Study p         indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> 0 VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias       9/73 (12.3%)       RR 4.68 (1.05 to 20.96)       Study p         indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> 0 VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias       2/76 (2.6%)       9/73 (12.3%)       RR 4.68 (1.05 to 20.96)       Study p         ide to risk of bias, imprecision, publication bias       1/76 (2.6%)       9/73 (12.3%)       RR 4.68 (1.05 to 20.96)       Study p         ide to risk of bias, imprecision, publication bias       1/76 (2.6%)       9/73 (12.3%)       RR 4.68 (1.05 to 20.96)       Study p         ide to risk of bias, imprecision, publication bias       1/76 (2.6%)       9/73 (12.3%)       1/76 (12.3%)       1/76 (12.3%)

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly		1/76 (1.3%)	8/73 (11%)	<b>RR 8.33</b> (1.07 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			64.95)	13 per 1000	96 more per 1000 (from 1 more to 841 more)
										Moderat	e
										13 per 1000	<b>95 more per 1000</b> (from 1 more to 831 more)
Diarrhoea	a or loc	ose stools (as	sessed with: Saf	ety Monitoring	g Uniform Report F	Form)	1		I	1	Į.
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly		9/76 (11.8%)	19/73 (26%)	<b>RR 2.2</b> (1.06 to	Study p	opulation
12 weeks		inconsistency	indirectiless		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(11.070)	(2070)	4.54)	118 per 1000	<b>142 more per 1000</b> (from 7 more to 419 more)
										Moderat	e
										118 per 1000	<b>142 more per 1000</b> (from 7 more to 418 more)
Abdomin	al disc	omfort (assess	sed with: Safety N	/ Ionitoring Uni	iform Report Form	)	I				
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		9/76	13/73 (17.8%)	<b>RR 1.5</b> (0.68 to	Study p	opulation
12 weeks		Inconsistency	munectness	Senous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(11.076)	(17.070)	3.3)	118 per 1000	59 more per 1000 (from 38 fewer to 272 more)
										Moderat	ie i
										118 per 1000	59 more per 1000 (from 38 fewer to 271 more)
Vomiting	or nau		with: Safety Moni	toring Uniform	Poport Form)	<u> </u>				1	ļ

serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		6/76 (7.9%)	14/73 (19.2%)	<b>RR 2.43</b> (0.99 to	Study p	opulation
				suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		<b>、</b> ,	5.98)	79 per 1000	<b>113 more per 1000</b> (from 1 fewer to 393 more)
									Modera	te
									79 per 1000	<b>113 more per 1000</b> (from 1 fewer to 393 more)
mnia (as	ssessed with: Saf	ety Monitoring Ur	niform Report	Form)		Į		<b>I</b>	_ <b>I</b>	
serious <sup>1</sup>	no serious	no serious	serious <sup>2</sup>	reporting bias		17/76 (22.4%)	28/73 (38.4%)	<b>RR 1.71</b> (1.03 to	Study p	opulation
				suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(22.170)	(00.175)	2.86)	224 per 1000	<b>159 more per 1000</b> (from 7 more to 416 more)
									Modera	te
									224 per 1000	<b>159 more per 1000</b> (from 7 more to 417 more)
omnia	or difficulty	falling asle	ep (assessed	d with: Safety Mon	itoring Uniform Repo	rt Form)				
serious <sup>1</sup>	no serious	no serious	serious <sup>2</sup>	reporting bias		7/76	17/73	<b>RR 2.53</b>	Study p	opulation
	inconsistency	maneetness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(3.270)	(23.376)	5.74)	92 per 1000	<b>141 more per 1000</b> (from 10 more to 437 more)
									Modera	te
									92 per 1000	<b>141 more per 1000</b> (from 10 more to 436 more)
	mnia (a: serious <sup>1</sup>	inconsistency mnia (assessed with: Saf serious <sup>1</sup> no serious inconsistency omnia or difficulty	inconsistency       indirectness         mnia       (assessed with: Safety Monitoring University Safety Monitoring University)         serious <sup>1</sup> no serious         inconsistency       no serious         indirectness       indirectness         omnia       or difficulty falling asle         serious <sup>1</sup> no serious         serious <sup>1</sup> no serious	inconsistency       indirectness       serious <sup>4</sup> mnia       (assessed with: Safety Monitoring Uniform Report         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> omnia or difficulty falling asleep (assessen serious <sup>1</sup> no serious       no serious <sup>2</sup>	inconsistency       indirectness       serious <sup>4</sup> strongly         suspected <sup>3</sup> mnia (assessed with: Safety Monitoring Uniform Report Form)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> omnia or difficulty falling asleep (assessed with: Safety Mon inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly	inconsistency       indirectness       serious <sup>4</sup> strongly       strongly         suspected <sup>3</sup> VERY LOW <sup>1,3,4</sup> due to risk of bias,       imprecision,         mnia (assessed with: Safety Monitoring Uniform Report Form)         serious <sup>1</sup> no serious         inconsistency       no serious         indirectness       serious <sup>2</sup> reporting bias       trongly         strongly       suspected <sup>3</sup> @OOO       VERY LOW <sup>1,2,3</sup> due to risk of bias,       imprecision,         publication bias       indirectness         serious <sup>1</sup> no serious         inconsistency       no serious         indirectness       serious <sup>2</sup> reporting bias       imprecision,         publication bias       imprecision,         out or difficulty falling asleep (assessed with: Safety Monitoring Uniform Repor         serious <sup>1</sup> no serious         inconsistency       no serious         indirectness       serious <sup>2</sup> reporting bias       trowy         strongly       suspected <sup>3</sup> with to risk of bias,       imprecision,	inconsistency       indirectness       serious <sup>4</sup> strongly suspected <sup>3</sup> VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       (7.9%)         mnia       (assessed with: Safety Monitoring Uniform Report Form)       Imprecision       17/76         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias       17/76         omnia or difficulty falling asleep (assessed with: Safety Monitoring Uniform Report Form)       serious <sup>3</sup> ⊕⊖⊖⊖       7/76         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       7/76         omnia or difficulty falling asleep (assessed with: Safety Monitoring Uniform Report Form)       90000       7/76         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕0000       7/76	inconsistency       indirectness       serious <sup>4</sup> strongly       VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       (7.9%)       (19.2%)         mnia       (assessed with: Safety Monitoring Uniform Report Form)       Imprecision, publication bias       (7.9%)       (19.2%)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias       17776       28/73         Omnia       or difficulty falling asleep       (assessed with: Safety Monitoring Uniform Report Form)       VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias       17776       28/73         omnia       or difficulty falling asleep       (assessed with: Safety Monitoring Uniform Report Form)       VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency       17/76       17/73         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖       7/76       17/73         (9.2%)       (23.3%)       (23.3%)       (23.3%)       (23.3%)       (23.3%)	inconsistency       indirectness       serious <sup>4</sup> strongly       VERY LOW <sup>1,3,4</sup> (7.9%)       (19.2%)       (0.99 to         mnia       (assessed with: Safety Monitoring Uniform Report Form)       publication bias       (7.9%)       (19.2%)       (19.2%)       (0.99 to         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inprecision, publication bias       17/76       28/73       RR 1.71         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ UERY LOW <sup>1,2,3</sup> due to risk of bias, inprecision, publication bias       28/73       RR 1.71         omnia       or difficulty falling asleep (assessed with: Safety Monitoring Uniform Report Form)       28/73       28/73       RR 2.53         omnia       or difficulty falling asleep (assessed with: Safety Monitoring Uniform Report Form)       28/73       28/73       28/73       28/73         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting Uniform Report Form)       7/76       17/73       RR 2.53         strongly       strongly       Strongly       Serious indirectness       111 to       5.74)	inconsistency       indirectness       serious <sup>4</sup> strongly suspected <sup>3</sup> VERY LOWI <sup>3.4</sup> due to risk of bias, imprecision bias       (7.9%)       (19.2%)       (0.99 to 5.98)       79 per 1000         mnla       cassessed with: Safety Monitoring Uniform Report Form)       moderation bias       (7.9%)       (19.2%)       (19.2%)       (1.03 to 5.98)       1000         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> the orisk of bias, imprecision, publication bias       17/76       28/73 (22.4%)       RR 1.71 (1.03 to 2.86)       Study p 224 per 1000         ommla       or difficulty falling asleep inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> the orisk of bias, indirection bias       17/76 (22.4%)       17/76 (38.4%)       RR 2.53 (1.11 to 5.74)       Study p 92 per 1000         serious <sup>1</sup> no serious inconsistency       no serious indirectness       serious <sup>2</sup> reporting bias strongly suspected <sup>3</sup> the orisk of bias, imprecision, publication bias       77.6 (2.2,%)       17.73 (2.2,%)       RR 2.53 (1.11 to 5.74)       Study p 92 per 1000

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		9/76 (11.8%)	13/73 (17.8%)	<b>RR 1.5</b> (0.68 to	Study p	opulation
12 weeks				Sonous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(11.070)	(11.070)	3.3)	118 per 1000	59 more per 1000 (from 38 fewer to 272 more)
										Moderat	e
										118 per 1000	59 more per 1000 (from 38 fewer to 271 more)
Cold, flu	or othe	er systemic i	nfection (ass	essed with: S	afety Monitoring L	Iniform Report Form)	1		I	-1	1
149 (1 study)	serious1	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		26/76 (34.2%)	31/73 (42.5%)	<b>RR 1.24</b> (0.82 to	Study p	opulation
12 weeks		inconsistency	maneetiless	301003	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(34.270)	(42.576)	1.87)	342 per 1000	82 more per 1000 (from 62 fewer to 298 more)
										Moderat	e
										342 per 1000	<b>82 more per 1000</b> (from 62 fewer to 298 more)
Decrease	ed appe	e <b>tite</b> (assessed v	vith: Safety Monit	L oring Uniform	Report Form)						
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		10/76	11/73 (15.1%)	<b>RR 1.15</b> (0.52 to	Study p	opulation
12 weeks		Inconsistency	Indirectiless	Senous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(13.276)	(13.1%)	(0.3210)	132 per 1000	20 more per 1000 (from 63 fewer to 201 more)
										Moderat	e
										132 per 1000	20 more per 1000 (from 63 fewer to 202 more)
Increase	d appet	: <b>ite</b> (assessed wi	th: Safety Monito	I pring Uniform I	Report Form)	1	I	•	<b> </b>		<u> </u>

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		8/76 (10.5%)	7/73 (9.6%)	<b>RR 0.91</b> (0.35 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		()	2.38)	105 per 1000	<b>9 fewer per 1000</b> (from 68 fewer to 145 more)
										Moderat	ie
										105 per 1000	<b>9 fewer per 1000</b> (from 68 fewer to 145 more)
Rash (ass	essed with	: Safety Monitorin	g Uniform Repor	t Form)	-1	1	1		I	-1	1
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		8/76 (10.5%)	12/73 (16.4%)	<b>RR 1.56</b> (0.68 to	Study p	opulation
12 weeks		lineonoisteney	maneotriess	5011000	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.070)	(10.470)	3.6)	105 per 1000	<b>59 more per 1000</b> (from 34 fewer to 274 more)
										Moderat	e
										105 per 1000	<b>59 more per 1000</b> (from 34 fewer to 273 more)
Other sk	in or su	Ibcutaneous	tissue disc	order (asse	ssed with: Safety N	I Monitoring Uniform Re	eport Forr	n)			
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly		1/76 (1.3%)	9/73 (12.3%)	<b>RR 9.37</b> (1.22 to	Study p	opulation
12 weeks		inconsistency	indirectiless		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(1.576)	(12.570)	72.12)	13 per 1000	<b>110 more per 1000</b> (from 3 more to 936 more)
										Moderat	e
										13 per 1000	<b>109 more per 1000</b> (from 3 more to 925 more)
	<u> </u>	ļ	oring Uniform Re	1	-	1	L	•		ļ	Į

serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		10/76 (13.2%)	10/73 (13.7%)	<b>RR 1.04</b> (0.46 to	Study p	opulation
				suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			2.35)	132 per 1000	<b>5 more per 1000</b> (from 71 fewer to 178 more)
									Moderat	te
									132 per 1000	5 more per 1000 (from 71 fewer to 178 more)
(assessed	d with: Safety Mo	nitoring Uniform F	Report Form)			1	-	I	_	
serious <sup>1</sup>	no serious	no serious	very	reporting bias		11/76	15/73	<b>RR 1.42</b>	Study p	opulation
	inconsistency	maneethess	301003	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(14.570)	(20.378)	2.88)	145 per 1000	61 more per 1000 (from 43 fewer to 272 more)
									Moderat	te
									145 per 1000	61 more per 1000 (from 43 fewer to 273 more)
ssessed wi	th: Safety Monito	ring Uniform Rep	ort Form)							
serious <sup>1</sup>	no serious	no serious	very	reporting bias		5/76	10/73	<b>RR 2.08</b>	Study p	opulation
	inconsistency	maneethess	301003	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.070)	(10.770)	5.8)	66 per 1000	71 more per 1000 (from 16 fewer to 316 more)
									Moderat	te
									66 per 1000	71 more per 1000 (from 16 fewer to 317 more)
	(assessed	inconsistency (assessed with: Safety Mon serious <sup>1</sup> no serious inconsistency sessed with: Safety Monito	inconsistency       indirectness         (assessed with: Safety Monitoring Uniform F         serious <sup>1</sup> no serious inconsistency       no serious indirectness         sesses with: Safety Monitoring Uniform Rep         sesses with: Safety Monitoring Uniform Rep         serious <sup>1</sup> no serious         serious <sup>1</sup> no serious         serious <sup>1</sup> no serious	inconsistency       indirectness       serious <sup>4</sup> (assessed with: Safety Monitoring Uniform Report Form)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> sessesed with: Safety Monitoring Uniform Report Form)       serious <sup>1</sup> no serious       very serious <sup>4</sup> sessesed with: Safety Monitoring Uniform Report Form)       serious <sup>1</sup> no serious       very very	inconsistency       indirectness       serious <sup>4</sup> strongly suspected <sup>3</sup> (assessed with: Safety Monitoring Uniform Report Form)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> sesessed with: Safety Monitoring Uniform Report Form)       serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> sesessed with: Safety Monitoring Uniform Report Form)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly	inconsistency       indirectness       serious <sup>4</sup> strongly       strongly         suspected <sup>3</sup> VERY LOW <sup>1,3,4</sup> due to risk of bias,       imprecision,         publication bias         (assessed with: Safety Monitoring Uniform Report Form)         serious <sup>1</sup> no serious         inconsistency       no serious         indirectness       very         serious <sup>1</sup> no serious         inconsistency       no serious         indirectness       very         suspected <sup>3</sup> ⊕⊙⊙⊙         VERY LOW <sup>1,3,4</sup> due to risk of bias,         imprecision,       publication bias         suspected <sup>3</sup> imprecision,         suspected <sup>3</sup> Imprecision,         serious <sup>1</sup> no serious         no serious       no serious         indirectness       very         serious <sup>1</sup> no serious         inconsistency       no serious         indirectness       very         serious <sup>1</sup> no serious         indirectness       very         serious <sup>1</sup> no serious         indirectness       very         serious <sup>1</sup> no serious	inconsistency       indirectness       serious <sup>4</sup> strongly suspected <sup>3</sup> VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       (13.2%)         (assessed with: Safety Monitoring Uniform Report Form)       serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       11/76 (14.5%)         sessed with: Safety Monitoring Uniform Report Form)       serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       11/76 (14.5%)         sessed with: Safety Monitoring Uniform Report Form)       serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, inconsistency       5/76 (6.6%)	inconsistency       indirectness       serious <sup>4</sup> strongly suspected <sup>3</sup> VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       (13.2%)       (13.7%)         (assessed with: Safety Monitoring Uniform Report Form)       (assessed with: Safety Monitoring Uniform Report Form)       reporting bias strongly serious <sup>1</sup> ©©© VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       11/76       15/73         serious <sup>1</sup> no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕©⊖⊙ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       11/76       15/73         sessesed with: Safety Monitoring Uniform Report Form)       serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊙⊖⊙ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       10/73 (6.6%)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊙⊝⊙ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	inconsistency       indirectness       serious <sup>4</sup> strongly suspected <sup>3</sup> VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       (13.2%)       (13.7%)       (0.46 to 2.35)         (assessed with: Safety Monitoring Uniform Report Form)       reporting bias strongly inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       11/76 (20.5%)       15/73 (20.5%)       RR 1.42 (0.7 to 2.88)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias       11/76 (20.5%)       15/73 (20.5%)       RR 1.42 (0.7 to 2.88)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, inconsistency       10/73 (13.7%)       RR 2.08 (0.75 to 5.8)	inconsistency       indirectness       serious <sup>4</sup> strongly suspected <sup>3</sup> VERY LOWI <sup>3.4</sup> due to risk of bias, imprecision bias       (13.2%)       (13.7%)       (0.46 to 2.35)       132 per 1000         (assessed with: Safety Monitoring Uniform Report Form)       serious <sup>1</sup> no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> $\oplus \ominus \ominus \ominus$ VERY LOWI <sup>3.4</sup> due to risk of bias, imprecision, publication bias       11/76       15/73 (14.5%)       RR 1.42 (0.7 to 2.88)       Study p 145 per 1000         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> $\oplus \ominus \ominus \ominus$ VERY LOWI <sup>3.4</sup> due to risk of bias, imprecision, publication bias       11/76       15/73 (14.5%)       RR 1.42 (0.7 to 2.88)       Study p 1000         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> $\oplus \ominus \ominus \ominus$ VERY LOW <sup>1.34</sup> VERY LOW <sup>1.34</sup> (14.5%)       10/73 (13.7%)       RR 2.08 (0.75 to 5.8)       Study p 66 per 1000

no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly		0/76 (0%)	1/73 (1.4%)	<b>RR 3.12</b> (0.13 to	Study p	opulation
,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	()	()	75.42)	0 per 1000	N/A
								Modera	te
								0 per 1000	N/A
					imprecision, publication bias	imprecision, publication bias	imprecision, publication bias	imprecision,	imprecision, publication bias 0 per 1000

### 1.33.3 Adverse events associated with antihistamines

#### Adverse events associated with cyproheptadine and haloperidol versus placebo and haloperidol

		Q	uality assessr	nent				Sun	nmary of I	Findings	;
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study e	event rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Adverse events associated with combined antihistamines and antipsychotics	effect (95% CI)	Risk with Control	Risk difference with Adverse events associated with combined antihistamines and antipsychotics (95% Cl)
Extrapyra	amidal	symptoms (a	ssessed with: Ex	trapyramidal S	Symptoms Rati	ng Scale (ESRS	): Total)				
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		6/20 (30%)	2/20 (10%)	<b>RR 0.33</b> (0.08 to	Study pe	opulation
8 weeks						due to risk of bias, imprecision		< ,	1.46)	300 per 1000	201 fewer per 1000 (from 276 fewer to 138 more)
										Moderat	e
										300 per 1000	<b>201 fewer per 1000</b> (from 276 fewer to 138

											more)		
Trouble	swallow	<b>/ing</b> (assessed v	vith: Study-specif	fic side effect of	checklist)		1						
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		4/20 (20%)	2/20 (10%)	<b>RR 0.5</b> (0.1 to	Study p	opulation		
8 weeks		inconsistency		Sellous		due to risk of bias, imprecision	(2078)	(1078)	2.43)	200 per 1000	<b>100 fewer per 1000</b> (from 180 fewer to 286 more)		
										Moderat	e		
										200 per 1000	<b>100 fewer per 1000</b> (from 180 fewer to 286 more)		
Stiffness	S (assessed	d with: Study-spec	ific side effect ch	ecklist)	ł	1	I			. <b>ļ</b>	Į		
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		3/20 (15%)	1/20 (5%)	<b>RR 0.33</b> (0.04 to	Study p	Study population		
8 weeks						due to risk of bias, imprecision	(10,0)		2.94)	150 per 1000	<b>101 fewer per 1000</b> (from 144 fewer to 291 more)		
										Moderate			
										150 per 1000	101 fewer per 1000 (from 144 fewer to 291 more)		
Slow mo	vement	(assessed with: S	Study-specific sid	e effect check	list)		1		I				
l0 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		3/20 (15%)	1/20 (5%)	<b>RR 0.33</b> (0.04 to	Study p	opulation		
3 weeks						due to risk of bias, imprecision	(		2.94)	150 per 1000	<b>101 fewer per 1000</b> (from 144 fewer to 291 more)		
										Moderat	e		
										150 per	101 fewer per 1000		

										1000	(from 144 fewer to 291 more)
Constip	ation (as	sessed with: Study	/-specific side eff	ect checklist)							
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/20 (10%)	4/20 (20%)	<b>RR 2</b> (0.41 to	Study p	opulation
8 weeks		lineonoiotonoy				due to risk of bias, imprecision	(10,0)	(2070)	9.71)	100 per 1000	<b>100 more per 1000</b> (from 59 fewer to 871 more)
										Modera	te
										100 per 1000	<b>100 more per 1000</b> (from 59 fewer to 871 more)
Diarrho	ea (assess	ed with: Study-spe	ecific side effect of	hecklist)							
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		3/20 (15%)	2/20 (10%)	<b>RR 0.67</b> (0.12 to	Study p	opulation
8 weeks						due to risk of bias, imprecision			3.57)	150 per 1000	<b>49 fewer per 1000</b> (from 132 fewer to 386 more)
										Moderate	
										150 per 1000	<b>49 fewer per 1000</b> (from 132 fewer to 386 more)
Increase	ed appet	t <b>ite</b> (assessed wi	th: Study-specific	side effect ch	necklist)	I	1	-	Į		•
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		4/20 (20%)	9/20 (45%)	<b>RR 2.25</b> (0.83 to	Study p	opulation
8 weeks		Inconsistency	Indirectiless	Senous		due to risk of bias, imprecision	(20%)	(4570)	6.13)	200 per 1000	<b>250 more per 1000</b> (from 34 fewer to 1000 more)
										Modera	te
										200 per	<b>250 more per 1000</b> (from 34 fewer to 1000

										1000	more)
Morning	l drowsi	ness (assessed	with: Study-spe	cific side effect	t checklist)	1	L				
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/20 (10%)	3/20 (15%)	<b>RR 1.5</b> (0.28 to	Study p	opulation
8 weeks						due to risk of bias, imprecision	(10,0)	(()	8.04)	100 per 1000	50 more per 1000 (from 72 fewer to 704 more)
						Improviolent				Modera	te
										100 per 1000	<b>50 more per 1000</b> (from 72 fewer to 704 more)
Day time	e drows	ness (assesse	d with: Study-spe	cific side effec	t checklist)						
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/20 (10%)	1/20 (5%)	<b>RR 0.5</b> (0.05 to		opulation
8 weeks						due to risk of bias, imprecision			5.08)	100 per 1000	<b>50 fewer per 1000</b> (from 95 fewer to 408 more)
										Modera	te
										100 per 1000	50 fewer per 1000 (from 95 fewer to 408 more)
Restless	sness (as	sessed with: Stuc	ly-specific side e	ffect checklist)							
40 (1 study)	serious1	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		4/20 (20%)	1/20 (5%)	<b>RR 0.25</b> (0.03 to	Study p	opulation
8 weeks						due to risk of bias, imprecision	(2070)	(675)	2.05)	200 per 1000	<b>150 fewer per 1000</b> (from 194 fewer to 210 more)
										Modera	te
										200 per 1000	<b>150 fewer per 1000</b> (from 194 fewer to 210 more)
Fatigue	(assessed v	vith: Study-specifi	c side effect cheo	cklist)				•			

40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/20 (10%)	3/20 (15%)	<b>RR 1.5</b> (0.28 to	Study p	opulation
8 weeks						due to risk of bias, imprecision			8.04)	100 per 1000	<b>50 more per 1000</b> (from 72 fewer to 704 more)
										Moderat	te
										100 per 1000	50 more per 1000 (from 72 fewer to 704 more)
		bias as unclear if f CI crosses both li						r term adverse events .25)			

## **1.33.4** Adverse events associated with antioxidants

## Adverse events associated with N-acetylcysteine versus placebo

		(	Quality assess	nent				Su	mmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study ev	vent rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Adverse events associated with antioxidants	effect (95% CI)	Risk with Control	Risk difference with Advers events associated with antioxidants (95% Cl)
Any gast	rointes	tinal side effe	ect (assessed wi	th: Dosage Re	cord and Treat	ment Emergent Sy	mptom S	cale (DOTES))			
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		7/15 (46.7%)	11/14 (78.6%)	<b>RR 1.68</b> (0.92 to	Study po	opulation
(1 study) 12 weeks						due to risk of bias, imprecision		( )	3.09)	467 per 1000	<b>317 more per 1000</b> (from 37 fewer to 975 more)
										Moderat	e
										467 per 1000	<b>318 more per 1000</b> (from 37 fewer to 976 more)

29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/15 (13.3%)	3/14 (21.4%)	<b>RR 1.61</b> (0.31 to	Study po	opulation
12 weeks						due to risk of bias, imprecision	()	(,	8.24)	133 per 1000	81 more per 1000 (from 92 fewer to 965 more)
										Moderat	e
										133 per 1000	81 more per 1000 (from 92 fewer to 963 more)
Nausea (	assessed w	vith: Dosage Reco	rd and Treatment	Emergent Syr	nptom Scale (D	OTES))	4		<b>!</b>		1
29 (1 study)	serious <sup>1</sup>	inconsistency indirectness serious <sup>2</sup> VERY LOW <sup>1,2</sup> (20%) (42.9%)				<b>RR 2.14</b> (0.66 to	Study po	opulation			
12 weeks		inconsistency		3011003		due to risk of bias, imprecision	(2070)	(42.378)	6.97)	200 per 1000	<b>228 more per 1000</b> (from 68 fewer to 1000 more)
										Moderate	
										200 per 1000	<b>228 more per 1000</b> (from 68 fewer to 1000 more)
Diarrhoe	<b>a</b> (assesse	ed with: Dosage R	ecord and Treatme	ent Emergent	Symptom Scale	e (DOTES))					
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		1/15 (6.7%)	3/14 (21.4%)	<b>RR 3.21</b> (0.38 to	Study po	opulation
12 weeks		inconsistency		3011003		due to risk of bias, imprecision	(0.770)	(21.470)	27.4)	67 per 1000	<b>147 more per 1000</b> (from 41 fewer to 1000 more)
				Moderat	e						
										67 per 1000	<b>148 more per 1000</b> (from 42 fewer to 1000 more)

29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		0/15 (0%)	2/14 (14.3%)	<b>RR 5.33</b> (0.28 to	Study po	opulation
12 weeks						due to risk of bias, imprecision			102.26)	0 per 1000	N/A
						Imprecision				Moderate	e
										0 per 1000	N/A
Decrease	ed appe	tite (assessed wi	th: Dosage Recor	d and Treatme	ent Emergent S	ymptom Scale (D	OTES))		<b>I</b>	1	
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		3/15 (20%)	2/14 (14.3%)	<b>RR 0.71</b> (0.14 to	Study po	opulation
12 weeks		inconsistency		Schous		due to risk of bias, imprecision	(2070)	(14.070)	3.66)	200 per 1000	58 fewer per 1000 (from 172 fewer to 532 more)
										Moderate 200 per 58 fewer per 1000	
										200 per 1000	<b>58 fewer per 1000</b> (from 172 fewer to 532 more)
Akathisia	<b>a</b> (assesse	d with: Dosage Re	cord and Treatme	I ent Emergent S	Symptom Scale	(DOTES))	1	· ·		1	1
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		0/15 (0%)	1/14 (7.1%)	<b>RR 3.2</b> (0.14 to	Study po	opulation
12 weeks		inconsistency	indirectriess	3611003		due to risk of bias, imprecision	(078)	(7.176)	72.62)	0 per 1000	N/A
						Imprecision				Moderate	e
										0 per 1000	N/A
Increase	d motor	activity (asse	ssed with: Dosage	e Record and	Treatment Eme	rgent Symptom S	cale (DO	TES))	,		
	serious <sup>1</sup>	no serious	no serious	very	undetected	000	3/15	2/14	RR 0.71	Study po	opulation
29 (1 study)	senous	inconsistency	indirectness	serious <sup>2</sup>		VERY LOW <sup>1,2</sup>	(20%)	(14.3%)	(0.14 to		

						bias, imprecision				1000	(from 172 fewer to 532 more)
										Moderat	e
										200 per 1000	58 fewer per 1000 (from 172 fewer to 532 more)
Tremor (a	assessed w	ith: Dosage Record	d and Treatment E	Emergent Sym	ptom Scale (D	OTES))					
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		1/15 (6.7%)	0/14 (0%)	<b>RR 0.36</b> (0.02 to	Study po	opulation
12 weeks						due to risk of bias, imprecision	(0.170)		8.07)	67 per 1000	43 fewer per 1000 (from 65 fewer to 471 more)
										Moderate	
										67 per 1000	<b>43 fewer per 1000</b> (from 66 fewer to 474 more)
Dizzines	S (assesse	d with: Dosage Re	cord and Treatme	nt Emergent S	Symptom Scale	(DOTES))	1	·		1	1
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		1/15 (6.7%)	0/14 (0%)	<b>RR 0.36</b> (0.02 to	Study po	opulation
12 weeks		inconsistency		301003		due to risk of bias, imprecision	(0.770)	(070)	8.07)	67 per 1000	<b>43 fewer per 1000</b> (from 65 fewer to 471 more)
										Moderat	9
										67 per 1000	43 fewer per 1000 (from 66 fewer to 474 more)
Exciteme	ent/agita	ation (assessed v	with: Dosage Reco	ord and Treatr	nent Emergent	Symptom Scale (	DOTES))		I	1	
29	serious <sup>1</sup>	no serious	no serious	very	undetected	<b>@</b> @@@	3/15	2/14	RR 0.71	Study po	pulation

(1 study) 12 weeks		inconsistency indirectness serious <sup>2</sup> VERY LOW <sup>1,2</sup> (20%) (14.3%) due to risk of bias, imprecision		(14.3%)	(0.14 to 3.66)	200 per 1000	58 fewer per 1000 (from 172 fewer to 532 more)				
										Moderat	e
										200 per 1000	<b>58 fewer per 1000</b> (from 172 fewer to 532 more)
Depress	ed affec	<b>t</b> (assessed with: I	Dosage Record ar	nd Treatment E	Emergent Sym	ptom Scale (DOTE	ES))		- 1		1
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		0/15 (0%)	1/14 (7.1%)	<b>RR 3.2</b> (0.14 to	Study po	opulation
12 weeks						due to risk of bias, imprecision			72.62)	0 per 1000	N/A
										Moderate	9
										0 per 1000	N/A
Nasal co	ngestio	<b>n</b> (assessed with:	Dosage Record a	Ind Treatment	Emergent Sym	I optom Scale (DOT	ES))				<u> </u>
29 (1 study)	serious <sup>1</sup>	no serious	no serious	very serious	undetected		6/15	4/14	RR 0.71	Study po	pulation
12 weeks		inconsistency	indirectness			due to risk of bias, imprecision	(40%)	(28.6%)	(0.25 to 2.01)	400 per 1000	<b>116 fewer per 1000</b> (from 300 fewer to 404 more)
										Moderate	9
										400 per 1000	<b>116 fewer per 1000</b> (from 300 fewer to 404 more)
Increase	d saliva	tion (assessed v	vith: Dosage Reco	ord and Treatm	ent Emergent	Symptom Scale ([	DOTES))				
	serious <sup>1</sup>	no serious	no serious	very serious <sup>2</sup>	undetected		2/15 (13.3%)	0/14 (0%)	<b>RR 0.21</b> (0.01 to	Study po	opulation
29 (1 study)		inconsistency	indirectness	sorious			112 2021				

						bias, imprecision				1000	(from 132 fewer to 412 more)
										Moderate	3
										133 per 1000	<b>105 fewer per 1000</b> (from 132 fewer to 411 more)
Sweating	) (assessed	d with: Dosage Rec	cord and Treatmer	nt Emergent S	ymptom Scale	(DOTES))					
29 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		1/15 (6.7%)	0/14 (0%)	<b>RR 0.36</b> (0.02 to	Study po	pulation
2 weeks						due to risk of bias, imprecision		. ,	8.07)	67 per 1000	<b>43 fewer per 1000</b> (from 65 fewer to 471
						Imprecision					more)
						Imprecision				Moderate	, 

## **1.33.5** Adverse events associated with antipsychotics

## Adverse events associated with antipsychotics versus placebo

			Quality ass	essment	Summary of Findings						
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study With	event rates (%) With Adverse events associated	Relative effect (95% CI)	Risk	Dated absolute effects Risk difference with Adverse events associated with
Any side	offoct	Arininrazok	halonerid	lol or rispe	ridone) (acco	and with: Non evetor		with antipsychotics			antipsychotics (95% Cl) re or study-specific report)

528 (5 studies)	serious <sup>1</sup>	serious <sup>2</sup>	no serious indirectness	no serious imprecision	reporting bias strongly		130/195 283/333 (66.7%) (85%)	<b>RR 1.27</b> (1.14 to	Study	population
6-12 weeks					suspected <sup>3</sup>	due to risk of bias, inconsistency, publication bias		1.42)	667 per 1000	<b>180 more per 1000</b> (from 93 more to 280 more)
									Mode	rate
									720 per 1000	<b>194 more per 1000</b> (from 101 more to 302 more)
Any side	effect	(Aripiprazol	<b>e)</b> (assessed wi	th: Study-specif	ic report of adver	rse events)		I	_ <b>I</b>	Į
313 (2 studies)	serious1	ct (Aripiprazole) (assessed with: Study-specific report of adverse events)         us <sup>1</sup> no serious indirectness       serious <sup>4</sup> reporting bias strongly suspected <sup>3</sup> \$\$\$\$\mathcal{O} \overline{O} \overline{O} \$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$			<b>RR 1.23</b> (1.08 to	Study	v population			
8 weeks		Inconsistency		indirectness strongly suspected <sup>3</sup> VERY LOW <sup>1,3,4</sup> (72.3%) (88.7%) due to risk of bias, imprecision, publication bias	1.41)	723 per 1000	<b>166 more per 1000</b> (from 58 more to 296 more)			
									Mode	rate
									723 per 1000	<b>166 more per 1000</b> (from 58 more to 296 more)
Any side	effect	(Haloperido	) (assessed with	n: Outcome me	asure not reporte	ed)				
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		5/20 16/20 (25%) (80%)	<b>RR 3.2</b> (1.45 to	Study	v population
12 weeks		Inconsistency	Indirectriess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(23%) (80%)	7.05)	250 per 1000	<b>550 more per 1000</b> (from 113 more to 1000 more)
						Mode	rate			
									250 per 1000	<b>550 more per 1000</b> (from 113 more to 1000 more)
Any side	effect	(Risperidon	<b>e)</b> (assessed wi	th: Non-system	atic assessment	or study-specific outco	ome measure )		<u> </u>	1

175 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		52/74 (70,3%)	79/101 (78.2%)	<b>RR 1.17</b> (0.98 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.070)	(101270)	1.39)	703 per 1000	<b>119 more per 1000</b> (from 14 fewer to 274 more)
										Mode	ate
										697 per 1000	<b>118 more per 1000</b> (from 14 fewer to 272 more)
Disconti	nuation	due to adve	erse events	(Aripipraz	ole)) (assessed	d with: Study-specific r	eport)		ł		4
98 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		3/51 (5.9%)	5/47 (10.6%)	<b>RR 1.81</b> (0.46 to	Study	population
1 study) weeks				suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	()	( )	7.16)	59 per 1000	<b>48 more per 1000</b> (from 32 fewer to 362 more)	
										Mode	ate
										59 per 1000	48 more per 1000 (from 32 fewer to 363 more)
Disconti	nuation	due to droc	oling (Aripip	orazole) (ass	sessed with: Stud	ly-specific report)					
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		0/51 (0%)	3/165 (1.8%)	<b>RR 2.19</b> (0.12 to	Study	population
3 weeks		lineerisisteriey			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0,0)	(1.070)	41.76)	0 per 1000	N/A
										Mode	ate
										0 per 1000	N/A
Disconti	nuation	due to seda	ation (Aripi	prazole) (as	sessed with: Stur	l	ļ		<u> </u>	1	<u> </u>

216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		0/51 (0%)	7/165 (4.2%)	<b>RR 4.7</b> (0.27 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			80.88)	0 per 1000	N/A
										Mode	rate
										0 per 1000	N/A
Disconti	nuation	due to tren	or (Aripipr	azole) (asses	sed with: Study-	specific report)	1				
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		0/51 (0%)	4/165 (2.4%)	<b>RR 2.82</b> (0.15 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0,0)	(=::,0)	51.5)	0 per 1000	N/A
										Mode	rate
										0 per 1000	N/A
Clinicall	y releva	nt (>=7%) w	veight gain (	(Aripiprazo	le) (assessed v	l <i>v</i> ith: Weight assessme	nt)				
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		7/101 (6.9%)	56/212 (26.4%)	<b>RR 3.80</b> (1.79 to	Study	population
8 weeks		inconsistency	Indirectriess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.978)	(20.476)	8.05)	69 per 1000	<b>194 more per 1000</b> (from 55 more to 489 more)
										Mode	rate
										60 per 1000	<b>168 more per 1000</b> (from 47 more to 423 more)
Weight g	gain (Ar	ipiprazole o	r risperidor	1e) (assessed v	with: Non-system	atic assessment, stud	y-specific	outcome measure	or study-sp	ecific re	port)
391 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		4/125 (3.2%)	18/266 (6.8%)	<b>RR 2.43</b> (0.85 to	Study	population
6-8 weeks		noonoioionoy			suspected <sup>3</sup>	due to risk of bias,	(0.270)	(0.070)	(0.83 to 6.98)	32	46 more per 1000

						imprecision, publication bias				per 1000	(from 5 fewer to 191 more)
										Mode	rate
										26 per 1000	<b>37 more per 1000</b> (from 4 fewer to 155 more)
Weight g	jain (Ari	ipiprazole) (a	ssessed with: S	tudy-specific rep	port)	1	1		1		
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		1/51 (2%)	7/165 (4.2%)	<b>RR 2.16</b> (0.27 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(270)	(,)	17.17)	20 per 1000	23 more per 1000 (from 14 fewer to 317 more)
					Moderate						
									20 pe	20 per 1000	23 more per 1000 (from 15 fewer to 323 more)
Weight g	jain (Ris	speridone) (a	I Issessed with: N	l on-systematic a	assessment or st	l udy-specific outcome n	neasure )		<u> </u>	1	
175 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		3/74 (4.1%)	11/101 (10.9%)	<b>RR 2.55</b> (0.75 to	Study	population
6-8 weeks		inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(4.170)	(10.070)	8.66)	41 per 1000	<b>63 more per 1000</b> (from 10 fewer to 311 more)
										Mode	rate
										41 per 1000	64 more per 1000 (from 10 fewer to 314 more)
Weight g	jain (Ari	ipiprazole o	r risperidon	e) (measured	with: Weight ass	essment (in kg); Better	indicated	d by lower values)	1		1
541 (6 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias strongly	⊕⊕⊝⊝ LOW <sup>1,3</sup>	206	335	-		The mean weight gain (aripiprazole or risperidone)

6-26 weeks					suspected <sup>3</sup>	due to risk of bias, publication bias					in the intervention groups was <b>0.69 standard deviations</b> <b>higher</b> (0.51 to 0.88 higher)
Weight g	ain (Ari	i <b>piprazole)</b> (n	neasured with: V	Veight gain (in k	g); Better indicat	ed by lower values)					
216 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>6</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,6</sup> due to risk of bias, imprecision, publication bias	51	165	-		The mean weight gain (aripiprazole) in the intervention groups was <b>0.48 standard deviations</b> higher (0.16 to 0.8 higher)
Weight g	ain (Ris	speridone) (n	neasured with: V	Veight gain (in k	g); Better indicat	ed by lower values)	•		•		
325 (5 studies) 6-26 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>6</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,6</sup> due to risk of bias, imprecision, publication bias	155	170	-		The mean weight gain (risperidone) in the intervention groups was <b>0.8 standard deviations</b> higher (0.57 to 1.03 higher)
BMI char	nge (Ari	<b>piprazole)</b> (n	neasured with: B	MI change (kg/r	n-squared); Bett	er indicated by lower va	alues)		<u> </u>		
216 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,7</sup> due to risk of bias, imprecision, publication bias	51	165	-		The mean bmi change (aripiprazole) in the intervention groups was <b>0.31 standard deviations</b> higher (0 to 0.63 higher)
Clinically	/ releva	nt prolactin	elevation (a	above upp	er limit of n	ormal for age &	gende	er) (Aripiprazo	ole) (asses	sed wit	h: Laboratory assessment)
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		5/101 (5%)	1/212 (0.5%)	<b>RR 0.19</b> (0.04 to	Study	population
8 weeks		· · · · · · · · · · · · · · · · · · ·			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	x/		0.98)	50 per 1000	40 fewer per 1000 (from 1 fewer to 48 fewer)

										Mode	ate
										50 per 1000	41 fewer per 1000 (from 1 fewer to 48 fewer)
Prolactin	conce	ntration (ng	/ml) (Rispe	ridone) (mea	sured with: Labo	oratory assessment; Be	etter indica	ated by lower val	ues)		•
124 (2 studies) 8-24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>6</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,6</sup> due to risk of bias, imprecision	64	60	-		The mean prolactin concentration (ng/ml) (risperidone) in the intervention groups was <b>1.8 standard deviations</b> higher (1.38 to 2.22 higher)
Any treat	tment-e	emergent ex	trapyramid	al sympton	n (Aripipraz	ole) (assessed with:	Study-spe	ecific report of a	dverse event)		
	serious <sup>1</sup>	no serious inconsistency		very serious <sup>5</sup>	reporting bias strongly		10/101 (9.9%)	44/212 (20.8%)	<b>RR 1.89</b> (0.98 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			3.67)	99 per 1000	88 more per 1000 (from 2 fewer to 264 more
										Mode	ate
										99 per 1000	88 more per 1000 (from 2 fewer to 264 more
Extrapyra	amidal	symptoms (	Risperidon	I I <b>e)</b> (measured v	l with: Abnormal Ir	I voluntary Movements	Scale (Al	MS): Total; Bette	er indicated by	lower va	alues)
92 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>6</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,6</sup> due to risk of bias, imprecision, publication bias	34	58	-		The mean extrapyramidal symptoms (risperidone) in the intervention groups wa <b>0.46 standard deviations</b> <b>lower</b> (0.89 to 0.03 lower)

313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly		0/101 (0%)	13/212 (6.1%)	<b>RR 6.02</b> (0.7 to	Study population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		<b>`</b> ,	51.91)	0 per N/A 1000
						publication bias				Moderate
										0 per N/A 1000
Fasting	glucose	e (mg/dL) ch	ange score	(Risperido	<b>ne)</b> (measured	with: Laboratory asse	essment; E	Better indicated I	by lower values	;)
68 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,7</sup> due to risk of bias, imprecision, publication bias	22	46	N/A	N/A The mean fasting glucose (mg/dl) change score (risperidone) in the intervention groups was 0.02 standard deviations higher (0.49 lower to 0.53 higher)
Fasting	glucose	e (=>115 mg/	/dL) - Aripip	orazole (asse	ssed with: Labor	atory assessment)	1		<b>I</b>	<b>↓</b>
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		0/101 (0%)	2/212 (0.9%)	<b>RR 1.57</b> (0.08 to	Study population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0,0)	(0.070)	32.11)	0 per N/A 1000
						publication bias				Moderate
										0 per N/A 1000
Fasting t	triglyce	rides (=>120	) mg/dL for	females or	160 mg/dL	for males) (Ari	piprazo	<b>ble)</b> (assessed	I with: Laborato	ry assessment)
313 (2 studies) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly suspected <sup>3</sup>	$\bigcirc \bigcirc \bigcirc \bigcirc$ <b>VERY LOW</b> <sup>1,3,5</sup> due to risk of bias,	7/101 (6.9%)	23/212 (10.8%)	<b>RR 1.8</b> (0.74 to 4.35)	Study population 69 55 more per 1000
						imprecision, publication bias				per (from 18 fewer to 232 1000 more)
	1	1	1	1			1		1	· · · ·

										70 per 1000	<b>56 more per 1000</b> (from 18 fewer to 234 more)
Insulin re	esistan	ce (HOMA-IF	R) change s	core (Risp	eridone) (me	asured with: Laborator	y assess	ment; Better indicate	ed by lower	values)	
65 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,7</sup> due to risk of bias, imprecision, publication bias	22	43	N/A	N/A	The mean insulin resistance (homa-ir) change score (risperidone) in the intervention groups was <b>0.12 standard deviations</b> <b>lower</b> (0.63 lower to 0.4 higher)
Leptin (n	ng/L) cł	nange score	(Risperido	<b>ne)</b> (measured	with: Laboratory	assessment; Better in	dicated I	oy lower values)			
104 (2 studies) 8-24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>6</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,6</sup> due to risk of bias, imprecision	52	52	N/A	N/A	The mean leptin (mg/l) change score (risperidone) in the intervention groups was <b>0.64 standard deviations</b> higher (0.24 to 1.04 higher)
Diastolic	blood	pressure (m	m Hg) char	nge scores	(Risperido	ne) (measured with: P	hysical e	exam; Better indicate	ed by lower	values)	
78 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,7</sup> due to risk of bias, imprecision, publication bias	38	40	N/A	N/A	The mean diastolic blood pressure (mm hg) change scores (risperidone) in the intervention groups was <b>0.15 standard deviations</b> higher (0.29 lower to 0.6 higher)
Systolic	blood p	pressure (mr	n Hg) chan	ge scores	(Risperidon	(measured with: Pr	nysical ex	am; Better indicated	d by lower v	alues)	
78 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,7</sup> due to risk of bias, imprecision, publication bias	38	40	N/A	N/A	The mean systolic blood pressure (mm hg) change scores (risperidone) in the intervention groups was <b>0.44 standard deviations</b>

											higher (0.01 lower to 0.89 higher)
Pulse (bp	om) cha	inge score (	Risperidon	e) (measured v	with: Physical exa	am; Better indicated by	lower val	ues)			
78 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>6</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,6</sup> due to risk of bias, imprecision, publication bias	38	40	N/A	N/A	The mean pulse (bpm) change score (risperidone) in the intervention groups was <b>0.7 standard deviations</b> higher (0.24 to 1.15 higher)
Somnole study-specific		•	ripiprazole	or risperid	<b>lone)</b> (assesse	d with: Non-systematic	c assessn	nent, study-specific	outcome m	easure,	study-specific report or
588 (5 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		14/226 (6.2%)		<b>RR 4.81</b> (2.85 to	Study	population
6-8 weeks		incondictorey			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.270)		8.13)	62 per 1000	<b>236 more per 1000</b> (from 115 more to 442 more)
										Mode	rate
										40 per 1000	<b>152 more per 1000</b> (from 74 more to 285 more)
Somnole	nce/Dr	owsiness (A	ripiprazole	(assessed with	h: Study-specific	report of adverse ever	nt)				
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		4/101 (4%)	22/212 (10.4%)	<b>RR 2.98</b> (1.07 to	Study	population
8 weeks		inconsistency	indirectress		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(470)	(10.476)	8.31)	40 per 1000	78 more per 1000 (from 3 more to 290 more)
										Mode	rate
										40 per 1000	<b>79 more per 1000</b> (from 3 more to 292 more)

275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		10/125 (8%)	60/150 (40%)	<b>RR 5.71</b> (3.08 to	Study	population
6-8 weeks		Inconsistency	indirectriess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0 %)	(4078)	10.6)	80 per 1000	<b>377 more per 1000</b> (from 166 more to 768 more)
										Mode	rate
										77 per 1000	<b>363 more per 1000</b> (from 160 more to 739 more)
Fatigue ( checklist)	Aripira	zole or rispe	eridone) (ass	essed with: Nor	n-systematic asse	essment, study-specifi	c outcome	e measure, study	-specific repor	t or stuc	ly-specific side effect
588 (5 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		17/226 (7.5%)	69/362 (19.1%)	<b>RR 3.16</b> (1.95 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(,		(1.95 to 5.13)	75 per 1000	<b>162 more per 1000</b> (from 71 more to 311 more)
										Mode	rate
										26 per 1000	<b>56 more per 1000</b> (from 25 more to 107 more)
Fatigue (	Aripipr	azole) (assess	ed with: Study-s	pecific report of	adverse event)						
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		2/101 (2%)	35/212 (16.5%)	<b>RR 8.33</b> (2.11 to	Study	population
8 weeks		inconciency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(270)	(10.075)	32.9)	20 per 1000	<b>145 more per 1000</b> (from 22 more to 632 more)
										Mode	rate
										20 per	<b>147 more per 1000</b> (from 22 more to 638 more)

										1000		
Fatigue	(Risperi	i <b>done)</b> (assesse	ed with: Non-sys	tematic assessr	nent, study-spec	ific outcome measure,	or study-	specific side effe	ect checklist)	1		
275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		15/125 (12%)	34/150 (22.7%)	<b>RR 2.25</b> (1.38 to	Study	population	
6-8 weeks		Inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(1270)	(22.170)	3.68)	120 per 1000	<b>150 more per 1000</b> (from 46 more to 322 more)	
										Mode	rate	
										26 per 1000	<b>32 more per 1000</b> (from 10 more to 70 more)	
Lethargy	/ (Aripip	prazole) (asses	ssed with: Study	specific report o	of adverse event	)	1	·		1	1	
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		0/51 (0%)	10/165 (6.1%)	<b>RR 6.58</b> (0.39 to	Study	population	
8 weeks		lineensisteney			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0,0)	) (6.1%)		110.35)	0 per 1000	N/A
						publication bias				Mode	rate	
										0 per 1000	N/A	
Sedatior	n (Aripip	orazole or ris	speridone) (	assessed with:	Non-systematic	assessment or study-s	pecific re	port)		1	1	
409 (2. studies)	serious <sup>1</sup>	no serious	no serious	serious <sup>4</sup>	reporting bias		4/136	53/273	RR 4.94	Study	population	
(3 studies) 6-8 weeks		inconsistency	indirectness		strongly suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2.9%)	(19.4%)	(1.94 to 12.58)	29 per 1000	<b>116 more per 1000</b> (from 28 more to 341 more)	
										Mode	rate	
										20 per	<b>79 more per 1000</b> (from 19 more to 232 more)	

							]			1000	
Sedation	(Aripir	azole) (assesse	ed with: Study-sp	Decific report of	adverse event)		1			1	
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		4/101 (4%)	44/212 (20.8%)	<b>RR 4.25</b> (1.57 to	Study	population
8 weeks		inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(+,0)	(20.070)	11.51)	40 per 1000	<b>129 more per 1000</b> (from 23 more to 416 more)
										Moder	ate
										39 per 1000	<b>127 more per 1000</b> (from 22 more to 410 more)
Sedation	(Rispe	ridone) (asses	sed with: Non-s	ystematic asses	ssment)	1	1		-	J	
96 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly		0/35 (0%)	9/61 (14.8%)	<b>RR 11.03</b> (0.66 to	Study	population
6 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0,0)	(110,0)	183.98)	0 per 1000	N/A
										Moder	ate
										0 per 1000	N/A
	-	ry tract infect side effect checkli	• • •	orazole or I	risperidone	(assessed with: Non	-systemat	tic assessment, stu	dy-specific o	outcome	e measure, study-specific
588 (5 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly		14/226 (6.2%)	30/362 (8.3%)	<b>RR 1.78</b> (0.97 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		()	3.25)	62 per 1000	<b>48 more per 1000</b> (from 2 fewer to 139 more)
										Moder	ate
										39 per	30 more per 1000

										1000	(from 1 fewer to 88 more)
Upper res	spirato	ry tract infed	ction (Aripi	prazole) (as	sessed with: Stud	dy-specific report of adv	verse eve	ent)		1	
313 (2 studies)	serious <sup>1</sup>	serious <sup>2</sup>	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		5/101 (5%)	6/212 (2.8%)	<b>RR 0.65</b> (0.16 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, inconsistency, imprecision, publication bias		< <i>'</i>	2.58)	50 per 1000	<b>17 fewer per 1000</b> (from 42 fewer to 78 more)
										Mode	rate
										50 per 1000	<b>18 fewer per 1000</b> (from 42 fewer to 79 more)
Upper res	spirato	ry tract infed	ction (Rispe	eridone) (as	sessed with: Non	-systematic assessme	nt, study-	specific outcome m	easure, or s	study-sp	becific side effect checklist)
275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,4</sup>	9/125 (7.2%)	24/150 (16%)	<b>RR 2.45</b> (1.21 to	Study	population
6-8 weeks		,				due to risk of bias, imprecision			4.96)	72 per 1000	<b>104 more per 1000</b> (from 15 more to 285 more)
										Mode	rate
										39 per 1000	<b>57 more per 1000</b> (from 8 more to 154 more)
Rhinitis/r	hinorrh	nea (Aripipra	zole or ris	peridone) (a	assessed with: St	udy-specific outcome r	neasure	or study-specific rep	port)	•	1
295 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		5/90 (5.6%)	19/205 (9.3%)	<b>RR 2.62</b> (1.02 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	()	()	6.77)	56 per 1000	<b>90 more per 1000</b> (from 1 more to 321 more)
										Mode	rate
										61	99 more per 1000

										per 1000	(from 1 more to 352 more)
Rhinitis/	/rhinorrl	hea (Aripipra	azole) (assess	sed with: Study-s	specific report of	adverse event)					
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		1/51 (2%)	8/165 (4.8%)	<b>RR 2.47</b> (0.32 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(270)	(11070)	19.3)	20 per 1000	<b>29 more per 1000</b> (from 13 fewer to 359 more)
										Mode	rate
										20 per 1000	29 more per 1000 (from 14 fewer to 366 more)
Rhinitis/	rhinorrl	hea (Risperi	done) (assess	sed with: Study-	specific outcome	measure)	-1			<u> </u>	1
79 (1 study)					reporting bias strongly		4/39	11/40 (27.5%)	<b>RR 2.68</b> (0.93 to	Study	population
8 weeks		Inconsistency	Indirectiless		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.3%)	(21.376)	7.71)	103 per 1000	<b>172 more per 1000</b> (from 7 fewer to 688 more)
										Mode	rate
										103 per 1000	173 more per 1000 (from 7 fewer to 691 more)
Nasal co	ongestic	on (Aripirazo	le or risper	r <b>idone)</b> (asse	essed with: Study	-specific report or stud	dy-specific	side effect che	ecklist)	<u> </u>	1
413 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected		22/152 (14.5%)		<b>RR 1.42</b> (0.92 to	Study	population
8 weeks						due to risk of bias, imprecision	(,	()	2.19)	145 per 1000	61 more per 1000 (from 12 fewer to 172 more)
	1			1		1	1				

										20 per 1000	8 more per 1000 (from 2 fewer to 24 more)
Nasal co	ongestic	on (Aripipraz	ole) (assessed	with: Study-sp	ecific report of ac	dverse event)					
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		2/101 (2%)	9/212 (4.2%)	<b>RR 2.37</b> (0.52 to	Study	population
3 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(= /0)	(	10.77)	20 per 1000	27 more per 1000 (from 10 fewer to 193 more)
										Mode	rate
										20 per 1000	<b>27 more per 1000</b> (from 10 fewer to 195 more)
Nasal co	ongestic	on (Risperido	one) (assessed	with: Study-sp	ecific side effect	checklist)			I		
_	serious <sup>1</sup>			very serious <sup>5</sup>	undetected		20/51 (39.2%)	25/49 (51%)	<b>RR 1.3</b> (0.84 to	Study	population
weeks						due to risk of bias, imprecision	(00.270)	(0170)	2.02)	392 per 1000	<b>118 more per 1000</b> (from 63 fewer to 400 more)
										Mode	rate
										392 per 1000	<b>118 more per 1000</b> (from 63 fewer to 400 more)
Nasopha	aryngitis	s (Aripiprazo	ole or rispe	<b>idone)</b> (asse	essed with: Non-	systematic assessmen	nt or study-	specific report)	P		•
409 3 studies) 5-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision, publication bias	7/136 (5.1%)	24/273 (8.8%)	<b>RR 1.65</b> (0.68 to 3.97)	Study 51 per 1000	<b>33 more per 1000</b> (from 16 fewer to 153 more)
										Mode	

										57 per 1000	<b>37 more per 1000</b> (from 18 fewer to 169 more)
Nasopha	aryngitis	s (Aripiprazo	<b>ble)</b> (assessed	with: Study-spe	cific report of adv	verse event)					
313 (2 studies)	serious <sup>1</sup>	no serious inconsistencv	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly			18/212 (8.5%)	<b>RR 1.61</b> (0.55 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		(0.070)	4.71)	50 per 1000	<b>30 more per 1000</b> (from 22 fewer to 184 more)
										Mode	rate
										50 per 1000	<b>31 more per 1000</b> (from 22 fewer to 186 more)
Nasopha	aryngitis	s (Risperido	ne) (assessed	with: Non-syste	matic assessme	nt)			<b>I</b>		
96 (1 study)	serious <sup>1</sup>			very serious <sup>5</sup>	reporting bias strongly			6/61 (9.8%)	<b>RR 1.72</b> (0.37 to	Study	population
6 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.170)	(0.070)	8.07)	57 per 1000	41 more per 1000 (from 36 fewer to 404 more)
										Mode	rate
										57 per 1000	<b>41 more per 1000</b> (from 36 fewer to 403 more)
Nose ble	ed (Ari	piprazole or	risperidon	<b>e)</b> (assessed w	ith: Non-systema	atic assessment or stu	dy-specific	report)		1	
	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias			7/226	<b>RR 3.2</b> (0.4 to	Study	population
6-8 weeks		inconsistency indirectness strongly suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0%) (3.1%) S,	25.77)	0 per 1000	N/A				
						publication bias				Mode	rate

										0 per 1000	N/A
Nose ble	eed (Ari	piprazole) (a	ssessed with: St	udy-specific rep	ort of adverse ev	vent)					
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		0/51 (0%)	5/165 (3%)	<b>RR 3.45</b> (0.19 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0,0)	(070)	61.28)	0 per 1000	N/A
						publication bias				Mode	rate
										0 per 1000	N/A
Nose ble	ed (Ris	peridone) (a	ssessed with: No	n-systematic as	ssessment)				ł		1
96 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		0/35 (0%)	2/61 (3.3%)	<b>RR 2.9</b> (0.14 to	Study	population
6 weeks				suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	()	()	58.81)	0 per 1000	N/A	
						publication blas				Mode	rate
										0 per 1000	N/A
Coughin	ng (Aripi	prazole or r	isperidone)	(assessed with	I i: Non-systematic	c assessment, study-s	pecific out	come measure o	r study-specif	ic report	t)
391 (3 studies)	serious1	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly		6/125 (4.8%)	18/266 (6.8%)	<b>RR 1.63</b>	Study	population
5-8 weeks		inconsistency	Indirectiless		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(4.070)	(0.078)	<b>RR 1.63</b> (0.65 to 4.12)	48 per 1000	<b>30 more per 1000</b> (from 17 fewer to 150 more)
										Mode	rate
										39 per 1000	25 more per 1000 (from 14 fewer to 122 more)

216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		2/51 (3.9%)	12/165 (7.3%)	<b>RR 1.85</b> (0.43 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.070)	(1.070)	8.01)	39 per 1000	<b>33 more per 1000</b> (from 22 fewer to 275 more)
										Mode	rate
Coughing (F										39 per 1000	33 more per 1000 (from 22 fewer to 273 more)
Coughin	ig (Risp	eridone) (ass	essed with: Non	-systematic asse	essment or study	-specific outcome me	asure)				1
175 (2 studies)	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias strongly		4/74 (5.4%)	6/101 (5.9%)	<b>RR 1.46</b> (0.45 to	Study	population
(2 studies) 6-8 weeks		inconsistency indired		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.170)	(0.070)	4.79)	54 per 1000	<b>25 more per 1000</b> (from 30 fewer to 205 more)	
										Mode	rate
									51 per 1000	23 more per 1000 (from 28 fewer to 193 more)	
Increase side effect c		tite (Aripipra	azole or ris	peridone) (a	ssessed with: No	on-systematic assessr	ment, study	y-specific outco	ome measure, s	tudy-spe	ecific report or study-specific
588 (5 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		15/226 (6.6%)	64/362 (17.7%)	<b>RR 3.01</b> (1.73 to	Study	population
6-8 weeks			indirectness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.070)	(,0)	5.24)	66 per 1000	<b>133 more per 1000</b> (from 48 more to 281 more)
										Mode	rate
	1			1						57	115 more per 1000

										1000	
Increase	d appet	tite (Aripipra	zole) (assesse	ed with: Study-s	specific report of	adverse event)	1				
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		7/101 (6.9%)	27/212 (12.7%)	<b>RR 2.11</b> (0.89 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		(,5)	5.01)	69 per 1000	77 more per 1000 (from 8 fewer to 278 more)
										Mode	rate
Incroased										70 per 1000	78 more per 1000 (from 8 fewer to 281 more)
Increase	d appet	tite (Risperio	<b>lone)</b> (assesse	ed with: Non-sy	stematic assessr	nent, study-specific ou	utcome me	asure, or study-	specific side e	ffect ch	ecklist)
275 (3 studies)	serious1	no serious	no serious	serious <sup>4</sup>	reporting bias strongly		8/125 (6.4%)	37/150 (24.7%)	<b>RR 3.83</b> (1.84 to	Study	population
6-8 weeks		inconsistency indir	indirectness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(01.70)	( , 3)	8.01)	64 per 1000	<b>181 more per 1000</b> (from 54 more to 449 more
										Mode	rate
										57 per 1000	<b>161 more per 1000</b> (from 48 more to 400 more)
Decrease	ed appe	etite (Aripipr	azole or ris	peridone)	assessed with: S	Study-specific report of	r study-spe	ecific side effect	checklist)		
316 (2 studies)	serious <sup>1</sup>	serious <sup>2</sup>	no serious indirectness	very serious <sup>5</sup>	undetected		6/102 (5.9%)	16/214 (7.5%)	<b>RR 1.43</b> (0.5 to	Study	population
8 weeks						due to risk of bias, inconsistency, imprecision		<b>、</b>	4.13)	59 per 1000	25 more per 1000 (from 29 fewer to 184 more)
										Mode	rate
										59	25 more per 1000

										per 1000	(from 30 fewer to 185 more)
Decreas	ed appe	etite (Aripipr	azole) (asses	sed with: Study	specific report o	f adverse event)					
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		1/51 (2%)	13/165 (7.9%)	<b>RR 4.02</b> (0.54 to	Study	population
8 weeks		Inconsistency	Indirectiless		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(276)	(7.9%)	29.98)	20 per 1000	<b>59 more per 1000</b> (from 9 fewer to 568 more)
										Mode	rate
		d appetite (Risperi	idono) (concord with							20 per 1000	60 more per 1000 (from 9 fewer to 580 more)
Decreas	ed appe	etite (Risperi	idone) (asses	sed with: Study	specific side effe	ect checklist)	-		<b>I</b>		
100 (1 study)	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	undetected		5/51 (9.8%)	3/49 (6.1%)	<b>RR 0.62</b> (0.16 to	Study	population
• • •			stency indirectness			-	(9.6%)	(0.1%)	,		
8 weeks						due to risk of bias, imprecision			2.47)	98 per 1000	<b>37 fewer per 1000</b> (from 82 fewer to 144 more)
8 weeks									2.47)	per	(from 82 fewer to 144 more)
8 weeks									2.47)	per 1000	(from 82 fewer to 144 more)
Abdomi	-	I/Stomachac	he (Aripipr	azole or ris	speridone) (	imprecision	vstematic a	assessment, stu		per 1000 Mode 98 per 1000	(from 82 fewer to 144 more) rate 37 fewer per 1000 (from 82 fewer to 144 more)
Abdomi	-		he (Aripipr	azole or ris	peridone) (	imprecision		assessment, stu 23/315 (7.3%)		per 1000 Mode 98 per 1000	(from 82 fewer to 144 more) rate 37 fewer per 1000 (from 82 fewer to 144 more)
Abdomi or study-spe 491	ecific side e	ffect checklist)	no serious	-	·	imprecision assessed with: Non-sy ⊕⊖⊖⊝	13/176	23/315	udy-specific out	per 1000 Mode 98 per 1000	(from 82 fewer to 144 more) rate 37 fewer per 1000 (from 82 fewer to 144 more) easure, study-specific repor

										48 per 1000	<b>17 more per 1000</b> (from 15 fewer to 79 more)
Abdomir	nal pain	/Stomachac	he (Aripipr	azole) (asses	sed with: Study-	specific report of adve	rse event)				
216 (1. study)	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias		1/51 (2%)	7/165	<b>RR 2.16</b> (0.27 to	Study	population
(1 study) 8 weeks		inconsistency	indirectness		strongly suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2%)	(4.2%)	17.17)	20 per 1000	23 more per 1000 (from 14 fewer to 317 more)
										Moder	rate
										20 per 1000	23 more per 1000 (from 15 fewer to 323 more)
Abdomir	nal pain	/Stomachac	he (Risperi	done) (asses	sed with: Non-sy	rstematic assessment,	study-spe	ecific outcome r	measure, or stud	dy-speci	fic side effect checklist)
275 (3 studies)	serious <sup>1</sup>	serious <sup>2</sup>	no serious indirectness	very serious <sup>5</sup>	undetected			16/150 (10.7%)	<b>RR 1.25</b> (0.61 to	Study	population
6-8 weeks			Indirectiless			due to risk of bias, inconsistency, imprecision	(3.078)	(10.776)	2.54)	96 per 1000	24 more per 1000 (from 37 fewer to 148 more)
										Moder	ate
										Moder 77 per 1000	<b>19 more per 1000</b> (from 30 fewer to 119 more)
Abdomir	nal disc	comfort (Risp	peridone) (as	ssessed with: No	on-systematic as	sessment)				77 per	<b>19 more per 1000</b> (from 30 fewer to 119
96	nal disc	no serious	no serious	ssessed with: No	reporting bias	$\oplus \Theta \Theta \Theta$	3/35 (8,6%)	0/61	RR 0.08	77 per 1000	<b>19 more per 1000</b> (from 30 fewer to 119
			1		-		3/35 (8.6%)	0/61 (0%)	<b>RR 0.08</b> (0 to 1.56)	77 per 1000	<b>19 more per 1000</b> (from 30 fewer to 119 more)

										86 per 1000	<b>79 fewer per 1000</b> (from 86 fewer to 48 more)
Vomiting checklist)	(Aripip	orazole or ris	speridone) (	assessed with:	Non-systematic	assessment, study-spe	cific outco	ome measure, stud	ly-specific r	eport or	study-specific side effect
588 (5 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly	⊕⊖⊝⊖ VERY LOW <sup>1,3,5</sup>	26/226 (11.5%)	55/362 (15.2%)	<b>RR 1.5</b> (0.97 to	Study	population
6-8 weeks		inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(11.570)	(13.270)	2.34)	115 per 1000	58 more per 1000 (from 3 fewer to 154 more)
										Mode	rate
										78 per 1000	<b>39 more per 1000</b> (from 2 fewer to 105 more)
Vomiting	(Aripip	orazole) (asses	ssed with: Study	-specific report	of adverse event	)					
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		6/101 (5.9%)	29/212 (13.7%)	<b>RR 2.19</b> (0.95 to	Study	population
8 weeks		incondictoricy			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.070)	(10.170)	5.03)	59 per 1000	71 more per 1000 (from 3 fewer to 239 more)
										Mode	rate
										59 per 1000	70 more per 1000 (from 3 fewer to 238 more)
Vomiting	(Rispe	ridone) (asses	ssed with: Non-s	ystematic asses	ssment, study-sp	ecific outcome measur	e, or study	y-specific side effe	ct checklist)	1	1
275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected		20/125 (16%)	26/150 (17.3%)	<b>RR 1.23</b> (0.74 to	Study	population
6-8 weeks		meenoloconoy				due to risk of bias, imprecision		(	2.07)	160 per 1000	<b>37 more per 1000</b> (from 42 fewer to 171 more)

										Mode	rate
										154 per 1000	<b>35 more per 1000</b> (from 40 fewer to 165 more)
Nausea (	(Aripipr	azole or risp	<b>peridone)</b> (as	ssessed with: No	on-systematic as	sessment, study-speci	fic report	or study-specific s	ide effect ch	ecklist)	1
412 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	undetected		7/137 (5.1%)	15/275 (5.5%)	<b>RR 1.3</b> (0.51 to	Study	population
6-8 weeks		lineonoisteney				due to risk of bias, imprecision	(0.170)	(0.076)	3.37)	51 per 1000	<b>15 more per 1000</b> (from 25 fewer to 121 more)
										Mode	rate
										29 per 1000	9 more per 1000 (from 14 fewer to 69 more)
Nausea (	(Aripipr	azole) (assess	l ed with: Study-s	Decific report of	adverse event)						
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		1/51 (2%)	8/165 (4.8%)	<b>RR 2.47</b> (0.32 to	Study	population
8 weeks		inconsistency	onsistency indirectness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(270)	(4.070)	19.3)	20 per 1000	<b>29 more per 1000</b> (from 13 fewer to 359 more)
										Mode	rate
										20 per 1000	29 more per 1000 (from 14 fewer to 366 more)
Nausea (	(Risperi	i <b>done)</b> (assess	ed with: Non-sys	tematic assessr	nent or study-sp	ecific side effect check	list)	·	_	1	1
196 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected		6/86 (7%)	7/110 (6.4%)	<b>RR 1.02</b>	Study	population
6-8 weeks		inconsistency				due to risk of bias, imprecision	(1 /0)	(0.770)	pe	70 per 1000	1 more per 1000 (from 46 fewer to 140 more)

							]			Moder	rate
										63 per 1000	1 more per 1000 (from 42 fewer to 126 more)
Gastroen	teritis	viral (Aripipi	azole) (asses	sed with: Study	-specific report of	of adverse event)	1		1		•
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly		0/51 (0%)	5/165 (3%)	<b>RR 3.45</b> (0.19 to	Study	population
8 weeks	eks				suspected <sup>3</sup>	due to risk of bias, imprecision,			61.28)	0 per 1000	N/A
		publication bias			Moder	rate					
										0 per 1000	N/A
Constipa	tion (R	isperidone)	l (assessed with: I	Non-systematic	assessment, stu	l Idy-specific outcome m	leasure, c	r study-specific side	e effect che	cklist)	Į
275 (3 studies)	serious1	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected		8/125 (6.4%)	21/150 (14%)	<b>RR 2.53</b> (1.19 to	Study	population
6-8 weeks		inconsistency				due to risk of bias, imprecision	(0.478)	(1470)	5.39)	64 per 1000	<b>98 more per 1000</b> (from 12 more to 281 more)
										Moder	rate
										29 per 1000	44 more per 1000 (from 6 more to 127 more)
Diarrhoe	a (Aripi	prazole or ri	isperidone)	(assessed with	: Non-systemation	c assessment, study-sp	pecific rep	ort or study-specific	side effect	checkli	st)
293 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	undetected		17/136 (12.5%)	14/157 (8.9%)	<b>RR 0.83</b> (0.43 to	Study	population
6-8 weeks						due to risk of bias, imprecision		()	1.59)	125 per 1000	21 fewer per 1000 (from 71 fewer to 74 more)

							]			Mode	rate
										64 per 1000	11 fewer per 1000 (from 36 fewer to 38 more)
Diarrhoe	a (Aripi	prazole) (ass	essed with: Stud	y-specific repor	t of adverse ever	nt)					
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly		5/50 (10%)	4/47 (8.5%)	<b>RR 0.85</b> (0.24 to	Study	population
8 weeks		inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(1070)	(0.070)	2.98)	100 per 1000	15 fewer per 1000 (from 76 fewer to 198 more)
										Mode	rate
										100 per 1000	<b>15 fewer per 1000</b> (from 76 fewer to 198 more)
Diarrhoe	a (Risp	eridone) (asse	essed with: Non-	-systematic asse	essment or study	-specific side effect che	ecklist)				1
196 (2 studies)	serious <sup>1</sup>	no serious	no serious	very serious⁵	undetected		12/86 (14%)	10/110 (9.1%)	<b>RR 0.82</b> (0.39 to	Study	population
6-8 weeks	serious inconsistency	sistency indirectness			due to risk of bias, imprecision	(1478)	(9.176)	1.75)	140 per 1000	25 fewer per 1000 (from 85 fewer to 105 more)	
										Mode	rate
										29 per 1000	5 fewer per 1000 (from 18 fewer to 22 more)
Fever (A	ripipraz	ole or rispe	ridone) (asse	I essed with: Non-	systematic asse	ssment, study-specific	outcome	measure or study-s	pecific repo	ort)	1
488 (4 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		8/175 (4.6%)	29/313 (9.3%)	<b>RR 2.25</b> (1.04 to	Study	population
6-8 weeks		Inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(+.0 %)	(3.370)	4.87)	46 per 1000	57 more per 1000 (from 2 more to 177 more)

										Mode	rate
										10 per 1000	12 more per 1000 (from 0 more to 39 more)
Fever (A	ripipraz	cole) (assessed	with: Study-spec	cific report of ad	verse event)				-		
313 (2 studies)	serious1	no serious inconsistency	no serious indirectness	serious⁵	reporting bias strongly		1/101 (1%)	19/212 (9%)	<b>RR 6.66</b> (1.13 to	Study	population
8 weeks		inconsistency	Indirectriess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(170)	(378)	39.2)	10 per 1000	<b>56 more per 1000</b> (from 1 more to 378 more)
										Mode	rate
										10 per 1000	57 more per 1000 (from 1 more to 382 more)
Fever (R	isperide	one) (assessed	with: Non-syster	natic assessme	I nt or study-speci	fic outcome measure)					<u> </u>
175 (2 studies)	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias strongly		7/74 (9.5%)	10/101 (9.9%)	<b>RR 1.26</b> (0.53 to	Study	population
6-8 weeks	inconsistency	ncy indirectness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(3.378)	(3.376)	3.02)	95 per 1000	<b>25 more per 1000</b> (from 44 fewer to 191 more)	
										Mode	rate
										90 per 1000	23 more per 1000 (from 42 fewer to 182 more)
Influenza	a-like sy	/mptoms (Ri	isperidone)	(assessed with	: Study-specific o	outcome measure)	Į			1	1
79 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		2/39 (5.1%)	4/40 (10%)	<b>RR 1.95</b> (0.38 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(,0)	(,	10.04)	51 per 1000	<b>49 more per 1000</b> (from 32 fewer to 464 more)

										Mode	rate
										51 per 1000	48 more per 1000 (from 32 fewer to 461 more)
Insomnia checklist)	a (Aripi	prazole or ri	speridone)	(assessed with:	Non-systematic	assessment, study-sp	pecific outo	ome measure	, study-specific ı	report or	study-specific side effect
372 (4 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected		27/175 (15.4%)		<b>RR 0.59</b> (0.34 to	Study	population
6-8 weeks		lineonoisteney				due to risk of bias, imprecision	(10.470)	(0.170)	1.04)	154 per 1000	63 fewer per 1000 (from 102 fewer to 6 more)
										Mode	rate
										117 per 1000	48 fewer per 1000 (from 77 fewer to 5 more)
Insomnia	a (Aripi	prazole) (asse	essed with: Study	v-specific report	of adverse even	t)		-	<b>I</b>	<u> </u>	
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly		4/50 (8%)	3/47 (6.4%)	<b>RR 0.8</b> (0.19 to	Study	population
8 weeks		lineonoisteney			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(070)	(0.+70)	3.38)	80 per 1000	<b>16 fewer per 1000</b> (from 65 fewer to 190 more)
										Mode	rate
										80 per	<b>16 fewer per 1000</b> (from 65 fewer to 190

Insomnia (Risperidone) (assessed with: Non-systematic assessment, study-specific outcome measure, or study-specific side effect checklist)

275 (3 studies)	 	no serious indirectness	serious <sup>4</sup>	undetected	0000	23/125 (18.4%)	 <b>RR 0.56</b> (0.31 to	Study	population
6-8 weeks					due to risk of bias, imprecision		1.03)	-	81 fewer per 1000 (from 127 fewer to 6 more)
					Imprecision			per	

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

1000

more)

							]			1000	
										Moderate	
										154 per 1000	68 fewer per 1000 (from 106 fewer to 5 more)
Hyperson	nnia (A	ripiprazole	or risperido	ne) (assessed	d with: Non-syste	matic assessment or s	tudy-spe	cific report)	ł		
312 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision, publication bias	1/86 (1.2%)	7/226 (3.1%)	<b>RR 2.01</b> (0.33 to 12.16)	Study population	
										12 per 1000	12 more per 1000 (from 8 fewer to 130 more)
										Moderate	
										14 per 1000	<b>14 more per 1000</b> (from 9 fewer to 156 more)
Hyperson	Hypersomnia (Aripiprazole) (assessed with: Study-specific report of adverse event)										
216 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision, publication bias	0/51 (0%)	(3%)	<b>RR 3.45</b> (0.19 to 61.28)	Study population	
										0 per 1000	N/A
										Moderate	
										0 per 1000	N/A
Hyperson	Hypersomnia (Risperidone) (assessed with: Non-systematic assessment )										
96 serious (1 study) 6 weeks	serious <sup>1</sup>		no serious indirectness	very serious⁵	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision,	1/35 (2.9%)	2/61 (3.3%)	<b>RR 1.15</b> (0.11 to 12.2)	Study population	
										29 per	<b>4 more per 1000</b> (from 25 fewer to 320

						publication bias				1000	more)
										Moderate	
										29 per 1000	4 more per 1000 (from 26 fewer to 325 more)
Sleep pr	oblems	(Risperidor	<b>1e)</b> (assessed w	ith: Study-speci	fic side effect ch	ecklist)	· · ·		4		1
100 (1 study) 8 weeks		no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖ VERY LOW <sup>1,5</sup> due to risk of bias, imprecision		11/49 ) (22.4%)	<b>RR 1.27</b> (0.58 to 2.8)	Study population	
										176 per 1000	<b>48 more per 1000</b> (from 74 fewer to 318 more)
										Moderate	
										177 per 1000	<b>48 more per 1000</b> (from 74 fewer to 319 more)
											more)
Headach checklist)	ne (Aripi	iprazole or r	isperidone)	(assessed with	: Non-systemation	c assessment, study-s	pecific outco	ome measure, stu	dy-specific		or study-specific side effect
checklist) 588	serious <sup>1</sup>	no serious	no serious	(assessed with	reporting bias	000	22/226	34/362	RR 1.1	report o	,
checklist)		- 1	. ,		-		22/226			report o	r study-specific side effect
checklist) 588 (5 studies)		no serious	no serious		reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision,	22/226	34/362	<b>RR 1.1</b> (0.65 to	report o Study 97 per	population 10 more per 1000 (from 34 fewer to 86 more)
checklist) 588 (5 studies)		no serious	no serious		reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision,	22/226	34/362	<b>RR 1.1</b> (0.65 to	Study 97 per 1000	population 10 more per 1000 (from 34 fewer to 86 more)
checklist) 588 (5 studies) 6-8 weeks	serious <sup>1</sup>	no serious	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision, publication bias	22/226	34/362	<b>RR 1.1</b> (0.65 to	Study 97 per 1000 Moder 114 per	or study-specific side effect population 10 more per 1000 (from 34 fewer to 86 more) rate 11 more per 1000 (from 40 fewer to 100

(2 studies) 8 weeks			indirectness		strongly suspected <sup>3</sup>	VERY LOW <sup>1,3,5,8</sup> due to risk of bias, inconsistency, imprecision,	(9.9%)	(7.5%)	(0.35 to 2.07)	99 per 1000	<b>15 fewer per 1000</b> (from 64 fewer to 106 more)
						publication bias				Moderate	
										100 per 1000	15 fewer per 1000 (from 65 fewer to 107 more)
Headache (Risperidone) (assessed with: Non-systematic assessment, study-specific outcome measure, or study-specific side effect checklist)											
275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected		12/125 (9.6%)	18/150 (12%)	<b>RR 1.31</b> (0.67 to	Study population	
6-8 weeks		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,				due to risk of bias, imprecision		((275)	2.57)	96 per 1000	<b>30 more per 1000</b> (from 32 fewer to 151 more)
										Moderate	
										114 per 1000	<b>35 more per 1000</b> (from 38 fewer to 179 more)
Dizziness (Risperidone) (assessed with: Study-specific side effect checklist)											
100 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,5</sup> due to risk of bias, imprecision	2/51 (3.9%)	8/49 (16.3%)	<b>RR 4.16</b> (0.93 to 18.64)	Study population	
										39 per 1000	124 more per 1000 (from 3 fewer to 692 more)
										Moderate	
										39 per 1000	123 more per 1000 (from 3 fewer to 688 more)
Increased salivation (Aripiprazole or risperidone) (assessed with: Study-specific outcome measure or study-specific report)											
295	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias	$\oplus \Theta \Theta \Theta$	2/90	15/205	RR 3.6	Study	population

(2 studies) 8 weeks		inconsistency	indirectness		strongly suspected <sup>3</sup>	VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision, publication bias	(2.2%)	(7.3%)	(0.82 to 15.82)	22 per 1000	58 more per 1000 (from 4 fewer to 329 more)
										Moder	ate
										23 per 1000	<b>60 more per 1000</b> (from 4 fewer to 341 more)
Increased	d saliva	ation (Aripip	r <b>azole)</b> (asses	ssed with: Study	y-specific report of	of adverse event)	-		•	,	•
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly	⊕⊖⊝⊖ VERY LOW <sup>1,3,5</sup>	1/51 (2%)	11/165 (6.7%)	<b>RR 3.4</b> (0.45 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		```	25.7)	20 per 1000	<b>47 more per 1000</b> (from 11 fewer to 484 more)
										Moder	ate
										20 per 1000	<b>48 more per 1000</b> (from 11 fewer to 494 more)
Increased	d saliva	ation (Risper	idone) (asses	ssed with: Study	y-specific outcom	e measure)	•				
79 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		1/39 (2.6%)	4/40 (10%)	<b>RR 3.9</b> (0.46 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		< <i>'</i>	33.36)	26 per 1000	74 more per 1000 (from 14 fewer to 830 more)
										Moder	ate
										26 per 1000	75 more per 1000 (from 14 fewer to 841 more)
Drooling	(Aripip	razole or ris	peridone) (	assessed with:	Study-specific re	port or study-specific s	ide effect	checklist)			
413	serious <sup>1</sup>	no serious	no serious	serious <sup>4</sup>	undetected	$\oplus \oplus \ominus \ominus$	3/152	32/261	RR 6.04	Study	population

(3 studies) 8 weeks		inconsistency	indirectness			<b>LOW</b> <sup>1,4</sup> due to risk of bias, imprecision	(2%)	(12.3%)	(2.1 to 17.39)	20 per 1000	<b>99 more per 1000</b> (from 22 more to 323 more)
										Mode	rate
										0 per 1000	N/A
Drooling	(Aripip	razole) (asses	sed with: Study-	specific report c	of adverse event)		1			•	
313 (2 studies)	serious1	no serious	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		0/101 (0%)	19/212 (9%)	<b>RR 9.65</b> (1.24 to	Study	population
8 weeks		inconsistency	Indirectriess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0%)	(9%)	74.91)	0 per 1000	N/A
						publication bias				Mode	rate
							0 per 1000	N/A			
Drooling	(Rispe	ridone) (asses	sed with: Study-	specific side eff	ect checklist)		1				
100 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,4</sup>	3/51 (5.9%)	13/49 (26.5%)	<b>RR 4.51</b> (1.37 to	Study	population
8 weeks		Inconsistency	Indirectriess			due to risk of bias, imprecision	(3.376)	(20.3%)	14.86)	59 per 1000	<b>206 more per 1000</b> (from 22 more to 815 more)
										Mode	rate
										59 per 1000	<b>207 more per 1000</b> (from 22 more to 818 more)
Dry mou	th (Risp	<b>peridone)</b> (ass	sessed with: Stu	dy-specific side	effect checklist)						
100 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected		5/51 (9.8%)	9/49 (18.4%)	<b>RR 1.87</b> (0.68 to	Study	population
8 weeks						due to risk of bias, imprecision		()	5.2)	98 per	85 more per 1000 (from 31 fewer to 412

										1000	more)
										Mode	rate
										98 per 1000	85 more per 1000 (from 31 fewer to 412 more)
Increase	d thirst	(Aripiprazo	le or risper	idone) (asses	ssed with: Non-s	ystematic assessment,	study-sp	ecific report or stud	y-specific s	ide effe	ct checklist)
412 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected		6/137 (4.4%)	13/275 (4.7%)	<b>RR 1.46</b> (0.57 to	Study	population
6-8 weeks						due to risk of bias, imprecision	(,0)	(	3.74)	44 per 1000	<b>20 more per 1000</b> (from 19 fewer to 120 more)
										Mode	rate
										20 per 1000	9 more per 1000 (from 9 fewer to 55 more)
Increase	d thirst	(Aripiprazo	<b>le)</b> (assessed w	l /ith: Study-speci	fic report of adve	erse event)	1		1		
216	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias	$\oplus \Theta \Theta \Theta$	1/51	5/165	RR 1.55		population
(A)				-		VEDV LOW1.3.5		(20())		Study	population
• • •		inconsistency	indirectness		strongly suspected <sup>3</sup>	VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision, publication bias	(2%)	(3%)	(0.18 to 12.93)	20 per 1000	11 more per 1000 (from 16 fewer to 234 more)
(1 study) 8 weeks					strongly	due to risk of bias, imprecision,		(3%)	(0.18 to	20 per	11 more per 1000 (from 16 fewer to 234 more)
•••					strongly	due to risk of bias, imprecision,		(3%)	(0.18 to	20 per 1000	11 more per 1000 (from 16 fewer to 234 more)
8 weeks	d thirst	inconsistency	indirectness		strongly suspected <sup>3</sup>	due to risk of bias, imprecision,	(2%)		(0.18 to	20 per 1000 Mode 20 per	11 more per 1000 (from 16 fewer to 234 more)rate11 more per 1000 (from 16 fewer to 239
8 weeks	d thirst	inconsistency	indirectness		strongly suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2%)		(0.18 to	20 per 1000 Mode 20 per 1000	11 more per 1000 (from 16 fewer to 234 more)rate11 more per 1000 (from 16 fewer to 239

						imprecision				per 1000	(from 28 fewer to 180 more)
										Mode	ate
										49 per 1000	22 more per 1000 (from 24 fewer to 151 more)
Tachyca	rdia (Ri	speridone) (	assessed with: S	Study-specific ou	utcome measure	or study-specific side	effect che	cklist)	I		
179 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected		1/90	11/89 (12.4%)	<b>RR 7.77</b> (1.45 to	Study	population
8 weeks						due to risk of bias, imprecision	(1170)	(12.+70)	41.72)	11 per 1000	<b>75 more per 1000</b> (from 5 more to 452 more)
										Mode	rate
										10 per 1000	68 more per 1000 (from 5 more to 407 more)
Anorexia	a (Rispe	eridone) (asse	ssed with: Study	-specific outcon	ne measure)		<u> </u>			ļ	
79	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias		1/39	4/40	RR 3.9	Study	population
(1 study) 8 weeks		inconsistency	indirectness		strongly suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2.6%)	(10%)	(0.46 to 33.36)	26 per 1000	<b>74 more per 1000</b> (from 14 fewer to 830 more)
										Mode	rate
										26 per 1000	<b>75 more per 1000</b> (from 14 fewer to 841 more)
Anxiety	(Risperi	idone) (assess	ed with: Study-s	pecific side effe	ct checklist)	I	1		I	1	1
100	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	undetected	<b>000</b>	10/51	12/49	RR 1.25	Study	population

(1 study) 3 weeks	inconsistency	cy indirectness	indirectness			VERY LOW <sup>1,5</sup> due to risk of bias, imprecision	(19.6%)	(24.5%)	(0.59 to 2.62)	196 per 1000	<b>49 more per 1000</b> (from 80 fewer to 318 more)
										Mode	rate
										196 per 1000	<b>49 more per 1000</b> (from 80 fewer to 318 more)
Depressi	ion (Ris	<b>peridone)</b> (a:	ssessed with: No	on-systematic as	ssessment)	1		•	<b>I</b>	ļ	1
96 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		0/35 (0%)	2/61 (3.3%)	<b>RR 2.9</b> (0.14 to	Study	population
6 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision,	()	· /	58.81)	0 per 1000	N/A
						publication bias				Mode	rate
									0 per 1000	N/A	
Apathy (	Risperi	done) (assesse	d with: Study-sp	ecific outcome	measure)	1				I	
79 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		0/39 (0%)	5/40 (12.5%)	<b>RR 10.73</b> (0.61 to	Study	population
8 weeks		inconsistency	indirectricss		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(070)	(12.370)	187.79)	0 per 1000	N/A
						publication bias				Mode	rate
										0 per 1000	N/A
Aggress	ion (Ari	piprazole or	risperidon	<b>e)</b> (assessed w	vith: Non-system	atic assessment or stud	dy-specific	c report)	1		1
193 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		6/85 (7.1%)	1/108 (0.9%)	<b>RR 0.2</b> (0.04 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision,	(,0)	(0.070)	1.11)	71 per	56 fewer per 1000 (from 68 fewer to 8 more)

						publication bias				1000	
										Moder	ate
										69 per 1000	55 fewer per 1000 (from 66 fewer to 8 more)
Aggress	sion (Ari	piprazole) (a	ssessed with: St	udy-specific rep	ort of adverse ev	/ent)	<u> </u>		<b>I</b>	ļ	
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		4/50 (8%)	1/47 (2.1%)	<b>RR 0.27</b> (0.03 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		(2.173)	2.29)	80 per 1000	<b>58 fewer per 1000</b> (from 78 fewer to 103 more)
										Moder	ate
										80 per 1000	58 fewer per 1000 (from 78 fewer to 103 more)
Aggress	sion (Ris	s <b>peridone)</b> (a	I ssessed with: No	I on-systematic as	ssessment)					I	
96 (4 study)	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias		2/35	0/61	RR 0.12	Study	population
(1 study) 6 weeks		inconsistency	indirectness		strongly suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(5.7%)	(0%)	(0.01 to 2.35)	57 per 1000	50 fewer per 1000 (from 57 fewer to 77 more)
										Moder	ate
										57 per 1000	50 fewer per 1000 (from 56 fewer to 77 more)
Agitatio	n (Rispe	eridone) (asse	ssed with: Non-s	ystematic asses	ssment)	1			1		
96 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias strongly		2/35 (5.7%)	1/61 (1.6%)	<b>RR 0.29</b> (0.03 to	Study	population
6 weeks		moonoloconoy			suspected <sup>3</sup>	due to risk of bias,	(0.1 /0)	(1.070)	3.05)	57	41 fewer per 1000

						imprecision, publication bias				per 1000	(from 55 fewer to 117 more)
										Moder	ate
										57 per 1000	40 fewer per 1000 (from 55 fewer to 117 more)
Restlessr	ness (A	ripiprazole	or risperido	one) (assessed	d with: Non-syste	matic assessment, stu	dy-specif	ic report or study-sp	ecific side	effect ch	necklist)
509 (4 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		8/187 (4.3%)	8/322 (2.5%)	<b>RR 0.63</b> (0.25 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		()	1.57)	43 per 1000	16 fewer per 1000 (from 32 fewer to 24 more)
										Moder	ate
										44 per 1000	16 fewer per 1000 (from 33 fewer to 25 more)
Restless	ness (A	ripiprazole)	(assessed with:	Study-specific	report of adverse	event)	ł	·			
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		4/101 (4%)	3/212 (1.4%)	<b>RR 0.32</b> (0.08 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		<b>`</b>	1.32)	40 per 1000	27 fewer per 1000 (from 36 fewer to 13 more)
										Moder	ate
										39 per 1000	27 fewer per 1000 (from 36 fewer to 12 more)
Restlessr	ness (R	(isperidone)	(assessed with:	Non-systematio	assessment or	study-specific side effe	ct checkl	ist)			
196	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	undetected	$\oplus \Theta \Theta \Theta$	4/86	5/110	RR 1.07	Study	population

(2 studies) 6-8 weeks		inconsistency	indirectness			VERY LOW <sup>1,5</sup> due to risk of bias, imprecision	(4.7%)	(4.5%)	(0.29 to 3.93)	47 per 1000	<b>3 more per 1000</b> (from 33 fewer to 136 more)
										Moder	ate
										44 per 1000	3 more per 1000 (from 31 fewer to 129 more)
Psychom	otor hy	peractivity	(Aripiprazo	le or rispe	ridone) (asses	ssed with: Non-system	atic asse	ssment or study-spe	cific report	)	
193 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		4/85 (4.7%)	3/108 (2.8%)	<b>RR 0.56</b> (0.13 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		、 <i>,</i>	2.47)	47 per 1000	21 fewer per 1000 (from 41 fewer to 69 more)
										Moder	ate
										49 per 1000	22 fewer per 1000 (from 43 fewer to 72 more)
Psychom	otor hy	peractivity	(Aripiprazo	le) (assessed	with: Study-spec	fic report of adverse ev	vent)				
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		2/50 (4%)	1/47 (2.1%)	<b>RR 0.53</b> (0.05 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			5.67)	40 per 1000	<b>19 fewer per 1000</b> (from 38 fewer to 187 more)
										Moder	ate
										40 per 1000	<b>19 fewer per 1000</b> (from 38 fewer to 187 more)
Psychom	otor hy	peractivity	(Risperidor	1e) (assessed	with: Non-system	natic assessment)					
96	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias	$\oplus \Theta \Theta \Theta$	2/35	2/61	RR 0.57	Study	population

(1 study) 6 weeks		inconsistency	indirectness		strongly suspected <sup>3</sup>	VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision, publication bias	(5.7%)	(3.3%)	(0.08 to 3.9)	57 per 1000	25 fewer per 1000 (from 53 fewer to 166 more)
										Moder	ate
										57 per 1000	25 fewer per 1000 (from 52 fewer to 165 more)
Tremor (A	Aripipra	azole or risp	<b>eridone)</b> (as	sessed with: St	udy-specific outc	ome measure, study-sp	pecific rep	port or study-specifi	c side effec	t checkl	ist)
492 (4 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		1/191 (0.5%)	32/301 (10.6%)	<b>RR 8.99</b> (2.4 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(*****)	(,	33.64)	5 per 1000	<b>42 more per 1000</b> (from 7 more to 171 more)
										Moder	ate
										0 per 1000	N/A
Tremor (A	Aripipra	azole) (assesse	d with: Study-sp	ecific report of a	adverse event)						
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		0/101 (0%)	21/212 (9.9%)	<b>RR 10.42</b> (1.33 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		(0.070)	81.48)	0 per 1000	N/A
										Moder	ate
										0 per 1000	N/A
Tremor (F	Risperi	done) (assesse	d with: Study-sp	ecific outcome	measure or study	/-specific side effect ch	ecklist)				
179 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious⁵	undetected	⊕⊕⊝⊝ LOW <sup>1,5</sup>	1/90 (1.1%)	11/89 (12.4%)	<b>RR 7.79</b> (1.46 to	Study	population
8 weeks						due to risk of bias, imprecision	(,0)	(	41.7)	11 per	<b>75 more per 1000</b> (from 5 more to 452 more)

										1000	
										Mode	ate
										10 per 1000	68 more per 1000 (from 5 more to 407 more)
Dyskine	sia/Hyp	erkinesia (A	ripiprazole	or risperid	one) (assesse	d with: Study-specific	report or s	study-specific sid	le effect checkl	ist)	1
197 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected		4/101 (4%)	6/96 (6.3%)	<b>RR 1.51</b> (0.47 to	Study	population
8 weeks		due to risk of bias, imprecision	(0.070)	4.82)	40 per 1000	<b>20 more per 1000</b> (from 21 fewer to 151 more)					
					Mode	ate					
									39 per 1000	20 more per 1000 (from 21 fewer to 149 more)	
Dyskine	sia/Hyp	l erkinesia (A	l ripiprazole)	(assessed with	: Study-specific	report of adverse ever	nt)				
97	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias	$\oplus \ominus \ominus \ominus$	1/50	0/47	RR 0.35	Study	population
(1 study) 8 weeks		inconsistency	indirectness		strongly suspected <sup>3</sup>	VERY LOW <sup>1,3,5</sup> due to risk of bias, imprecision, publication bias	(2%)	(0%)	(0.01 to 8.48)	20 per 1000	13 fewer per 1000 (from 20 fewer to 150 more)
										Mode	ate
										20 per 1000	13 fewer per 1000 (from 20 fewer to 150 more)
Dyskine	sia/Hyp	erkinesia (R	isperidone	(assessed with	n: Study-specific	side effect checklist)				20 per	<b>13 fewer per 1000</b> (from 20 fewer to 150
Dyskine 100 (1 study)	sia/Hyp	erkinesia (R	isperidone)	) (assessed with very serious <sup>5</sup>	n: Study-specific undetected	side effect checklist) ⊕⊖⊖⊖ VERY LOW <sup>1,5</sup>	3/51 (5.9%)	6/49 (12.2%)	RR 2.08 (0.55 to	20 per 1000	<b>13 fewer per 1000</b> (from 20 fewer to 150

						imprecision				per 1000	(from 26 fewer to 404 more)
										Moder	rate
										59 per 1000	64 more per 1000 (from 27 fewer to 405 more)
Hypokin	esia (Ar	ripiprazole) (	assessed with: S	Study-specific re	port of adverse	event)					
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		0/50 (0%)	1/47 (2.1%)	<b>RR 3.19</b> (0.13 to	Study	population
8 weeks		lineonaisteney	indirectricss		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(070)	(2.170)	76.36)	0 per 1000	N/A
						publication blas				Moder	rate
										0 per 1000	N/A
Muscle r	igidity (	Arininrazole	or risporie			pecific report or study-		ide offect abacklist)			
	0 7		e or risperic	ione) (assess	ed with: Study-s	pecilic report of study-	specific s	side effect checklist)			
197 (2 studies)	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	undetected	$\oplus \Theta \Theta \Theta$	1/101	6/96	<b>RR 4.54</b>	Study	population
197 (2 studies) 8 weeks	-		-		-	The second se	-		<b>RR 4.54</b> (0.79 to 26.12)	Study 10 per 1000	<b>35 more per 1000</b> (from 2 fewer to 249 more)
(2 studies)	-	no serious	no serious	- ·	-	<ul> <li>⊕⊖⊖⊖</li> <li>VERY LOW<sup>1,5</sup></li> <li>due to risk of bias,</li> </ul>	1/101	6/96	(0.79 to	10 per	35 more per 1000 (from 2 fewer to 249 more)
(2 studies)	-	no serious	no serious	- ·	-	<ul> <li>⊕⊖⊖⊖</li> <li>VERY LOW<sup>1,5</sup></li> <li>due to risk of bias,</li> </ul>	1/101	6/96	(0.79 to	10 per 1000	35 more per 1000 (from 2 fewer to 249 more)
(2 studies) 8 weeks	serious <sup>1</sup>	no serious	no serious indirectness	very serious⁵	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,5</sup> due to risk of bias, imprecision	1/101	6/96	(0.79 to	10 per 1000 Moder 10 per	35 more per 1000 (from 2 fewer to 249 more) rate 35 more per 1000
(2 studies) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,5</sup> due to risk of bias, imprecision	1/101	6/96	(0.79 to	10 per 1000 Moder 10 per 1000	35 more per 1000 (from 2 fewer to 249 more) rate 35 more per 1000

						imprecision, publication bias				1000	
										Moder	ate
										0 per 1000	N/A
Muscle r	igidity (	Risperidone	e) (assessed wit	h: Study-specifi	c side effect cheo	cklist)					
100 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected		1/51 (2%)	5/49 (10.2%)	<b>RR 5.2</b> (0.63 to	Study	population
8 weeks		inconsistency	indirectriess			due to risk of bias, imprecision	(270)	(10.270)	42.96)	20 per 1000	82 more per 1000 (from 7 fewer to 823 more)
										Moder	ate
										20 per 1000	84 more per 1000 (from 7 fewer to 839 more)
Muscle s	spasms	(Aripiprazol	<b>e)</b> (assessed w	ith: Study-speci	fic report of adve	rse event)				1	
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		1/50 (2%)	0/47 (0%)	<b>RR 0.35</b> (0.01 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(270)	(070)	8.48)	20 per 1000	<b>13 fewer per 1000</b> (from 20 fewer to 150 more)
										Moder	ate
										20 per 1000	<b>13 fewer per 1000</b> (from 20 fewer to 150 more)
Enuresis	s (Aripip	orazole or ris	speridone) (	assessed with:	Non-systematic a	assessment, study-spe	cific repo	rt or study-specific	side effect o	checklist	;)
509 (4 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious⁵	undetected		20/187 (10.7%)		<b>RR 1.14</b> (0.67 to	Study	population
6-8 weeks		,				due to risk of bias, imprecision	()	(- ···)	1.93)	107 per	15 more per 1000

										1000	(from 35 fewer to 99 more)
										Mode	ate
										50 per 1000	7 more per 1000 (from 16 fewer to 46 more)
Enuresis	(Aripip	orazole) (asses	ssed with: Study	-specific report of	of adverse event	)	4		- 1	<u>,</u>	
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		5/101 (5%)	7/212 (3.3%)	<b>RR 0.92</b> (0.28 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			3.05)	50 per 1000	<b>4 fewer per 1000</b> (from 36 fewer to 101 more)
										Mode	ate
										50 per 1000	4 fewer per 1000 (from 36 fewer to 102 more)
Enuresis	s (Rispe	eridone) (asses	ssed with: Non-s	l ystematic asses	sment or study-	specific side effect che	cklist)			1	
196 (2 studies)	serious <sup>1</sup>	no serious	no serious	very serious⁵	undetected		15/86	19/110	RR 1.21	Study	population
(2 studies) 6-8 weeks		inconsistency	indirectness			due to risk of bias, imprecision	(17.4%)	(17.3%)	(0.68 to 2.18)	174 per 1000	<b>37 more per 1000</b> (from 56 fewer to 206 more)
										Mode	ate
		1	1							147	31 more per 1000
										per 1000	(from 47 fewer to 173 more)
Skin irrit	ation/R	ash (Aripipr	azole or ris	peridone) (	assessed with: N	lon-systematic assess	ment, stud	ly-specific report	or study-spec	1000	more)
Skin irrit 412 (3 studies)	ation/R	ash (Aripipr	azole or ris	<b>peridone)</b> ( very serious⁵	assessed with: N undetected	Ion-systematic assess	ment, stud 8/137 (5.8%)	dy-specific report 17/275 (6.2%)	or study-spec	1000	more)

						imprecision				per 1000	(from 14 fewer to 152 more)
										Mode	rate
										20 per 1000	13 more per 1000 (from 5 fewer to 52 more)
Skin irrit	ation/R	ash (Aripipr	azole) (assess	sed with: Study-	specific report of	fadverse event)					
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly		1/51 (2%)	4/165 (2.4%)	<b>RR 1.24</b> (0.14 to	Study	population
8 weeks		inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(270)	(2.770)	10.81)	20 per 1000	5 more per 1000 (from 17 fewer to 192 more)
										Mode	rate
										20 per 1000	5 more per 1000 (from 17 fewer to 196 more)
Skin irrit	ation/R	ash (Risperi	done) (assess	l sed with: Non-s	l ystematic assess	I ment or study-specific	side effe	ct checklist)			<u> </u>
196 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected		7/86 (8.1%)	13/110 (11.8%)	<b>RR 1.74</b> (0.76 to	Study	population
6-8 weeks		inconsistency				due to risk of bias, imprecision	(0.176)	(11.0%)	4.01)	81 per 1000	60 more per 1000 (from 20 fewer to 245 more)
										Mode	rate
										69 per 1000	<b>51 more per 1000</b> (from 17 fewer to 208 more)
Earache	/Ear infe	ection (Risp	eridone) (ass	essed with: No	n-systematic ass	essment or study-spec	cific side e	effect checklist)			
196	serious1	no serious	no serious	very serious <sup>5</sup>	undetected	$\oplus \Theta \Theta \Theta$	4/86	4/110	RR 0.85	Study	population

(2 studies) 6-8 weeks		inconsistency	indirectness			VERY LOW <sup>1,5</sup> due to risk of bias, imprecision	(4.7%)	(3.6%)	(0.22 to 3.3)	47 per 1000	7 fewer per 1000 (from 36 fewer to 107 more)
										Moder	rate
										39 per 1000	6 fewer per 1000 (from 30 fewer to 90 more)
Sore thr	oat (Ris	peridone) (as	ssessed with: Stu	udy-specific side	e effect checklist)	)	4		4		
100 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected		1/51 (2%)	5/49 (10.2%)	<b>RR 5.2</b> (0.63 to	Study	population
8 weeks		inconsistency				due to risk of bias, imprecision	(270)	(10.270)	42.96)	20 per 1000	82 more per 1000 (from 7 fewer to 823 more)
										Moder	rate
										20 per 1000	84 more per 1000 (from 7 fewer to 839 more)
unclear <sup>2</sup> I-squared v <sup>3</sup> Trial funde <sup>4</sup> Events<30 <sup>5</sup> Events<30 <sup>6</sup> N<400 <sup>7</sup> N<400 and	value indica d by pharm 0 0 and 95% 1 95% CI cr	ates moderate het aceutical compar Cl crosses both l	erogeneity ny and/or study d ine of no effect a no effect and m	rugs were provi	ded by pharmace appreciable bene	bserve potential longer eutical company and/or efit or harm (RR 0.75/1. harm (SMD -0.5/0.5)	authors		-	•	me outcome measures

## Adverse events associated with low dose antipsychotics versus placebo

Quality assessment	Summary of Findings

` '	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e	vent rates (%)	Relative effect	Anticipat	ed absolute effects
Follow up							With Control	With Adverse events associated with low dose antipsychotics versus placebo	(95% CI)	Risk with Control	Risk difference with Adverse events associated with low dose antipsychotics versus placebo (95% Cl)
Any side	effect	(Aripiprazo	ole or risp	eridone)	(assessed with:	Non-systematic asse	essment o	r study-specific repo	rt of advers	e event)	
168 (2 studies)	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		58/86 (67.4%)	58/82 (70.7%)	<b>RR 1.03</b> (0.84 to	Study po	pulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, inconsistency, imprecision, publication bias			1.26)	674 per 1000	<b>20 more per 1000</b> (from 108 fewer to 175 more)
						publication blab				Moderate	1
										663 per 1000	20 more per 1000 (from 106 fewer to 172 more)
Any side	effect	(Aripiprazo	ole 5mg/da	<b>ay)</b> (assesse	d with: study-sp	ecific report of advers	se event)		1	J	1
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious⁵	reporting bias strongly		37/51 (72,5%)	46/52 (88.5%)	<b>RR 1.22</b> (1 to	Study po	pulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(1 210 70)	(001070)	1.48)	725 per 1000	<b>160 more per 1000</b> (from 0 more to 348 more)
										Moderate	
										726 per 1000	<b>160 more per 1000</b> (from 0 more to 348 more)
Any side	effect	(Risperido	ne 0.125-0	).175mg/	day) (assesse	ed with: Non-systema	tic assess	sment)			1
65	serious1	no serious	no serious	very	reporting bias	⊕⊖⊖⊖	21/35	12/30	RR 0.67	Study po	pulation

(1 study) 6 weeks		inconsistency	indirectness	serious <sup>3</sup>	strongly suspected <sup>4</sup>	VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	(60%)	(40%)	(0.4 to 1.12)	600 per 1000	<b>198 fewer per 1000</b> (from 360 fewer to 72 more)
										Moderate	
										600 per 1000	<b>198 fewer per 1000</b> (from 360 fewer to 72 more)
Disconti	inuatio	n due to se	dation (Ar	ipiprazo	le 5mg/day	/) (assessed with: St	udy-spec	cific report of adverse	event)		•
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/51 (0%)	1/52 (1.9%)	<b>RR 2.94</b> (0.12 to	Study po	pulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	()	()	70.61)	0 per 1000	-
										Moderate	•
										0 per 1000	-
Disconti	inuatio	n due to dr	ooling (Ar	ipiprazol	e 5mg/day	(assessed with: St	udy-spec	ific report of adverse	event)		
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/51 (0%)	1/52 (1.9%)	<b>RR 2.94</b> (0.12 to	Study po	pulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	()		70.61)	0 per 1000	-
										Moderate	•
										0 per 1000	-
Disconti	inuatio	n due to tre	emor (Arip	iprazole	5mg/day)	assessed with: Study	/-specific	report of adverse eve	ent)		
103	serious <sup>1</sup>	no serious	no serious	very	reporting bias	$\oplus \ominus \ominus \ominus$	0/51	2/52	RR 4.91	Study po	pulation

(1 study) 8 weeks		inconsistency	indirectness	serious <sup>3</sup>	strongly suspected <sup>4</sup>	VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	(0%)	(3.8%)	(0.24 to 99.74)	0 per 1000 Moderate 0 per 1000	-
Any trea	tment-	emergent e	extrapyran	nidal sym	nptoms (A	ripiprazole 5n	ng/day	/) (assessed with: S	tudy-specif	ic report of	adverse event)
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		6/51 (11.8%)	12/52 (23.1%)	<b>RR 1.96</b> (0.8 to	Study po	pulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(11070)	()	4.83)	118 per 1000	<b>113 more per 1000</b> (from 24 fewer to 451 more)
										Moderate	
										118 per 1000	<b>113 more per 1000</b> (from 24 fewer to 452 more)
Extrapy	ramidal	symptoms	s (Risperio	lone 0.12	25-0.175mg	g/day) (measured	with: Non	-systematic assessm	ient; Better	indicated b	y lower values)
63 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>6</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,4,6</sup> due to risk of bias, imprecision, publication bias	34	29	-		The mean extrapyramidal symptoms (risperidone 0.125-0.175mg/day) in the intervention groups was <b>0.37 standard deviations</b> <b>lower</b> (0.87 lower to 0.13 higher)
Extrapy	ramidal	disorder (	Aripiprazo	ole 5mg/d	lay) (assessed	with: Study-specific	report of a	adverse event)			
103 (1 study)	serious1	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/51 (0%)	2/52 (3.8%)	<b>RR 4.91</b> (0.24 to	Study po	pulation
						due to risk of bias,	. ,	· · ·		0 per	-

					suspected <sup>4</sup>	imprecision, publication bias			99.74)	1000	
										Moderate	)
										0 per 1000	-
remor	(Aripip	razole 5mg	/day) (assess	sed with: Study	y-specific report	of adverse event)					
03 I study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/51 (0%)	4/52 (7.7%)	<b>RR 8.83</b> (0.49 to	Study po	pulation
weeks		inconsistency	maneotress	5011005	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(0,0)	(1.170)	159.93)	0 per 1000	-
										Moderate	)
										0 per 1000	-
03	ly relev	no serious	no serious	<b>tin (Aripip</b> serious⁵	reporting bias		4/51	17/52	RR 4.17	Study po	pulation
03 1 study)	1		Т		I	Γ	1			Study po 78 per 1000	pulation       249 more per 1000 (from 40 more to 827 more)
03 1 study)	1	no serious	no serious		reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,4,5</sup> due to risk of bias, imprecision,	4/51	17/52	<b>RR 4.17</b> (1.51 to	78 per	<b>249 more per 1000</b> (from 40 more to 827 more)
Clinical 103 (1 study) 8 weeks	1	no serious	no serious		reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,4,5</sup> due to risk of bias, imprecision,	4/51	17/52	<b>RR 4.17</b> (1.51 to	78 per 1000	<b>249 more per 1000</b> (from 40 more to 827 more)
03 1 study) weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>5</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,4,5</sup> due to risk of bias, imprecision,	4/51 (7.8%)	17/52 (32.7%)	<b>RR 4.17</b> (1.51 to 11.54)	78 per 1000 Moderate 78 per 1000	249 more per 1000 (from 40 more to 827 more) 247 more per 1000 (from 40 more to 822
103 1 study) 3 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>5</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,4,5</sup> due to risk of bias, imprecision, publication bias	4/51 (7.8%)	17/52 (32.7%)	<b>RR 4.17</b> (1.51 to 11.54)	78 per 1000 Moderate 78 per 1000	249 more per 1000 (from 40 more to 827 more) 247 more per 1000 (from 40 more to 822 more)

6-8 weeks					suspected <sup>4</sup>	imprecision, publication bias			9.51)	1000	(from 12 fewer to 297 more)
										Moderat	e
										38 per 1000	<b>58 more per 1000</b> (from 13 fewer to 323 more)
Weight	gain (A	ripiprazole	5mg/day)	(assessed wit	th: Study-specific	c report of adverse ev	ent)			1	
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/51 (2%)	4/52 (7.7%)	<b>RR 3.92</b> (0.45 to	Study po	opulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(= / - )	()	33.92)	20 per 1000	<b>57 more per 1000</b> (from 11 fewer to 645 more)
										Moderat	e
										20 per 1000	<b>58 more per 1000</b> (from 11 fewer to 658 more)
Weight	gain (R	isperidone	0.125-0.17	75mg/day	/) (assessed wit	th: Non-systematic as	sessmer	nt)		1	
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		2/35 (5.7%)	3/30 (10%)	<b>RR 1.75</b> (0.31 to	Study po	opulation
5 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias		(,)	9.79)	57 per 1000	<b>43 more per 1000</b> (from 39 fewer to 502 more)
										Moderat	e
										57 per 1000	<b>43 more per 1000</b> (from 39 fewer to 501

160 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>7</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,4,7</sup> due to risk of bias, imprecision, publication bias	84	76	-	The mean weight gain (in kg) (aripiprazole or risperidone) in the intervention groups was <b>0.45 standard deviations</b> higher (0.13 to 0.76 higher)
Weight	gain (ir	n kg) - Aripi	iprazole (5	mg/day)	(measured with:	Weight assessment;	Better ir	ndicated by lowe	er values)	
103 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>7</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,4,7</sup> due to risk of bias, imprecision, publication bias	51	52	-	The mean weight gain (in kg) - aripiprazole (5mg/day) in the intervention groups was <b>0.46 standard deviations</b> higher (0.07 to 0.85 higher)
Weight	gain (ir	n kg) - Risp	eridone (0	.125-0.1	75mg/day)	(measured with: Weig	ht asse	ssment; Better i	ndicated by lower va	alues)
57 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>6</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,4,6</sup> due to risk of bias, imprecision, publication bias	33	24	-	The mean weight gain (in kg) - risperidone (0.125- 0.175mg/day) in the intervention groups was <b>0.42 standard deviations</b> <b>higher</b> (0.11 lower to 0.96 higher)
BMI cha	ange (k	g/m-square	ed) - Aripip	prazole (	5 <b>mg/day)</b> (m	leasured with: Weight	assess	ment; Better inc	licated by lower valu	ies)
	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>6</sup>	reporting bias strongly		51	52	-	The mean bmi change (kg/m-squared) -

						publication bias					0.28 standard deviations higher (0.11 lower to 0.66 higher)
Increas	ed appe	etite (Aripip	orazole or	risperid	one) (assessed	with: Non-systemation	c assessr	ment or study-sp	pecific report of a	adverse ev	vent)
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious⁵	reporting bias strongly		4/86 (4.7%)	15/82 (18.3%)	<b>RR 3.95</b> (1.36 to	Study p	opulation
6-8 weeks		lineensieteney			suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	( /0)	(10.070)	11.51)	47 per 1000	<b>137 more per 1000</b> (from 17 more to 489 more)
										Moderat	te
										48 per 1000	<b>142 more per 1000</b> (from 17 more to 504 more)
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious⁵	reporting bias strongly		2/51 (3.9%)	10/52 (19.2%)	<b>RR 4.9</b> (1.13 to	Study p	opulation
(1 study) 8 weeks		inconsistency	indirectness		strongly suspected <sup>4</sup>	<b>VERY LOW</b> <sup>1,4,5</sup> due to risk of bias, imprecision,	(3.9%)	(19.2%)	(1.13 to 21.29)	39 per 1000	153 more per 1000 (from 5 more to 796 more
						publication bias				Moderat	te
										39 per 1000	152 more per 1000 (from 5 more to 791 more)
Increas	ed appe	etite (Rispe	eridone 0.1	25-0.17	5mg/day) (as	sessed with: Non-sys	stematic a	assessment)	I	1	
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>3</sup>	reporting bias strongly		2/35 (5.7%)	5/30 (16.7%)	<b>RR 2.92</b> (0.61 to	Study p	opulation
6 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision,		(,)	13.96)	57 per 1000	<b>110 more per 1000</b> (from 22 fewer to 741

						publication bias				Moderate	
										57 per 1000	<b>109 more per 1000</b> (from 22 fewer to 739 more)
Decrea	sed app	etite (Aripi	prazole 5r	ng/day) (	assessed with: St	udy-specific report o	f advers	e event)	·		•
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/51 (2%)	5/52 (9.6%)	<b>RR 4.9</b> (0.59 to	Study po	pulation
8 weeks		inconsistency	Indirectiless	3611003	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(270)	(3.078)	40.53)	20 per 1000	76 more per 1000 (from 8 fewer to 775 more)
										Moderate	1
										20 per 1000	<b>78 more per 1000</b> (from 8 fewer to 791
											more)
Fasting lower values		se (mg/dL)	(Change S	icore) - F	Risperidone	e (0.125-0.175	img/d	ay) (measured wi	th: Laborator	y assessme	more)
-		no serious inconsistency	(Change S	Score) - F	Risperidone	€ (0.125-0.175 ⊕⊖⊖⊖ VERY LOW <sup>1,4,6</sup> due to risk of bias, imprecision, publication bias	22	<b>ay)</b> (measured wi	th: Laborator	y assessme	, , , , , , , , , , , , , , , , , , ,
45 (1 study) 6 weeks	s)	no serious inconsistency	no serious indirectness	very serious <sup>6</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,4,6</sup> due to risk of bias, imprecision,	22	23	th: Laborator	y assessme	The mean fasting glucose (mg/dl) (change score) - risperidone (0.125- 0.175mg/day) in the intervention groups was 0.03 standard deviations higher

## Fasting triglycerides (=>120 mg/dL for females or 160 mg/dL for males) - Aripiprazole (5mg/day) (assessed with: Laboratory assessment)

103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		2/51 (3.9%)	6/52 (11.5%)	<b>RR 2.94</b> (0.62 to	Study po	pulation
3 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(0.070)	(11.070)	13.9)	39 per 1000	<b>76 more per 1000</b> (from 15 fewer to 506 more)
										Moderate	)
										39 per 1000	<b>76 more per 1000</b> (from 15 fewer to 503 more)

Insulin Resistance (HOMA-IR) (Change Score) - Risperidone (0.125-0.175mg/day) (measured with: Laboratory assessment; Better indicated by lower values)

	-					1			
43 (1 study) 6 weeks		no serious indirectness	serious <sup>6</sup>	suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,4,6</sup> due to risk of bias, imprecision, publication bias	22	21	-	The mean insulin resistance (homa-ir) (change score) - risperidone (0.125- 0.175mg/day) in the intervention groups was <b>0.3 standard deviations</b> <b>lower</b> (0.9 lower to 0.3 higher)

Aggression (Risperidone 0.125-0.175mg/day) (assessed with: Non-systematic assessment)

65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	·		2/35 (5.7%)	0/30 (0%)	<b>RR 0.23</b> (0.01 to	Study po	oulation
6 weeks					due to risk of bias, imprecision, publication bias			4.66)	57 per 1000	44 fewer per 1000 (from 57 fewer to 209 more)
									Moderate	•

										57 per 1000	44 fewer per 1000 (from 56 fewer to 209 more)
Agitatic	on (Risp	eridone 0.	125-0.175r	ng/day) (a	assessed with: No	on-systematic assess	sment)		1	1	1
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		2/35 (5.7%)	0/30 (0%)	<b>RR 0.23</b> (0.01 to	Study po	pulation
6 weeks		lineensistency	manoothoos	Schous	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(0.17)	(0,0)	4.66)	57 per 1000	44 fewer per 1000 (from 57 fewer to 209 more)
										Moderate	
										57 per 1000	44 fewer per 1000 (from 56 fewer to 209 more)
Depres	sion (Ri	speridone	0.125-0.17	′5mg/day	(assessed with	n: Non-systematic as	sessment	;)			
65 (1 study) 6 weeks	1					See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
Abdom	inal dis	comfort (R	isperidone	e 0.125-0.	.175mg/da	<b>y)</b> (assessed with: N	lon-syste	matic assessmen	t)	1	1
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		3/35 (8.6%)	0/30 (0%)	<b>RR 0.17</b> (0.01 to	Study po	pulation
6 weeks				Sonouo	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(0.070)		3.09)	86 per 1000	71 fewer per 1000 (from 85 fewer to 179 more)
										Moderate	1
										86 per 1000	<b>71 fewer per 1000</b> (from 85 fewer to 180 more)

168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/86 (1.2%)	3/82 (3.7%)	<b>RR 2.44</b> (0.37 to	Study po	opulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias			15.99)	12 per 1000	<b>17 more per 1000</b> (from 7 fewer to 174 more)
										Moderat	e
										10 per 1000	<b>14 more per 1000</b> (from 6 fewer to 150 more)
Abdomi	inal pai	n (upper) -	Aripiprazo	ole (5mg/	/day) (assesse	ed with: Study-specific	c report o	f adverse event)	)		
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/51 (2%)	2/52 (3.8%)	<b>RR 1.96</b> (0.18 to	Study po	opulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	()	()	20.97)	20 per 1000	<b>19 more per 1000</b> (from 16 fewer to 392 more)
										Moderat	e
										20 per 1000	<b>19 more per 1000</b> (from 16 fewer to 399 more)
Abdomi	inal pai	n (upper) -	Risperido	ne (0.12	5-0.175mg/	day) (assessed wit	h: Non-sy	ystematic asses	sment )	1	
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/35 (0%)	1/30 (3.3%)	<b>RR 3.48</b> (0.15 to	Study po	opulation
5 weeks		Inconsistency	Indirectriess	senous	suspected <sup>4</sup>	due to risk of bias, imprecision,	(0 %)	(3.376)	82.48)	0 per 1000	-
0						publication bias					

										0 per 1000	-
Constip	oation (I	Risperidon	e 0.125-0.′	175mg/da	<b>ay)</b> (assessed w	vith: Non-systematic a	assessme	ent)			
65 (4. aturtu)	serious <sup>1</sup>	no serious	no serious	very serious <sup>3</sup>	reporting bias strongly		1/35 (2.9%)	0/30 (0%)	<b>RR 0.39</b> (0.02 to	Study po	opulation
(1 study) 6 weeks		inconsistency	indirectness	senous	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(2.9%)	(0%)	9.16)	29 per 1000	<b>17 fewer per 1000</b> (from 28 fewer to 233 more)
										Moderat	e
										29 per 1000	<b>18 fewer per 1000</b> (from 28 fewer to 237 more)
Nausea	(Aripip	razole or r	isperidone	hassassad	with: Non-system	etia accomment or a		-ific non-out of only	(oroo overt)	•	
168	serious <sup>1</sup>	no serious	no serious	very	reporting bias	<b>000</b>	2/86	2/82	RR 1.07	Study po	opulation
168 (2 studies)			•			1				Study po 23 per 1000	2 more per 1000
168 (2 studies)		no serious	no serious	very	reporting bias strongly	⊕⊝⊝⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	2/86	2/82	<b>RR 1.07</b> (0.15 to	23 per	<b>2 more per 1000</b> (from 20 fewer to 149 more)
168 (2 studies) 6-8 weeks		no serious	no serious	very	reporting bias strongly	⊕⊝⊝⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	2/86	2/82	<b>RR 1.07</b> (0.15 to	23 per 1000	2 more per 1000 (from 20 fewer to 149 more) e 2 more per 1000
168 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊝⊝⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	2/86	2/82	<b>RR 1.07</b> (0.15 to	23 per 1000 Moderat 24 per	2 more per 1000 (from 20 fewer to 149 more) e 2 more per 1000 (from 20 fewer to 153
168 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	2/86	2/82	<b>RR 1.07</b> (0.15 to	23 per 1000 Moderat 24 per 1000	2 more per 1000 (from 20 fewer to 149 more) e 2 more per 1000 (from 20 fewer to 153

						publication bias					more)
										Moderat	e
										20 per 1000	<b>0 fewer per 1000</b> (from 19 fewer to 285 more)
Nausea	(Rispe	ridone 0.12	5-0.175mg	<b>g/day)</b> (ass	essed with: Non	-systematic assessm	ent)		<b>I</b>	-	<u>.</u>
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/35 (2.9%)	1/30 (3.3%)	<b>RR 1.17</b> (0.08 to	Study po	opulation
6 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(,		17.86)	29 per 1000	5 more per 1000 (from 26 fewer to 482 more)
										Moderat	e
										29 per 1000	<b>5 more per 1000</b> (from 27 fewer to 489 more)
								•		1	
Vomitin	g (Aripi	iprazole or	risperidor	ne) (assesse	d with: Non-syst	ematic assessment o	r study-sp	pecific report of ad	verse event)		
168	<b>g (Arip</b> i	no serious	no serious	very	reporting bias	<b>000</b>	6/86	7/82	RR 1.21	Study po	opulation
		-	-	•	-	1	1			Study po 70 per 1000	<b>15 more per 1000</b> (from 40 fewer to 170 more)
168 (2 studies)		no serious	no serious	very	reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	6/86	7/82	<b>RR 1.21</b> (0.42 to	70 per	<b>15 more per 1000</b> (from 40 fewer to 170 more)

103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		4/51 (7.8%)	5/52 (9.6%)	<b>RR 1.23</b> (0.35 to	Study po	opulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias		()	4.31)	78 per 1000	<b>18 more per 1000</b> (from 51 fewer to 260 more)
										Moderate	e
										78 per 1000	<b>18 more per 1000</b> (from 51 fewer to 258 more)
Vomitin	g (Risp	eridone 0.1	25-0.175n	n <b>g/day)</b> (a	ssessed with: No	n-systematic assess	sment)			J	4
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		2/35 (5.7%)	2/30 (6.7%)	<b>RR 1.17</b> (0.17 to	Study po	opulation
6 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias			7.79)	57 per 1000	<b>10 more per 1000</b> (from 47 fewer to 388 more)
										Moderate	e
										57 per 1000	<b>10 more per 1000</b> (from 47 fewer to 387 more)
Gastroe	enteritis	viral (Arip	iprazole 5	mg/day) (	assessed with: S	Study-specific report of	of advers	e event)	I	1	
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/51 (0%)	1/52 (1.9%)	<b>RR 2.94</b> (0.12 to	Study po	opulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision,			70.61)	0 per 1000	-
						publication bias				Moderate	e
										0 per 1000	-

65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/35 (2.9%)	1/30 (3.3%)	<b>RR 1.17</b> (0.08 to	Study po	opulation
6 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias		()	17.86)	29 per 1000	5 more per 1000 (from 26 fewer to 482 more)
										Moderat	e
										29 per 1000	5 more per 1000 (from 27 fewer to 489 more)
-			-	e) (assessed		natic assessment or s	1				
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/86 (0%)	3/82 (3.7%)	<b>RR 6.87</b> (0.36 to	Study po	opulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias			129.7)	0 per 1000	-
										Moderat	e
										0 per 1000	-
Pyrexia	(Aripip	razole 5mg	<b>j/day)</b> (asses	sed with: Stu	dy-specific report	of adverse event)	1		I	<u>,</u>	
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/51 (0%)	3/52 (5.8%)	<b>RR 6.87</b> (0.36 to		opulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias			129.7)	0 per 1000	-
										Moderat	e
										0 per	-

Pyrexia	(Rispe	ridone 0.12	5-0.175mç	g <b>/day)</b> (ass	essed with: Non-	-systematic assessm	ent)				
65 (1 study) 6 weeks						See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
Drooling	g (Aripi	prazole 5m	g/day) (asse	essed with: Stu	udy-specific repo	ort of adverse event)				•	
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/51 (0%)	2/52 (3.8%)	<b>RR 4.91</b> (0.24 to	Study po	pulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	()	(,	99.74)	0 per 1000	-
										Moderate	
										0 per 1000	-
Increase	ed saliv	ation (Arip	iprazole 5	mg/day) (	assessed with:	Study-specific report	of advers	se event)			
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/51 (2%)	1/52 (1.9%)	<b>RR 0.98</b> (0.06 to	Study po	oulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias			15.26)	20 per 1000	<b>0 fewer per 1000</b> (from 18 fewer to 280 more)
										Moderate	
										20 per 1000	<b>0 fewer per 1000</b> (from 19 fewer to 285 more)
Thirst (A	Aripipra	zole or ris	peridone)	(assessed with	n: Non-systemati	c assessment or stu	dy-specifi	c report of adverse e	vent)		
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/86 (1.2%)	3/82 (3.7%)	<b>RR 2.94</b> (0.32 to	Study po	oulation
. ,						due to risk of bias,		. ,		12 per	23 more per 1000

6-8 weeks					suspected <sup>4</sup>	imprecision, publication bias			27.36)	1000	(from 8 fewer to 307 more)
										Moderate	
										10 per 1000	<b>19 more per 1000</b> (from 7 fewer to 264 more)
Thirst (/	Aripipra	azole 5mg/o	<b>day)</b> (assesse	d with: Study-	specific report of	adverse event)					
03 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/51 (2%)	3/52 (5.8%)	<b>RR 2.94</b> (0.32 to	Study po	pulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias		、 <i>,</i>	27.36)	20 per 1000	38 more per 1000 (from 13 fewer to 517 more)
										Moderate	
										20 per 1000	<b>39 more per 1000</b> (from 14 fewer to 527 more)
Thirst (I	Risperio	done 0.125	-0.175mg/o	day) (asses	sed with: Non-sy	stematic assessment	:)				
65 (1 study) 6 weeks						See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
Fatigue	(Aripip	razole or ri	speridone	e) (assessed	with: Non-system	l natic assessment or s	tudy-spe	ecific report of ad	verse event)	1	
	-	no serious	no serious	very serious <sup>3</sup>	reporting bias strongly		0/86 (0%)	2/82 (2.4%)	<b>RR 4.91</b> (0.24 to	Study po	pulation
	serious <sup>1</sup>	inconsistencv	indirectness	senous							
168 (2 studies) 6-8 weeks	serious <sup>1</sup>	inconsistency	indirectness	senous	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias		· · ·	99.74)	0 per 1000	-

										0 per 1000	-
Fatigue	(Aripip	razole 5mg	<b>/day)</b> (asses	sed with: Stuc	ly-specific report	of adverse event)					
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/51 (0%)	2/52 (3.8%)	<b>RR 4.91</b> (0.24 to	Study po	oulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(-,-,	()	99.74)	0 per 1000	-
						publication bias				Moderate	
										0 per 1000	-
65 (1 study) 6 weeks	no serious risk of bias					See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
Lethargy	y (Aripi	prazole 5m	ng/day) (ass	essed with: St	udy-specific repo	ort of adverse event)					
103	y (Aripi	no serious	no serious	very	reporting bias	<b>000</b>	0/51	4/52 (7.7%)	<b>RR 8.83</b>	Study po	oulation
Lethargy 103 (1 study) 8 weeks	1	-		1		⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	0/51 (0%)	4/52 (7.7%)	<b>RR 8.83</b> (0.49 to 159.93)	Study pop 0 per 1000	oulation
103 (1 study)	1	no serious	no serious	very	reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias,			(0.49 to	0 per	-

168 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	3/86 (3.5%)	4/82 (4.9%)	<b>RR 1.32</b> (0.33 to 5.26)	Study population	
										35 per 1000	11 more per 1000 (from 23 fewer to 149 more)
										Moderat	e
										34 per 1000	<b>11 more per 1000</b> (from 23 fewer to 145 more)
Somnol	ence (A	Aripiprazole	e 5mg/day	(assessed w	<i>i</i> ith: Study-specif	ic report of adverse e	vent)	-			
103 (1 study)	serious <sup>1</sup>			very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	2/51 (3.9%)	4/52 (7.7%)	<b>RR 1.96</b> (0.38 to 10.24)	Study population	
8 weeks										39 per 1000	<b>38 more per 1000</b> (from 24 fewer to 362 more)
										Moderate	
										39 per 1000	<b>37 more per 1000</b> (from 24 fewer to 360 more)
Somnol	ence (F	Risperidone	e 0.125-0.1	75mg/da	I <b>y)</b> (assessed w	ith: Non-systematic a	ssessme	nt)	I		
65 (1.study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/35 (2.9%)	0/30 (0%)	<b>RR 0.39</b> (0.02 to	Study population	
(1 study) 6 weeks			indirectiless	Senous	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(2.070)	(076)	9.16)	29 per 1000	<b>17 fewer per 1000</b> (from 28 fewer to 233 more)
										Moderate	
										29 per 1000	<b>18 fewer per 1000</b> (from 28 fewer to 237

Sedatio	n (Arini	prazole or	risperido	ne) (assesse	d with: Non-syste	ematic assessment o	r study-sr	pecific report of	adverse )		more)
168 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	3/86 (3.5%)	10/82 (12.2%)	<b>RR 3.01</b> (0.94 to 9.62)	Study population	
										35 per 1000	<b>70 more per 1000</b> (from 2 fewer to 301 more)
										Moderate	
										29 per 1000	58 more per 1000 (from 2 fewer to 250 more)
103 (1 study) 8 weeks	serious <sup>1</sup>		no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	<ul> <li>⊕⊖⊖⊖</li> <li>VERY LOW<sup>1,3,4</sup></li> <li>due to risk of bias,</li> <li>imprecision,</li> <li>publication bias</li> </ul>	3/51 (5.9%)	9/52 (17.3%)	<b>RR 2.94</b> (0.84 to 10.25)	Study po	opulation
					suspected	imprecision,			`	59 per 1000	<b>114 more per 1000</b> (from 9 fewer to 544 more)
					suspected	imprecision,			`	1000 Moderat	(from 9 fewer to 544 more) e
					suspected	imprecision,			`	1000	(from 9 fewer to 544 more) e 114 more per 1000
Sedatio	n (Risp	eridone 0.1	125-0.175r	ng/day) (a		imprecision,	ment)		`	1000 Moderat 59 per	(from 9 fewer to 544 more) e 114 more per 1000 (from 9 fewer to 546
Sedatio	n (Risp	eridone 0.1	125-0.175r	ng/day) (a		imprecision, publication bias	0/35 (0%)	1/30 (3.3%)	`	1000 Moderat 59 per 1000	(from 9 fewer to 544 more) e 114 more per 1000 (from 9 fewer to 546

						publication bias				Moderat	e
										0 per 1000	-
leadac	he (Arij	piprazole o	r risperido	one) (assess	sed with: Non-sys	stematic assessment	or study-	specific report of	f adverse event	)	
168 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	<ul> <li>⊕⊖⊖⊖</li> <li>VERY LOW<sup>1,3,4</sup></li> <li>due to risk of bias, imprecision, publication bias</li> </ul>	6/86 (7%)	5/82 (6.1%)	<b>RR 0.9</b> (0.28 to 2.86)	Study population	
										70 per 1000	7 fewer per 1000 (from 50 fewer to 130 more)
										Moderat	e
										77 per 1000	8 fewer per 1000 (from 55 fewer to 143 more)
		 T		1		port of adverse even		3/52	BR 1.47	Study po	opulation
103 (1 study)	he (Arij serious <sup>1</sup>	no serious inconsistency	mg/day) (as no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		t) 2/51 (3.9%)	3/52 (5.8%)	<b>RR 1.47</b> (0.26 to		opulation
Headac 103 (1 study) 8 weeks		no serious	no serious	very	reporting bias	<b>000</b>	2/51			Study po 39 per 1000	18 more per 1000
103 (1 study)		no serious	no serious	very	reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	2/51		(0.26 to	39 per	<b>18 more per 1000</b> (from 29 fewer to 292 more)
103 (1 study)		no serious	no serious	very	reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	2/51		(0.26 to	39 per 1000	18 more per 1000           (from 29 fewer to 292 more)           e           18 more per 1000
103 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	2/51 (3.9%)		(0.26 to	39 per 1000 Moderat 39 per	18 more per 1000           (from 29 fewer to 292 more)           e           18 more per 1000           (from 29 fewer to 290
103 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	2/51 (3.9%) ssment)		(0.26 to	39 per 1000 Moderat 39 per 1000	18 more per 1000           (from 29 fewer to 292 more)           e           18 more per 1000           (from 29 fewer to 290

6 weeks					suspected 4	imprecision, publication bias			2.96)	1000	(from 102 fewer to 224 more)
										Moderate	· ·
										114 per 1000	<b>48 fewer per 1000</b> (from 101 fewer to 223 more)
Ear infe	ction (F	Risperidon	e 0.125-0.1	75mg/da	<b>ay)</b> (assessed w	<i>i</i> ith: Non-systematic a	assessme	ent)			
65 (1 study) 6 weeks						See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
Inner r	snirat	orv tract in	fection (A	ripiprazo	le or rispe	ridone) (assesse	d with: No	on-systematic asse	essment or stu	udy-specific	report of adverse event
	1	1		T	1	1	1/86	3/82		Study po	
168	serious <sup>1</sup>	no serious	no serious indirectness	very serious <sup>3</sup>	reporting bias		1/86	3/82 (3.7%)	RR 2.49	Study po	
168 (2 studies)	1	1	no serious	very	1	000	1/86 (1.2%)	3/82 (3.7%)		Study po 12 per 1000	
168 (2 studies)	1	no serious	no serious	very	reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,			<b>RR 2.49</b> (0.36 to	12 per	pulation 17 more per 1000 (from 7 fewer to 186 more)
168 (2 studies)	1	no serious	no serious	very	reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,			<b>RR 2.49</b> (0.36 to	12 per 1000	pulation 17 more per 1000 (from 7 fewer to 186 more)
68 2 studies) S-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	(1.2%)	(3.7%)	<b>RR 2.49</b> (0.36 to 17.01)	12 per 1000 Moderate 14 per	17 more per 1000         (from 7 fewer to 186 more)         21 more per 1000         (from 9 fewer to 224
168 (2 studies) 5-8 weeks <b>Upper re</b>	serious <sup>1</sup>	no serious inconsistency Ory tract in no serious	no serious indirectness fection (Au no serious	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup> Ie 5mg/day	<ul> <li>⊕⊖⊖⊖</li> <li>VERY LOW<sup>1,3,4</sup></li> <li>due to risk of bias, imprecision, publication bias</li> <li>(assessed with: St</li> <li>⊕⊖⊖⊖</li> </ul>	(1.2%) udy-spec	(3.7%) cific report of adver	RR 2.49 (0.36 to 17.01)	12 per 1000 Moderate 14 per	17 more per 1000         (from 7 fewer to 186 more)         21 more per 1000         (from 9 fewer to 224 more)
168 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness fection (Au	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	<ul> <li>Contract Contract Contract</li></ul>	(1.2%)	(3.7%) cific report of adver	RR 2.49 (0.36 to 17.01)	12 per 1000 Moderate 14 per 1000	17 more per 1000         (from 7 fewer to 186 more)         21 more per 1000         (from 9 fewer to 224 more)

										0 per 1000	-
Upper r	espirat	ory tract in	fection (R	isperido	ne 0.125-0.	175mg/day) (a	ssessed	with: Non-syster	natic assessme	nt)	
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/35 (2.9%)	1/30 (3.3%)	<b>RR 1.17</b> (0.08 to	Study po	opulation
6 weeks		inconsistency	maneothess	3011003	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(2.370)	(0.076)	17.86)	29 per 1000	<b>5 more per 1000</b> (from 26 fewer to 482 more)
										Moderat	e
										29 per 1000	<b>5 more per 1000</b> (from 27 fewer to 489 more)
• ·											
168	(Aripira	no serious	no serious	very	reporting bias	C assessment or stud	2/86	8/82	RR 3.92	Study po	opulation
168 (2 studies)	` •	-	-		-	T	 T	•		Study po 23 per 1000	68 more per 1000 (from 3 fewer to 386 more)
Cough 168 (2 studies) 6-8 weeks	` •	no serious	no serious	very	reporting bias strongly	⊕⊝⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	2/86	8/82	<b>RR 3.92</b> (0.87 to	23 per	68 more per 1000 (from 3 fewer to 386 more)
168 (2 studies)	` •	no serious	no serious	very	reporting bias strongly	⊕⊝⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	2/86	8/82	<b>RR 3.92</b> (0.87 to	23 per 1000	68 more per 1000 (from 3 fewer to 386 more)
168 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	2/86	8/82	<b>RR 3.92</b> (0.87 to	23 per 1000 Moderat 20 per	68 more per 1000 (from 3 fewer to 386 more)           e           58 more per 1000 (from 3 fewer to 332
168 (2 studies) 6-8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	2/86	8/82	<b>RR 3.92</b> (0.87 to	23 per 1000 Moderat 20 per 1000	68 more per 1000 (from 3 fewer to 386 more)           e           58 more per 1000 (from 3 fewer to 332

						publication bias					more)
										Moderate	•
										39 per 1000	<b>114 more per 1000</b> (from 5 fewer to 647 more)
Cough	(Risper	idone 0.125	5-0.175mg	<b>/day)</b> (asse	ssed with: Non-s	systematic assessme	nt)		I		
65 (1 study) 6 weeks						See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
Rhinorı	rhea (Ar	ipiprazole :	5mg/day) (	assessed with	: Study-specific	report of adverse eve	ent)				1
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/51 (2%)	2/52 (3.8%)	<b>RR 1.96</b> (0.18 to	Study po	pulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision,	(_ / 0)	(0.070)	20.97)	20 per 1000	<b>19 more per 1000</b> (from 16 fewer to 392
						publication bias					more)
										Moderate	more)
											more)
Nasal c	congesti	ion (Aripipr	razole 5mç	<b>J/day)</b> (asso	essed with: Stud		dverse e	vent)		Moderate 20 per	more) <b>19 more per 1000</b> (from 16 fewer to 399
103	congesti	ion (Aripipr	razole 5mg	I/day) (asso very serious <sup>3</sup>	reporting bias	publication bias	1/51	1/52	RR 0.98 (0.06 to	Moderate 20 per	more) <b>19 more per 1000</b> (from 16 fewer to 399 more)
Nasal c 103 (1 study) 8 weeks		no serious	no serious	very	T	y-specific report of ac	T		RR 0.98 (0.06 to 15.26)	Moderate 20 per 1000	more) <b>19 more per 1000</b> (from 16 fewer to 399 more)

										20 per 1000	<b>0 fewer per 1000</b> (from 19 fewer to 285 more)
Nasoph	aryngit	is (Aripipra	zole or ris	speridon	<b>e)</b> (assessed wi	h: Non-systematic as	ssessmer	nt or study-speci	fic report of adve	erse event	
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		4/86 (4.7%)	8/82 (9.8%)	<b>RR 2.09</b> (0.65 to	Study po	pulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(,0)	(0.075)	6.79)	47 per 1000	51 more per 1000 (from 16 fewer to 269 more)
										Moderat	3
										48 per 1000	52 more per 1000 (from 17 fewer to 278 more)
-	aryngit	is (Aripipra	no serious	very	ssed with: Study	specific report of adv ⊕⊝⊝⊝	2/51	nt) 6/52	RR 2.94	Study po	pulation
(1 study) 8 weeks		inconsistency	indirectness	serious <sup>3</sup>	strongly suspected <sup>4</sup>	VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	(3.9%)	(11.5%)	(0.62 to 13.9)	39 per 1000	<b>76 more per 1000</b> (from 15 fewer to 506 more)
										Moderate	9
										39 per 1000	<b>76 more per 1000</b> (from 15 fewer to 503 more)
Nasoph	aryngit	is (Risperio	done 0.125	5-0.175m	g/day) (asses	ssed with: Non-syster	matic asso	essment)		<u> </u>	L
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		2/35 (5.7%)	2/30 (6.7%)	<b>RR 1.17</b> (0.17 to	Study po	pulation
6 weeks		Theorisistericy		3011003	suspected <sup>4</sup>	due to risk of bias,	(3.770)	(0.7 /0)	(0.17 10 7.79)	57 per	10 more per 1000

						publication bias				1000	more)
										Moderate	1 !
										57 per 1000	<b>10 more per 1000</b> (from 47 fewer to 387 more)
Nose bl	eed (Ar	ipiprazole	or risperid	lone) (asse	essed with: Non-s	systematic assessme	nt or stud	y-specific report	of adverse ever	nt)	
168 (2 studies) 6-8 weeks						See comment	0/86 (0%)	0/82 (0%)	not pooled	See comment	See comment
Nose bl	eed (Ar	ipiprazole	5mg/day) (	assessed with	n: Study-specific	report of adverse eve	ent)			<u> </u>	
103 (1 study) 8 weeks						See comment	0/51 (0%)	0/52 (0%)	not pooled	See comment	See comment
Nose bl	eed (Ri	speridone	0.125-0.17	5mg/day	) (assessed with	I Non-systematic ass	sessment)	)		<u> </u>	
65 (1 study) 6 weeks						See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
Akathis	ia (Arip	iprazole or	risperido	ne) (assesse	ed with: Non-syst	tematic assessment o	or study-s	pecific report of	adverse event)		
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		4/86 (4.7%)	1/82 (1.2%)	<b>RR 0.35</b> (0.06 to	Study po	pulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(,	< /	2.14)	47 per 1000	<b>30 fewer per 1000</b> (from 44 fewer to 53 more)
										Moderate	<u> </u>

										44 per 1000	<b>29 fewer per 1000</b> (from 41 fewer to 50 more)
Akathis	sia (Arip	iprazole 5r	ng/day) (as	sessed with: S	Study-specific rep	port of adverse event)	)				
03 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		3/51 (5.9%)	1/52 (1.9%)	<b>RR 0.33</b> (0.04 to	Study po	opulation
3 weeks		incensionaly			suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias		(1.070)	3.04)	59 per 1000	<b>39 fewer per 1000</b> (from 56 fewer to 120 more)
										Moderat	e
										59 per 1000	40 fewer per 1000 (from 57 fewer to 120 more)
55 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	on-systematic asses ⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias,	1/35 (2.9%)	0/30 (0%)	<b>RR 0.39</b> (0.02 to 9.16)	Study po	opulation
) weeks					suspected	imprecision, publication bias			9.10)	1000	(from 28 fewer to 233 more)
										Moderat	e
										29 per 1000	<b>18 fewer per 1000</b> (from 28 fewer to 237 more)
Insomn	ia (Risp	peridone 0.	125-0.175r	mg/day) (	assessed with: N	on-systematic asses	sment)				
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		2/35 (5.7%)	0/30 (0%)	<b>RR 0.23</b> (0.01 to	Study po	opulation
	1			20040	suspected <sup>4</sup>	due to risk of bias,	(0.1 /0)	(0,0)	4.66)	57 per	44 fewer per 1000

						publication bias				1000	more)
										Moderat	e
										57 per 1000	<b>44 fewer per 1000</b> (from 56 fewer to 209 more)
Hypers	omnia (	Aripiprazol	le or rispe	ridone) (a	assessed with: No	on-systematic assess	ment or s	study-specific rep	port of adverse	event)	
168 (2 studies)	serious <sup>1</sup>	serious <sup>8</sup>	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/86 (1.2%)	3/82 (3.7%)	<b>RR 2.12</b> (0.38 to	:0	
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, inconsistency, imprecision, publication bias	(		11.88)	12 per 1000	<b>13 more per 1000</b> (from 7 fewer to 127 more)
						publication bias				Moderat	e
										14 per 1000	<b>16 more per 1000</b> (from 9 fewer to 152 more)
Hyperso	omnia (	Aripiprazol	le 5mg/day	<b>/)</b> (assessed	with: Study-spec	ific report of adverse	event)				
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/51 (0%)	3/52 (5.8%)	<b>RR 6.87</b> (0.36 to	Study po	opulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	()	()	129.7)	0 per 1000	-
						publication blac				Moderat	e
										0 per 1000	-
			1			L	I	ont)		1	
Hyperso	omnia (	Risperidon	e 0.125-0.	175mg/d	ay) (assessed	with: Non-systematic	assessm	ent)			

(1 study) 6 weeks		inconsistency	indirectness	serious <sup>3</sup>	strongly suspected <sup>4</sup>	VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	(2.9%)	(0%)	(0.02 to 9.16)	29 per 1000	<b>17 fewer per 1000</b> (from 28 fewer to 233 more)
										Moderate	•
										29 per 1000	<b>18 fewer per 1000</b> (from 28 fewer to 237 more)
Psychor	notor h	yperactivit	y (Risperi	done 0.1	25-0.175m	g/day) (assessed	with: No	n-systematic assess	ment)		
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		2/35 (5.7%)	1/30 (3.3%)	<b>RR 0.58</b> (0.06 to	Study po	pulation
6 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	()	()	6.12)	57 per 1000	24 fewer per 1000 (from 54 fewer to 293 more)
										Moderate	•
										57 per 1000	24 fewer per 1000 (from 54 fewer to 292 more)
Enuresi	s (Aripi	prazole or	risperidor	IE) (assessed	d with: Non-syste	ematic assessment o	r study-sp	pecific report of adve	rse event)	I	1
168 (2 studies)	serious <sup>1</sup>	serious <sup>8</sup>	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/86 (1.2%)	2/82 (2.4%)	<b>RR 1.61</b> (0.29 to	Study po	pulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, inconsistency, imprecision,	<b>、</b>	· · ·	9.04)	12 per 1000	7 more per 1000 (from 8 fewer to 93 more)
						publication bias				Moderate	9
										10 per 1000	6 more per 1000 (from 7 fewer to 80 more)
Enuresis	s (Aripi	prazole 5m	g/day) (asso	essed with: St	udy-specific repo	ort of adverse event)			1		1

103 (1 study)	serious1	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/51 (2%)	0/52 (0%)	<b>RR 0.33</b> (0.01 to	Study po	opulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(270)		7.85)	20 per 1000	<b>13 fewer per 1000</b> (from 19 fewer to 134 more)
										Moderat	e
										20 per 1000	<b>13 fewer per 1000</b> (from 20 fewer to 137 more)
Enuresi	s (Risp	eridone 0.1	25-0.175n	ng/day) (a	assessed with: No	n-systematic assess	ment)			1	
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		0/35 (0%)	2/30 (6.7%)	<b>RR 5.81</b> (0.29 to	Study po	opulation
6 weeks					suspected 4	due to risk of bias, imprecision, publication bias			116.41)	0 per 1000	-
						publication bias				Moderat	e
										0 per 1000	-
Rash (A	ripipra	zole or risp	eridone) (a	assessed with	n: Non-systematic	assessment or study	-specific	report of advers	e event)	1	
168 (2 studies)	serious <sup>1</sup>	serious <sup>8</sup>	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/86 (1.2%)	2/82 (2.4%)	<b>RR 1.61</b> (0.29 to	Study po	opulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, inconsistency, imprecision,	(1.270)	(2.170)	9.04)	12 per 1000	7 more per 1000 (from 8 fewer to 93 more)
						publication bias				Moderat	e
										10 per 1000	6 more per 1000 (from 7 fewer to 80 more)
Rash (A	 .ripipra:	zole 5mg/d	<b>ay)</b> (assessed	with: Study-s	pecific report of a	adverse event)					

103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly		1/51 (2%)	0/52 (0%)	<b>RR 0.33</b> (0.01 to	Study p	opulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(_ /0)	(0.0)	7.85)	20 per 1000	<b>13 fewer per 1000</b> (from 19 fewer to 134 more)
										Moderat	e
										20 per 1000	<b>13 fewer per 1000</b> (from 20 fewer to 137 more)
Rash (R	isperid	one 0.125-	0.175mg/d	ay) (assess	ed with: Non-sys	tematic assessment)	1		I		
65 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly suspected <sup>4</sup>	<ul> <li>⊕⊖⊖⊖</li> <li>VERY LOW<sup>1,3,4</sup></li> <li>due to risk of bias,</li> </ul>	0/35 (0%)	2/30 (6.7%)	<b>RR 5.81</b> (0.29 to 116.41)	0 per	opulation
						imprecision, publication bias				1000	
										Moderat	e
										0 per 1000	-
adverse even	-	no serious	no serious	very	reporting bias	000	2/51	0/52	RR 0.2		with: Study-specific report of
(1 study) 8 weeks		inconsistency	indirectness	serious <sup>3</sup>	strongly suspected <sup>4</sup>	<b>VERY LOW</b> <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	(3.9%)	(0%)	(0.01 to 3.99)	39 per 1000	31 fewer per 1000 (from 39 fewer to 117 more)
										Moderat	e
										39 per 1000	<b>31 fewer per 1000</b> (from 39 fewer to 117 more)

<sup>1</sup> High risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse eventsand reliability/validity of some outcome measures unclear

<sup>2</sup> I-squared value indicates substantial to considerable heterogeneity

<sup>3</sup> Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25)

<sup>4</sup> Trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies <sup>5</sup> Events<300

<sup>6</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

<sup>7</sup> N<400

<sup>3</sup> I-squared value indicates moderate heterogeneity

#### Adverse events associated with risperidone versus placebo

			Quality assessment					Summary of Findings			
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study	event rates (%)	Relative effect	Anticip	ated absolute effects
Follow up							With Control	With Adverse events associated with risperidone versus haloperidol	(95% CI)	Risk with Control	Risk difference with Adverse events associated with risperidone versus haloperidol (95% CI)
Treatme lower values)	nt-eme	ergent extra	apyramidal	symptor	ns (measured v	u with: Chouinard Extra	apyramic	dal Symptoms Rating	Scale (ES	RS): Sec	tion I; Better indicated by
28 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	15	13	-		The mean treatment- emergent extrapyramidal symptoms in the intervention groups was <b>0.83 standard deviations</b> <b>lower</b> (1.61 to 0.05 lower)
Prolactir	n conc	entration (r	ng/ml) Cha	nge Scor	<b>'ES</b> (measured v	vith: Laboratory asse	essment;	; Better indicated by I	ower value	s)	1
28 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of	15	13	-		The mean prolactin concentration (ng/ml) change scores in the

12 weeks					suspected <sup>3</sup>	bias, imprecision, publication bias				intervention groups <b>1.01 standard dev</b> <b>Iower</b> (1.80 to 0.22 lower	viations
Liver pr	roblems	s (change ii	n alanine ti	ransamin	ase [ALT])	(measured with: Lal	oorator	y assessment;	Better indicated	by lower values)	
28 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	15	13	-	The mean liver pro (change in alanine transaminase [alt]) intervention groups <b>0.83 standard dev</b> <b>Iower</b> (1.60 to 0.05 lower	in the s was <b>/iations</b>
<sup>2</sup> N<400		bias as unclear if ed by the pharma				rve potential longer t sted	erm ac	lverse effects	1		

## 1.33.6 Adverse events associated with antivirals

## Adverse events associated with amantadine hydrochloride versus placebo

			Quality asse	essment			Summary of Findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study e	event rates (%)	Relative effect	Anticipa	ted absolute effects
Follow up									(95% CI)	Risk with Control	Risk difference with Adverse events associated with antivirals (95% CI)
Any adv	erse ev	<b>/ent</b> (assessed w	vith: Study-specifi	c report of adv	verse event)		•			•	
39	serious <sup>1</sup>	no serious	no serious	very	reporting bias	$\oplus \Theta \Theta \Theta$	14/20	14/19	RR 1.05	Study po	opulation

(1 study) 5 weeks	inconsistency in	indirectness	serious <sup>2</sup> strongly suspected <sup>3</sup>		<b>VERY LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision, publication bias	(70%)	(73.7%)	(0.71 to 1.56)	700 per 1000	<b>35 more per 1000</b> (from 203 fewer to 392 more)			
						publication blas				Moderat	e		
										700 per 1000	<b>35 more per 1000</b> (from 203 fewer to 392 more)		
Insomn	i <b>a</b> (assess	ed with: Study-sp	ecific report of ad	verse event)		-1	_			1	1		
39 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		2/20 (10%)	4/19 (21.1%)	<b>RR 2.11</b> (0.43 to	Study po	opulation		
5 weeks		inconsisioney	manocinoss	301003	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(1070)	(21.170)	10.19)	100 per 1000	<b>111 more per 1000</b> (from 57 fewer to 919 more)		
										Moderat	derate		
										100 per 1000	<b>111 more per 1000</b> (from 57 fewer to 919 more)		
Antisoc	ial beh	aviour (asses	sed with: Study-s	pecific report	of adverse event)								
39 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		4/20 (20%)	2/19 (10.5%)	<b>RR 0.53</b> (0.11 to	Study po	opulation		
5 weeks				conode	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2070)	(10.075)	2.55)	200 per 1000	94 fewer per 1000 (from 178 fewer to 310 more)		
										Moderat	e		
										200 per 1000	<b>94 fewer per 1000</b> (from 178 fewer to 310		

<sup>2</sup> Events<300 and 95% CI crosses both line of no effect and measure of significant benefit or harm (RR 0.75/1.25) <sup>3</sup> Trial funded by pharmaceutical company

## **1.33.7** Adverse events associated with cognitive enhancers

### Adverse events associated with piracetam and risperidone versus placebo and risperidone

		Q	uality assessi	nent				Sun	nmary of I	Findings	3
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	event rates (%)	Relative effect	Anticipa	ated absolute effects
Follow up						evidence	With Control	With Adverse events associated with combined piracetam and risperidone versus combined placebo and risperidone	(95% CI)	Risk with Control	Risk difference with Adverse events associated with combined piracetam and risperidone versus combined placebo and risperidone (95% Cl)
Any trea	T	-emergent e	extrapyran	nidal sym	ptom (asse	essed with: Extra	apyramic	lal Symptoms Rating Scale	(ESRS))	I	
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		8/20 (40%)	6/20 (30%)	<b>RR 0.75</b> (0.32 to	Study p	opulation
10 weeks		lineeneisteney				due to risk of bias, imprecision	(10,0)		1.77)	400 per 1000	<b>100 fewer per 1000</b> (from 272 fewer to 308 more)
						Imprecision				Modera	te
										400 per 1000	<b>100 fewer per 1000</b> (from 272 fewer to 308 more)
Constip	ation (a	I ssessed with: Stu	dy-specific side	effect checklist	t)	1	Į			,	
40 (1 study)	ation (a	no serious	dy-specific side	effect checklist very serious <sup>2</sup>	t) undetected		3/20 (15%)	4/20 (20%)	<b>RR 1.33</b> (0.34 to	Study p	opulation

10 weeks						bias, imprecision			5.21)	1000	(from 99 fewer to 632 more)
										Moderat	te
										150 per 1000	50 more per 1000 (from 99 fewer to 632 more)
Nervous	sness (a	assessed with: Stu	udy-specific side	effect checklis	st)		<u> </u>				
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/20 (10%)	1/20 (5%)	<b>RR 0.5</b> (0.05 to	Study p	opulation
10 weeks						due to risk of bias,			5.08)	100 per 1000	50 fewer per 1000 (from 95 fewer to 408 more)
						imprecision				Moderat	te
										100 per 1000	50 fewer per 1000 (from 95 fewer to 408 more)
Day time	e drow	siness (asses	sed with: Study-	specific side e	ffect checklist)						
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		9/20 (45%)	7/20 (35%)	<b>RR 0.78</b> (0.36 to	Study p	opulation
10 weeks		inconsistency	indirectiness	3011003		due to risk of bias, imprecision	(4070)		1.68)	450 per 1000	<b>99 fewer per 1000</b> (from 288 fewer to 306 more)
						Imprecision				Moderat	te
										450 per 1000	<b>99 fewer per 1000</b> (from 288 fewer to 306 more)
Morning	drows	siness (assess	sed with: Study-s	specific side ef	fect checklist)		I		- 1	<u>,</u>	1
40 (1. atudu)	serious <sup>1</sup>	no serious	no serious	very serious <sup>2</sup>	undetected		8/20	11/20	RR 1.38	Study p	opulation
(1 study) 10 weeks		inconsistency	indirectness	Senous		due to risk of bias,	(40%)	(55%)	(0.71 to 2.68)	400 per 1000	152 more per 1000 (from 116 fewer to 672 more)

						imprecision				Moderat	te
										400 per 1000	152 more per 1000 (from 116 fewer to 672 more)
Increase	ed app	etite (assessed	with: Study-spe	cific side effec	ct checklist)						
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		6/20 (30%)	7/20 (35%)	<b>RR 1.17</b> (0.48 to	Study p	opulation
10 weeks		,				due to risk of bias,	()	()	2.86)	300 per 1000	<b>51 more per 1000</b> (from 156 fewer to 558 more)
						imprecision				Moderat	te
										300 per 1000	<b>51 more per 1000</b> (from 156 fewer to 558 more)
		te (assessed wit				1	ļ				I
40	appeti	te (assessed wit	h: Study-specific no serious indirectness	side effect ch very serious <sup>2</sup>	undetected		1/20	1/20 (5%)	<b>RR 1</b> (0.07 to	Study p	opulation
		no serious	no serious	very	-	VERY LOW <sup>1,2</sup> due to risk of bias,				Study p 50 per 1000	opulation 0 fewer per 1000 (from 47 fewer to 695 more)
40 (1 study)		no serious	no serious	very	-	VERY LOW <sup>1,2</sup> due to risk of			(0.07 to	50 per	<b>0 fewer per 1000</b> (from 47 fewer to 695 more)
40 (1 study)		no serious	no serious	very	-	VERY LOW <sup>1,2</sup> due to risk of bias,			(0.07 to	50 per 1000	<b>0 fewer per 1000</b> (from 47 fewer to 695 more)
40 (1 study) 10 weeks	serious <sup>1</sup>	no serious	no serious indirectness	very serious <sup>2</sup>	-	VERY LOW <sup>1,2</sup> due to risk of bias,			(0.07 to	50 per 1000 Moderat	0 fewer per 1000 (from 47 fewer to 695 more) te 0 fewer per 1000
40 (1 study) 10 weeks <b>Dry mou</b> 40	serious <sup>1</sup>	no serious inconsistency ssed with: Study- no serious	no serious indirectness specific side effe no serious	very serious <sup>2</sup> oct checklist)	-	VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	(5%)	(5%)	(0.07 to 14.9)	50 per 1000 Moderat 50 per 1000	0 fewer per 1000 (from 47 fewer to 695 more) te 0 fewer per 1000
40 (1 study) 10 weeks	serious <sup>1</sup>	no serious inconsistency ssed with: Study-	no serious indirectness specific side effe	very serious <sup>2</sup>	undetected	VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	(5%)	(5%)	(0.07 to 14.9)	50 per 1000 Moderat 50 per 1000 Study p	0 fewer per 1000 (from 47 fewer to 695 more) te 0 fewer per 1000 (from 47 fewer to 695 more)

										150 per 1000	<b>50 more per 1000</b> (from 99 fewer to 632 more)
Fatigue (a	assessed	with: Study-speci	fic side effect che	ecklist)							
40 (1 study)		no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		3/20 (15%)	5/20 (25%)	<b>RR 1.67</b> (0.46 to	Study p	opulation
10 weeks						due to risk of bias,		· · /	6.06)	150 per 1000	<b>100 more per 1000</b> (from 81 fewer to 759 more)
						imprecision				Moderat	e
										150 per 1000	<b>100 more per 1000</b> (from 81 fewer to 759 more)

### 1.33.8 Adverse events associated with melatonin

### Adverse events associated with melatonin versus placebo

		(	Quality assess	ment			Summary of Findings					
Participants (studies)	dies) bias	of Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study ev		Relative effect	Anticipate	ed absolute effects	
Follow up							With Control	With Adverse events associated with melatonin	(95% CI)	Risk with Control	Risk difference with Adverse events associated with melatonin (95% CI)	
Coughin	<b>g</b> (assess	sed with: Study-spe	cific report of adv	erse event)	I	1	<u> </u>		<u> </u>	1	- <u>-</u>	
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		13/33 (39.4%)	6/30 (20%)	RR 0.51 Study	Study pop	ly population	
(1 51009)		niconcional		001000		due to risk of	(00.470)	(2070)	(0.22 10	394 per	193 fewer per 1000	

12 weeks						bias, imprecision			1.17)	1000	(from 307 fewer to 67 more)
										Moderate	, ,
										394 per 1000	<b>193 fewer per 1000</b> (from 307 fewer to 67 more)
Mood s	wings (a	assessed with: Stud	dy-specific report	of adverse eve	ent)		1			-	
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		6/33 (18.2%)	7/30 (23.3%)	<b>RR 1.28</b> (0.49 to	Study po	pulation
12 weeks		,				due to risk of bias, imprecision	. ,	()	3.39)	182 per 1000	<b>51 more per 1000</b> (from 93 fewer to 435 more)
										Moderate	
										182 per 1000	<b>51 more per 1000</b> (from 93 fewer to 435 more)
Vomitin	<b>g</b> (assesse	ed with: Study-spec	Lific report of adve	erse event)	1		1		I	<u> </u>	
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		7/33 (21.2%)	7/30 (23.3%)	<b>RR 1.1</b> (0.44 to	Study pop	pulation
12 weeks		inconsistency	indirectiness	301003		due to risk of bias, imprecision	. ,	(20.070)	2.77)	212 per 1000	<b>21 more per 1000</b> (from 119 fewer to 375 more)
										Moderate	
										212 per 1000	<b>21 more per 1000</b> (from 119 fewer to 375 more)

63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		6/33 (18.2%)	5/30 (16.7%)	<b>RR 0.92</b> (0.31 to	Study po	pulation
12 weeks						due to risk of bias, imprecision	, ,		2.7)	182 per 1000	<b>15 fewer per 1000</b> (from 125 fewer to 309 more)
										Moderate	•
										182 per 1000	<b>15 fewer per 1000</b> (from 126 fewer to 309 more)
Headac	<b>he</b> (asses	sed with: Study-sp	ecific report of ad	verse event)	•					1	•
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/33 (6.1%)	2/30 (6.7%)	<b>RR 1.1</b> (0.17 to	Study po	pulation
12 weeks		lineeneisteney				due to risk of bias, imprecision		(0.176)	7.33)	61 per 1000	6 more per 1000 (from 50 fewer to 384 more)
										Moderate	•
										61 per 1000	6 more per 1000 (from 51 fewer to 386 more)
Rash (as	sessed with	: Study-specific re	port of adverse ev	/ent)							
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		3/33 (9.1%)	4/30 (13.3%)	<b>RR 1.47</b> (0.36 to	Study po	pulation
12 weeks		inconsistency	Indirectiless	361003		due to risk of bias, imprecision		(13.370)	6.03)	91 per 1000	<b>43 more per 1000</b> (from 58 fewer to 457 more)
										Moderate	

										91 per 1000	<b>43 more per 1000</b> (from 58 fewer to 458 more)
Somno	lence (as	sessed with: Stud	y-specific report o	of adverse ever	nt)	I	1				
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		5/33 (15.2%)	3/30	<b>RR 0.66</b> (0.17 to	Study po	oulation
12 weeks		inconsistency		301003		due to risk of bias, imprecision	, ,	(10,0)	2.53)	152 per 1000	52 fewer per 1000 (from 126 fewer to 232 more)
										Moderate	
										152 per 1000	<b>52 fewer per 1000</b> (from 126 fewer to 233 more)
(1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		6/33 (18.2%)	1/30 (3.3%)	<b>RR 0.18</b> (0.02 to	Study po	- T
63 (1 study) 12 weeks	serious <sup>1</sup>				undetected		(18.2%)			Study po 182 per 1000	149 fewer per 1000 (from 178 fewer to 80
											more)
										Moderate	
										182 per 1000	<b>149 fewer per 1000</b> (from 178 fewer to 80 more)
Hypoth	ermia (a	ssessed with: Stud	ly-specific report of	of adverse eve	nt)				ł		
				1		000	2/33	1/30	RR 0.55	Study po	aulation
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		(6.1%)	(3.3%)	(0.05 to	orady por	Julation

						bias, imprecision				1000	more)
										Moderate	e
										61 per 1000	<b>27 fewer per 1000</b> (from 58 fewer to 290 more)
ncreas	ed activ	vity (assessed w	ith: Study-specific	report of adve	erse event)	1	1		ŀ	_ <b>I</b>	-
3 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		3/33 (9.1%)	3/30 (10%)	<b>RR 1.1</b> (0.24 to	Study po	pulation
12 weeks						due to risk of bias, imprecision		(1070)	5.04)	91 per 1000	<b>9 more per 1000</b> (from 69 fewer to 367 more)
										Moderate	
										91 per 1000	<b>9 more per 1000</b> (from 69 fewer to 368 more)
Nausea	(assessed	with: Study-specif	ic report of advers	se event)	1	1	I		I		
53 [1 study]	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/33 (6.1%)	1/30 (3.3%)	<b>RR 0.55</b> (0.05 to	Study po	pulation
12 weeks		meenelectroy		Sonedo		due to risk of bias, imprecision		(0.070)	5.76)	61 per 1000	<b>27 fewer per 1000</b> (from 58 fewer to 288 more)
										Moderate	9

63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/33 (6.1%)	0/30 (0%)	<b>RR 0.22</b> (0.01 to	Study pop	ulation
12 weeks						due to risk of bias, imprecision			4.39)	61 per 1000	<b>47 fewer per 1000</b> (from 60 fewer to 205 more)
										Moderate	
										61 per 1000	<b>48 fewer per 1000</b> (from 60 fewer to 207 more)
Breathle	essnes	<b>S</b> (assessed with:	Study-specific rep	port of adverse	event)			-		•	1
63 (1 study) 12 weeks						See comment	0/33 (0%)	0/30 (0%)	not pooled	See comment	See comment
Hung-o	ver feel	ing (assessed w	vith: Study-specific	c report of adve	erse event)	1	<u> </u>		<b>I</b>	1	1
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		0/33 (0%)	1/30 (3.3%)	<b>RR 3.29</b> (0.14 to	Study pop	ulation
12 weeks		lineerioioterioy		conouc		due to risk of bias, imprecision	. ,	(0.070)	77.82)	0 per 1000	-
										Moderate	ļ
										0 per 1000	-
Tremor	(assessed v	with: Study-specifi	c report of advers	e event)	1	1	I			1	1
63						See comment	0/33 (0%)	0/30 (0%)	not pooled	See comment	See comment

63 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		1/33 (3%)	0/30 (0%)	<b>RR 0.37</b> (0.02 to	Study po	pulation	
12 weeks						due to risk of bias, imprecision	. ,		8.65)	30 per 1000	<b>19 fewer per 1000</b> (from 30 fewer to 232 more)	
										Moderate		
										30 per 1000	<b>19 fewer per 1000</b> (from 29 fewer to 229 more)	
oulei (a	ssessea wit	h: Study-specific r	eport of adverse e	event)						Study population		
63		no serious	eport of adverse e	very	undetected		20/33	15/30 (50%)	<b>RR 0.82</b> (0.53 to	Study po	pulation	
63 (1 study) 12 weeks					undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	(60.6%)	15/30 (50%)	<b>RR 0.82</b> (0.53 to 1.3)	Study po 606 per 1000	pulation 109 fewer per 1000 (from 285 fewer to 182 more)	
63 (1 study)		no serious	no serious	very	undetected	VERY LOW <sup>1,2</sup> due to risk of	(60.6%)		(0.53 to	606 per	<b>109 fewer per 1000</b> (from 285 fewer to 182 more)	

## 1.33.9 Adverse events associated with opioid antagonists

#### Adverse events associated with naltrexone versus placebo

Quality assessment

Summary of Findings

Participants		Inconsistency	Indirectness	Imprecision		Overall quality of	Study ev	vent rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	evidence	With Control	With Adverse events associated with opioid antagonists	effect (95% CI)	Risk with Control	Risk difference with Adverse events associated with opioid antagonists (95% Cl)
Any side	effect (	assessed with: Stu	udy-specific side	effect checklis	t)						
41 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		7/18 (38.9%)	13/23 (56.5%)	<b>RR 1.45</b> (0.74 to	Study po	opulation
6 weeks		Inconsistency	Indirectriess	senous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(30.9%)	(30.3%)	2.87)	389 per 1000	<b>175 more per 1000</b> (from 101 fewer to 727 more)
										Moderat	e
										389 per 1000	<b>175 more per 1000</b> (from 101 fewer to 727 more)
Aggressi	veness	(assessed with: S	l Study-specific sid	e effect checkl	ist)						
41 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		5/18	4/23 (17.4%)	<b>RR 0.63</b> (0.2 to 2)	Study po	opulation
6 weeks		linconsistency		Sellous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(27.076)	(17.470)	(0.2 10 2)	278 per 1000	<b>103 fewer per 1000</b> (from 222 fewer to 278 more)
										Moderat	e
										278 per 1000	<b>103 fewer per 1000</b> (from 222 fewer to 278 more)
Self-injur	ious be	<b>haviour</b> (asse	ssed with: Study	-specific side e	effect checklist)		1	·	<u> </u>	1	
41 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		2/18 (11.1%)	1/23	<b>RR 0.39</b> (0.04 to	Study po	opulation
6 weeks			11101100110055	301003	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(11.170)	(4.570)	3.98)	111 per 1000	<b>68 fewer per 1000</b> (from 107 fewer to 331 more)

										Moderat	te
										111 per 1000	68 fewer per 1000 (from 107 fewer to 331 more)
Hyperac	<b>tivity</b> (as	sessed with: Study	/-specific side eff	ect checklist)	•		•	•	•	•	•
41 (1. atudu)	serious <sup>1</sup>	no serious	no serious	very serious <sup>2</sup>	reporting bias strongly		3/18 (16.7%)	2/23	<b>RR 0.52</b> (0.1 to	Study p	opulation
(1 study) 6 weeks		inconsistency	indirectness	senous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(16.7%)	(8.7%)	(0.1 to 2.8)	167 per 1000	80 fewer per 1000 (from 150 fewer to 300 more)
										Moderat	te
										167 per 1000	80 fewer per 1000 (from 150 fewer to 301 more)
Temper	tantrum	S (assessed with:	Study-specific si	de effect chec	klist)					1	
41 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		1/18 (5.6%)	2/23 (8.7%)	<b>RR 1.57</b> (0.15 to	Study p	opulation
6 weeks		Inconsistency	Indirectiness	senous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(5.0%)	(0.7 %)	15.92)	56 per 1000	<b>32 more per 1000</b> (from 47 fewer to 829 more)
										Moderat	te
										56 per 1000	<b>32 more per 1000</b> (from 48 fewer to 836 more)
Stereoty	<b>pies</b> (ass	essed with: Study	-specific side effe	ct checklist)	<u> </u>		<u> </u>	·		1	Į.
41 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		3/18 (16.7%)	2/23 (8.7%)	<b>RR 0.52</b> (0.1 to	Study p	opulation
6 weeks		literiolecitely			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.170)	(0 /0)	2.8)	167 per 1000	80 fewer per 1000 (from 150 fewer to 300 more)

							]			Moderat	te
										167 per 1000	80 fewer per 1000 (from 150 fewer to 301 more)
Irritabili	ty (assesse	ed with: Study-spe	cific side effect c	hecklist)	•	•	•			-	
41 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		2/18 (11.1%)	3/23	<b>RR 1.17</b> (0.22 to	Study p	opulation
6 weeks		Inconsistency	Indirectriess	Serious	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(11.176)	(13%)	6.3)	111 per 1000	<b>19 more per 1000</b> (from 87 fewer to 589 more)
										Moderat	te
										111 per 1000	<b>19 more per 1000</b> (from 87 fewer to 588 more)
Decreas	sed trans	sient verbal	production	assessed with	: Study-specific si	de effect checklist)			I		
41 (1 study)	serious1	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		0/18 (0%)	1/23 (4.3%)	<b>RR 2.38</b> (0.1 to	Study p	opulation
6 weeks		Inconsistency	maneciness	senous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0%)	(4.3%)	55.06)	0 per 1000	-
						publication bias				Moderat	te
										Moderat 0 per 1000	te -
Slight s	leepines	S (assessed with	: Study-specific s	ide effect chea	cklist)					0 per	te -
41	leepines	no serious	no serious	very	reporting bias	- 	0/18	1/23	RR 2.38	0 per 1000	te - opulation
Slight s 41 (1 study) 6 weeks	-			1	· ·		0/18 (0%)	1/23 (4.3%)	<b>RR 2.38</b> (0.1 to 55.06)	0 per 1000	-

										0 per 1000	-
Falling a	sleep (a	ssessed with: Stu	dy-specific side e	ffect checklist	)		1		1	1	
41 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		0/18 (0%)	2/23 (8.7%)	<b>RR 3.96</b> (0.2 to	Study p	opulation
6 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision,	(0,0)	(0.1.70)	77.63)	0 per 1000	-
						publication bias				Modera	te
										0 per 1000	-
Decrease	ed appe	etite (assessed w	vith: Study-specifi	c side effect c	checklist)				1		
41 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		0/18 (0%)	2/23 (8.7%)	<b>RR 3.96</b> (0.2 to	Study p	opulation
6 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		%) (8.7%)	77.63)	0 per 1000	-
						publication blas				Modera	te
										0 per 1000	-
Vomiting	(assessed	d with: Study-spec	ific side effect ch	ecklist)	4		1			<u> </u>	-
41 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		0/18 (0%)	3/23 (13%)	<b>RR 5.54</b> (0.3 to	Study p	opulation
6 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0,0)	(,)	100.86)	0 per 1000	-
										Modera	te
										0 per 1000	-

<sup>2</sup> Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25) <sup>3</sup> Potential conflict of interest as drug and placebo were supplied by the manufacturer

## 1.33.10 Adverse events associated with SNRIs

Adverse events associated with atomoxetine versus placebo

			Quality asses	ssment				Sum	mary of F	indings		
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study ev	vent rates (%)	Relative	Anticipa	ated absolute effects	
(studies) Follow up	bias				bias	of evidence	With Control	With Adverse events associated with selective noradrenaline reuptake inhibitors	effect (95% CI)	Risk with Control	Risk difference with Adverse events associated with selective noradrenaline reuptake inhibitors (95% CI)	
Any adve	erse eve	ent (assessed wi	th: Study-specifi	c open-ended	questionning for	adverse events)						
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		32/49 (65.3%)	39/48 (81.3%)	<b>RR 1.24</b> (0.97 to	Study p	opulation	
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			1.59)	653 per 1000	<b>157 more per 1000</b> (from 20 fewer to 385 more)	
										Moderate		
										653 per 1000	<b>157 more per 1000</b> (from 20 fewer to 385 more)	
Discontin	nuation	due to adve	erse events	assessed with	n: Study-specific	I open-ended questic	onning for	adverse events)	<u> </u>	1		
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		0/49 (0%)	1/48 (2.1%)	<b>OR 3.13</b> (0.12 to	Study p	opulation	
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	<b>`</b> ,	· · ·	78.66)	0 per 1000	-	
										Modera	te	
										0 per	-	

							]			1000	
Abdomir	nal pain	(assessed with: S	L Study-specific op	en-ended que	stionning for adve	erse events)	•			I	
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		3/49 (6.1%)	4/48 (8.3%)	<b>RR 1.36</b> (0.32 to	Study p	opulation
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.170)		5.76)	61 per 1000	22 more per 1000 (from 42 fewer to 291 more)
										Modera	te
										61 per 1000	22 more per 1000 (from 41 fewer to 290 more)
Upper at	odomina	al pain (assess	ed with: Study-s	pecific open-e	nded questionnin	g for adverse event	s)			<u>I</u>	1
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		3/49 (6.1%)	9/48 (18.8%)	<b>RR 3.06</b> (0.88 to	Study p	opulation
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	()	(()))	10.63)	61 per 1000	<b>126 more per 1000</b> (from 7 fewer to 590 more)
										Modera	te
										61 per 1000	<b>126 more per 1000</b> (from 7 fewer to 587 more)
Diarrhoe	a (assesse	ed with: Study-spe	ecific open-ended	d questionning	for adverse ever	nts)	<b>I</b>			1	1
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		3/49 (6.1%)	1/48 (2.1%)	<b>RR 0.34</b> (0.04 to	Study p	opulation
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.170)	(//)	3.16)	61 per 1000	40 fewer per 1000 (from 59 fewer to 132 more)
										Modera	te
										61 per	40 fewer per 1000

										1000	(from 59 fewer to 132 more)
Nausea	(assessed v	vith: Study-specifi	ic open-ended q	uestionning fo	r adverse events)						
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		4/49 (8.2%)	14/48 (29.2%)	<b>RR 3.57</b> (1.27 to	Study p	opulation
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			10.08)	82 per 1000	<b>210 more per 1000</b> (from 22 more to 741 more)
										Modera	te
										82 per 1000	<b>211 more per 1000</b> (from 22 more to 745 more)
Vomiting	g (assesse	d with: Study-spe	cific open-ended	questionning	for adverse event	s)	<u> </u>			1	Į
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		5/49 (10.2%)	7/48 (14.6%)	<b>RR 1.43</b> (0.49 to	Study p	opulation
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			4.19)	102 per 1000	44 more per 1000 (from 52 fewer to 326 more)
										Modera	te
										102 per 1000	<b>44 more per 1000</b> (from 52 fewer to 325 more)
Fatigue	(assessed v	vith: Study-specifi	ic open-ended q	uestionning for	r adverse events)	•	1			1	ł
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		4/49 (8.2%)	11/48 (22.9%)	<b>RR 2.81</b> (0.96 to	Study p	opulation
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		. ,	8.21)	82 per 1000	148 more per 1000 (from 3 fewer to 589 more)
										Modera	te

										82 per 1000	<b>148 more per 1000</b> (from 3 fewer to 591 more)
Pyrexia	(assessed v	with: Study-specifi	ic open-ended qu	uestionning for	adverse events)				I.		1
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		3/49 (6.1%)	0/48 (0%)	<b>RR 0.15</b> (0.01 to	Study p	opulation
8 weeks		Inconsistency	Indirectiless	Sellous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.176)	(0 %)	2.75)	61 per 1000	52 fewer per 1000 (from 61 fewer to 107 more)
										Modera	te
										61 per 1000	52 fewer per 1000 (from 60 fewer to 107 more)
Influenz	a (assesse	d with: Study-spe	cific open-ended	questionning	for adverse event	s)					
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		0/49 (0%)	3/48 (6.3%)	<b>RR 7.14</b> (0.38 to	Study p	opulation
8 weeks		lineeneisteney		5011005	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(070)	(0.070)	134.69)	0 per 1000	-
						publication blab				Modera	te
										0 per 1000	-
Decease	ed appet	t <b>ite</b> (assessed w	ith: Study-specifi	c open-ended	questionning for	adverse events)				<u> </u>	
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly		3/49 (6.1%)	13/48 (27.1%)	<b>RR 4.42</b> (1.34 to	Study p	opulation
3 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(01170)	(,0)	14.55)	61 per 1000	<b>209 more per 1000</b> (from 21 more to 830 more)
										Modera	te
										61 per	209 more per 1000

										1000	(from 21 more to 827 more)
Myalgia	(assessed	with: Study-specif	ic open-ended q	uestionning for	adverse events)				· · ·		
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		0/49 (0%)	3/48 (6.3%)	<b>RR 7.14</b> (0.38 to	Study p	opulation
3 weeks		linconsistency	indirectriess	Serious	suspected <sup>3</sup>	due to risk of bias, imprecision,	(078)	(0.3%)	134.69)	0 per 1000	-
						publication bias				Modera	te
										0 per 1000	-
Dizzines	S (assesse	ed with: Study-spe	cific open-ended	l questionning	for adverse even	ts)	•				1
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		1/49 (2%)	3/48 (6.3%)	<b>RR 3.06</b> (0.33 to	Study p	opulation
3 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			28.42)	20 per 1000	<b>42 more per 1000</b> (from 14 fewer to 560 more)
										Modera	te
										20 per 1000	<b>41 more per 1000</b> (from 13 fewer to 548 more)
Headach	1e (assess	ed with: Study-spe	ecific open-ende	d questionning	for adverse ever	nts)	1			1	1
97 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		9/49 (18.4%)	12/48	<b>RR 1.36</b> (0.63 to	Study p	opulation
3 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	()	()	2.93)	184 per 1000	<b>66 more per 1000</b> (from 68 fewer to 354 more)
										Modera	te
										184 per	<b>66 more per 1000</b> (from 68 fewer to 355

										1000	more)
Psychor	notor h	peractivity	assessed with: S	Study-specific	open-ended ques	stionning for adverse	e events)		I		
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		4/49 (8.2%)	1/48 (2.1%)	<b>RR 0.26</b> (0.03 to	Study p	oopulation
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	()	()	2.2)	82 per 1000	<b>60 fewer per 1000</b> (from 79 fewer to 98 more)
										Modera	ite
										82 per 1000	61 fewer per 1000 (from 80 fewer to 98 more)
Aggress	sion (asse	ssed with: Study-	specific open-en	ded questionni	ing for adverse ev	vents)	1		I	Į	1
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		3/49 (6.1%)	2/48 (4.2%)	<b>RR 0.68</b> (0.12 to	Study p	oopulation
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(01170)	(	3.89)	61 per 1000	<b>20 fewer per 1000</b> (from 54 fewer to 177 more)
										Modera	ite
										61 per 1000	<b>20 fewer per 1000</b> (from 54 fewer to 176 more)
Early mo	orning a	wakening (as	ssessed with: Stu	udy-specific op	ben-ended question	onning for adverse e	events)		<b>I</b>	I	
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		0/49 (0%)	5/48 (10.4%)	<b>RR 11.22</b> (0.64 to	Study p	oopulation
8 weeks		lineensisteney		5011005	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(070)	(10.470)	197.6)	0 per 1000	-
										Modera	ite
										0 per	-

97 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly		5/49 (10.2%)	3/48 (6.3%)	<b>RR 0.61</b> (0.15 to	Study po	opulation
8 weeks		inconsistentely			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.270)	(0.070)	2.42)	1000	<b>40 fewer per 1000</b> (from 87 fewer to 145 more)
										Moderat	e
										-	<b>40 fewer per 1000</b> (from 87 fewer to 145 more)

# **1.34ADVERSE EVENTS ASSOCIATED WITH BIOMEDICAL INTERVENTIONS**

## 1.34.1 Adverse events associated with medical procedures

Adverse events associated with HBOT versus attention-placebo

Quality assessment							Summary of Findings					
	Risk of bias	Inconsistency	Indirectness	Imprecision		of evidence	Study e With Control		effect	Anticipa Risk with Control	Ated absolute effects Risk difference with Adverse events associated with hyperbaric oxygen treatment (HBOT) versus attention- placebo control (95% Cl)	
Any adve	Any adverse event (assessed with: Study-specific daily treatment logbooks)											

62 (1 study) 4 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW <sup>1.2,3</sup> due to risk of bias, imprecision, publication bias		3/33 (9.1%)	<b>RR 1.32</b> (0.24 to 7.35)	Study population	
										69 per 1000	<b>22 more per 1000</b> (from 52 fewer to 438 more)
										Moderate	
										69 per 1000	<b>22 more per 1000</b> (from 52 fewer to 438 more)
Minor-gr	ade ear	barotrauma	l (assessed with:	Not reported)	)		1		4	1	
58 (1 study) 4 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious⁵	undetected	⊕⊕⊖⊖ LOW <sup>4,5</sup> due to risk of bias, imprecision		11/29 6) (37.9%)	<b>RR 3.67</b> (1.14 to 11.79)	Study population	
										103 per 1000	<b>276 more per 1000</b> (from 14 more to 1000 more)
										Moderate	
										103 per 1000	<b>275 more per 1000</b> (from 14 more to 1000 more)
administrator <sup>2</sup> Events<300 <sup>3</sup> Potential co <sup>4</sup> High risk of	r who was 0 and 95% onflict of int detection plinding, ar	non-blind to treatn Cl crosses both li erest as study fun	nent assignment ne of no effect a ded by the Interi 4 weeks was a s	and to other p nd measure of national Hyper	potentially confour f appreciable ben rbarics Association	Inding factors lefit or harm (RR 0. on and authors profi	75/1.25) t from the	e events and adverse events and adverse events and adverse events and out	ment in thei	r clinical p	practices

## **1.34.2** Adverse events associated with nutritional interventions

### Adverse events associated with multivitamin/mineral supplement versus placebo

Quality assessment								Summary of Findings					
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative	Anticipated absolute effects			
							With Control	With Adverse events associated with multivitamin and mineral supplement	effect (95% CI)	Risk with Control	Risk difference with Adverse events associated with multivitamin and mineral supplement (95% CI)		
Discontir	nuation	due to adver	<b>se events</b> (a	ssessed with:	Number of par	ticipants who dis	scontinue	d due to adverse events)					
141 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	5/69 (7.2%)	3/72 (4.2%)	<b>RR 0.57</b> (0.14 to 2.31)	Study population			
										72 per 1000	<b>31 fewer per 1000</b> (from 62 fewer to 95 more)		
										Moderate			
										73 per 1000	<b>31 fewer per 1000</b> (from 63 fewer to 96 more)		
Disconti	nuation	due to diarrh	IOEA (assessed	with: Number	of participants	who discontinue	ed due to	diarrhoea)	1	<u> </u>	1		
141 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1</sup> due to imprecision	3/69 (4.3%)	1/72 (1.4%)	<b>RR 0.32</b> (0.03 to 3)	Study population			
										43 per 1000	<b>30 fewer per 1000</b> (from 42 fewer to 87 more)		
										Moderate			
										44 per 1000	<b>30 fewer per 1000</b> (from 43 fewer to 88 more)		
Disconti	nuation	due to increa	ased stimmi	i <b>ng</b> (assessed	d with: Number	of participants	who disco	ntinued due to increased	d stimming)	Į	1		
(1 study) ris	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1</sup> due to imprecision	1/69 (1.4%)	0/72 (0%)	<b>RR 0.32</b> (0.01 to 7.72)	Study population			
										14 per 1000	<b>10 fewer per 1000</b> (from 14 fewer to 97 more)		

										15 per 1000	<b>10 fewer per 1000</b> (from 15 fewer to 101 more)
Disconti	inuation of	due to behav	viour proble	ems (assesse	ed with: Numbe	r of participants	who disc	ontinued due to	behaviour problems	)	
141 (1 study)		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	$\oplus \oplus \ominus \ominus$ LOW <sup>1</sup>	1/69 (1.4%)	2/72 (2.8%)	<b>RR 1.92</b> (0.18 to	Study p	opulation
(1 study) 13 weeks	bias					due to imprecision		<b>、</b> ,	20.66)	14 per 1000	<b>13 more per 1000</b> (from 12 fewer to 285 more)
										Modera	te
										15 per 1000	14 more per 1000 (from 12 fewer to 295 more)

#### Adverse events associated with omega-3 fatty acids versus placebo

		C	Quality assessi	ment				Su	mmary of	Findings	;
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study ev	vent rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Adverse events associated with omega-3 fatty acids	effect (95% CI)	Risk with Control	Risk difference with Adverse events associated with omega-3 fatty acids (95% CI)
Any adve	erse eve	ent (assessed with	n: Study-specific r	eport of advers	se event)				F		
27 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		4/13 (30.8%)	5/14 (35.7%)	<b>RR 1.16</b> (0.4 to	Study po	opulation
12 weeks						due to risk of bias, imprecision		````	3.41)	308 per 1000	<b>49 more per 1000</b> (from 185 fewer to 742 more)
										Moderat	e
										308 per	49 more per 1000

										1000	(from 185 fewer to 742 more)
Rashes (	assessed w	vith: Study-specific	report of adverse	event)		•					
27 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		0/13 (0%)	2/14 (14.3%)	<b>RR 4.67</b> (0.24 to	Study p	opulation
12 weeks		Inconsistency	Indirectriess	Senous		due to risk of bias,	(078)	(14.370)	(0.24 to 88.96)	0 per 1000	-
						imprecision				Moderat	ie
										0 per 1000	-
Upper re	spirato	ry infection (a	assessed with: Stu	udy-specific re	port of adverse	event)					
27 [1 study]	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		0/13 (0%)	1/14 (7.1%)	<b>RR 2.8</b> (0.12 to	Study p	opulation
12 weeks			63.2)	0 per 1000	-						
										Moderat	ie
										0 per 1000	-
Nose ble	eds (asse	essed with: Study-	specific report of a	adverse event)	)		1			<u> </u>	1
27 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		0/13 (0%)	1/14 (7.1%)	<b>RR 2.8</b> (0.12 to	Study p	opulation
12 weeks		lineerioleteriey				due to risk of bias, imprecision	(0,0)	(11173)	63.2)	0 per 1000	-
						Imprecision				Moderat	te
										0 per 1000	-
GI svmn	toms (as	sessed with: Study	-specific report of	adverse ever	l	1	<u> </u>			ļ	

27 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		0/13 (0%)	1/14 (7.1%)	<b>RR 2.8</b> (0.12 to	Study po	opulation
12 weeks						due to risk of bias, imprecision		<b>、</b> ,	63.2)	0 per 1000	-
						Imprecision				Moderat	e
										0 per 1000	-
Hyperac	tivity (as:	sessed with: Stud	y-specific report c	of adverse eve	nt)						
27 (1 study)	serious <sup>1</sup>	inconsistency indirectness serious <sup>2</sup> VERY LOW <sup>1,2</sup> (23.1%) (0%)						<b>RR 0.13</b> (0.01 to	Study po	opulation	
12 weeks						due to risk of bias, imprecision		(070)	2.36)	231 per 1000	201 fewer per 1000 (from 228 fewer to 314 more)
										Moderat	e
										231 per 1000	201 fewer per 1000 (from 229 fewer to 314 more)
Self-stin	nulatory	behaviour (a	assessed with: St	udy-specific re	port of adverse	event)					
27 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		1/13 (7.7%)	0/14 (0%)	<b>RR 0.31</b> (0.01 to	Study po	opulation
12 weeks		Inconsistency	muneciness	3611043		due to risk of bias, imprecision	(1.170)	(078)	7.02)	77 per 1000	53 fewer per 1000 (from 76 fewer to 463 more)
										Moderat	e
							77 per 1000	<b>53 fewer per 1000</b> (from 76 fewer to 464 more)			

### Adverse events associated with immunoglobulin (dosages combined) versus placebo

		Q	uality assessr	nent				Sun	nmary of F	indings	
		Inconsistency	Indirectness	Imprecision		Overall	Study e	vent rates (%)	Relative	Anticipa	ited absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Adverse events associated with immunoglobulin (dosages combined)	effect (95% CI)	Risk with Control	Risk difference with Adverse events associated with immunoglobulin (dosages combined) (95% Cl)
Any adve	erse eve	ent (assessed wi	th: Study-specific	report of adve	erse event)						
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW <sup>1,2</sup>	25/31 (80.6%)	71/94 (75.5%)	<b>RR 0.94</b> (0.76 to	Study p	opulation
12 weeks						due to risk of bias, imprecision			1.15)	806 per 1000	<b>48 fewer per 1000</b> (from 194 fewer to 121 more)
										Moderat	ie
										807 per 1000	<b>48 fewer per 1000</b> (from 194 fewer to 121 more)
Discontir	nuation	due to adve	rse events	assessed with	: Study-specif	ic report of adve	rse event)	)	1	<u>,</u>	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		1/31 (3.2%)	7/94 (7.4%)	<b>RR 2.31</b> (0.3 to	Study p	opulation
12 weeks		lineensisteney		001000		due to risk of bias, imprecision	(0.270)	(1.470)	18.03)	32 per 1000	<b>42 more per 1000</b> (from 23 fewer to 549 more)
						Imprecision				Moderat	te
										32 per 1000	<b>42 more per 1000</b> (from 22 fewer to 545 more)
Infection	s/Infest	ations (assess	ed with: Study-s	pecific report o	f adverse ever	nt)	ļ		•	ļ	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		16/31	46/94 (48.9%)	<b>RR 0.95</b> (0.64 to	Study p	opulation
12 weeks						due to risk of bias,	(3.1070)	(,)	1.41)	516 per	<b>26 fewer per 1000</b> (from 186 fewer to 212

						imprecision				1000	more)	
										Moderat	e	
										516 per 1000	<b>26 fewer per 1000</b> (from 186 fewer to 212 more)	
Gastroin	testinal	disorders (a	ssessed with: St	udy-specific re	port of adverse	e event)	ļ		1	,		
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		9/31 (29%)	36/94 (38.3%)	<b>RR 1.32</b> (0.72 to	Study p	opulation	
12 weeks						due to risk of bias, imprecision	· · ·	< , , , , , , , , , , , , , , , , , , ,	2.42)	290 per 1000	<b>93 more per 1000</b> (from 81 fewer to 412 more)	
										Moderat	e	
										290 per 1000	<b>93 more per 1000</b> (from 81 fewer to 412 more)	
Psychiat	ric diso	orders (assesse	d with: Study-spe	ecific report of	adverse event	)	I			1	l .	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		6/31 (19.4%)	17/94	<b>RR 0.93</b> (0.4 to	Study p	dy population	
12 weeks						due to risk of bias, imprecision	(10.170)	(10.176)	2.16)	194 per 1000	<b>14 fewer per 1000</b> (from 116 fewer to 225 more)	
										Moderat	e	
										194 per 1000	<b>14 fewer per 1000</b> (from 116 fewer to 225 more)	
Respirat	ory/Tho	oracic/Media:	stinal disor	ders (assess	ed with: Study	-specific report o	f adverse	event)	1	I		
125	serious <sup>1</sup>	no serious	no serious	very	undetected		4/31	15/94	RR 1.24	Study p	opulation	
(1 study) 12 weeks		inconsistency	indirectness	serious <sup>3</sup>		VERY LOW <sup>1,3</sup> due to risk of bias,	(12.9%)	(10%)	(0.44 to 3.45)	129 per 1000	<b>31 more per 1000</b> (from 72 fewer to 316 more)	

						imprecision	]			Moderat	te
								<u>.</u>		129 per 1000	31 more per 1000 (from 72 fewer to 316 more)
	ocutane	ous tissue o	lisorders (as	sessed with: S	Study-specific r	eport of adverse	1			T	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		3/31 (9.7%)	12/94 (12.8%)	<b>RR 1.32</b> (0.4 to	Study p	opulation
12 weeks						due to risk of bias, imprecision	(011 /0)	(,	4.37)	97 per 1000	31 more per 1000 (from 58 fewer to 326 more)
										Moderat	te
										97 per 1000	31 more per 1000 (from 58 fewer to 327 more)
General	disorde	ers/Administ	ration site o	onditions	(assessed wi	th: Study-specific	report of	f adverse event)	<b>I</b>	<u> </u>	1
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		2/31 (6.5%)	9/94 (9.6%)	<b>RR 1.48</b> (0.34 to	Study population	
12 weeks		lineeneisteney				due to risk of bias,	(0.070)	(0.070)	6.5)	65 per 1000	<b>31 more per 1000</b> (from 43 fewer to 355 more)
						imprecision				Modera	te
										65 per 1000	<b>31 more per 1000</b> (from 43 fewer to 357 more)
Nervous	system	n disorders (	assessed with: Si	tudy-specific r	eport of advers	se event)	1	•			1
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		0/31 (0%)	7/94 (7.4%)	<b>RR 5.05</b> (0.3 to	Study p	opulation
12 weeks						due to risk of bias, imprecision			86.01)	0 per 1000	-
						Imprecision				Moderat	te
										0 per 1000	-

Injury/Po	isoning	g/Procedural	complicati	ONS (assesse	ed with: Study	-specific report of	fadverse	event)			
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		1/31 (3.2%)	5/94 (5.3%)	<b>RR 1.65</b> (0.2 to	Study p	opulation
12 weeks						due to risk of bias, imprecision	(===,=,	()	13.58)	32 per 1000	21 more per 1000 (from 26 fewer to 406 more)
										Moderat	te
										32 per 1000	21 more per 1000 (from 26 fewer to 403 more)
Investiga	tions (a	ssessed with: Stu	dy-specific repor	t of adverse ev	vent)						
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		1/31 (3.2%)	3/94 (3.2%)	<b>RR 0.99</b> (0.11 to	Study p	opulation
12 weeks						due to risk of bias, imprecision			9.17)	32 per 1000	<b>0 fewer per 1000</b> (from 29 fewer to 264 more)
										Moderat	te
										32 per 1000	<b>0 fewer per 1000</b> (from 28 fewer to 261 more)
Metabolis	sm/Nut	rition disord	ers (assessed)	with: Study-spe	ecific report of	adverse event)					
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		1/31 (3.2%)	3/94 (3.2%)	<b>RR 0.99</b> (0.11 to	Study p	opulation
12 weeks						due to risk of bias, imprecision	()		9.17)	32 per 1000	<b>0 fewer per 1000</b> (from 29 fewer to 264 more)
										Moderat	te
										32 per 1000	<b>0 fewer per 1000</b> (from 28 fewer to 261 more)
Eye disor	ders (a	ssessed with: Stud	dy-specific report	of adverse ev	ent)						
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		0/31 (0%)	3/94 (3.2%)	<b>RR 2.36</b> (0.13 to	Study p	opulation
12 weeks		,				due to risk of	· · /	、 <i>,</i>	44.42)	0 per	-

						bias, imprecision				1000	
										Modera	te
										0 per 1000	-
Blood/Ly	/mphati	c system dis	sorders (asse	essed with: Stu	dy-specific rep	port of adverse ev	vent)				
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		1/31 (3.2%)	1/94 (1.1%)	<b>RR 0.33</b> (0.02 to	Study p	opulation
12 weeks						due to risk of bias, imprecision	(0.270)	(,0)	5.12)	32 per 1000	22 fewer per 1000 (from 32 fewer to 133 more)
										Modera	te
										32 per 1000	<b>21 fewer per 1000</b> (from 31 fewer to 132 more)
Renal/U	inary di	isorders (asse	essed with: Study	-specific repor	t of adverse ev	vent)			4		
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		2/31 (6.5%)	0/94 (0%)	<b>RR 0.07</b> (0 to	Study p	opulation
12 weeks		lineensisteney				due to risk of bias, imprecision	(0.070)	(0,0)	1.37)	65 per 1000	60 fewer per 1000 (from 65 fewer to 24 more)
										Modera	te
										65 per 1000	60 fewer per 1000 (from 65 fewer to 24 more)
Ear/Laby	rinth di	i <b>sorders</b> (asse	essed with: Study	-specific repor	t of adverse ev	vent)	<b>I</b>			1	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		0/31 (0%)	1/94 (1.1%)	<b>RR 1.01</b> (0.04 to	Study p	opulation
12 weeks						due to risk of bias, imprecision		· · /	24.19)	0 per 1000	-
										Modera	te

									0 per 1000	-
system	disorders (a	assessed with: St	udy-specific re	eport of advers	e event)			I		1
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>1,3</sup> due to risk of	0/31 (0%)	1/94 (1.1%)	<b>RR 1.01</b> (0.04 to 24.19)		opulation
					bias, imprecision				1000	
									Modera	te
									0 per 1000	-
r disord	ers (assessed v	vith: Study-specif	ic report of adv	verse event)					1	
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected		0/31 (0%)	1/94 (1.1%)	<b>RR 1.01</b> (0.04 to	Study p	opulation
					due to risk of bias,			24.19)	0 per 1000	-
					imprecision					
									Modera	te
	serious <sup>1</sup>	serious <sup>1</sup> no serious inconsistency r disorders (assessed v serious <sup>1</sup> no serious	serious <sup>1</sup> no serious inconsistency       no serious indirectness         r       disorders serious <sup>1</sup> (assessed with: Study-specif         serious <sup>1</sup> no serious       no serious	serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>3</sup> r       disorders serious <sup>1</sup> (assessed with: Study-specific report of adv no serious       very	serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>3</sup> undetected         r       disorders serious <sup>1</sup> (assessed with: Study-specific report of adverse event)         serious <sup>1</sup> no serious       very undetected	inconsistency       indirectness       serious <sup>3</sup> VERY LOW <sup>1,3</sup> due to risk of bias, imprecision         r disorders (assessed with: Study-specific report of adverse event)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>3</sup> undetected VERY LOW <sup>1,3</sup> due to risk of bias, indirectness	serious1no serious inconsistencyno serious indirectnessvery serious3undetected $\bigoplus \bigcirc \bigcirc \bigcirc \bigcirc$ VERY LOW1.3 due to risk of bias, imprecision0/31 (0%)r disorders serious1(assessed with: Study-specific report of adverse event)undetected $\bigoplus \bigcirc \bigcirc \bigcirc \bigcirc$ VERY LOW1.3 due to risk of bias, imprecision0/31 (0%)serious1no serious inconsistencyno serious indirectnessvery serious3undetected VERY LOW1.3 due to risk of bias, indirectness0/31 (0%)	$ \begin{array}{ c c c c c } \hline serious^{1} & no \ serious \\ inconsistency \\ inconsistency \\ indirectness \\ indirectness \\ indirectness \\ indirectness \\ serious^{3} \\ \hline serious^{3} \\ \hline very \\ serious^{3} \\ \hline very \\ very \\ imprecision \\ \hline very \\ serious^{1} \\ no \ serious \\ inconsistency \\ \hline no \ serious \\ inconsistency \\ \hline no \ serious \\ indirectness \\ \hline very \\ serious^{3} \\ \hline very \\ very \\ serious^{3} \\ \hline very \\ ver$	serious1no serious inconsistencyno serious indirectnessvery serious3undetected $\bigcirc \bigcirc \bigcirc \bigcirc$ VERY LOW13 due to risk of bias, imprecision $0/31$ (0.0%)1/94 (0%)RR 1.01 (0.04 to 24.19)r disorders (assessed with: Study-specific report of adverse event)undetected $\bigcirc \bigcirc \bigcirc \bigcirc$ VERY LOW13 due to risk of bias, imprecision $0/31$ (1.1%) $1/94$ (0%)RR 1.01 (0.04 to 24.19)serious1no serious inconsistencyno serious indirectnessvery serious3undetected very serious3 $\bigcirc \bigcirc \bigcirc \bigcirc$ very serious3 $0/31$ (1.1%) $1/94$ (0%)RR 1.01 (0.04 to 24.19)	system disorders (assessed with: Study-specific report of adverse event) <ul> <li>serious<sup>1</sup> no serious inconsistency</li> <li>no serious inconsistency</li> <li>no serious indirectness</li> <li>very serious<sup>3</sup></li> <li>undetected bias, imprecision</li> <li>very serious<sup>1</sup> and to risk of bias, imprecision</li> </ul> 0/31 (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)             (1.1%)

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

		Qı	ality assessn	nent				Sum	mary of F	indings	i
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	•	bias	Overall quality of evidence	Study e With Control	With Adverse events	<b>effect</b> (95% CI)	Anticip Risk with Control	Ated absolute effects Risk difference with Adverse events associated with combined ginkgo biloba and risperidone versus combined placebo and risperidone

								risperidone			(95% CI)
Daytime of	drowsi	ness (assessed	with: Study-spe	cific side effec	t checklist)		•				
47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		7/24 (29.2%)	6/23 (26.1%)	<b>RR 0.89</b> (0.35 to	Study p	oopulation
10 weeks						due to risk of bias, imprecision		<b>`</b>	2.26)	292 per 1000	<b>32 fewer per 1000</b> (from 190 fewer to 368 more)
										Modera	te
										292 per 1000	<b>32 fewer per 1000</b> (from 190 fewer to 368 more)
Morning	drowsi	<b>NESS</b> (assessed	with: Study-spe	cific side effec	t checklist)	1	Į		H	1	1
47 (1 study) 10 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias,	0/24 (0%)	2/23 (8.7%)	<b>RR 5.21</b> (0.26 to 102.98)	Study p 0 per 1000	oopulation
						imprecision				Modera	te
										0 per 1000	-
Constipat	tion (ass	sessed with: Study	/-specific side ef	fect checklist)		•	•			4	
47 (1 study) 10 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>1,2</sup> due to risk of	3/24 (12.5%)	3/23 (13%)	<b>RR 1.04</b> (0.23 to 4.65)	-	5 more per 1000
						bias, imprecision				1000	(from 96 fewer to 456 more)
										Modera	te
										125 per 1000	5 more per 1000 (from 96 fewer to 456 more)
Dizziness	(assesse	ed with: Study-spe	cific side effect of	checklist)	1	ł	1		ł		

serious <sup>1</sup>	no serious	no serious	very serious <sup>2</sup>	undetected		3/24 (12.5%)	1/23 (4.3%)	<b>RR 0.35</b>	Study population		
			conouc		due to risk of bias, imprecision	(12:070)	(,)	3.11)	125 per 1000	<b>81 fewer per 1000</b> (from 120 fewer to 264 more)	
									Moderate		
									125 per 1000	81 fewer per 1000 (from 120 fewer to 264 more)	
vement	(assessed with:	Study-specific s	ide effect chec	cklist)	4			ł	1	•	
serious <sup>1</sup>	no serious	no serious	very serious <sup>2</sup>	undetected		1/24 (4.2%)	2/23 (8.7%)	<b>RR 2.09</b>	Study p	opulation	
	lineonoisteney				due to risk of bias,	(4.270)	(0.775)	21.48)	42 per 1000	45 more per 1000 (from 33 fewer to 853 more)	
									Moderate		
									42 per 1000	46 more per 1000 (from 34 fewer to 860 more)	
ness (as	sessed with: Stud	dy-specific side e	effect checklist	i)	1	<u> </u>		I		1	
serious <sup>1</sup>	no serious	no serious	very	undetected		1/24	5/23	RR 5.22	Study p	opulation	
	inconsistency		Senous		due to risk of bias, imprecision	(4.270)	(21.776)	41.32)	42 per 1000	<b>176 more per 1000</b> (from 14 fewer to 1000 more)	
									Modera	te	
									42 per 1000	<b>177 more per 1000</b> (from 14 fewer to 1000 more)	
	vement serious <sup>1</sup>	inconsistency         inconsistency         inconsistency         vement         (assessed with:         serious <sup>1</sup> no serious inconsistency         ness         (assessed with:         State	inconsistency       indirectness         vement       (assessed with: Study-specific side sinconsistency         serious <sup>1</sup> no serious indirectness         no serious       no serious indirectness         no serious       no serious indirectness         serious <sup>1</sup> no serious indirectness         ness       (assessed with: Study-specific side side side side side side side side	inconsistency       indirectness       serious <sup>2</sup> vement       (assessed with: Study-specific side effect check side inconsistency       no serious indirectness       very serious <sup>2</sup> serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> ness       (assessed with: Study-specific side effect checklist serious <sup>1</sup> no serious       very serious <sup>2</sup> ness       (assessed with: Study-specific side effect checklist serious <sup>1</sup> no serious       no serious       very serious	inconsistency       indirectness       serious <sup>2</sup> vement       (assessed with: Study-specific side effect checklist)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected         ness       (assessed with: Study-specific side effect checklist)       serious <sup>2</sup> undetected         ness       (assessed with: Study-specific side effect checklist)       undetected         serious <sup>1</sup> no serious       no serious       very         serious <sup>1</sup> no serious       no serious       very	inconsistency       indirectness       serious <sup>2</sup> VERY LOW <sup>1,2</sup> due to risk of bias, imprecision         vement (assessed with: Study-specific side effect checklist)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected bias, imprecision       ⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision         nesss (assessed with: Study-specific side effect checklist)       serious <sup>2</sup> undetected bias, imprecision       ⊕⊖⊖⊖ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected Undetected       ⊕⊖⊝⊖ VERY LOW <sup>1,2</sup> due to risk of bias,	inconsistency       indirectness       serious <sup>2</sup> VERY LOW <sup>1,2</sup> due to risk of bias, imprecision       (12.5%)         vement       (assessed with: Study-specific side effect checklist)       Imprecision       1/24         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected bias, imprecision       Imprecision         nesses       (4.2%)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected bias, imprecision       Imprecision         ness       (assessed with: Study-specific side effect checklist)       Imprecision       1/24       (4.2%)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       Imprecision         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       Imprecision         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected       Imprecision       1/24	inconsistency       indirectness       serious <sup>2</sup> VERY LOW <sup>1/2</sup> due to risk of bias, imprecision       (12.5%)       (4.3%)         vement       (assessed with: Study-specific side effect checklist)       very       very       very         serious <sup>1</sup> no serious inconsistency       no serious <sup>2</sup> very serious <sup>2</sup> undetected bias, imprecision       t/24 (4.2%)       2/23 (8.7%)         nesss (assessed with: Study-specific side effect checklist)       serious <sup>2</sup> undetected bias, imprecision       t/24 (4.2%)       2/23 (8.7%)         no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected were the risk of bias, imprecision       t/24 (4.2%)       2/23 (8.7%)         serious <sup>1</sup> no serious inconsistency       no serious indirectness       very serious <sup>2</sup> undetected Were to risk of bias,       t/24 (4.2%)       5/23 (21.7%)	Inconsistencyindirectnessserious2VERY LOW12 due to risk of bias, imprecision(12.5%)(4.3%)(0.04 to 3.11)Vement(assessed with: Study-specific side effect checklist)serious1no serious inconsistencyno serious indirectnessvery serious2undetected bias, imprecision $D \oplus O \oplus O$ VERY LOW12 due to risk of bias, imprecision $1/24$ (4.2%) $2/23$ (8.7%)RR 2.09 (0.2 to 21.48)serious1no serious inconsistencyno serious2undetected serious2 $D \oplus O \oplus O$ VERY LOW12 due to risk of bias, imprecision $1/24$ (4.2%) $2/23$ (8.7%)RR 2.09 (0.2 to 21.48)serious1no serious inconsistencyno serious indirectnessvery serious2undetected $D \oplus O \oplus O$ VERY LOW12 due to risk of bias, imprecision $1/24$ (21.7%) $2/23$ (21.7%)RR 5.22 (0.66 to 41.32)	inconsistency       indirectness       serious <sup>2</sup> VERY LOW <sup>1/2</sup> due to risk of bias, imprecision       (12.5%)       (4.3%)       (0.04 to 3.11)       Image: Constant of the constex of the constant of the constant of the constant of t	

47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		5/24 (20.8%)	3/23 %) (13%)	<b>RR 0.63</b> (0.17 to	Study population		
10 weeks				Schous		due to risk of bias, imprecision	(20.070)		2.33)	208 per 1000	<b>77 fewer per 1000</b> (from 173 fewer to 277 more)	
										Moderate		
										208 per 1000	<b>77 fewer per 1000</b> (from 173 fewer to 277 more)	
Increase	d appet	t <b>ite</b> (assessed w	ith: Study-specifi	ic side effect c	hecklist)	н			I	<u>.</u>		
47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>1,2</sup>	10/24 (41.7%)	6/23 (26.1%)	<b>RR 0.63</b> (0.27 to	Study p	opulation	
10 weeks						due to risk of bias, imprecision	· · ·	`````	1.44)	417 per 1000	<b>154 fewer per 1000</b> (from 304 fewer to 183 more)	
										Modera	te	
										417 per 1000	<b>154 fewer per 1000</b> (from 304 fewer to 183 more)	
Loss of a	appetite	(assessed with:	Study-specific si	ide effect chec	klist)	1			<b>I</b>			
47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		4/24 (16.7%)	3/23	<b>RR 0.78</b> (0.2 to	Study p	opulation	
10 weeks		inconsistency	indirectiless	Senous		due to risk of bias, imprecision	(10.778)	(1376)	3.12)	167 per 1000	<b>37 fewer per 1000</b> (from 133 fewer to 353 more)	
										Modera	ie	
										167 per 1000	<b>37 fewer per 1000</b> (from 134 fewer to 354 more)	
	I		1	ļ				•				

47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		2/24 (8.3%)	5/23 (21.7%)	<b>RR 2.61</b> (0.56 to	Study p	opulation		
10 weeks			due to risk of bias, imprecision	(,)	12.13)	83 per 1000	<b>134 more per 1000</b> (from 37 fewer to 927 more)						
						Imprecision				Moderate			
										83 per 1000	<b>134 more per 1000</b> (from 37 fewer to 924 more)		
Diarrhoe	a (assess	ed with: Study-sp	ecific side effect	checklist)	-								
47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		3/24 (12.5%)	3/23 (13%)	<b>RR 1.04</b> (0.23 to	Study p	opulation		
10 weeks		inconcionational				due to risk of bias, imprecision	(12.070)	(10,0)	4.65)	125 per 1000	5 more per 1000 (from 96 fewer to 456 more)		
						Impredictor				Moderate			
										125 per 1000	5 more per 1000 (from 96 fewer to 456 more)		
Twitches	S (assesse	d with: Study-spe	cific side effect c	hecklist)		1							
47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		0/24 (0%)	3/23 (13%)	<b>RR 7.29</b> (0.4 to	Study population			
10 weeks		inconcionationaly				due to risk of bias, imprecision	(070)	(10,0)	133.82)	0 per 1000	-		
						Imprecision				Modera	te		
										0 per 1000	-		
Dry mou	ith (asses	sed with: Study-sp	becific side effect	t checklist)	<u> </u>	<u> </u>	I		I				
47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		1/24 (4.2%)	1/23 (4.3%)	<b>RR 1.04</b> (0.07 to	Study p	opulation		
10 weeks						due to risk of bias,	(-1.2 /0)	(1.070)	15.72)	42 per 1000	2 more per 1000 (from 39 fewer to 613 more)		

						imprecision				Modera	te
										42 per 1000	2 more per 1000 (from 39 fewer to 618 more)
Trouble	swallow	/ing (assessed	with: Study-spec	ific side effect	checklist)	4	I			1	1
47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		3/24 (12.5%)	1/23	<b>RR 0.35</b> (0.04 to	Study p	opulation
10 weeks		inconsistency	indirectiless	Senous		due to risk of bias, imprecision	(12.070)	(4.370)	3.11)	125 per 1000	<b>81 fewer per 1000</b> (from 120 fewer to 264 more)
										Modera	te
										125 per 1000	81 fewer per 1000 (from 120 fewer to 264 more)
Sore thr	oat/tong	<b>JUE</b> (assessed w	vith: Study-specif	ic side effect o	checklist)					1	1
47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		5/24 (20.8%)	1/23	<b>RR 0.21</b> (0.03 to	Study p	opulation
10 weeks				Sonouo		due to risk of bias, imprecision	(20.070)	(	1.65)	208 per 1000	165 fewer per 1000 (from 202 fewer to 135 more)
										Moderate	
											<b>164 fewer per 1000</b> (from 202 fewer to 135 more)
Abdomiı	hal pain	(assessed with:	Study-specific sid	de effect checl	klist)	1	Į			<u> </u>	1
47 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected		3/24 (12.5%)	2/23 (8.7%)	<b>RR 0.7</b> (0.13 to	Study p	opulation
10 weeks						due to risk of bias, imprecision	(12.070)	(0,0)	3.79)	125 per 1000	<b>38 fewer per 1000</b> (from 109 fewer to 349 more)

							Modera	te
							•	<b>38 fewer per 1000</b> (from 109 fewer to 349 more)
reliability and v	validity of	to record adver	se events is u	nclear, and the	e checklist is bas	a sufficient follow-up duration to obse sed on parental report and parents w SMD -0.5/0.5)		

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

		Q	uality asses	sment			Summary of Findings					
Participants		Inconsistency	Indirectness	•				Study event rates (%)		Anticipated absolute effects		
(studies) Follow up	of bias				bias	quality of evidence	With Control	With Adverse events	effect (95% CI)	Risk with Control	Risk difference with Adverse events associated with gluten- free and casein-free diet (95% Cl)	
Any adve	erse ev	vent (assessed	with: Outcome	e measure not	reported)							
72 (1 study) 35 weeks						See comment	0/34 (0%)		not pooled	Effect size not estimable	Effect size not estimable	

# **2 ECONOMIC EVIDENCE PROFILES**

# 2.1 CLINICAL/ECONOMIC QUESTION: RECIPROCAL-SOCIAL COMMUNICATION ADDED TO STANDARD CARE VERSUS STANDARD CARE ALONE FOR PRESCHOOL CHILDREN WITH AUTISM

Evidence	Evidence profile - economic evidence												
Study & country	Limitations	Applicabili ty	Other comments	Incremental cost (£) <sup>1</sup>	Incrementa 1 effect	ICER (£/effect)	Uncertainty <sup>1</sup>						
Byford et al., Unpublishe d UK	Minor limitations <sup>2</sup>	Partially applicable <sup>3</sup>	<ul> <li>Measure of outcome: proportion of children with clinically meaningful improvement expressed by an ADOS-G score improvement ≥ 4 points</li> <li>Time horizon: 13 months</li> <li>ICER and probabilistic analysis based on bootstrapping techniques</li> </ul>	£5,121 (£4,109 to £6,135)	12%	£297	Compared with standard care alone, intervention plus standard care has greater probability of being cost-effective above willingness to pay of £293 per 1% increase in % of children with clinically meaningful improvement						

1. Costs uplifted to 2012 UK pounds using the hospital and community health services pay and prices inflation index (Curtis, 2012).

2. Economic analysis conducted alongside an RCT, all relevant costs included, unit costs based mostly on national sources, HRQoL not considered, sensitivity analysis undertaken including probabilistic sensitivity analysis, time horizon of 13 months

3. Conducted in the UK, perspective including statutory and non-statutory health and social services, no QALYs estimated

2.2 Clinical / economic question: antipsychotics versus placebo for the management of behaviour that challenges in children and young people with autism

Evide	Evidence profile - economic evidence												
Study & count ry	Limitation s	Applicability	Other comments	Incremental cost (£) <sup>1</sup>	Incremental effect (QALY)	ICER (£/QALY)	Uncertainty <sup>1</sup>						
Guide line model	Potentially serious limitations 2	Partially applicable <sup>3</sup>	• Time horizon: 32 weeks	Risperidone: • tablets: £8.47 • oral solution: £144 • orodispersi ble tablets: £205 Aripiprazole tablets: £510	All antipsychotic s: 0.008	Risperidone: • tablets: £1,004 • oral solution: £17,083 • orodispersi ble tablets: £24,267 Aripiprazole tablets: £60,527	PSA: probability of antipsychotics being cost-effective at £20,000/QALY: Risperidone tablets: 0.63 Risperidone oral solution: 0.47 Risperidone orodispersible tablets: 0.40 Aripiprazole tablets: 0.10						

1. Costs expressed in 2012 UK pounds

2. Only intervention costs considered consisting of drug acquisition costs, efficacy data from 4 trials, PSA performed

3. NHS & PSS perspective, QALYs based on HUI3 (valuations elicited from Canadian population)

## 2.3 CLINICAL / ECONOMIC QUESTION: EARLY INTENSIVE BEHAVIOURAL INTERVENTION VERSUS STANDARD EDUCATIONAL SERVICE (SPECIAL EDUCATION) FOR CHILDREN WITH AUTISM

Evidend	Evidence profile - economic evidence											
Study & country	Limitatio ns	Applicability	Other comments	Incremen tal cost (£) <sup>1</sup>	Incremental effect	ICER (£/effect) <sup>1</sup>	Uncertainty <sup>1</sup>					
Chasson et al., 2007 US	Potentially serious limitations 2	Partially applicable <sup>3</sup>	<ul><li>Cost analysis</li><li>Time horizon: 18 years</li></ul>	-£99,039	NA	NA	Not estimated					

 Costs converted and uplifted to 2012 UK pounds – converted using PPP exchange rates (<u>http://www.oecd.org/std/ppp</u>) and UK PPS local authorities adults and children's services pay and prices inflation index (Curtis, 2012).

2. Simple economic model including education costs only, cost estimates based on personal communication and further assumptions, clinical model parameters based on published literature and further assumptions; local state costs, no sensitivity analysis

3. Conducted in the US, public perspective including state, local, federal and private costs, no discounting although time horizon was 18 years

# 2.4 CLINICAL / ECONOMIC QUESTION: EARLY INTENSIVE BEHAVIOURAL INTERVENTION VERSUS NO INTERVENTION FOR PRESCHOOL CHILDREN WITH AUTISM

Evide	Evidence profile - economic evidence												
Study & countr y	Limitations	Applicabilit y	Other comments	Increment al cost (£) <sup>1</sup>	Incremental effect	ICER (£/effect)	Uncertainty <sup>1</sup>						
Motiw ala et al., 2006 US	Potentially serious limitations <sup>2</sup>	Partially applicable <sup>3</sup>	<ul> <li>Measure of outcome: number of dependency- free years</li> <li>Time horizon: up to 65 years of age</li> </ul>	-£37,450	4.4	Interventi on dominant	Findings sensitive to discount rate and EIBI efficacy (net costs and not savings, with discount rate of 5%)						

 Costs converted and uplifted to 2012 UK pounds – converted using PPP exchange rates (<u>http://www.oecd.org/std/ppp</u>) and UK PPS local authorities adults and children's services pay and prices inflation index (Curtis, 2012).

2. Economic model over lifetime, provincial government resource use estimates and prices, all relevant costs included, but efficacy estimates were judgements based on literature review

3. Conducted in Canada, public perspective, discounting 3%, no QALYs but intervention dominant

# 2.5 CLINICAL/ECONOMIC QUESTION: EARLY INTENSIVE BEHAVIOURAL INTERVENTION VERSUS TREATMENT AS USUAL FOR PRESCHOOL CHILDREN WITH AUTISM

Eviden	Evidence profile - economic evidence											
Study & country	Limitation s	Applicabili ty	Other comments	Increment al cost (£) <sup>1</sup>	Incremental effect	ICER (£/effect)	Uncertainty <sup>1</sup>					
Peters- Scheffer et al., 2012 Netherla nds	Potentially serious limitations <sup>2</sup>	Partially applicable <sup>3</sup>	• Time horizon: up to 65 years of age	-£925,338	NA	NA	Using more optimistic TAU efficacy data: -£210,358					

1. Costs converted and uplifted to 2012 UK pounds – converted using PPP exchange rates (<u>http://www.oecd.org/std/ppp</u>) and UK PPS local authorities adults and children's services pay and prices inflation index (Curtis, 2012).

2. Economic model over lifetime, resource use and unit cost data based on national sources and assumptions, all relevant costs included, efficacy estimates based on review of meta-analyses, selection of studies based on their applicability to the Dutch context, and naïve addition of meta-analytic data across same treatment arms

3. Conducted in the Netherlands, public sector perspective, no discounting

## 2.6 CLINICAL / ECONOMIC QUESTION: CBT VERSUS WAIT LIST FOR THE MANAGEMENT OF ANXIETY IN CHILDREN AND YOUNG PEOPLE WITH AUTISM

Evide	Evidence profile - economic evidence												
Study & countr y	Limitations	Applicabilit y	Other comments	Increment al cost (£) <sup>1</sup>	Incremental effect (QALY)	ICER (£/QALY)	Uncertainty <sup>1</sup>						
Guidel ine model	Potentially serious limitations <sup>2</sup>	Partially applicable <sup>3</sup>	• Time horizon: 38 weeks	Group- CBT: £387 Individual CBT: £2712	0.028	Group- CBT: £13,910 Individual CBT: £97,367	PSA: probability of CBT being cost-effective at £20,000/QALY: group-CBT: 0.53; individual CBT: 0						

1. Costs expressed in 2012 UK pounds

2. Only intervention costs considered, resource use from RCTs included in guideline systematic review, efficacy data from 2 trials, PSA performed

3. NHS & PSS perspective, QALYs based on HUI3 (valuations elicited from Canadian population)