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#### 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

		Qı	ıality assessm	ent				5	Summary o	of Findings	
Participants		Inconsistency	Indirectness	Imprecision			Study event	rates (%)	Relative	Anticipated a	absolute effects
(studies) Follow up	bias				bias	of evidence	With Treatment-as- usual	With Behavioural intervention	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Behavioural intervention (95% CI)
Overall a	utistic be	haviours (me	asured with: Autis	sm Diagnostic	Observation S	chedule (ADOS/A	ADOS-G): Sta	ndardised seve	rity score; B	etter indicated	by lower values)
45 (1 study) 104 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <sup>1</sup> due to imprecision	21	24	N/A	N/A	The mean overall autistic behaviours in the intervention groups was  0.16 standard deviations lower (0.75 lower to 0.43 higher)
DSM-IV C	linical D	iagnosis (asse	essed with: Numb	er of participa	nts who showe	d improvement in	diagnosis fro	m autistic disor	der to PDD-	NOS)	
45 (1 study)	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup>	1/21 (4.8%)	7/24 (29.2%)	January population		
104 weeks						due to risk of bias, imprecision			73.79)	48 per 1000	345 more per 1000 (from 4 fewer to 1000 more)

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				Moderate		
				N/A	N/A	

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

#### 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	attainn	nent for targ	eted object	ives (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	⊕⊕⊖⊝ <b>LOW</b> <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 1.42 standard deviations higher (0.63 to 2.2 higher)	

<sup>&</sup>lt;sup>1</sup> High risk of performance bias as intervention administrators were non-blind. There was also a high risk of detection bias as the primary outcome assessor was the non-blind investigator with a blinded secondary outcome assessor only rating 20% of behavioural observations. In addition, because only 20% of observations were double-coded and a standardized observation measure was not used the relaibility and validity of this outcome measure is unclear <sup>2</sup> N<400

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<sup>&</sup>lt;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

<sup>&</sup>lt;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)

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

		Q	uality assess	ment				Sur	nmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study event	rates (%)	Relative	Anticipated a	bsolute 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% CI)
Overall a	utistic	behaviours (	measured with:	Childhood Auti	sm Rating Sca	ale (CARS): Tota	al; 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,	117	177	N/A	N/A	The mean overall autistic behaviours in the intervention

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants non-blind. In addition, risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported

<sup>&</sup>lt;sup>2</sup> N<400

#### 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

		C	Quality assess	ment	Summary of Findings						
Participants		Inconsistency	Indirectness	Imprecision			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% CI)
Overall a		ehaviours (F	PEC+PEBM	combine	<b>d)</b> (measured wi	ith: Developmenta	al Behav	iour Checklist (DBC): Au	utism Scree	ning Algo	orithm (ASA); Better indicated
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 lower</b> (0.47 lower to 0.34 higher)
Overall a	utistic b	ehaviours (m	neasured with: C	hildhood Autis	m Rating Scale (	(CARS): Total; Be	tter indic	cated by lower values)	ļ	ļ	1
-	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 lower</b> (0.81 to 0.03 lower)
Overall a	utistic b	ehaviours (F	PEBM grou	<b>p)</b> (measured	with: Childhood	Autism Rating Sc	ale (CAI	RS): Total; Better indicat	ted by lowe	r values)	-
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>	⊕⊖⊖ <b>VERY LOW</b> <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

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						publication bias					0.44 standard deviations lower (0.92 lower to 0.03 higher)
Overall a	utistic b	ehaviours (m	neasured with: C	hildhood Autis	m Rating Scale (	CARS): Total; Be	tter indic	ated by lower values)			
32 (1 study) 13 weeks		no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊖⊝ LoW³ due to imprecision	16	16	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.38 standard deviations lower (1.08 lower to 0.32 higher)

<sup>&</sup>lt;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 parent-rated and parents were non-blind and involved in the intervention

#### 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	bias of evidence With With Parent effect	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% CI)
Overall a	utistic be	ehaviour (meas	sured with: Autism	Behaviour Ch	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	⊕⊕⊖ <b>LOW</b> <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 lower</b> (1.08 lower to 0.27 higher)
<sup>1</sup> N<400 and 9	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	1	1

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;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)

<sup>&</sup>lt;sup>4</sup> Risk of selective reporting bias in TONGE2006/2012 as trial protocol is not registered on ClinicalTrials.gov or ISRCTN and there is a potential conflict of interest as the manuals used in this study have been published by Jessica Kingsley Publishers, and the authors receive royalties (5%) from sales

#### 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

		Qu	ality assessm	ent			Summary of 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 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% CI)
Overall a	utistic k	ehaviours (n	neasured with: A	utism Diagnos	stic Observation	n Schedule (AI	OS/ADOS-	G): Total score; Better in	ndicated by	lower values)	)
_	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> ¹ due to imprecision	14	14	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.76 standard deviations lower</b> (1.53 lower to 0.01 higher)
<sup>1</sup> N<400 and 9	95% CI cro	sses both line of r	no effect and me	asure of appre	ciable benefit	or harm (SMD	-0.5/0.5)		l	L	

## 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

		Qı	uality assessr	nent				Sun	nmary of I	indings	
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study ev	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 Diagnostic	C Observation	Schedule (AD	OS/ADOS-G): C	Communica	tion (odds of being in a h	igher sever	ity category	on ADOS-G))
84 (1 study)		no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖ VERY LOW <sup>1,2</sup>	N/A	N/A	OR 0.52 (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 in	teractio	n (assessed with	: Autism Diagno	stic Observation	on Schedule (A	ADOS/ADOS-G)	: Social Inte	eraction (odds of being in	a higher s	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	⊕⊝⊝ VERY LOW <sup>1,2</sup>	N/A	N/A	OR 0.55 (0.25 to	Study pop	oulation
33 weeks						due to risk of bias,			1.2)	N/A	N/A
						imprecision				Moderate	

										0 per 1000	N/A
Social in	teractio	n (assessed with	: Autism Diagno	stic Observation	on Schedule (A	ADOS/ADOS-G)	Social Int	teraction (odds of being in	a higher s	everity cated	gory on ADOS-G))
53 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1,3</sup>	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
	o and 95%	nce, response and CI crosses both li					d outcome	assessors were non-blin	d	I	1

## 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

			Quality asse	essment					Summary	of Finding	js			
<b>(</b>	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study ev (%)	ent rates	Relative effect	Anticipate	d absolute effects			
Follow up							With Waitlist control	Waitlist Horseback		Risk with Waitlist control	Risk difference with Horseback riding (95% CI)			
Social im	Social impairment (measured with: Social Responsiveness Scale (SRS): Total; Better indicated by lower values)													
34 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious 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,	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	ognition	(measured with:	Social Responsiv	eness Scale	(SRS): Social Cogn	ition ; Better indicated b	y lower va	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 LOW¹,3,4 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 deviations lower</b> (1.13 lower to 0.24 higher)
Social a	warenes	SS (measured with	h: Social Respons	siveness Scal	e (SRS): Social Awa	areness ; Better indicate	ed 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 awareness in the intervention groups was <b>0.4 standard deviations lower</b> (1.08 lower to 0.28 higher)
Social m	notivatio	n (measured with	n: Social Respons	siveness Scal	e (SRS): Social Mot	ivation ; Better indicated	d by lower	r values)		L	
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 LOW¹,3,4 due to risk of bias, imprecision, publication bias	15	19	N/A	N/A	The mean social motivation in the intervention groups was 0.58 standard deviations lower (1.27 lower to 0.12 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants non-blind. There is also a high risk of detection bias as outcome measures are parent-rated and parents non-blind

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</sup> High risk of selective reporting bias as data not reported for selected subscales: the social communication and autistic mannerisms subscales of the Social Responsiveness Scale (SRS) <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)

### 1.2.3 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				Summ	ary of Find	dings				
` ,	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study eve (%)		Relative effect	Anticipate	ed absolute effects			
Follow up							With Waitlist control	With Music therapy	(95% CI)	Risk with Waitlist control	Risk difference with Music therapy (95% CI)			
	ocial communication (measured with: Childhood Autism Rating Scale (CARS): Social communication (composite score from imitation, verbal and non-verbal communication, insistency of intellectual responses and general impressions); Better indicated by lower values)													
	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to imprecision	12	12	N/A	N/A	The mean social communication in the intervention groups was 0.23 standard deviations higher (0.58 lower to 1.03 higher)			
<sup>1</sup> N<400 and 9	N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)													

### 1.2.4 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			Summary of Findings					
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	bias	quality of	With	` '	effect (95% CI)	Anticip Risk with Control	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% CI)
Examine	er-child	joint/shared	attention	measured wit	h: EScs (Early	Social Commu	nication	Scales): Initiating Joint Attent	tion (IJA);	Better inc	dicated by lower values)
27 (1 study) 10 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <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)	er-child	joint/shared	attention	(Copy) (me	asured with: E	Scs (Early Soc	ial Com	munication Scales): Initiating	Joint Atten	tion (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	⊕⊕⊖⊝ <b>LOW</b> <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 higher</b> (0.06 to 1.65 higher)
Social a	nd emo	tional devel	opment (me	asured with: B	ayley Scales o	of Infant Develo	pment: \$	Social-Emotional ; Better indic	ated 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 higher</b> (0.36 lower to 1.17 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and the risk of detection bias is also high as outcome assessors were not blinded

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

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and the risk of detection bias is also high as parent-report measue and parents non-blind

<sup>&</sup>lt;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)

		Q	uality assessi	ment				Sı	ımmary o	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% CI)
Social aff	ect (mea	asured with: Autisr	n Diagnostic Obs	servation Sche	dule for Toddle	ers (ADOS-T): So	ocial Affect; I	Better indicated by Id	wer values)		
98 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖ <b>LOW</b> <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 0.07 standard deviations lower (0.46 lower to 0.33 higher)
Imitation	(measure	d with: Imitation ta	sks (Rogers et a	I., 2003): Imitat	tive sequences	; Better indicated	d by lower va	alues)			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 deviations higher</b> (0.16 lower to 0.63 higher)
Orienting	to soc	ial stimuli (m	easured with: So	cial engageme	ent task (Daws	on et al., 2004):	ı Mean Social	Orient I; Better indic	ated by low	er values)	Į.
98 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊝⊖ <b>VERY LOW</b> <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 deviations higher</b> (0.27 lower to 0.52 higher)
Orienting	to join	t attention (n	neasured with: S	ocial engagem	ent task (Daws	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	⊕⊕⊖⊖ <b>LOW</b> <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		0 standard deviations higher (0.4 lower to 0.4 higher)

<sup>&</sup>lt;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 assessor reported only as 'laboratory personnel' with no information about blinding <sup>2</sup> N<400

### 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 effect	Anticip	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With With Emotion recognition  Control training versus treatment-as- usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome		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% CI)
	_	,		•		•		Spence, 1995) or Situation-Flicated by lower values)	Facial Expr	ession M	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 higher</b> (0.27 to 1.03 higher)

<sup>&</sup>lt;sup>3</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 the identity and blinding of outcome assessors not reported and reliability and validity of outcome measure unclear

<sup>&</sup>lt;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)

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 higher</b> (0.4 lower to 0.73 higher)
Emotion	unders	standing (mea	asured with: Em	otional vocab	ulary (study-sp	ecific); Better indic	ated b	y lower values)	•	•	,
38 (1 study) 4 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊝ LOW <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 higher</b> (0.34 to 1.7 higher)
Emotion	regula	tion and so	cial skills (n	neasured with	Emotion Reg	ulation and Social	Skills (	Questionnaire (ERSS	Q; 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 i the intervention groups was 1.39 standard deviations higher (0.76 to 2.02 higher)
Anxiety	coping	<b>skills</b> (measur	ed with: James	and the Maths	Test (Attwoo	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	⊕⊕⊖⊝ 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 1.23 standard deviations higher (0.62 to 1.85 higher)
Bullying	coping	<b>skills</b> (measu	red with: Dylan	is Being Teas	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	⊕⊕⊖⊝ LOW <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 1.29 standard deviations

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											<b>higher</b> (0.67 to 1.91 higher)
Social sk	ill <b>s</b> (mea	sured with: Socia	I 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 indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖ LOW <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)

<sup>&</sup>lt;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 blinding of outcome assessors is unclear

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

		C	uality assess	sment			Summary of Findings						
•	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With	weet rates (%)  With Face 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 difference with Face recognition training versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome (95% CI)		
Face reco	Face recognition (measured with: The Let's Face It! Skills Battery: Matching identity across masked features (percent correct); Better indicated by lower values)												

<sup>&</sup>lt;sup>2</sup> Substantial to considerable heterogeneity (I-squared value of 77%, p = 0.01)

 $<sup>^{3}</sup>$  N<400

<sup>&</sup>lt;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)

<sup>&</sup>lt;sup>5</sup> High risk of performance and response bias as intervention adminstrators and participants were non-blind and high risk of detection bias as outcome assessor was non-blind investigator and study-specific outcome measure with no independent measures of reliability or validity data

<sup>&</sup>lt;sup>6</sup> High risk of performance and response bias as intervention adminsitrators and participants were non-blind and high risk of detection bias as outcome assessor was non-blind parent and study-specific outcome measure with no independent measures of reliability or validity data

<sup>&</sup>lt;sup>7</sup> High risk of performance and response bias as intervention adminsitrators and participants were non-blind and high risk of detection bias as only 33% of responses were independently and blindly coded

<sup>&</sup>lt;sup>8</sup> High risk of performance, response and detection bias. The questionnaire was parent-rated and parents were not blind and participated in the intervention

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 LOW¹,2,3 due to risk of bias, imprecision, publication bias	37	41	N/A	N/A	The mean face recognition in the intervention groups was 0.07 standard deviations lower (0.52 lower to 0.37 higher)
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 LOW¹,3,4 due to risk of bias, imprecision, publication bias	37	ions (percent correct); Better 41	N/A	N/A	The mean face recognition in the intervention groups was 0.02 standard deviations lower (0.47 lower to 0.42 higher)
Face rec	ognitio	n (measured with	n: The Let's Fac	e It! Skills Batt	ery: Matching id	dentity across exp	ression	(percent correct); Better ind	cated by lo	wer valu	es)
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 LOW¹,2,3 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 lower</b> (0.88 lower to 0.02 higher)
Face rec	ognitio	<b>n</b> (measured with	n: The Let's Fac	e It! Skills Batt	ery: Parts/whole	e identity (percen	t correct	); Better indicated by lower v	alues)	1	<u> </u>
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 0.06 standard deviations higher (0.39 lower to 0.51 higher)
Face rec	ognitio	n (measured with	n: The Let's Fac	e It! Skills Batt	ery: Immediate	memory for faces	s (perce	nt correct); Better indicated b	y lower va	lues)	1
77 (1 study) 19 weeks	serious <sup>1</sup>	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,	36	41	N/A	N/A	The mean face recognition in the intervention groups was 0.26 standard deviations

									_	
						imprecision				lower
										(0.71 lower to 0.19 higher)
1 High risk of	performan	ce and response	bias as interver	ntion administr	ator and particip	oants non-blind, a	and risk of detection bias unclear/unk	nown as id	l lentity an	d blinding of outcome
		and no independ	,	,			2.5(2.5)			
		and no independ	,	,			2.6/0.6)			

<sup>&</sup>lt;sup>3</sup> The paper states that other experimental measures were taken that are not reported <sup>4</sup> N<400

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

		Qı	uality assessr	ment				Sum	mary of F	indi	ngs
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Stud	dy 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 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	mind	(measured with: T	heory of Mind (	ToM) Test: To	al; Better indic	cated by lower v	values	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 theory of mind in the intervention groups was <b>0.04 standard deviations higher</b> (0.61 lower to 0.7 higher)
Empathy	(measure	d with: Index of E	mpathy for Child	dren and Adole	scents: Total;	Better indicate	d by l	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	ıl awar	eness (measur	ed with: Levels	of Emotional A	wareness Sca	ale for Children	(LEA	S-C): Total; Better indicated by le	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 LOW¹,² 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 higher</b> (0.2 lower to 1.13 higher)
Maladapt	ive soc	ial behaviou	ur (measured w	vith: Children's	Social Behavi	or Questionnai	re (CS	SBQ): Total; Better indicated by	lower value	es)	
36	serious <sup>4</sup>	no serious	no serious	very	undetected	⊕⊖⊝⊝	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>		behaviour in the intervention groups was
				due to risk o bias, imprecision		<b>0.31 standard deviations lower</b> (0.97 lower to 0.35 higher)

<sup>&</sup>lt;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 assessor not reported

### 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				Sumn	nary of F	indings	;
Participants		Inconsistency	Indirectness	Imprecision			Study	` '	Relative	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	effect (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	recogn	ition (IQ <70	and >70 c	ombined)	(measured w	ith: Ekman emoti	on reco	gnition photographs; Better inc	dicated by	lower va	lues)
49 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <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> higher (0.37 to 1.56 higher)
Emotion	recogn	ition (IQ <70	and >70 c	ombined)	(measured w	ith: Study-specifi	c emotic	n recognition in drawings test	; Better inc	dicated b	y 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

<sup>&</sup>lt;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>&</sup>lt;sup>3</sup> High risk of performance and response bias as intervention administrators and participants non-blind, and high risk of detection bias as self-completed

<sup>4</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

	_	inconsistency  ition (IQ <70		-	(measured w	LOW <sup>2,3</sup> due to risk of bias, imprecision	core fro	om Ekman emotion recogni	tion photogra	ohs and	recognition (iq <70 and >70 combined) in the intervention groups was  1.1 standard deviations higher  (0.5 to 1.7 higher)
49 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 1.09 standard deviations higher (0.48 to 1.69 higher)
Face rec	ognitio	n (IQ <70 an	d >70 com	bined) (mea	asured with: B	enton Facial Red	ognitio	n Test: Short Form; Better	indicated by l	ower valu	ues)
49 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW¹.² 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> higher (0.29 to 1.47 higher)
Face rec	ognitio	n (IQ <70 an	d >70 com	bined) (mea	asured with: B	enton Facial Red	ognitio	n Test: Long Form; Better i	ndicated by lo	wer valu	ies)
49 (1 study) 8 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	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 sl	⊔ kills (lQ	<70 and >70	ı O combined	(measured	l with: Social S	l kills Rating Syste	ım (SSI	RS): Social skills (standard	ized score); B	etter ind	icated by lower values)
49 (1 study) 8 weeks	no serious risk of bias	very serious <sup>5</sup>	no serious indirectness	very serious <sup>6</sup>	undetected	⊕⊖⊖⊖ <b>VERY LOW</b> <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 0.29 standard deviations

						imprecision					higher (0.29 lower to 0.88 higher)
Social s	kills (IQ	<b>&lt;70)</b> (measure	d with: Social S	kills Rating Sy	stem (SSRS):	Social skills (sta	ndardiz	ed score); Better indicate	ed by lower valu	ies)	
25 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² 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 indicate	ed by lower valu	ies)	
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> lower (1.09 lower to 0.52 higher)
Positive lower values		nteractions	(IQ <70 an	d >70 con	nbined) (m	easured with: Be	haviour	al observation: Initiating	or maintaining	social into	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	⊕⊕⊕⊝ MODERATE² due to imprecision	24	25	N/A	N/A	The mean positive social interactions (iq <70 and >70 combined) in the intervention groups was  0.6 standard deviations higher  (0.02 to 1.17 higher)
Positive Better indica			(IQ <70 an	d >70 con	nbined) (m	easured with: Be	haviour	al observation: Social in	tention without i	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	⊕⊕⊖⊖ <b>LoW</b> <sup>6</sup> due to imprecision	25	24	N/A	N/A	The mean positive social interactions (iq <70 and >70 combined) in the intervention groups was  0.12 standard deviations lower

											(0.68 lower to 0.45 higher)
Negative lower values		interactions	s (IQ <70 ar	nd >70 cor	<b>mbined)</b> (m	neasured with: Be	haviou	ral observation: Negative socia	al interactio	n behavi	iours; Better indicated by
49 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	25	24	N/A	N/A	The mean negative social interactions (iq <70 and >70 combined) in the intervention groups was  0.88 standard deviations lower  (1.47 to 0.29 lower)

<sup>&</sup>lt;sup>1</sup> High risk of performance bias as intervention administrator non-blind and risk of detection bias is unclear/unknown as identity of outcome assessor is not reported

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

	Quality assessment cipants Risk of Inconsistency Indirectness Imprecision Publication Overall						Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	-	bias	Overall quality of evidence	With		Relative effect (95% CI)	Anticip 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 impaired reciprocal social communication and interaction as a direct outcome (95% CI)

<sup>&</sup>lt;sup>3</sup> High risk of performance bias as intervention administrator non-blind and risk of detection bias is unclear/unknown as identity of outcome assessor is not reported and no independent reliability or validity data for this outcome measure

<sup>&</sup>lt;sup>4</sup> High risk of performance bias as intervention administrator non-blind and risk of detection bias is unclear/unknown as identity of outcome assessor is not reported and no reliability or validity data for the long form

<sup>&</sup>lt;sup>5</sup> Substantial to considerable heterogeneity with an I-squared value of 76% (p = 0.04)

<sup>&</sup>lt;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)

25 (1 study) 3 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW¹,² due to risk of bias, imprecision	12	13	N/A	N/A	The mean emotion recognition in the intervention groups was <b>1.2 standard deviations higher</b> (0.34 to 2.07 higher)
Emotion	recogn	nition (measure	d with: Develop	mental Neuro	psychological	Assessment (I	NEPSY-	II): Affect Recognition; Better i	ndicated by	lower va	alues)
25 (1 study) 3 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	12	13	N/A	N/A	The mean emotion recognition in the intervention groups was 1.55 standard deviations higher (0.63 to 2.46 higher)
Positive	social l	behaviours	measured with	Social Comm	unication Que	estionnaire (SC	Q): Soc	cial peer interest; Better indicat	ed by lower	values)	<u>'</u>
25 (1 study) 3 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW³,4 due to risk of bias, imprecision	12	13	N/A	N/A	The mean positive social behaviours in the intervention groups was  0.33 standard deviations higher  (0.46 lower to 1.12 higher)
Positive	social l	behaviours	measured with	Social Comm	unication Que	estionnaire (SC	Q): Eye	contact; Better indicated by Ic	wer values	)	•
25 (1 study) 3 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	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)
Gaze av	ersion (r	measured with: S	ocial Communic	cation Question	nnaire (SCQ):	Gaze aversion	n; Better	indicated by lower values)	1		
25 (1 study) 3 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	12	13	N/A	N/A	The mean gaze aversion in the intervention groups was 0.14 standard deviations lower (0.93 lower to 0.64 higher)
<sup>1</sup> High risk o	f performar	nce bias as interv	ention adminste	ered by non-bli	nd parents an	d risk of detect	tion bias	s is unclear/unknown as identit	y (beyond s	tating 're	esearcher') and blinding of

#### DRAFT FOR CONSULTATION

outcome assessor unclear and the reliability and validity of this outcome measure is unclear

<sup>2</sup> 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

		Q	uality assessr	nent				Sur	nmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study event i	rates (%)	Relative	Anticipated a	bsolute 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% CI)
Social sk	ills (mea	sured with: Social	Skills Rating Sy	stem (SSRS):	Positive socia	l skills (percentil	e rank score); E	Better indicated by lo	wer values	)	
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>1,2</sup> due to risk of	117	177	N/A	N/A	The mean social skills in the

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants non-blind. In addition, risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported

<sup>&</sup>lt;sup>2</sup> N<400

#### 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 assessr	nent				Sur	nmary of	of Findings		
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	(ills (mea	sured with: Brigar	nce Inventory of	Child Develop	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 lower</b> (0.68 lower to 0.48 higher)	
Social sk	ills (pre	eschool sub	group analy	<b>ysis)</b> (meası	red with: Briga	ance Inventory o	f Child	Development: Social skills;	Better indica	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	⊕⊝⊝⊝ <b>VERY LOW</b> <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 <b>0.18 standard deviations</b> lower (1 lower to 0.64 higher)	
Social sk	ills (K-	1 subgroup	analysis) (m	easured with:	I Brigance Inver	I ntory of Child De	velopr	ment: Social skills; Better indi	cated by lo	ver val	ues)	
23 (1 study) 13 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW¹,² 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 lower</b> (0.85 lower to 0.79 higher)	

<sup>&</sup>lt;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)

### 1.2.7 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	ıality assessr	ment				Sum	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% CI)
Reciproc values)	al soci	al interaction	n (direct ou	utcome) (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	⊕⊝⊖⊝ VERY LOW¹,² due to risk of bias, imprecision	12	12	N/A	N/A	The mean reciprocal social interaction (direct outcome) in the intervention groups was <b>0.38 standard deviations</b> lower (1.19 lower to 0.43 higher)
Nonverba	al comi	munication (	direct outc	ome) (meas	sured with: Aut	tism Diagnostic	Intervie	w-Revised (ADI-R): Nonverb	al Commur	nication;	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 0.37 standard deviations lower (1.18 lower to 0.44 higher)

71 (2 studies) 10-12 weeks		no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ LOW³,4 due to risk of bias, imprecision	25	46	N/A	N/A	The mean social skills (indirect outcome) in the intervention groups was  0.77 standard deviations higher  (0.25 to 1.28 higher)
indicated by I	•		me; combi	nea work	snop + inc	iividuai se	SSION	<b>IS)</b> (measured wit	h: Social Skills Ques	stionnaire	(Spence, 1995): Total ; Better
51 (1 study) 10 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>4,5</sup> due to risk of bias, imprecision	15	36	N/A	N/A	The mean social skills (indirect outcome; combined workshop + individual sessions) in the intervention groups was 0.98 standard deviations higher (0.34 to 1.61 higher)
Social sk	ills (ind	direct outco	me) (measure	d with: Scales	of Independer	nt Behavior-Rev	ised (S	SIB-R): Social intera	action; Better indicat	ed by low	er values)
20 (1 study) 12 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>2,6</sup> due to risk of bias, imprecision	10	10	N/A	N/A	The mean social skills (indirect outcome) in the intervention groups was  0.37 standard deviations higher  (0.52 lower to 1.25 higher)

<sup>&</sup>lt;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>&</sup>lt;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

		(	Quality asses	sment	Summary of Findings						
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study eve	ent rates (%)		Anticipated 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% CI)
		n (Caregive r indicated by low		social co	mmunicat	ion intervent	ion) (mea	sured with: Autism D	iagnostic C	observation S	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	⊕⊕⊖⊝ <b>LOW</b> <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 0.29 standard deviations lower (0.59 lower to 0 higher)
		(Caregiver- indicated by lowe		social com	nmunicatio	n interventio	<b>n)</b> (measu	red with: Autism Diaç	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 lower</b> (0.35 lower to 0.29 higher)

202 (2 studies) 39-56 weeks	bias	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	100	102	N/A	N/A	The mean social interaction and communication (caregived mediated social communication intervention) in the intervention groups was <b>0 standard deviations higher</b> (0.28 lower to 0.27 higher
			•	_		by lower values)	mouno		ion) (measur	od With. Ooi	mindinoation and Cymbolic
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 social communication intervention) in the intervention groups was <b>0.39 standard deviations</b> higher (0.06 to 0.71 higher)
			d'			cation interv	-		: Behavioural o	bservation:	Child communication acts or
223 (3 studies) 22-56 weeks	no serious	serious <sup>1</sup>	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖ Low¹¹² 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	⊕⊕⊕⊝ MODERATE² 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> lower (0.43 lower to 0.32 higher)
	•						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	⊕⊕⊝⊝ LOW⁵ 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> lower (0.68 lower to 0.43 higher)
	•	joint/shared		-			ial com	munication in	terventi	on) (measi	ured 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	⊕⊕⊖⊝ LOW⁵ 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 higher</b> (0.51 lower to 0.51 higher)
	-	nt/shared att	•	_	-		ediated	social-commu	ınicatio	n interve	ention) (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 0.30 standard deviations higher (0.07 to 0.53 higher)
	-	nt/shared att ion; Better indicat	-	_	ediated so	ocial commu	nicatio	n intervention	) (measured	with: Behav	ioural observation: Parent-
241 (4 studies) 8-56 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² 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 higher</b> (0.07 to 0.59 higher)
	_	nt/shared att	· -			ediated socia	ıl comn	nunication int	erventior	<b>1)</b> (measure	ed with: Behavioural
61 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <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 0.17 standard deviations higher (0.33 lower to 0.68 higher)
	-	nt attention   etter indicated by	-	(Caregive	er-mediate	d social com	munica	ation interven	tion) (meas	sured with: E	Behavioural 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

8-52 weeks	risk of bias					due to inconsistency, imprecision					(caregiver-mediated social communication intervention) in the intervention groups was 2.25 standard deviations higher (1.57 to 2.93 higher)
		nt engagement: Joint engagement				acher- media	ted soc	ial-communica	ation int	erventio	(measured with:
99 (2 studies) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	46 ion inte	53  rvention) (measu	N/A	N/A Sehavioural o	The mean parent-child joint engagement (caregiver- or preschool-teacher-mediated social-communication intervention) in the intervention groups was 0.55 standard deviations higher (0.14 to 0.95 higher)
38 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	19	19	N/A	N/A	The mean parent-child joint engagement (caregiver-mediated social communication intervention) in the intervention groups was 0.85 standard deviations higher (0.18 to 1.52 higher)
	-	nt engageme er indicated by lov	•	ool-teach	er-mediate	ed social com	nmunica	tion intervent	i <b>on)</b> (mea	sured with: I	Behavioural observation:
61 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW⁵ due to imprecision	27	34	N/A	N/A	The mean parent-child joint engagement (preschool-teacher-mediated social communication

											intervention) in the intervention groups was <b>0.37 standard deviations higher</b> (0.14 lower to 0.88 higher)
	-	int/shared a teacher-child play	•				al comn	nunication inte	rventio	<b>n)</b> (measure	ed with: Behavioural
61 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖  MODERATE²  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 0.57 standard deviations higher (0.05 to 1.08 higher)
	-	I <b>nt engagen</b> d play): Joint enga				ated social co	mmuni	cation interver	ition) (m	easured with	h: Behavioural observation
61 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊖ <b>Low</b> <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)
		ests (Caregi BR); Better indica			communic	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 serious <sup>5</sup>	undetected	⊕⊕⊖⊝ <b>LoW</b> <sup>5</sup> due to imprecision	23	28	N/A	N/A	The mean behaviour requests (caregiver-mediated social communication intervention) in the

Behavio	ur reque	ests (Caregi	ver-mediat	ed social	communic	cation interve	ntion)	(Conv) (measured	with: FScs	(Farly Socia	intervention groups was  0.18 standard deviations higher (0.37 lower to 0.73 higher)  Communication Scales):
	-	equests (IBR); Be						(COPY) (measured	With Locs	(Larry Godia	Communication Scales).
49 (1 study) 39 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW⁵ 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 higher</b> (0.49 lower to 0.63 higher)
		munication mmunication; Bet	•			mmunication	interv	ention) (measured	with: Parer	nt Interview fo	or Autism-Clinical Version
47 (1 study) 22 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖⊝ <b>VERY LOW</b> <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 0.09 standard deviations lower (0.67 lower to 0.49 higher)
		munication mmunication; Bet				mmunication	interve	ention) (measured	with: Parer	nt Interview f	or Autism-Clinical Version
47 (1 study) 39 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 ndicated by	_	•	er-mediate	ed social o	communic	ation interve	<b>ntion)</b> (r	neasured with:	Behavioural obse	ervation (P.	IAM): 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	⊕⊕⊕⊝ MODERATE² due to imprecision	12	11	N/A	N/A	The mean focusing on faces (caregiver-mediated social communication intervention) in the intervention groups was 1.87 standard deviations higher (0.86 to 2.88 higher)
Focusin Indicated by	•	•	er-mediate	ed social o	communic	ation interve	<b>ntion)</b> (r	neasured with:	Behavioural obse	ervation (P.	JAM): 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	⊕⊕⊕⊝ MODERATE² 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 higher</b> (0.05 to 1.78 higher)
Turn-tak	• •	regiver-med	iated socia	al commu	nication in	itervention) (	measured	with: Behaviour	al observation (P	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	⊕⊕⊝⊝ <b>LoW</b> <sup>5</sup> due to imprecision	12	11	N/A	N/A	The mean turn-taking (caregiver-mediated social communication intervention) in the intervention groups was 0.73 standard deviations higher (0.12 lower to 1.58 higher)
Turn-tak	•	egiver-medi	ated socia	l commun	ication int	t <b>ervention)</b> (m	easured w	rith: Behavioura	l observation (P.	AM): Turn-	Taking; Better indicated by
23	no	no serious	no serious	very	undetected	⊕⊕⊝⊝	12	11	N/A	N/A	The mean turn-taking

(1 study)	serious	inconsistency	indirectness	serious <sup>5</sup>	LOW <sup>5</sup>		caregiver-mediated social
60 weeks	risk of				due to		communication
	bias				imprecision		intervention) in the
							intervention groups was
							0.14 standard deviations
							lower
							(0.96 lower to 0.68 higher)
	1						, ,

Moderate to substantial heterogeneity

N<400

High risk of selective reporting bias as data could not be extracted from ALDRED2001/2004 for the ADOS communication subdomain

High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measure was parent-reported and parents were non-blind and involved in the delivery of the intervention

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

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	nt rates (%)	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			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 LOW¹.2,3 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> higher (0.31 to 1.08 higher)
time in joint e	ngagemer	nt in playground ;	Better indicated	by lower valu	es)	ı	1			T	havioural observations of %
29 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊕⊝ LOW⁴ due to imprecision	14	15	N/A	N/A	The mean peer-child joint engagement (therapist-mediated social-communication intervention) in the intervention groups was  0.03 standard deviations higher  (0.7 lower to 0.76 higher)

29 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊕⊖⊝ LOW⁴ due to imprecision	14	15	N/A	N/A	The mean peer-child joint engagement (peer-mediated social-communication intervention) in the intervention groups was <b>0.12 standard deviations higher</b> (0.61 lower to 0.84 higher)
	•	t engagem	•	•	•			al-commu	nication i	nterven	tion) (measured with:
29 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊕⊝⊝ LOW⁴ due to imprecision	14	15	N/A	N/A	The mean peer-child joint engagement (both therapist-and peer- mediated social-communication intervention) in the intervention groups was  0 standard deviations higher (0.73 lower to 0.73 higher)
	_	t engagem nt in playground;		-		cial-commu	ınicatio	on interve	<b>ntion)</b> (mea	sured with:	Behavioural observations of %
30 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>4</sup> due to imprecision	15	15	N/A	N/A	The mean peer-child joint engagement (therapist-mediated social-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	⊕⊕⊝⊝ LOW⁴ 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 higher</b> (0 to 1.51 higher)
	•		•	•	•	er- mediated ed by lower values		l-commu	nication ii	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	⊕⊕⊕⊝ MODERATE² 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  0.86 standard deviations higher  (0.11 to 1.62 higher)
		social inte	•				nicatio	n interve	ntion) (mea	sured with:	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  (0.21 to 1.09 higher)

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	ion in	48	N/A N/A	N/A	The mean child-initiated social interactions (peer-mediated social-communication intervention in the intervention groups was  0.68 standard deviations higher  (0.24 to 1.12 higher)  Network Survey (SNS): Social
		; Better indicated	•		o coolai c	oaoac			) (measured w	iti i. Oociai i	Network ourvey (GNO). Goelar
30 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊝ <b>VERY LOW</b> <sup>4,5</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean social network salience (therapist-mediate social-communication intervention) in the intervention groups was 0.05 standard deviations lower (0.77 lower to 0.66 higher)
		salience (		iated so	cial-comm	unication ir	nterve	e <b>ntion)</b> (mea	sured with: Soc	al Network	Survey (SNS): Social Network
30 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊝ <b>VERY LOW</b> <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 0.42 standard deviations higher

			·		undetected	⊕⊕⊝⊖ Low <sup>2.5</sup> due to risk of bias, imprecision	ion in	15 terventio	N/A  1) (measured w	N/A ith: Social N	The mean social network salience (both therapist-mediated and peer-mediated social-communication intervention) in the intervention groups was 1.15 standard deviations higher (0.37 to 1.93 higher)
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> lower (1.25 lower to 0.23 higher)
		no serious inconsistency		very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision	nterve	e <b>ntion)</b> (mea	sured with: Soc	al Network	Survey (SNS): Social Network  The mean social network salience (peer-mediated social-communication intervention) in the intervention groups was 0.03 standard deviations higher (0.68 lower to 0.75 higher)

Social Netwo	ork Survey	(SNS): Social Ne	twork Salience	Ratio; Better i	ndicated by low	ver values)					
			•		•	⊕⊖⊝ VERY LOW <sup>4,5</sup> due to risk of bias, imprecision  st-mediated er indicated by lowe		15 -communica	N/A	N/A tervent	The mean social network salience (both therapist-mediated and peer-mediated social-communication intervention) in the intervention groups was 0.32 standard deviations higher (0.4 lower to 1.04 higher)
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  0.18 standard deviations lower  (0.9 lower to 0.54 higher)
			•		•	ediated soci		munication	interve	ntion)	measured with: Social Network
30 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 0.96 standard deviations higher (0.19 to 1.72 higher)

			•		•		socia		N/A nication in	N/A ntervent	The mean number of received friendship nominations (both therapist-mediated and peer-mediated social-communication intervention) in the intervention groups was <b>0.51 standard deviations higher</b> (0.22 lower to 1.24 higher)
29 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	er indicated by lower than the second of the	15	14	N/A	N/A	The mean number of received friendship nominations (therapist-mediated social-communication intervention) in the intervention groups was  0.1 standard deviations lower  (0.83 lower to 0.63 higher)
Survey (SNS	s): Number	of received friend	dship nominatio	ns (Indegrees	); Better indicat	ed by lower values	)				measured with: Social Network
30 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊝⊝ <b>VERY LOW</b> <sup>4,5</sup> due to risk of bias, imprecision	15	15	N/A	N/A	The mean number of received friendship nominations (peer-misocial-communication intervention) in the intervention groups of the second

											higher (0.39 lower to 1.05 higher)
			-		•	erapist-med		-			communication
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 0.25 standard deviations higher (0.47 lower to 0.97 higher)
										Therapis	st-mediated social-
Commu	inicatio	n intervent	(measur	ed with: Socia	Network Surv	ey (SNS): Rejectior	ns; Better	indicated by lowe	r 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  0.44 standard deviations higher  (0.32 lower to 1.21 higher)
						hildren don' ey (SNS): Rejection		_	•	Peer-me	ediated social-
29 (1 study)	serious <sup>5</sup>	no serious	no serious	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>2,5</sup>	14	15	N/A	N/A	The mean number of times child identified as someone

								<b>hang out v</b> Survey (SNS): Reje	•		other children don't like to 'hang out with' (peer- mediated social- communication intervention) in the intervention groups was 0.94 standard deviations higher (0.17 to 1.72 higher)  rapist-mediated and
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 peermediated social-communication intervention) in the intervention groups was  0.35 standard deviations higher  (0.38 lower to 1.09 higher)
								hang out valued by lower value 12	=	herapis N/A	The mean number of times child identified as someone other children don't like to 'hang out with' (therapistmediated social-
											communication intervention) in the intervention groups was 0.17 standard deviations

											lower (0.94 lower to 0.61 higher)
						hildren don' ey (SNS): Rejection		_	•	Peer-me	ediated social-
29 1 study) 2 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' (peermediated social-communication intervention in the intervention groups was  0.14 standard deviations
								_	=		higher (0.59 lower to 0.87 higher)  erapist-mediated and by lower values)

		no serious inconsistency social skill by lower values)	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖ VERY LOW <sup>4,6</sup> due to risk of bias, imprecision	13	13 rvention)	N/A Measured with:	N/A Teacher Pe	The mean teacher-rated social skills (therapist-mediated social-communication intervention) in the intervention groups was  0.11 standard deviations lower (0.88 lower to 0.66 higher)
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 ed social-o	N/A Sommunic	N/A sation ir	The mean teacher-rated social skills (peer-mediated social-communication intervention) in the intervention groups was 0.36 standard deviations higher (0.39 lower to 1.11 higher)
with: Teache 28 (1 study) 6 weeks	serious <sup>6</sup>	no of Social Skills 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 0.32 standard deviations higher (0.43 lower to 1.06 higher)

25 (1 study) 12 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ <b>VERY LOW</b> <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  0.02 standard deviations lower  (0.81 lower to 0.77 higher)
			ls (Peer-m	ediated	social-co	mmunicatio	n inte	rvention)	measured with:	Teacher Pe	erception of Social Skills (TPSS):
Total; Better	r indicated b	by lower values)									
29 (1 study) 12 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊝⊖ <b>VERY LOW</b> <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 higher</b> (0.59 lower to 0.87 higher)
with: Teache	er Perceptio	on of Social Skills	s (TPSS): Total;	Better indicat	ted by lower val	ues)	ı				ntervention) (measured
29 (1 study) 12 weeks	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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>

<sup>&</sup>lt;sup>3</sup> High risk of selective reporting bias for ROEYERS1996 as data cannot be extracted for the Social Behavior Rating Scale which was designed to measure generalization of gains in social behaviour to larger school setting

<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)

#### DRAFT FOR CONSULTATION

<sup>&</sup>lt;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>&</sup>lt;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					Summai	y of Find	lings
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e	vent rates (%)	Relative effect	Anticipa	ted 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	JA) (measui	red with: EScs (Ea	rly Social	Communication S	Scales): Cod	rdinated J	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	⊕⊕⊝⊝ LOW¹ 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 lower</b> (0.74 lower to 0.56 higher)
Examin	er-child	l joint attent	tion (Child	-initiated	<b>JA)</b> (measui	l red 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	⊕⊕⊝⊝ LOW¹ due to imprecision	17	20	N/A	N/A	The mean examiner-child joint attention (child-initiated ja) in the intervention groups was 0.55 standard deviations higher (0.11 lower to 1.21 higher)
Examino	er-child	l joint attent	tion (Child-	-initiated	<b>JA)</b> (measui	l red with: EScs (Ea	I Irly Social	Communication S	Scales): Poir	I 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	⊕⊕⊕⊝ MODERATE² due to	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-child	joint atten	tion (Child	-initiated	<b>JA)</b> (measu	red with: EScs (E	arly Soci	al Communica	ation Scales): G	iving; 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	⊕⊕⊝⊝ LOW¹ due to imprecision	17	20	N/A	N/A	The mean examiner-child join attention (child-initiated ja) in the intervention groups was <b>0.48 standard deviations higher</b> (0.18 lower to 1.14 higher)
		l joint atten ter indicated by lo	•	-initiated	JA) (measu	red with: Commu	inication a	and Symbolic	Behavior Scale	s Developn	nental Profile (CSBS DP): Initiating
48 (1 study) 26 weeks	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to	24	24	N/A	N/A	The mean examiner-child join attention (child-initiated ja) in the intervention groups was <b>0.31 standard deviations</b>
	bias					imprecision					higher (0.26 lower to 0.88 higher)
Examin	er-child	l <b>joint atten</b>	•	-initiated	<b>JA)</b> (measu		inication a	and Symbolic	Behavior Scale	s Developm	higher

mental Profile (C	no I	shared positive affective mental Profile (CSBS DP): Shared no serious inconsistency no serious indirectness	•	•	•		cales): JA &	shared positive	-	
	serious i		serious <sup>2</sup>	1				snareu positive	affect or C	communication and Symbolic
	DIAS			undetected	⊕⊕⊕⊝ MODERATE² 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 higher</b> (0.39 lower to 0.47 higher)
•		shared positive affect mental Profile (CSBS DP): Share	,	•	•		,	shared positive	affect or C	communication and Symbolic
		no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	40	44	N/A	N/A	The mean examiner-child shared positive affect in the intervention groups was <b>0.43 standard deviations higher</b> (0 to 0.87 higher)
shared po	er-child :	shared positive affect	Ct (measured	with: EScs (Ear	ly Social Commu	unication So	cales): JA &	shared positive	affect; Bet	ter indicated by lower values)
	_	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	16	20	N/A	N/A	The mean examiner-child shared positive affect in the intervention groups was <b>0.6 standard deviations higher</b> (0.08 lower to 1.27 higher)
n	no l serious i risk of bias	n ir	o serious no serious indirectness	o serious no serious very indirectness serious serious	o serious no serious very undetected indirectness serious¹	no serious indirectness very serious serious undetected to imprecision	o serious indirectness very serious undetected $\bigoplus \bigoplus \ominus \ominus$ LOW <sup>1</sup> due to imprecision	o serious indirectness very serious serious loops aconsistency indirectness loops aconsistency loops are loops as loops are loops as loops are loo	o serious indirectness very serious looserious indirectness very serious looserious indirectness looserious lo	indirectness serious¹ LOW¹ due to

36 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to imprecision	16	20	N/A	N/A	The mean examiner-child joint attention, shared positive affec & utterance in the intervention groups was <b>0.04 standard deviations higher</b> (0.62 lower to 0.7 higher)
		-		ed positiv	e affect 8	utterance	(measure	ed with: EScs	(Early Social C	ommunica	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	⊕⊕⊝⊝ LOW¹ 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)
		l joint atten er indicated by low		ed positiv	e affect 8	utterance	(measure	ed with: EScs	(Early Social C	ommunica	tion Scales): JA & shared positive
36 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	16	20	N/A	N/A	The mean examiner-child joint attention, shared positive affect witterance in the intervention groups was 0.77 standard deviations higher (0.09 to 1.46 higher)
	ner-child	l socially er	ngaged imi	itation (me	easured with: Be	ehavioural observ	ation: Soc	cially engage	d imitation (SEI)	); Better inc	dicated by lower values)
Examir							24	24	N/A	N/A	

	bias					imprecision					higher (0.28 lower to 0.86 higher)
Examin	ner-child	socially er	ngaged imi	tation (me	easured with: Be	ehavioural observ	vation: So	cially engaged	d imitation (SEI)	; Better inc	dicated by lower values)
48 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² 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 higher</b> (0.15 to 1.32 higher)
Mother- ower value:	-	int attentio	n (Child-in	itiated J	<b>A)</b> (measured	with: Behavioura	l observat	tion: Mother-c	hild interaction	(Coordinate	ed 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	⊕⊕⊝⊝ Low¹ 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 higher</b> (0.18 lower to 1.13 higher)
Mother-	-child jo	int attentio	n (Child-in	itiated J	<b>A)</b> (measured	uith: Behavioura	l observat	tion: Mother-c	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	⊕⊕⊖⊝ Low¹ due to imprecision	17	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) in the intervention groups was <b>0.51 standard deviations</b> higher (0.15 lower to 1.16 higher)
Mother-	-child jo	int attentio	n (Child-in	itiated J	<b>A)</b> (measured	l with: Behavioura	l observat	tion: Mother-c	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	⊕⊕⊖⊝ <b>LOW</b> <sup>1</sup> due to	17	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) in the intervention groups was <b>0.39 standard deviations</b>

	bias					imprecision					lower (1.04 lower to 0.27 higher)
Mother-	-child jo	int attentio	n (Child-in	itiated J	(measured	with: Behavioural	observati	on: Mother-cl	nild interaction (	(Giving); Be	etter 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	⊕⊕⊝⊝ LOW¹ 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 higher</b> (0.3 lower to 1.01 higher)
Mother- by lower val	_	int attentio	n (Child-in	itiated J	(measured	with: Behavioural	observati	on: Mother-cl	nild 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	⊕⊕⊕⊝ MODERATE² 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 higher</b> (0.1 to 1.45 higher)
Mother- by lower val	_	oint attentio	n (Child-in	itiated J	<b>A)</b> (measured	with: Behavioural	observati	on: Mother-cl	nild 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	⊕⊕⊝⊝ LOW¹ due to imprecision	17	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) in the intervention groups was <b>0.19 standard deviations higher</b> (0.46 lower to 0.83 higher)
Mother- by lower val	_	int attentio	n (Child-in	itiated J	(measured	with: Behavioural	observati	on: Mother-cl	nild interaction -	- Duration	of JA (seconds); Better indicated
36 (1 study)	no serious	no serious	no serious	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup>	16	20	N/A	N/A	The mean mother-child joint attention (child-initiated ja) in

52 weeks	risk of bias	inconsistency	indirectness			due to imprecision					the intervention groups was  0.81 standard deviations higher  (0.13 to 1.5 higher)
		and mothe	_	nt attenti	on (JA ini	tiation con	nposite	e) (measured	d with: EScs a	nd mother-c	child 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	⊕⊕⊖ LOW¹ 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 higher</b> (0.15 lower to 1.17 higher)
		and mothe ter indicated by lov		nt attenti	on (JA ini	tiation con	nposite	<b>e)</b> (measured	d with: EScs a	nd mother-c	child 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	⊕⊕⊝⊝ LOW¹ 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 higher</b> (0.13 lower to 1.18 higher)
		and mothe	•	nt attenti	on (JA ini	tiation con	nposite	e) (measured	d with: EScs ar	nd mother-c	shild interaction observations: JA
36 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² 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 <b>0.99 standard deviations higher</b> (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	⊕⊕⊕⊝ MODERATE² 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 1.11 standard deviations higher (0.41 to 1.81 higher)
		and mothe Better indicated by	=	nt attenti	on (JA re	sponses co	mpos	site) (measu	red with: EScs	and mothe	er-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	⊕⊕⊕⊝ MODERATE² 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 higher</b> (0.12 to 1.47 higher)
responses (		I and mothe Better indicated by	-	nt attenti	on (JA re		_	•	-		er-child interaction observations:
36 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	16	20	N/A	N/A	The mean examiner-child and mother-child joint attention (jaresponses composite) in the intervention groups was 0.17 standard deviations higher

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

		Q	uality assess	ment					Summ	ary of Findings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rat	es (%)	Relative effect	Anticipated abso	olute 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% CI)
Social in	teract	ion (measured v	vith: Gilliam Auti	sm Rating Sca	le (GARS): So	cial interaction; I	Better indicated by	/ lower va	lues)		
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  0.73 standard deviations lower  (1.46 lower to 0 higher)
Frequen	cy of c	child-initiate	ed social i	nteraction	ns with T	D peers (me	easured with: Beha	avioural o	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 higher</b> (0.63 lower to 1.09 higher)
Duration	of all	social inter	ractions w	ith TD pe	ers (measure	ed with: Behavio	ural observation; l	Better ind	icated by lo	wer values)	
21 (1 study) 18 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊝⊝ <b>VERY LOW</b> <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

I				imprecision		0.27 standard deviations	i
						higher (0.59 lower to 1.13 higher)	ì
						(0.59 lower to 1.15 fligher)	1

<sup>&</sup>lt;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 as parent-rated and blinding of parents was not reported

### 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	Quality assessment					Summary of Findings				
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			Tr	With Treatment- as-usual	With Social skills group	(95% CI)	Risk with Treatment-as- usual	Risk difference with Social skills group (95% CI)					
		asured with: Socia	al Skills Rating S	vstem (SSRS)	· Assertion or So	oial Ckilla Dating Cyat	om (CCDC).	0:-1-1:11-	/- (   -       -     -				
System for C	hildren, 2n	d ed., parent rated					em (SSRS).	Social skills	(standardiz	ed score) or E	Behavior Assessment		

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias due to non-blinded behavioural observations which were carried out by the investigator and there was no reliability or validity data reported for observation measures

<sup>&</sup>lt;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)

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 LOW¹.2.3 due to risk of bias, imprecision,	17	18	N/A	N/A	The mean social impairment in the intervention groups was <b>0.69 standard deviations</b>
Adamti		I bakasia				publication bias					(1.37 lower to 0 higher)
Adaptiv	ve socia	ii benaviou	f (measured with	h: Social Com	petence Inventory	(SCI): Pro-social inde	ex; Better	indicated by	lower value	s)	
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 adaptive social behaviour in the intervention groups was <b>0.11 standard deviations</b> higher (0.51 lower to 0.73 higher)
Capaci	ty for so	ocial intera	ctions (meas	ured with: So	cial Competence I	nventory (SCI): Social	l initiation	index; Bette	r indicated b	y lower value	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 <b>0.03 standard deviations</b> lower
											(0.65 lower to 0.58 higher)
Study-s	specific	targeted se	ocial skills	(measured w	vith: Adapted Skills	treaming Checklist (A	SC): Tota	al; Better ind	icated by low	ver values)	(0.65 lower to 0.58 higher)

69 (2 studies) 6-12 weeks	serious <sup>6</sup>	very serious <sup>7</sup>	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 1.58 standard deviations higher (1.03 to 2.14 higher)
Social s	kills kr	owledge (s	self-rated)	(measured wi	th: Test of Adoles	scent Social Skills Know	wledge (T	ASSK): Tota	al; Better ind	icated by low	ver 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 kr	owledge (r	esearcher	-rated) (n	neasured with: Sk	illstreaming Knowledge	e Assessi	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 (researcherrated) in the intervention groups was 1.19 standard deviations higher (0.48 to 1.91 higher)
	s of Ion	eliness (mea	asured with: Lone	eliness Scale:	Total; Better indi	cated by lower values)					
Feeling											

											(1.16 to 0.18 lower)
Populai	rity (sel	f-rated) (mea	sured with: Piers	-Harris Self-C	Concept Scale (Pl	HS): Popularity; Better	indicated	d by lower va	lues)		
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  0.56 standard deviation higher  (0.07 to 1.04 higher)
Numbe	r of time	es child inv	rited to a p	lay date	(parent-rat	(measured with:	Quality of	of Play Quest	ionnaire (QI	PQ): Host; Be	etter indicated by lower values)
97 (2 studies) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝  VERY LOW¹.5  due to risk of bias, imprecision	45	52	N/A	N/A	The mean number of time child invited to a play date (parent-rated) in the intervention groups was <b>0.36 standard deviations higher</b> (0.04 lower to 0.77 higher)
Numbe	r of time	es child inv	rited to a p	lay date	(Self-rated	(measured with: Qua	lity of Pl	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 serious <sup>5</sup>	undetected	⊕⊝⊖⊝ VERY LOW <sup>5,8</sup> due to risk of bias, imprecision	16	17	N/A	N/A	The mean number of time child invited to a play date (self-rated) in the intervention groups was  0.26 standard deviations lower  (0.95 lower to 0.42 higher)
Time sp	pent in i	nteractive	activities (r	neasured with	n: Quality of Play	Questionnaire (QPQ):	Engage;	; Better indica	ted by lowe	r values)	
62 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝⊝ <b>VERY LOW</b> <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 <b>0.2 standard deviations</b>

					imprecision					higher (0.31 lower to 0.7 higher)
nt in r	ninimally i	nteractive	activities	(measured with	n: Quality of Play Quest	tionnaire (	QPQ): Diseng	age; Better i	ndicated by l	ower values)
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	27	35	N/A	N/A	The mean time spent in minimally interactive activities in the intervention groups was 1.31 standard deviations lower (1.87 to 0.75 lower)
f frien	dships (se	If-rated) (me	easured with:	Friendship Qualii	ties Scale (FQS): Total	; Better in	dicated by low	er values)	1	+
serious <sup>8</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	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)
treatm	ent respon	ISE (assessed	with: Dichoton	nous measure of	number of participants	'much im	proved/very in	nproved' on	I Clinical Globa	al Impression-Improvement
serious <sup>9</sup>	no serious	no serious	serious <sup>10</sup>	undetected	⊕⊕⊖⊖ LOW <sup>9,10</sup>	0/18	16/23		Study popu	ulation
	mocriciotomoy	indirectines.			due to risk of bias,	(0,0)	(00.070)	407.99)	0 per 1000	N/A
					Impredicion				Moderate	
									0 per 1000	N/A
	f frien serious8	f friendships (se	serious no serious inconsistency indirectness  f friendships (self-rated) (messerious inconsistency indirectness  serious no serious inconsistency indirectness  treatment response (assessed to serious) no serious  serious no serious no serious	serious no serious inconsistency indirectness serious serious friendships (self-rated) (measured with:  serious no serious no serious very indirectness serious serious inconsistency indirectness serious serious no serious serious serious no serious serious serious no serious se	serious no serious inconsistency indirectness serious undetected indirectness serious undetected indirectness serious friendships (self-rated) (measured with: Friendship Qualities no serious no serious inconsistency indirectness serious serious serious no serious inconsistency indirectness serious serious no serious serious no serious serious no serious serious undetected serious no serious serious undetected serious no serious serious undetected undetected	serious¹ no serious inconsistency indirectness serious² undetected ⊕⊕⊝⊝ LOW¹.² due to risk of bias, imprecision  f friendships (self-rated) (measured with: Friendship Qualities Scale (FQS): Total serious³ no serious inconsistency indirectness serious⁵ undetected very serious⁵ very serious⁵ due to risk of bias, imprecision  ireatment response (assessed with: Dichotomous measure of number of participants inconsistency indirectness serious¹ undetected ⊕⊕⊝ LOW³.¹²  ireatment response (assessed with: Dichotomous measure of number of participants inconsistency indirectness serious¹ undetected ⊕⊕⊝ LOW³¹.¹o	serious no serious inconsistency indirectness serious serious indirectness serious indirectness serious indirectness indirectness serious indirectness serious indirectness serious indirectness serious indirectness serious inconsistency indirectness serious inconsistency inconsisten	serious no serious indirectness serious serious indirectness serious serious indirectness serious serious indirectness serious indirectness serious serious indirectness serious serious indirectness serious serious indirectness serious serious inconsistency serious serious indirectness serious serious indirectness serious serious indirectness serious serious indirectness serious s	serious¹ no serious inconsistency indirectness serious² undetected \$\begin{array}{c} \pmo \operatorname{\text{phi} \opera	inconsistency indirectness   LOW <sup>1,2</sup>   due to risk of bias, imprecision

36 (1 study)		no serious indirectness	very serious⁵	undetected	⊕⊝⊝ VERY LOW <sup>5,11</sup>	18	18	N/A	The mean emotion recognition in the
6 weeks	ĺ				due to risk of bias, imprecision				intervention groups was  0.44 standard deviations
									higher (0.22 lower to 1.1 higher)

<sup>&</sup>lt;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>&</sup>lt;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>&</sup>lt;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

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

<sup>&</sup>lt;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>&</sup>lt;sup>7</sup> Moderate to substantial heterogeneity

<sup>&</sup>lt;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>&</sup>lt;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>&</sup>lt;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 non-blind 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	ment				Sur	nmary 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						evidence	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% CI)
Social s	kills (me	easured with: Soc	ial Responsiven	ess Scale (SR	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	⊕⊕⊖⊝ LOW¹,2 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 (SRS	S): Social Cog	l nition (standardi	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	Imunication (sta	I ndardized ch	nange score); Better inc	licated by lo	ower values)	
50 (1 study)	serious <sup>1</sup>	no serious	no serious	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <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	skills (me	easured with: Soc	ial Responsiven	ess Scale (SR	S): Social Moti	vation (standard	ized char	nge score); Bette	indicated by lower	values)	
50 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖ LOW¹,2 due to risk of bias, imprecision	26	24	N/A	N/A	The mean social skills in the intervention groups was 0.66 standard deviations lower (1.23 to 0.08 lower)
Social	skills (me	easured with: Soc	cial Responsiven	ess Scale (SR	S): Autistic Ma	nnerisms (stand	ardized c	hange score); Be	tter indicated by lo	wer values)	
50 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW¹,2 due to risk of bias, imprecision	26	24	N/A	N/A	The mean social skills in the intervention groups was  0.67 standard deviations lower  (1.24 to 0.1 lower)
Social	self-effi	cacy (self-ı	rated) (measu	red with: Soci	al Self-efficacy	Scale (standard	lized char	nge score); Bette	r indicated by lowe	r values)	
52 (1 study) 19 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖⊝ <b>VERY LOW</b> <sup>3,4</sup> due to risk of bias, imprecision	28	24	N/A	N/A	The mean social self- efficacy (self-rated) in the intervention groups was  0.12 standard deviations lower (0.67 lower to 0.42 higher)
Feeling	s of lor	n <b>eliness</b> (me	asured with: Soc	ial Dissatisfac	ion Questionn	l aire (standardize	l d change	e score); Better in	dicated by lower va	alues)	
52 (1 study)	serious <sup>4</sup>	no serious	no serious	very	undetected	⊕⊝⊝⊝ VERY LOW <sup>3,4</sup>	28	24	N/A	N/A	The mean feelings of loneliness in the

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)
1 High rick of	nerformar	ca and recnonce	hiae ae intervent	ion administra	tore and nartic	inante ware non	-hlind and high risk of detection his	e se naren	t-completed s	and parents were non blind

<sup>&</sup>lt;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 parent-completed and parents were non-blind and involved in the intervention

# 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		Overall quality	Study event	` ′		Anticipated a	absolute effects			
(studies) Follow up	bias	Treatment-as- ES usual P-f		With ESDM or P-ESDM	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with ESDM or P- ESDM (95% CI)							
-	Repetitive behaviour (ESDM or P-ESDM) (measured with: Repetitive Behavior Scale (RBS): Total or Autism Diagnostic Observation Schedule for Toddlers (ADOS-T): Restricted, Repetitive Behaviours; Better indicated by lower values)													
143 (2 studies) 12-104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW¹.² 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			

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;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)

<sup>&</sup>lt;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 measure self-rated

							]				(0.39 lower to 0.27 higher)
Repetitiv	e behav	/iour (ESDM)	(measured with:	Repetitive Beh	navior Scale (R	BS): Total; Better	indicated by	lower value	es)		
15 1 study) 104 weeks Repetitiv	serious <sup>3</sup> e behav	no serious inconsistency	no serious indirectness  M) (measured wi	very serious <sup>4</sup> th: Autism Dia	undetected gnostic Observ	⊕⊖⊖ VERY LOW <sup>3,4</sup> due to risk of bias, imprecision  ation Schedule fo	21 r Toddlers (A	24 ADOS-T): Re	N/A	N/A	The mean repetitive behaviour (esdm) in the intervention groups was 0.35 standard deviations lower (0.95 lower to 0.24 higher) naviours; Better indicated by low
98 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <sup>2.5</sup> due to risk of bias, imprecision	49	49	N/A	N/A	The mean repetitive behaviour (p-esdm) in the intervention groups was <b>0.07 standard deviations higher</b> (0.32 lower to 0.47 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and unclear/unknown risk of detection bias as blinding ofoutcome assessors was either not reported or the outcome measure was parent-completed and parents were non-blind and involved in the intervention

# 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

<sup>&</sup>lt;sup>3</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as this outcome measure was parent-completed and parents were non-blind and involved in the intervention

 <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)</li>
 5 High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as the outcome assessor

High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as the outcome assessor reported as 'laboratory personnel' with no detail regarding blinding of outcome assessors reported

		Qı	uality assessr	ment				Sun	nmary of I	inding	s
Participants studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	event rates (%)	Relative effect	Anticip	ated absolute effects
ollow up						evidence	With Control	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)	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 be	ehaviour (m	easured with: S	ocial Commun	ication Questi	ionnaire (SCQ)	: Stereot	typed behaviour; Better indica	ated by lowe	er values	s)
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 0.31 standard deviations lower (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 (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	` '	Relative effect	Anticip	ated absolute effects
Follow up						evidence	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: C	hildren's Yale-B	rown Obsessiv	ve Compulsive	Scales-PDD (	CYBOC	S-PDD): Compulsions; Better	indicated b	y lower v	values)
95 (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	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)

<sup>&</sup>lt;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, but unclear who the interviewee is but if parental interview then non-blind. There was also a high risk of attrition bias due to higher dropout rates in the experimental (combined risperidone and parent training) group (N=20; 27% attrition) than the control (risperidone only) group (N=9; 18% attrition)
<sup>2</sup> N<400

## 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

		Qı	uality assessr	nent				Su	mmary of	Findings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study ever	nt rates (%)	Relative effect	Anticipated	d absolute effects
Follow up						evidence	With Treatment- as-usual	With Caregiver- mediated social- communication intervention (PACT)	(95% CI)	Risk with Treatment- as-usual	Risk difference with Caregiver-mediated social- communication intervention (PACT) (95% CI)
B 4141								Repetitive Behaviours			<del>.</del>

# 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

		Qı	uality assessm	ent				S	ummary o	f Findings	5
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study ev	ent 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 (gloement [CGI-I]: Autisn	•	nent) (asses	ssed with: Posi	tive treatment respo	onse (num	ber of participant	s 'much impr	oved/very i	mproved' on Clinical
	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1</sup>	0/11 (0%)	2/16 (12.5%)	RR 3.53 (0.19 to	Study po	pulation
12 weeks						due to imprecision		()	67.1)	0 per 1000	NA
										Moderate	1
										0 per 1000	NA
<sup>1</sup> Events<300	and 95% CI	crosses both line of	no effect and mea	sure of appred	ı ciable benefit o	r 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

		Qı	uality assessm	ent					Summa	ry of Find	lings
articipants R		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study e	vent rates (%)	Relative	Anticipa	ted absolute effects
ollow up	oias				bias	of evidence	With Placebo	With Antidepressant	effect (95% CI)	Risk with Placebo	Risk difference with Antidepressant (95% CI)
		chaviours (gl dren's Yale-Brown									ent Scale Adapted to Global
study) ris		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ 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 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

		Qı	uality assessi	ment				Sum	nmary of I	indings	
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study event rat	tes (%)	Relative	Anticipated abs	olute effects
(studies) Follow up	bias				bias		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% CI)
Overall a	utistic k	ehaviours (r	neasured with: (	Childhood Auti	sm Rating Sca	le (CARS): Total	[change score]; I	Better indicated by	lower valu	es)	
_	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	20	20	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.96 standard deviations lower (1.62 to 0.3 lower)
<sup>1</sup> N<400			L	L					l	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				Sur	nmary of	Finding	s
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study	event rates (%)	Relative	Anticipa	ated absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Antipsychotics versus placebo for overall autistic behaviours	effect (95% CI)	Risk with Control	Risk difference with Antipsychotics versus placebo for overall autistic behaviours (95% CI)
Overall a	utistic b	ehaviours (a	ssessed with: Did	chotomous: Po	sitive treatment	response (>20% im	proveme	nt on CARS))			
39 (1 study)	no serious	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	reporting bias strongly	⊕⊕⊝⊝ <b>LOW</b> <sup>1,2</sup>	0/20 (0%)	12/19 (63.2%)	RR 26.25 (1.66 to	Study p	opulation
26 weeks	bias	,			suspected <sup>2</sup>	due to imprecision, publication bias	,	` ,	414.57)	0 per 1000	N/A
										Modera	te
										0 per 1000	N/A
Overall a	utistic b	ehaviours (as	ssessed with: Did	chotomous: Po	sitive treatment	response (>20% im	proveme	nt on Children's Globa	l Assessme	nt Scale))	
39 (1 study)	no serious	no serious inconsistency	no serious	serious <sup>1</sup>	reporting bias strongly	⊕⊕⊝⊝ <b>LOW</b> <sup>1,2</sup>	2/20 (10%)	17/19 (89.5%)	RR 8.95 (2.38 to	Study p	opulation
26 weeks	bias	modification	muncoures:		suspected <sup>2</sup>	due to imprecision, publication bias	(1070)	(65.576)	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)
Overall a	utistic b	ehaviours (m	l neasured with: Cl	l hildhood Autisr	n Rating Scale (	L CARS): Total or Rity	vo-Freem	nan Real-life Rating Sc	l ale (RLRS)	: Total; Be	etter indicated by lower

/alues)											
2 studies)	no serious risk of bias	very serious <sup>3</sup>	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊖⊝ <b>VERY LOW</b> <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 deviations lower</b> (1.25 to 0.5 lower)
Overall au	utistic b	ehaviours (d	lirect outco	me) (measu	red with: Childho	od Autism Rating So	cale (CA	ARS): Total; Better ind	icated by lov	ver value	s)
23 s (1 study) 24 weeks		no serious inconsistency	no serious indirectness	very serious <sup>6</sup>	undetected	⊕⊖⊝ <b>VERY LOW</b> <sup>5,6</sup> due to risk of bias, imprecision	12	11	N/A	N/A	The mean overall autistic behaviours (direct outcome) in the intervention groups was <b>0.31 standard deviations higher</b> (0.51 lower to 1.14 higher)
Overall au	utistic b	ehaviours (i	ndirect out	come) (mea	sured with: Ritvo	-Freeman Real-life	Rating S	Scale (RLRS): Total; B	etter indicat	ed by low	ver values)
1 study)		no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE⁴ due to imprecision	52	49	N/A	N/A	The mean overall autistic behaviours (indirect outcome) in the intervention groups was 1.19 standard deviations lower (1.61 to 0.76 lower)

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

Substantial to considerable heterogeneity with an I-squared value of 90%

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>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)

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

		Q	uality assessr	nent				Sur	nmary of	Finding	s
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study 6	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% CI)
Overall a	utistic	behaviours (r	neasured 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	⊕⊖⊝ <b>VERY LOW</b> <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 0.35 standard deviations lower (1.1 lower to 0.4 higher)
Overall a	utistic	behaviours (r	measured with: F	Ritvo-Freeman	Real-life Ratin	g Scale (RLRS):	Social; I	Better indicated by lower v	/alues)	•	
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 lower</b> (1 lower to 0.49 higher)
Overall a	utistic	behaviours (r	neasured with: F	ı Ritvo-Freeman	Real-life Ratin	g Scale (RLRS):	Motor; E	Better indicated by lower v	alues)		
28 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝⊖ VERY LOW¹.² 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> lower (1.09 lower to 0.41 higher)
Overall a	utistic	behaviours (r	neasured with: F	Ritvo-Freeman	Real-life Ratin	g 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	⊕⊝⊝ VERY LOW <sup>1,2</sup>	15	13	N/A	N/A	The mean overall autistic behaviours in the

12 weeks						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>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	n Real-life Ratir undetected	ng Scale (RLRS):	Sensory 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> lower (0.92 lower to 0.57 higher)
Overall a 28 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	measured with: I	very serious <sup>2</sup>	n Real-life Ratir undetected	mg Scale (RLRS):  ⊕⊖⊖⊝  VERY LOW¹.²  due to risk of bias, imprecision	Langua 15	ge; Better indicat	ed by lower value	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.22 standard deviations higher</b> (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	ıality assessm	ent				Su	ımmary of	Finding	5
Participants		Inconsistency	Indirectness	•		Overall quality	Study e	vent rates (%)		Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Placebo	With Selective noradrenaline reuptake inhibitors	1 (95% CI)	Risk with Placebo	Risk difference with Selective noradrenaline reuptake inhibitors (95% CI)
Overall a	utistic be	ehaviours (mea	asured with: Child	dren's Social B	Behavior Questi	onnaire (CSBQ):	Total; Be	etter indicated by lowe	r values)		

	no serious risk of bias		no serious indirectness	very serious <sup>1</sup>		⊕⊕⊖⊖ <b>LOW</b> ¹ due to imprecision	46	43	N/A		The mean overall autistic behaviours in the intervention groups was <b>0.27 standard deviations lower</b> (0.68 lower to 0.15 higher)		
<sup>1</sup> N<400 and	<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)												

# 1.5 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 assessm				Summa	ry of Finc	lings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study e (%)	vent rates	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	veness Scale (	SRS): Total; Be	etter indicated by l	ower valu	es)			
29 (1 study)	no serious	no serious	no serious	very	undetected	⊕⊕⊝⊝ LOW¹	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 0.14 standard deviations lower (0.87 lower to 0.59 higher)
Social /	Awarenes	SS (measured wit	h: Social Respons	siveness Scale	e (SRS): Social A	\wareness ; Bette	er indicate	ed 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	⊕⊕⊝⊝ LOW¹ due to imprecision	15	14	N/A	N/A	The mean social awareness in the intervention groups was <b>0.45 standard deviations lower</b> (1.19 lower to 0.29 higher)
Social (	Cognition	(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	⊕⊕⊝⊝ LOW¹ due to imprecision	15	14	N/A	N/A	The mean social cognition in the intervention groups was <b>0.02 standard deviations lower</b> (0.74 lower to 0.71 higher)
Social (	Commun	ication (meas	ured with: Social F	Responsivene	ss Scale (SRS):	Social Communic	cation ; B	etter indicate	ed by lower v	alues)	
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ 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	n: 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	⊕⊕⊝⊝ <b>LOW</b> ¹ 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	isms (measured	with: Social Resp	onsiveness Sc	cale (SRS): Auti	istic Mannerisms ;	Better in	ndicated by lov	ver values)		
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	15	14	N/A	N/A	The mean autistic mannerisms in the intervention groups was <b>0.64 standard deviations</b> lower (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 Finding	gs
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	of evidence	Study ev With Placebo	(.,	Relative effect (95% CI)	•	Risk difference with Antidepressants (95% CI)

149 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹	26/76 (34.2%)	24/73 (32.9%)	<b>RR 0.96</b> (0.61 to	Study po	pulation
12 weeks		,				due to imprecision	(= 1.2,0)	(==:073)	1.51)	342 per 1000	14 fewer per 1000 (from 133 fewer to 174 more)
										Moderate	9
										342 per 1000	<b>14 fewer per 1000</b> (from 133 fewer to 174 more)
improved' or	n CGI-improve	ment))	•					•			uch improved/very
149 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹	10/76 (13.2%)	15/73 (20.5%)	RR 1.56 (0.75 to	Study po	pulation
12 weeks		,				due to imprecision		,	3.25)	132 per 1000	<b>74 more per 1000</b> (from 33 fewer to 296 more)
										Moderate	•
										132 per 1000	74 more per 1000 (from 33 fewer to 297 more)
		asured with: Child	Iren's Yale-Brown	Obsessive C	ompulsive Scale	s-PDD (CYBOCS-F	PDD): Com	pulsions or Ch	nildren's Yale-E	Brown Obse	ssive Compulsive Scale
		Better indicated b									

											higher)
Compu	I <b>lsive</b> (meas	L sured with: Repetit	ive Behavior Scal	e (RBS): Com	pulsive; Better i	ndicated by lower	/alues)				
149 (1 study) 12 days	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖  MODERATE²  due to imprecision	76	73	N/A	N/A	The mean compulsive in the intervention groups was 0.09 standard deviations higher (0.23 lower to 0.42 higher)
Restric	tive (measu	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	⊕⊕⊕⊝  MODERATE²  due to imprecision	76	73	N/A	N/A	The mean restrictive in the intervention groups was  0.34 standard deviations higher (0.01 to 0.66 higher)
Ritualis	StiC (measure	ed with: Repetitive	Behavior Scale (F	RBS): Ritualist	ic; Better indica	ted by lower value	s)		I		
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	76	73	N/A	N/A	The mean ritualistic in the intervention groups was <b>0 standard deviations higher</b> (0.32 lower to 0.32 higher)
Samen	<b>ess</b> (measur	ed with: Repetitive	e Behavior Scale (	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	⊕⊕⊕⊖  MODERATE²  due to imprecision	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-inj	urious (me	easured with: Repo	etitive Behavior So	cale (RBS): Se	elf-injurious; Bet	ter indicated by lov	ver values	s)	1	1	
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖  MODERATE²  due to imprecision	76	73	N/A	N/A	The mean self-injurious in the intervention groups was 0.15 standard deviations higher (0.17 lower to 0.47 higher)
Stereot	yped (mea	sured with: Repeti	tive 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	⊕⊕⊕⊝ MODERATE² 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)
<sup>1</sup> Events<30 <sup>2</sup> N<400	<u> </u> 00 and 95% Cl	crosses both line	of no effect and r	l measure of ap	l preciable benefi	t or harm (RR 0.75	/1.25)				

## 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	uality assessm	ent				Summar	ry 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)
Compul	Isions (me	asured with: Repe	titive Behavior Sca	ale (RBS): Cor	mpulsions; Bette	er indicated by lov	ver values)			-	•
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	15	14	N/A	N/A	The mean compulsions in the intervention groups was <b>0.68 standard deviations lower</b> (1.43 lower to 0.08 higher)
Restrict	ted (measure	ed with: Repetitive	Behavior Scale (F	RBS): Restricte	ed; Better indica	ted by lower valu	es)		·	-	1
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LoW¹ due to imprecision	15	14	N/A	N/A	The mean restricted in the intervention groups was <b>0.42 standard deviations 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)				ļ	1
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LoW¹ due to imprecision	15	14	N/A	N/A	The mean rituals in the intervention groups was <b>0.3 standard deviations lower</b> (1.03 lower to 0.44 higher)
Samene	SS (measure	ed with: Repetitive	Behavior Scale (F	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	⊕⊕⊝⊝ LoW¹ due to imprecision	15	14	N/A	N/A	The mean sameness in the intervention groups was <b>0.46 standard deviations lower</b> (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	⊕⊕⊖ LOW¹ due to imprecision	15	14	N/A	N/A	The mean self-injurious behaviour in the interventior groups was <b>0.26 standard deviations lower</b> (0.99 lower to 0.48 higher)
Stereot	ypic beha	aviour (measu	red with: Repetitiv	e Behavior Sc	ale (RBS): Stere	otypies; Better in	idicated b	y lower value	s)		
29	no serious	no serious	no serious	very	undetected	$\oplus \oplus \ominus \ominus$	15	14	N/A	N/A	The mean stereotypic

## 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	•	Overall quality of evidence	Study (	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)
•		(risperidoned by lower values)		razole) (m	easured with: (	L Children's Yale-B	rown Ob	sessive Compulsive Scale	(CYBOCS)	: Compu	Isions (Endpoint or Change
85 3 studies) -8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	130	255	N/A	N/A	The mean compulsions (risperidone or aripiprazoli in the intervention groups was  0.42 standard deviations lower  (0.64 to 0.2 lower)
compu	lsions (	(risperidon	<b>e)</b> (measured w	ith: Children's	Yale-Brown Ol	bsessive Compul	sive Sca	le (CYBOCS): Compulsion	s; Better in	dicated b	y lower values)
93	no	no serious	no serious	serious <sup>1</sup>	undetected	⊕⊕⊕⊝	86	107	N/A	N/A	The mean compulsions
2 studies) -8 weeks	serious risk of bias	inconsistency	indirectness			MODERATE <sup>1</sup> due to imprecision					(risperidone) in the intervention groups was <b>0.49 standard deviations lower</b> (0.79 to 0.20 lower)
2 studies) -8 weeks	risk of bias			vith: Children's	Yale-Brown C	due to imprecision	Ilsive Sca	ale (CYBOCS): Compulsion	ns (Change	Score);	intervention groups was 0.49 standard deviations lower (0.79 to 0.20 lower)

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

		Qı	ality assessr	nent				Sum	mary of F	inding	s
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	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 by lower values)		razole) (m	easured with:	Children's Yale	e-Brown	Obsessive Compulsive Scale	(CYBOCS	): Comp	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	⊕⊕⊝⊝ <b>LOW</b> <sup>1</sup> due to imprecision	78	75	N/A	N/A	The mean compulsions (risperidone or aripiprazole) in the intervention groups was <b>0.27 standard deviations lower</b> (0.59 lower to 0.04 higher)
Compuls	sions (	risperidon	e) (measured w	ith: Children's	Yale-Brown C	Dbsessive Com	pulsive S	Scale (CYBOCS): Compulsion	ns; Better ir	ndicated	by lower values)
63 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	34	29	N/A	N/A	The mean compulsions (risperidone) in the intervention groups was <b>0.29 standard deviations lower</b> (0.79 lower to 0.21 higher)

90 (1 study) 8 weeks	_			very serious <sup>1</sup>		⊕⊕⊝⊝ <b>LOW</b> <sup>1</sup> due to imprecision	44	46	N/A	The mean compulsions (aripiprazole) in the intervention groups was 0.27 standard deviations lower (0.68 lower to 0.15 higher)
<sup>1</sup> N<400 and	95% CI cro	osses both line of	no effect and me	easure of appr	reciable benef	it or harm (SMI	D -0.5/0	5)		

## 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 assessr	nent					Summa	ry of Fin	dings
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e	event rates	Relative effect	Anticipat	ted absolute effects
Follow up							With Waitlist	With Acupressure	(95% CI)	Risk with Waitlist	Risk difference with Acupressure (95% CI)
Overall a	utistic l	pehaviours (me	easured with: Stud	y-specific pare	ent-rated questi	onnaire: Total score	e; Better	indicated by lo	wer values)		
32 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW¹.² 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	utistic l	oehaviours (me	easured with: Stud	y-specific pare	ent-rated questi	onnaire: Language;	Better in	ndicated by low	er 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 1.33 standard deviations higher (0.55 to 2.1 higher)
Overall	autistic	behaviours (r	measured with: Stu	udy-specific pa	rent-rated quest	tionnaire: Social inte	raction	; Better indic	ated 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 interventior groups was <b>0.98 standard deviations higher</b> (0.24 to 1.72 higher)
Overall	autistic l	behaviours (r	neasured with: Stu	udy-specific pa	rent-rated quest	tionnaire: Social inte	raction	; Better indic	ated by lower	values)	
32 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	16	16	N/A	N/A	The mean overall autistic behaviours in the interventior groups was <b>0.23 standard deviations higher</b> (0.47 lower to 0.92 higher)
Overall	autistic l	L behaviours (r	neasured with: tud	l ly-specific pare	ent-rated questic	nnaire: Motor function	I oning; I	Better indica	ted by lower v	/alues)	
32 (1 study) 6 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	16	16	N/A	N/A	The mean overall autistic behaviours in the interventior groups was <b>0.45 standard deviations higher</b> (0.25 lower to 1.15 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as participants and intervention administrators were non-blind, and high risk of detection bias as outcome measure was parent-rated and parents were non-blind

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

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;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)

		Q	uality assess	sment				Sumn	nary of F	indings	
•		Inconsistency	Indirectness	Imprecision		Overall quality	Study event	rates (%)		Anticipated a	absolute effects
(studies) Follow up	bias				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% CI)
Overall a	utistic	behaviours	(measured with	n: Autism Eval	uation Treatm	ent Checklist (AT	EC): Total; Bet	ter indicated by lower va	alues)		
36 (1 study) 8 weeks	serious <sup>1</sup>	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	18	18	N/A	N/A	The mean overall autistic behaviours in the intervention groups was  0.25 standard deviations higher (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	n; 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 LOW¹,² due to risk of bias, imprecision	18	18	N/A	N/A	The mean overall autistic behaviours in the intervention groups was  0.06 standard deviations lower (0.71 lower to 0.59 higher)
Overall a	utistic	behaviours	(measured with	n: Autism Eval	uation Treatm	ent Checklist (AT	EC): Sociability	; Better indicated by lov	ver values)	)	
36 (1 study) 8 weeks	serious <sup>1</sup>	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	18	18	N/A	N/A	The mean overall autistic behaviours in the intervention groups was  0.14 standard deviations higher (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	areness; 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 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 indicate	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  0.18 standard deviations higher (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;	Better indicated by	y lower values)	<u> </u>	1
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  0.28 standard deviations higher (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	⊕⊖⊖ <b>VERY LOW</b> <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  0.16 standard deviations higher (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  0.2 standard deviations lower (0.69 lower to 0.28 higher)
Overall a	utistic	behaviours	(measured with	n: Ritvo-Freem	nan Real-life R	ating Scale (RLR	S): Affecti	ve; Better indicate	d by lower values)	•	
66 (2 studies) 8 weeks	serious <sup>1</sup>	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	33	33	N/A	N/A	The mean overall autistic behaviours in the intervention groups was  0.17 standard deviations higher (0.32 lower to 0.66 higher)
Overall a	utistic	behaviours	(measured with	n: Ritvo-Freem	nan Real-life R	ating Scale (RLR	S): Senso	ry; Better indicated	d by lower values)		<u> </u>
66 (2 studies) 8 weeks	serious <sup>1</sup>	serious <sup>3</sup>	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ <b>VERY LOW</b> <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  0.12 standard deviations higher (0.36 lower to 0.61 higher)
Overall a	utistic	behaviours	(measured with	n: Ritvo-Freem	nan Real-life R	tating Scale (RLR	S): Langu	age; Better indicat	ed 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 0.35 standard

											deviations higher (0.13 lower to 0.84 higher)
Overall a	autistic	behaviours	(measured with	h: Clinical Glol	bal Impression	Scale (CGI): Tot	al; Better ind	icated by lower value	es)		
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <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 0.9 standard deviations lower (1.58 to 0.21 lower)
Overall a	autistic	behaviours	(measured wit	h: Clinical Glol	bal Impression	Scale (CGI): Re	sponse to so	cial interaction; Bette	r indicated by I	ower 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 0.2 standard deviations lower (0.91 lower to 0.52 higher)
Overall a	autistic	behaviours	(measured with	h: Clinical Glol	bal Impression	Scale (CGI): So	cial initiation;	Better indicated by lo	ower 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  0.1 standard deviations lower  (0.81 lower to 0.62 higher)
Overall a	autistic	behaviours	(measured with	h: Clinical Glol	bal Impressior	Scale (CGI): Use	e of speech;	Better indicated by lo	wer 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

30 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ <b>Low</b> <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 a	utistic	behaviours	(measured wit	h: Clinical Glo	bal Impression	Scale (CGI): Be	naviour pro	bblem; Better indic	ated by lower value	es)	<u>'</u>
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 a	utistic	behaviours	(measured wit	h: Clinical Glo	bal Impression	Scale (CGI): Act	ivity 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 a	utistic	behaviours	(measured wit	h: Clinical Glo	bal Impression	Scale (CGI): Sle	ep problen	n; Better indicated	by lower values)	1	
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 a	utistic	behaviours	(measured wit	h: Clinical Glo	bal Impression	Scale (CGI): Dig	estive prol	blem; Better indica	ited by lower value	s)	<u> </u>
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

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind and potential for care confounds as the conventional education programme differed for each participant which may introduce bias. There was also an unclear risk of detection bias as although all outcomes were measured by blinded assessors, some outcomes involved input from parents who were not blind to treatment allocation or confounding variables and systematic review from which data was extracted does not report which outcome measures relied on non-blind parental report

<sup>&</sup>lt;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>&</sup>lt;sup>3</sup> Moderate to substantial heterogeneity

<sup>4</sup> N<400

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

		Q	uality assess	sment				Summ	ary 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	(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 deviations lower</b> (0.69 lower to 0.09 higher)
Overall a	utistic	behaviours	(measured w	ith: Ritvo-Free	man Real-life	Rating Scale (R	LRS): Motor (chang	e 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 deviations lower</b> (0.49 lower to 0.28 higher)
Overall a	utistic	behaviours	6 (measured w	ith: Ritvo-Free	man Real-life	Rating Scale (R	LRS): Social (chang	ge scores); Better inc	licated by I	ower 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>0.16 standard deviations lower</b> (0.55 lower to 0.22

											higher)
Overall a	autistic	behaviour	<b>S</b> (measured w	ith: Ritvo-Free	eman Real-life	Rating Scale (R	LRS):	Affective (change scores); Better in	ndicated 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 deviations lower</b> (0.66 lower to 0.11 higher)
Overall a	autistic	behaviours	<b>S</b> (measured w	ith: Ritvo-Free	eman Real-life	Rating Scale (R	LRS):	Sensory (change scores); Better in	ndicated by	y lower values)	
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 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): I	Language (change scores); Better	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 deviations lower</b> (0.7 lower to 0.07 higher)
Positive	treatm	ent respon	Se (assessed	with: Number	of participants	showing much	improve	ement on CGI-I for autistic behavio	ours)		
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊝⊝⊝ VERY LOW <sup>2,5</sup>	1/25 (4%)		<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	193 more per 1000 (from 9 fewer to

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					bias					1000 more)		
									Moderate			
									40 per 1000	193 more per 1000 (from 9 fewer to 1000 more)		
treatm	ent respon	Se (assessed	with: Number	of participants	showing minima	al improvemer	nt on CGI-I for autistic	behaviours)				
no serious	no serious	no serious	very serious <sup>5</sup>	reporting	⊕⊝⊝⊝ VFRY LOW <sup>2,5</sup>	14/25 (56%)	20/30	RR 1.19	Study population	tion		
risk of bias			55.1535	strongly suspected <sup>2</sup>	due to imprecision, publication bias	(6676)	(65.1.75)	1.83)	560 per 1000	106 more per 1000 (from 129 fewer to 465 more)		
									Moderate			
									560 per 1000	106 more per 1000 (from 129 fewer to 465 more)		
			ial related	Iness (asse	ssed with: Dicho	tomous: Positi	ive treatment response	e for social rela	tedness - Social r	esponse (study-		
no	no serious	no serious	very	reporting		5/25	4/30		Study population	n		
risk of bias	inconsistency	indirectiness	School	strongly suspected <sup>2</sup>	due to imprecision, publication	(2076)	(13.370)	2.22)	200 per 1000	66 fewer per 1000 (from 160 fewer to 244 more)		
					Diag				Moderate			
									200 per 1000	66 fewer per 1000 (from 160 fewer to 244 more)		
	no serious risk of bias  treatment-reported no serious risk of	no serious inconsistency risk of bias no serious inconsistency risk of bias no serious ent-reported better than be no serious risk of no serious inconsistency risk of	no serious inconsistency risk of bias no serious inconsistency risk of bias no serious indirectness indirectness indirectness indirectness indirectness indirectness inconsistency risk of no serious inconsistency risk of no serious indirectness indirect	no serious inconsistency risk of bias no serious inconsistency indirectness serious serious serious serious serious inconsistency indirectness serious serious inconsistency inconsistency indirectness serious serious inconsistency indirectness serious serious inconsistency indirectness serious serious serious inconsistency indirectness serious serious serious serious serious serious inconsistency indirectness serious inconsistency indirectness serious serious serious serious serious serious serious inconsistency indirectness serious serious serious serious serious indirectness serious seriou	no serious risk of bias no serious indirectness serious serious risk of bias no serious indirectness serious serious serious strongly suspected 2  **Treatment response for social relatedness** (assertion temporated better than before))  no serious risk of no serious inconsistency reporting bias strongly serious serious risk of no serious inconsistency reporting bias strongly	treatment response (assessed with: Number of participants showing minimal no serious serious risk of bias  treatment response for social relatedness (assessed with: Dicho intreported better than before'))  no no serious inconsistency risk of bias inconsistency risk of bias  treatment response for social relatedness (assessed with: Dicho intreported better than before'))  no no serious serious inconsistency risk of bias inconsistency risk of bias  no serious serious inconsistency risk of bias strongly suspected bias strongly suspected imprecision, inconsistency risk of bias strongly suspected imprecision, impr	treatment response (assessed with: Number of participants showing minimal improvement of participants showing	treatment response (assessed with: Number of participants showing minimal improvement on CGI-I for autistic  no serious sirsk of bias  risk of bias  treatment response for social relatedness (assessed with: Dichotomous: Positive treatment response inconsistency)  no serious indirectness  very serious strongly suspected 2 very serious bias strongly suspected 2 very serious inconsistency inco	treatment response (assessed with: Number of participants showing minimal improvement on CGI-I for autistic behaviours)  no serious inconsistency indirectness serious of bias    Participants showing minimal improvement on CGI-I for autistic behaviours	treatment response (assessed with: Number of participants showing minimal improvement on CGI-I for autistic behaviours)  no serious serious inconsistency indirectness indirectness in a serious of bias  treatment response for social relatedness (assessed with: Dichotomous: Positive treatment response for social relatedness - Social neteroporated better than before!)  no no serious strongly suspected 2 bias strongly serious 3 bias inconsistency indirectness		

55	no	no serious	no serious	very	reporting	$\oplus \ominus \ominus \ominus$	0/25	7/30	RR	Study population		
(1 study) 4 weeks	serious risk of	inconsistency	indirectness	serious <sup>5</sup>	bias strongly	VERY LOW <sup>2,5</sup> due to	(0%)	(23.3%)	<b>12.58</b> (0.75 to	0 per 1000		
4 Weeks	bias				suspected <sup>2</sup>	imprecision,			209.98)	o per 1000	-	
						publication bias				Moderate		
										0 per 1000	-	
		-	se for soc	ial related	dness (asses	ssed with: Dicho	tomous: Posit	ive treatment respons	e for social rela	tedness - Eye cor	ntact (study-specific	
		than before'))			T .		1.,		1			
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊝⊝⊝ VERY LOW <sup>2,5</sup>	4/25 (16%)	7/30 (23.3%)	<b>RR 1.46</b> (0.48 to	Study population	on	
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision, publication bias			4.42)	160 per 1000	<b>74 more per 1000</b> (from 83 fewer to 547 more)	
										Moderate		
										160 per 1000	<b>74 more per 1000</b> (from 83 fewer to 547 more)	
		•	se for soc	ial related	dness (asses	ssed with: Dicho	tomous: Posit	ive treatment respons	e for social rela	tedness - Share (	study-specific parent-	
reported 'be	1	1			T		1.05	0/00	DD 0 00	01		
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊖⊖ VERY LOW <sup>2,5</sup>	1/25 (4%)	0/30 (0%)	RR 0.28 (0.01 to	Study population	on	
4 weeks	risk of bias	, ,			strongly suspected <sup>2</sup>	due to imprecision, publication bias		` ,	6.58)	40 per 1000	29 fewer per 1000 (from 40 fewer to 223 more)	
										Moderate		
										40 per 1000	29 fewer per 1000 (from 40 fewer to 223 more)	

55	no	no serious	no serious	very	reporting	⊕⊖⊖⊖	1/25 (4%)	0/30	RR 0.28	Study population	n
(1 study) 4 weeks	serious risk of bias	of	nconsistency indirectness	serious <sup>5</sup>	bias strongly suspected <sup>2</sup>	very Low <sup>2,5</sup> due to imprecision, publication bias	(+70)	(0%)	(0.01 to 6.58)	40 per 1000	29 fewer per 1000 (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: Positi	ive treatment respons	e for social rela	tedness - Patienc	e (study-specific
55 (1 study)	no tudy) serious	no serious inconsistency			reporting bias	⊕⊝⊝ VERY LOW <sup>2,5</sup>	0/25 (0%)	1/30 (3.3%)	RR 2.52 (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	-
		-				communicater than before'))	,	sed with: Dichotomou	s: Positive treat	ment response fo	r non-verbal and
54 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias	⊕⊝⊝ VERY LOW <sup>2,5</sup>	7/24 (29.2%)	11/30 (36.7%)	RR 1.26 (0.58 to	Study population	on
4 weeks	risk of bias	Inconsistency	indirectriess	Sellous	strongly suspected <sup>2</sup>	due to imprecision, publication bias	(29.276)	(30.7 %)	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)

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%)	RR 2.83 (1.22 to	Study population	
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision, publication bias		(000.00)	6.59)	200 per 1000	366 more per 1000 (from 44 more to 1000 more)
										Moderate	
										200 per 1000	366 more per 1000 (from 44 more to 1000 more)
		ent respon - Pointing (study					ation (asses	sed with: Dichotomou	s: Positive treat	ment response fo	r non-verbal and
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊝⊝⊝ VERY LOW <sup>2,5</sup>	0/25 (0%)	1/30 (3.3%)	RR 2.52 (0.11 to	Study population	on
4 weeks	risk of bias				strongly suspected <sup>2</sup>	due to imprecision,		,	59.18)	0 per 1000	-
					i i	publication bias				Moderate	
										0 per 1000	-
verbal comi	munication	- Imitation (stud	y-specific pare	nt-reported 'b	etter than befor	re'))	,	sed with: Dichotomou			
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>2,5</sup>	0/25 (0%)	1/30 (3.3%)	(0.11 to	Study population	on
4 1	risk of bias				strongly suspected <sup>2</sup>	due to imprecision,			59.18)	0 per 1000	•
4 weeks	Dias					publication				Moderate	
4 weeks	Dias					bias				Wioderate	

55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>2,5</sup>	5/25 (20%)	8/30 (26.7%)	<b>RR 1.33</b> (0.5 to	Study population		
4 weeks	risk of bias			Concuc	strongly suspected <sup>2</sup>	due to imprecision, publication bias	(2070)	(23.176)	3.56)	200 per 1000	<b>66 more per 1000</b> (from 100 fewer to 512 more)	
						Diag				Moderate		
										200 per 1000	<b>66 more per 1000</b> (from 100 fewer to 512 more)	
		ent respons ve behaviour (stu					(assessed with	h: Dichotomous: Positiv	e treatment	response for stere	eotypy interest and	
55 (1 study)	serious inconsistency		very reporting bias		1/25 (4%)	1/30 (3.3%)	RR 0.83 (0.05 to	Study population				
4 weeks	risk of bias	in continued in the second		Concuc	strongly suspected <sup>2</sup>	due to imprecision, publication bias	(170)	(6.676)	12.66)	40 per 1000	7 fewer per 1000 (from 38 fewer to 466 more)	
										Moderate		
										40 per 1000	7 fewer per 1000 (from 38 fewer to 466 more)	
		ent respons n to change (stud					(assessed with	h: Dichotomous: Positiv	re treatment	response for stere	eotypy interest and	
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	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			56.1545	strongly suspected <sup>2</sup>	due to imprecision, publication bias	(170)	(673)	6.58)	40 per 1000	<b>29 fewer per 1000</b> (from 40 fewer to 223 more)	
										Moderate	'	
										40 per 1000	29 fewer per 1000 (from 40 fewer to	

											223 more)
Positive before'))	treatm	ent respon	se for cog	nition (asse	essed with: Did	L chotomous: Posi	tive treatmer	it response for cognition	n - Memory (stu	ıdy-specific pareı	nt-reported 'better than
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting	⊕⊝⊝ VERY LOW <sup>2,5</sup>	2/25 (8%)	1/30 (3.3%)	<b>RR 0.42</b> (0.04 to	Study populati	on
4 weeks	risk of bias		nconsistency indirectness :	Sellous	strongly suspected <sup>2</sup>	due to imprecision, publication bias	(070)	(3.376)	4.33)	80 per 1000	46 fewer per 1000 (from 77 fewer to 266 more)
						Dias				Moderate	
							80 per 1000	46 fewer per 1000 (from 77 fewer to 266 more)			
Positive better than		no serious	se for cog	nition (asse	reporting	chotomous: Posi	tive treatmer	at response for cognition	n - Learning ab	ility (study-specif	
(1 study)	serious				serious <sup>5</sup> bias strongly suspected <sup>2</sup>		(8%)	8%) (6.7%) (0.13 to		Study populati	
4 weeks	risk of bias								80 per 1000	14 fewer per 1000 (from 70 fewer to 360 more)	
										Moderate	
										80 per 1000	<b>14 fewer per 1000</b> (from 70 fewer to 360 more)
		nent respon r than before'))	se for mot	or abnorr	nalities (as	sessed with: Did	chotomous: F	ositive treatment respo	nse for motor a	ı abnormalities - Mo	otor skill (study-specific
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>2,5</sup>	0/25 (0%)	5/30 (16.7%)	RR 9.23 (0.53 to	Study populati	on
4 weeks	risk of bias	inconsistency	mancomcos	Scrious	strongly suspected <sup>2</sup>	due to imprecision,	(070)	(10.770)	159.14)	0 per 1000	N/A
	Dias				Suspected	publication				Moderate	

						bias				0 per 1000	N/A
		nent respon ed 'better than be		or abnor	malities (as	sessed with: Did	chotomous: P	ositive treatment respo	nse for motor a	abnormalities - Co	ordination (study-
55 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>2,5</sup>	2/25 (8%)	8/30 (26.7%)	RR 3.33 (0.78 to	Study population	n
4 weeks	weeks risk of bias			Conodo	strongly	due to imprecision, publication bias		(2011 70)	14.29)	80 per 1000	186 more per 1000 (from 18 fewer to 1000 more)
										Moderate	
										80 per 1000	186 more per 1000 (from 18 fewer to 1000 more)
		r than before')) no serious	no serious	very serious <sup>5</sup>	reporting bias	⊕⊖⊖⊖ VERY LOW <sup>2,5</sup>	1/25 (4%)	2/30 (6.7%)	RR 1.67	Study population	
4 weeks	risk of bias	of		s	strongly suspected <sup>2</sup>	due to imprecision, publication bias	(478)	(6.178)	17.32)	40 per 1000	27 more per 1000 (from 34 fewer to 653 more)
										Moderate	
										40 per 1000	
										40 per 1000	<b>27 more per 1000</b> (from 34 fewer to 653 more)
		nent respon		-	reported o	changes (ass	sessed with: [	Dichotomous: Positive t	treatment respo	·	(from 34 fewer to 653 more)
	tudy-specif no			-	reported (	changes (ass	1/25 (4%)	Dichotomous: Positive to 3/30 (10%)	RR 2.5 (0.28 to	·	653 more) ent-reported changes

						publication bias					862 more)
										Moderate	
										40 per 1000	60 more per 1000 (from 29 fewer to 862 more)
		nent respon specific parent-re		•	reported (	changes (ass	sessed with: Dic	hotomous: Positive	treatment respo	onse for other par	ent-reported changes -
55 (1 study)	no	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>2,5</sup>	0/25 (0%)	9/30 (30%)	RR 15.94	Study population	on
4 weeks	risk of	inconsistency	mancetress	3011003	strongly suspected <sup>2</sup>	due to imprecision,	(070)	(5070)	(0.97 to 260.91)	0 per 1000	N/A
	bias				Suspected	publication bias			200.01)	Moderate	
						Diag				0 per 1000	N/A
Sleeping pa		-		-	-	cnanges (ass	sessed with: Dic	hotomous: Positive	treatment respons	onse for other par	ent-reported changes -
55 (1 study)	no serious	no serious	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊖⊝⊝ VERY LOW <sup>2,5</sup>	3/25 (12%)	7/30 (23.3%)	RR 1.94 (0.56 to	Study population	on
	no	no serious	no serious	very	reporting					Study population	113 more per 1000 (from 53 fewer to 690 more)
(1 study)	no serious risk of	no serious	no serious	very	reporting bias strongly	VERY LOW <sup>2,5</sup> due to imprecision, publication			(0.56 to		113 more per 1000 (from 53 fewer to
(1 study)	no serious risk of	no serious	no serious	very	reporting bias strongly	VERY LOW <sup>2,5</sup> due to imprecision, publication			(0.56 to	120 per 1000	113 more per 1000 (from 53 fewer to
(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>2</sup>	VERY LOW <sup>2,5</sup> due to imprecision, publication bias	(12%)	(23.3%)	(0.56 to 6.75)	120 per 1000 Moderate 120 per 1000	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>	strongly	very Low <sup>2,5</sup> due to imprecision, publication	(4%)	(6.7%)	(0.16 to 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)

#### 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 6 (%)	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% CI)
		<b>Dehaviours</b> (mo			sm Behaviour (	Checklist (ABC): Total	or Paren	t-rated Pervas	sive Develop	ment 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	⊕⊖⊝ <b>VERY LOW</b> <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  0.85 standard deviations lower  (1.32 to 0.39 lower)
Overall au	utistic k	ehaviours (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	⊕⊕⊝⊝ <b>LOW</b> <sup>2,3</sup>	21	25	N/A	N/A	The mean overall autistic behaviours in the intervention

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

High risk of selective reporting bias as trial protocol for WONG2010B states that follow-up measurements will be taken but these are not reported

Moderate heterogeneity

Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25)

Events<300

22 weeks						due to risk of bias, imprecision					groups was 0.91 standard deviations lower (1.52 to 0.3 lower)
Overall a	utistic b	ehaviours (mo	easured with: Par	ent-rated Perva	sive Developm	nent Disorder Behavior	Inventor	y (PDDBI): A	Autism Com	posite; Be	tter indicated by lower values)
33 (1 study) 17 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LoW</b> <sup>2,4</sup> due to risk of bias, imprecision	18	15	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.77 standard deviations</b> lower (1.49 to 0.06 lower)
•		, and commu Better indicated by		lities (measu	red with: Teac	ther-rated Pervasive De	evelopme	ent Disorder	Behavior In	ventory (P	DDBI): Social, language and
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  0.82 standard deviations higher (0.22 to 1.43 higher)
•	•	, and commu Better indicated by		<b>lities</b> (measu	I ured with: Pare	nt-rated Pervasive Dev	relopmer	t Disorder B	ehavior Inve	entory (PD	DBI): Social, language and
79 (2 studies) 17-22 weeks	very serious <sup>1</sup>	very serious <sup>5</sup>	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW¹,2,5 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  0.53 standard deviations higher  (0.07 to 1 higher)
Maladapt	ive beh	aviour (measure	ed with: Teacher-r	ated Pervasive	Development	L Disorder Behavior Inve	I entory (Pl	DDBI): Malac	daptive beh	aviour; Be	tter 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	d with: Parent-rate	ed Pervasive D	evelopment Dis	sorder Behavior Invent	ory (PD	DBI): Maladap	tive behavio	ur; Bette	r 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	⊕⊖⊝ <b>VERY LOW</b> <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)

<sup>&</sup>lt;sup>1</sup> High risk of selection bias in SILVA2009 as groups were assigned using a random number generator but 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 risk of detection bias was high for the parent-rated outcome measure as parents were non-blind and involved in the intervention.

#### 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				Summary of Findings				
(	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study ev		Relative effect	Anticipa	ted absolute effects	
Follow up							With Placebo	With Secretin		Risk with Placebo	Risk difference with Secretin (95% CI)	
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 po	ppulation	
3 weeks					suspected <sup>3</sup>	due to risk of bias,	( 1,0)	(	à a\	241 per	152 more per 1000	

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</sup> High risk of selection bias in SILVA2009 as groups were assigned using a random number generator but 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.

<sup>&</sup>lt;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 parent-rated and parents were non-blind and involved in intervention

<sup>&</sup>lt;sup>5</sup> Substantial to considerable heterogeneity

<sup>&</sup>lt;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)

						imprecision, publication bias				1000	(from 63 fewer to 628 more)
										Moderat	e
										241 per 1000	<b>152 more per 1000</b> (from 63 fewer to 627 more)
		nt response ( roved' on CGI-imp		Dichotomous: I	Positive treatmen	t response (decrease	of >4.07 p	oints CAF	(S) or Dich	otomous: F	Positive treatment response (
109 (2 studies)	serious <sup>1</sup>	no serious	no serious indirectness	very serious <sup>2</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,2,3</sup>	15/54	19/55	<b>RR 1.24</b> (0.71 to	Study po	opulation
4-6 weeks		inconsistency	Indirectiess	serious	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(27.0%)		2.19)	278 per 1000	67 more per 1000 (from 81 fewer to 331 more)
										Moderat	re
										278 per 1000	67 more per 1000 (from 81 fewer to 331 more)
Overall a	utistic b	ehaviours (m	easured with: Ch	ı nildhood Autisı	n Rating Scale (0	CARS): Total (endpoin	t or chang	e scores):	Better indi	cated by lo	ower values)
137 (2 studies) 3-6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE⁴ due to imprecision	71	66	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.14 standard deviations higher (0.2 lower to 0.48 higher)
Overall a	utistic b	ehaviours (m	easured with: Au	ıtism Behaviou	ır Checklist (ABC	:): Total (change score	ı); Better iı	ndicated b	y lower val	ues)	
145 (2 studies) 1-3 weeks	1	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	ıtism Behaviou	ur Checklist (ABC	:): Total (change score	); Better ii	ndicated b	y lower val	ues)	
52 (1 study) 4 weeks	T	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ 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 (2 studies)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE⁴	70	70	N/A	N/A	The mean sensory function in the intervention groups was
1-3 weeks	bias	,				due to imprecision					<b>0.09 standard deviations lower</b> (0.42 lower to 0.25 higher)
Sensory	function	(measured with:	Autism Behavio	ur Checklist (A	ABC): Sensory (c	hange score); Better in	dicated	by lower v	alues)		<u> </u>
52 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ 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 Checklist	(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	⊕⊕⊕⊝ MODERATE⁴ 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 Checklist	(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 serious <sup>5</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> ⁵ 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>USC</b> (measured	with: Autism Bel	navior Checkli	st (ABC): Body a	nd object use (change	score);	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	⊕⊕⊕⊖ <b>MODERATE</b> <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>USC</b> (measured	with: Autism Bel	navior Checkli	st (ABC): Body a	nd object use (change	score);	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	⊕⊕⊖⊝ LOW⁵ 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	<b>Je</b> (measured	d with: Autism Be	haviour Checklis	t (ABC): Lang	uage (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	⊕⊕⊖⊖ <b>LOW</b> <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

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						inconsistency, imprecision					(0.35 lower to 0.33 higher)
Languag	<b>Je</b> (measure	d with: Autism Bel	naviour Checklis	(ABC): Langu	age (change sco	re); Better indicated b	y lower v	alues)			
52 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ 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 (mea	sured with: Autism	Behaviour Che	cklist (ABC): S	ocialization (chan	ige score); Better indic	cated by	ower value	es)		
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 (mea	sured with: Autism	Behaviour Che	cklist (ABC): S	ocialization (char	ige score); Better indic	cated by	lower value	es)		+
52 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ 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	easured with: Gi	lliam Autism F	ating Scale (GAF	RS): Autism Quotient;	Better inc	dicated by	lower value	s)	
98 (2 studies) 4-6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ due to imprecision	51	47	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.34 standard deviations higher (0.06 lower to 0.74 higher)
Overall a	autistic b	ehaviours (m	easured with: Gi	Iliam Autism R	Lating Scale (GAF	RS): Social Interaction	; Better ir	ndicated by	/ lower valu	es)	
56 (1 study) 4 weeks		no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ 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	easured with: Gi	lliam Autism F	ating Scale (GAF	RS): Stereotyped beha	viours; B	etter indica	ated by low	er values)	
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>5</sup> due to imprecision	28	28	N/A	N/A	The mean overall autistic behaviours in the intervention groups was

											0.17 standard deviations higher (0.36 lower to 0.69 higher)
Overall	autistic b	ehaviours (m	neasured with: G	illiam Autism f	Rating Scale (GA	RS): Communication; E	Better in	dicated by	lower valu	es)	<del>-</del>
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW⁵ due to imprecision	28	28	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.38 standard deviations higher (0.15 lower to 0.9 higher)
Overall	autistic b	ehaviours (m	neasured with: Cl	inical Global I	mpression (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 serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW⁵ due to imprecision	28	28	N/A	N/A	The mean overall autistic behaviours in the intervention groups was  0.23 standard deviations higher  (0.29 lower to 0.76 higher)
Respons	se to soc	ial interaction	<b>on</b> (measured wi	th: Clinical Gl	obal 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 serious <sup>5</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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)
Respons	se to soc	ial interaction	n (measured wi	th: Clinical Gl	obal 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 serious <sup>5</sup>	undetected	⊕⊕⊖⊝ <b>LoW</b> <sup>5</sup> due to imprecision	24	25	N/A	N/A	The mean response to social interaction in the intervention groups was  0.34 standard deviations lower (0.9 lower to 0.23 higher)
Social in	nitiation (n	neasured with: Cl	inical Global Imp	ression (CGI)	Social initiation	(change score); Better	indicate	d by lowe	r values)	ı	
52 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊖ <b>LoW</b> <sup>5</sup> 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 ir	nitiation (n	I neasured with: Cl	I inical Global Imp	ression (CGI)	L : 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 serious <sup>5</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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: Clini	cal Global Impre	ssion (CGI): U	se 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 serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ due to imprecision	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	easured with: Clini	cal Global Impre	ssion (CGI): U	se of speech (cha	ange score); Better ind	dicated by	lower val	ues)	-	1
49 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ 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 of	repetitiv	e behaviour	(measured with	: Clinical Globa	al Impression (CC	GI): Types of repetitive	behavio	ur (change	score); Be	ter indica	ited 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	⊕⊕⊖⊝ LOW⁵ 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 of	f repetitiv	∟ ⁄e behaviour	I (measured with	: Clinical Glob	al Impression (CC	I): Types of repetitive	behavio	ur (change	score); Be	ter indica	ted 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  0.26 standard deviations lower (0.82 lower to 0.3 higher)
Behavio	ur proble	e <b>ms</b> (measured v	ı vith: Clinical Glol	oal Impression	(CGI): Behaviou	r problems (change so	core); Bet	ter indicate	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	⊕⊕⊖⊝ <b>LOW</b> <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	ems (measured v	vith: Clinical Glob	oal Impression	(CGI): Behaviou	r 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 serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ due to imprecision	24	25	N/A	N/A	The mean behaviour problems in the intervention groups was <b>0.42 standard deviations</b>

											higher (0.14 lower to 0.99 higher)
Activity	level (meas	sured with: Clinica	al Global Impress	sion (CGI): Act	ivity level (change	e score); Better indicat	ed by lo	wer values	)		
52 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ due to imprecision	25	27	N/A	N/A	The mean activity level in the intervention groups was 0.32 standard deviations higher (0.23 lower to 0.87 higher)
Activity	level (meas	sured with: Clinica	al Global Impress	sion (CGI): Act	ivity level (change	e score); Better indicat	ted by lo	wer values	)		
49 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ due to imprecision	24	25	N/A	N/A	The mean activity level in the intervention groups was 0.08 standard deviations higher (0.48 lower to 0.64 higher)
Sleep p	roblems (r	neasured with: Cl	inical Global Imp	ression (CGI)	: Sleep problems	(change score); Better	r indicate	ed by lower	values)		
49 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ due to imprecision	24	25	N/A	N/A	The mean sleep problems in the intervention groups was <b>0.16 standard deviations</b> higher (0.41 lower to 0.72 higher)
Sleep p	roblems (r	measured with: Cl	inical Global Imp	ression (CGI)	: Sleep problems	(change score); Better	r indicate	ed by lower	values)		
48 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 lower</b> (0.79 lower to 0.34 higher)
Digestiv	e probler	<b>ns</b> (measured wi	th: Clinical Globa	al Impression	(CGI): Digestive p	roblems (change scor	e); Bette	r indicated	by lower v	values)	L
50 (1 study) 1 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 lower</b> (0.74 lower to 0.37 higher)
Digestiv	e probler	<b>ns</b> (measured wi	th: Clinical Globa	al Impression	(CGI): Digestive p	roblems (change scor	e); Bette	r indicated	by lower v	values)	,
48 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> ⁵ due to imprecision	24	24	N/A	N/A	The mean digestive problems in the intervention groups was <b>0</b> standard deviations higher

											(0.57 lower to 0.57 higher)
		ehaviours (p Better indicated b		synthetic	secretin gr	oups combined	<b>d)</b> (mea	sured with:	Parent-rate	ed Secret	in Outcome Survey-Modified (SO
8 1 study) weeks	risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ 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  0.1 standard deviations lowe (0.56 lower to 0.35 higher)
		ehaviours (p score); Better indic			secretin gr	oups combined	<b>d)</b> (mea:	sured with:	Teacher-ra	ted Secre	etin Outcome Survey-Modified
56 1 study) I weeks	no serious risk of bias	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 0.17 standard deviations higher (0.37 lower to 0.71 higher)
	orcine a		secretin g	oups con	nbined) (meas	sured with: Parent-rate	d Secre	tin Outcom	e Survey-M	odified (S	SOS-M): Social (change score);
78 1 study) I 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 social (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.07 standard deviations</b> higher (0.38 lower to 0.53 higher)
Social (p	orcine a	nd synthetic	secretin gi	oups con	nbined) (meas	sured with: Teacher-ra	ted Secr	etin Outco	me Survey-	Modified	(SOS-M): Social (change score);
66 1 study) I weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 <b>0.25 standard deviations higher</b> (0.28 lower to 0.79 higher)

78	no serious	score); Better indi	no serious	very	undetected	$\oplus \oplus \ominus \ominus$	31	47	N/A	N/A	The mean communication
(1 study) 4 weeks	risk of bias	inconsistency	indirectness	serious <sup>5</sup>	undetected	Low <sup>5</sup> due to imprecision	31	47	IN/A	IV/A	(porcine and synthetic secretin groups combined) in the intervention groups was 0.25 standard deviations higher (0.2 lower to 0.71 higher)
<b>Communica</b>	nication ( ation (change	porcine and score); Better indi	synthetic sticated by lower v	secretin g alues)	roups comb	<b>Dined)</b> (measured w	ith: Tead	cher-rated	Secretin O	utcome Su	urvey-Modified (SOS-M):
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW⁵ due to imprecision	22	34	N/A	N/A	The mean communication (porcine and synthetic secretin groups combined) in the intervention groups was  0.5 standard deviations higher (0.05 lower to 1.04 higher)
		iour (porcine			etin groups	combined) (meas	ured wit	h: Parent-	rated Secre	etin Outcor	me Survey-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	⊕⊕⊖⊖ <b>Low</b> <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  0.2 standard deviations lower (0.65 lower to 0.25 higher)
		iour (porcine ange score); Bette			etin groups	combined) (meas	ured wit	h: Teache	r-rated Sec	cretin Outc	ome Survey-Modified (SOS-M):
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <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 <b>0.18 standard deviations</b> higher (0.36 lower to 0.72 higher)
Digostiv			etic secreti	n groups	combined)	measured with: Paren	t-rated S	Secretin O	utcome Su	rvey-Modif	ied (SOS-M): Digestive (change
score); Bett	er indicated b	y lower values)									

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 synthous () () () () () () () () () () () () ()	etic secretii	n groups	combined) (r	neasured with: Teach	er-rated	Secretin O	utcome Su	rvey-Modi	fied (SOS-M): Digestive (change
35 (1 study) 4 weeks	no serious risk of bias	inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊖⊝ LOW⁵ 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> higher (0.39 lower to 0.96 higher)
Mood (point indicated by			secretin gr	oups com	<b>ibined)</b> (measi	red with: Parent-rated	d Secreti	n Outcome	Survey-Mo	odified (SC	OS-M): Mood (change score); Better
77 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝ LOW⁵ 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 lower</b> (0.51 lower to 0.4 higher)
Mood (po			secretin gr	oups com	<b>ibined)</b> (measu	red with: Teacher-rate	ed Secre	etin Outcom	ne Survey-N	Nodified (S	SOS-M): Mood (change score);
47 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	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 0.33 standard deviations higher (0.26 lower to 0.93 higher)
Sensory Better indica			tic secretin	groups c	ombined) (m	easured with: Parent-r	ated Se	cretin Outc	ome Surve	/-Modified	d (SOS-M): Sensory (change score);
77 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <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 lower

											(0.85 lower to 0.07 higher)
		and synthe y lower values)	etic secretin	groups	combined) (r	neasured with: Teache	r-rated S	Secretin C	utcome Su	rvey-Modif	ied (SOS-M): Sensory (change
46 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖ LOW⁵ due to imprecision	18	28	N/A	N/A	The mean sensory (porcine and synthetic secretin groups combined) in the intervention groups was  0 standard deviations higher (0.59 lower to 0.59 higher)
		rcine and sy		retin gro	ups combin	ed) (measured with: I	Parent-r	ated Secr	etin Outcor	ne Survey-	Modified (SOS-M): Hyperactivity
77 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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	<b>ed)</b> (measured with:	Teacher	-rated Sed	cretin Outco	ome Surve	y-Modified (SOS-M): Hyperactivity
43 (1 study) 4 weeks	no serious risk of bias	-	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊖⊖ LOW⁵ due to imprecision	16	27	N/A	N/A	The mean hyperactivity (porcine and synthetic secretin groups combined) in the intervention groups was <b>0.14 standard deviations higher</b> (0.48 lower to 0.76 higher)
			etic secretii	n groups	combined) (	 measured with: Parent	rated S	ecretin O	utcome Sur	vey-Modifi	ed (SOS-M): Lethargy (change
76 (1 study) 4 weeks	no serious risk of bias	y lower values) no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>5</sup> due to imprecision	30	46	N/A	N/A	The mean lethargy (porcine and synthetic secretin groups combined) in the intervention groups was 0.09 standard deviations higher

41 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious⁵	undetected	⊕⊕⊖⊖ <b>LOW</b> <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)
Sleep (po			secretin gr	oups com	<b>bined)</b> (measu	red with: Parent-rated	Secretin	Outcome	Survey-Mo	dified (SO	OS-M): Lethargy (change score);
76 (1 study) 4 weeks	risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>		⊕⊕⊕⊝ MODERATE⁴ due to imprecision	31	45	N/A	N/A	The mean sleep (porcine and synthetic secretin groups combined) in the intervention groups was  0.02 standard deviations higher  (0.44 lower to 0.48 higher)

<sup>2</sup> Risk of detection bias is unclear/unknown in CONIGLIO2001 as the paper reports that it was 'double-blind study' but it is not clear whether outcome assessors 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			
•	Risk of bias	Inconsistency	Indirectness	•	bias	quality of evidence	With Short- term chelation	` ,	effect (95% CI)	Risk with Short-term chelation		

Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25)

<sup>&</sup>lt;sup>3</sup> High risk of selective reporting bias in CONIGLIO2001 as data could not be extracted for the CARS (continuous measure), GARS or PLS

<sup>&</sup>lt;sup>4</sup> N<400

<sup>&</sup>lt;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)

Moderate heterogeneity

							therapy and 6-rounds of placebo)			therapy and 6-rounds of placebo)	
Overall	autisti	c behavio	U <b>rs</b> (measure	d with: Autism	Evaluation Tre	eatment Check	list (ATEC):	Total; Better indicate	ed by lower	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 LOW¹,² due to imprecision, publication bias	10	14	N/A	N/A	The mean overall autistic behaviours in the intervention groups was  0.25 standard deviations higher (0.57 lower to 1.06 higher)
Speech values)	/Langı	iage/Comr	nunicatio	<b>n</b> (measured	with: Autism Ev	valuation Trea	tment Check	dist (ATEC): Speech	/Language	/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 LOW¹,² 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	I asured with: Autis	I sm Evaluation T	reatment Che	ecklist (ATEC):	Sociability; Be	tter 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 LOW¹.² 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)

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/	Physic	al/Behavio	r (measured w	vith: Autism E	valuation Treatr	ment Checklist	t (ATEC):	Health/Physical	/Behavior; Bette	r 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 LOW¹,² 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	autisti	c behavio	J <b>rs</b> (measure	d with: Pervas	I sive Developme	L ent Disorder Be	ehavior Inv	entory (PDDBI	): Autism Compo	site; Better	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 LOW¹.² due to imprecision, publication bias	15	25	N/A	N/A	The mean overall autistic behaviours in the intervention groups was  0.24 standard deviations higher (0.41 lower to 0.88 higher)
Overall	autisti	c behavio	J <b>rs</b> (measure	d with: Severi	ty of Autism Sc	l ale (SAS): Tot	al; Better i	ndicated by low	ver values)		
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>	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)
1 N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5) 2 High risk of selective reporting bias as efficacy data cannot be extracted for the Parent Global Impressions scale as no measure of variability reported										

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

		Q	uality assess	ment					Sun	nmary of F	indings
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study eve	ent rates (%)	Relative	Anticipate	ed 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% CI)
Positive t	reatme	ent response	e (assessed wit	h: Number of p	participants wh	no showed impro	vement in A	ADOS Total so	ore)		
34 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>1</sup>	4/16 (25%)	5/18 (27.8%)	RR 1.11 (0.36 to	Study pop	pulation
15 weeks	risk of bias					due to imprecision	,	,	3.44)	250 per 1000	28 more per 1000 (from 160 fewer to 610 more)
										Moderate	
										250 per 1000	28 more per 1000 (from 160 fewer to 610 more)
Overall a	utistic	behaviours	(measured with	: Autism Diagr	nostic Observa	ation Schedule (A	DOS): Tota	al score; Better	r indicated	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	⊕⊕⊖⊝ LOW² due to imprecision	26	30	N/A	N/A	The mean overall autistic behaviours in the intervention groups was  0.16 standard deviations lower (0.69 lower to 0.37 higher)
Overall a	utistic	behaviours	(parent-rat	ed) (measure	ed with: Autisr	n Evaluation Trea	atment 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	<b>d)</b> (measured	MODERATE <sup>3</sup> due to imprecision with: Autism Eva	luation Ti	reatment Chec	klist (ATE	C): Speech/	(parent-rated) in the intervention groups was 0.05 standard deviations lower (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	⊕⊕⊕⊖ MODERATE³ due to imprecision	55	59	N/A	N/A	The mean speech/language/communication (parent-rated) in the intervention groups was  0.10 standard deviations higher (0.27 lower to 0.47 higher)
Sociabil	ity (par	ent-rated) (m	easured with: A	utism Evaluat	ion 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	⊕⊕⊕⊝  MODERATE³  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	-rated) (m	easured with:	Autism Evaluation	Treatme	ent Checklist (A	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	⊕⊖⊖⊖ <b>VERY LOW</b> <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  0.25 standard deviations lower (0.62 lower to 0.13 higher)
Health/P	hysical	/Behavior (p	oarent-rate	<b>d)</b> (measured	d with: Autism	L Evaluation Treatn	nent Che	cklist (ATEC):	—l 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	⊕⊕⊕⊝ MODERATE³ due to imprecision	55	59	N/A	N/A	The mean health/physical/behavior (parent-rated) in the intervention groups was  0.02 standard deviations higher (0.35 lower to 0.39 higher)
Overall a	autistic	behaviours	(clinician-	r <b>ated)</b> (mea	I asured with: Au	I itism Evaluation 1	reatment	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

-	_	_	indirectness	serious <sup>2</sup>	ted) (measu	LOW <sup>2</sup> due to imprecision red with: Autism	Evaluatio	n Treatment C	hecklist (A	TEC): Spee	(clinician-rated) in the intervention groups was  0.03 standard deviations lower (0.54 lower to 0.49 higher)  ch/Language/Communication; 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	⊕⊕⊝⊝ LOW² 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)
Sociabil	lity (clin	ician-rated)	(measured with	: Autism Evalu	uation Treatme	ent Checklist (AT	EC): Soc	iability; Better	ndicated 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	⊕⊕⊖⊝ LOW² due to imprecision	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 lower value	•	ive Awaren	ess (clinici	an-rated)	(measured wit	h: Autism Evalua	ation Trea	tment Checklis	st (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	⊕⊕⊖⊝ LOW² 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	rated) (meas	ured with: Aut	tism Evaluation <sup>-</sup>	- Γreatmen	t Checklist (AT	EC): Healt	h/Physical/E	Behavior; 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	⊕⊕⊝⊝ LOW² due to imprecision	29	29	N/A	N/A	The mean health/physical/behaviour (clinician-rated) in the intervention groups was  0.2 standard deviations lower (0.72 lower to 0.31 higher)
Global s	severity	(parent-rate	ed) (measured	uith: Clinical (	I Global Impress	ion Scale (CGI-	S): Sever	ity; Better indic	ated by lov	ver values)	
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	severity	(clinician-ra	<b>ited)</b> (measur	ed with: Clinic	al Global Impr	ession Scale (CG	I-S): Sev	verity; Better inc	dicated 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	⊕⊕⊝⊝ LOW² due to imprecision	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 i	mprove	ment (paren	t-rated) (me	easured with:	Clinical Global	Impression Scale	(CGI-I):	Improvement;	Better ind	icated by lov	ver values)
58 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW² due to imprecision	29	29	N/A	N/A	The mean global improvement (parent-rated) in the intervention groups was  0.28 standard deviations lower (0.8 lower to 0.23 higher)
Global i	mprove	ment (cinici	<b>an-rated)</b> (r	neasured with	: Clinical Glob	al Impression Sca	ale (CGI-	I): Improvemen	t; Better ir	ndicated by	ower values)
58 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE³ due to imprecision	29	29	N/A	N/A	The mean global improvement (cinician-rated) in the intervention groups was  0.57 standard deviations lower (1.1 to 0.05 lower)
<sup>1</sup> Events<30 <sup>2</sup> N<400 and	00 and 95% d 95% CI c	CI crosses both rosses both line o	line of no effect f no effect and I	and measure measure of ap	of appreciable opreciable	e benefit or harm efit or harm (SMD	(RR 0.75 ) -0.5/0.5	5/1.25)	I	I	

 $<sup>^{3}</sup>$  N<400

#### 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

<sup>&</sup>lt;sup>4</sup> I-squared value indicates substantial to considerable heterogeneity

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e	vent rates (%)	Relative effect	Anticipa	ted absolute effects
Follow up							With Placebo	With Multivitamin and mineral supplement	(95% CI)	Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% CI)
Average	improv	ement (measu	red with: Parent 0	Global Impress	ions-Revised (	PGI-R): Average in	nproveme	ent (average of all s	ubscales); E	Better 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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	51	53	N/A	N/A	The mean average improvement in the intervention groups was <b>0.55 standard deviations higher</b> (0.16 to 0.94 higher)
Overall i	mprove	ment (measure	d with: Parent Glo	obal Impressio	ns-Revised (Po	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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	51	53	N/A	N/A	The mean overall improvement in the intervention groups was <b>0.49 standard deviations higher</b> (0.1 to 0.88 higher)
Overall a	autistic	behaviours	(measured with:	Autism Evalua	tion 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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	51	53	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.04 standard deviations higher</b> (0.34 lower to 0.43 higher)
Overall a	autistic	behaviours	(measured with:	Severity of Aut	ism Scale (SAS	S): Total; Better ind	licated by	lower values)	1	1	
104 (1 study)	no serious	no serious	no serious	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹	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: F	Pervasive Dev	elopment Disor	rder Behavior Inver	ntory (PI	DDBI): Total; Better i	ndicated by	lower valu	es)
104 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	51	53	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.02 standard deviations higher</b> (0.37 lower to 0.4 higher)
<sup>1</sup> N<400						1			1		

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

		C	Quality assessi	ment				S	ummary c	of Finding	js .
Participants		Inconsistency	Indirectness	Imprecision		•	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	<b>ent</b> (measured w	ith: Parent Global	Impressions-I	mprovement (F	PGI-I): Overall impro	vement a	cross subscales; B	etter indicat	ed by lowe	r values)
31 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ <b>LoW</b> ¹ due to imprecision	17	14	N/A	N/A	The mean global improvement in the intervention groups was <b>0.47 standard deviations higher</b> (0.25 lower to 1.19 higher)
Overall a	utistic be	ehaviours (me	easured with: Child	dhood Autism	Rating Scale (0	CARS): Total; Better	indicated	d 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	⊕⊝⊝ VERY LOW <sup>1,2</sup>	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 (me	easured with: Gilli	am Autism Ra	ting Scale (GA	RS): Total; Better inc	licated by	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	⊕⊕⊖⊖ <b>LoW</b> ¹ due to imprecision	17	14	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.34 standard deviations lower</b> (1.05 lower to 0.38 higher)
		ses both line of no		ure of apprecia	able benefit or I	narm (SMD -0.5/0.5)	•			•	

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

		Q	uality assessn	nent					Sumr	nary of Fin	dings
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study eve (%)	nt rates	Relative effect (95% CI)	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% CI)
Pervasiv	e Deve	elopmental	Disorder (P	PDD) sym	ptoms (me	easured with: Chil	d Behavior (	Checklist 1.5	5 - 5 (CBCL/	(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	⊕⊕⊖⊝ LOW¹.² due to risk of bias, imprecision	13	10	N/A	N/A	The mean pervasive developmental disorder (pdd) symptoms in the intervention groups was 0.98 standard deviations lower

Ī									(1.86 to 0.1 lower)
1	High risk of p measure was N<400		as as interventior	n administratoi	s and participa	ants were non-blin	d, and high risk of detec	ction bias as	s the outcome assessor for this outcome

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

			luality assessr	nent					Summary	of Findings	
•	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event	rates (%)	Relative effect	Anticipated a	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% CI)
Overall a	utistic	behaviours	(measured with:	Diagnose of Ps	sykotisk Adferd	hos Børn (Diagno	osis of Psycho	tic Behaviour	in Children;	DIPAB): Total;	Better indicated by lower

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 N<400

#### 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 asses	ssment				5	Summary	of Findings	
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-ra	ated o	verall autis	tic behavio	D <b>Urs</b> (measu	red with: Social (	Communication Que	L stionnaire (S	CQ): Total; Bett	er indicated	l by lower valu	ies)
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>	⊕⊖⊖ <b>VERY LOW</b> <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 1.85 standard deviations lower (2.94 to 0.77 lower)
Teacher-	-rated	overall auti	stic behav	<b>iours</b> (mea	Lusured with: Socia	al Communication Q	l uestionnaire	(SCQ): Total; B	l etter indicat	ed 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 LOW¹,3,4 due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rate overall autistic behaviours in the intervention groups was 0.29 standard deviations lower (1.18 lower to 0.59 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance, response and detection bias as intervention administrators, participants and outcome assessors were non-blind. The risk of other bias due to potential conflict of interest is also high as neurofeedback equipment provided by manufacturer for trial.

<sup>2</sup> N~400

<sup>&</sup>lt;sup>3</sup> High risk of selective reporting bias as data cannot be extracted for 6-month follow-up

<sup>&</sup>lt;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)

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

		Qı	uality assessn	nent				S	ummary c	of Findings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rat	es (%)	Relative effect	Anticipated abs	olute effects
Follow up						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)
Overall a	autistic	behaviours	(measured with	n: Autism Beha	L aviour Checklis	t (ABC): Total;	Better indicated by	/ lower values)		<u> </u>	
80 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to imprecision	40	40	N/A	N/A	The mean overall autistic behaviours in the intervention groups was <b>0.1 standard deviations higher</b> (0.34 lower to 0.54 higher)
Overall a	autistic	behaviours	6 (measured with	n: Autism Beha	aviour Checklis	t (ABC): Total;	Better indicated by	/ lower values)			
80 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to imprecision	40	40	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.22 standard deviations higher (0.22 lower to 0.66 higher)
Overall a	autistic	behaviours	<b>S</b> (measured with	n: Autism Beha	aviour Checklis	et (ABC): Total;	Better indicated by	/ lower values)			deviations high (0.22 lower to 0

(1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖ LOW¹ due to imprecision	40	40	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.25 standard deviations higher (0.19 lower to 0.69 higher)
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ Low¹ due to imprecision	3etter indicated 40	by lower values) 40	N/A	N/A	The mean overall autistic behaviours in the intervention groups was 0.27 standard deviations higher (0.17 lower to 0.71 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

	Qu	ality assessr	ment			Summary of Findings					
Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rates (%)		Relative effect	Anticipated absolute effects		
					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)	
nicatio	<b>n</b> (measured wi	th: Autism Diag	nostic Observ	ation Schedul	e (ADOS/ADO	DS-G): C	Communication (change score);	Better indic	ated by	lower values)	
no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	18	18	N/A	N/A	The mean communication in the intervention groups was 0.19 standard deviations lower (0.85 lower to 0.46 higher)	
teract	i <b>on</b> (measured	with: Autism D	iagnostic Obse	I ervation Sched	L dule (ADOS/A	DOS-G)	: Social Interaction (change sco	re); Better	indicated	d by lower values)	
no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	18	18	N/A	N/A	The mean social interaction in the intervention groups was <b>0 standard deviations higher</b> (0.65 lower to 0.65 higher)	
	no serious risk of bias teract	Risk of bias Inconsistency  no no serious risk of bias inconsistency  teraction (measured with teraction (measured moserious risk of bias inconsistency risk of inconsistency	Risk of bias Inconsistency Indirectness  nication (measured with: Autism Diagono no serious inconsistency risk of bias inconsistency indirectness  teraction (measured with: Autism Diagono no serious indirectness inconsistency indirectness inconsistency indirectness indirectness indirectness indirectness	no serious inconsistency indirectness very serious¹  teraction (measured with: Autism Diagnostic Observation of the serious inconsistency indirectness inconsistency indirectness inconsistency indirectness very serious¹  no serious inconsistency indirectness very serious¹	Risk of bias    Inconsistency   Indirectness   Imprecision   Publication bias	Risk of bias Inconsistency Indirectness Imprecision bias Overall quality of evidence  Nication (measured with: Autism Diagnostic Observation Schedule (ADOS/ADO no serious inconsistency risk of bias no serious of bias no serious inconsistency risk of bias no serious of bias no serious inconsistency risk of bias no serious of bias no serious inconsistency risk of bias no serious of bias no se	Risk of bias Inconsistency Indirectness Imprecision   Publication   Overall quality of evidence   With Control    NiCation (measured with: Autism Diagnostic Observation Schedule (ADOS/ADOS-G): Output (ADOS/ADOS-G): Outp	Risk of bias  Inconsistency bias  Indirectness Imprecision bias  Imprecision bias  Publication duality of evidence  With With Acupuncture/electro-Control 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  Publication With With Acupuncture/electro-Control 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  Inconsistency inconsistency indirectness very serious very serious inconsistency indirectness very serious very serious inconsistency indirectness very serious very serious very serious very serious inconsistency indirectness very serious very seri	Risk of bias    Inconsistency   Indirectness   Imprecision   Publication   Dias   Quality of evidence   With   With Acupuncture/electro-   (95% CI)   (95% CI)	Risk of bias    Inconsistency   Indirectness   Imprecision   Publication   Dias   Overall quality of evidence   With With Acupuncture and conventional educational programme versus conventional educational autism feature of impaired reciprocal social communication and interaction as an indirect outcome   Inconsistency   Inconsistency	

### 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

		G	tuality assess	ment			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 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)	
Commui	nicatio	<b>n</b> (measured wit	h: Autism Diagn	ostic Observat	ion Schedule	(ADOS/ADOS-G)	: Commu	unication (endpoint and cha	nge scores	); Better	indicated by lower values)	
141 (2 studies)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝  MODERATE¹  due to  imprecision	61	80	N/A	N/A	The mean communication in the intervention groups was <b>0.1 standard deviations</b> lower	
4 weeks	bias					Imprecision					(0.44 lower to 0.24 higher)	
		n (measured wit	h: Gilliam Autisr	n Rating Scale	(GARS): Con		er indicat	ed by lower values)				

141 (2 studies) 4 weeks	no serious risk of bias	very serious <sup>3</sup>	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <sup>1,3</sup> due to inconsistency, imprecision	61	80	N/A	N/A	The mean social interaction in the intervention groups was 0.46 standard deviations higher (0.12 to 0.8 higher)
Social i	nteract	cion (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	⊕⊕⊖⊖ LOW² due to imprecision	28	28	N/A	N/A	The mean social interaction in the intervention groups was  0.42 standard deviations higher  (0.11 lower to 0.95 higher)
		on and Soc by lower values)		tion (measu	red with: Autis	n Diagnostic Obs	ervatio	n Schedule (ADOS	S/ADOS-G): Comm	unication	& Social Interaction (change
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝  MODERATE¹  due to  imprecision	28	28	N/A	N/A	The mean communication and social interaction in the intervention groups was <b>0.55 standard deviations higher</b> (0.02 to 1.09 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

		Qı	uality assessm	nent			Summary of Findings					
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study ever	nt rates (%)	Relative	Anticipated	l 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 treatment (HBOT) (95% CI)	
Positive t	treatme	nt response	assessed with: N	lumber of parti	cipants who s	nowed improven	nent in ADOS	Communication)				
34 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹	2/16 (12.5%)	3/18 (16.7%)	RR 1.33 (0.25 to	Study popu	ılation	
15 weeks	risk of bias	inconsistency	indirectriess	Sellous		due to imprecision	(12.370)		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	lumber of parti	cipants who s	nowed improven	nent in ADOS	S Socialization)				
34 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹	2/16 (12.5%)	3/18 (16.7%)	OR 1.4 (0.2 to	Study popu	ılation	
15 weeks	risk of bias	inconcional in the second		Solicus		due to imprecision	(12.070)	(10.176)	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 Responsi	iveness Scale	(SRS): Social	Awareness (cha	nge score); E	Better indicated by	lower value	es)	1	
29 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW² due to imprecision	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:	Social Responsiv	eness Scale (	SRS): Social C	ognition (change	score); Bett	er indicated by lo	wer values)	-	
29 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝ LOW² due to imprecision	15	14	N/A	N/A	The mean social cognition in the intervention groups was <b>0.53 standard deviations higher</b> (0.21 lower to 1.27 higher)
Social C	ommun	ication (measur	ed with: Social R	esponsivenes	s Scale (SRS):	Social Commun	ication (chan	nge score); Better	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	⊕⊕⊖⊝ LOW² due to imprecision	15	14	N/A	N/A	The mean social communication in the intervention groups was <b>0.32 standard deviations lower</b> (1.05 lower to 0.41 higher)
Social N	lotivatio	n (measured with:	Social Responsi	veness Scale	(SRS): Social I	Motivation (chan	ge score); Be	etter indicated by	lower values	s)	
29 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW² due to imprecision	15	14	N/A	N/A	The mean social motivation in the intervention groups was <b>0.06 standard deviations higher</b> (0.67 lower to 0.79 higher)
Autistic	Manneri	isms (measured	with: Social Resp	oonsiveness S	cale (SRS): Au	tistic Mannerism	s (change so	core); Better indica	ated by lowe	er values)	
29 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW² due to imprecision	15	14	N/A	N/A	The mean autistic mannerisms in the intervention groups was <b>0.36 standard deviations higher</b> (0.38 lower to 1.09

									higher)
vocalization (me	asured with: Beha	vioural observ	ation: Appropri	ate vocalization	(change sco	ore); Better inc	dicated by lower	values)	
,	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW² due to imprecision	16	18	N/A	N/A	The mean appropriate vocalization in the intervention groups was <b>0.17 standard deviations higher</b> (0.51 lower to 0.84 higher)
	no serious	no serious no serious inconsistency indirectness	no serious no serious very inconsistency indirectness serious²	no serious no serious very undetected inconsistency indirectness serious²	no serious inconsistency indirectness very serious² undetected ⊕⊕⊝⊝ LOW² due to	no serious inconsistency indirectness very serious² undetected ⊕⊕⊝⊝ LOW² due to	no serious inconsistency indirectness indirectness very serious² undetected below b	no serious inconsistency indirectness indirectness very serious² undetected below below to low low low low low low low low low lo	us inconsistency indirectness serious <sup>2</sup> LOW <sup>2</sup> due to

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					
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study event	rates (%)		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% 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 deviations higher</b> (0.13 lower to 1.17	

											higher)
Social A	pproac	h Behaviou	rs (measured v	with: Pervasive	e Development [	Disorder Behav	ior Invento	ry (PDDBI): Socia	I Approach; Bette	er indicated by	lower values)
40 (1 study) 17 weeks		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 approach behaviours in the intervention groups was <b>0.08 standard deviations lower</b> (0.72 lower to 0.56 higher)

<sup>&</sup>lt;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)

### 1.8.4 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					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)	
Commun	ication	measured with: Au	utism Diagnostic	Observation So	chedule (ADOS	s): Communicatio	n (change sc	ore); Better in	dicated by	ower values)		
55 (1 study) 35 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	29	26	N/A	N/A	The mean communication in the intervention groups was <b>0.42 standard deviations lower</b> (0.95 lower to 0.12 higher)	

<sup>&</sup>lt;sup>2</sup> High risk of selective reporting bias as efficacy data cannot be extracted for the ADOS Communication, Sociability, and Communication+Sociability or the Parent Global Impressions scale as no measure of variability reported

Commun	nication	(measured with: G	Billiam Autism Rat	ing Scale (GAF	RS): Communi	cation (change so	core); Bette	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 in the intervention groups was <b>0.34 standard deviations lower</b> (0.87 lower to 0.19 higher)
Social In	teractio	n (measured with	: Autism Diagnos	tic Observation	Schedule (AD	OOS): Social Inter	action (cha	ange 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 LOW¹.² 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 lower</b> (0.54 lower to 0.52 higher)
Social In	teractio	n (measured with	: Gilliam Autism F	Rating Scale (G	ARS): Social I	nteraction (chang	e score); I	Better indicat	ed by lower	/alues)	
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 ([	Diagnosis (	of Psychotic I	Behaviour in	Children; DIF	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 1.19 standard deviations higher (0.22 to 2.15 higher)
		ommunicatio cation and interact					k Adferd h	os Børn (Dia	ignosis of Ps	ychotic Beha	viour in Children; DIPAB):
20 (1 study) 52 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>4,5</sup> due to risk of	10	10	N/A	N/A	The mean resistance to communication and interaction in the intervention

					bias, imprecision					groups was 1.58 standard deviations lower (2.61 to 0.55 lower)
Social iso		agnose of Psykot	isk Adferd hos	Børn (Diagnos	is of Psychotic Bo	ehaviour in Chi	ldren; DIPA	B): Social ir	teraction or is	olation (I-scores); Better
20 (1 study) 52 weeks	serious <sup>5</sup>	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <sup>4,5</sup> due to risk of bias, imprecision	10 1	10	N/A	N/A	The mean social isolation in the intervention groups was 1.35 standard deviations lower (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)

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

		Q	uality assessm	ent				Summary	of Findir	ngs	
(	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study e	vent rates	Relative effect	Anticipate	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% CI)
Social sk	ills (measure	ed with: Social Resp	oonsiveness Scale	(SRS): Total;	Better indicated	d by lower values)					
		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ due to imprecision	11	11	N/A	N/A	The mean social skills in the intervention groups was 0.06 standard deviations higher

<sup>&</sup>lt;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>&</sup>lt;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>&</sup>lt;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

								(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 o	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
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study ever	nt rates (%)		Anticipated	d absolute effects
(studies) Follow up	bias				bias	of evidence	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 pos	itive vocaliza	ations (measur	ed with: Behav	rioural observa	tion; Better indica	ted by lower	values)		•	
23 (1 study) 13 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ <b>Low</b> ¹ 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 higher</b> (0.62 lower to 1.03 higher)
Frequenc	y of soc	ial initiations	(measured with:	Behavioural o	bservation; Be	tter indicated by lo	wer values)				
23 (1 study) 13 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> ¹ 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)

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

		Q	uality assessm	ent				5	Summary o	of Finding	gs
Participants		Inconsistency	Indirectness	Imprecision		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% CI)
Sociabili	ty improv	ement (measu	red with: Parent G	Blobal Impressi	ons-Revised (I	PGI-R): Sociability	/ improve	ment; Better indicat	ed by lower	values)	
104 (1 study) 13 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ <b>LoW</b> <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 higher</b> (0.24 lower to 0.53 higher)
Eye cont	act impro	ovement (meas	sured with: Parent	Global Impres	sions-Revised	(PGI-R): Eye cor	ntact impr	ovement; Better ind	icated 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	⊕⊕⊖⊝ <b>LOW</b> <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 higher</b> (0.11 lower to 0.67 higher)
<sup>1</sup> N<400 and	95% CI cross	ses both line of no	effect and measu	re of appreciat	ole benefit or h	arm (SMD -0.5/0.	5)			1	1

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

		Qı	uality assessm	ent					Summary	of Findin	gs
Participants		Inconsistency	Indirectness	Imprecision		•	Study ev			Anticipate	ed absolute effects
(studies) Follow up	bias				bias of evidence		With Placebo	With L carnocino	effect (95% CI)	Risk with Placebo	Risk difference with L- carnosine supplement (95% CI)
Commun	ication (m	neasured with: Gillia	m Autism Rating	Scale (GARS)	: Communication	on; Better indicate	d by lowe	r values)			
31 (1 study)			no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹	17	14	N/A	· ·	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	teraction	(measured with: G	illiam Autism Rati	ng Scale (GAF	RS): Social Inte	raction; Better indi	cated 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	⊕⊕⊖⊝ <b>LOW</b> <sup>1</sup> due to imprecision	17	14	N/A	N/A	The mean social interaction in the intervention groups was  0.51 standard deviations lower  (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				;	Summary	of Findings	;		
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study even	` '	Relative	Anticipated	absolute effects		
(studies) Follow up	bias				bias		With Treatment- as-usual	With Neurofeedback	effect (95% CI)	Risk with Treatment- as-usual	Risk difference with Neurofeedback (95% CI)		
Parent-ra	arent-rated reciprocal social interaction (measured with: Social Communication Questionnaire (SCQ): Reciprocal social interactions; Better indicated by lower values)												
20 (1 study) 20 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, publication bias	10	10	N/A	N/A	The mean parent-rated reciprocal social interaction in the intervention groups was 1.54 standard deviations lower (2.57 to 0.52 lower)		

Teacher- values)	rated re	eciprocal so	cial interact	t <b>ion</b> (measur	red with: Social C	ommunication Ques	stionnaire (S	CQ): Reciproca	I social inte	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>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖ <b>VERY LOW</b> <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean teacher-rated reciprocal social interaction in the intervention groups was <b>0.39 standard deviations lower</b> (1.28 lower to 0.49 higher)
Parent-ra	ated co	mmunication	n (measured with	n: Social Com	munication Quest	ionnaire (SCQ): Co	mmunicatio	n; Better indicate	ed 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 communication in the intervention groups was 1.14 standard deviations lower (2.1 to 0.18 lower)
Teacher-	rated c	ommunicati	on (measured v	vith: Social Co	mmunication Que	estionnaire (SCQ): (	Communicat	ion; Better indica	ated by low	er values)	1
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>	⊕⊖⊖ <b>VERY LOW</b> <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>0.19 standard deviations lower</b> (1.07 lower to 0.69 higher)
Parent-ra	ated co	mmunication	n (measured with	n: Children's C	communication Cl	necklist (CCC-2): To	otal; Better i	ndicated 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>	⊕⊖⊖ <b>VERY LOW</b> <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	10	10	N/A	N/A	The mean parent-rated communication in the intervention groups was <b>0.88 standard deviations lower</b> (1.81 lower to 0.04 higher)

Teacher	-rated c	ommunicati	ion (measured v	with: Children's	s Communication	Checklist (CCC-2):	Total; Bet	tter indicated b	y lower values	s)	
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 LOW¹,3,4 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 deviations lower</b> (0.93 lower to 0.83 higher)
Parent-r	ated so	cial impairm	nent (measured	with: Social R	esponsiveness S	cale (SRS): Total; E	Better indi	cated 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 LOW¹,3,4 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 deviations lower</b> (1.85 lower to 0.02 higher)
Teacher	-rated s	ocial impair	ment (measur	ed with: Social	Responsiveness	Scale (SRS): Total	; Better in	dicated by low	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 LOW¹,3,4 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 deviations higher</b> (0.87 lower to 0.88 higher)
Parent-r	ated so	cial awarene	ess (measured	with: Social Re	esponsiveness So	cale (SRS): Social A	wareness	; Better 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 LOW¹.3,4 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 deviations lower</b> (1.55 lower to 0.26 higher)
Teacher	-rated s	ocial aware	ness (measure	d with: Social	Responsiveness	Scale (SRS): Social	Awarene	ss ; Better indi	cated by lowe	r 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 LOW¹.3.4 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 deviations higher</b> (0.66 lower to 1.1 higher)
Parent-r	ated so	cial cognitio	n (measured wi	th: Social Res	ponsiveness Sca	le (SRS): Social Co	gnition ; B	etter indicated	by lower valu	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 LOW¹.2.3 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 1.38 standard deviations lower (2.38 to 0.38 lower)
Teacher	-rated s	ocial cognit	ion (measured	with: Social R	esponsiveness S	cale (SRS): Social (	Cognition;	Better indicate	d 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 LOW¹.3.4 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 deviations higher</b> (0.53 lower to 1.24 higher)
Parent-r	ated so	cial commu	nication (mea	asured with: S	ocial Responsiver	ness Scale (SRS): S	Social Com	nmunication ; B	etter indicate	d by lower v	ralues)
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	neasured with:	Social Responsiv	veness Scale (SRS)	: Social Co	ommunication :	Better indica	ited by lowe	r 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>	⊕⊖⊖ <b>VERY LOW</b> <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 v	with: Social Re	sponsiveness Sc	ale (SRS): Social M	lotivation; B	etter indicated b	y lower valu	ies)	
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 deviations lower</b> (1.43 lower to 0.36 higher)
Teacher	-rated s	ocial motiva	tion (measure	d with: Social	Responsiveness	Scale (SRS): Social	Motivation	; Better indicated	by lower va	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>	⊕⊖⊖ <b>VERY LOW</b> <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 deviations higher</b> (0.44 lower to 1.34 higher)
Parent-r	ated aut	tistic manne	risms (measu	red with: Socia	al Responsivenes	ss Scale (SRS): Auti	istic Manne	risms ; Better inc	licated by Ic	wer 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 LOW¹.2.3 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 deviations lower</b> (1.92 to 0.04 lower)
Teacher	-rated a	tistic manne	erisms (measu	red with: Soci	al Responsivenes	ss Scale (SRS): Aut	istic Manne	risms ; Better in	dicated 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>	⊕⊖⊖ <b>VERY LOW</b> <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 deviations lower</b> (1.3 lower to 0.48 higher)

20	serious <sup>1</sup>	no serious	no serious	very	reporting bias	⊕⊖⊝⊝	10	10	N/A	N/A	The mean parent-rated
(1 study) 20 weeks		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					social relations in the intervention groups was 0.37 standard deviations lower (1.26 lower to 0.51 higher)
Teacher	-rated s	ocial relatio	ns (measured v	with: Children	's Communication	Checklist (CCC-2):	Social re	ations; Better i	ndicated by le	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>	⊕⊖⊖ <b>VERY LOW</b> <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 higher</b> (0.88 lower to 0.88 higher)
Parent-r	rated int	<b>erests</b> (measu	red with: Childre	n's Communi	cation Checklist (0	CCC-2): Interests; Bo	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>	⊕⊖⊖ <b>VERY LOW</b> <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 1.18 standard deviations lower (2.15 to 0.21 lower)
Teacher	r-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>	⊕⊖⊖ <b>VERY LOW</b> <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 higher</b> (0.88 lower to 0.88 higher)
Parent-r	rated ina	ppropriate i	nitializatio	<b>1</b> (measured	with: Children's Co	ommunication Check	klist (CCC	C-2): Inappropri	ate initializati	on; Better in	dicated by lower values)
20	serious1	no serious	no serious	serious <sup>2</sup>	reporting bias	<b>⊕</b> ⊖⊖⊖	10	10	N/A	N/A	The mean parent-rated

(1 study) 20 weeks		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 1.08 standard deviations lower (2.03 to 0.13 lower)
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>	Communication Che  ⊕⊖⊖⊖  VERY LOW¹,3,4  due to risk of bias, imprecision, publication bias	ecklist (CC	CC-2): Inappro	N/A	N/A	The mean teacher-rated inappropriate initialization in the intervention groups was  0.15 standard deviations lower  (1.03 lower to 0.73 higher)
Parent-r 20 (1 study) 20 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	(measured w very serious <sup>4</sup>	rith: Children's Co reporting bias strongly suspected <sup>3</sup>	mmunication Check  ⊕⊖⊖  VERY LOW¹,3,4  due to risk of  bias, imprecision,  publication bias	list (CCC-	-2): Stereotype	N/A	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)
Teacher 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>	⊕⊖⊖ <b>VERY LOW</b> <sup>1,3,4</sup> due to risk of bias, imprecision,	cklist (CC	CC-2): Stereoty	ped conversat	ion; Better i	The mean teacher-rated stereotyped conversation in the intervention groups was
Parent-r	ated co	ntext use (me	easured with: Chi	ldren's Comm	nunication Checkli	publication bias	t use; Bet	ter indicated by	o lower values	)	0.31 standard deviations higher (0.58 lower to 1.19 higher)

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 LOW¹.2.³ 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 1 standard deviations lower (1.94 to 0.06 lower)
Teacer-r	ated co	ntext use (me	easured with: Ch	ildren's Comm	nunication Checkl	ist (CCC-2): Contex	t use; Bet	ter 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 LOW¹.3.4 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 deviations higher</b> (0.6 lower to 1.17 higher)
Parent-r	ated no	n-verbal cor	nmunicatio	<b>n</b> (measured	with: Children's C	Communication Chec	cklist (CC0	C-2): Non-verb	al communica	tion; Better	indicated 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>	⊕⊖⊖ <b>VERY LOW</b> <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 1.05 standard deviations lower (2 to 0.1 lower)
Teacher	-rated n	on-verbal co	ommunicat	ion (measure	ed with: Children's	Communication Ch	necklist (C	CCC-2): Non-ve	erbal communi	cation; Bett	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 LOW¹.3.4 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 deviations higher</b> (0.55 lower to 1.22 higher)
Parent-r	ated pra	agmatics (mea	asured with: Chil	dren's Commi	unication Checklis	st (CCC-2): Pragma	tics; Bette	r indicated 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>	⊕⊖⊝ <b>VERY LOW</b> <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	easured with: Ch	nildren's Comn	nunication Check	list (CCC-2): Pragm	atics; Bette	er indicated by lo	wer values)		
20 (1 study) 20 weeks		no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖⊖ VERY LOW¹,3,4 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 deviations higher</b> (0.64 lower to 1.13 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance, response and detection bias as intervention administrators, participants and outcome assessors were non-blind. The risk of other bias due to potential conflict of interest is also high as neurofeedback equipment provided by manufacturer for trial.

# 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				S	ummary	of Find	ings
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness		Publication bias	quality of	With	With Secretin versus	effect (95% CI)	Anticip Risk with	Risk difference with Secretin versus placebo for the core autism feature of

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</sup> High risk of selective reporting bias as data cannot be extracted for 6-month follow-up

<sup>&</sup>lt;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)

								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% CI)
Stereoty values)	yped bel	naviour/inte	r <b>ests</b> (measur	ed with: Autisn	n Diagnostic C	bservation Sch	nedule (	ADOS/ADOS-G): Stereoty	yped behav	viour/inte	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	⊕⊕⊝⊝ LOW¹ 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	ped bel	naviours (mea	asured with: Gilli	am Autism Rat	ting Scale (GA	RS): Stereotyp	ed beha	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	⊕⊕⊖⊝ LOW¹ 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 and	d 95% CI cr	osses both line of	no effect and m	easure of app	reciable benef	it or harm (SMI	O -0.5/0	.5)			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	mary of	Findings			
•		Inconsistency	Indirectness	•		, ,		Study event rates (%)			Anticipated a	absolute effects
(studies) Follow up	bias				Lavidanca		With Long-term chelation (7-rounds of Dimercaptosuccinic	(95% CI)	Risk with Short-term chelation (1-	Risk difference with Long- term chelation (7-rounds of Dimercaptosuccinic Acid		

							DMSA therapy and 6-rounds of placebo)	Acid [DMSA] therapy)		round of DMSA therapy and 6- rounds of placebo)	[DMSA] therapy) (95% CI)
Sensory/ Better indicate			ach Behavi	OURS (measu	ured with: Per	vasive Develo	oment Disorde	r Behavior Inventory (P	DDBI): Ser	nsory/Perceptua	ll Approach Behaviours;
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖ <b>LOW</b> <sup>1</sup> due to imprecision	15	25	N/A		The mean sensory/perceptual approach behaviours in the intervention groups was <b>0.29 standard deviations higher</b> (0.35 lower to 0.94 higher)
Ritualisn lower values		stance to C	hange (meas	sured with: Per	vasive Develo	ppment Disord	er Behavior In	ventory (PDDBI): Rituali	isms/Resis	tance to Chang	e; Better indicated by
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LoW</b> ¹ due to imprecision	15	25	N/A		The mean ritualisms/resistance to change in the intervention groups was 0.18 standard deviations lower (0.83 lower to 0.46 higher)
<sup>1</sup> N<400 and	95% CI cr	osses both line o	f no effect and r	neasure of app	oreciable bene	efit or harm (S	MD -0.5/0.5)		•	•	

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

		(	Quality assess	sment			Su	mmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision		 Study even			Anticipated	absolute effects
(studies) Follow up	bias				bias	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% 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 deviations lower</b> (0.97 lower to 0.39 higher)
Physica	l stereot	ypy (measured v	with: Behavioural	observation: I	Physical stereotypy reporting bias	/ (change score); E	Better indic	cated by lower v	values)	N/A	The mean physica

#### 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 assessn	nent	Summary of Findings						
Participants		Inconsistency	Indirectness	•		•	Study event	Study event rates (%)		Anticipated absolute effects	
(studies) Follow up	bias				bias	of evidence	With Treatment-as- usual	With Kata	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Kata exercise training (95% CI)

30 (1 study) 15 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW¹.² 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 lower</b> (1.66 to 0.15 lower)
30 (1 study) 19 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	Autism Rating serious <sup>2</sup>	Scale (GARS): undetected	Stereotyped behaviors  ⊕⊕⊖  LOW¹.²  due to risk of bias, imprecision	15	ter indicated by	N/A	N/A	The mean stereotyped behaviour in the intervention groups was <b>0.76 standard deviations lower</b> (1.51 to 0.02 lower)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind. The risk of detection bias was also high as the outcome measure was based on interview with carers and teachers who were non-blind and blinding of examiner not reported.

## 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

		Q	uality assessn	nent					Summary	of Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study event	` '		Anticipated a	absolute effects
(studies) Follow up	bias				bias		With Treatment-as- usual	With Gluten-	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Gluten- free and casein-free diet (95% CI)

**Unusual or bizarre behaviour** (measured with: Diagnose of Psykotisk Adferd hos Børn (Diagnosis of Psychotic Behaviour in Children; DIPAB): Unusual or bizarre behaviour (B-scores); Better indicated by lower values)

<sup>&</sup>lt;sup>2</sup> N<400

20 (1 study) 52 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW¹.² 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 deviations lower</b> (1.9 to 0.02 lower)
Repetitiv	e behav	riours (measured	with: Autism Dia	gnostic Observ	ation Schedule	(ADOS): Repetiti	ve Behaviou	rs (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	⊕⊖⊖ <b>VERY LOW</b> <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 deviations lower</b> (0.86 lower to 0.2 higher)
Stereoty	ed beh	aviour (measure	d with: Gilliam Au	itism Rating Sc	ale (GARS): S	tereotyped behavi	our (change	score); Better	indicated by	lower values)	
55 (1 study) 35 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 deviations lower</b> (0.61 lower to 0.45 higher)

<sup>&</sup>lt;sup>1</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

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

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>13</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>&</sup>lt;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)

<sup>&</sup>lt;sup>5</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)

		Qı	uality assessm	ent			Summary of Findings				ıgs		
Participants		Inconsistency	Indirectness	Imprecision			Study e	vent rates (%)	Relative	Anticipat	ed absolute effects		
(studies) Follow up	bias				bias	of evidence	With Placebo	With L-carnosine supplement	1(95% CI)	Risk with Placebo	Risk difference with L- carnosine supplement (95% CI)		
Stereotyp	itereotyped behaviours (measured with: Gilliam Autism Rating Scale (GARS): Stereotyped behaviour; Better indicated by lower values)												
_		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	17	14	N/A	N/A	The mean stereotyped behaviours in the intervention groups was <b>0.41 standard deviations lower</b> (1.13 lower to 0.3 higher)		
<sup>1</sup> N<400 and 9	<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)												

## 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			Summary of Findings						
Participants		Inconsistency	Indirectness	Imprecision			Study even	t rates (%)	Relative	Anticipated	absolute effects		
(studies) Follow up	bias			as-usual	With Neurofeedback	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Neurofeedback (95% CI)					
Parent-ra	Parent-rated stereotyped behaviour (measured with: Social Communication Questionnaire (SCQ): Stereotyped behaviour; Better indicated by lower values)												
20 (1 study) 20 weeks		no serious inconsistency	no serious indirectness		reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖ <b>VERY LOW</b> <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-	Teacher-rated stereotyped behaviour (measured with: Social Communication Questionnaire (SCQ): Stereotyped behaviour; Better 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>	⊕⊖⊝ <b>VERY LOW</b> <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  0.56 standard deviations higher (0.33 lower to 1.46 higher)			

<sup>&</sup>lt;sup>1</sup> High risk of performance, response and detection bias as intervention administrators, participants and outcome assessors were non-blind. The risk of other bias due to potential conflict of interest is also high as neurofeedback equipment provided by manufacturer for trial.

# 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 Fii	ndings
Participants (studies) Follow up	Risk of bias	Inconsistency	istency Indirectness Imprecision Publication bias Overall quality of evidence (%)				Anticipated absolute effects			
						With Waitlist control	With Horseback riding		Risk with Waitlist control	Risk difference with Horseback riding (95% CI)

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</sup> High risk of selective reporting bias as data cannot be extracted for 6-month follow-up

<sup>&</sup>lt;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)

34 (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 LOW¹.2.3 due to risk of bias, imprecision, publication bias	15	19	N/A	N/A	The mean inattention/distractability in the intervention groups was 1.2 standard deviations higher (0.46 to 1.94 higher)	
Sedentary (measured with: Sensory Profile: Sedentary; Better indicated by lower values)												
34 (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,	15	19	N/A	N/A	The mean sedentary in the intervention groups was 1.14 standard deviations higher	

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants non-blind. There is also a high risk of detection bias as outcome measures are parent-rated and parents non-blind

#### 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

		Qı	uality assessn	nent				Sun	nmary of I	Finding	IS
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	bias	Overall quality of evidence	Study With Control	With Behaviour-focused	effect	Anticip Risk with Control	Risk difference with Behaviour- focused intervention versus treatment-as-usual for behaviour that challenges as a direct

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</sup> High risk of selective reporting bias as not all subscales that measure behaviour that challenges are reported, for instance, data are missing for the emotionally reactive subscale

<sup>2</sup> N<400

								as a direct outcome			outcome (95% CI)
Illness-r	elated	problem be	ehaviour (m	easured with:	Study-specific	questionnaire; E	Better in	ndicated by lower values)			
21 (1 study) 43 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	11	10	N/A	N/A	The mean illness-related problem behaviour in the intervention groups was 1.65 standard deviations lower (2.64 to 0.66 lower)

intervention administrators and the outcome measure was designed specifically for the study and as such lacked formal assessments of reliability and validity

		Q	uality assessr	nent			Summary of Findings					
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study 6	` ,	Relative effect	Anticipa	ted absolute effects	
Follow up						evidence	With Control	With EIBI versus parent training for behaviour that challenges as an indirect outcome	(95% CI) Risk v		Risk difference with EIBI versus parent training for behaviour that challenges as an indirect outcome (95% CI)	
Aggress	Aggression (parent-rated) (measured with: Achenbach Child Behavior Checklist (Parent report): Aggression; Better indicated by lower values)											
28 (1 study) 260 weeks	serious <sup>1</sup>	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	13	15	N/A	N/A	The mean aggression (parent-rated) in the intervention groups was <b>0.36 standard deviations</b> lower (1.1 lower to 0.39 higher)	

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

Aggress	Aggression (teacher-rated) (measured with: Achenbach Child Behavior Checklist (Teacher report): Aggression; Better indicated by lower values)													
28 (1 study) 260 weeks	serious <sup>1</sup>	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	13	15	N/A	N/A	The mean aggression (teacher-rated) in the intervention groups was <b>0.47 standard deviations</b> higher (0.28 lower to 1.23 higher)			

<sup>&</sup>lt;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 measure was non-blind parent- or teacher- completed checklist and checklist was not validated in autism population

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

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

			Quality asses	ssment			Summary of Findings						
(	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	1(95% CI)	Risk with Control	Risk difference with CBT for anger management versus waiting-list control for behaviour that challenges (95% CI)		
	Parent-reported instances of child anger (measured with: Study-specific parent monitoring of anger: Parent-reported instances of child anger over a week; Better indicated by lower values)												
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 0.92 standard deviations lower		

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

										(1.54 to 0.3 lower)
•		s of child	anger (me	easured with: Study	/-specific parent mor	nitoring	of anger: Parer	t-reported instanc	es of child	anger over a week; Better
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 1.03 standard deviations lower (1.65 to 0.4 lower)
		_	ng own a	nger (measured	d with: Study-specific	paren	nt monitoring of a	nger: Parent-repo	rted confid	ence in their child managin
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖ VERY LOW¹.2,3 due to risk of bias, imprecision, publication bias	21	24	N/A	N/A	The mean parent confidence in child managing own anger in the intervention groups was  0.61 standard deviations higher (0 to 1.21 higher)
		•	ng own a	i <b>nger</b> (measured	I with: Study-specific	paren	nt monitoring of a	inger: Parent-repo	rted confid	ence in their child managir
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 in the intervention groups was  1.1 standard deviation higher
	serious¹  confide ger; Better  confide	serious¹ no serious inconsistency  confidence in chil ager; Better indicated by lower serious¹ no serious inconsistency  confidence in chil ager; Better indicated by lower serious¹ no serious inconsistency	serious no serious inconsistency no serious indirectness  confidence in child managir nger; Better indicated by lower values)  serious no serious inconsistency indirectness  confidence in child managir nger; Better indicated by lower values)  serious no serious indirectness  serious no serious indirectness	serious¹ no serious inconsistency indirectness serious²  confidence in child managing own anger; Better indicated by lower values)  serious¹ no serious indirectness serious²  serious¹ no serious indirectness serious²  confidence in child managing own anger; Better indicated by lower values)  serious¹ no serious indirectness serious²  serious¹ no serious serious serious²	serious¹ no serious indirectness serious² reporting bias strongly suspected ³  confidence in child managing own anger (measured ager; Better indicated by lower values)  serious¹ no serious inconsistency indirectness serious² reporting bias strongly suspected ³  confidence in child managing own anger (measured ager; Better indicated by lower values)  confidence in child managing own anger (measured ager; Better indicated by lower values)  serious¹ no serious inconsistency indirectness serious² reporting bias strongly suspected ³	serious¹ no serious inconsistency indirectness serious² reporting bias strongly suspected ³ due to risk of bias, imprecision, publication bias  confidence in child managing own anger (measured with: Study-specific ager; Better indicated by lower values)  serious¹ no serious inconsistency indirectness serious² reporting bias strongly suspected ³ due to risk of bias, imprecision, publication bias  confidence in child managing own anger (measured with: Study-specific ager; Better indicated by lower values)  serious¹ no serious inconsistency indirectness serious² reporting bias strongly suspected ³ due to risk of bias, imprecision, publication bias  confidence in child managing own anger (measured with: Study-specific ager; Better indicated by lower values)  serious¹ no serious inconsistency indirectness serious² reporting bias strongly suspected ³ VERY LOW¹.2.3 due to risk of bias, imprecision, publication bias strongly suspected ³ very Low¹.2.3 due to risk of bias, imprecision, publication bias indirectness strongly suspected ³ very Low¹.2.3 due to risk of bias, imprecision,	serious¹ no serious inconsistency indirectness serious² reporting bias strongly suspected ³ suspected ° suspected	serious¹ no serious inconsistency   no serious indirectness   serious²   reporting bias strongly suspected³   very Low¹²²³   due to risk of bias, imprecision, publication bias   publication bias   publication bias   very Low¹²²³   very Low¹²²³   due to risk of bias, imprecision, publication bias   very Low²²²   reporting bias strongly suspected³   very Low²²³   very Low²³³   very Low³³³   very Low³³   very Low³   very Lo	serious¹ no serious indirectness serious² reporting bias strongly suspected³ serious² loconfidence in child managing own anger (measured with: Study-specific parent monitoring of anger: Parent-reporting bias strongly suspected³ serious¹ no serious indirectness serious² reporting bias strongly suspected³ serious² loconfidence in child managing own anger (measured with: Study-specific parent monitoring of anger: Parent-reporting bias strongly suspected³ suspected³ serious² loconfidence in child managing own anger (measured with: Study-specific parent monitoring of anger: Parent-reporting bias strongly suspected³ suspected³ suspected suspect	Serious   no serious   no serious   no serious   indirectness   serious   serious   strongly   suspected   strongly   suspected   suspected   strongly   suspected   suspect

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

		C	Quality assessr	ment					Sum	mary of Fi	indings
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study ev	vent rates	Relative effect (95% CI)	Anticipate	ed absolute effects
							With Waitilist control	With CBT for anxiety		Risk with Waitilist control	Risk difference with CBT for anxiety (95% CI)
Hyperac	tivity a	nd conduct	problems	parent-ra	ated) (meas	ured with: Strengtl	hs and Dif	ficulties Que	stionnaire: E	Externalising	g; 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	⊕⊕⊖⊖ LOW¹.² 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	ind conduct	problems	(teacher-	rated) (mea	Lasured with: Streng	l gths and D	Difficulties Qu	l lestionnaire	Externalisi	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	⊕⊕⊖⊖ <b>LOW</b> <sup>2,3</sup> due to risk of bias, imprecision	19	28	N/A	N/A	The mean hyperactivity and conduct problems (teacher-rated in the intervention groups was <b>0.62 standard deviations lowe</b> (1.21 to 0.02 lower)

<sup>&</sup>lt;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 meausre parent- rated and parents non-blind

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;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

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</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 teacher-rated and blinding of teachers is not reported

### 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 Findir	ngs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	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 aviours; Better ind	•		orkshop -	+ individua	l ses	sions) (measured v	ı with: Eyberç	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	⊕⊕⊝ LOW¹.² 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 1.26 standard deviations lower (1.91 to 0.61 lower)
	•	blem behav aviours; Better ind	•		orkshop -	+ individua	l ses	sions) (measured v	ı with: Eyberç	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	⊕⊕⊝ LOW¹.² 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 1.23 standard deviations lower (1.88 to 0.58 lower)

Intensit indicated by			viours (inc	lividual s	essions)	(measured with:	Eyberg	Child Behaviour Inver	tory (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)
Intensit indicated by	•		viours (inc	lividual s	essions)	(measured with:	Eyberg	Child Behaviour Inver	tory (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	⊕⊕⊖⊝ <b>LOW</b> <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 1.35 standard deviations lower (2.12 to 0.59 lower)
Intensit values)	ty of pro	oblem beha	viours (wo	rkshop) (	measured with	: Eyberg Child B	ehaviou	r Inventory (ECBI): Int	ensity of pro	blem beh	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 lower</b> (1.30 lower to 0.10 higher)
Intensit	ty of pro	oblem beha	viours (wo	rkshop) (	I measured with	: Eyberg Child B	ehaviou	r Inventory (ECBI): Int	ensity of pro	blem beh	aviours; Better indicated by lower
33 (1 study)	serious <sup>1</sup>	no serious	no serious	very serious <sup>3</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,3</sup>	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)
Problen by lower value		iour (PEC+	PEBM con	nbined) (m	easured with:	Developmental I	3ehavio	our Checklist (DBC)	: Total Behav	iour Probler	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	⊕⊖⊖ <b>VERY LOW</b> <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 0.35 standard deviations lower (0.76 lower to 0.06 higher)
intervention <sup>2</sup> N<400		Lace bias as intervelosses both line of			_			outcome assessor	s were non-b	I lind parents	who were involved in the

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

	udies) bias q							Sun	nmary of	Finding	IS
•		Inconsistency	Indirectness	Imprecision	bias	quality of	Study 6 With Control	With Combined	Relative effect (95% CI)	Anticipa Risk with Control	Risk difference with Combined antipsychotic and parent training versus antipsychotic only for behaviour that challenges as a direct outcome (95% CI)
Noncomp 95 (1 study) 24 weeks	1 1	ehaviour in no serious inconsistency	everyday c no serious indirectness	ircumstar very serious <sup>2</sup>	undetected		40	outcome  ns Questionnaire (HSQ): Se  55	everity; Bett	er indica	ted by lower values)  The mean noncompliant behaviour in everyday circumstances in the intervention groups was

						imprecision					0.33 standard deviations lower (0.74 lower to 0.08 higher)
Noncom	pliant b	ehaviour in	everyday o	ircumsta	nces (measu	red with: Home	Situation	ons Questionnaire (	HSQ): Severity; B	etter indic	eated by lower values)
87 (1 study) 80 weeks	serious <sup>1</sup>	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	36	51	N/A	N/A	The mean noncompliant behaviour in everyday circumstances in the intervention groups was <b>0.17 standard deviations lower</b> (0.6 lower to 0.26 higher)
	-	ehaviour in			nces (measu	red with: Study	-specific	c noncompliance in	dex based on the	Vineland A	Adaptive Behaviour Scale (VABS
124 (1 study) 24 weeks	serious <sup>1</sup>		no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊖ LOW¹,3 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> lower (0.83 to 0.1 lower)
Irritabilit	: <b>y</b> (measur	ed with: Aberrant	Behaviour Chec	klist (ABC): Irı	itability & Agita	ation; Better ind	icated b	by lower values)		<u> </u>	
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 irritability in the intervention groups was <b>0.43 standard deviations lower</b> (0.85 to 0.02 lower)
Irritabilit	: <b>y</b> (measur	ed with: Aberrant	Behaviour Chec	klist (ABC): Irı	itability & Agita	ation; Better ind	icated b	by lower values)	<u>_</u>		
87 (1 study) 80 weeks	serious <sup>1</sup>	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	36	51	N/A	N/A	The mean irritability in the intervention groups was 0.33 standard deviations lower (0.75 lower to 0.1 higher)

	y/ Octial	withidiawai	(measured with	. Abeliani ben	1	isi (ADC). Letha			Better indicated by I		ico)
95 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW¹.² due to risk of bias, imprecision	40	55	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was  0.36 standard deviations lower  (0.77 lower to 0.06 higher)
Lethargy	y/Social	withdrawal	(measured with	: Aberrant Beh	aviour Checkl	ist (ABC): Letha	rgy & S	Social Withdrawal;	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	⊕⊕⊝⊝ LOW¹,3 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 lower</b> (0.89 to 0.03 lower)
Stereoty	pic beh	aviour (measu	red with: Aberra	nt Behaviour (	Checklist (ABC	C): Stereotypic E	Behavio	ur; Better indicate	d by lower values)		
95 (1 study) 24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 0.63 standard deviations lower (1.04 to 0.21 lower)
Stereoty	pic beh	aviour (measu	red with: Aberra	nt Behaviour	Checklist (ABC	C): Stereotypic E	Behavio	ur; Better indicate	d 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 LOW¹,² 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> lower (0.78 lower to 0.08 higher)
Hyperac	tivity (m	easured with: Abe	errant Behaviour	Checklist (AB	C): Hyperactiv	rity & Noncompli	iance; E	Better indicated by	v 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,	40	55	N/A	N/A	The mean hyperactivity in the intervention groups was 0.48 standard deviations lower

						imprecision					(0.89 to 0.07 lower)
Hyperac	tivity (m	easured with: Ab	errant Behaviou	Checklist (AB	C): Hyperactiv	ity & Noncompli	ance; E	Better indicated by I	ower values)	I	- 1
87 (1 study) 80 weeks	serious <sup>1</sup>	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	36	51	N/A	N/A	The mean hyperactivity in the intervention groups was 0.13 standard deviations lower (0.56 lower to 0.29 higher)
Inappro	priate s <sub>l</sub>	peech (measu	red with: Aberra	nt Behaviour C	hecklist (ABC)	: Inappropriate S	Speech	; Better indicated b	/ 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, imprecision	40	55	N/A	N/A	The mean inappropriate speech in the intervention groups was 0.23 standard deviations lower (0.63 lower to 0.18 higher)
Inappro	priate s	peech (measu	red with: Aberra	nt Behaviour C	hecklist (ABC)	: Inappropriate S	Speech	; Better indicated b	y lower values)		
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 inappropriate speech in the intervention groups was <b>0.02 standard deviations higher</b> (0.41 lower to 0.44 higher)

control (risperidone only) group (N=9; 18% attrition)

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

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
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N<400

•		Inconsistency	Indirectness	-		Overall quality	Study	event rates (%)		Anticip	ated absolute effects
Follow up	bias	l hohaviour	that challo			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	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% CI)  3SQ): Total; Better indicated by
lower values)	-	i bellavioui	tilat Cilalie	iiges (iiiiz	CCU ASD C		c) (IIIea	sured with behavior Screen	ng Questio	illialle (i	55Q). Total, better indicated by
58 (1 study) 40 weeks		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 lower</b> (0.54 lower to 0.49 higher)
Parent-re lower values)	portec	l behaviour	that challe	nges (mix	ed ASD 8	& DD sample	<b>e)</b> (mea	sured with: Behavior Screeni	ng Questio	nnaire (E	BSQ): Total; Better indicated by
50 (1 study) 108 weeks		no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ VERY LOW¹.2,3 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 lower</b> (0.71 lower to 0.4 higher)
Teacher-I	rated b	ehaviour th	at challeng	ges (mixe	d ASD & I	DD sample)	(measu	red with: Preschool Behavior	Checklist (	PBCL): <sup>-</sup>	Total; Better indicated by lower
53 (1 study) 40 weeks		no serious inconsistency	serious <sup>2</sup>	serious <sup>5</sup>	undetected	⊕⊖⊖ VERY LOW <sup>2,4,5</sup> due to risk of bias, indirectness, imprecision	26	27	N/A	N/A	The mean teacher-rated behaviour that challenges (mixed asd & dd sample) in the intervention groups was <b>0.67 standard deviations lower</b> (1.23 to 0.12 lower)
Teacher-	rated b	ehaviour th	at challeng	jes (ASD-	only sam	<b>ple)</b> (measured	with: Pr	eschool Behavior Checklist (	PBCL): Tot	al; Bette	r indicated by lower values)

34 (1 study) 40 weeks		no serious inconsistency	no serious indirectness	serious <sup>5</sup>	undetected	⊕⊕⊖⊝ LOW <sup>4,5</sup> due to risk of bias, imprecision	18	16	N/A	N/A	The mean teacher-rated behaviour that challenges (asd-only sample) in the intervention groups was <b>0.98 standard deviations lower</b> (1.69 to 0.26 lower)
Teacher- values)	rated b	ehaviour th	nat challen	ges (mixe	d ASD &	DD sample)	measu	red with: Preschool B	ehavior Checklist	(PBCL):	Total; Better indicated by lower
46 (1 study) 108 weeks		no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>	undetected	⊕⊖⊖⊖ 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 lower</b> (0.68 lower to 0.47 higher)

psychologist outcome assessor this outcome measure relied on non-blind parental report

2 Population was indirect (as the sample included participants with developmental delay or language delay without autism)

### 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

	Quality assessment								Summary of Findings				
-	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	With	With Social skills	effect (95% CI)	Riek	Risk difference with Social skills groups versus treatment-as-usual for behaviour that challenges as an indirect outcome (95% CI)		
Conflict (	Dnflict (parent-rated) (measured with: Quality of Play Questionnaire (QPQ): Conflict; Better indicated by lower values)												

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

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 teachers N<400

95 (2 studies) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW¹.² 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	<b>ted)</b> (measured	with: Quality of	Play Question	nnaire (QPQ):	Conflict; Better indic	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	⊕⊖⊖⊖ <b>VERY LOW</b> <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 cated by lower va	<b>``</b>	it-rated) (n	neasured with	: Social Skills Rating	Syste	m (SSRS): Externalizir	ng or Social	Skills Ra	ating System (SSRS): Problem
101 (2 studies) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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	/aggres	ssive behav	iour (teach	er-rated)	measured wit	h: Pupil Evaluation I	nvento	ry (PEI): Aggression; E	Better indica	ted by lo	ower values)
59 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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)
		ral (parent-ra awal; Better indic			I al Skills Ratinເ	g System (SSRS): In	ternaliz	ting or Behavior Asses	ssment Syste	em for C	hildren, 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  0.68 standard deviations lower (1.08 to 0.28 lower)
Social wi	ithdraw	al (teacher-	rated) (meas	ured with: Pur	oil Evaluation	Inventory (PEI): With	ndrawa	; Better indicated by lo	ower values)		
59 (1 study) 12 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊝⊝⊝ <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		0.04 standard deviations lower
					(0.55 lower to 0.47 higher)

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.

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

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

<sup>&</sup>lt;sup>3</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>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)

High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as teacher-rated and teachers were non-blind

Substantial to considerable heterogeneity

# 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			Summary of Findings					
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study	event rates (%)	Relative effect (95% CI)	Anticipated absolute effects		
(studies) Follow up	bias				bias	of evidence	With Control	With Anticonvulsants versus placebo for behaviour that challenges as a direct outcome		Risk with Control	Risk difference with Anticonvulsants versus placebo for behaviour that challenges as a direct outcome (95% CI)	
Irritability	(measure	ed with: Aberrant E	Behaviour Check	dist (ABC): Irrit	ability & Agitatio	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 LOW¹,² due to inconsistency, imprecision	25	32	N/A	N/A	The mean irritability in the intervention groups was <b>0.05 standard deviations lower</b> (0.58 lower to 0.48 higher)	
Irritability	/ (measure	ed with: Overt Agg	ression Scale (C	DAS): Irritability	; Better indicate	d by lower values)					1	
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 lower</b> (1.21 lower to 0.35 higher)	
Aggressi	on (meas	ured with: Overt A	Aggression Scale	e (OAS): Total;	Better indicated	by lower values)			<u>I</u>	<u>!</u>	1	
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	

											(0.69 lower to 0.75 higher
Global s	severity (	measured with: C	linical Global Im	pression Scal	e (CGI-S): Sever	rity; Better indicated	d by lowe	r values)		<u> </u>	1
30 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <sup>2</sup> due to imprecision	14	16	N/A	N/A	The mean global severity in the intervention groups was  0 standard deviations higher  (0.72 lower to 0.72 higher)
Global i	mprover	ment (measured	d with: Clinical G	lobal Impressi	ion Scale (CGI-I)	: Improvement; Be	tter indica	ited by lower values	)		
30 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>2</sup> due to imprecision	14	16	N/A	N/A	The mean global improvement in the intervention groups was <b>0.43 standard deviation lower</b> (1.16 lower to 0.29 higher
Global i	mprover	ment (assessed	with: Dichotomo	•	reatment respons	se ( 'much improve	d/very im	proved' on CGI-imp	rovement))	,	
27	no serious	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE⁴	1/11 (9.1%)	10/16 (62.5%)	RR 6.88 (1.02 to	Study p	oopulation
(1 study)						due to	,	,	46.28)	91 per	535 more per 1000
(1 study) 12 weeks	risk of bias					imprecision			40.20)	1000	(from 2 more to 1000 more)
									40.20)		(from 2 more to 1000 more)

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

Events<300

		Qı	uality assess	ment				Sum	mary of F	indings	5		
Participants	Risk of	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% CI)		
Irritability	(measure	ed with: Aberrant	Behaviour Chec	cklist (ABC): Irı	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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	20	20	N/A	N/A	The mean irritability in the intervention groups was 1.88 standard deviations lower (2.63 to 1.12 lower)		
Lethargy	Lethargy/Social withdrawal (measured with: Aberrant Behaviour Checklist (ABC): Lethargy & Social Withdrawal; Better indicated by lower values)												
40 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊖ <b>LoW</b> <sup>2</sup> due to imprecision	20	20	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was 0.25 standard deviations lower (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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	20	20	N/A	N/A	The mean stereotypic behaviour in the intervention groups was 2.02 standard deviations lower (2.8 to 1.25 lower)		
Hyperact	ivity (me	easured with: Abe	rrant Behaviour	Checklist (AB	C): Hyperactiv	rity & Noncomplia	ance; Be	etter indicated by lower values	5)				
40 (1 study) 8 weeks	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ <b>MODERATE</b> <sup>1</sup> due to	20	20	N/A	N/A	The mean hyperactivity in the intervention groups was 1.87 standard deviations		

	bias					imprecision					lower (2.63 to 1.12 lower)
Inappro	priate s <sub>l</sub>	peech (measur	ed with: Aberran	t Behaviour C	hecklist (ABC)	: Inappropriate S	peech;	; Better indicated by lower	values)		
40 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝ LOW² due to imprecision	20	20	N/A	N/A	The mean inappropriate speech in the intervention groups was 0.16 standard deviations lower (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	no effect and m	easure of app	reciable benef	fit or harm (SMD	-0.5/0.	5)	1		,

# 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 assessi	ment				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 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% CI)
Irritability	(measure	d with: Aberrant B	ehaviour Check	list (ABC): Irrit	ability & Agitat	ion; Better indicat	ed by lo	wer values)		•	
(1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝  MODERATE¹  due to  imprecision	76	73	N/A	N/A	The mean irritability in the intervention groups was <b>0.01 standard deviations lower</b> (0.33 lower to 0.31 higher)
Lethargy /Social withdrawal (measured with: Aberrant Behaviour Checklist (ABC): Lethargy & Social Withdrawal; Better indicated by lower 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 lower</b> (0.33 lower to 0.31 higher)
Stereoty	pic beh	aviour (measu	ed with: Aberrar	t Behaviour C	hecklist (ABC)	: Stereotypic Beha	aviour; E	Better indicated by lower va	lues)	L	1
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖  MODERATE¹  due to  imprecision	76	73	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0.05 standard deviations higher</b> (0.27 lower to 0.37 higher)
Hyperac	tivity (me	easured with: Abe	rant Behaviour (	Checklist (ABC	): Hyperactivity	y & Noncompliand	e; Bette	er indicated by lower values	5)		
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖  MODERATE¹  due to  imprecision	76	73	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.09 standard deviations</b> higher (0.23 lower to 0.41 higher)
Inappro	priate sp	peech (measure	d with: Aberrant	Behaviour Ch	ecklist (ABC):	Inappropriate Spe	ech; Be	etter indicated by lower valu	es)		1
149 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	76	73	N/A	N/A	The mean inappropriate speech in the intervention groups was 0.06 standard deviations higher (0.26 lower to 0.38 higher)
<sup>1</sup> N<400		<u> </u>	<u>l</u>		1	<u> </u>				<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 assessi	ment				Sum	mary of F	inding	s		
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study	event rates (%)		Anticip	ated absolute effects		
(studies) Follow up	bias				bias	of evidence	With Control	With Combined antihistamine and antipsychotic versus combined antipsychotic and placebo for behaviour that challenges as a direct outcome	effect (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% CI)		
Behaviou	Sehaviour that challenges (measured with: Aberrant Behaviour Checklist (ABC): Total (Change Score); Better indicated by lower values)												
(1 study) 8 weeks	no serious risk of bias		no serious indirectness	serious <sup>1</sup>		⊕⊕⊕⊝  MODERATE¹ due to imprecision	20	20	N/A	N/A	The mean behaviour that challenges in the intervention groups was 0.98 standard deviations lower (1.64 to 0.32 lower)		
<sup>1</sup> N<400				•	•		•			•			

## 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 Fin	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	ир					With Placebo	With Antioxidants	(95% CI)	Risk with Placebo	Risk difference with Antioxidants (95% CI)			
Irritability	rritability (measured with: Aberrant Behaviour Checklist (ABC): Irritability & Agitation; Better indicated by lower values)												
_		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	15	14	N/A	N/A	The mean irritability in the intervention groups was <b>0.7 standard deviations lower</b> (1.46 lower to 0.05 higher)		

29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> ¹ due to imprecision	15	14	N/A	N/A	The mean lethargy/social withdrawal in the interventior groups was <b>0.31 standard deviations higher</b> (0.43 lower to 1.04 higher)
Stereoty	pic behav	iour (measured	with: Aberrant B	ehaviour Chec	klist (ABC): Ste	reotypic Behavio	ur; Better	indicated by	lower values	s)	
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> ¹ due to imprecision	15	14	N/A	N/A	The mean stereotypic behaviour in the intervention groups was 0.36 standard deviations lower (1.1 lower to 0.37 higher)
Hyperac	tivity (meas	sured with: Aberra	nt Behaviour Che	cklist (ABC): H	lyperactivity & N	loncompliance; E	Better indi	cated by low	er values)		
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	15	14	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.73 standard deviations lower</b> (1.49 lower to 0.03 higher)
Inappro	priate spe	ech (measured	with: Aberrant Bel	naviour Checkl	list (ABC): Inapp	oropriate Speech	; Better in	ndicated by le	ower values)		
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	15	14	N/A	N/A	The mean inappropriate speech in the intervention groups was 0.34 standard deviations lower (1.07 lower to 0.4 higher)
Global s	severity (m	easured with: Clin	ical Global Impres	ssion Scale (C	GI-S): Severity;	Better indicated	by lower v	values)			
29 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW¹ due to imprecision	15	14	N/A	N/A	The mean global severity in the intervention groups was 0.46 standard deviations lower

											(1.19 lower to 0.28 higher)
Global im	nproveme	ent (measured wit	th: Clinical Global	Impression So	cale (CGI-I): Imp	provement; Bette	r indicate	d by lower va	alues)		
-		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	15	14	N/A	N/A	The mean global improvement in the intervention groups was <b>0.29 standard deviations</b> lower (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 asses	sment				Sui	mmary 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% CI)
		-			azole) (ass	essed with: Positive	treatment	response (clinician-ra	ated: >25%	improve	ment on ABC-Irritability with
or without 'mu	ıch improve	d/very improved' o	n CGI-improven	nent))						1	
	no serious risk of bias	very serious <sup>1</sup>	no serious indirectness	no serious imprecision	undetected	⊕⊕⊝⊝ LOW¹	44/184 (23.9%)	183/317 (57.7%)	RR 2.27 (1.75 to	Study p	population
6-8 weeks				·		due to inconsistency		,	2.94)	239 per 1000	<b>304 more per 1000</b> (from 179 more to 464 more)
										Modera	nte
										245 per 1000	311 more per 1000 (from 184 more to 475 more)

2 studies) risk	no serious risk of bias	very serious <sup>1</sup>	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,2</sup>	20/86 73/107 (23.3%) (68.2%)	<b>RR 2.72</b> (1.85 to	Study	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)
									Modera	ate
									245 per 1000	<b>421 more per 1000</b> (from 208 more to 733 more)
mproved/ve	ry improved'	on CGI-improvem	nent))	le) (assessed		, ,	Clinician-rated: >25% imp	PRR 1.95		
808 2 studies)	no serious risk of bias	,	no serious indirectness	serious	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	(24.5%) (52.4%)	(1.37 to	Study	population
weeks						due to inconsistency, imprecision		2.78)	245 per 1000	233 more per 1000 (from 91 more to 436 more)
									Modera	ate
									245 per 1000	233 more per 1000 (from 91 more to 436 more)
		nt response	(risperidon	e) (assessed v	with: Dichotom	ous: Positive treatme	ent response (<3 "definite	ely improved" or b	per 1000	(from 91 more to 436
ymptom sca	no serious	no serious	no serious	e) (assessed v	with: Dichotom	$\oplus\oplus\ominus\ominus$	9/43 31/44	RR 3.37	per 1000 etter on 9	(from 91 more to 436 more)
Positive symptom sca 37 (1 study) 3 weeks	no serious	- 1	` ·	, ,					per 1000 etter on 9	(from 91 more to 436 more) 9-point parent-defined target

										209 per 1000	<b>495 more per 1000</b> (from 173 more to 1000 more)
Maladapt	tive beha	viour (measure	ed with: Vineland	d Adaptive Beha	aviour Scale (V	/ABS): Maladaptive I	Behaviou	ur Index; Better indicate	ed by lower	values)	
101 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE³ due to imprecision	52	49	N/A	N/A	The mean maladaptive behaviour in the intervention groups was 1.17 standard deviations lower (1.59 to 0.75 lower)
Irritability values)	y (risperi	done or arip	oiprazole) (n	neasured with: A	Aberrant Beha	viour Checklist (ABC	): Irritabi	lity & Agitation (Endpo	int 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	⊕⊕⊕⊝ MODERATE³ due to imprecision	173	190	N/A	N/A	The mean irritability (risperidone or aripiprazole) in the intervention groups was 0.92 standard deviations lower (1.14 to 0.7 lower)
Irritability	y (risperi	i <b>done)</b> (measur	ed with: Aberrar	L nt Behaviour Ch	ecklist (ABC):	Irritability & Agitation	(Endpo	int or Change score); E	Better indica	ated by lo	ower values)
268 (3 studies) 6-8 weeks		no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊖ MODERATE³ due to imprecision	124	144	N/A	N/A	The mean irritability (risperidone) in the intervention groups was <b>0.96 standard deviations lower</b> (1.22 to 0.71 lower)
Irritability	y (aripipr	razole) (measu	red with: Aberra	nt Behaviour Ch	necklist (ABC):	Irritability & Agitation	n (Endpo	oint or Change score);	Better indic	ated by I	ower values)
95 (1 study) 8 weeks		no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE³ due to imprecision	49	46	N/A	N/A	The mean irritability (aripiprazole) in the intervention groups was 0.81 standard deviations lower (1.23 to 0.39 lower)

		vithdrawal (I	-	or aripipra	azole) (meas	sured with: Aberrant	Behavio	our Checklist (ABC): Le	thargy & So	ocial With	drawal (Endpoint and
486 (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	188	298	N/A	N/A	The mean lethargy/social withdrawal (risperidone or aripiprazole) in the intervention groups was <b>0.28 standard deviations lower</b> (0.47 to 0.08 lower)
Lethargy indicated by		•	risperidone	(measured wi	th: Aberrant Bo	ehaviour Checklist (A	BC): Le	ethargy & Social Withdo	awal (Endp	oint and	Change scores); Better
178 (2 studies) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE³ due to imprecision	90	88	N/A	N/A	The mean lethargy/social withdrawal (risperidone) in the intervention groups was 0.45 standard deviations lower (0.75 to 0.15 lower)
Lethargy indicated by		•	aripiprazol	e) (measured w	vith: Aberrant E	Behaviour Checklist (	ABC): L	ethargy & Social Without	drawal (End	point and	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)
Stereoty Better indica	-		ridone or a	ripiprazole)	(measured w	ith: Aberrant Behavio	our Che	cklist (ABC): Stereotyp	ic Behaviou	ır (Endpoi	int and Change scores);
485 (4 studies) 8 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to risk of bias	188	297	N/A	N/A	The mean stereotypic behaviour (risperidone or aripiprazole) in the intervention groups was <b>0.48 standard deviations</b> lower

											(0.68 to 0.29 lower)
Stereoty	pic beha	viour (rispe	ridone) (mea	sured with: Aber	rrant Behaviou	ır Checklist (ABC): S	ereotyp	ic Behaviour (Endpoin	t and Chan	ge scores	s); 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	⊕⊕⊕⊝ MODERATE³ due to imprecision	90	87	N/A	N/A	The mean stereotypic behaviour (risperidone) in the intervention groups was 0.34 standard deviations lower (0.64 to 0.05 lower)
Stereoty  values)	pic beha	viour (aripip	<b>orazole)</b> (mea	sured with: Abe	rrant Behavio	ur Checklist (ABC): S	tereotyp	oic Behaviour (Endpoir	nt and Char	nge score	s); Better indicated by lower
308 (2 studies) 8 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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)
Hyperact indicated by	• •		aripiprazol	<b>e)</b> (measured v	with: Aberrant	Behaviour Checklist	(ABC): I	Hyperactivity & Nonco	mpliance (E	Endpoint o	or Change score); Better
484 (4 studies) 8 weeks	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖  MODERATE⁴  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> lower (1.04 to 0.64 lower)
Hyperact	tivity (ris	p <b>eridone)</b> (m	easured with: Al	L perrant Behavio	Lur Checklist (A	LABC): Hyperactivity &	Noncor	mpliance (Endpoint or	Change sc	ore); Bette	er indicated by lower values)
176 (2 studies) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ <b>MODERATE</b> <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	tivity (ari	<b>piprazole)</b> (n	neasured with: A	berrant Behavio	ur Checklist (	ABC): Hyperactivity &	k Nonco	mpliance (Endpoint or	Change sc	ore); Bett	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	⊕⊖⊖ <b>VERY LOW</b> <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> lower (0.97 to 0.46 lower)
Inapprop Better indica	-	· · ·	idone or ari	piprazole)	(measured wit	h: Aberrant Behaviou	ır Check	klist (ABC): Inappropria	ate Speech	(Endpoin	t and Change scores);
485 (4 studies) 8 weeks	serious <sup>4</sup>	serious <sup>5</sup>	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ <b>LOW</b> <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 lower</b> (0.74 to 0.35 lower)
Inapprop	oriate Sp	eech (risper	idone) (meas	ured with: Aberr	ant Behaviour	Checklist (ABC): Ina	appropria	ate Speech (Endpoint a	and Change	e scores)	; Better indicated by lower
178 (2 studies) 8 weeks		no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE³ due to imprecision	90	88	N/A	N/A	The mean inappropriate speech (risperidone) in the intervention groups was <b>0.66 standard deviations lower</b> (0.96 to 0.36 lower)
Inapprop	oriate Sp	eech (aripip	razole) (meas	ured with: Aber	rant Behaviou	r Checklist (ABC): In	appropri	ate Speech (Endpoint	and Chang	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	⊕⊖⊖ <b>VERY LOW</b> <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)
	efined ta	• • •	oms (measured	d with: Parent-d	defined target sy	ymptom scale (9-poir	nt) or Visu	ial Analog Scale	for the most tro	ublesom	e symptom (VAS-MS); Bet
63 2 studies) s weeks	serious <sup>7</sup>	very serious <sup>8</sup>	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <sup>3,7,8</sup> due to risk of bias, inconsistency, imprecision	80	83	N/A	N/A	The mean parent-define target symptoms in the intervention groups was <b>0.96 standard deviatio lower</b> (1.29 to 0.63 lower)
Slobal st		sitive treatm	ent respons	se (risperio	done) (asses	sed with: Dichotomo	us: Positiv	ve treatment res	sponse ( 'much in	nproved/	very improved' on CGI-
71 2 studies)	serious <sup>9</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>2,9</sup>	12/72 (16.7%)	45/99 (45.5%)	<b>RR 2.83</b> (1.61 to	Study	population
-8 weeks						due to risk of bias, imprecision		( )	4.95)	167 per 1000	<b>305 more per 1000</b> (from 102 more to 658 more)
										Moderate	
										166 per 1000	<b>304 more per 1000</b> (from 101 more to 656 more)
	tate: Syn	•	rity (risperio	done or ar	ipiprazole)	(measured with: Cli	nical Glob	oal Impression S	scale (CGI-S): Se	verity (E	ndpoint or Change Scores
73 2 studies) -8 weeks	serious <sup>10</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖ <b>LOW</b> <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		inconsistency	no serious indirectness	very serious <sup>3,11</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <sup>3,11</sup> due to imprecision	34	58	N/A	N/A	The mean global state: symptom severity (risperdione) in the intervention groups was <b>0.28 standard deviations</b> lower (0.71 lower to 0.14 higher)
181 (1 study) 8 weeks	serious <sup>10</sup>	no serious inconsistency	no serious indirectness	very serious <sup>11</sup>	1	1	n Scale	(CGI-S): Severity; Bet	er indicated	N/A	The mean global state: symptom severity (aripiprazole) in the intervention groups was 0.34 standard deviations lower (0.69 lower to 0.01 higher)
Global s	tate: Imp	rovement (ri	speridone)	(measured with	n: Clinical Glob	oal Impression Scale	(CGI-I):	Improvement; Better i	ndicated by	lower va	alues)
77 (1 study) 8 weeks	serious <sup>9</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊖⊝ LOW <sup>3,9</sup> due to risk of bias, imprecision	38	39	N/A	N/A	The mean global state: improvement (risperidone) in the intervention groups was 0.98 standard deviations lower (1.45 to 0.51 lower)

<sup>&</sup>lt;sup>1</sup> Substantial to considerable heterogeneity

<sup>&</sup>lt;sup>2</sup> Events<300

<sup>&</sup>lt;sup>3</sup> N<400

<sup>&</sup>lt;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>&</sup>lt;sup>5</sup> Moderate heterogeneity

<sup>&</sup>lt;sup>6</sup> Substantial heterogeneity

<sup>&</sup>lt;sup>7</sup> In RUPPRISPERIDONE2001 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>&</sup>lt;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>&</sup>lt;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>&</sup>lt;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

		Q	uality assess	ment				Sun	nmary of	Finding	S
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study e	vent rates (%)	Relative	Anticipa	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% CI)
Positive	treatmer	nt response	(risperidor	e or aripi	prazole) (a	ssessed with: Dich	notomous	: Positive treatment resp	onse (>25%	% improve	ement on ABC-Irritability) or
Dichotomous	: Positive tre	eatment response	(>25% improve	ment on ABC-	Irritability & 'm	uch improved/very	/ improve	d' on CGI-improvement))	)		
164 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>1,2</sup>	31/83 (37.3%)	44/81 (54.3%)	RR 1.46 (1.03 to	Study p	opulation
6-8 weeks						due to risk of bias, imprecision		(6.116.73)	2.06)	373 per 1000	172 more per 1000 (from 11 more to 396 more)
										Modera	te
										379 per 1000	174 more per 1000 (from 11 more to 402 more)
Positive	treatmer	nt response	risperidor	i <b>e)</b> (assessed	with: Dichotor	nous: Positive trea	atment re	sponse (>25% improvem	l ent on AB0	L C-Irritabilit	ty))
63 (1 study)		no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>2,3</sup>	14/34	15/29 (51.7%)	RR 1.26 (0.74 to	Study p	opulation
6 weeks	bias			00000		due to imprecision	( / 0 /	(6.11.76)	2.14)	412 per 1000	<b>107 more per 1000</b> (from 107 fewer to 469 more)
										Modera	te
										379 per	99 more per 1000

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101 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision		29/52 (55.8%)	RR 1.61 (1.02 to 2.53)	347 per 1000 Modera	212 more per 1000 (from 7 more to 531 more)  te  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; Bet	tter indicated by lower va	lues)	1	
63 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE⁴ due to imprecision	34	29	N/A	N/A	The mean irritability (risperidone) in the intervention groups was <b>0.52 standard deviations</b> lower (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	indicated l	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> lower (0.46 lower to 0.32 higher)
Stereoty	⊣ /pic beha	⊥ ıviour (aripi <sub>l</sub>	orazole) (mea	I asured with: Al	l berrant Behavi	I iour Checklist (AB0	L C): Stered	otypic behaviour (Change	e Score); B	etter indic	ated 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 0.55 standard deviations lower (0.95 to 0.15 lower)
Hyperac	tivity (ar	ipiprazole) (	measured with: A	Aberrant Behav	iour Checklist	(ABC): Hyperactiv	ity (Char	nge Score); Better indica	ted by lowe	er 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 hyperactivity (aripiprazole) in the intervention groups was <b>0.53 standard deviations</b>

											lower (0.93 to 0.14 lower)
Inappro	priate Sp	eech (aripip	razole) (mea	sured with: Abo	errant Behavio	our Checklist (ABC	): Inappro	opriate Speech (Chan	ge Score); Be	tter indica	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 LOW¹,5 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> lower (0.65 lower to 0.14 higher)
Global s	state: Pos	sitive treatm	ent respon	Se (assessed	with: Dichotor	nous: Positive trea	itment res	sponse ( 'much improv	/ed/very impro	oved' on C	CGI-improvement))
64 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊝⊝ LOW³	5/34 (14.7%)	5/30 (16.7%)	<b>RR 1.13</b> (0.36 to	Study p	opulation
6 weeks	bias	,				due to imprecision	(		3.54)	147 per 1000	<b>19 more per 1000</b> (from 94 fewer to 374 more)
										Modera	te
										147 per 1000	19 more per 1000 (from 94 fewer to 373 more)
Global s	severity (ı	risperidone	or aripipraz	z <b>ole)</b> (measu	red with: Clini	L cal Global Impress	ion Scale	e (CGI-S): Severity (Er	ndpoint or Ch	ange Sco	res); 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	⊕⊖⊖ <b>VERY LOW</b> <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 0.09 standard deviations lower (0.41 lower to 0.24 higher)
Global s	everity (	risperidone)	(measured with	: Clinical Globa	l al Impression	L Scale (CGI-S): Se	L verity; Be	tter indicated by lower	· values)		
63 (1 study) 6 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW⁵ 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> higher (0.39 lower to 0.6 higher)

Global se	Global severity (aripiprazole) (measured with: Clinical Global Impression Scale (CGI-S): Severity (Change Scores); Better indicated by lower values)											
85 (1 study) 8 weeks			no serious indirectness	very serious <sup>5</sup>		⊕⊖⊖ VERY LOW <sup>1,5</sup> due to risk of bias, imprecision	41	44		N/A		The mean global severity (aripiprazole) in the intervention groups was 0.23 standard deviations lower (0.65 lower to 0.2 higher)

<sup>&</sup>lt;sup>1</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.

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

		Q	uality assessr	nent					Summa	ry of Findi	ngs
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study eve	` '	Relative	Anticipate	d absolute effects
(studies) Follow up	bias				bias	of evidence		With Continued antipscyhotic	effect (95% CI)	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-Irritability	and rated	as 'worse/v	ery much worse' on CGI-I)
		no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹	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	463 fewer per 1000 (from 231 fewer to 566 fewer)
										Moderate	
										646 per 1000	465 fewer per 1000 (from 233 fewer to 568 fewer)
Time to r	elapse a	after discont	inuation (in	weeks) (m	neasured with:	Time to relapse (i	n weeks); B	etter indicated b	y lower val	ues)	
(1 study)		no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² 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>

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<sup>&</sup>lt;sup>2</sup> Events<300

<sup>&</sup>lt;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>&</sup>lt;sup>4</sup> N<400

<sup>&</sup>lt;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)

											higher (0.11 to 1.82 higher)
Irritabili	<b>ty</b> (measured	d with: Aberrant E	Behaviour Checkl	ist (ABC): Irrit	ability & Agitat	ion; Better indicate	ed by lowe	er values)		ļ.	
24 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊝⊝ LOW³ due to imprecision	12	12	N/A	N/A	The mean irritability in the intervention groups was 0.74 standard deviations lower (1.58 lower to 0.09 higher)
Letharg	y/Social v	withdrawal (	measured with: A	berrant Beha	viour Checklist	(ABC): Lethargy 8	& Social W	/ithdrawal; Bet	ter indicated	by lower va	lues)
24 (1 study) 32 weeks		no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊖⊝ LOW³ due to imprecision	12	12	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was 0.58 standard deviations lower (1.4 lower to 0.24 higher)
Stereoty	pic beha	viour (measur	ed with: Aberrant	Behaviour C	hecklist (ABC):	Stereotypic Beha	viour; Bett	ter indicated by	/ lower value	s)	
24 (1 study) 32 weeks		no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊝⊝ LOW³ due to imprecision	12	12	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0.02 standard deviations</b> lower (0.82 lower to 0.78 higher)
Hyperac	ctivity (mea	asured with: Aber	rant Behaviour C	hecklist (ABC	): Hyperactivity	& Noncompliance	e; Better ir	ndicated by lov	ver values)		
24 (1 study) 32 weeks		no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊝⊝ LOW³ due to imprecision	12	12	N/A	N/A	The mean hyperactivity in the intervention groups was 0.23 standard deviations lower (1.03 lower to 0.58 higher)
Inappro	priate sp	eech (measure	d with: Aberrant I	Behaviour Ch	ecklist (ABC): I	nappropriate Spe	ech; Better	r indicated by I	ower values)		
24 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊖⊝ LOW³ due to imprecision	12	12	N/A	N/A	The mean inappropriate speech in the intervention groups was 0 standard deviations higher

										(0.8 lower to 0.8 higher)			
<sup>1</sup> Events<300	Events<300												
<sup>2</sup> N<400	<sup>2</sup> N<400												
<sup>3</sup> N<400 and 9	<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)												

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

		Q	uality assess	ment				Su	mmary of	Finding	IS .
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall	Study	event rates (%)	Relative	Anticipa	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Risperidone versus haloperidol for behaviour that challenges as an indirect outcome	effect (95% CI)	Risk with Control	Risk difference with Risperidone versus haloperidol for behaviour that challenges as an indirect outcome (95% CI)
Behaviou	ır that	<b>challenges</b> (r	neasured with: A	Aberrant Behav	viour Checklist	(ABC): Total; Be	etter indi	icated 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	15	13	N/A	N/A	The mean behaviour that challenges in the intervention groups was

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

## 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			;	Summary o	f Findings	;
(studies)	Risk of bias	Inconsistency	Indirectness	Imprecision		Study ev (%)	ent rates	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	⊕⊕⊝⊝ <b>LOW</b> <sup>1</sup>	7/19 (36.8%)	9/19 (47.4%)	<b>RR 1.29</b> (0.6 to	Study po	pulation	
5 weeks						due to imprecision	,	,	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	⊕⊝⊝ VERY LOW <sup>1,2</sup>	5/20 (25%)	10/19 (52.6%)	RR 2.11 (0.88 to	Study population		
5 weeks		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,				due to risk of bias, imprecision	(==72)	(====,	5.03)	250 per 1000	277 more per 1000 (from 30 fewer to 1000 more)	
o wooks											,	
o wooks										Moderate	,	

## 1.11.7 Cognitive 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 assess	ment				Sun	nmary of	Findin	gs
Participants		Inconsistency	Indirectness	Imprecision			Study	event rates (%)		Antici	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% CI)
Behavio	ur that o	challenges (m	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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	20	20	N/A	N/A	The mean behaviour that challenges in the intervention groups was 1.93 standard deviations lower (2.69 to 1.16 lower)
<sup>1</sup> N<400		1	•	•					•		

# 1.11.8Methylxanthines 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	indings	5
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study ( With Control	weet rates (%)  With Combined methylxanthine and antipsychotic versus combined antipsychotic and placebo for behaviour that challenges as a direct outcome	Relative effect (95% CI)	Anticipo Risk with Control	Risk difference with Combined methylxanthine and antipsychotic versus combined antipsychotic and placebo for behaviour that challenges as a direct outcome (95% CI)
40 (1 study)	no serious risk of bias			klist (ABC): Irr	itability & Agit	ation; Better indice  ⊕⊕⊕⊖  MODERATE¹  due to  imprecision	cated by	lower values)	N/A	N/A	The mean irritability in the intervention groups was 1.71 standard deviations lower

											(2.44 to 0.97 lower)
Lethargy	/ & Soci	al Withdraw	/al (measured v	with: Aberrant	Behaviour Che	ecklist (ABC): Let	hargy 8	& 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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	20	20	N/A	N/A	The mean lethargy & social withdrawal in the interventio groups was 1.69 standard deviations lower (2.42 to 0.96 lower)
Stereoty	pic Beh	aviour (meas	ured with: Aberra	ant Behaviour	Checklist (AB	C): Stereotypic B	ehaviou	ır; 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	⊕⊕⊖ MODERATE¹ due to imprecision	20	20	N/A	N/A	The mean stereotypic behaviour in the intervention groups was 1.55 standard deviations lower (2.27 to 0.83 lower)
Hyperac	tivity (me	easured with: Abe	errant Behaviour	Checklist (AB	BC): Hyperactiv	vity & Noncomplia	ınce; B	etter 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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	20	20	N/A	N/A	The mean hyperactivity in the intervention groups was 1.14 standard deviations lower (1.81 to 0.47 lower)
Inapprop	oriate S <sub>I</sub>	peech (measur	red with: Aberrar	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	⊕⊕⊕⊖ MODERATE¹ due to imprecision	20	20	N/A	N/A	The mean inappropriate speech in the intervention groups was 2.1 standard deviations lower (2.89 to 1.31 lower)
<sup>1</sup> N<400		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

		Qı	uality assessme	ent				S	ummary of	f Findings	;
-	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality	Study ev	ent rates (%)	Relative	Anticipate	ed absolute effects
(studies) Follow up					bias	of evidence	With Placebo	With Opioid antagonists	effect (95% CI)	Risk with Placebo	Risk difference with Opioid antagonists (95% CI)
Global po		<del>-</del>	nse for beha	viour that	challenge	S (assessed with: [	Dichotomo	us measure of 'n	nuch improve	ed/very impi	roved' on Clinical Global
	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1</sup>	7/18 (38.9%)	13/23 (56.5%)	<b>RR 1.45</b> (0.74 to	Study pop	oulation
6 weeks		,				due to imprecision		` ,	2.87)	389 per 1000	<b>175 more per 1000</b> (from 101 fewer to 727 more)
										Moderate	Ļ
										389 per 1000	<b>175 more per 1000</b> (from 101 fewer to 727 more)
<sup>1</sup> Events<300	and 95% CI c	rosses both line of r	no effect and meas	ure of appreci	able benefit or l	harm (RR 0.75/1.25	5)		1		1

# 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 assess	ment		Summary of Findings				
Participant (studies) Follow up	Risk of bias	Inconsistency	Indirectness	•	Overall quality of evidence	With	With Selective	effect	Anticip Risk with	Risk difference with Selective 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): Irri	tability & Agita	tion; Better indica	ated 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	⊕⊕⊝⊝ LOW¹ due to imprecision	46	43	N/A	N/A	The mean irritability in the intervention groups was 0.09 standard deviations lower (0.51 lower to 0.32 higher)
Letharg	y/Social	withdrawal	(measured with:	Aberrant Beha	aviour Checklis	st (ABC): Letharg	y & So	cial Withdrawal; Better indic	ated by low	er values	)
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	46	43	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was 0.05 standard deviations lower (0.46 lower to 0.37 higher)
Stereoty	ypic beh	<b>aviour</b> (measu	red with: Aberra	nt Behaviour C	hecklist (ABC)	): Stereotypic Bel	naviour	; Better indicated by lower v	values)	1	
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	46	43	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0 standard deviations higher</b> (0.42 lower to 0.42 higher)
Hyperac	ctivity (me	easured with: Abe	rrant Behaviour	Checklist (ABC	): Hyperactivi	ty & Noncompliar	nce; Be	tter indicated by lower value	es)	<u>.</u>	<del> </del>
88 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	45	43	N/A	N/A	The mean hyperactivity in the intervention groups was 0.19 standard deviations lower (0.61 lower to 0.22 higher)
Inappro	priate sp	peech (measure	ed with: Aberran	t Behaviour Ch	necklist (ABC):	Inappropriate Sp	eech; I	Better indicated by lower va	lues)	1	1
89	no	no serious	no serious	very	undetected	$\oplus\oplus\ominus\ominus$	46	43	N/A	N/A	The mean inappropriate

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 0.22 standard deviations lower (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 I	no effect and me	easure of appre	eciable benefit	or harm (SMD -0	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				Sum	nmary of	Finding	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 Thai massage and sensory integration therapy versus sensory integration therapy only for behaviour that challenges as a direct outcome	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-ı	Teacher-rated behaviour that challenges (measured with: Conners Teacher Rating Scales (CTRS): Conduct problem; Better indicated 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	⊕⊕⊖⊝ LoW¹ 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 lower</b> (0.73 lower to 0.28 higher)			
Teacher-i	rated be	haviour that	tchallenge	<b>S</b> (measured	with: Conners	Teacher Rating S	cales (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 0.56 standard deviations lower (1.08 to 0.04 lower)
Teacher	-rated be	ehaviour tha	t challenge	S (measured	with: Conners	Teacher Rating S	Scales (CTRS): Inattenti	on-passivity; Better in	dicated	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	⊕⊕⊖⊝ LoW¹ 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 lower</b> (0.87 lower to 0.15 higher)
Teacher	-rated be	ehaviour tha	t challenge	S (measured	with: Conners	Teacher Rating S	Scales (CTRS): Hyperac	tivity index; Better inc	licated b	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	⊕⊕⊝ LOW¹ 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 lower</b> (0.91 lower to 0.11 higher)
Parent-r	ated beh	naviour that	_ challenges	(measured w	ith: Conners P	arent Rating Scal	es (CPRS): Conduct pro	blem; Better indicate	d by low	rer values)
60 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊝⊖ VERY LOW¹,3 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 lower</b> (0.61 lower to 0.41 higher)
Parent-r	ated beh	naviour that	 challenges	(measured w	ith: Conners P	arent Rating Scal	es (CPRS): Learning Pr	oblem; Better indicate	d 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 lower</b> (0.72 lower to 0.29 higher)

Parent-r	ated bel	naviour that	challenges	(measured w	ith: Conners P	arent Rating Scal	es (CPI	RS): Psychosomatic	c; 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	⊕⊖⊝ <b>VERY LOW</b> <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 higher</b> (0.44 lower to 0.57 higher)
Parent-r	ated bel	naviour that	challenges	(measured w	ith: Conners P	arent Rating Scal	es (CPI	RS): Impulsivity-hyp	peractivity; Better i	ndicated	by lower values)
60 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊝ <b>VERY LOW</b> <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> lower (1.02 lower to 0.01 higher)
Parent-r	ated bel	naviour that	challenges	(measured w	ith: Conners P	arent Rating Scal	es (CPI	RS): Anxiety; Better	indicated by lowe	r values)	
60 (1 study) 8 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊝ <b>VERY LOW</b> <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> lower (0.71 lower to 0.3 higher)
Parent-r	ated bel	naviour that	challenges	(measured w	ith: Conners P	arent Rating Scal	es (CPI	RS): Hyperactivity;	Better indicated by	/ 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 LOW¹,3 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> lower (0.75 lower to 0.27 higher)
Parent-r	ated sle	ep-related p	roblems (me	easured with: \$	Sleep Diary (Sl	D): Sleep behavio	ur; Bett	er indicated by low	er values)		
60 (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,	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			(1.04 to 0.01 lower)
<sup>2</sup> N<400	performanc	e and response b		`	,	as outcome	measure parent-rated and parents

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

	-				•	•			•		
		Q	uality assess	ment				Sumi	nary of F	inding	S
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)		Anticip	ated absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Acupuncture/Electro- acupuncture versus sham acupuncture/electro- acupuncture for behaviour that challenges as an indirect outcome	(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% CI)
Irritability	(measur	ed with: Aberrant	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 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 irritability in the intervention groups was <b>0.18 standard deviations higher</b> (0.36 lower to 0.71 higher)
Lethargy	/Social	withdrawal	(measured wit	h: Aberrant Be	ehaviour Check	list (ABC): Leth	argy & S	Social Withdrawal; Better indica	ated by low	er value	s)
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 lethargy/social withdrawal in the intervention groups was 0.02 standard deviations lower (0.56 lower to 0.51 higher)
Stereotyp	oic 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	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				'	due to imprecision, publication bias					groups was 0.05 standard deviations higher (0.48 lower to 0.58 higher)
Hyperact	t <b>ivity</b> (m	easured with: Ab	errant Behaviou	ur Checklist (A	BC): Hyperacti	vity & Noncomp	liance;	Better indicated by lower value	es)		
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</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 lower</b> (0.54 lower to 0.52 higher)
Inapprop	riate s	peech (measu	red with: Aberra	ant Behaviour	Checklist (ABC	): Inappropriate	Speed	h; Better indicated by lower va	lues)	•	
55 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	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 0.14 standard deviations lower (0.68 lower to 0.39 higher)
<sup>1</sup> N<400 and <sup>2</sup> High risk of	95% CI co selective	I rosses both line o reporting bias as	f no effect and trial protocol fo	measure of ap r WONG2010	ppreciable bene B states that fo	ı efit or harm (SM llow-up measur	D -0.5/ ements	0.5) will be taken but these are no	t reported	1	1

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

		Qua	ality assessr	ment				Sumr	nary of F	inding	s
-	Risk of bias	Inconsistency	Indirectness	_	bias	quality of	With	With Acupuncture/electro-	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% CI)
Behaviou	Behaviour that challenges (measured with: Aberrant Behaviour Checklist (ABC)							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 LOW¹,² due to risk of bias, imprecision	18	18	N/A	N/A	The mean behaviour that challenges in the intervention groups was  0.3 standard deviations higher (0.36 lower to 0.95 higher)
Irritabilit	<b>y</b> (measu	red with: Aberran	t Behaviour Ch	ecklist (ABC):	Irritability (Cl	nange Score);	Better i	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 higher</b> (0.24 lower to 1.08 higher)
Lethargy	/Socia	withdrawa	(measured wi	th: Aberrant B	ehaviour Che	ecklist (ABC): L	ethargy	(Change Score); Better indicate	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 lethargy/social withdrawal in the intervention groups was 0.23 standard deviations higher (0.42 lower to 0.89 higher)
Stereoty	pic ber	aviour (meas	ured with: Abe	rrant Behaviou	ır Checklist (A	ABC): Stereoty	py (Cha	inge Score); Better indicated by	lower value	es)	
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY LOW¹.² due to risk of bias, imprecision	18	18	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0.29 standard deviations</b> higher (0.37 lower to 0.94 higher)
Hyperact	tivity (m	easured with: Ab	errant Behavio	ur Checklist (A	ABC): Hypera	ctivity (Change	Score	; Better indicated by lower value	es)	ļ	
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW¹.² due to risk of bias, imprecision	18	18	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.06 standard deviations lower</b> (0.72 lower to 0.59 higher)
Inapprop	oriate s	peech (measu	red with: Aberr	ant Behaviour	Checklist (Al	BC): Inappropr	iate Sp	eech (Change Score); Better ind	icated by lo	ower val	ues)
36	serious <sup>1</sup>	no serious	no serious	very	undetected	$\oplus \ominus \ominus \ominus$	18	18	N/A	N/A	The mean inappropriate speech

(1 study) 8 weeks	inconsistency	indirectness	serious <sup>2</sup>	VERY LOW <sup>1,2</sup>	in the intervention groups was <b>0.58 standard deviations</b>
				due to risk of bias, imprecision	higher (0.09 lower to 1.25 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind and potential for care confounds as the conventional education programme differed for each participant which may introduce bias. There was also an unclear risk of detection bias as although all outcomes were measured by blinded assessors, some outcomes involved input from parents who were not blind to treatment allocation or confounding variables and systematic review from which data was extracted does not report which outcome measures relied on non-blind parental report

#### 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	mmary of	Finding	js
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study 6	event rates (%)	Relative	Anticipa	ted 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% CI)
Behaviou	ir that c	hallenges (P	arent-rated)	(measured w	ith: Aberrant E	ehaviour Checklis	t (ABC):	Total (change score); E	Better indica	ted by lov	ver values)
77 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ 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 lower</b> (0.59 lower to 0.33 higher)
Behaviou	ır that c	hallenges (To	eacher-rate	<b>d)</b> (measured	with: Aberran	t Behaviour Check	list (ABC	c): Total (change score)	; Better indi	cated by	ower values)
65 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² 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

<sup>&</sup>lt;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)

											(0 to 1.01 higher)
rritabilit	y (Paren	ı <b>t-rated)</b> (meas	sured with: Aberr	ant Behaviour	Checklist (ABC	LC): Irritability & Ag	itation (e	endpoint and ch	ange scores); Bette	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	⊕⊕⊕⊝ MODERATE² due to imprecision	57	76	N/A	N/A	The mean irritability (parent rated) in the intervention groups was  0.11 standard deviations lower  (0.45 lower to 0.24 higher)
rritabilit	y (Teach	ner-rated) (me	easured with: Abe	errant Behavio	our Checklist (A	BC): Irritability & A	Agitation	(change score	s); 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	⊕⊕⊝ LOW¹ due to imprecision	26	39	N/A	N/A	The mean irritability (teacher-rated) in the intervention groups was <b>0.2 standard deviations higher</b> (0.3 lower to 0.69 higher)
Lethargy	/ (Parent	t-rated) (meas	ured with: Aberra	nt Behaviour (	Checklist (ABC	): Lethargy & Soc	ial Withd	rawal (endpoin	t and change score	s); 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	⊕⊕⊕⊝ MODERATE² due to imprecision	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: Aberran	t Behaviour Checl	dist (ABC	C): Lethargy &	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	⊕⊕⊕⊝  MODERATE²  due to imprecision	26	22	N/A	N/A	The mean lethargy (teacher rated porcine secretin) in the intervention groups was 0.74 standard deviations 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	⊕⊕⊝⊝ LOW¹ 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> <b>higher</b> (0.56 lower to 0.67 higher)
Stereoty values)	pic beha	aviour (Pare	nt-rated) (me	asured with:	Aberrant Behav	iour Checklist (AE	BC): Ster	eotypic Behavi	our (endpoint and cl	nange sc	ores); 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	⊕⊕⊕⊝ <b>MODERATE</b> <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> higher (0.25 lower to 0.45 higher)
Stereoty	pic beha	aviour (Teac	<b>her-rated)</b> (r	neasured with	n: Aberrant Beh	aviour Checklist (	ABC): St	ereotypic Beha	viour (change score	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	⊕⊕⊝ LOW¹ 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 (Pa	arent-rated)	(measured with:	Aberrant Beh	aviour Checklis	t (ABC): Hyperact	ivity & N	oncompliance (	endpoint and chang	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	⊕⊕⊕⊝ MODERATE² due to imprecision	57	76	N/A	N/A	The mean hyperactivity (parent-rated) in the intervention groups was <b>0.01 standard deviations lower</b> (0.36 lower to 0.34 higher)
Hyperac	tivity (Te	eacher-rated	(measured with	n: Aberrant Be	ehaviour Check	list (ABC): Hypera	activity &	Noncomplianc	e (change scores);	Better inc	licated by lower values)
65 (1 study) 4 weeks	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ <b>MODERATE</b> <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> higher (0.03 to 1.04 higher)
napprop ralues)	riate sp	eech (Paren	<b>t-rated)</b> (mea	sured with: Ab	perrant Behavio	our Checklist (ABC	): Inapp	ropriate Speech (end	point and cha	inge score	es); Better indicated by lower
31 2 studies) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² 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> lower (0.75 to 0.04 lower)
napprop 55 1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	Aberrant Behav	wiour Checklist (AE  ⊕⊕⊖⊝  LOW¹  due to  imprecision	26	opropriate Speech (cl	nange scores	); Better in	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 asses	ssment			\$	Summary	of Findings	5
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	evidence	Study ever With Attention- placebo	With Hyperbaric oxygen treatment	effect (95% CI)	Anticipated Risk with Attention- placebo	Risk difference with Hyperbaric oxygen treatment (HBOT) (95% CI)

							control	(HBOT)		control	
<b>Behavio</b> by lower value		challenges	(measured with	n: Aberrant Be	I haviour Checklis	t (ABC): Total or Beh	I avioural obs	servation: Chall	enging 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 LOW¹,2,3 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 deviations lower</b> (0.59 lower to 0.24 higher)
Behavio	ur that	challenges	direct ou	itcome) (i	measured with: A	berrant Behaviour Ch	necklist (AB	C): Total; Bette	r indicated b	y lower value	es)
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW² 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 deviations higher</b> (0.48 lower to 0.57 higher)
Behavio	our that	challenges	s (indirect	outcome	) (measured with	n: Behavioural observ	ation: Chall	enging behavio	urs (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 deviations lower</b> (1.23 lower to 0.15 higher)

56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ <b>LoW</b> <sup>2</sup> due to imprecision	26	30	N/A	N/A	The mean irritability in the intervention groups was  0.11 standard deviations lower  (0.64 lower to 0.41 higher)
Letharg	y/Socia	al withdraw	al (measured w	vith: Aberrant	Behaviour Check	klist (ABC): Lethargy; B	Better ind	icated by lower	values)	I	
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ <b>LoW</b> <sup>2</sup> due to imprecision	26	30	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was 0.06 standard deviations higher (0.46 lower to 0.59 higher)
Stereoty	<b>ypy</b> (mea	sured with: Aberra	ant Behaviour Cl	hecklist (ABC)	): Stereotypy; Be	tter indicated by lower	values)		<b>- 1</b>	- 1	
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ <b>LoW</b> <sup>2</sup> due to imprecision	26	30	N/A	N/A	The mean stereotypy in the intervention groups was  0.17 standard deviations higher  (0.36 lower to 0.7 higher
Hyperac	<b>ctivity</b> (r	neasured with: Ab	Derrant Behaviou	ır Checklist (A	ABC): Hyperactivi	ty or Behavioural obse	rvation: I	Hyperactivity (c	hange score)	Better indic	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>	⊕⊕⊖⊝ <b>LOW</b> <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 indicated	l by lower valu	ıes)	
no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW² due to imprecision	26	30	N/A	N/A	The mean hyperactivity (direct outcome) in the intervention groups was <b>0.12 standard deviations higher</b> (0.41 lower to 0.64 higher)
ctivity (	indirect ou	tcome) (mea	asured with: B	Behavioural observ	vation: Hyperactivity (d	change so	core); Better in	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 deviations lower</b> (0.72 lower to 0.63 higher)
priate	speech (meas	sured with: Aber	rant Behaviou	r Checklist (ABC)	: Inappropriate Speecl	h; Better	indicated by lo	wer values)		
no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW² due to imprecision	26	30	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>0.24 standard 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 inconsistency risk of bias no serious risk of bias no serious inconsistency risk of bias no serious inconsistency risk of bias no serious risk of serious risk of no serious inconsistency risk of no serious risk of no se	no serious inconsistency risk of bias  no serious inconsistency indirectness  risk of bias  no serious inconsistency indirectness  no serious inconsistency indirectness  no serious inconsistency indirectness  priate speech (measured with: Aberrance inconsistency indirectness inconsistency indirectness inconsistency indirectness indirectness indirectness indirectness indirectness	no serious risk of bias  no serious inconsistency indirectness serious²  ctivity (indirect outcome) (measured with: Elementary indirectness serious inconsistency indirectness serious²  no serious risk of bias  no serious inconsistency indirectness serious²  priate speech (measured with: Aberrant Behavious inconsistency inconsistency indirectness serious²  no serious inconsistency indirectness serious²	no serious inconsistency indirectness serious² undetected  ctivity (indirect outcome) (measured with: Behavioural observable)  no serious inconsistency indirectness serious² reporting bias strongly serious² strongly suspected³  priate speech (measured with: Aberrant Behaviour Checklist (ABC)  no serious inconsistency indirectness serious very serious² undetected inconsistency serious very serious² undetected inconsistency indirectness very serious² undetected	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 bias   no serious serious risk of bias   no serious risk of   no seriou	no serious risk of bias  no serious inconsistency risk of bias  no serious inconsistency risk of bias  no serious risk of bias  no serious indirectness wery serious² undetected LOW² due to imprecision  no serious risk of bias  no serious inconsistency risk of bias  no serious risk of bias  no serious indirectness wery serious² reporting bias strongly suspected ³ due to imprecision, publication bias  priate speech (measured with: Aberrant Behaviour Checklist (ABC): Inappropriate Speech; Better no no serious inconsistency risk of ris	no serious risk of bias   no serious inconsistency   no serious serious²   undetected   ⊕⊕⊖⊖   26   30	no serious risk of bias   no serious   no serious   no serious   serious²   undetected   ⊕⊕⊖   LOW²   due to imprecision     26   30   N/A	serious risk of bias inconsistency indirectness serious²

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				Sumi	mary of F	indings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	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 indicated by I			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	⊕⊕⊝ LOW¹ due to imprecision	15	25	N/A	N/A	The mean maladaptive behaviours composite in the intervention groups was <b>0.17 standard deviations higher</b> (0.47 lower to 0.81 higher)
Arousal values)	Regul	ation Prob	lems (measu	red with: Perva	asive Develop	ment 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	⊕⊕⊝ LOW¹ due to imprecision	15	25	N/A	N/A	The mean arousal regulation problems in the intervention groups was  0.2 standard deviations higher (0.44 lower to 0.85

Aggressiveness (measured with: Pervasive Development Disorder Behavior I	r Inventory (PDDBI): Aggressiveness; Better indicate		
		d by lower values)	
(1 study) serious inconsistency indirectness serious du	⊕⊕⊖⊝ 15 25  LOW¹ due to mprecision	N/A N/A	The mean aggressiveness in the intervention groups was <b>0.2 standard 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

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

		Qı	uality assessm	ent					Summa	ary of Fin	dings
` ,	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study ev (%)	ent rates	Relative effect	Anticipate	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% CI)
Irritability	(measured	with: Aberrant Beha	viour Checklist (A	.BC): Irritability	& Agitation; B	etter indicated by I	ower valu	es)			
24 (1 study) 12 weeks	no serious risk of bias		no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	12	12	N/A	N/A	The mean irritability in the intervention groups was <b>0.09 standard deviations lower</b> (0.89 lower to 0.71 higher)
Lethargy	Social w	ithdrawal (mea	sured with: Aberra	ant Behaviour	Checklist (ABC	): 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 indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to	12	12	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was

						imprecision					0.28 standard deviations lower (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	s)	
24 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ Low¹ due to imprecision	12	12	N/A	N/A	The mean stereotypic behaviour in the intervention groups was <b>0.81 standard deviations lower</b> (1.65 lower to 0.03 higher)
Hyperac	tivity (meas	sured with: Aberra	nt Behaviour Ched	cklist (ABC): H	lyperactivity & N	oncompliance; B	etter indic	ated by low	er values)	<u> </u>	
24 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ Low¹ due to imprecision	12	12	N/A	N/A	The mean hyperactivity in the intervention groups was <b>0.42 standard deviations lower</b> (1.23 lower to 0.39 higher)
Inappro	priate spe	ech (measured v	with: Aberrant Beh	naviour Check	list (ABC): Inapp	ropriate Speech;	Better in	dicated by l	ower values)	<u> </u>	
24 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	12	12	N/A	N/A	The mean inappropriate speech in the intervention groups was <b>0.68 standard deviations</b> lower (1.51 lower to 0.14 higher)
External	_ l <b>izing</b> (meas	ured with: Behavio	or Assessment Sy	stem for Child	lren (BASC): Ex	L ternalizing; Better	· indicated	d 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	⊕⊕⊝ LOW¹ due to imprecision	12	12	N/A	N/A	The mean externalizing in the intervention groups was <b>0.44 standard deviations lower</b> (1.25 lower to 0.37 higher)
Behavio	ural symp	otoms (measure	ed with: Behavior A	Assessment S	ystem for Childr	en (BASC): Beha	vioral syr	nptoms; Be	tter indicated	by lower va	ilues)
23	no serious	no serious	no serious	very	undetected	$\oplus \oplus \ominus \ominus$	11	12	N/A	N/A	The mean behavioural

12 weeks						due to imprecision					groups was 0.24 standard deviations lower (1.06 lower to 0.58 higher)
24 (1 study) 12 weeks	no serious	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	en (BASC): Hypundetected	eractivity; Better in the second seco	ndicated 12	12	es) N/A	N/A	The mean hyperactivity in the intervention groups was 0.19 standard deviations lower (0.99 lower to 0.61 higher)
N<400 and	d 95% CI cross	es both line of no	effect and measure	e of appreciable	e benefot or ha	ırm (SMD -0.5/0.5)	)		1		1

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

		Q	uality assessn	nent					Summ	ary of Find	lings
<b>(</b> - · · · · · · · · · · · · · · · · · ·	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study eve	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% CI)
Total pro	blem s	COre (measured v	vith: Child Behavi	or Checklist 1.	5 - 5 (CBCL/1.	5-5): Total probler	n score; Bet	ter indicated	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	⊕⊖⊖ <b>VERY LOW</b> <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 lower</b> (0.99 lower to 0.66 higher)
Externalia	zing (me	easured 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)

Emotion	al regul	ation (measure	d with: Child Beha	avior Checklist	1.5 - 5 (CBCL/	1.5-5): Emotional	regulatior	n; Better indi	cated 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	⊕⊝⊝ <b>VERY LOW</b> <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 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 lowe	er values)	·		
23 (1 study) 13 weeks	serious <sup>1</sup>	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	13	10	N/A	N/A	The mean withdrawn in the intervention groups was <b>0.81 standard deviations lower</b> (1.67 lower to 0.05 higher)
Attentio	n proble	ems (measured v	with: Child Behavi	or Checklist 1.	5 - 5 (CBCL/1.5	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	⊕⊖⊖ <b>VERY LOW</b> <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 lower</b> (1.37 lower to 0.31 higher)
Aggress	ive beh	aviours (meas	ured with: Child B	ehavior Check	dist 1.5 - 5 (CB)	L CL/1.5-5): Aggres	sive beha	viours; Bette	er indicated b	y lower valu	es)
23 (1 study) 13 weeks	serious <sup>1</sup>	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	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)
Oppositi	ional De	fiant Disord	er (ODD) syı	mptoms (n	neasured with:	Child Behavior Ch	ecklist 1.	5 - 5 (CBCL/	′1.5-5): ODD	; Better indic	cated by lower values)
23 (1 study) 13 weeks	serious <sup>1</sup>	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	13	10	N/A	N/A	The mean oppositional defiant disorder (odd) symptoms in the intervention groups was <b>0.04 standard deviations</b> lower (0.87 lower to 0.78 higher)
<sup>1</sup> High risk o	f performan	ce and response	bias as intervention	on administrato	ors and participa	ants were non-blir	nd, and hi	gh risk of de	tection bias	as the outco	me assessor for this outcome

measure was not blinded.

<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)

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

		Qı	ıality assessn	nent				S	ummary c	f Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study event r	ates (%)	Relative	Anticipated a	bsolute 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% CI)
Irritability	(measure	d with: Aberrant B	ehaviour Checkl	ist (ABC): Irrita	ability & Agitati	on; Better indica	ated by lower va	lues)			
10 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>1</sup> due to imprecision	24	23	N/A	N/A	The mean irritability in the intervention groups was <b>0.1 standard 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 ind	dicated 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	⊕⊕⊖⊝ LOW¹ due to imprecision	24	23	N/A	N/A	The mean lethargy/social withdrawal in the intervention groups was 0.08 standard deviations lower (0.65 lower to 0.49 higher)
Stereotyp	oic Beha	aviour (measure	ed with: Aberrant	t Behaviour Ch	necklist (ABC):	Stereotypic Bel	naviour; Better i	ndicated by lowe	r values)	1	
47 (1 study) 10 weeks	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1</sup> due to	24	23	N/A	N/A	The mean stereotypic behaviour in the intervention groups

Autism: the management and support of children and young people on the autism spectrum (March 2013)

(1 study)   10 weeks   risk of bias		bias					imprecision					was 0.02 standard deviations lower (0.59 lower to 0.55 higher)
(1 study) 10 weeks risk of bias inconsistency risk of bias	Hyperact	tivity (me	easured with: Aber	rant Behaviour C	hecklist (ABC	): Hyperactivity	& Noncompliar	nce; Better inc	licated by lower va	ues)	·	
47   no   no serious   no serious   no serious   no serious   inconsistency   no serious   no se	(1 study)	serious risk of				undetected	LOW <sup>1</sup> due to	24	23	N/A	N/A	0.22 standard deviations higher (0.35 lower to 0.8
(1 study) 10 weeks risk of bias inconsistency indirectness serious due to imprecision  LOW¹ due to imprecision  LOW¹ due to imprecision  0.21 standard deviations lower to 0.79 lower to 0.50 for the intervention of the interven	Inapprop	oriate Sp	peech (measure	ed with: Aberrant	Behaviour Ch	ecklist (ABC): I	Inappropriate Sp	eech; Better	indicated by lower	values)	<u>.</u>	
	(1 study)	serious risk of			,	undetected	LOW <sup>1</sup> due to	24	23	N/A	N/A	inappropriate speech in the intervention groups was

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

			Quality assess	sment				Sui	mmary of I	indings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision			Study ev With Placebo	vent rates (%) With Dimethylglycine	effect	•	Risk difference with Dimethylglycine (95% CI)	
Positive t	Positive treatment response (assessed with: Parental report)											

38 (1 study)		no serious inconsistency	no serious indirectness		⊕⊝⊝ VERY LOW <sup>1,2</sup>	10/19 (52.6%)	11/19 (57.9%)	<b>RR 1.1</b> (0.62 to	Study po	pulation
4 weeks	non or side	eo.ioisioney		suspected <sup>2</sup>	due to imprecision, publication bias	(02.070)	(61.676)	1.95)	1000	53 more per 1000 (from 200 fewer to 500 more)
									Moderate	
									526 per 1000	53 more per 1000 (from 200 fewer to 500 more)

<sup>&</sup>lt;sup>1</sup> Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25)

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

ı		Q	uality assessn	nent				5	Summary	of Findin	gs
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 Multivitamin and mineral supplement	effect (95% CI)	Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% CI)
Hyperact	ivity imp	provement (me	easured with: Pare	ent Global Imp	ressions-Revi	sed (PGI-R): Hype	activity in	nprovement; Better	indicated by	y lower val	ues)
104 (1 study) 13 weeks	no serious risk of bias		no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	51	53	N/A	N/A	The mean hyperactivity improvement in the intervention groups was <b>0.6 standard deviations higher</b> (0.2 to 0.99 higher)
Tantrumi	ming imp	provement (me	easured with: Par	ent Global Im	pressions-Revi	ised (PGI-R): Tantr	umming i	mprovement; Bette	r indicated b	y lower va	llues)
104 (1 study) 13 weeks	no serious risk of bias		no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	51	53	N/A	N/A	The mean tantrumming improvement in the intervention groups was 0.52 standard deviations higher

<sup>&</sup>lt;sup>2</sup> High risk of selective reporting bias as data could not be extracted for the Aberrant Behavior Checklist (Irritability, Lethargy/Social Withdrawal, Stereotypic Behavior, Hyperactivity and Inappropriate Speech subscales) or the Maladaptive Behavior Domain of the Vineland Adaptive Behavior Scale and potential conflict of interest as trial funded by manufacturer of supplement

					(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% CI)
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	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	reporting bias strongly	⊕⊕⊖⊝ LOW <sup>1,2</sup>	11/28	17/83 (20.5%)	RR 0.52 (0.28 to	Study po	ppulation
` ,	bias	,			suspected <sup>2</sup>	due to imprecision, publication bias	(00000)	(2000)	0.97)	393 per 1000	189 fewer per 1000 (from 12 fewer to 283 fewer)
										Moderate	e
										393 per 1000	189 fewer per 1000 (from 12 fewer to 283 fewer)
Positive	∟ parent-ra	ı ated treatme	⊥ nt response	l (assessed wi	l ith: Dichotomous r	l neasure of 'much i	improved/\	very improved' on Par	rent Global	Impression	n-Improvement (PGI-I))
	no serious	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	reporting bias	⊕⊕⊖⊝ <b>LOW</b> <sup>1,2</sup>	16/29 (55.2%)	25/83 (30.1%)	RR 0.55 (0.34 to	Study po	ppulation
` ,	bias	Inconsistency	munectness		suspected <sup>2</sup>	due to imprecision, publication bias	(33.276)	(30.176)	0.87)	552 per 1000	248 fewer per 1000 (from 72 fewer to 364 fewer)
										Moderate	<b>e</b>
										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	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	ment				s	ummary o	of Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study event ra	tes (%)	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% CI)
Parent-ra	ated beh	naviour that	challenges	(measured wit	h: Developme	ntal Behaviour Ch	ecklist (DBC): To	otal; Better indi	cated by lov	wer values)	
80 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ <b>LoW</b> ¹ due to imprecision	40	40	N/A	N/A	The mean parent- rated behaviour that challenges in the intervention groups was 0.06 standard deviations higher (0.38 lower to 0.5 higher)
Parent-ra	ated ber	naviour that	challenges	(measured wit	h: Developme	ntal Behaviour Ch	ecklist (DBC): To	otal; Better indi	cated by lov	wer values)	
80 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ 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	hecklist (DBC	c): Total; Better in	dicated by lo	ower values)	1
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> ¹ due to imprecision	40	40	N/A	N/A	The mean parent-rated behaviour that challenges in the intervention groups was  0.26 standard deviations higher  (0.18 lower to 0.7 higher)
Parent-r	ated bel	naviour that	challenges	(measured wi	th: Developme	ntal Behaviour C	hecklist (DBC	c): Total; Better in	dicated by lo	ower values)	
80 (1 study) 56 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ <b>LOW</b> <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean parent- rated behaviour that challenges in the intervention groups was 0.24 standard deviations higher (0.2 lower to 0.68 higher)
Teacher	-rated be	ehaviour tha	t challenge	<b>S</b> (measured	with: Developr	mental Behaviour	Checklist (DE	BC): 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	⊕⊕⊝ LOW¹ due to imprecision	40	40	N/A	N/A	The mean teacher- rated behaviour that challenges in the intervention groups was 0.16 standard deviations lower (0.6 lower to 0.28 higher)
Teacher	rated be	ehaviour tha	t challenge	S (measured	with: Developr	nental Behaviour	Checklist (DE	BC): Total; Better	indicated by	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	inconsistency	indirectness	serious <sup>1</sup>	I with: Developr	LOW <sup>1</sup> due to imprecision	Checklist (DI	BC): Total; Bett	er indicated	by lower value	rated behaviour that challenges in the intervention groups was 0.15 standard deviations lower (0.59 lower to 0.29 higher)
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝  MODERATE²  due to imprecision	40	40	N/A	N/A	The mean teacher- rated behaviour that challenges in the intervention groups was 0.04 standard deviations lower (0.48 lower to 0.39 higher)
Teacher-	rated b	ehaviour tha	at challenge	S (measured	with: Developr	nental Behaviour	Checklist (DI	BC): Total; Bett	er indicated	by 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	⊕⊕⊝⊝ <b>LOW</b> ¹ due to imprecision	40	40	N/A	N/A	The mean teacher- rated behaviour that challenges in the intervention groups was 0.09 standard deviations higher (0.35 lower to 0.53 higher)

Autism: the management and support of children and young people on the autism spectrum (March 2013)

### 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	ımmary o	f Findin	gs
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study 6	event rates (%)	Relative	Anticip	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	our (measured	with: Vineland A	daptive Behavi	our Scale (VAE	BS/VABS II): Adaptiv	e behavi	our composite score; E	Better indica	ated 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	⊕⊖⊖ <b>VERY LOW</b> <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 higher</b> (0.31 lower to 0.36 higher)
Daily livi	ng skills	(measured with	: Vineland Adapt	ive Behaviour	Scale (VABS/\	/ABS II): Daily living	skills; Be	etter 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  0.1 standard deviations higher  (0.23 lower to 0.43 higher)
Socializa	tion (mea	asured with: Vine	land Adaptive Be	ehaviour Scale	(VABS/VABS	I): Socialization; Bet	ter indica	ated by lower values)			
143	serious <sup>1</sup>	very serious <sup>2</sup>	no serious	serious <sup>3</sup>	undetected	$\oplus \ominus \ominus \ominus$	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 143 (2 studies) 12-104 weeks	serious <sup>1</sup>	(measured with: very serious <sup>2</sup>	vineland Adaptiv no serious indirectness	ve Behaviour S serious <sup>3</sup>	cale (VABS/VA undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2,3</sup> due to risk of bias, inconsistency,	70	ter indicated by lower v	values)	N/A	The mean communication in the intervention groups was 0.11 standard deviations higher

<sup>&</sup>lt;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 the outcome measure was based on interview with (non-blind) parent rather than direct observation

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

		Q	uality assessr	nent			Summary of Findings				gs		
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study 6	` '	Relative	Anticipa	ted absolute effects		
(studies) Follow up	bias				bias	quality of evidence	With With EIBI versus parent Control training for adaptive behaviour as a direct outcome		(95% CI)	Risk with Control	Risk difference with EIBI versus parent training for adaptive behaviour as a direct outcome (95% CI)		
Adaptive	Adaptive behaviour (measured with: Vineland Adaptive Behaviour Scale (VABS): Total; Better indicated by lower 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 adaptive behaviour in the intervention groups was <b>0.11 standard deviations higher</b> (0.64 lower to 0.85 higher)		

<sup>&</sup>lt;sup>2</sup> I-squared value indicates substantial to considerable heterogeneity

<sup>&</sup>lt;sup>3</sup> N<400

28 (1 study) 260 weeks	serious <sup>1</sup>	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	13	15	N/A	N/A	The mean daily living skills in the intervention groups was <b>0.03 standard deviations</b> lower (0.77 lower to 0.71 higher)
Socializa	<b>ation</b> (me	asured with: Vinel	and Adaptive Bel	naviour Scale	(VABS): Social	lization; Better inc	licated b	by lower values	)		
28 (1 study) 260 weeks	serious <sup>1</sup>	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	13	15	N/A	N/A	The mean socialization in the intervention groups was 0.12 standard deviations lower (0.86 lower to 0.63 higher)
Commur	nication	(measured with: \	/ineland Adaptive	Behaviour So	cale (VABS): C	ommunication; B	etter ind	licated by lower	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 higher</b> (0.47 lower to 1.02 higher)

<sup>&</sup>lt;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 although outcome assessors were blinded the outcome measure was based on interview with (non-blind) parent rather than direct observation

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

		Qı	uality assessn	nent			Summary of Findings					
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	bias	Overall quality of evidence	Study 6 With Control	With Home-based	Relative effect (95% CI)	Risk with Control	Risk difference with Home-based versus Centre-based EBI for adaptive behaviour as a direct outcome (95% CI)	
Socializa	Socialization (measured with: Vineland Adaptive Behaviour Scale (VABS): Socialization; Better indicated by lower values)											

<sup>&</sup>lt;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)

56 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝ LOW¹,2 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 lower</b> (1.17 to 0.09 lower)
Commur	nication	(measured with: \	/ineland Adaptive	e Behaviour Sc	cale (VABS): C	ommunication; E	Better indicated by lowe	r values)		
55 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 lower</b> (1 lower to 0.07 higher)
Adaptive	function	ning and ps	ychopathol	ogy (measur	ed with: Devel	opmental Behav	iour Checklist (DBC): T	otal; Better indica	ted by low	er 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 lower</b> (0.7 lower to 0.48 higher)

<sup>&</sup>lt;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, despite blinding outcome assessors, the outcome measure relies on interview with parent and parents were non-blind to group assignment and other potentially confounding factors and were also part of the intervention so problems with self-assessment

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

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

		Qı	uality assessn	nent				Summary of Findings				
•		Inconsistency	Indirectness	•	Publication		Study		Relative	Anticipated absolute effects		
(studies) Follow up	bias				bias	quality of evidence	With Control	With CBT for anxiety versus waitlist control for adaptive behaviour as an	effect (95% CI)	Risk with Risk difference with CBT for Control anxiety versus waitlist control for adaptive behaviour as an indirect		

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>13</sup> N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

								indirect outcome			outcome (95% CI)
Adaptive	behavi	our (self-car	<b>e)</b> (measured w	ith: Vineland A	daptive Behav	riour Scale (VAB	S): Daily	Living Skills; Better indic	ated by low	er values)	
40 (1 study) 16 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	20	20	N/A		The mean adaptive behaviour (slef-care) in the intervention groups was 0.63 standard deviations higher (0.01 lower to 1.26 higher)

<sup>&</sup>lt;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

## 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	nent				S	ummary c	of Findir	igs
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall	Study 6	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% CI)
Function	al emoti	ional develo	oment (clini	ician-rated	(measured	with: Functional	Emotion	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	⊕⊕⊖⊝ LOW¹ 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>

<sup>&</sup>lt;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)

32 (1 study) 13 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊝⊝⊝ VERY LOW¹,² 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> lower (0.9 lower to 0.49 higher)
Daily livi	ng skills	(PEBM) (mea	sured with: Vine	land Adaptive	Behaviour Sca	ale (VABS): Dail	y Living	Skills; Better indicated b	y lower val	ues)	
70 (1 study) 46 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 0.46 standard deviations higher (0.01 lower to 0.94 higher)
Daily livi	ng skills	(PEC) (measu	red with: Vinelar	nd Adaptive Be	ehaviour Scale	(VABS): Daily L	iving Sk	ills; Better indicated by	ower 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 0.14 standard deviations lower (0.61 lower to 0.34 higher)
Socializa	ation (PE	BM) (measured	with: Vineland A	Adaptive Behav	viour Scale (V	ABS): Socializati	on; Bett	er indicated by lower va	lues)		
70 (1 study) 46 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊝⊝⊝ <b>VERY LOW</b> <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 0.35 standard deviations higher (0.12 lower to 0.83 higher)
Socializa	ation (PE	(measured w	th: Vineland Ada	aptive Behavio	ur Scale (VAB	S): Socialization	Better	indicated by lower value	es)		1
68 (1 study) 46 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 lower</b> (0.74 lower to 0.21 higher)

70 (1 study) 46 weeks	serious <sup>3</sup>	(PEBM) (meas no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	ehaviour Scale undetected	(VABS): Comm  (H) (H) (H) (H)  VERY LOW <sup>1,3</sup> due to risk of bias, imprecision	35	on; Better indicated by l	ower values	N/A	The mean communication (pebm) in the intervention groups was  0.1 standard deviations higher  (0.37 lower to 0.57 higher)
68 (1 study) 46 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	aviour Scale (\u00ed	/ABS): Commur ⊕⊕⊖ LOW <sup>3,4</sup> due to risk of bias, imprecision	ication;	Better indicated by low 33	er values)	N/A	The mean communication (pec) in the intervention groups was 0.56 standard deviations lower (1.04 to 0.07 lower)

<sup>&</sup>lt;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)

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

		Qu	ality assess	ment		Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Overall quality of evidence	With	With Combined parent training and early intervention centre programme versus early intervention centre programme only for adaptive behaviour as a direct outcome	Relative effect (95% CI)	Anticip Risk with Control	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)

<sup>&</sup>lt;sup>2</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 so problems with self-assessment. There was also no independent reliability and validity data for the Thai-version of this outcome measure which was used in the study.

<sup>&</sup>lt;sup>3</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 the outcome assessor was a blinded clinician the measure is based on parental interview and simultaneous child observation and parents non-blind and involved in intervention

58 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>	undetected	⊕⊖⊖ VERY LOW¹1,2,3 due to risk of bias, indirectness, imprecision	28	30	N/A	N/A	The mean parent-reported adaptive behaviour (mixed asd & dd sample) in the intervention groups was <b>0.25 standard deviations higher</b> (0.27 lower to 0.77 higher)
Parent-re	eported	adaptive be	haviour (	mixed ASI	D & DD sa	mple) (measure	ed with:	Vineland Adaptive	Behaviour Scale (V	ABS): To	otal; Better indicated by lower
51 (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	28	N/A	N/A	The mean parent-reported adaptive behaviour (mixed asd & dd sample) in the intervention groups was <b>0.31 standard deviations higher</b> (0.24 lower to 0.87 higher)
Clinician	-rated a	daptive ber	aviour (m	nixed ASD	& DD sam	<b>ple)</b> (measured	with: E	ayley Behavior Rat	ing Scale (BRS): To	otal; Bett	er 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>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 higher</b> (0.12 lower to 0.93 higher)
Clinician	-rated a	daptive beh	aviour (n	nixed ASD	& DD sam	ple) (measured	with: E	ayley Behavior Rat	ing Scale (BRS): To	otal; Bett	er indicated by lower values)
47 (1 study) 108 weeks	no serious risk of bias	no serious inconsistency	serious <sup>2</sup>	serious <sup>4</sup>	undetected	⊕⊕⊖ <b>LOW</b> <sup>2,4</sup> due to indirectness, imprecision	23	24	N/A	N/A	The mean clinician-rated adaptive behaviour (mixed asd & dd sample) in the intervention groups was <b>0.62 standard deviations higher</b> (0.04 to 1.21 higher)

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

		Qu	ality assessm	nent				Sui	mmary of	Finding	gs		
Participants		Inconsistency	Indirectness	Imprecision			Study	event rates (%)	Relative	Anticipa	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% CI)		
Self-care	Self-care (measured with: Early Intervention Developmental Profile (EIDP)/Preschool Developmental Profile (PSDP): Self-Care; Better indicated by lower values)												
35 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	19	16	N/A	N/A	The mean self-care in the intervention groups was <b>0.04 standard deviations lower</b> (0.7 lower to 0.63 higher)		
<sup>1</sup> N<400 and	95% CI cro	sses both line of n	o effect and mea	asure of appre	ciable benefit	or harm (SMD -	0.5/0.5)						

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

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

<sup>&</sup>lt;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>&</sup>lt;sup>2</sup> Population was indirect (as the sample included participants with developmental delay or language delay without autism)

<sup>&</sup>lt;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)

<sup>4</sup> N<400

								indirect outcome			
Adaptiv	e behav	iour (measured	with: Vineland A	daptive Behav	viour Scale (VA	ABS): Adaptive (	Compos	ite; 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 0.56 standard deviations higher (0.19 to 0.93 higher)
Daily liv	ing skill	<b>S</b> (measured with	n: Vineland Adap	tive Behaviou	r Scale (VABS	): Daily Living S	kills; Be	tter 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)
Socializ	ation (me	asured with: Vine	land Adaptive B	ehaviour Scale	e (VABS): Soci	alization; Better	indicat	ed 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 socialization in the intervention groups was <b>0.6 standard deviations higher</b> (0.23 to 0.96 higher)
Commu	nication	(measured with:	Vineland Adapti	ı ve Behaviour :	Scale (VABS):	Communication	; Better	indicated by lower value	ıes)		
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 communication in the intervention groups was <b>0.47 standard deviations higher</b> (0.11 to 0.84 higher)

<sup>&</sup>lt;sup>1</sup> High risk of selection bias as significant group differences at baseline on this outcome measure. High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measure based on interview with parents who were non-blind. Also high risk of attrition bias due to higher dropout rates in the experimental (combined risperidone and parent training) group (N=20; 27% attrition) than the control (risperidone only) group (N=9; 18% attrition)

<sup>2</sup> N<400

## 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

		Qι	ıality assessn	nent				Sun	nmary of l	Finding	s
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 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	<b>OU</b> (measured	with: Vineland A	daptive Behav	riour Scale (VA	ABS): Total; Bet	ter 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 lower</b> (0.48 lower to 0.15 higher)
Daily Livi	ng Skil	IS (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 0.55 standard deviations higher (0.09 lower to 1.19 higher)
Socializa	tion (me	asured with: Vine	land Adaptive B	ehaviour Scale	(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 0.1 standard deviations higher (0.53 lower to 0.73 higher)

Commun	ication	(measured with:	Vineland Adapti	ve Behaviour S	Scale (VABS):	Communication	n; Bette	r indicated by lower values)		
245 (4 studies) 39-56 weeks			no serious indirectness	serious <sup>2</sup>		⊕⊕⊖⊝ LOW <sup>2,5</sup> due to risk of bias, imprecision	122	123	N/A	The mean communication in the intervention groups was <b>0.04 standard deviations lower</b> (0.29 lower to 0.22 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrator and participants were non-blind, and unclear/unknown risk of detection bias as teacher-rated and blinding of teacher not reported

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

		C	uality assessn	nent					Summary	of Findings	
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication		Study event	rates (%)	Relative	Anticipated a	bsolute effects
(studies) Follow up	bias				bias	of evidence	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	ol (measu	red with: Social Ski	lls Rating System	(SSRS): Self-c	ontrol; Better in	dicated by lower va	alues)				
68 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW¹.² 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 deviations higher</b> (0.14 to 1.11 higher)

<sup>&</sup>lt;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 parent-rated and parents were non-blind and involved in the intervention. There was also a high risk of attrition bias due to a greater drop-out rate in the experimental (N=14; 35%) than in the control (N=5; 14%) group <sup>2</sup> N<400

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</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 outcome measure based on interview with non-blind parent rather than direct behavioural observation

<sup>&</sup>lt;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)

b High risk of performance and response bias as intervention administrators and participants were non-blind, and unclear/unknown risk of detection bias as blinding of outcome assessment is unclear

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

		Qı	uality assessn	nent				Su	mmary of	Findin	gs
•		Inconsistency	Indirectness	Imprecision	Publication	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% CI)
Socializa	tion (me	asured with: Vine	land Adaptive Be	ehaviour Scale	(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	⊕⊖⊖⊖ <b>VERY LOW</b> <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	e Behaviour S	Scale (VABS):	Communication	; Better	indicated 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 communication in the intervention groups was 0.48 standard deviations higher (0.23 lower to 1.2 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrator and participants were non-blind, and risk of detection bias is unclear/unknown as although the interviewer was a blinded research assistant, the outcome measure was based on non-blind parent report

## 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

<sup>&</sup>lt;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)

Participants		Inconsistency	Indirectness	Imprecision		Overall quality of	Study 6	event rates (%)	Relative	Anticipa	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% CI)
Adaptive	behavi	iour (aripipra	azole) (measu	red with: Peds	QL: Total (cha	ange score); Better in	dicated b	by lower values)			
243 (2 studies) 8 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 higher</b> (0.21 to 0.8 higher)
Emotiona	al funct	ioning (aripi	orazole) (me	asured with: F	PedsQL: Emoti	onal functioning (cha	nge scor	re); 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 higher</b> (0.12 to 0.7 higher)
Social fu	nctioni	ng (aripioraz	zole) (measure	d with: PedsQ	L: Social funct	ioning (change score	); Better	indicated by lower value	s)		1
243 (2 studies) 8 weeks	serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊖⊖⊖ VERY LOW¹,2,4 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	functi	oning (aripi	orazole) (mea	asured with: Po	edsQL: Cognit	ive functioning (chan	ge score	); Better indicated by low	er values)	1	
242 (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,	75	167	N/A	N/A	The mean cognitive functioning (aripiprazole) in the intervention groups

				imprecision		was 0.4 standard deviations higher (0.11 to 0.69 higher)
<sup>1</sup> Risk of detection bia: <sup>2</sup> I-squared value indic <sup>3</sup> N<400 <sup>4</sup> N<400 and 95% CLC	ates substantial to	considerable het	erogeneity	 (0.15 - 5.0		

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

		Qı	uality assessr	ment				Sun	nmary of F	indings	6
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticipa	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	iour (low dos	se aripipraz	ole 5mg/d	lay) (measur	ed with: PedsQL	: Total (d	change score); Better indica	ated by lowe	er values)	
80 (1 study) 8 weeks	serious <sup>1</sup>	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	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 higher</b> (0.23 lower to 0.65 higher)
Emotiona	al funct	ioning (low o	dose aripip	razole 5m	g/day) (mea	asured with: Ped	sQL: Em	notional 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	ay) (measured	d with: PedsQL:	Social f	functioning (change	e score); Better indi	cated by I	ower values)
80 (1 study) 8 weeks		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 functionin (low dose aripiprazole 5mg/day) in the intervention groups was <b>0 standard deviations higher</b> (0.43 lower to 0.44 higher)
	T .		1	<u> </u>		1	1				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	⊕⊖⊝ <b>VERY LOW</b> <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 0.32 standard deviations 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

		(	Quality asses	sment	Summary of Findings					
•	Risk of bias	Inconsistency	Indirectness	•		of evidence	Study event rates (%)  With With Acupuncture/Electro- Control acupuncture versus sham	effect	Antici Risk with	Risk difference 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% CI)
Adaptive	behav	iour (measured	with: Function	al Independen	ce Measure for	Children (WeeFIM	): Total	(change score); Better indi	cated by low	er values	s)
105 (2 studies) 4-9 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 LOW¹,2,3 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 higher</b> (0.19 to 0.98 higher)
Self-care	(measure	ed with: Functiona	al Independence	Measure for	Children (WeeF	IM): Self-care (cha	ange sco	ore); Better indicated by lov	ver values)	1	
105 (2 studies) 4-9 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	50	55	N/A	N/A	The mean self-care in the intervention groups was <b>0.56 standard deviations higher</b> (0.17 to 0.96 higher)
Mobility	(measured	with: Functional	Independence	Measure for C	hildren (WeeFIN	M): Mobility (chang	e score)	; Better indicated by lower	values)		
105 (2 studies) 4-9 weeks	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 0.08 standard deviations lower (0.46 lower to 0.31 higher)
Cognitic	n (measu	red with: Function	nal Independend	ce Measure fo	r Children (Wee	FIM): Cognition (c	hange s	core); Better indicated by le	ower 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 cognition in the intervention groups was <b>0.48 standard deviations higher</b> (0.09 to 0.87 higher)
Compre	hensior	(measured with	: Functional Ind	ependence Me	easure for Child	ren (WeeFIM): Co	mpehen	sion (change score); Bette	r indicated b	y lower v	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 comprehension in the intervention groups was <b>0.51 standard deviations higher</b> (0.03 lower to 1.05 higher)
Expressi	on (mea	sured with: Functi	onal Independe	ence 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 serious <sup>5</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊖ <b>VERY LOW</b> <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 higher</b> (0.36 lower to 0.7 higher)
Social in	teraction	on (measured wi	th: Functional Ir	ndependence	Measure for Ch	ildren (WeeFIM): S	Social in	nteraction (change score); Bet	ter indicate	ed by lov	ver 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 interaction in the intervention groups was  0.23 standard deviations lower  (0.77 lower to 0.3 higher)
Problem	solving	g (measured with	: Functional Ind	lependence M	easure for Child	dren (WeeFIM): Pr	oblem s	solving (change score); 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>	⊕⊖⊖ <b>VERY LOW</b> <sup>3,5</sup> due to imprecision, publication bias	25	30	N/A	N/A	The mean problem solving in the intervention groups was  0.24 standard deviations lower  (0.77 lower to 0.3 higher)
Memory	(measured	with: Functional	Independence	Measure for C	hildren (WeeFI	M): Memory (chan	ge scor	e); Better indicated by lower v	alues)	1	
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 memory in the intervention groups was 0.13 standard deviations higher (0.4 lower to 0.67 higher)

Self-care	e (funct	ional skill) (r	measured with:	Pediatric Eval	uation of Disabil	lity Inventory (PED	l): Self-	care; Better indicated by lo	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 (functional skill) in the intervention groups was 0.22 standard deviations lower (0.75 lower to 0.31 higher)
Self-care	e (indep	endence) (m	neasured with: F	Pediatric Evalu	ation of Disabili	ty Inventory (PEDI	): Self-d	care (caregiver assistant); E	Better indica	ted by lo	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>	⊕⊖⊖ <b>VERY LOW</b> <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> lower (0.97 lower to 0.1 higher)
Mobility	(function	onal skill) (m	easured with: P	ediatric Evalu	ation of Disabilit	y Inventory (PEDI)	: Mobili	ty; Better indicated 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>	⊕⊖⊖ <b>VERY LOW</b> <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> lower (0.64 lower to 0.42 higher)
Mobility	(indepe	endence) (me	easured with: Pe	ediatric Evalua	ition of Disability	Inventory (PEDI):	Mobilit	y (caregiver assistant); Bet	ter indicated	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> lower (0.72 lower to 0.35 higher)
Social fu	unction	(functional	<b>skill)</b> (measu	red with: Pedia	atric Evaluation	of Disability Inven	tory (PE	EDI): Social function; Better	indicated by	/ lower v	alues)
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>	⊕⊝⊝⊝ <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 <b>0.04 standard deviations</b>

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						publication bias					higher (0.49 lower to 0.57 higher)
Social fur	Social function (independence) (measured with: Pediatric Evaluation of Disability Inventory (PEDI): Social function (caregiver assistant); Better indicated by lower values)										
(1 study) 4 weeks	-		no serious indirectness	serious <sup>5</sup>	3,	⊕⊖⊝ 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 lower</b> (0.67 lower to 0.39 higher)

<sup>1</sup> I-squared value indicates substantial to considerable heterogeneity

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

		Q	uality assess	sment	Summary of Findings						
Participants	Risk of	Inconsistency	Indirectness	Imprecision		Overall quality	Study event rates (%)			Anticipated 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	(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% CI)
Adaptive	behav	iour (measured	with: Functions	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 LOW¹.2.3 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 higher</b> (0.11 lower to 0.93 higher)

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</sup> High risk of selective reporting bias as trial protocol for WONG2010B states that follow-up measurements will be taken but these are not reported

<sup>&</sup>lt;sup>4</sup> I-squared value indicates moderate heterogeneity

<sup>&</sup>lt;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)

Self-care	(measure	ed with: Function	al Independenc	e Measure for	Children (We	eFIM): Self-care (	change	score); Better indica	ted by lower values	s)	
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 higher</b> (0.35 lower to 0.67 higher)
<b>Mobility</b>	(measured	with: Functional	Independence	Measure for C	Children (Weel	FIM): Mobility (cha	ange sc	ore), Better indicated	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 mobility in the intervention groups was <b>0.52 standard deviations higher</b> (0 to 1.05 higher)
Cognitio	<b>n</b> (measu	red with: Function	nal Independen	ce Measure fo	or Children (W	eeFIM): Cognition	(chang	ge score); Better indic	cated 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 higher</b> (0.1 to 1.14 higher)
Compre	nensior	(measured with	: Functional Inc	dependence M	easure for Ch	ildren (WeeFIM):	Compel	hension (change sco	re); Better indicated	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 lower</b> (1.13 lower to 0.19 higher)
Expressi	ion (meas	sured with: Funct	tional Independ	ence Measure	for Children (	WeeFIM): Expres	sion (ch	nange score); Better	indicated 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 expression in the intervention groups was <b>0.4 standard deviations 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 higher</b> (0.26 lower to 1.06 higher)
Problem 36 (1 study) 8 weeks	1	no serious inconsistency	n: Functional Ind no serious indirectness	very serious <sup>3</sup>	leasure for Ch undetected	ildren (WeeFIM):	Problen 18	n solving (change sc	ore); Better indicat	N/A	The mean problem solving in the intervention groups was 0.33 standard deviations higher (0.32 lower to 0.99 higher)
Memory	(measured	with: Functional	Independence	Measure for C	hildren (WeeF	I IM): Memory (ch	ange sc	ore); Better indicated	by lower values)	<b>.</b>	
36 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and the conventional education programme differed for each participant which may introduce bias. The risk of detection bias was also unclear/unknown as all outcome measures were rated by blinded assessors, but some outcome measures involved input from parents who were not blind to treatment allocation or confounding variables and systematic review from which data was extracted does not report which outcome measures relied on non-blind parental report

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

Secretin versus placebo for adaptive behaviour as an indirect outcome

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

<sup>&</sup>lt;sup>2</sup> I-squared value indicates considerable heterogeneity

<sup>&</sup>lt;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)

<sup>4</sup> N<400

(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% CI)
Adaptive	e behavi	<b>OU</b> (measured w	vith: Vineland Ada	aptive Behavio	our Scale (VAB	S): Adaptive Con	nposite; E	Better indicated by lov	ver values)	•	
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	28	28	N/A	N/A	The mean adaptive behaviour in the intervention groups was <b>0.08 standard deviations lower</b> (0.61 lower to 0.44 higher)
Daily livi	ing skills	(measured with:	Vineland Adaptiv	ve Behaviour S	Scale (VABS): [	Daily Living Skills	; Better i	ndicated by lower value	ues)	L	1
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	28	28	N/A	N/A	The mean daily living skills in the intervention groups was <b>0.11 standard deviations higher</b> (0.42 lower to 0.63 higher)
Socializa	ation (mea	asured with: Vinela	and Adaptive Beh	aviour Scale	(VABS): Sociali	zation; Better ind	licated by	/ lower values)	· I		
56 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	28	28	N/A	N/A	The mean socialization in the intervention groups was 0.26 standard deviations lower (0.78 lower to 0.27 higher)
Commu	nication	(measured with: V	ineland Adaptive	Behaviour So	cale (VABS): Co	ommunication; Be	etter indi	cated by lower values	)		
112 (2 studies) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	56	56	N/A	N/A	The mean communication in the intervention groups was 0.28 standard deviations lower (0.65 lower to 0.1 higher)
<sup>1</sup> N<400 and	I 95% CI cro	sses both line of r	no effect and mea	sure of appre	ciable benefit o	r harm (SMD -0.	5/0.5)			1	

### 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				Sumr	nary of F	indings	
Participants		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)	(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	ptive 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	⊕⊕⊖⊖ <b>Low</b> ¹ due to imprecision	15	25	N/A	N/A	The mean adaptive behaviour in the intervention groups was <b>0.2 standard deviations lower</b> (0.84 lower to 0.44 higher)
<sup>1</sup> N<400 and 9	95% CI cr	osses both line of	no effect and n	neasure of app	reciable bene	efit or harm (SI	MD -0.5/0.5)		ı	ı	1

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

	Cipants Risk of bias   Inconsistency   Indirectness   Imprecision   Publication   Overall   quality of							Summary of Findings			
•		Inconsistency	Indirectness	•			Study event		Relative	Anticipated a	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 treatment (HBOT) (95% CI)
Adaptive	behavio	<b>DUI</b> (measured wit	h: Vineland Adar	otive Behaviou	r Scale (VABS	s): Adaptive Com	tive 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	⊕⊕⊖⊝ <b>LOW</b> <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 deviations lower</b> (0.85 lower to 0.5 higher)
Daily livi	ing skills	(measured with:	Vineland Adaptiv	ve Behaviour S	Scale (VABS): [	Daily Living Skills	change s	score); Better in	dicated by low	er values)	
34 (1 study) 15 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	16	18	N/A	N/A	The mean daily living skills in the intervention groups was <b>0.11 standard deviations higher</b> (0.56 lower to 0.78 higher)
Socializa	ation (mea	asured with: Vinela	and Adaptive Beh	naviour Scale	(VABS): Sociali	zation (change s	core); Bett	ter 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	⊕⊕⊖⊝ <b>LoW</b> ¹ due to imprecision	16	18	N/A	N/A	The mean socialization in the intervention groups was <b>0.38 standard 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	⊕⊕⊝⊖ LOW¹ due to imprecision	16	18	N/A	N/A	The mean communication in the intervention groups was <b>0.23 standard deviations higher</b> (0.45 lower to 0.9

56 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW²	2/26 (7.7%)	9/30 (30%)	<b>RR 3.9</b> (0.92 to	Study popula	Study population	
4 weeks	risk of bias	inconsistency	munectness	Serious		due to imprecision	(1.170)	(50 %)	16.45)	77 per 1000	223 more per 1000 (from 6 fewer to 1000 more)	
										Moderate	<u>L</u>	
										77 per 1000	<b>223 more per 1000</b> (from 6 fewer to 1000 more)	
			•		ith. Niah an af		ah imananad/	vary improved' a	n Dorontol C	labat tarana ara-tara		
overall function	no	no serious	no serious	very	undetected	⊕⊕⊝⊝	4/26	9/30	RR 1.95	Study popula		
overall function	oning)	T	T	T						Study popula		
overall function 56 (1 study)	no serious risk of	no serious	no serious	very		⊕⊕⊝⊝ <b>LOW</b> <sup>2</sup> due to	4/26	9/30	RR 1.95 (0.68 to	Study popula	<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	ent	Summary of Findings			
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision		 	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% CI)
Adaptive	skill (meas	ured with: Behavior	Assessment Syste	em for Childrer	n (BASC): Adap	tive skill; Better inc	licated by	lower values)			
24 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	12	12	N/A	N/A	The mean adaptive skill in the intervention groups was  0.2 standard deviations lower  (1 lower to 0.6 higher)
<sup>1</sup> N<400 and	95% CI cross	es both line of no eff	fect and measure of	of appreciable	benefit or harm	(SMD -0.5/0.5)					

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

		Qı	uality assessm	ent		Summary of Fig			ary of Findi	ngs			
Participants		Inconsistency	Indirectness	Imprecision			Study event rates (%)			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)		
Frequenc	Frequency of attending to task/activity (measured with: Behavioural observation; Better indicated by lower values)												
23 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ <b>LoW</b> <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 higher</b> (0.2 lower to 1.5 higher)		
<sup>1</sup> N<400 and	N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)												

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

		Q	uality assessn	nent		Summary 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	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 Liv	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	⊕⊖⊝ <b>VERY LOW</b> <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 0.32 standard deviations higher (0.21 lower to 0.85 higher)
Socializa	ation (mea	sured with: Vinelar	nd Adaptive Beha	viour Scale (VA	BS): Socializat	ion (change score	); Better indica	ated by lower	values)	1	
55 (1 study) 35 weeks	serious <sup>1</sup>	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	29	26	N/A	N/A	The mean socialization in the intervention groups was <b>0.05 standard deviations higher</b> (0.48 lower to 0.58 higher)
Commur	nication	(measured with: Vii	neland Adaptive E	Behaviour Scale	(VABS): Comr	munication (chang	e score); Bett	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	⊕⊖⊖ <b>VERY LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	29	26	N/A	N/A	The mean communication in the intervention groups was 0.12 standard deviations lower (0.65 lower to 0.41 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators (parents) and participants were non-blind and high risk of detection bias as parent-reported and non-blind to treatment allocation and other potentially confounding factors. There was also a 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>&</sup>lt;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)

#### 1.16PSYCHOSOCIAL 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 assessr	ment				Sun	nmary of I	Findings	
(	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 i	nitiations	(assessed w	ith: Behavioural	observatio	n (odds of being in a high	ner initiation	category))	
0 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>1,2</sup>	N/A	N/A	OR 2.73 (1.22 to	Study pop	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 i	nitiations	(assessed w	ith: Behavioural	observatio	n (odds of being in a high	ner initiation	category))	
0 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	undetected	⊕⊝⊝⊝ VERY	N/A	N/A	<b>OR 1.08</b> (0.3 to	Study pop	pulation
78 weeks		,				LOW <sup>1,2,3</sup> due to risk of			3.89)	N/A	N/A
						bias, imprecision			<u> </u>	Moderate	
										0 per	N/A

										1000	
PECS u	ISE (asses	sed with: Behavio	oural observation	(odds of beir	ng in a higher ca	ategory for rate o	f PECS u	use))			
0 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1,2</sup>	N/A	N/A	OR 3.90 (1.75 to	Study po	opulation
33 weeks		,				due to risk of			8.69)	N/A	N/A
						bias, imprecision				Moderat	e
										0 per 1000	N/A
PECS u	ISE (asses	sed with: Behavio	oural observation	(odds of bein	ng in a higher ca	ategory for rate o	f PECS u	use))		1	
0 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,3</sup>	N/A	N/A	OR 1.56 (0.46 to	Study pe	opulation
78 weeks		Inconsistency	indirectiness	3011003		due to risk of			5.3)	N/A	N/A
						bias, imprecision				Moderat	е
										0 per 1000	N/A
Speech	/vocalis	sation use	(assessed with: I	I Behavioural ol	oservation (odd	s of being in a hi	gher cate	egory for rate of sp	peech/vocalisation u	se))	
) (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,3</sup>	N/A	N/A	OR 1.10 (0.46 to	Study po	opulation
33 weeks		moonsistemey	indirectiness	Scrious		due to risk of			2.63)	N/A	N/A
						bias, imprecision				Moderat	е
										0 per 1000	N/A
Recepti	ve lang	Juage (assess	ed with: British P	ricture Vocabu	lary test (BPVS	S): Receptive lan	guage (o	dds of being in a h	higher category on B	PVS))	
	1	no serious	no serious	T		⊕⊖⊝⊝	N/A	N/A	OR 1.54		opulation

(1 study) 33 weeks		inconsistency	indirectness	serious <sup>3</sup>		VERY LOW <sup>1,3</sup> due to risk of bias,			(0.52 to 4.55)	N/A Moderate	N/A
						imprecision				0 per 1000	N/A
Express	ive lan	iguage (asses	sed with: Expres	ssive One Wor	d Picture Voca	abulary Test (EO	WPVT) E	xpressive language (odds	of being in	a higher cat	egory on EOWPVT))
) (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1,2</sup>	N/A	N/A	<b>OR 1.01</b> (0.89 to	Study pop	pulation
33 weeks						due to risk of			1.15)	N/A	N/A
						bias, imprecision				Moderate	
										0 per 1000	N/A
Events<300	o <sup>.</sup>	nce, response and					d outcome	e assessors were non-blin	d		1

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

		Qı	uality assess	ment				Sum	mary of F	Findings	
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 n	onimitative	spoken a	acts (measu	red with: Behav	vioural observa	ion; Better indicate	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	⊕⊝⊝ <b>VERY LOW</b> <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 deviations higher</b> (0.06 lower to 1.28 higher)
Frequen	cy of n	onimitative	e spoken a	acts (measu	red with: Beha	vioural observation	on; Better in	dicated by lower	/alues)		,
36 (1 study) 52 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝⊖  VERY LOW¹.²  due to risk of bias, imprecision	17	19	N/A	N/A	The mean frequency of nonimitative spoken acts in the intervention groups was 0.03 standard deviations higher (0.62 lower to 0.68 higher)
Number	of diffe	erent nonin	nitative w	ords (meas	ured with: Beha	vioural observat	on; Better ir	ndicated 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 LOW¹.²  due to risk of bias, imprecision	17	19	N/A	N/A	The mean number of different nonimitative words in the intervention groups was <b>0.49 standard deviations higher</b> (0.18 lower to 1.15 higher)

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 number of different nonimitative words in the intervention groups was <b>0.08 standard deviations higher</b> (0.57 lower to 0.74 higher)
Number values)	no no	no serious	nges (measur	ed with: EScs	-Abridged (Early	Social Commu ⊕⊕⊖⊝	nication Scales-A	Abridged): Number o	of picture e	xchanges; Better	The mean number
(1 study) 26 weeks	serious risk of bias	inconsistency	indirectness		strongly suspected <sup>4</sup>	LOW <sup>3,4</sup> due to imprecision, publication bias					of picture exchanges in the intervention groups was 0.8 standard deviations higher (0.12 to 1.48 higher)
								e same care apart for addition, the number			 (parents in the RPMT ion' increased

<sup>&</sup>lt;sup>1</sup> High risk of performance bias as intervention administrators were non-blind and comparison groups did not receive the same care apart from the intervention studied (parents in the RPMT group chose to receive more hours of training [mean: 10.6 hours] than parents in the PECS group [mean 7.9 hours]. In addition, the number of hours of 'other intervention' increased between the treatment and follow-up periods, and this increase was greater for the PECS group [4 hours] than for the RPMT group [-0.3 hours]). There was also a high risk of response bias as participants were non-blind and detection bias as identity and blinding of outcome assessors is not reported

#### 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

<sup>&</sup>lt;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> N<400

<sup>&</sup>lt;sup>4</sup> High risk of selective reporting bias as only post-intervention (and not 6-month post-intervention follow-up) reported for the only outcome where significant treatment effects observed (number of picture exchanges as assessed by the EScs-Abridged)

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	ommui	nication (mea	sured with: Child	hood Autism R	ating Scale (C	:ARS): Verbal com	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	⊕⊕⊝⊝ LOW¹ due to imprecision	12	12	N/A	N/A	The mean verbal communication in the intervention groups was <b>0.09 standard deviations lower</b> (0.89 lower to 0.71 higher)
Non-ver	bal con	nmunicatio	n (measured with	n: Childhood A	utism Rating S	Scale (CARS): Nor	n-verbal commu	nication; E	Better 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	⊕⊕⊖⊝ LOW¹ due to imprecision	12	12	N/A	N/A	The mean non-verbal communication in the intervention groups was <b>0.35 standard deviations higher</b> (0.45 lower to 1.16 higher)
Express values)	ive lan	guage (mus	ic therapy	(measured w	ith: Verbal Pro	oduction Evaluation	n Scale (VPES;	study-spe	cific): Expre	essive language;	Better indicated by lower
32 (1 study) 4 days	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	14	18	N/A	N/A	The mean expressive language (music therapy) in the intervention groups was 1.22 standard deviations higher (0.45 to 1.99 higher)
Express	ive lan	⊥ guage (spe	ech therap	<b>y)</b> (measured	with: Verbal P	l Production Evaluat	I ion Scale (VPES	S; study-sp	l pecific): Exp	ressive language	e; Better indicated by lower

		1 .		. 2	1		Taa		- INI/A		
32	no	no serious	no serious	serious <sup>2</sup>	undetected		14	18	N/A	N/A	The mean expressive
(1 study)	serious	inconsistency	indirectness			MODERATE <sup>2</sup>					language (speech therapy)
4 days	risk of					due to					in the intervention groups
	bias					imprecision					was
						'					1.09 standard deviations
											higher
											_
											(0.33 to 1.84 higher)

# 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	uality assessm	ent					Summa	ry of Findinຸ	gs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	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% CI)
Receptive	e languaç	ge (ESDM) (me	easured with: Mull	en Scales of E	arly Learning (I	MSEL): Receptive	Language; E	Better indica	ated by lowe	er values)	
45 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ <b>LoW</b> ¹ due to imprecision	21	24	N/A	N/A	The mean receptive language (esdm) in the intervention groups was <b>0.6 standard deviations higher</b> (0 to 1.2 higher)
Expressiv	ve langua	age (ESDM) (r	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 risk of bias	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	ood (measured w	th: MacArthur Co	mmunication D	evelopmental Ir	nventories (CDI):	Phrases und	lerstood; Be	etter indicate	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 lower</b> (0.63 lower to 0.16 higher)
Vocabul	ary comp	rehension (m	easured with: Ma	Arthur Comm	unication Devel	opmental Inventor	ies (CDI): V	ocabulary 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 lower</b> (0.58 lower to 0.21 higher)
Vocabul	ary prod	uction (measure	d with: MacArthur	Communication	on Development	tal Inventories (CI	OI): Vocabul	ary producti	on; Better in	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 higher</b> (0.35 lower to 0.45 higher)
Total ge	stures pr	oduced (measu	red with: MacArth	ur Communica	ation Developme	ental Inventories (	CDI): Total	gestures 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	⊕⊝⊝ <b>VERY LOW</b> <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	•	as intervention a			bias as com	ne measure was	s parent-rated and parents
were non-blin 3 N<400	d and involve	ed in the intervention	on					

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

		Qı	uality assessn	nent				Sı	ımmary o	f Finding	js .
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	event rates (%)	Relative effect	Anticipa	ted 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)
Recepti	ve lang	uage (measured	with: Reynell De	evelopmental L	anguage Scal	e: Comprehension	on; Better	ndicated 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	⊕⊕⊝⊝ LOW¹ due to imprecision	13	15	N/A	N/A	The mean receptive language in the intervention groups was 0.48 standard deviations higher (0.28 lower to 1.23 higher)
Express	ive lan	guage (measur	ed with: Reynell	Developmenta	Language Sc	ale: Expressive I	_anguage	e; Better indicated by lo	wer values)	•	1
28 (1 study) 260 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ 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	ve + Ex	pressive lar	nguage (mea	sured with: Re	ynell Developr	nental Language	Scale:	Total; Better indicated	oy lower valu	ies)	
28 (1 study) 260 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to imprecision	13	15	N/A	N/A	The mean receptive + expressive language in the intervention groups was 0.63 standard deviations higher (0.13 lower to 1.39 higher)
N<400 and	95% CI cro	sses both line of n	o effect and mea	sure of apprec	iable benefit o	r harm (SMD -0.	5/0.5)				

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

		Qı	ıality assessm	ent				Su	mmary of	Findin	gs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	` '	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)
Receptiv	e langu	Iage (measured	with: Reynell De	velopmental L	anguage Scal	e: Comprehension	on; Bette	r indicated by lower valu	es)		
53 (1 study) 40 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	26	27	N/A	N/A	The mean receptive language in the intervention groups was 0.42 standard deviations lower (0.96 lower to 0.13 higher)
Express	ive lang	Juage (measure	I ed with: Reynell [	I Developmental	Language Sc	ale: Expressive I	_anguag₀	e; Better indicated by lov	ver values)		

53 (1 study) 40 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ due to imprecision	26	27	N/A	N/A	The mean expressive language in the intervention groups was <b>0.26 standard deviations lower</b> (0.8 lower to 0.28 higher)
56 (1 study) 40 weeks	serious <sup>2</sup>	no serious inconsistency	ning (measure no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊖⊖⊖ VERY LOW¹.² due to risk of bias, imprecision	29	cated by lower values)  27	N/A	N/A	The mean everyday language functioning in the intervention groups was 0.52 standard deviations lower (1.06 lower to 0.01 higher)

<sup>&</sup>lt;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)

## 1.16.4 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

	Quality assessment							Sun	nmary of I	Findin	egs
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	bias	Overall quality of evidence	Study With IBI- only	,		Antic Risk with IBI- only	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	bulary Test, 3r	d Ed. (PPVT-III)	: Total	; Better indicated by lower va	lues)		

<sup>&</sup>lt;sup>2</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias in unclear/unknown as although the outcome assessors were blinded, this outcome measure was based on interview with parent and parents were non-blind and were part of the intervention

46 (1 study) 13 weeks	serious <sup>1</sup>	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	24	22	N/A	N/A	The mean receptive language in the intervention groups was <b>0.33 standard deviations higher</b> (0.25 lower to 0.92 higher)
Recepti values)	ive lang	juage (pres	school sub	group a	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	⊕⊖⊖⊖ VERY LOW¹.² 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>0.4 standard deviations higher</b> (0.43 lower to 1.22 higher)
Recepti	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> higher (0.55 lower to 1.09 higher)
Recepti	ive lang	Juage (measu	red with: Brigand	e Inventory of	Child Develop	ment: Receptive	langu	age; Better indicate	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 <b>0.09 standard deviations higher</b> (0.49 lower to 0.67 higher)
Reception values)	ive lang	uage (pres	 school sub	group a	nalysis) (m	easured with: Bri	gance	e Inventory of Child	Development: Rece	eptive la	nguage; Better indicated by low

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> lower (0.84 lower to 0.8 higher)
Recepti	ve lang	juage (K-1	subgroup	analysis)	(measured wi	th: Brigance Inve	entory	of Child Development: Re	ceptive langu	age; Be	tter 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	⊕⊝⊝ <b>VERY LOW</b> <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)
Express	sive lan	guage (meas	ured with: Expre	ssive Vocabul	ary Test (EVT)	: Total; Better ind	dicate	d by lower values)	,		•
46 (1 study) 13 weeks	serious <sup>1</sup>	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	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)
Express	sive lan	guage (pre	school su	bgroup a	nalysis) (	l measured with: I	Expre	ssive Vocabulary Test (EV	Γ): Total; Bett	er 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	⊕⊝⊝⊝ <b>VERY LOW</b> <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 <b>0.33 standard deviations</b> higher (0.5 lower to 1.15 higher)
Express	sive lan	guage (K-1	subgroup	analysis	(measured	with: Expressive	Voca	bulary Test (EVT): Total; B	etter indicate	d by low	ver values)
23 (1 study)	serious <sup>1</sup>	no serious	no serious	very	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,2</sup>	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)
Expres	sive lan	<b>iguage</b> (meas	ured with: Briga	nce Inventory	of Child Develo	ppment: Expressi	ve lan	guage; Better indica	ated by lower value	s)	
46 (1 study) 13 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ <b>VERY LOW</b> <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 higher</b> (0.57 lower to 0.59 higher)
Express lower values		iguage (pre	school su	bgroup a	analysis) (	measured with: I	Brigan	ce Inventory of Chil	d Development: Ex	pressive	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	⊕⊖⊖ <b>VERY LOW</b> <sup>2,3</sup> due to risk of bias, imprecision	12	11	N/A	N/A	The mean expressive languag (preschool subgroup analysis) in the intervention groups was <b>0.07 standard deviations</b> higher (0.75 lower to 0.89 higher)
											(0.75 lower to 0.09 flighter)
Expres	sive lan	iguage (K-1	subgroup	analysi	S) (measured	l with: Brigance In	vento	ry of Child Developr	nent: Expressive la	inguage;	Better indicated by lower values

<sup>&</sup>lt;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.

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

<sup>&</sup>lt;sup>3</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

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

		Q	uality assessr	nent				Su	mmary of	Findings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event	rates (%)	Relative effect	Anticipated at	osolute 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)
Languaç	ge (meas	ured with: Prescho	ool Language Sc	ale-4 (PLS-4):	Total; Better i	ndicated by lowe	er values)				
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW¹.² due to risk of bias, imprecision	117	177	N/A	N/A	The mean language in the intervention groups was <b>0.94 standard deviations higher</b> (0.7 to 1.19 higher)
Receptiv	ve lang	Juage (measure	ed with: Mullen S	cales of Early	Learning (MS	EL): Receptive L	anguage Age	(months); Better ind	icated by lo	wer values)	
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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	I <b>guage</b> (measi	Lured with: Mullen	Scales of Ear	l ly Learning (M	SEL): Expressiv	l re Language A	ge (months); Better	I 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,	117	177	N/A	N/A	The mean expressive language in the intervention groups was 0.49 standard

						imprecision				deviations higher (0.25 to 0.73 higher)
<sup>1</sup> High risk of outcome asse <sup>2</sup> N<400	•	•	pias as interventi	on administrat	ors and partici	pants non-blind.	In addition, risk of detection bias is	unclear/ur	nknown 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				S	ummary c	of Findin	igs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study 6	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		acArthur Communica	ation Develo	pmental I	inventories (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 LOW¹.2.3 due to risk of bias, inconsistency, imprecision	57	90	N/A	N/A	The mean receptive language in the intervention groups was 0.2 standard deviations lower (0.54 lower to 0.14 higher)
Receptiv	e lang	uage (direc	t outcome	) (measured v	vith: Mullen Sc	ales of Early Learning	g (MSEL)	: Receptive Languag	e; Better ind	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	⊕⊖⊖ <b>VERY LOW</b> <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	ne) (measur	red with: MacAr	rthur Communication I	Develop	mental Invento	ories (CDI): Voca	abulary 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-	⊦РЕВМ co	ombined) (meas	ured with	n: Reynell Dev	elopmental Lan	guage Sca	le: Comprehension; Better
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>6</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <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 the intervention groups was <b>0.5 standard deviations</b> lower (0.91 to 0.08 lower)
								ommunication [	Developme	ental Inventories (CDI):
serious <sup>1</sup>	serious <sup>7</sup>	no serious indirectness	serious <sup>6</sup>	undetected	⊕⊝⊝ <b>VERY LOW</b> <sup>1,6,7</sup> due to risk of bias,	57	90	N/A	N/A	The mean expressive language in the intervention groups was
	serious <sup>5</sup> ve lang lower value serious <sup>1</sup>	serious no serious inconsistency  ve language (indivervalues)  serious no serious inconsistency  ive language (measoroduction or Reynell Development)	serious no serious inconsistency indirectness  ve language (indirect outcor lower values)  serious no serious inconsistency indirectness  ive language (measured with: Muller production or Reynell Developmental Language)	serious no serious indirectness very serious very serious no serious indirectness very serious no serious serious no serious serious no serious inconsistency indirectness serious serious serious inconsistency indirectness serious serious serious indirectness serious ser	serious no serious no serious very serious very serious no serious indirectness very serious we language (indirect outcome; PEC+PEBM colower values)  serious no serious no serious inconsistency indirectness serious undetected inconsistency indirectness serious no serious inconsistency indirectness serious serious serious serious inconsistency indirectness serious	ye language (indirect outcome) (measured with: MacArthur Communication (es)    serious   no serious inconsistency   no serious indirectness   very serious   undetected   ⊕⊖⊖	ye language (indirect outcome) (measured with: MacArthur Communication Developes)  serious⁵ no serious inconsistency indirectness very serious³ undetected ∀⊖⊖⊖ ∀ERY LOW³.5 due to risk of bias, imprecision  ye language (indirect outcome; PEC+PEBM combined) (measured with lower values)  serious¹ no serious inconsistency indirectness serious⁶ undetected ⊕⊕⊖ LOW¹.6 due to risk of bias, imprecision  ive language (measured with: Mullen Scales of Early Learning (MSEL): Expressive Language of Production or Reynell Developmental Language Scale: Expressive Language; Better indicated by lower	serious   no serious   no serious   no serious   serious   serious     language (indirect outcome; very   serious   serious   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   serious   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined) (measured with: Reynell Developmental Inventors)   language (indirect outcome; PEC+PEBM combined	Serious   No serious   no serious   no serious   indirectness   very   serious   very   serious   very   serious   very   serious   very   serious   very   serious   very   v	ve language (indirect outcome) (measured with: MacArthur Communication Developmental Inventories (CDI): Vocabulary Cores

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, imprecision	10	10	N/A	N/A	The mean expressive language (direct outcome) in the intervention groups was <b>0.15 standard deviations lower</b> (1.03 lower to 0.73 higher)
lower values)		gaago (iiiai	ioot outoo	mo) (measo	irea with. ivide/	Artiful Communication	1 Develo	princinal inventories (	ODI). Voca	odiary i ro	duction, Better indicated by
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  0.56 standard deviations higher  (0.26 lower to 1.38 higher)
Express Better indicat			rect outco	me; PEC	+PEBM c	c <b>ombined)</b> (mea	sured w	ith: Reynell Developn	nental Lang	uage Scal	e: Expressive Language;
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 (0.72 lower to 0.1 higher)
Overall I non-verbal (<	_	ge rating of	non-verba	al (<5 wo	rds) (indi	rect outcome)	) (asses	sed with: Dichotomou	I is: Overall I	anguage r	rating (based on ADI-R) of
24 (1 study)	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>8</sup>	undetected	⊕⊝⊝ VERY LOW <sup>5,8</sup>	9/12 (75%)	4/12 (33.3%)	RR 0.44 (0.19 to	Study p	opulation
52 weeks		,				due to risk of bias, imprecision		,,	1.05)	750 per 1000	<b>420 fewer per 1000</b> (from 608 fewer to 37 more)
										Moderat	ie

										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 ratir	ng (based on ADI-R) of single
24 (1 study)	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>8</sup>	undetected	⊕⊖⊝⊖ VERY LOW <sup>5,8</sup>	3/12 (25%)	5/12 (41.7%)	RR 1.67 (0.51 to	Study p	opulation
52 weeks		inconsistency	munectiess	Serious		due to risk of bias, imprecision	(2376)	(41.170)	5.46)	250 per 1000	<b>167 more per 1000</b> (from 123 fewer to 1000 more)
										Modera	te
										250 per 1000	167 more per 1000 (from 123 fewer to 1000 more)
speech)  24 (1 study)	serious <sup>5</sup>	no serious inconsistency	no serious	very serious <sup>8</sup>	undetected	⊕⊝⊝ VERY LOW <sup>5,8</sup>	0/12 (0%)	3/12 (25%)	RR 7 (0.4 to		d on ADI-R) of phrase
52 weeks		inconsistency	man comess	School		due to risk of bias, imprecision	(070)	(2370)	122.44)	0 per 1000	N/A
										Modera	te
										0 per 1000	N/A
Total ge		•	(indirect o	utcome)	(measured with	: MacArthur Commur	nication [	Developmental In	ventories (CDI):	Total ges	stures produced; Better
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,	12	12	N/A	N/A	The mean total gestures produced (indirect outcome in the intervention groups

imprecisior	0.58 standard deviations
	higher
	(0.24 lower to 1.4 higher)

<sup>&</sup>lt;sup>1</sup> High risk of selection bias as baseline differences in TONGE2006/2012 between groups on this outcome measure

#### 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	f Findin	gs
,	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% CI)
Langua 35	ge (measu	ured with: Early Int	ervention Develo	ppmental Profil	e (EIDP)/Preso	chool Developm	ental Pro	ofile (PSDP): Language; I	Better indica	ated by Id	ower values)  The mean language in the

<sup>&</sup>lt;sup>2</sup> I-squared value indicates considerable heterogeneity

<sup>&</sup>lt;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)

<sup>&</sup>lt;sup>4</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 the identity and blinding of outcome assessor/s are not reported

<sup>&</sup>lt;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 outcome measure was parent-rated and parents were non-blind and involved in the intervention

<sup>&</sup>lt;sup>6</sup> N<400

<sup>&</sup>lt;sup>7</sup> I-squared value indicates moderate heterogeneity

<sup>&</sup>lt;sup>8</sup> Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1,25)

### 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	ment				Sum	mary of F	indings	5
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 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% CI)
•	_	age (clinician; Better indicated	, ,		Mullen Scales	of Early Learning	(MSEL)	: Receptive Language Age (	months) or	Prescho	ool Language Scale-3 (PLS-3):
225 (3 studies) 39-56 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ 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 higher</b> (0.23 lower to 0.30 higher)
Receptive values)	e langu	age (parent-	rated) (meas	ured with: Mad	Arthur Comm	unication Develop	omental	Inventories (CDI): Vocabula	ry Compre	hension;	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	⊕⊕⊖⊖ <b>LOW</b> <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 higher</b> (0.13 lower to 0.45 higher)
		uage (clinici mmunication; Bett			Mullen Scale	s of Early Learnin	g (MSEI	_): 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	⊕⊕⊕⊝ <b>MODERATE</b> <sup>1</sup> due to	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> higher (0.23 lower to 0.29 higher)
Expressi	ve lang	uage (paren	t-rated) (mea	asured with: M	lacArthur Com	munication Deve	lopmen	tal Inventories (C	DI): Vocabulary P	roduction;	Better indicated by lower values
180 (2 studies) 52-56 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	89	91	N/A	N/A	The mean expressive language (parent-rated) in the intervention groups was <b>0.05 standard deviations higher</b> (0.24 lower to 0.34 higher)
<sup>1</sup> N<400 <sup>2</sup> High risk of parents were		ce and response I	bias as intervent	ion administra	ators and partic		-blind, a	and high risk of d	etection bias as th	s outcome	•

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

		C	Quality 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							With Treatment-as- usual	With Social (reatment-as- skills		Risk with Treatment-as- usual	Risk difference with Social skills group (95% CI)
Idiomati	c langı	Jage (measured	with: Comprehens	sive Assessme	nt of Spoken L	anguage (CASL): I	diomatic Lang	uage; Bette	r indicated t	y lower values)	
34 (1 study) 6 weeks	serious <sup>1</sup>	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	16	18	N/A	N/A	The mean idiomatic language in the intervention groups was <b>0.05 standard deviations higher</b> (0.62 lower to 0.73

							higher)
	ce and response bia			and high risk of detection	bias as res	earcher-rated ar	nd researchers were non-
	sses both line of no			5)			

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

		Qı	ıality assessn	nent				Su	mmary 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 [	Developmental	Language Sc	ale: Comprehe	nsion or	Mullen Scales of Early Lea	arning (MSE	L): Rece	eptive 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	⊕⊕⊝⊝ LOW¹ due to imprecision	41	44	N/A	N/A	The mean receptive language in the intervention groups was <b>0.27 standard deviations higher</b> (0.16 lower to 0.69 higher)
Receptive by lower value		uage (measure	d with: Reynell [	I Developmental	Language Sc	ale: Comprehe	nsion or	Mullen Scales of Early Lea	arning (MSE	EL): Rece	eptive language; Better indicated
85 (2 studies) 26-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	41	44	N/A	N/A	The mean receptive language in the intervention groups was <b>0.23 standard deviations 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	⊕⊕⊝⊝ LOW¹ 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	ive Lang	guage or Mullen S	Scales of Early Lear	ning (MSE	EL): Expressive Language; Bette
85 (2 studies) 6-26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	41	44	N/A	N/A	The mean expressive language in the intervention groups was 0.19 standard deviations higher
											(0.23 lower to 0.62 higher)
Express indicated by			ured with: Reyne	ell Developme	intal Language	Scale: Express	ive Lanç	guage or Mullen S	Scales of Early Lear	ning (MSE	(0.23 lower to 0.62 higher)  EL): Expressive Language; Bette
	no serious		no serious indirectness	very serious <sup>1</sup>	undetected	Scale: Express      Output  Description  Des	41	guage or Mullen S	Scales of Early Lear	ning (MSE	
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	⊕⊕⊜⊝ <b>LOW</b> ¹ 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

		Qu	ality assessn	nent				Summ	mmary of Findings		
Participants		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% CI)
Receptive	e sema	ntics (measur	ed with: Arabic	Language Tes	st: Receptive S	Semantics; Be	tter indica	ated by lower values)			
20 (1 study) 39 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW¹,² 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 higher</b> (0.24 lower to 1.57 higher)
Expressi	ve sem	nantics (measi	ured with: Arabi	c Language T	est: Expressiv	e Semantics;	Better ind	dicated by lower values)			
20 (1 study) 39 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	10	10	N/A	N/A	The mean expressive semantics in the intervention groups was 0.08 standard deviations lower (0.96 lower to 0.79 higher)
Attention	level (	measured with: A	rabic Language	e Test: Attention	on Level; Bette	er indicated by	lower va	alues)			
20	serious <sup>1</sup>	no serious	no serious	very	undetected	⊕⊖⊝⊝	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 0.36 standard deviations higher (0.53 lower to 1.24 higher)
		- T	T .	,	ı	ı		ey of improvement in basic deve			<u> </u>
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY	2/14 (14.3%)	1/16 (6.3%)	RR 0.44 (0.04 to	Study	population
39 weeks		,				LOW <sup>1,3</sup> due to risk of bias, imprecision			4.32)	143 per 1000	80 fewer per 1000 (from 137 fewer to 474 more)
										Modera	ate
										143 per 1000	80 fewer per 1000 (from 137 fewer to 475 more)
Positive	treatme	ent respons	e for babb	l <b>ing</b> (assess	L ed with: Dicho	tomous: Freq	l uency of i	mprovement in basic developm	l ental asse	ssment)	
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY	4/14 (28.6%)	2/16	RR 0.44 (0.09 to	Study	population
39 weeks		inconsistency	man couriess	Schous		LOW <sup>1,3</sup> due to risk of bias,	(20.070)	(12.070)	2.04)	286 per 1000	<b>160 fewer per 1000</b> (from 260 fewer to 297 more)
						imprecision				Modera	ate
										286 per 1000	<b>160 fewer per 1000</b> (from 260 fewer to 297 more)
Positive	treatme	ent respons	e for speed	<b>ch</b> (assessed	with: Dichoto	mous: Freque	ncy of im	provement in basic developmer	ntal assess	ment)	
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY	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,	(1110,0)	()	13.82)	143 per 1000	357 more per 1000 (from 16 fewer to 1000 more)

						imprecision				Modera	ate
										143 per 1000	358 more per 1000 (from 16 fewer to 1000 more)
		ent respons	•	ch compr	ehension	(assessed wit	h: Dichot	omous: Frequency o	of improvement in Chir	na Rehal	cilitation Research Council
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY	5/14	5/16 (31.3%)	<b>RR 0.88</b> (0.32 to	Study	population
39 weeks		inconsistency	indirectriess	Schous		LOW <sup>1,3</sup> due to risk of bias, imprecision	(55.176)	(31.3%)	2.4)	357 per 1000	<b>43 fewer per 1000</b> (from 243 fewer to 500 more)
						Imprecision				Moderate	
										357 per 1000	<b>43 fewer per 1000</b> (from 243 fewer to 500 more)
Positive sign-signification		•	e for spee	ch expres	ssion (asses	sed with: Dich	notomous	: Frequency of impro	vement in China Reh	abilitatio	n Research Council (CRRC)
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY	3/14 (21.4%)	4/16 (25%)	<b>RR 1.17</b> (0.31 to	Study	population
39 weeks		inconsistency	indirectriess	Schous		LOW <sup>1,3</sup> due to risk of bias, imprecision	(21.470)	(2370)	4.34)	214 per 1000	36 more per 1000 (from 148 fewer to 716 more)
										Modera	ate
										214 per 1000	36 more per 1000 (from 148 fewer to 715 more)
Positive significance		-	e for spee	ch imitation	on (assessed	with: Dichoto	mous: Fr	equency of improven	ment in China Rehabil	itation R	esearch Council (CRRC) sign-
30	serious <sup>1</sup>	no serious	no serious	very	undetected	⊕⊖⊝⊖	2/14	1/16	RR 0.44	Study	population

(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				Moder	ate
										143 per 1000	80 fewer per 1000 (from 137 fewer to 475 more)
		ent respons nce relations scale		bulary co	mprehens	sion (assess	ed with: [	Dichotomous: Frequency of im	provement i	n China	Rehabilitation Research Council
30 (1 study) 39 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,3</sup>	0/14 (0%)	5/16 (31.3%)	RR 9.71 (0.58 to 161.31)		population
39 weeks						due to risk of bias,			161.31)	0 per 1000	N/A
						imprecision				Moder	ate
										0 per 1000	N/A
		ent respons		bulary ex	pression (	assessed with	n: Dichoto	mous: Frequency of improven	nent in Chin	a Rehab	ilitation Research Council
30 (1 study)		no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY	0/14 (0%)	5/16 (31.3%)	RR 9.71 (0.58 to	Study	population
39 weeks		inconsistency	manectness	serious		LOW <sup>1,3</sup> due to risk of bias,	(0%)	(31.3%)	161.31)	0 per 1000	N/A
						imprecision				Moder	ate
										0 per 1000	N/A
D !!!	treatme		-	se compr	ehension	(assessed with	h: Dichoto	omous: Frequency of improve	ment in Chir	a Rehal	bilitation Research Council
(CRRC) sign	-significan	ice relations scale	<del>2</del> )								

(1 study) 39 weeks		inconsistency	indirectness	serious <sup>3</sup>		VERY LOW <sup>1,3</sup> due to risk	(0%)	(6.3%)	(0.12 to 60.21)	0 per 1000	N/A
						of bias, imprecision				Moder	ate
										0 per 1000	N/A
Positive sign-significa		•	e for phras	se expres	sion (assess	sed with: Dich	otomous:	Frequency of improvement	in China Reha	abilitation	n 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%)	RR 2.65 (0.12 to	Study	population
39 weeks		inconsistency	indirectiness	Schous		LOW <sup>1,3</sup> due to risk of bias,	(070)	(0.076)	60.21)	0 per 1000	N/A
						imprecision				Moder	ate
										0 per 1000	N/A
		ent respons ce relations scale		nunicatio	n attitude	· -	th: Dichot	omous: Frequency of improv	vement in Chi	T	
(1 study)	serious	inconsistency	indirectness	senous	unaetectea	⊕⊕⊝⊝ LOW <sup>1,4</sup>		(93.8%)	(1.02 to	Study	population
39 weeks						due to risk of bias, imprecision			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 ass	essors no 95% CI ci and 95%	nce and response t reported and no rosses both line of CI crosses both	independent real for the independent real for	eliability or vali measure of ap	dity data for the preciable ben	nis outcome m refit or harm (\$	easure SMD -0.5		is unclear/un	known a	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		Publication bias	Overall quality of evidence			Relative	Anticipated absolute effects		
							With Control	With Acupuncture/Electro- acupuncture versus sham acupuncture/electro- acupuncture for speech and language as an indirect outcome	effect (95% CI)	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)												
50 (1 study) 9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ due to imprecision	25	25	N/A	N/A	The mean receptive language in the intervention groups was <b>0.18 standard deviations lower</b> (0.73 lower to 0.38 higher)	
Receptiv	e langı	lage (measured	I with: Reynell D	Developmental	Language Sca	le (change scor	e): Com	prehension age (years); Bette	r 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 receptive language in the intervention groups was 0.39 standard deviations higher (0 to 0.78 higher)	
Expressive language (measured with: Reynell Developmental Language Scale (change score): Expression score; 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	⊕⊕⊖⊝ LoW¹ due to imprecision	25	25	N/A	N/A	The mean expressive language in the intervention groups was  0.42 standard deviations higher  (0.14 lower to 0.98 higher)	

Autism: the management and support of children and young people on the autism spectrum (March 2013)

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 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 higher</b> (0.28 lower to 0.49 higher)

<sup>&</sup>lt;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)

#### 1.17.2Hormones 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% CI)		
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	serious <sup>1</sup>	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 lower</b> (0.31 lower to 0.27 higher)		
<b>Expressive language</b> (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 inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>2</sup>	100	112	N/A	N/A	The mean expressive language in the		

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;sup>3</sup> High risk of selective reporting bias in WONG2010B as trial protocol includes a follow-up but no follow-up data reported

										Moderat	more)
3 weeks	risk of bias	,				due to imprecision	(====,	(2 172)	3.23)	208 per 1000	<b>131 more per 1000</b> (from 35 fewer to 465
95 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> ⁴	10/48 (20.8%)	16/47 (34%)	<b>RR 1.63</b> (0.83 to	Study p	opulation
Positive	treatme	ent response	(assessed with:	Dichotomous:	Positive treatm	nent response (imp	rovement >	>=4 points on PL	_S-3))		
(2 studies) 4-6 weeks	serious risk of bias	inconsistency	indirectness			MODERATE <sup>2</sup> due to imprecision					the intervention groups was  0.06 standard deviations lower  (0.43 lower to 0.31 higher
15	no	no serious	no serious	serious <sup>2</sup>	undetected	$\oplus \oplus \oplus \ominus$	53	62	N/A	N/A	The mean vocabulary in
Vocabulation ower values	• '	ured with: Behavio	oural observation	: Type token r	atio or MacArth	ur Communication	Developm	ental Inventories	s (CDI): Vocabula	ary (chang	e score); Better indicated t
											higher (0.15 lower to 0.71 highe
weeks	bias					due to imprecision					0.28 standard deviation
35 1 study) 3 weeks	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊕⊝⊝ LOW³	44	41	N/A	N/A	The mean receptive and expressive language in the intervention groups was
Receptiv	e and e	xpressive la	nguage (mea	sured with: Pr	eschool Langua	age Scale-3 (PLS-3	B): Total (cl	hange score); Be	etter indicated by	lower valu	ies)
	bias					improdicion					lower (0.43 lower to 0.11 higher
3-6 weeks	risk of bias					due to imprecision					intervention groups was 0.16 standard deviation

N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5) Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25)

# 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	•	Publication		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% CI)
Semantic values)	Pragn	natic Proble	<b>ms</b> (measured	l with: Pervasiv	ve Developme	ent Disorder Be	havior Invento	ry (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	⊕⊕⊖⊝ LOW¹ due to imprecision	15	25	N/A	N/A	The mean semantic pragmatic problems in the intervention groups was  0.44 standard deviations higher (0.2 lower to 1.09 higher)
Expressi	ve Lan	guage (measu	red with: Pervas	sive Developm	ent Disorder E	Behavior Inven	tory (PDDBI): E	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	⊕⊕⊝⊝ <b>LOW</b> ¹ due to imprecision	15	25	N/A	N/A	The mean expressive language in the intervention groups was <b>0.26 standard deviations lower</b> (0.91 lower to 0.38 higher)

Learning, Memory, and Receptive Language (measured with: Pervasive Development Disorder Behavior Inventory (PDDBI): Learning, Memory, and Receptive Language; Better indicated by lower values)													
(1 study) 17 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ 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 deviations lower</b> (0.76 lower to 0.52 higher)		

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

		Q	uality assessm	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study even	t 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% CI)
						(DD) (T III) T I	/ 1	\ D # : # +			
Receptive	e langua	<b>ige</b> (measured w	ith: Peabody Pict	ure Vocabulary	lest, 3rd Ed.	(PPV1-III): Total	(change scor	e); Better indicated	d by lower v	alues)	

# 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

		Q	uality assessm	ent					Summa	ry of Find	ings
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study e	vent rates	Relative effect	Anticipate	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% CI)
Receptive	e languaç	<b>G</b> (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	⊕⊕⊖⊝ <b>LOW</b> ¹ due to imprecision	12	13	N/A	N/A	The mean receptive language in the intervention groups was 0.52 standard deviations lower (1.32 lower to 0.28 higher)
Expressi	ve langua	ige (measured with	h: Expressive Voc	abulary 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	⊕⊕⊝⊝ <b>LOW</b> ¹ due to imprecision	12	13	N/A	N/A	The mean expressive language in the intervention groups was 0.69 standard deviations lower (1.51 lower to 0.12 higher)
<sup>1</sup> N<400 and	95% CI cross	es both line of no ef	fect and measure	of appreciable	benefit or harr	m (SMD -0.5/0.5)	•		•	•	

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

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

Receptiv	e langu	age (measured wi	ith: Mullen Scales	of Early Learn	ning (MSEL): Re	eceptive Language	Better indi	cated by lowe	r 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 receptive language in the intervention groups was <b>0.21 standard deviations higher</b> (0.61 lower to 1.04 higher)
Expressi	ve lang	uage (measured	with: Mullen Scale	es of Early Lea	rning (MSEL): I	Expressive Langua	ge; Better i	ndicated by lo	wer values)		
23 (1 study) 13 weeks	serious <sup>1</sup>	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	13	10	N/A	N/A	The mean expressive language in the intervention groups was <b>0.36 standard deviations higher</b> (0.47 lower to 1.19 higher)

<sup>&</sup>lt;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 the outcome assessor for this outcome measure was not blinded.

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

li		Q	uality assessn	nent		Summary of Findings							
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	effect (95% CI)	Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% CI)		
Receptive	eceptive language improvement (measured with: Parent Global Impressions-Revised (PGI-R): Receptive language improvement; Better indicated by lower values)												
-	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	51	53	N/A	N/A	The mean receptive language improvement in the intervention groups was <b>0.43 standard deviations higher</b> (0.04 to 0.82 higher)		

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

-	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <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 higher</b> (0.02 lower to 0.76 higher)
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## L-carnosine supplement versus placebo for speech and language as an indirect outcome

		C	uality assessn	nent					Summary	of Findir	ngs
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 L-carnosine supplement	effect (95% CI)	Risk with Placebo	Risk difference with L- carnosine supplement (95% CI)
Receptive	e langua	<b>ge</b> (measured with	n: Receptive One-	Word Picture V	ocabulary Test	(ROWPVT) Rece	ptive lang	uage (raw score)	; Better indi	cated by lo	wer values)
-	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	17	14	N/A	N/A	The mean receptive language in the intervention groups was <b>0.25 standard deviations higher</b> (0.46 lower to 0.96 higher)
Receptive	e langua	<b>ge</b> (measured with	n: Receptive One-	Word Picture V	ocabulary Test	(ROWPVT) Rece	ptive lang	uage (age adjust	ed score); E	etter indica	ated by lower values)
	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	17	14	N/A	N/A	The mean receptive language in the intervention groups was <b>0.2 standard deviations higher</b> (0.5 lower to 0.91 higher)

(1 study) ri 8 weeks	isk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>		⊕⊕⊝⊝ LoW¹ due to imprecision	17	14	N/A	N/A	The mean expressive language in the intervention groups was <b>0.2 standard deviations higher</b> (0.51 lower to 0.91 higher)
31 n	no serious	no serious	no serious	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	17	anguage (age ad	N/A	N/A	The mean expressive language in the intervention groups was 0.21 standard deviations higher (0.5 lower to 0.92 higher)

# 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	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision		•	Study event rat	` '	Relative	Anticipated abs	olute effects
(studies) Follow up	bias				bias		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% CI)
Receptive	e langua	age (measured w	vith: Peabody Pic	ture Vocabula	ry Test (PPVT	): Total; Better ind	icated by lower v	alues)		·	
(1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	40	40	N/A	N/A	The mean receptive language in the intervention groups was 0.24 standard deviations lower

											(0.68 lower to 0.2 higher)
Receptiv	ve langu	age (measured v	vith: Peabody Pi	cture Vocabula	ary Test (PPVT	): Total; Better inc	dicated by low	ver values)			
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖ <b>LOW</b> <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean receptive language in the intervention groups was 0.32 standard deviations lower (0.76 lower to 0.12 higher)
-	ve langu	age (measured v	vith: Peabody Pi			T	ı		T		T
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊖ MODERATE² due to imprecision	40	40	N/A	N/A	The mean receptive language in the intervention groups was  0.5 standard deviations lower  (0.94 to 0.05 lower)
<sup>1</sup> N<400 and <sup>2</sup> N<400	d 95% CI cro	sses both line of r	I no effect and mea	I asure of appre	L ciable benefit	or harm (SMD -0.5	5/0.5)				

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

			Quality asses	ssment				S	Summary o	of Findings	
Participants		Inconsistency	Indirectness	•		Overall quality of	Study even	` '	Relative	Anticipated	absolute effects
(studies) Follow up	bias				bias		With With I		(95% CI)	Risk with Treatment-as- usual	Risk difference with Neurofeedback (95% CI)
Parent-ra	ited spe	eech produc	tion (measured	d with: Childrer	n's Communicatio	n Checklist (CCC-2)	: Speech pro	duction; 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	-rated s	peech prod	<b>uction</b> (measu	red with: Chil	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	-2): Spee	ech production:	Better indicat	ed by lower	the intervention groups was 0.38 standard deviations lower (1.26 lower to 0.51 higher)
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 LOW¹.2,3  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  0.75 standard deviations higher (0.16 lower to 1.67 higher)
Parent-r	ated sy	ntax (measured	with: Children's	Communicati	on Checklist (CCC	:-2): Syntax; Better in	dicated b	by lower values	5)		
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 LOW¹,2,3 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 deviations lower</b> (1.44 lower to 0.35 higher)
Teacher	-rated s	yntax (measur	ed with: Children	's Communic	ation Checklist (C0	CC-2): Syntax; Better	indicate	d by lower valu	es)		
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 LOW¹,2,3 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 deviations higher</b> (0.68 lower to 1.08 higher)
Parent-r	ated se	mantics (mea	sured with: Child	ren's Commu	nication Checklist	(CCC-2): Semantics;	Better in	ndicated by low	rer 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 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	ldren's Comn	nunication Checkli	st (CCC-2): Semantic	s; Better	indicated by le	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>	⊕⊖⊝ <b>VERY LOW</b> <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 1.12 standard deviations higher (0.17 to 2.08 higher)
Parent-ra	ated co	herence (mea	sured with: Child	ren's Commu	ınication Checklist	(CCC-2): Coherence	; Better in	ndicated by lo	wer 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 LOW¹.2.3 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 deviations lower</b> (1.59 lower to 0.23 higher)
Teacher-	-rated c	oherence (m	easured with: Ch	ildren's Comr	munication Checkl	st (CCC-2): Coheren	ce; Bette	r indicated 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 LOW¹.2.3 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 deviations higher</b> (0.04 lower to 1.82 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance, response and detection bias as intervention administrators, participants and outcome assessors were non-blind. The risk of other bias due to potential conflict of interest is also high as neurofeedback equipment provided by manufacturer for trial.

<sup>&</sup>lt;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>&</sup>lt;sup>3</sup> High risk of selective reporting bias as data cannot be extracted for 6-month follow-up

<sup>&</sup>lt;sup>4</sup> N<400

# 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	ary of Findin	gs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study even (%)	t rates	Relative	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	developn	nental quoti	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 pesdm) in the intervention groups was  0.25 standard deviations higher  (0.08 lower to 0.58 higher)
Verbal de	velopm	ental quotie	nt (P-ESDM)	(measured wi	th: Mullen Scal	es of Early Learning (	(MSEL): Verb	al develop	mental quot	tient; Better inc	dicated 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 (pesdm) in the intervention groups was  0.1 standard deviations higher  (0.3 lower to 0.5 higher)
Non-verb	al deve	lopmental qu	otient (P-E	SDM) (measu	ured with: Mulle	en Scales of Early Lea	arning (MSEL)	): Non-ver	bal develop	mental quotien	nt; Better indicated by lower
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,	49	49	N/A	N/A	The mean non-verbal developmental quotient (pesdm) in the intervention

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						imprecision				groups was  0.08 standard deviations higher  (0.31 lower to 0.48 higher)
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<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants were nonblind, and risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported

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

		Q	uality assessn	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	d with: Bayle	ey Scales of Infant	Development: Me	ental Developr	ment Index; Be	tter indicated by lo	wer value	es)			
-	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	13	15	N/A	N/A	The mean iq in the intervention groups was <b>0.74 standard deviations higher</b> (0.04 lower to 1.51 higher)
Academi	c skills (n	neasured with: We	chsler Individualiz	zed Achievem	ent Test (WIAT	): Total; Better indi	cated by	lower values)		•	
-	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	13	15	N/A	N/A	The mean academic skills in the intervention groups was <b>0.84 standard deviations higher</b> (0.06 to 1.62 higher)
<sup>1</sup> N<400 and	95% CI cros	ses both line of no	effect and measu	re of apprecia	ble benefit or l	harm (SMD -0.5/0.	5)		1		·

<sup>&</sup>lt;sup>2</sup> I-squared value indicates moderate heterogeneity

<sup>&</sup>lt;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)

<sup>4</sup> N<400

<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 assessn	nent				Sur	nmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study event i	rates (%)	Relative	Anticipated a	bsolute 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% CI)
IQ (measure	d with: Mu	llen Scales of Ear	ly Learning (MSI	EL): Early-lear	ning composite	e score; Better i	ndicated by low	er values)			•
294 (1 study) 104 weeks		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 deviations higher</b> (0.63 to 1.12 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants non-blind. In addition, risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported <sup>2</sup> N<400

## 1.18.3 Parent training for IQ as an indirect outcome

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

			Quality assess	sment			Sı	ummary o	f Finding	S
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Study 6 With Control	With Parent training versus treatment-as-usual for IQ	effect	Risk with	Risk difference with Parent training versus treatment-as-usual for IQ (95% CI)

			tal Development: mental quotient;				cational	Profile-Revised (PEP	'-R): Develo	omental Q	uotient (DQ) or Mullen
	no serious risk of bias		no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW¹.2 due to inconsistency, imprecision	57	90	N/A		The mean iq in the intervention groups was <b>0.04 standard deviations higher</b> (0.3 lower to 0.38 higher)
<sup>1</sup> I-squared va <sup>2</sup> N<400	alue indicate	s moderate heter	rogeneity								

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

		Q	uality assessi	ment				Sun	nmary of	Findings	
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall	Study event ra	ates (%)	Relative	Anticipated ab	solute effects
(studies) Follow up	bias				bias	quality of evidence	With Early intervention centre programme only	With Combined parent training and early intervention centre programme	effect (95% CI)	Risk with Early intervention centre programme only	Risk difference with Combined parent training and early intervention centre programme (95% CI)
		<b>&amp; DD sample</b> cated by lower value		h: Bayley Scal	les of Infant De	evelopment-Seco	ond Edition or W	echsler Preschool	and Primar	y Scale of Intellig	ence-Revised
	no serious	no serious inconsistency	serious <sup>1</sup>	very serious <sup>2</sup>	undetected	⊕⊖⊝ VERY LOW <sup>1,2</sup>	29	30	N/A	N/A	The mean iq (mixed asd & dd sample) in
40 weeks	risk of bias					due to indirectness, imprecision					the intervention groups was 0.35 standard deviations higher (0.17 lower to 0.86 higher)
40 weeks	bias only sa		ed with: Bayley S	Scales of Infant	t Developmen	indirectness, imprecision	or Wechsler Pre	eschool and Primar	y Scale of I	ntelligence-Revis	the intervention groups was 0.35 standard deviations higher (0.17 lower to 0.86

(1 study) 40 weeks	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 deviations higher</b> (0.21 lower to 1.07 higher)
(WPPSI-R);		S DD sample cated by lower value	• `	th: Bayley Sca	lles of Infant D				Ţ		ntelligence-Revised
54 (1 study) 108 weeks	no serious risk of bias	no serious inconsistency	serious <sup>1</sup>	very serious <sup>2</sup>	undetected	⊕⊖⊝ VERY LOW <sup>1,2</sup> due to indirectness, imprecision	26	28	N/A	N/A	The mean iq (mixed asd & dd sample) in the intervention groups was <b>0.37 standard deviations higher</b> (0.17 lower to 0.91 higher)
		ct (as the sample i						autism)		<u>L</u>	l

# 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

	Quality assessment							Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision	Publication		Study			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	(95% CI)	Risk with Control	Risk difference with Reciprocal social-communication interventions versus treatment- as-usual for IQ as an indirect outcome (95% CI)	
IQ (measure	d with: Mu	llen Scales of Ear	ly Learning (MS	(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>		⊕⊖⊖ <b>VERY LOW</b> <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 lower</b> (0.62 lower to 0.5 higher)	
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<sup>&</sup>lt;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

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

		Qu	ality assessm	ent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision			Study e		Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Combined joint	(95% CI)	Risk with Control	Risk difference with Combined joint attention training and EIBI versus EIBI only for IQ as an indirect outcome (95% CI)
IQ (measure	d with: Mul	len Scales of Early	Learning (MSEL	): Developme	ntal quotient; E	Better indicated b	y lower	values)		•	
36 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ due to imprecision	16	20	N/A	N/A	The mean iq in the intervention groups was <b>0.54 standard deviations higher</b> (0.13 lower to 1.21 higher)
<sup>1</sup> N<400 and	95% CI cro	sses both line of no	o effect and mea	sure of appred	iable benefit c	r harm (SMD -0.	5/0.5)		ı	1	1

## 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

<sup>&</sup>lt;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)

		Qı	uality assessm	nent				Sui	mmary of	Findings	3
Participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study e	event rates (%)	Relative	Anticipa	ted absolute effects
(studies) Follow up	bias				bias	of evidence	With Control	With Antipsychotics versus placebo for academic skills	effect (95% CI)	Risk with Control	Risk difference with Antipsychotics versus placebo for academic skills (95% CI)
Maths pro	oblem-s	olving (measure	ed with: Classroon	m Analogue Ta	ask: Total num	ber of maths prob	lems cor	rrectly calculated; Better	indicated b	y lower va	ilues)
	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	18	20	N/A	N/A	The mean maths problem- solving in the intervention groups was <b>0.45 standard deviations</b> <b>lower</b> (1.1 lower to 0.19 higher)

# 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 Control	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)
Reasoning: B	-	Composite Score				lues)	General (	Quotient or Leiter Internationa		nce Scal	le-Revised: Visualization and The mean general

(2 studies) 4-9 weeks	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					quotient/fiq in the intervention groups was <b>0.23 standard deviations higher</b> (0.15 lower to 0.62 higher)
Mental a	ge in m	onths (measu	red with: Griffith	s Mental Deve	elopment Scale	(change score):	Mental	age (months); Bette	er indicated by lowe	er values)	
50 (1 study) 9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> ¹ due to imprecision	25	25	N/A	N/A	The mean mental age in months in the intervention groups was 0.43 standard deviations higher (0.13 lower to 0.99 higher)
Locomo	tor (meas	ured with: Griffith	s Mental Develo	opmental Scal	e: Locomotor (c	hange score); B	etter in	dicated by lower val	ues)		
50 (1 study) 9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ Low¹ due to imprecision	25	25	N/A	N/A	The mean locomotor in the intervention groups was <b>0.2 standard deviations lower</b> (0.76 lower to 0.35 higher)
Persona	I-Social	(measured with:	Griffiths Mental	Development	al Scale: Perso	nal-Social (chan	ge sco	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	⊕⊕⊝⊝ LOW¹ due to imprecision	25	25	N/A	N/A	The mean personal-social in the intervention groups was <b>0.53 standard deviations higher</b> (0.03 lower to 1.1 higher)
Hearing	and spe	eech (measured	d with: Griffiths I	I Mental Develo	pmental Scale:	Hearing & Spee	ch (cha	ange score); Better in	ndicated by lower v	ralues)	
50 (1 study) 9 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	25	25	N/A	N/A	The mean hearing and speech in the intervention groups was  0.15 standard deviations 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	⊕⊕⊝ LOW¹ 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 higher</b> (0.44 lower to 0.67 higher)
Perform	ance (me	easured with: Grif	fiths Mental Dev	velopmental S	cale: Performano	ce (change scor	e); Bett	ter 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	⊕⊕⊝⊝ LOW¹ due to imprecision	25	25	N/A	N/A	The mean performance in the intervention groups was <b>0.41 standard deviations higher</b> (0.15 lower to 0.97 higher)
Practica	l reasor	ning (measured	with: Griffiths M	lental Develor	omental Scale: P	ractical Reason	ing (ch	ange score); Better in	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	⊕⊕⊝ LOW¹ due to imprecision	25	25	N/A	N/A	The mean practical reasoning in the intervention groups was 0.32 standard deviations higher (0.23 lower to 0.88 higher)
Attentio	n and m	n <b>emory</b> (meas	ured with: Leiter	International	Performance Sc	ale-Revised: At	ention	and Memory: Battery	/ (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 LOW¹,² 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 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

Control   placebo for IQ as an indirect outcome   Control   placebo for IQ as an indirect outcome   Control   placebo for IQ as an indirect outcome   Control   versus placebo for IQ as indirect outcome   Control   Control   Versus placebo for IQ as indirect outcome   Control			Qı	uality assessm	ent				S	ummary c	f Finding	js
Follow up    With Secretin versus placebo for IQ as an indirect outcome   (95% CI)   Risk with Control   versus placebo for IQ as indirect outcome   (95% CI)   Risk with Control   versus placebo for IQ as indirect outcome   (95% CI)   Risk with Control   versus placebo for IQ as indirect outcome   (95% CI)   (95% CI)   Risk with Control   versus placebo for IQ as indirect outcome   (95% CI)	•		Inconsistency	Indirectness	•			Study 6	event rates (%)		Anticipa	ted absolute effects
42 no serious risk of bias inconsistency indirectness serious¹ undetected to imprecision lower l	` ,	bias				bias	of evidence	-	placebo for IQ as an			Risk difference with Secretin versus placebo for IQ as an indirect outcome (95% CI)
(1 study) risk of bias inconsistency indirectness serious¹ LOW¹ due to imprecision intervention groups we consistency indirectness serious¹ LOW¹ due to imprecision intervention groups we consistency indirectness serious¹ LOW¹ due to imprecision intervention groups we consistency indirectness serious¹ LOW¹ due to imprecision lower	IQ (measure	d with: Merri	II-Palmer Scale; Be	etter indicated by	lower values)							
	(1 study)					undetected	LOW <sup>1</sup> due to	23	19	N/A	N/A	intervention groups was  0.31 standard deviations

# 1.20.3 Nutritional intervention for IQ as an indirect outcome

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

		Qı	uality assessm	ent				S	ummary c	f Finding	js
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	effect (95% CI)	Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% CI)
Cognition	improv	ement (measure	d with: Parent Glo	obal Impressio	ns-Revised (P	GI-R): Cognition in	mprovem	ent; Better indicated	by lower va	lues)	
104 (1 study) 13 weeks		no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>Low</b> ¹ due to imprecision	51	53	N/A	N/A	The mean cognition improvement in the intervention groups was <b>0.32 standard deviations higher</b> (0.06 lower to 0.71 higher)
<sup>1</sup> N<400 and 9	95% CI cross	ses both line of no	ı effect and measuı	re of appreciat	l ble benefit or h	ı arm (SMD -0.5/0.5	5)		1	1	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

		Qı	uality assessn	nent				Su	mmary of	Findings	
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study event rat	es (%)	Relative	Anticipated abso	olute 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% CI)
PIQ (measu	ured with: L	eiter International I	Performance Sca	ale (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	⊕⊕⊝ <b>LOW</b> <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean piq in the intervention groups was 0.16 standard deviations lower (0.6 lower to 0.28 higher)
PIQ (measu	ured with: L	eiter International I	Performance Sca	ile (LIPS): Tota	al; Better indica	ted by lower val	ues)	_			1
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖ <b>LOW</b> <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean piq in the intervention groups was <b>0.17 standard deviations lower</b> (0.61 lower to 0.26 higher)
PIQ (measu	ured with: L	eiter International I	Performance Sca	le (LIPS): Tota	al; Better indica	ated by lower val	ues)	•	ļ.	1	
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> ¹ due to imprecision	40	40	N/A	N/A	The mean piq in the intervention groups was 0.22 standard deviations lower (0.66 lower to 0.22 higher)

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<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
(,	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	ns (measured wit	th: Sensory Profile	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 deviations higher</b> (0.23 lower to 1.14 higher)
Sensory	seeking	(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 deviations higher</b> (0.17 to 1.6 higher)
Sensory	sensitiv	vity (measured w	vith: Sensory Profi	le: Sensory se	nsitivity; Better indic	cated by lower values)	)		1		
34	serious <sup>1</sup>	no serious	no serious	very	reporting bias	⊕⊖⊝⊝	15	19	N/A	N/A	The mean sensory

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imprecision, publication bias 0.39 standard deviations higher	(1 study) 12 weeks	inconsistency	indirectness	serious <sup>2</sup>	strongly suspected <sup>3</sup>	'		deviations higher (0.29 lower to 1.08
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<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants non-blind. There is also a high risk of detection bias as outcome measures are parent-rated and parents non-blind

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

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

		Qı	uality assessn	nent				Sun	nmary of	Findir	ngs
Participants		Inconsistency	Indirectness	Imprecision		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)
Auditory	proces	sing (measured	with: Brigance I	nventory of Ch	nild Developme	ent: Auditory pro	cessir	g; Better indicated by lower v	/alues)		
46 (1 study) 13 weeks	serious <sup>1</sup>	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	24	22	N/A	N/A	The mean auditory processing in the intervention groups was <b>0.21 standard deviations 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 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	12	11	N/A	N/A	The mean auditory processing (preschool subgroup analysis) in the intervention groups was

<sup>&</sup>lt;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>&</sup>lt;sup>3</sup> High risk of selective reporting bias as data not reported for selected subscales: low endurance/tone, oral sensory sensitivity, and poor registration subscales of the Sensory Profile scale

						bias, imprecision					0.13 standard deviations higher (0.69 lower to 0.95 higher)
Auditory	proces	sing (K-1 su	bgroup and	<b>alysis)</b> (mea	sured with: Br	igance Inventory	of Ch	ild Development: Auditory pro	ocessing; B	Better in	dicated by lower values)
23 (1 study) 13 weeks			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		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>&</sup>lt;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

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	uality assessn	nent			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision			Study	event rates (%)	Relative	Anticipa	ated absolute effects
(studies) Follow up	bias					quality of evidence	With Control	With Qigong massage versus waitlist for the coexisting problem or disorder of sensory sensitivities as a direct outcome	effect (95% CI)	Risk with Control	Risk difference with Qigong massage versus waitlist for the coexisting problem or disorder of sensory sensitivities as a direct outcome (95% CI)
Sensory i	impairr	nent (measured	with: Pervasive	Development	Disorder Beha	avior Inventory (F	PDDBI):	Sensory; Better indicated b	y lower val	ues)	
79 (2 studies) 17-22 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW¹,² due to risk of bias,	39	40	N/A	N/A	The mean sensory impairment in the intervention groups was 0.8 standard deviations

						imprecision					lower (1.27 to 0.34 lower)
Sensory i	impairn	nent (measured	with: Sense and	Self-Regulation	on Checklist (S	SSC): Sense che	ecklist; E	Better indicated by lower val	ues)		
87 (2 studies) 17-22 weeks			no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	39	48	N/A	N/A	The mean sensory impairment in the intervention groups was 1.11 standard deviations lower (1.56 to 0.65 lower)

<sup>&</sup>lt;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 coassigned 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	ment			Summary of Findings				
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	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	(95% CI)	Risk with Attention-placebo (structured listening) control	Risk difference with Auditory integration training (95% CI)
Sound se	ensitivit	<b>y</b> (measured with:	Sound Sensitivi	ty Questionna	re (SSQ): Tota	al; 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	⊕⊕⊖⊝ LOW¹ 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	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	⊕⊕⊝ <b>LOW</b> <sup>1</sup> due to imprecision	40	40	N/A	N/A	The mean sound sensitivity in the intervention groups was 0.13 standard deviations lower (0.57 lower to 0.31 higher)
Sound s	ensitivit	<b>y</b> (measured with	: Sound Sensitiv	ity Questionna	ire (SSQ): Tota	al; Better indicated	by lower val	ues)	•		•
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ <b>LoW</b> <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 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	by lower val	ues)		·	
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ Low¹ due to imprecision	40	40	N/A	N/A	The mean sound sensitivity in the intervention groups was <b>0.2 standard deviations higher</b> (0.24 lower to 0.64 higher)
Sound d	listress (	I measured with: So	ound Sensitivity	Questionnaire	I (SSQ): Sound	distress; Better in	dicated by lov	wer values)			
80 (1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝  MODERATE²  due to imprecision	40	40	N/A	N/A	The mean sound distress in the intervention groups was

											<b>0.02 standard deviations lower</b> (0.46 lower to 0.41 higher)
Sound d	listress (	measured with: So	ound Sensitivity (	Questionnaire	(SSQ): Sound	distress; Better in	dicated by Ic	ower values)			
80 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	40	40	N/A	N/A	The mean sound distress in the intervention groups was  0 standard deviations higher (0.44 lower to 0.44 higher)
Sound d	listress (	measured with: So	ound Sensitivity (	Questionnaire	(SSQ): Sound	distress; Better in	dicated by Ic	ower values)			
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ due to imprecision	40	40	N/A	N/A	The mean sound distress in the intervention groups was 0.43 standard deviations higher (0.01 lower to 0.87 higher)
Sound d	listress (	measured with: So	ound Sensitivity (	Questionnaire	(SSQ): Sound	distress; Better in	dicated by Ic	ower values)			<u> </u>
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	40	40	N/A	N/A	The mean sound distress in the intervention groups was  0.2 standard deviations higher (0.24 lower to 0.63 higher)
Sensory	self-stir	l <b>nulation</b> (mea	I sured with: Sens	ory Problems	I Checklist (SP)	: Total; Better indi	cated by low	ver values)			
80 (1 study)	no serious	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW¹	40	40	N/A	N/A	The mean sensory self-stimulation in

4 weeks	risk of bias					due to imprecision					the intervention groups was 0.07 standard deviations higher (0.36 lower to 0.51 higher)
Sensory	self-sti	mulation (mea	sured with: Sens	ory Problems	Checklist (SP)	: Total; Better indi	cated by low	er values)			
80 (1 study) 13 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LoW</b> ¹ due to imprecision	40	40	N/A	N/A	The mean sensory self-stimulation in the intervention groups was <b>0.1 standard deviations higher</b> (0.34 lower to 0.54 higher)
Sensory	self-sti	nulation (mea	sured with: Sens	ory Problems	Checklist (SP)	: Total; Better indi	cated by low	er values)			
80 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊕⊝ MODERATE² due to imprecision	40	40	N/A	N/A	The mean sensory self-stimulation in the intervention groups was <b>0.05 standard deviations higher</b> (0.39 lower to 0.49 higher)
Sensory	self-sti	mulation (mea	sured with: Sens	ory Problems	Checklist (SP)	: Total; Better indi	cated by low	er values)			
80 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ due to imprecision	40	40	N/A	N/A	The mean sensory self-stimulation in the intervention groups was <b>0.22 standard deviations higher</b> (0.22 lower to 0.66 higher)
<sup>1</sup> N<400 and <sup>2</sup> N<400	l 1 95% CI cro	sses both line of r	I no effect and me	asure of appre	Leciable benefit	or harm (SMD -0.:	5/0.5)				[

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

		Q	uality assessr	nent			Summary of Findings					
Participants		Inconsistency	Indirectness	•	Publication	Overall quality	Study event	rates (%)	Relative	Anticipated a	bsolute effects	
(studies) Follow up	bias				bias	of evidence	With Treatment-as- usual	therapy	effect (95% CI)	Risk with Treatment-as- usual	Risk difference with Sensory integration therapy (95% CI)	
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	⊕⊕⊖⊝ LOW <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>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants non-blind, and risk of detection bias is unclear/unknown as the identity and blinding of outcome assessor is not reported

#### 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 assessn	nent					Summa	ry of Find	ings	
Participants		Inconsistency	Indirectness	Imprecision			Study ev	rent rates (%)		Anticipate	d absolute effects	
(studies) Follow up	bias				bias	of evidence	With Waitlist control	With Horseback riding	effect (95% CI)	Risk with Waitlist control	Risk difference with Horseback riding (95% CI)	
Fine moto	Fine motor/perception (measured with: Sensory Profile: Fine motor/perception; Better indicated by lower values)											

<sup>&</sup>lt;sup>2</sup> N<400

34 (1 study) 12 weeks	serious <sup>1</sup>		no serious indirectness	very serious <sup>2</sup>		⊕⊖⊝ <b>VERY LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	15	19	N/A	N/A	The mean fine motor/perception in the intervention groups was <b>0.22 standard deviations</b> higher (0.45 lower to 0.9 higher)
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<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants non-blind. There is also a high risk of detection bias as outcome measures are parent-rated and parents non-blind

#### 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	ent				Sun	nmary of	Finding	S
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticip	ated absolute effects
(studies) Follow up	bias	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% CI)			
Fine mote	or skills	(measured with: N	Mullen Scales of	Early Learning	g (MSEL): Fine	e Motor; Better i	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	⊕⊕⊝⊝ LoW¹ due to imprecision	21	24	N/A	N/A	The mean fine motor skills in the intervention groups was <b>0.45 standard deviations higher</b> (0.15 lower to 1.04 higher)
Motor ski	ills (measu	ured with: Vineland	d Adaptive Beha	viour Scale (V	ABS): Motor S	kills; Better indi	cated by	lower values)			
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 higher</b> (0.17 to 1.39 higher)

<sup>&</sup>lt;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)

#### 1.23.3 Educational interventions for motor skills as an indirect outcome

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

		Qı	uality assessr	ment			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% CI)	
Fine moto	or skills	<b>S</b> (measured with:	Mullen Scales of	of Early Learnin	ng (MSEL): Fir	ne Motor Age (m	onths); Better i	indicated by lower va	alues)			
294 (1 study) 104 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊖ LOW¹.² 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 deviations higher</b> (0.45 to 0.93 higher)	

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants non-blind. In addition, risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported
<sup>2</sup> N<400

## 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

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

<sup>&</sup>lt;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>&</sup>lt;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

N<400

(studies) Follow up	bias				bias	quality of evidence	With Control	With Parent training versus treatment-as- usual for motor skills as an indirect outcome		Risk with Control	Risk difference with Parent training versus treatment-as- usual for motor skills as an indirect outcome (95% CI)
Motor sk	ills (PE	C+PEBM cor	<b>mbined)</b> (mea	sured with: Vi	neland Adaptiv	e Behaviour Sca	le (VABS	S): Motor Skills; Better in	dicated by lo	ower value	es)
103 (1 study) 46 weeks	serious <sup>1</sup>	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	35	68	N/A	N/A	The mean motor skills (pec+pebm combined) in the intervention groups was <b>0.11 standard deviations higher</b> (0.3 lower to 0.52 higher)

<sup>&</sup>lt;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 although the study included a blinded clinician outcome assessor this outcome measure was based on parental interview and simultaneous child observation and parents 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)

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

		Qu	ality assessm	nent			Summary of Findings					
Participants		Inconsistency	Indirectness	Imprecision			Study	event rates (%)	Relative	Anticipa	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 fine and gross motor skills as 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% CI)	
Fine moto values)	or skills	(measured with:	Early Interventio	n Developmer	ntal Profile (EII	OP)/Preschool D	evelopn	nental Profile (PSDP): Per	ceptual/Fin	e Motor;	Better indicated by lower	
35 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ <b>LOW</b> <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 higher</b> (0.66 lower to 0.67 higher)	
Gross mo	otor ski	IIS (measured wit	h: Early Interven	tion Developm	nental Profile (I	EIDP)/Preschoo	l Develo	pmental Profile (PSDP): 0	Gross Motor	r; Better i	ndicated by lower values)	
35	no	no serious	no serious	very	undetected	$\oplus \oplus \ominus \ominus$	19	16	N/A	N/A	The mean gross motor skills	

(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	N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit 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

		Qι	ıality assessn	nent			Summary of Findings				
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 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% CI)
Fine mote	or skill	<b>S</b> (measured with	: Mullen Scales	of Early Learn	ing (MSEL): F	ine Motor Age	(months)	; Better indicated by lower va	lues)		
50 (1 study) 39 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	25	25	N/A	N/A	The mean fine motor skills in the intervention groups was <b>0.02 standard deviations higher</b> (0.53 lower to 0.58 higher)
Motor ski	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 higher</b> (0.44 lower to 0.82 higher)

#### 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

		Qu	ality assessm	ent	Summary of Findings						
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study e	event rates (%)	Relative	Anticipa	nted absolute effects
(studies) Follow up	bias				bias	quality of evidence	With Control	With Secretin versus placebo for fine and gross motor skills as an indirect outcome	(95% CI)	Risk with Control	Risk difference with Secretin versus placebo for fine and gross motor skills as an indirect outcome (95% CI)
Fine mot	or skills	(measured with: M	fullen/DTVP-2: F	ine motor (mo	nths); Better ir	dicated by lower	values)		•	•	
(1 study) 4 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	28	28	N/A	N/A	The mean fine motor skills in the intervention groups was <b>0.04 standard deviations lower</b> (0.57 lower to 0.48 higher)
<sup>1</sup> N<400 and	95% CI cros	sses both line of no	effect and meas	sure of apprec	iable benefit o	harm (SMD -0.5	5/0.5)			l	

#### 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

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

<sup>&</sup>lt;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

<sup>&</sup>lt;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>&</sup>lt;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

(studies) Follow up	bias				bias		_	With Omega- 3 fatty acids		Risk with Healthy diet control	Risk difference with Omega-3 fatty acids (95% CI)
Fine mot	<b>Or</b> (measu	red with: Mullen Sca	ales of Early Learr	ning (MSEL): F	Fine 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	⊕⊖⊝ <b>VERY LOW</b> <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 deviations lower</b> (0.86 lower to 0.79 higher)

<sup>&</sup>lt;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 the outcome assessor for this outcome measure was not blinded.

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

		Q	nent		Summary of Findings						
Participants		Inconsistency	Indirectness	Imprecision		Overall quality	Study event	rates (%)	Relative	Anticipated a	bsolute 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)
Motor imp	pairme	<b>1t</b> (measured with:	Movement Asses	ssment Battery	for Children:	Test of Motor Impa	airment (TOMI	); 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	⊕⊖⊖⊖ VERY LOW¹.² 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 deviations lower</b> (1 lower to 0.76 higher)

<sup>&</sup>lt;sup>1</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 identity and blinding of outcome assessors not reported

<sup>&</sup>lt;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>&</sup>lt;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)

# 1.25PSYCHOSOCIAL 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 assess	sment	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 a	bsolute effects
							With Waitlist or treatment- as-usual	With CBT		Risk with Waitlist or treatment-as- usual	Risk difference with CBT (95% CI)
No longe	er meet	anxiety disc	order diagi	10SiS (asses	ssed with: Num	nber of participants wh	no no longer m	et DSM-I\	/ criteria for	anxiety disorde	er)
_	no serious	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹	2/42 (4.8%)	29/45 (64.4%)	<b>RR 11.82</b> (3.14 to	Study popula	tion
16-24 weeks						due to imprecision	(11070)	(0 , 6)	44.5)	48 per 1000	515 more per 1000 (from 102 more to 1000 more)
										Moderate	
										44 per 1000	<b>476 more per 1000</b> (from 94 more to 1000 more)
Improve	ment in	anxiety syr	nptoms (ass	sessed with: Cl	inical global im	npressions scale: Impr	rovement rating	gs)			
83	no serious	no serious	no serious	serious <sup>1</sup>	undetected	$\oplus\oplus\ominus\ominus$	4/46	23/37	RR 7.2	Study popula	ition

(2 studies) 16-24 weeks	risk of bias	inconsistency	indirectness		MODERATE <sup>1</sup> 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	1
										87 per 1000	<b>539 more per 1000</b> (from 151 more to 1000 more)
Self-repo	orted an	xiety (measure	ed with: Spence C	L Childrens Anxid	ety Scale (SCA	.S) or Multidimensiona	Il Anxiety Scal	e 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 1.06 standard deviations lower (1.58 to 0.55 lower)
Parent-re Better indicate			asured with: Sper	nce Childrens	Anxiety Scale:	Parent Version (SCAS	S-P) or Multidi	mensional	Anxiety Sc	ale for Children	(MASC): Parent version;
149 (3 studies) 6-24 weeks	serious <sup>5</sup>	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 0.99 standard deviations lower (1.39 to 0.6 lower)
		-				lle for Children - Clinic ated by lower values)	al Severity Ra	ting Scale	(ADIS-CSF	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	⊕⊖⊖⊝ <b>VERY LOW</b> <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 Children	n's Manifest Ai	nxiety Scale (R	CMAS); Better indicate	ed by lowe	r values)			
17 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 chronic anxiety in the intervention groups was 3.29 standard deviations lower (4.19 to 2.38 lower)
	nxiety (i		pence Child Anxie	ety Scale-Pare	ent (SCAS-P): S	ocial phobia or Anxiet	y Disorders	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 anxiet in the intervention groups was <b>0.2 standard deviations lower</b> (0.59 lower to 0.2 higher)
•		iety (measured value	•	d Anxiety Sca	le-Parent (SCA	S-P): Separation or A	nxiety Disc	orders Intervi	iew Schedu	lule for Childre	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	⊕⊖⊖ <b>VERY LOW</b> <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 <b>0.39 standard deviations lower</b> (0.78 lower to 0.01 higher)

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 deviations lower</b> (1.1 to 0.22 lower)
relating	to a specif	ic phobia	measured with	n: Anxiety Disor	ders Interview Schedu	ule for Childr	en - Parent	Version (AI	DIS-P): Speci	fic phobia; Better indicated
serious <sup>8</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 deviations lower</b> (1.63 to 0.36 lower)
asured with	: Spence Child Ar	xiety Scale-Pare	ent (SCAS-P):	Panic; Better in	dicated by lower value	es)		-		
serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊖⊝ <b>VERY LOW</b> <sup>5,7</sup> due to risk of bias, imprecision	20	46	N/A	N/A	The mean panic in the intervention groups was 0.15 standard deviations higher (0.37 lower to 0.68 higher)
easured with	n: Spence Child Ar	nxiety Scale-Pare	ent (SCAS-P):	Panic; Better in	dicated by lower value	es)				
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)
	relating es) serious <sup>8</sup> easured with	inconsistency  relating to a specifies)  serious <sup>8</sup> no serious inconsistency  resured with: Spence Child Armserious <sup>5</sup> no serious inconsistency  resured with: Spence Child Armserious <sup>5</sup> no serious	relating to a specific phobia (es)  serious <sup>8</sup> no serious no serious inconsistency indirectness  assured with: Spence Child Anxiety Scale-Pare inconsistency indirectness  serious <sup>5</sup> no serious no serious inconsistency indirectness  easured with: Spence Child Anxiety Scale-Pare serious <sup>5</sup> no serious no serious inconsistency indirectness	relating to a specific phobia (measured with es)  serious <sup>8</sup> no serious no serious inconsistency indirectness  serious <sup>5</sup> no serious no serious inconsistency indirectness  serious <sup>5</sup> no serious no serious very indirectness  serious <sup>5</sup> no serious no serious inconsistency indirectness  serious <sup>5</sup> no serious no serious very serious <sup>7</sup> serious <sup>5</sup> no serious no serious very	inconsistency indirectness  relating to a specific phobia (measured with: Anxiety Disores)  serious <sup>8</sup> no serious inconsistency indirectness serious <sup>4</sup> undetected indirectness  assured with: Spence Child Anxiety Scale-Parent (SCAS-P): Panic; Better in serious <sup>5</sup> no serious inconsistency indirectness serious <sup>7</sup> undetected seasured with: Spence Child Anxiety Scale-Parent (SCAS-P): Panic; Better in serious <sup>5</sup> no serious no serious very undetected	inconsistency indirectness   LOW <sup>4,5</sup> due to risk of bias, imprecision    serious <sup>8</sup>   no serious inconsistency   no serious indirectness   serious <sup>4</sup>   undetected   ⊕⊕⊖	inconsistency indirectness   LOW <sup>4,5</sup>   due to risk of bias, imprecision    relating to a specific phobia (measured with: Anxiety Disorders Interview Schedule for Childres)  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    asured with: Spence Child Anxiety Scale-Parent (SCAS-P): Panic; Better indicated by lower values)  serious <sup>5</sup>   no serious inconsistency   no serious indirectness   very   undetected   ⊕⊕⊕⊕   VERY LOW <sup>5,7</sup>   due to risk of bias, imprecision    assured with: Spence Child Anxiety Scale-Parent (SCAS-P): Panic; Better indicated by lower values)  serious <sup>5</sup>   no serious inconsistency   no serious inconsistency   no serious inconsistency   no serious indirectness   very   undetected   ⊕⊕⊕⊕   VERY LOW <sup>5,7</sup>   due to risk of bias, imprecision   20   VERY LOW <sup>5,7</sup>   due to risk of bias, inconsistency   very   undetected   ⊕⊕⊕⊕   VERY LOW <sup>5,7</sup>   due to risk of bias, inconsistency   very   undetected   ⊕⊕⊕⊕   very   ver	inconsistency indirectness   LOW <sup>4.5</sup>   due to risk of bias, imprecision    relating to a specific phobia (measured with: Anxiety Disorders Interview Schedule for Children - Parent es)  serious <sup>8</sup>   no serious indirectness   serious <sup>4</sup>   undetected   ⊕⊕⊕   LOW <sup>4.8</sup>   due to risk of bias, imprecision    assured with: Spence Child Anxiety Scale-Parent (SCAS-P): Panic; Better indicated by lower values)  serious <sup>5</sup>   no serious indirectness   very   undetected   ⊕⊕⊕⊕   VERY LOW <sup>5.7</sup>   due to risk of bias, imprecision    serious <sup>5</sup>   no serious indirectness   no serious indirectness   very   undetected   ⊕⊕⊕⊕   VERY LOW <sup>5.7</sup>   due to risk of bias, imprecision    serious <sup>5</sup>   no serious   no serious indirectness   very   undetected   ⊕⊕⊕⊕   VERY LOW <sup>5.7</sup>   due to risk of bias, imprecision   very   ver	Inconsistency   Indirectness   LOW <sup>4.5</sup>   due to risk of bias, imprecision	Inconsistency   Indirectness   In

66 (1 study) 6 weeks	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 deviations higher</b> (0.32 lower to 0.73 higher)
Fear of	persona	al injury (mea	sured with: Spen	ce Child Anxie	ty Scale-Paren	t (SCAS-P): Personal	Injury; Bett	er indicated b	oy lower va	ilues)	
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 fear of personal injury in the intervention groups was <b>0.31 standard deviations lower</b> (0.84 lower to 0.22 higher)
OCD (mea	asured with:	Spence Child Anx	iety Scale-Paren	t (SCAS-P): O	CD; Better indic	cated by lower values)	)		<del>'</del>		
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 ocd in the intervention groups was 0.33 standard deviations lower (0.86 lower to 0.19 higher)
OCD (me	asured with:	Spence Child Anx	kiety Scale-Paren	it (SCAS-P): O	CD; Better indi	cated by lower values	)		1		
66 (1 study) 12 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	20	46	N/A	N/A	The mean ocd in the intervention groups was 1 standard deviations lower (1.55 to 0.45 lower)

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 deviations lower</b> (5.37 to 3.21 lower)
Emotio	nal sym <sub>l</sub>	ptoms (measu	red with: Strength	ns and Difficul	ties Questionna	ire: Teacher Version:	Emotional;	Better indica	ted by lowe	er 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	egative thou	ughts (measu	red with: Child	dren's Automatic	Thoughts Scale (CAT	ΓS): Interna	lising; Better	indicated b	by lower value	es)
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 <b>4.61 standard deviations lower</b> (5.75 to 3.48 lower)
Outward	d-direct	ed negative	thoughts	measured wit	h: Children's Au	tomatic Thoughts Sca	le (CATS):	Hostile Inter	t; Better in	dicated by lov	ver values)
47 (1 study) 24 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>7</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 0.33 standard deviations lower (0.91 lower to 0.26 higher)

<sup>&</sup>lt;sup>3</sup> I squared value is considerable at 96% (p=0.00001)

# 1.26PHARMACOLOGICAL INTERVENTIONS AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

#### 1.26.1SNRIs for ADHD as a direct outcome

Atomoxetine versus placebo for ADHD as a direct outcome

	Quality assessment						Sumi	mary of F	indings	5	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study	` '	Relative effect	Anticip	ated absolute effects
Follow up						evidence	With Control	/ith With Selective noradrenaline		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			y lower v	/alues)
88 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LoW</b> ¹ due to imprecision	45	43	N/A	N/A	The mean hyperactivity (parent-rated) in the intervention groups was <b>0.19 standard deviations lower</b> (0.61 lower to 0.22 higher)

<sup>&</sup>lt;sup>4</sup> Total N less than 400

<sup>&</sup>lt;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>&</sup>lt;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>&</sup>lt;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.

72 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ 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> lower (0.59 lower to 0.34 higher)
ADHD :	sympto	ms (parent	:-rated) (mea	asured with: D	SM-IV ADHD I	Rating Scale (AD	)HD-RS	s): 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	⊕⊕⊕⊝ MODERATE² 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> lower (0.9 to 0.06 lower)
VDHD .		<u> </u>									
ADIID	sympto	ms (teache	er-rated) (m	easured with:	Conners' Tead	ther Rating Scale	e - Revis	sed: Short Form (C	CTRS-R:S): ADHD; E	Better indi	cated by lower values)
72 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	Conners' Teac	⊕⊕⊖⊝ LOW¹ due to imprecision	36	sed: Short Form (C 36	CTRS-R:S): ADHD; E	N/A	The mean adhd symptom (teacher-rated) in the intervention groups was 0.15 standard deviations lower
72 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to imprecision	36	36	N/A	N/A	The mean adhd symptoms (teacher-rated) in the intervention groups was <b>0.15 standard deviations</b>

72 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to imprecision	36	36	N/A	N/A	The mean oppositional (teacher-rated) in the intervention groups was <b>0.1 standard deviations higher</b> (0.36 lower to 0.56 higher
Improve	ement i	n ADHD sy	mptoms (	Clinician	- <b>rated)</b> (me	easured with: Cl	inical Gl	lobal Impression S	Scale-ADHD-Improve	ment (CG	I-ADHD-I); Better indicated b
lower values		no serious	no serious	very	undetected	<b>⊕⊕⊝⊝</b>	46	43	N/A	N/A	The mean improvement in

# 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

		G	Quality assessn	nent		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		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 lower</b> (1.13 lower to 0.53 higher)

<sup>&</sup>lt;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 the outcome assessor for this outcome measure was not blinded.

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

		C	Quality 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 a	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% CI)		
Inattenti	<b>ON</b> (measu	ured with: Attention-	Deficit Hyperactiv	ity Disorder-IV	rating scale bas	sed on DSM-IV cri	teria (ADHD-l	V): Inattention	(change sco	ore); Better indi	cated by lower values)		
55 (1 study) 35 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW¹.² due to risk of bias,	29	26	N/A	N/A	The mean inattention in the intervention groups was 0.59 standard deviations lower		

<sup>&</sup>lt;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)

						imprecision					(1.13 to 0.05 lower)
Hyperactivalues)	tivity (m	easured with: Attent	I ion-Deficit Hypera	ctivity Disorder	-IV rating scale	based on DSM-I	≀ √ criteria (ADH	HD-IV): Hypera	ctivity (chan	ge score); Bett	er 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		The mean hyperactivity in the intervention groups was <b>0.5 standard deviations lower</b> (1.04 lower to 0.04 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators (parents) and participants were non-blind and high risk of detection bias as parent-reported and non-blind to treatment allocation and other potentially confounding factors. There was also a 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)

### 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			Study e		Relative effect (95% CI)	Anticipat	ed absolute effects
							With Placebo	With Omega- 3 fatty acids		Risk with Placebo	Risk difference with Omega-3 fatty acids (95% CI)
Internalia	zing (meas	ured with: Behavior	Assessment Syste	em for Childrer	n (BASC): Interr	nalizing; Better indi	cated by I	ower values)			

<sup>&</sup>lt;sup>2</sup> N<400

<sup>&</sup>lt;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)

	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ due to imprecision	12	12	N/A	N/A	The mean internalizing in the intervention groups was <b>0.48 standard deviations lower</b> (1.3 lower to 0.33 higher)
<sup>1</sup> N<400 and	95% CI cross	es both line of no ef	fect and measure	of appreciable	benefit or harm	(SMD -0.5/0.5)				<u> </u>	

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

		C	Quality assessi	ment					Summa	ary of Findi	ngs
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)
Internali	izing (m	easured with: Child	Behavior Checkli	st 1.5 - 5 (CBC	L/1.5-5): Inter	nalizing; Better ind	licated by lov	wer values)			
23 (1 study) 13 weeks	serious <sup>1</sup>	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	13	10	N/A	N/A	The mean internalizing in the intervention groups was <b>0.17 standard deviations lower</b> (0.99 lower to 0.66 higher)
Anxious	/Depre	essed (measured	d with: Child Beha	vior Checklist	1.5 - 5 (CBCL/	1.5-5): Anxious/De	epressed; Be	etter 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	⊕⊝⊖ VERY LOW¹,2 due to risk of bias, imprecision	13	10	N/A	N/A	The mean anxious/depressed in the intervention groups was <b>0.23 standard deviations 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	⊕⊖⊖ <b>VERY LOW</b> <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 higher</b> (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	s)			

<sup>&</sup>lt;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 the outcome assessor for this outcome measure was not blinded

## 1.27.3 Medical procedures for anxiety as an indirect outcome

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

		Qu	ality assessn	nent				Sumr	nary of F	indings	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	quality of evidence	With Short- term chelation (1-round of DMSA therapy and 6-rounds	<b>,</b> ,	effect (95% CI)	•	Risk difference with Long- term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy) (95% CI)

<sup>&</sup>lt;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)

							of placebo)			placebo)	
Specific	Fears	(measured with:	Pervasive Deve	elopment Diso	rder Behavior	Inventory (PDI	DBI): Specific	Fears; Better indicated by	y lower val	ues)	
40 (1 study) 17 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>Low</b> ¹ due to imprecision	15	25	N/A	N/A	The mean specific fears in the intervention groups was <b>0.11 standard 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			Summary of Findings				
` ,	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study 6 (%)		Relative effect	Anticipat	ted absolute effects
Follow up							With Control	With CBT versus placebo	(95% CI)	Risk with Control	Risk difference with CBT versus placebo (95% CI)
Sleep on	set latend	(measured with:	Actigraph; Better	indicated by Id	ower values)				·		
	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ 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 aft	er sleep o	onset (measured	I with: Actigraph; E	Better indicated	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	⊕⊕⊝⊝ LOW² 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> lower (0.73 lower to 0.24 higher)
Nap time	(measured w	rith: 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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	33	N/A	N/A	The mean nap time in the intervention groups was <b>0.81 standard deviations lower</b> (1.32 to 0.3 lower)
Bedtime	(measured wi	th: Actigraph; Bette	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	⊕⊕⊖ MODERATE¹ due to imprecision	32	33	N/A	N/A	The mean bedtime in the intervention groups was <b>0.89 standard deviations</b> lower (1.4 to 0.38 lower)
Total sle	ep time (m	easured with: Acti	graph; Better indic	ated by lower	values)						
65 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	33	N/A	N/A	The mean total sleep time in the intervention groups was <b>0.62 standard deviations higher</b> (0.12 to 1.12 higher)
Sleep eff	ficiency (m	easured with: Acti	graph; Better indic	ated by lower	values)		1	·		<u> </u>	1
65 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖  MODERATE¹  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)
Sleep pr	roblems (m	neasured with: Chi	Idren's Sleep Habi	ts Questionnai	re (CSHQ): Tota	al score; Better indica	ated by I	ower values	;)		
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹,3 due to risk of bias, imprecision	32	33	N/A	N/A	The mean sleep problems in the intervention groups was 1.01 standard deviations lower (1.53 to 0.5 lower)
Bed resi	istance (me	easured with: Child	dren's Sleep Habits	s Questionnair	e (CSHQ): Bed	resistance; Better inc	dicated b	y lower valu	ıes)		
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹.³ due to risk of bias, imprecision	32	33	N/A	N/A	The mean bed resistance in the intervention groups was 1.18 standard deviations lower (1.71 to 0.65 lower)
Sleep or	nset delay	(measured with:	Children's Sleep H	abits Question	naire (CSHQ): \$	Sleep onset delay; B	etter ind	icated by lov	ver values)		
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖ LOW¹,3 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	nxiety (meas	sured with: Childre	en's Sleep Habits 0	Questionnaire (	CSHQ): Sleep a	anxiety; Better indica	ted by lo	ower values)			
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ <b>VERY LOW</b> <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 0.43 standard deviations lower (0.92 lower to 0.06 higher)
Night-wa	akings (me	asured with: Child	ren's Sleep Habits	Questionnaire	(CSHQ): Night	-wakings; Better indi	cated by	lower value	es)	1	
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <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)
Sleep du	uration (me	asured with: Child	ren's Sleep Habits	Questionnaire	e (CSHQ): Sleep	duration; Better ind	icated b	y lower valu	ıes)	ı	
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝ <b>VERY LOW</b> <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 higher</b> (0.26 lower to 0.71 higher)
Parason	nnias (meas	ured with: Children	n's Sleep Habits C	luestionnaire (	CSHQ): Parasoi	mnias; Better indicat	ed by lo	wer values)	<b>-</b>		
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝ <b>VERY LOW</b> <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 higher</b> (0.15 lower to 0.83 higher)
Sleep di	sordered	breathing (me	easured with: Child	dren's Sleep H	abits Questionna	aire (CSHQ): Sleep	disorder	ed breathin	g; Better indica	ated by lo	wer values)
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖ LOW¹,3 due to risk of bias, imprecision	32	33	N/A	N/A	The mean sleep disordered breathing in the intervention groups was  0 standard deviations higher  (0.49 lower to 0.49 higher)
Daytime	sleepines	SS (measured with	n: Children's Sleep	Habits Quest	ionnaire (CSHQ	): Daytime sleepines	s; Bette	er indicated l	by lower value	s)	
65 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖ LOW¹.3 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 lower</b> (1 to 0.01 lower)
		-	Sleep onset	latency (as	ssessed with: N	umber of participants	s who sh	nowed sleep	onset latency	<30 min	or reduction of sleep onset
-	1	actigraph data)	1 .	1	T		0/00	0/00	DD 0.50		
65	no serious	no serious	no serious	very	undetected	$\oplus \oplus \ominus \ominus$	0/32	3/33	RR 6.79	Study	population

(1 study) 12 weeks	risk of bias	inconsistency	indirectness	serious <sup>4</sup>		LOW <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
	T	<u> </u>	1	<del>-</del>		r of participants who	1		1	1	
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%)	RR 6.79 (0.36 to	Study po	opulation
2 weeks						due to imprecision			126.5)	0 per 1000	N/A
										Moderat	e

<sup>&</sup>lt;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)

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

Melatonin versus placebo for sleep problems as a direct outcome

		Q	uality assessn	nent				Sı	ummary of	f Finding	js .
Participants	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study	event rates (%)		Anticipa	ted absolute effects
(studies) Follow up	Dias				Dids		With Control	With Melatonin versus placebo for the coexisting problem of sleep	1(95% (:1)	Risk with Control	Risk difference with Melatonin versus placebo for the coexisting problem of sleep (95% CI)
Sleep ons	set laten	CY (measured wit	h: Actigraph; Bet	ter indicated b	y lower values	)					

<sup>&</sup>lt;sup>3</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>&</sup>lt;sup>4</sup> Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25)

66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	34	N/A	N/A	The mean sleep onset latency in the intervention groups was 1.23 standard deviations lower (1.75 to 0.7 lower)
Wake aft	er sleep	onset (measure	ed with: Actigraph	; Better indica	ited by lower va	alues)				1	
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	34	N/A	N/A	The mean wake after sleep onset in the intervention groups was  0.82 standard deviations lower  (1.32 to 0.31 lower)
Nap time	(measured	with: Actigraph; Be	etter 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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	34	N/A	N/A	The mean nap time in the intervention groups was 0.57 standard deviations lower (1.06 to 0.08 lower)
Bed time	(measured	with: Actigraph; Be	etter 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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	34	N/A	N/A	The mean bed time in the intervention groups was 1.08 standard deviations lower (1.6 to 0.56 lower)
Total sle	ep time	measured with: Ac	tigraph; Better in	dicated by low	er values)						
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	34	N/A	N/A	The mean total sleep time in the intervention groups was 1.45 standard deviations higher (0.9 to 1.99 higher)

Sleep ef	ficiency (	measured with: A	ctigraph; Better i	ndicated by lov	wer values)						
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝  MODERATE¹  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	neasured with: C	hildren's Sleep H	abits Question	naire (CSHQ):	Total score; Bette	r indicat	ed by lower va	lues)		·
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	34	N/A	N/A	The mean sleep problems in the intervention groups was 1.81 standard deviations lower (2.39 to 1.23 lower)
Bed resi	istance (m	easured with: Ch	ildren's Sleep Ha	bits Questionr	naire (CSHQ): E	Bed resistance; Be	tter indic	cated by lower	values)	L	
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE¹ due to imprecision	32	34	N/A	N/A	The mean bed resistance if the intervention groups wa 1.72 standard deviations lower (2.29 to 1.15 lower)
Sleep or	nset dela	/ (measured with	: Children's Slee	o Habits Ques	tionnaire (CSH	Q): Sleep onset de	lay; Bet	ter indicated b	y lower values)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝  MODERATE¹  due to  imprecision	32	34	N/A	N/A	The mean sleep onset delay in the intervention groups was 1.58 standard deviations lower (2.14 to 1.03 lower)
Sleep ar	nxiety (mea	Lasured with: Child	ren's Sleep Habi	ts Questionnai	re (CSHQ): Sle	eep anxiety; Better	indicate	d 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	⊕⊕⊝⊝ LOW² due to imprecision	32	34	N/A	N/A	The mean sleep anxiety in the intervention groups wa 0.37 standard deviations lower

											(0.86 lower to 0.12 higher)
Night-wa	akings (me	easured with: Child	dren's Sleep Hab	its Questionna	aire (CSHQ): N	ight-wakings; Bette	er indica	ted by lower v	ralues)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝  MODERATE¹  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	oits Questionn	aire (CSHQ): S	leep duration; Bett	er indic	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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	34	N/A	N/A	The mean sleep duration in the intervention groups was 1.39 standard deviations lower (1.93 to 0.85 lower)
Parason	nnias (mea	sured with: Childre	en's Sleep Habits	Questionnair	e (CSHQ): Par	asomnias; Better ir	ndicated	by lower valu	ies)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊝ Low² due to imprecision	32	34	N/A	N/A	The mean parasomnias in the intervention groups was <b>0.11 standard deviations higher</b> (0.37 lower to 0.6 higher)
Sleep di	sordered	breathing (m	Ineasured with: Cl	nildren's Sleep	Habits Questi	onnaire (CSHQ): S	leep dis	ordered breat	hing; Better indicate	d by low	er values)
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW² due to imprecision	32	34	N/A	N/A	The mean sleep disordered breathing in the intervention groups was  0.11 standard deviations lower  (0.59 lower to 0.38 higher)
Daytime	sleepine	SS (measured wi	th: Children's Sle	eep Habits Qu	estionnaire (CS	SHQ): Daytime slee	piness;	Better indicat	ed by lower values)		
66 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖ MODERATE¹ due to imprecision	32	34	N/A	N/A	The mean daytime sleepiness in the intervention groups was 0.72 standard deviations lower

							7				(1.21 to 0.22 lower)			
Sleep or	nset laten	IC <b>y</b> (measured wi	th: Sleep diary (s	tudy-specific);	Better indicate	l ed by lower values)	)							
49 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	24	25	N/A	N/A	The mean sleep onset latency in the intervention groups was <b>0.76 standard deviations lower</b> (1.35 to 0.18 lower)			
Total sle	ep time	measured with: Sl	eep diary (study-s	specific); Bette	r indicated by	lower values)	•		1	1				
47 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW² due to imprecision	24	23	N/A	N/A	The mean total sleep time in the intervention groups was <b>0.15 standard deviations higher</b> (0.43 lower to 0.72 higher)			
		nt response - actigraph data)	· Sleep onse	et latency	(assessed with	: Number of partic	ipants w	ho showed sleep onse	et latency <3	0 min or re	eduction of sleep onset			
66 (1 study)	no serious	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>3</sup>	0/32 (0%)	13/34 (38.2%)	RR 25.46 (1.58 to	Study po	opulation			
12 weeks	bias	inconsistency	indirectiness			due to imprecision	(070)	(00.278)	411.3)	0 per 1000	N/A			
										Moderat	ee			
										0 per 1000	N/A			
Positive	treatmer	nt response ·	Sleep effic	iency (asse	ssed with: Nun	nber of participants	s who sh	owed =>85% for sleep	efficiency b	ased on a	actigraph data)			
66 (1 study)	no serious	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>3</sup>	0/32 (0%)	16/34 (47.1%)	RR 31.11 (1.94 to	Study population				
12 weeks	bias	in conclusion by	manooniooo			due to imprecision	(676)	(11176)	498.04)	0 per 1000	N/A			
										Moderat	e			

							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 apprecia	able benefit or	harm (SMD -0.5/0.	.5)		

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

		Q	uality assessn	nent				Sı	ımmary 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% CI)
Sleep on	set laten	Cy (measured with	n: Actigraph; Bett	er indicated by	lower values)						
67 (1 study) 12 weeks		no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ 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 (measured	d with: Actigraph;	Better indicate	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	⊕⊕⊕⊝ MODERATE¹ 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 lower</b> (1.22 to 0.23 lower)
Nap time	(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	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <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	with: Actigraph; Be	etter indicated by	lower values)		1			1	<u> </u>	
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊝ LOW² due to imprecision	33	34	N/A	N/A	The mean bed time in the intervention groups was 0.23 standard deviations lower (0.71 lower to 0.25 higher)
Total sle	eep time (r	neasured with: Ac	tigraph; Better inc	dicated by low	er values)	1			1	<u> </u>	
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	33	34	N/A	N/A	The mean total sleep time in the intervention groups was 0.76 standard deviations higher (0.26 to 1.26 higher)
Sleep ef	ficiency (r	neasured with: Ac	tigraph; Better inc	dicated by low	er values)	1	ı		l		
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	33	34	N/A	N/A	The mean sleep efficiency in the intervention groups was <b>0.89 standard deviations higher</b> (0.39 to 1.4 higher)
Sleep pr	roblems (n	neasured with: Ch	ildren's Sleep Hal	bits Questionr	aire (CSHQ): 1	otal score; Better ir	ndicated	d 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 problems in the intervention groups was 0.94 standard deviations lower (1.45 to 0.44 lower)
Bed res	istance (m	easured with: Child	dren's Sleep Hab	its Questionna	aire (CSHQ): Be	ed resistance; Bette	r indica	ted by lower values)			
67 (1 study)	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <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 0.5 standard deviations lower (0.99 to 0.01 lower)
Sleep or	set delay	(measured with:	Children's Sleep I	Habits Questic	onnaire (CSHQ	): Sleep onset delay	r; Better	r indicated 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 onset delay in the intervention groups was <b>0.65 standard deviations</b> lower (1.14 to 0.15 lower)
Sleep an	nxiety (mea	asured with: Childre	en's Sleep Habits	Questionnaire	e (CSHQ): Slee	p anxiety; Better inc	dicated	by lower values)		<b>L</b>	-
67 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹.³ due to risk of bias, imprecision	33	34	N/A	N/A	The mean sleep anxiety in the intervention groups was 0.02 standard deviations higher (0.46 lower to 0.5 higher)
Night-wa	akings (me	easured with: Child	I Iren's Sleep Habit	s Questionnai	re (CSHQ): Nig	J ght-wakings; Better i	ndicate	d 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 night-wakings in the intervention groups was  1.86 standard deviations lower  (2.44 to 1.28 lower)
Sleep du	ıration (m	easured with: Child	dren's Sleep Habit	s Questionnai	ire (CSHQ): Sle	eep 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)

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

Positive	treatmen	t response -	Sleep effici	ency (asses	sed with: Num	ber of participants	who show	/ed =>85% for sleep	efficiency b	ased on a	ctigraph data)
67 (1 study)	no serious	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE⁴	3/33 (9.1%)	16/34 (47.1%)	RR 5.18 (1.66 to	Study p	opulation
12 weeks	now or blue		indirectiness.			due to imprecision	(6.176)	(,	16.13)	91 per 1000	380 more per 1000 (from 60 more to 1000 more)
										Moderat	e
										91 per 1000	<b>380 more per 1000</b> (from 60 more to 1000 more)

N<400

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

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

		Q	uality assessn	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 Combined melatonin and CBT versus placebo	effect (95% CI)	Risk with Control	Risk difference with Combined melatonin and CBT versus placebo (95% CI)			
Sleep on:	Sleep onset latency (measured with: Actigraph; Better indicated by lower values)													
-		no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	35	N/A	N/A	The mean sleep onset latency in the intervention groups was 1.86 standard deviations lower			

<sup>&</sup>lt;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>&</sup>lt;sup>3</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>&</sup>lt;sup>4</sup> Events<300

											(2.44 to 1.29 lower)
Wake af	ter sleep	o <b>nset</b> (measure	ed with: Actigraph	; Better indicat	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	⊕⊕⊕⊝  MODERATE¹  due to imprecision	32	35	N/A	N/A	The mean wake after sleep onset in the intervention groups was 1.29 standard deviations lower (1.82 to 0.76 lower)
Nap time	e (measured v	vith: Actigraph; Be	etter 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	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	35	N/A	N/A	The mean nap time in the intervention groups was 0.95 standard deviations lower (1.45 to 0.44 lower)
Bedtime	(measured w	ith: Actigraph; Be	tter indicated by lo	ower values)	_	1	"		<b>-</b>	ľ	
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	32	35	N/A	N/A	The mean bedtime in the intervention groups was 1.32 standard deviations lower (1.85 to 0.79 lower)
Total sle	eep time (n	neasured with: Ac	tigraph; Better inc	dicated by lowe	er values)	·	l				
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝  MODERATE¹  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: Ac	tigraph; Better inc	dicated by lowe	er values)				1	1	
67 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝  MODERATE¹  due to  imprecision	32	35	N/A	N/A	The mean sleep efficiency in the intervention groups was 2.8 standard deviations

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											higher (2.12 to 3.49 higher)
Sleep p	roblems (	measured with: Ch	ildren's Sleep Hal	oits Questionna	aire (CSHQ): T	otal score; Better in	dicated	by lower values	s)	<u> </u>	
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹.² 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: Chil	dren's Sleep Habi	its Questionna	ire (CSHQ): Be	d resistance; Better	indicat	ed by lower val	ues)	<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 3.34 standard deviations lower (4.09 to 2.58 lower)
Sleep or	nset dela	<b>y</b> (measured with:	Children's Sleep	Habits Questio	nnaire (CSHQ)	: Sleep onset delay	; Better	indicated by lo	wer values)		
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹.² 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 aı	n <b>xiety</b> (mea	asured with: Childre	en's Sleep Habits	Questionnaire	(CSHQ): Slee	p anxiety; Better ind	icated I	oy lower values	)		
67 (1 study)	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹,² due to risk of bias, imprecision	32	35	N/A	N/A	The mean sleep anxiety in the intervention groups was 1.74 standard deviations
12 weeks											<b>lower</b> (2.3 to 1.17 lower)
	akings (m	easured with: Child	lren's Sleep Habit	s Questionnair	re (CSHQ): Nig	ht-wakings; Better ii	ndicate	d by lower value	es)		

(1 study) 12 weeks		inconsistency	indirectness			LOW <sup>1,2</sup> due to risk of bias, imprecision					in the intervention groups was 3.96 standard deviations lower (4.8 to 3.12 lower)
Sleep du	<b>iration</b> (m	easured with: Child	ren's Sleep Habit	s Questionnai	re (CSHQ): Sle	ep duration; Better i	ndicate	d by lower value	es)	•	<u>'</u>
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 duration in the intervention groups was 1.73 standard deviations lower (2.29 to 1.16 lower)
Parason	nnias (mea	sured with: Childre	n's Sleep Habits (	Questionnaire	(CSHQ): Paras	somnias; Better indi	cated by	y lower values)	<b>.</b>		
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <sup>2,3</sup> due to risk of bias, imprecision	32	35	N/A	N/A	The mean parasomnias in the intervention groups was 0.16 standard deviations lower (0.64 lower to 0.32 higher)
Sleep di	sordered	breathing (me	I easured with: Chil	I Idren's Sleep F	I Habits Questior	nnaire (CSHQ): Slee	p disor	dered breathing;	Better indicate	ed by lowe	r values)
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝ <b>VERY LOW</b> <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 0.03 standard deviations higher (0.45 lower to 0.51 higher)
Daytime	sleepine	SS (measured with	n: Children's Slee	p Habits Ques	tionnaire (CSH	IQ): Daytime sleepir	ness; Be	etter indicated by	/ lower values)		
67 (1 study) 12 weeks	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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)

67 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE⁴	0/32 (0%)	30/35 (85.7%)	RR 55.92 (3.56 to	Study population
2 weeks						due to imprecision		,	878.39)	0 per N/A 1000
										Moderate
										0 per N/A 1000
Positive	treatmen	t response -	Sleep efficion	ency (asses	sed with: Numb	per of participants v	ho show	ved =>85% for sle	eep efficiency b	ased on actigraph data)
67 (1 study)	no serious risk of bias	no serious inconsistency	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 population
12 weeks						due to imprecision		,	653.27)	0 per 1000 N/A
										Moderate
										0 per N/A 1000

<sup>&</sup>lt;sup>1</sup> N<400

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

		Q	uality assessr	ment			Summary of Findings					
Participants		Inconsistency	Indirectness	•			Study	event rates (%)		Anticipated absolute effects		
(studies) Follow up	bias				bias	of evidence	With Control	With Combined melatonin and CBT versus CBT-only for coexisting problem of	1(95% CI)	Risk with Combined Control melatonin and CBT versus CBT-only for coexisting problem of sleep (95% CI)		

<sup>&</sup>lt;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>&</sup>lt;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)

<sup>&</sup>lt;sup>4</sup> Events<300

								sleep			
Sleep or	⊥ nset laten	I <b>CY</b> (measured w	ith: Actigraph; Be	tter indicated	by lower value	es)					
68 (1 study) 12 weeks	1	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	33	35	N/A	N/A	The mean sleep onset latency in the intervention groups was 1.15 standard deviations lower (1.67 to 0.64 lower)
Wake af	ter sleep	onset (measur	ed with: Actigrap	h; Better indic	ated by lower v	values)					
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝  MODERATE¹  due to  imprecision	33	35	N/A	N/A	The mean wake after sleep onset in the intervention groups was  1.4 standard deviations lower  (1.94 to 0.87 lower)
Nap time	e (measured	with: Actigraph; B	setter indicated by	/ lower values	)	1					<u>'</u>
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>2</sup> due to imprecision	33	35	N/A	N/A	The mean nap time in the intervention groups was 0.13 standard deviations lower (0.61 lower to 0.35 higher)
Bed time	<b>e</b> (measured	with: Actigraph; B	Better indicated by	/ lower values	)						
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW² due to imprecision	33	35	N/A	N/A	The mean bed time in the intervention groups was <b>0.47 standard deviations lower</b> (0.95 lower to 0.01 higher)
Total sle	eep time (	neasured with: A	ctigraph; Better in	ndicated by lov	wer values)		·		<u> </u>	1	1
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊖  MODERATE¹  due to imprecision	33	35	N/A	N/A	The mean total sleep time in the intervention groups was 1.46 standard deviations higher

											(0.93 to 2 higher)
Sleep ef	ficiency (	neasured with: Ac		ndicated by lov	ver values)						
68 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	33	35	N/A	N/A	The mean sleep efficiency in the intervention groups was 1.33 standard deviations higher (0.81 to 1.86 higher)
Sleep pr	oblems (r	neasured with: Ch	nildren's Sleep H	abits Question	naire (CSHQ):	Total score; Bette	r indicat	ted by lower va	alues)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 3.1 standard deviations lower (3.81 to 2.38 lower)
Bed resi	stance (m	easured with: Chi	ldren's Sleep Ha	bits Questionr	naire (CSHQ):	Bed resistance; Be	tter indi	cated by lower	r values)	1	
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 1.7 standard deviations lower (2.26 to 1.14 lower)
Sleep or	set delay	/ (measured with:	Children's Sleep	Habits Quest	tionnaire (CSH	Q): Sleep onset de	lay; Be	tter indicated b	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 1.23 standard deviations lower (1.75 to 0.71 lower)
Sleep ar	nxiety (mea	sured with: Childr	en's Sleep Habit	s Questionnai	re (CSHQ): Sle	eep anxiety; Better	indicate	ed by lower val	ues)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹,3 due to risk of	33	35	N/A	N/A	The mean sleep anxiety in the intervention groups was 1.55 standard deviations

						bias, imprecision					lower (2.1 to 1.01 lower)
Night-wa	akings (m	easured with: Chil	dren's Sleep Hab	its Questionn	aire (CSHQ): N	light-wakings; Bette	er indica	ited 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 night-wakings in the intervention groups was 2.66 standard deviations lower (3.32 to 2 lower)
Sleep du	uration (m	neasured with: Chi	ldren's Sleep Hat	oits Questionn	aire (CSHQ): S	Sleep duration; Bett	er 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	⊕⊕⊖⊝ LOW <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 lower</b> (2.68 to 1.49 lower)
Parason	nnias (mea	asured with: Child	en's Sleep Habits	Questionnai	re (CSHQ): Pai	asomnias; Better i	ndicated	d 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 parasomnias in the intervention groups was <b>0.48 standard deviations lower</b> (0.96 lower to 0 higher)
Sleep di	sordered	breathing (r	neasured with: C	hildren's Slee	p Habits Quest	onnaire (CSHQ): S	Sleep dis	sordered breathing; Bet	ter indicate	d by lowe	er values)
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ <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 higher</b> (0.45 lower to 0.5 higher)
Daytime	sleepine	SS (measured w	rith: Children's Sle	eep Habits Qu	estionnaire (CS	SHQ): Daytime slee	epiness;	Better indicated by low	ver values)		
68 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹,3 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>

										lower (1.09 to 0.12 lower)	
		nt response actigraph data)	- Sleep ons	et latency	(assessed wit	h: Number of part	icipants who showed slee	ep 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	⊕⊕⊕⊝ MODERATE <sup>4</sup>	3/33 30/35 (9.1%) (85.7%)	RR 9.43 (3.18 to	Study p	opulation	
12 weeks	bias	due to imprecision	(9.176) (63.776)	27.97)	91 per 1000	<b>766 more per 1000</b> (from 198 more to 1000 more)					
									Moderate		
									91 per 1000	<b>767 more per 1000</b> (from 198 more to 1000 more)	
	treatmer	-	- Sleep effic	ciency ( =:	>85% for s	sleep efficier	ncy) (assessed with: Nu	mber of participan	ts who sh	owed =>85% for sleep	
68 (1 study)	no serious	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>4</sup>	3/33 22/35 (9.1%) (62.9%)	RR 6.91 (2.28 to	Study population		
12 weeks	bias	incorrolations	mancomess			due to imprecision	(0.170) (02.070)	20.95)	91 per 1000	<b>537 more per 1000</b> (from 116 more to 1000 more)	
									Moderate		
									Wodera	te	

<sup>&</sup>lt;sup>3</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

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

<sup>&</sup>lt;sup>4</sup> Events<300

		Q	uality assess	ment				Su	mmary of	Finding	js
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall quality	Study e	event 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% CI)
Sleep on:	set laten	ICY (measured w	ith: Actigraph; B	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	⊕⊕⊕⊝  MODERATE¹  due to  imprecision	34	35	N/A	N/A	The mean sleep onset latency in the intervention groups was 0.59 standard deviations lower (1.07 to 0.11 lower)
Wake afte	er sleep	onset (measur	ed with: Actigrap	h; Better indica	ated by lower	values)			_	_	
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	34	35	N/A	N/A	The mean wake after sleep onset in the intervention groups was <b>0.68 standard deviations</b> lower (1.17 to 0.19 lower)
Nap time	(measured	with: Actigraph; B	etter indicated b	y lower values)	)	1				_	
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW² due to imprecision	34	35	N/A	N/A	The mean nap time in the intervention groups was <b>0.27 standard deviations</b> lower (0.75 lower to 0.2 higher)
Bed time	(measured	with: Actigraph; B	etter indicated b	y lower values)	)				1	1	4
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 lower</b> (0.69 lower to 0.25 higher)

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Total sle	ep time (	measured with: A	Actigraph; Better	indicated by Id	ower values)						
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊕⊝ MODERATE¹ due to imprecision	34	35	N/A	N/A	The mean total sleep time in the intervention groups was  0.61 standard deviations higher  (0.13 to 1.1 higher)
Sleep ef	ficiency (	measured with: A	Actigraph; Better	indicated by lo	ower values)						
69 (1 study) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊕⊝⊝ LOW² due to imprecision	34	35	N/A	N/A	The mean sleep efficiency in the intervention groups was  0.42 standard deviations higher  (0.06 lower to 0.9 higher)
Sleep pr	roblems (r	measured with: C	hildren's Sleep I	labits Questio	nnaire (CSHQ)	: Total score; Bet	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	⊕⊕⊖⊝ LOW¹,3 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	istance (m	neasured with: Ch	nildren's Sleep H	abits Question	nnaire (CSHQ):	Bed resistance; E	etter ind	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	⊕⊕⊖⊝ LOW¹,3 due to risk of bias, imprecision	34	35	N/A	N/A	The mean bed resistance in the intervention groups was  1.1 standard deviations lower  (1.61 to 0.59 lower)
Sleep or	nset dela	y (measured with	n: Children's Slee	p Habits Que	stionnaire (CSI	HQ): Sleep onset o	lelay; Be	etter indicated b	y lower values)		'
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW¹,3 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 an	nxiety (me	asured with: Child	Iren's Sleep Hab	its Questionna	ire (CSHQ): SI	eep anxiety; Bette	r indicate	ed by lower val	ues)	ı	1
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ LOW¹,3 due to risk of bias, imprecision	34	35	N/A	N/A	The mean sleep anxiety in the intervention groups was 1.33 standard deviations lower (1.85 to 0.8 lower)
Night-wa	akings (m	easured with: Chi	ldren's Sleep Ha	bits Questionn	aire (CSHQ): I	Night-wakings; Bet	ter indic	ated by lower v	alues)	•	
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	undetected	⊕⊕⊖⊖ <b>LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	34	35	N/A	N/A	The mean night-wakings in the intervention groups was <b>0.6 standard deviations lower</b> (1.08 to 0.12 lower)
Sleep du	<b>iration</b> (m	easured with: Ch	ildren's Sleep Ha	bits Questionr	naire (CSHQ):	Sleep duration; Be	tter indic	cated 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 0.44 standard deviations lower (0.92 lower to 0.03 higher)
Parason	nnias (mea	asured with: Child	ren's Sleep Habi	ts Questionnai	re (CSHQ): Pa	rasomnias; Better	indicate	d by lower valu	es)		
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 parasomnias in the intervention groups was 0.27 standard deviations lower (0.74 lower to 0.21 higher)
Sleep di	sordered	breathing (	measured with: 0	Children's Slee	p Habits Ques	tionnaire (CSHQ):	Sleep di	sordered breat	hing; Better indicate	ed 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	⊕⊖⊖⊖ VERY LOW <sup>2,3</sup> due to risk of bias, imprecision	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 Sl	eep Habits Qu	estionnaire (C	SHQ): Daytime sl	eepiness;	Better indicated by lov	ver values)		
69 (1 study) 12 weeks	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 lower</b> (0.74 lower to 0.21 higher)
		actigraph data)	- Sleep ons	et latency	(assessed wit	th: Number of part	icipants w	ho showed sleep onse	et latency <3	0 min or r	eduction of sleep onset
69 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊕⊝ MODERATE <sup>4</sup>	13/34 (38.2%)	30/35 (85.7%)	RR 2.24 (1.43 to	Study p	opulation
12 weeks	bias	,				due to imprecision		, ,	3.51)	382 per 1000	<b>474 more per 1000</b> (from 164 more to 960 more)
										Moderat	te
										382 per 1000	<b>474 more per 1000</b> (from 164 more to 959 more)
Positive	treatmer	nt response	- Sleep effic	ciency (ass	essed with: Nu	mber of participar	its who sh	owed =>85% for sleep	efficiency b	ased on a	actigraph data)
69 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊕⊝⊝ LOW⁵	16/34 (47.1%)	22/35 (62.9%)	RR 1.34 (0.86 to	Study p	opulation
12 weeks	bias	,				due to imprecision	,	,	2.07)	471 per 1000	<b>160 more per 1000</b> (from 66 fewer to 504 more
										Moderat	te
										471 per 1000	<b>160 more per 1000</b> (from 66 fewer to 504 mor
N<400						1					

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)

<sup>&</sup>lt;sup>3</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

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

Atomoxetine versus placebo for sleep problems as an indirect outcome

		Qı	ality assessn	nent				Sum	nmary of	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% CI)
Time to fa	all aslee	<b>ep</b> (measured wit	h: Sleep Measur	e Scale: Time	to fall asleep;	Better indicated	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	⊕⊕⊖⊝ LOW¹ 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	ırs of sl	eep (measured	with: Sleep Meas	sure Scale: To	tal hours of sle	eep; Better indic	ated by l	lower values)		1	1.
88 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	46	42	N/A	N/A	The mean total hours of sleep in the intervention groups was 0.13 standard deviations lower (0.55 lower to 0.29 higher)
Difficulty	falling	a <b>sleep</b> (measu	red with: Sleep I	L Measure Scale	L : Difficulty falli	ing asleep; Bett	er indica	ted by lower values)		<u> </u>	
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to imprecision	46	43	N/A	N/A	The mean difficulty falling asleep in the intervention groups was 0.17 standard deviations higher

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<sup>&</sup>lt;sup>4</sup> Events<300

<sup>&</sup>lt;sup>5</sup> Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25)

											(0.24 lower to 0.59 higher)
Quality	of sleep	(measured with: S	Sleep Measure S	cale: Quality o	of sleep; Better	indicated by lov	ver valu	ies)		1	
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup> with: Sleep M	undetected easure Scale:	⊕⊕⊖⊖ LOW¹ due to imprecision	46 ome du	43 ring day; Better indicated	N/A	N/A N/A	The mean quality of sleep in the intervention groups was <b>0.23 standard deviations lower</b> (0.65 lower to 0.18 higher)
89 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹ due to imprecision	46	43	N/A	N/A	The mean functional outcome during day in the intervention groups was <b>0.18 standard deviations</b> lower (0.6 lower to 0.24 higher)
<sup>1</sup> N<400 and	1 95% CL cro	sses both line of	I no effect and me	asure of appre	L eciable benefit	or harm (SMD	-0 5/0 5	)			

# 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					
` ,	Risk of bias	Inconsistency	Indirectness	Imprecision	Overall quality of evidence	Study e	,	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% CI)

Sleep improven	nent (measured	with: Parent Globa	al Impressions	-Revised (PGI-I	R): Sleep improve	ement; B	etter indicated	by lower values)	1	
	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ due to imprecision	51	53	N/A	N/A	The mean sleep improvement in the intervention groups was <b>0.18 standard deviations 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					Summar	y of Finding	ıs
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study even	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- fatty acids (95% CI)
Sleep pr	oblem	<b>S</b> (measured with:	Child Behavior Ch	necklist 1.5 - 5 (	(CBCL/1.5-5): §	Sleep problems; Be	tter indicated	by lower val	ues)		

measure was not blinded

<sup>&</sup>lt;sup>2</sup> N<400

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

Secretin versus placebo for gastrointestinal symptoms as an indirect outcome

		Qı	ıality assessn	nent			Summary of Findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study			Anticip	ated absolute effects
Follow up						evidence	With Control			Risk with Control	Risk difference with Secretin versus placebo for gastrointestinal symptoms as an indirect outcome (95% CI)
Number	of gas	trointestina	l problems	(measured w	rith: GI sympto	ms questionnai	re: Total	(change score); Better ind	icated by lo	wer valu	es)
95 (1 study) 3 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to imprecision	48 47		N/A	N/A	The mean number of gastrointestinal problems in the intervention groups was <b>0.18 standard deviations lower</b> (0.59 lower to 0.22 higher)
<sup>1</sup> N<400 and	95% CI cro	l esses both line of r	l o effect and mea	I asure of appre	l ciable benefit	I or harm (SMD -	0.5/0.5)		<u> </u>	<u> </u>	

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

Immunoglobulin versus placebo for gastrointestinal symptoms as a direct outcome

		,	Quality assess	sment		Sum	nmary of I	indings	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	of evidence	` ,	effect (95% CI)	•	Risk difference with Immunoglobulin (dosages

											combined) (95% CI)
		-			ous measure of 'mo		ntially impr	oved' on at lea	ast two of last 4 as:	sessments	or 'somewhat improve
125 1 study)	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,2</sup>	14/31 (45.2%)	31/94 (33%)	<b>RR 0.73</b> (0.45 to	Study po	ppulation
12 weeks	bias	inconsistency	munectress	Serious	suspected <sup>2</sup>	due to imprecision, publication bias	(43.270)	(3376)	1.18)	452 per 1000	<b>122 fewer per 1000</b> (from 248 fewer to 81 more)
										Moderate	e 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

		Qı	uality assessm	ent			Summary of Findings				ngs
Participants (studies)	Risk of bias	bias quality of		event rates (%)	Relative effect	Anticipa	ted absolute effects				
Follow up						evidence	With Placebo	With Multivitamin and mineral supplement	(95% CI)	Risk with Placebo	Risk difference with Multivitamin and mineral supplement (95% CI)
Gastroir	ntestina	symptom i	mproveme	<b>nt</b> (measured	with: Parent (	Global Impression	ns-Revise	ed (PGI-R): GI impr	ovement; Be	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	⊕⊕⊝⊝ <b>LOW</b> ¹ due to	51	53	N/A	N/A	The mean gastrointestinal symptom improvement in the intervention groups was 0.3 standard deviations

						imprecision			higher (0.09 lower to 0.68 higher)
<sup>1</sup> N<400 and	95% CI cros	ses both line of no	effect and measu	ure of apprecia	ble benefit or h	narm (SMD -0.5/0	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	uality assessr	ment				s	ummary o	of Findir	ngs
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 Home-based versus Centre-based EBI for improving the impact on the family as an indirect outcome	effect (95% CI)	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 Far	mily Quality of	Life Questionr	naire: Total; Bett	er indica	ated by lower values)	<u>-</u>	•	
44 (1 study) 40 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY LOW¹,² 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> higher (0.43 lower to 0.76 higher)
Family qu	uality o	f life (family	interaction	) (measured v	vith: Beach Fa	mily Quality of L	ife Ques	stionnaire: Family interac	tion; Better	indicated	by lower values)
44 (1 study) 40 weeks	serious <sup>1</sup>	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,	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>

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						imprecision					higher (0.45 lower to 0.73 higher)
Family q	uality o	f life (parent	t <b>ing)</b> (measure	d with: Beach	Family Quality	of Life Question	naire: Pa	arenting; Better indicated	d by lower v	/alues)	
44 (1 study) 40 weeks	serious <sup>1</sup>	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	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 (emotion	onal wellbe	ing) (measur	ed with: Beach	n Family Quality	of Life Q	uestionnaire: Emotional	wellbeing;	Better in	dicated by lower values)
44 (1 study) 40 weeks	serious <sup>1</sup>	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	23	21	N/A	N/A	The mean family quality of life (emotional wellbeing) in the intervention groups was 0.22 standard deviations higher (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 Que	estionnaire: Physical well	being; Bett	er indica	ted 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 LOW¹,² 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	t) (measured v	with: Beach Fa	mily Quality of L	ife Ques	tionnaire: Disability supp	ort; Better	indicated	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 LOW¹,² 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> higher (0.49 lower to 0.69 higher)
Parental	coping	<b>skills</b> (measur	ed with: Parent l	Perception Que	estionnaire: To	otal; Better indica	ted by Ic	ower 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	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	dence) (mea	sured with: Pa	rent Perceptio	n Questionnaire	: Confi	dence; Better indicated	by lower va	ues)	
46 (1 study) 40 weeks	serious <sup>1</sup>	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	23	23	N/A	N/A	The mean parental coping skills (confidence) in the intervention groups was  0 standard deviations higher (0.58 lower to 0.58 higher)
Parental	coping	skills (copir	ng) (measured	with: Parent P	erception Que	stionnaire: Copir	ng; Bet	ter indicated by lower va	alues)	•	
46 (1 study) 40 weeks	serious <sup>1</sup>	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	23	23	N/A	N/A	The mean parental coping skills (coping) in the intervention groups was  0.33 standard deviations higher  (0.25 lower to 0.91 higher)
Parental	coping	skills (know	ledge) (meas	sured with: Par	rent Perception	n Questionnaire:	Know	edge; Better indicated b	y lower val	ues)	
46 (1 study) 40 weeks	serious <sup>1</sup>	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	23	23	N/A	N/A	The mean parental coping skills (knowledge) in the intervention groups was 0.52 standard deviations lower (1.11 lower to 0.07 higher)
Parental	coping	skills (unde	rstanding)	(measured wit	h: Parent Perd	eption Question	naire: I	Understanding; Better in	dicated 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 LOW¹,² 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 lower</b> (0.84 lower to 0.32 higher)
Parental	coping	skills (famil	y issues) (m	neasured with:	Parent Percep	otion Questionna	ire: Fa	mily issues; Better indic	ated by low	er values)	
46 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	23	23	N/A	N/A	The mean parental coping skills (family issues) in the

					due to risk of bias, imprecision					intervention groups was 0.23 standard deviations higher (0.35 lower to 0.81 higher)
coping	skills (plan	ning) (measur	ed with: Paren	t Perception Q	uestionnaire: Pla	anning	Better indicated by	y lower values)		
serious <sup>1</sup>	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	23	23	N/A	N/A	The mean parental coping skills (planning) in the intervention groups was <b>0.09 standard deviations lower</b> (0.67 lower to 0.49 higher)
stress	(measured with: F	Parenting Stress	Index-3rd Edit	ion (PSI): Tota	l; Better indicate	d by lo	wer values)			
serious <sup>1</sup>	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	20	20	N/A	N/A	The mean parental stress in the intervention groups was <b>0.26 standard deviations lower</b> (0.89 lower to 0.36 higher)
stress	(defensive r	esponding)	(measured w	ith: Parenting	Stress Index (PS	I): Def	ensive responding;	Better indicated	by lower	values)
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW¹,² 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 lower</b> (0.83 lower to 0.42 higher)
stress	parental dis	s <b>tress)</b> (meas	ured with: Par	enting Stress I	ndex (PSI): Pare	ental di	stress; Better indica	ated by lower va	lues)	
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY LOW¹,² due to risk of bias, imprecision	20	20	N/A	N/A	The mean parental stress (parental distress) in the intervention groups was <b>0.22 standard deviations lower</b> (0.84 lower to 0.4 higher)
	stress serious¹  stress serious¹  stress serious¹	serious¹ no serious inconsistency  stress (measured with: F serious¹ no serious inconsistency  stress (defensive r serious¹ no serious inconsistency  stress (parental dis	serious no serious inconsistency no serious indirectness  stress (measured with: Parenting Stress serious no serious inconsistency indirectness  stress (defensive responding)  serious no serious inconsistency indirectness  stress (parental distress) (meas serious no serious inconsistency indirectness	serious no serious indirectness very serious serious no serious indirectness very serious serious no serious inconsistency no serious inconsistency indirectness very serious serious no serious inconsistency indirectness very serious serious no serious inconsistency no serious very indirectness very serious serious no serious inconsistency indirectness very serious serious no serious no serious very serious no serious very serious no serious very	serious¹ no serious inconsistency indirectness very serious² undetected serious¹ no serious inconsistency indirectness lndex-3rd Edition (PSI): Total serious¹ no serious inconsistency indirectness very serious² undetected serious¹ no serious inconsistency indirectness very serious² undetected indirectness very serious² undetected indirectness very serious² serious² undetected serious¹ no serious indirectness very serious² undetected serious¹ no serious indirectness very serious² undetected serious¹ no serious no serious very undetected serious¹ no serious no serious very undetected	bias, imprecision  Coping Skills (planning) (measured with: Parent Perception Questionnaire: Plate serious¹ no serious inconsistency indirectness very serious² undetected due to risk of obias, imprecision  Stress (measured with: Parenting Stress Index-3rd Edition (PSI): Total; Better indicate very serious¹ no serious inconsistency indirectness very serious² undetected when the parenting Stress Index (PSI): Total; Better indicate very very serious² undetected when the parenting Stress Index (PSI): Total; Better indicate very very serious² undetected when the parenting Stress Index (PSI): Total; Better indicate very very very undetected when the parenting Stress Index (PSI): Total; Better indicate very very undetected when the parenting Stress Index (PSI): Total; Better indicate very very undetected when the parenting Stress Index (PSI): Total; Better indicate very very undetected when the parenting Stress Index (PSI): Total; Better indicate very very undetected when the parenting Stress Index (PSI): Total; Better indicate very very very undetected when the parenting Stress Index (PSI): Parenting Str	bias, imprecision	Stress (defensive responding) (measured with: Parenting Stress Index (PSI): Defensive responding; serious¹   no serious inconsistency   no serious inconsistency   no serious   no serious   very serious²   undetected   ⊕⊖⊝   VERY LOW¹²   due to risk of bias, imprecision   very serious²   undetected   ⊕⊖⊝   VERY LOW¹²   due to risk of bias, imprecision   very serious²   undetected   ⊕⊖⊝   VERY LOW¹²   very very serious²   undetected   ⊕⊖⊝   very very very very very very very very	Serious	Stress (defensive responding) (measured with: Parenting Stress Index-dwith: Parenting Stress Index of bias, imprecision

lower values	)										
40 (1 study) 40 weeks		no serious inconsistency	no serious indirectness	very serious <sup>2</sup>		⊕⊖⊝ VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	20 ild; Bet	20 ter indicated by lower val	N/A	N/A	The mean parental stress (parent-child dysfunctional interaction) in the intervention groups was  0.15 standard deviations lower  (0.77 lower to 0.47 higher)
40 (1 study) 40 weeks	serious <sup>1</sup>	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	20	20	N/A	N/A	The mean parental stress (difficult child) in the intervention groups was <b>0.35 standard deviations lower</b> (0.98 lower to 0.27 higher)

<sup>&</sup>lt;sup>1</sup> High risk of performance and response bias as intervention administrators and participants were non-blind, and unclear/unknown risk of detection bias as although the outcome assessors were blinded, this outcome measure was based on interview with parent and parents were non-blind and were part of the intervention <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)

## 1.30.2Cognitive-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	ıality assessn	nent			Summary of Findings					
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	•		Overall quality of evidence	Study ( With Control		effect	Anticip Risk with Control	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>		⊕⊕⊝ LOW¹.² 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	performar	nce and response	bias as interven	tion administra	ators and parti	cipants were no	n-blind,	and high risk of detection	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				Sı	ummary o	f Findin	gs
Participants		Inconsistency	Indirectness	Imprecision		Overall	Study	event rates (%)	Relative	Anticipa	ated 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		me) (measu	red with: Parer	nting Stress The	rmomete	r or Parental Stress Inve	ntory: Total	or Paren	ting 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> lower (0.73 to 0.04 lower)
Parental s	stress	(direct outco	me; combi	ned PEBM	I+PEC pos	st-intervent	t <b>ion)</b> (m	neasured with: Parenting	Stress The	rmomete	r; Better indicated by lower
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 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	red with: Pare	ntal Stress Inv	entory: Total or	Parentin	g Stress Index-3rd Edition	on (PSI): To	tal; Better	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> lower (0.93 lower to 0.32 higher)
Parental	mental	health (com	bined PEB	/I+PEC gr	oups) (mea	sured with: Gene	ral Heal	th Questionnaire (GHQ-2	28): Total; E	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	⊕⊖⊖ <b>VERY LOW</b> <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  0.26 standard deviations lower  (0.67 lower to 0.15 higher)
Parental	mental	health (com	bined PEBI	/I+PEC gr	oups) (mea	sured with: Gene	ral Heal	th Questionnaire (GHQ-2	28): Total; E	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	⊕⊕⊝ LOW¹.² 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  0.45 standard deviations lower  (0.86 to 0.03 lower)
Parental lower values)		c symptoms	(combined	PEBM+PI	EC groups	(measured wi	th: Gene	eral 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 ower values		c symptoms	s (combined	PEBM+P	EC group	S) (measured wi	th: Ger	neral Health Question	nnaire (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	⊕⊖⊝ <b>VERY LOW</b> <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> lower (0.63 lower to 0.19 higher)
	l anxiety lower value		nia (combin	ed PEBM-	+PEC grou	ups) (measured	d with:	General Health Ques	tionnaire (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 lower</b> (0.57 lower to 0.25 higher)
	l anxiety lower value		nia (combin	ed PEBM-	+PEC grou	ups) (measured	d with:	General Health Ques	tionnaire (GHC	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	⊕⊕⊝⊝ <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> lower (0.95 to 0.12 lower)
Parental ower values		dysfunction	(combined	PEBM+PE	EC groups	(measured wit	h: Gen	eral Health Question	naire (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	⊕⊕⊖⊝ LOW¹.² 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 wit	h: Gene	eral Health Quest	ionnaire (GHQ-28)	: Social d	ysfunction; Better indicated by
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <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 lower</b> (0.78 lower to 0.04 higher)
Parental lower values		depression	(combined	PEBM+PE	EC groups	(measured wit	h: Gene	eral Health Quest	ionnaire (GHQ-28)	: Severe	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 0.09 standard deviations higher (0.32 lower to 0.49 higher)
Parental lower values		depression	(combined	PEBM+PE	EC groups	(measured wit	h: Gene	eral Health Quest	ionnaire (GHQ-28)	: Severe	depression; Better indicated by
103 (1 study) 46 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊝⊖ <b>VERY LOW</b> <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 <b>0.14 standard deviations lower</b> (0.55 lower to 0.27 higher)
General	family f	unction (co	nbined PEE	BM+PEC g	roups) (me	L asured with: Mcl	Master	Family Assessme	ent Device (FAD); I	Better ind	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+pec groups) in the intervention

						bias, imprecision					groups was  0.31 standard deviations lower (0.72 lower to 0.1 higher)
103 (1 study) 46 weeks	1 4	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	with: McI  Description  WERY LOW <sup>1,3</sup> due to risk of bias, imprecision	Master Fa	68	e (FAD); Be	N/A	The mean general family function (combined pebm+pec groups) in the intervention groups was  0.14 standard deviations lower  (0.55 lower to 0.27 higher)
intervention <sup>2</sup> N<400	and not blir				·		J	risk of detection bias as	parent-com	npleted a	nd 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

l		Qι	ıality assessn	nent				Sur	nmary of	Finding	js –
Participants		Inconsistency	Indirectness	Imprecision		Study	event rates (%)	Relative effect	Anticip	ated absolute effects	
(studies) Follow up	bias				bias	quality of evidence	With Control			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	ralues)			
35 (1 study) 12 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	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)
arousa	(measured with	h: Stress-Arousa	l Checklist: M	others' Arousal	; Better indicated	by lov	wer values)	<u> </u>		
serious <sup>1</sup>	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	19	16	N/A	N/A	The mean maternal arousal in the intervention groups was <b>0.18 standard deviations higher</b> (0.48 lower to 0.85 higher)
stress	(measured with:	Stress-Arousal C	hecklist: Fath	ers' Stress; Be	tter indicated by	lower v	values)	<u> </u>		
serious <sup>1</sup>	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	19	16	N/A	N/A	The mean paternal stress in the intervention groups was <b>0.14 standard deviations higher</b> (0.53 lower to 0.8 higher)
arousa	(measured with	n: Stress-Arousal	Checklist: Fa	thers' Arousal;	Better indicated	by low	er values)			
serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖  VERY LOW¹.²  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 higher</b> (0.16 lower to 1.19 higher)
	serious <sup>1</sup> stress serious <sup>1</sup>	serious¹ no serious inconsistency  stress (measured with: serious¹ no serious inconsistency  arousal (measured with serious¹ no serious	serious no serious inconsistency indirectness  stress (measured with: Stress-Arousal Consistency inconsistency inconsistency inconsistency indirectness inconsistency inconsistency indirectness inconsistency indirectness inconsistency indirectness inconsistency indirectness inconsistency inconsistency indirectness inconsistency inconsistency inconsistency indirectness inconsistency inconsistency inconsistency inconsistency inconsistency inconsistency inconsistency inconsistency indirectness indi	serious no serious inconsistency indirectness very serious serious no serious indirectness indirectness serious no serious inconsistency indirectness very serious serious inconsistency indirectness serious serious inconsistency indirectness serious serious no serious no serious very serious no serious no serious very	serious¹ no serious inconsistency indirectness very serious² undetected serious² undetected serious¹ no serious no serious inconsistency indirectness very serious² serious¹ no serious inconsistency indirectness very serious² undetected serious¹ (measured with: Stress-Arousal Checklist: Fathers' Arousal; serious¹ no serious no serious very undetected	serious¹ no serious indirectness very serious² undetected ⊕⊖⊖ VERY LOW¹¹² due to risk of bias, imprecision  stress (measured with: Stress-Arousal Checklist: Fathers' Stress; Better indicated by serious¹ no serious inconsistency indirectness very serious² undetected ∀⊕⊖⊖ VERY LOW¹¹² due to risk of bias, imprecision  arousal (measured with: Stress-Arousal Checklist: Fathers' Arousal; Better indicated serious¹ no serious inconsistency indirectness very serious² undetected ⊕⊖⊖ VERY LOW¹¹² due to risk of bias, imprecision  arousal (measured with: Stress-Arousal Checklist: Fathers' Arousal; Better indicated ⊕⊖⊖ VERY LOW¹¹² due to risk of bias, indirectness indirectness very serious² undetected ⊕⊖⊝ VERY LOW¹¹² due to risk of bias,	serious¹ no serious indirectness very serious² undetected ⊕⊖⊖⊖ VERY LOW¹¹² due to risk of bias, imprecision  stress (measured with: Stress-Arousal Checklist: Fathers' Stress; Better indicated by lower very serious¹ no serious indirectness very serious² undetected ⊕⊖⊖⊖ VERY LOW¹²² due to risk of bias, imprecision  arousal (measured with: Stress-Arousal Checklist: Fathers' Arousal; Better indicated by lower very serious² undetected ⊕⊖⊖⊖ VERY LOW¹²² due to risk of bias, imprecision  serious¹ no serious inconsistency indirectness very serious² undetected ⊕⊖⊖⊖ VERY LOW¹²² due to risk of bias, indirectness indirectness very serious² undetected ⊕⊖⊖⊖ VERY LOW¹²² due to risk of bias, indirectness indirectness very serious² very due to risk of bias, indirectness very serious² very serious² very due to risk of bias, indirectness very serious² very serious² very due to risk of bias, indirectness very serious² very due to risk of bias, indirectness very serious² very due to risk of bias, indirectness very serious² very due to risk of bias, indirectness very serious² very due to risk of bias, indirectness very serious² very due to risk of bias, indirectness very serious² very due to risk of bias, indirectness very serious² very due to risk of bias, indirectness very serious² very due to risk of bias, indirectness very serious² very due to risk of bias, indirectness very due to risk of bias, indirectnes very due to risk of bias, indirectness very due	inconsistency indirectness serious²  Stress (measured with: Stress-Arousal Checklist: Fathers' Stress; Better indicated by lower values)  serious¹ no serious inconsistency indirectness serious²  arousal (measured with: Stress-Arousal Checklist: Fathers' Arousal; Better indicated by lower values)  serious¹ no serious indirectness very serious²  arousal (measured with: Stress-Arousal Checklist: Fathers' Arousal; Better indicated by lower values)  serious¹ no serious inconsistency indirectness very serious²  undetected the control of the contr	serious¹ no serious inconsistency loserious indirectness loserious² loserious loserious² loserious l	serious¹ no serious indirectness serious² undetected to risk of bias, imprecision serious indirectness serious² undetected to risk of bias, imprecision serious indirectness serious¹ no serious indirectness indirectness indirectness serious² undetected to risk of bias, imprecision serious indirectness in

measure is unclear and parent-completed and parents involved in the intervention so non-blind  $^2$  N<400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

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

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

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

		Qu	ality assessn	nent				Sum	mary of F	indings	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	⊕⊕⊖⊝ <b>LoW</b> ¹ due to imprecision	46	43	N/A	N/A	The mean parental mental health in the intervention groups was 0.24 standard deviations lower (0.66 lower to 0.18 higher)
Parental :	stress (	measured with: N	ijmeegse Ouder	lijke Stress Ind	lex (NOSI): To	tal; Better indic	ated by	lower values)			
77 (1 study) 8 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊖⊝ LOW¹ due to imprecision	39	38	N/A	N/A	The mean parental stress in the intervention groups was <b>0.24 standard deviations lower</b> (0.69 lower to 0.21 higher)
<sup>1</sup> N<400 and	95% CI cro	sses both line of	no effect and me	easure of appr	eciable benefi	t or harm (SMD	0.5/0.5	5)	1		

# 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 6	event rates (%)	Relative	Anticipa	ted absolute effects	
(studies) Follow up	bias				bias	of evidence	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% CI)		
Parental :	stress (	measured with: Au	itism Parenting S	tress Index (A	SPI); Better in	dicated by lower v	values)					
41 (1 study) 17 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	undetected	⊕⊕⊖⊝ <b>LOW</b> <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 lower</b> (1.42 to 0.14 lower)	

<sup>&</sup>lt;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 parents who were delivering the intervention and the outcome measure was created for this study so reliability and validity is unknown
<sup>2</sup> N<400

## 1.33 ADVERSE EVENTS ASSOCIATED WITH PHARMACOLOGICAL INTERVENTIONS

#### 1.33.1 Adverse events associated with anticonvulsants

Adverse events associated with divalproex versus placebo

			Quality asses	ssment				Sum	mary of F	indings
Participants		Inconsistency	Indirectness	Imprecision		Overall quality of	Study e	• •	Relative	Anticipated absolute effects
(studies) Follow up	bias				bias	evidence	With Control	With Adverse events associated with anticonvulsants	effect (95% CI)	Risk with Control Adverse events associated with anticonvulsants (95% CI)
Any adve	rse eve	ent (assessed wit	h: Number of par	rticipants expe	riencing any side	effect during the tria	l (measur	ed using checklist deri	ved from Pl	hysicians' Desk Reference, 1997))
30 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	, ,	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,2,3</sup>	11/14 (78.6%)	15/16 (93.8%)	RR 1.19 (0.88 to	Study population
8 weeks		,			suspected 3	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)
More tha	n one a	dverse even	t (assessed with	n: Number of p	articipants experi	encing more than on	e adverse	event during the trial	(measured	using phy	sical examination))
27 (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>	2/11	5/16 (31.3%)	RR 1.72 (0.4 to	Study p	opulation
12 weeks				00.1000	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.270)	(61.675)	7.32)	182 per 1000	131 more per 1000 (from 109 fewer to 1000 more)
										Moderat	t <b>e</b>
										182 per 1000	<b>131 more per 1000</b> (from 109 fewer to 1000 more)
Disconti	nuation	due to adve	r <b>se event</b> (a	ssessed with:	Number of partici	pants who discontinu	l led due to	adverse event)	1		
57 (2 studies)	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>	0/25 (0%)	2/32 (6.3%)	RR 2.37 (0.26 to	Study p	opulation
8-12 weeks		inconsistency	indirectriess	Serious	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0 78)	(0.576)	21.43)	0 per 1000	N/A
						publication bias				Moderat	t <b>e</b>
										0 per 1000	N/A
Weight g	ain (mea	sured with: Number	er of kilograms o	r pounds that p	participants gaine	d during the trial; Bet	ter indica	ted by lower values)			
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>	⊕⊝⊖ <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)
			serve potential long	er term adverse events		

<sup>&</sup>lt;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>&</sup>lt;sup>3</sup> Trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies

## 1.33.2 Adverse events associated with antidepressants

Adverse events associated with citalogram versus placebo

			Quality asse	ssment				Sur	nmary of F	indings	
Participants		Inconsistency	Indirectness	Imprecision	Publication		Study e	vent rates (%)	Relative	Anticipa	ated 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% CI)
Any adve	erse eve	ent (assessed wi	th: Safety Monito	oring Uniform R	eport Form )						
149 (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>	66/76 (86.8%)	71/73 (97.3%)	RR 1.12 (1.02 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		(* 2)	1.23)	868 per 1000	104 more per 1000 (from 17 more to 200 more)
										Moderate	
										868 per 1000	<b>104 more per 1000</b> (from 17 more to 200 more)
Nightman	'es (asse	ssed with: Safety	Monitoring Unifo	rm Report Forr	n )		ļ		1		
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	0/76 (0%)	5/73 (6.8%)	RR 11.45 (0.64 to	Study p	opulation
12 weeks		inconsistency	mancomess.	Serious	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(070)	(0.070)	203.38)	0 per 1000	N/A
									Mod	Moderat	te
										0 per 1000	N/A
Increase	d energ	y level (assess	sed with: Safety I	I Monitoring Unif	orm Report Form	1)	1		1	1	

149 (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>	15/76 (19.7%)	28/73 (38.4%)	<b>RR 1.94</b> (1.13 to	Study pe	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(1011 70)	(65.176)	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	irritabi	lity (assessed w	ith: Safety Monit	oring Uniform	Report Form )	<del>,</del>			·	•	
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	13/76 (17.1%)	18/73 (24.7%)	<b>RR 1.44</b> (0.76 to	Study po	opulation
12 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			2.73)	171 per 1000	<b>75 more per 1000</b> (from 41 fewer to 296 more)
										Moderat	e
									1	171 per 1000	<b>75 more per 1000</b> (from 41 fewer to 296 more)
Aggress	ion or h	ostility (asses	sed with: Safety	Monitoring Un	iform Report Form	ı )					I
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	13/76 (17.1%)	17/73 (23.3%)	RR 1.36 (0.71 to	Study po	opulation
12 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		,	(0.71 to 2.6)	171 per 1000	<b>62 more per 1000</b> (from 50 fewer to 274 more)
										Moderat	e
										_	<b>62 more per 1000</b> (from 50 fewer to 274 more)
Headach	e or mi	g <b>raine</b> (assess	I ed with: Safety M	L Ionitoring Unif	orm Report Form	)					

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	10/76 (13.2%)	15/73 (20.5%)	RR 1.56 (0.75 to	Study p	opulation
12 weeks				3033	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.270)	(20.070)	3.25)	132 per 1000	<b>74 more per 1000</b> (from 33 fewer to 296 more)
										Moderat	te
										132 per 1000	74 more per 1000 (from 33 fewer to 297 more)
Restless	ness or	difficulty se	ettling dowr	assessed w	rith: Safety Monitor	ring Uniform Report I	Form )	•		•	<del>'</del>
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	7/76 (9.2%)	13/73 (17.8%)	RR 1.93 (0.82 to	Study p	opulation
12 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			4.57)	92 per 1000	86 more per 1000 (from 17 fewer to 329 more)
										Moderat	te
										92 per 1000	<b>86 more per 1000</b> (from 17 fewer to 328 more)
Disinhib	ited, im	pulsive, or i	ntrusive bel	naviour (as	ssessed with: Safe	ty Monitoring Uniforr	n Report I	Form )			
149 (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>	5/76 (6.6%)	14/73 (19.2%)	RR 2.92	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(6.676)	(13.273)	(1.11 to 7.68) 66 pc	66 per 1000	<b>126 more per 1000</b> (from 7 more to 439 more)
										Moderat	te
										66 per 1000	<b>127 more per 1000</b> (from 7 more to 441 more)
Silliness	(assessed	with: Safety Mon	I itoring Uniform R	eport Form )						1	

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	10/76 (13.2%)	9/73 (12.3%)	<b>RR 0.94</b> (0.4 to	Study p	opulation
12 weeks		""iounicional			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.270)	(12.070)	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)
Anxiety (	assessed v	vith: Safety Monito	oring Uniform Re	port Form )	•	,			<u> </u>	<u>'</u>	
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	9/76 (11.8%)	8/73 (11%)	RR 0.93 (0.38 to	Study population	
12 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			2.27)	118 per 1000	8 fewer per 1000 (from 73 fewer to 150 more)
										Moderat	e
										118 per 1000	8 fewer per 1000 (from 73 fewer to 150 more)
Mood lab	oility (ass	essed with: Safet	y Monitoring Unit	form Report F	orm )	<u> </u>					
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	9/76 (11.8%)	7/73 (9.6%)	RR 0.81 (0.32 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(**************************************	(ere.e)	2.06)	118 per 1000	<b>22 fewer per 1000</b> (from 81 fewer to 126 more)
										Moderat	ee
										_	22 fewer per 1000 (from 80 fewer to 125 more)
Increase	⊥ d speed	h (assessed with	l n: Safety Monitori	I ing Uniform R	eport Form )		<u> </u>				

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	4/76 (5.3%)	8/73 (11%)	RR 2.08 (0.66 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.070)	(/	6.62)	53 per 1000	<b>57 more per 1000</b> (from 18 fewer to 296 more)
										Modera	te
										53 per 1000	<b>57 more per 1000</b> (from 18 fewer to 298 more)
Decrease	ed atten	tion and co	ncentration	(assessed wit	th: Safety Monitori	ng Uniform Report F	orm )			•	-
149 (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>	2/76 (2.6%)	9/73 (12.3%)	RR 4.68 (1.05 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		,	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)
Hyperact	tivity (as:	sessed with: Safe	ty Monitoring Uni	form Report F	Form )	<u> </u>					
149 (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>	2/76 (2.6%)	9/73 (12.3%)	RR 4.68 (1.05 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(======================================	(12073)	20.96)	26 per 1000	<b>97 more per 1000</b> (from 1 more to 525 more)
										Moderate	
										26 per 1000	<b>96 more per 1000</b> (from 1 more to 519 more)
Stereoty	py (asses	L sed with: Safety N	I Monitoring Uniforr	I m Report Form	l n)					ļ	

149 (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>	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	( 211,		64.95)	13 per 1000	<b>96 more per 1000</b> (from 1 more to 841 more)
										Moderat	e
										13 per 1000	<b>95 more per 1000</b> (from 1 more to 831 more)
Diarrhoe	a or loo	se stools (as	ssessed with: Saf	ety Monitoring	Uniform Report F	Form )	1			'	
149 (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>	9/76 (11.8%)	19/73 (26%)	RR 2.2 (1.06 to	Study p	opulation
12 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		` ,	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)
Abdomir	nal disc	omfort (assess	sed with: Safety N	I Monitoring Unit	form Report Form	)					
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	9/76 (11.8%)	13/73 (17.8%)	RR 1.5 (0.68 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(111273)	(	3.3)	118 per 1000	<b>59 more per 1000</b> (from 38 fewer to 272 more)
										Moderat	e
										118 per 1000	<b>59 more per 1000</b> (from 38 fewer to 271 more)
Vomiting	or nau	Sea (assessed v	⊥ with: Safety Moni	toring Uniform	Report Form)	1	1				

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	6/76 (7.9%)	14/73 (19.2%)	<b>RR 2.43</b> (0.99 to	Study p	opulation
12 weeks				Conocc	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(7.070)	(10.270)	5.98)	79 per 1000	113 more per 1000 (from 1 fewer to 393 more)
										Moderat	te
										79 per 1000	113 more per 1000 (from 1 fewer to 393 more)
Any inso	mnia (as	ssessed with: Safe	ety Monitoring Ur	iform Report	Form)	•	•	•		•	
149 (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>	17/76 (22.4%)	28/73 (38.4%)	RR 1.71 (1.03 to	Study p	opulation
12 weeks		ŕ			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		,	2.86)	224 per 159 more per 1000 (from 7 more to 416 more)	
										Moderat	te
										224 per 1000	<b>159 more per 1000</b> (from 7 more to 417 more)
Initial ins	somnia	or difficulty	falling asle	<b>ep</b> (assessed	I with: Safety Mon	itoring Uniform Repo	rt Form)				
149 (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>	7/76 (9.2%)	17/73 (23.3%)	RR 2.53 (1.11 to	Study p	opulation
12 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		` ,	5.74)	92 per 1000	<b>141 more per 1000</b> (from 10 more to 437 more)
										Moderat	te
										92 per 1000	<b>141 more per 1000</b> (from 10 more to 436 more)
Midcycle	or othe	er insomnia	(assessed with: \$	L Safety Monitor	ing Uniform Repo	rt Form)	<u> </u>			<u> </u>	

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	9/76 (11.8%)	13/73 (17.8%)	<b>RR 1.5</b> (0.68 to	Study po	opulation	
12 weeks				30333	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(111676)	(1.13/3)	3.3)	118 per 1000	<b>59 more per 1000</b> (from 38 fewer to 272 more)	
										Moderate		
										118 per 1000	<b>59 more per 1000</b> (from 38 fewer to 271 more)	
Cold, flu	or othe	r systemic i	nfection (ass	essed with: S	afety Monitoring U	Iniform Report Form)		•		•		
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	26/76 (34.2%)	31/73 (42.5%)	RR 1.24 (0.82 to		opulation	
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			1.87)	342 per 1000	<b>82 more per 1000</b> (from 62 fewer to 298 more)	
										Moderat	е	
										342 per 1000	<b>82 more per 1000</b> (from 62 fewer to 298 more)	
Decrease	ed appe	etite (assessed v	vith: Safety Monit	oring Uniform	Report Form)						l	
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	10/76 (13.2%)	11/73 (15.1%)	RR 1.15 (0.52 to	Study po	opulation	
12 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		,	(0.52 to 2.53)	132 per 1000	20 more per 1000 (from 63 fewer to 201 more)	
										Moderat	e	
										132 per 1000	<b>20 more per 1000</b> (from 63 fewer to 202 more)	
Increase	d appet	i <b>te</b> (assessed w	ith: Safety Monito	ring Uniform F	Report Form)		1		<u> </u>	1		

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	8/76 (10.5%)	7/73 (9.6%)	<b>RR 0.91</b> (0.35 to	Study p	opulation
12 weeks		inconcincting,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.070)	(6.676)	2.38)	105 per 1000	9 fewer per 1000 (from 68 fewer to 145 more)
										Moderat	te
										105 per 1000	9 fewer per 1000 (from 68 fewer to 145 more)
Rash (asse	essed with:	Safety Monitoring	g Uniform Report	Form)		,	1		1	•	
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	8/76 (10.5%)	12/73 (16.4%)	RR 1.56 (0.68 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(1010,0)	(13111)	3.6)	105 per 1000	<b>59 more per 1000</b> (from 34 fewer to 274 more)
										Moderat	te
										105 per 1000	<b>59 more per 1000</b> (from 34 fewer to 273 more)
Other ski	in or su	bcutaneous	tissue disc	order (asses	sed with: Safety N	Ionitoring 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	⊕⊝⊝ VERY LOW <sup>1,2,3</sup>	1/76 (1.3%)	9/73 (12.3%)	RR 9.37 (1.22 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(11070)	()	72.12)	13 per 1000	110 more per 1000 (from 3 more to 936 more)
										Moderat	te
										13 per 1000	<b>109 more per 1000</b> (from 3 more to 925 more)
Fatigue (a	I assessed v	l vith: Safety Monito	I oring Uniform Re	port Form)							

149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	10/76	10/73 (13.7%)	<b>RR 1.04</b> (0.46 to	Study p	opulation
12 weeks				Semode	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.270)	(10.170)	2.35)	132 per 1000	<b>5 more per 1000</b> (from 71 fewer to 178 more)
										Moderat	ee
										132 per 1000	<b>5 more per 1000</b> (from 71 fewer to 178 more)
Allergies	(assessed	with: Safety Mon	itoring Uniform F	Report Form)	-	<b>.</b>			<b>!</b>	1	
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	11/76 (14.5%)	15/73 (20.5%)	<b>RR 1.42</b> (0.7 to	Study p	opulation
12 weeks				00.1300	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(1.11070)	(=0.070)	2.88)	145 per 1000 (from 43 fewer to 27 more)	
										Moderat	e
										145 per 1000	<b>61 more per 1000</b> (from 43 fewer to 273 more)
Cough (as	ssessed wi	th: Safety Monitor	ing Uniform Rep	ort Form)							
149 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	5/76 (6.6%)	10/73 (13.7%)	<b>RR 2.08</b> (0.75 to	Study p	opulation
12 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.075)	(121175)	5.8)	).75 to	<b>71 more per 1000</b> (from 16 fewer to 316 more)
										Moderat	ee
										66 per 1000	<b>71 more per 1000</b> (from 16 fewer to 317 more)
Any seri	⊔ ous adv	erse event (	assessed with: S	I afety Monitori	ng Uniform Repor	t Form)	<u> </u>			1	

149 (1 study)	serious <sup>1</sup>		no serious indirectness	very serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	0/76 (0%)		RR 3.12 (0.13 to	Study po	opulation
12 weeks		,			0,	due to risk of bias, imprecision, publication bias	` ,	` ,	75.42)	0 per 1000 Moderat	N/A
										0 per 1000	N/A

High risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events

#### 1.33.3 Adverse events associated with antihistamines

Adverse events associated with cyproheptadine and haloperidol versus placebo and haloperidol

		Qı	uality assessr	nent				Sun	nmary of I	indings	;
Participants		Inconsistency	Indirectness	Imprecision			Study 6	event rates (%)		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% CI)
Extrapyra	amidal	symptoms (as	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	⊕⊖⊝ VERY LOW <sup>1,2</sup>	6/20 (30%)	2/20 (10%)	RR 0.33 (0.08 to	Study po	opulation
8 weeks		·				due to risk of bias, imprecision	,		1.46)	300 per 1000	<b>201 fewer per 1000</b> (from 276 fewer to 138 more)
										Moderat	e
										300 per 1000	<b>201 fewer per 1000</b> (from 276 fewer to 138

Authors are consultants to pharmaceutical companies
Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25)

											more)
rouble	swallow	/ing (assessed v	vith: Study-speci	fic side effect of	checklist)						
0 I study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,2</sup>	4/20 (20%)	2/20 (10%)	<b>RR 0.5</b> (0.1 to	Study po	opulation
weeks						due to risk of bias, imprecision	(==70)	(1375)	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	(assessed	d with: Study-spec	ific side effect ch	ecklist)						Ļ	
10 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,2</sup>	3/20 (15%)	1/20 (5%)	<b>RR 0.33</b> (0.04 to	Study po	opulation
weeks						due to risk of bias, imprecision	(1070)	(073)	2.94)	150 per 1000	<b>101 fewer per 1000</b> (from 144 fewer to 291 more)
										Moderate	
										150 per 1000	<b>101 fewer per 1000</b> (from 144 fewer to 291 more)
Slow mo	vement	: (assessed with: \$	Study-specific sid	le effect check	:list)						
l0 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	3/20 (15%)	1/20 (5%)	<b>RR 0.33</b> (0.04 to	Study po	opulation
study) 8 weeks		inconsistency	indirectriess	Senous		due to risk of bias, imprecision	(1376)	(370)	2.94)	150 per 1000	<b>101 fewer per 1000</b> (from 144 fewer to 291 more)
										Moderate	
										150 per	101 fewer per 1000

										1000	(from 144 fewer to 291 more)
Constipa	ation (ass	sessed with: Study	-specific side eff	ect checklist)			l			·	
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	2/20 (10%)	4/20 (20%)	<b>RR 2</b> (0.41 to	Study p	opulation
8 weeks		inconsistency	manosinos	Schous		due to risk of bias, imprecision	(1070)	(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)
Diarrhoe	a (assess	ed with: Study-spe	cific side effect c	hecklist)		1	•		- 1	1	
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	3/20 (15%)	2/20 (10%)	RR 0.67 (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)
										Modera	te
										150 per 1000	49 fewer per 1000 (from 132 fewer to 386 more)
Increase	ed appet	i <b>ite</b> (assessed wit	h: Study-specific	side effect ch	ecklist)	1	<u> </u>				
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,2</sup>	4/20 (20%)	9/20 (45%)	RR 2.25 (0.83 to	Study p	opulation
8 weeks		inconsistency	muncouress	Schous		due to risk of bias, imprecision	(2070)	(4370)	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	drowsi	ness (assessed	with: Study-spec	cific side effect	checklist)		l			<u> </u>	
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	2/20 (10%)	3/20 (15%)	RR 1.5 (0.28 to	Study p	opulation
8 weeks		,				due to risk of bias, imprecision	( 333)	( 223)	8.04)	100 per 1000	50 more per 1000 (from 72 fewer to 704 more)
						Imprecision				Moderat	t <b>e</b>
										100 per 1000	50 more per 1000 (from 72 fewer to 704 more)
Day time	drowsi	iness (assessed	d with: Study-spe	cific side effec	t checklist)		l			<u> </u>	
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	2/20 (10%)	1/20 (5%)	<b>RR 0.5</b> (0.05 to	Study p	opulation
8 weeks						due to risk of bias, imprecision	(1070)	(676)	5.08)	100 per 1000	50 fewer per 1000 (from 95 fewer to 408 more)
						III production				Moderat	te
										100 per 1000	50 fewer per 1000 (from 95 fewer to 408 more)
Restless	iness (as	sessed with: Stud	y-specific side e	fect checklist)							
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	4/20 (20%)	1/20 (5%)	RR 0.25 (0.03 to	Study p	opulation
8 weeks		inconsistency	indirectiness.	School		due to risk of bias, imprecision	(2070)	(070)	2.05)	200 per 1000	<b>150 fewer per 1000</b> (from 194 fewer to 210 more)
										Moderat	te
										200 per 1000	<b>150 fewer per 1000</b> (from 194 fewer to 210 more)
Fatigue (	assessed v	ı vith: Study-specific	side effect chec	cklist)	1	1	1			1	

40 (1 study)	serious <sup>1</sup>		no serious indirectness	very serious <sup>2</sup>	⊕⊖⊝⊝ VERY LOW <sup>1,2</sup>	2/20 (10%)		<b>RR 1.5</b> (0.28 to	Study po	opulation
8 weeks		,			due to risk of bias, imprecision		, ,			<b>50 more per 1000</b> (from 72 fewer to 704 more)
										<b>50 more per 1000</b> (from 72 fewer to 704 more)
		pias as unclear if fo CI crosses both lin					r term adverse events .25)	•		

## 1.33.4 Adverse events associated with antioxidants

Adverse events associated with N-acetylcysteine versus placebo

		C	uality assessn	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 Adverse events associated with antioxidants (95% CI)
Any gast	rointest	tinal side effe	ect (assessed wit	h: 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	⊕⊝⊝ VERY LOW <sup>1,2</sup>	7/15 (46.7%)	11/14 (78.6%)	RR 1.68 (0.92 to	Study po	pulation
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)
										Moderate	e
										467 per 1000	318 more per 1000 (from 37 fewer to 976 more)
Constipa	tion (ass	essed with: Dosage	e Record and Trea	atment Emerg	ent Symptom S	cale (DOTES))		•	1	•	•

29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	2/15 (13.3%)	3/14 (21.4%)	RR 1.61 (0.31 to	Study po	ppulation
12 weeks						due to risk of bias, imprecision	(1010,0)	(=)	8.24)	133 per 1000	81 more per 1000 (from 92 fewer to 965 more)
										Moderate	e
										133 per 1000	81 more per 1000 (from 92 fewer to 963 more)
Nausea (a	assessed w	vith: Dosage Record	d and Treatment E	Emergent Sym	nptom Scale (D	OTES))	1	•		<del>-</del>	
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,2</sup>	3/15 (20%)	6/14 (42.9%)	RR 2.14 (0.66 to	Study po	pulation
12 weeks				Concuc		due to risk of bias, imprecision	(2070)	(12.070)	6.97)	200 per 1000	<b>228 more per 1000</b> (from 68 fewer to 1000 more)
										Moderate	9
										200 per 1000	228 more per 1000 (from 68 fewer to 1000 more)
Diarrhoe	<b>a</b> (assesse	ed with: Dosage Re	cord and Treatme	ent Emergent S	Symptom Scale	(DOTES))					
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	1/15 (6.7%)	3/14 (21.4%)	RR 3.21 (0.38 to	Study po	ppulation
12 weeks		linearisticiney		Solious		due to risk of bias, imprecision	(6.776)	(21.470)	27.4)	67 per 1000	<b>147 more per 1000</b> (from 41 fewer to 1000 more)
										Moderate	9
										67 per 1000	148 more per 1000 (from 42 fewer to 1000 more)
Increase	d appet	ite (assessed with	: Dosage Record	and Treatmer	nt Emergent Sy	mptom Scale (DO	TES))			1	

29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	0/15 (0%)	2/14 (14.3%)	<b>RR 5.33</b> (0.28 to	Study po	ppulation
12 weeks		·				due to risk of bias, imprecision		, ,	102.26)	0 per 1000	N/A
						Imprecision				Moderat	e
										0 per 1000	N/A
Decrease	ed appe	tite (assessed wi	th: Dosage Recor	d and Treatme	ent Emergent S	ymptom Scale (D0	OTES))		,	1	
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	3/15 (20%)	2/14 (14.3%)	RR 0.71 (0.14 to	Study po	ppulation
12 weeks						due to risk of bias, imprecision	(==73)	(**************************************	3.66)	200 per 1000	<b>58 fewer per 1000</b> (from 172 fewer to 532 more)
										Moderate	 
										200 per 1000	<b>58 fewer per 1000</b> (from 172 fewer to 532 more)
Akathisia	a (assesse	l d with: Dosage Re	L cord and Treatme	nt Emergent S	Symptom Scale	(DOTES))			_		
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	0/15 (0%)	1/14 (7.1%)	<b>RR 3.2</b> (0.14 to	Study po	ppulation
12 weeks		inconsistency	mancetress	Scrious		due to risk of bias, imprecision	(070)	(1.176)	72.62)	0 per 1000	N/A
										Moderat	e
										0 per 1000	N/A
Increase	d motor	activity (asse	ssed with: Dosage	Record and	reatment Eme	rgent Symptom So	cale (DOT	TES))	<u>.</u>	1	1
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	3/15 (20%)	2/14 (14.3%)	<b>RR 0.71</b> (0.14 to	Study po	ppulation
12 weeks		in contolocortoy	in directions	3311043		due to risk of	(2070)	(1.1.070)	3.66)	200 per	58 fewer per 1000

						bias, imprecision				1000	(from 172 fewer to 532 more)
										Moderat	e
										200 per 1000	<b>58 fewer per 1000</b> (from 172 fewer to 532 more)
Tremor (a	assessed w	ith: Dosage Record	d and Treatment E	Emergent Sym	ptom Scale (D	OTES))					1
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	1/15 (6.7%)	0/14 (0%)	RR 0.36 (0.02 to	Study po	ppulation
12 weeks		,				due to risk of bias, imprecision		()	8.07)	67 per 1000	<b>43 fewer per 1000</b> (from 65 fewer to 471 more)
										Moderat	e e
										67 per 1000	43 fewer per 1000 (from 66 fewer to 474 more)
Dizzines	S (assesse	d with: Dosage Re	cord and Treatme	ent Emergent S	Symptom Scale	(DOTES))	1			1	
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	1/15 (6.7%)	0/14 (0%)	RR 0.36 (0.02 to	Study po	ppulation
12 weeks		inconsistency	indirectives.	School		due to risk of bias, imprecision	(0.7 70)	(070)	8.07)	67 per 1000	43 fewer per 1000 (from 65 fewer to 471 more)
										Moderat	e
										67 per 1000	<b>43 fewer per 1000</b> (from 66 fewer to 474 more)
Exciteme	ent/agita	ation (assessed v	with: Dosage Rec	ord and Treatn	nent Emergent	Symptom Scale (	DOTES))				
29	serious <sup>1</sup>	no serious	no serious	very	undetected	$\oplus \ominus \ominus \ominus$	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> due to risk of bias, imprecision	(20%)	(14.3%)	(0.14 to 3.66)	200 per 1000	<b>58 fewer per 1000</b> (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	t (assessed with: I	Dosage Record ar	nd Treatment E	: Emergent Sym <sub>l</sub>	otom Scale (DOTE	S))			-	
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	0/15 (0%)	1/14 (7.1%)	<b>RR 3.2</b> (0.14 to	Study po	pulation
12 weeks						due to risk of bias, imprecision			72.62)	0 per 1000	N/A
						Improduction				Moderate	<del> </del>
										0 per 1000	N/A
Nasal co	ngestio	<b>n</b> (assessed with:	Dosage Record a	ind Treatment	Emergent Sym	ptom Scale (DOTI	ES))				
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious	undetected	⊕⊝⊝ VERY LOW¹	6/15 (40%)	4/14 (28.6%)	RR 0.71 (0.25 to	Study po	ppulation
12 weeks						due to risk of bias, imprecision	(1275)	(2000)	2.01)	400 per 1000	116 fewer per 1000 (from 300 fewer to 404 more)
										Moderate	e
										400 per 1000	<b>116 fewer per 1000</b> (from 300 fewer to 404 more)
Increase	d saliva	tion (assessed w	vith: Dosage Reco	ord and Treatm	ent Emergent	Symptom Scale (D	OTES))				
29 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	2/15 (13.3%)	0/14 (0%)	<b>RR 0.21</b> (0.01 to	Study po	ppulation
12 weeks		, , , , , , , , , , , , , , , , , , , ,				due to risk of	(1212,0)	\')	4.09)	133 per	105 fewer per 1000

						bias, imprecision				1000	(from 132 fewer to 412 more)
										Moderate	e
										133 per 1000	<b>105 fewer per 1000</b> (from 132 fewer to 411 more)
Sweating	g (assesse	d with: Dosage Red	cord and Treatmen	nt Emergent S	ymptom Scale	(DOTES))					
29	serious <sup>1</sup>	no serious	no serious	very	undetected	$\oplus \ominus \ominus \ominus$	1/15	0/14	RR 0.36	Study po	pulation
1 study)		inconsistency	indirectness	serious <sup>2</sup>		VERY LOW <sup>1,2</sup>	(6.7%)	(0%)	(0.02 to		
1 study) 2 weeks		inconsistency	indirectness	serious <sup>2</sup>		very Low <sup>1,2</sup> due to risk of bias, imprecision	(6.7%)	(0%)	(0.02 to 8.07)	67 per 1000	43 fewer per 1000 (from 65 fewer to 471 more)
		inconsistency	indirectness	serious <sup>2</sup>		due to risk of bias,	(6.7%)	(0%)		-	(from 65 fewer to 471 more)

## 1.33.5 Adverse events associated with antipsychotics

Adverse events associated with antipsychotics versus placebo

			Quality ass	essment				Su	mmary of	Findi	ings
Participants		Inconsistency	Indirectness		Publication	• •	Study			Antici	pated absolute effects
(studies) Follow up	bias				bias	evidence	With	With Adverse events associated with antipsychotics	effect (95% CI)	Risk with	Risk difference with Adverse events associated with antipsychotics (95% CI)
Any side	effect	(Aripiprazole	e, haloperid	lol or rispe	essed with: Non-system	natic asse	essment, study-spec	ific outcome	e meas	ure or study-specific report)	

528 (5 studies)	serious <sup>1</sup>	serious <sup>2</sup>	no serious indirectness	no serious imprecision	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,2,3</sup>	130/195 (66.7%)	283/333 (85%)	<b>RR 1.27</b> (1.14 to	Study	population
6-12 weeks				improdicion	suspected <sup>3</sup>	due to risk of bias, inconsistency, publication bias	(66.170)	(6676)	1.42)	667 per 1000	<b>180 more per 1000</b> (from 93 more to 280 more)
										Moder	rate
										720 per 1000	<b>194 more per 1000</b> (from 101 more to 302 more)
Any side	effect	(Aripiprazol	e) (assessed wi	th: Study-speci	fic report of adver	rse events)			<u>'</u>	1	
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>		188/212 (88.7%)	<b>RR 1.23</b> (1.08 to	Study	population
8 weeks		inconsistency	indirections.		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(12.570)	(00.770)	1.41)	723 per 1000	<b>166 more per 1000</b> (from 58 more to 296 more)
										Moder	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)				<u> </u>	
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	5/20 (25%)	16/20 (80%)	<b>RR 3.2</b> (1.45 to	Study	population
12 weeks		inconsistency	indirections.		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2370)	(50 70)	7.05)	250 per 1000	<b>550 more per 1000</b> (from 113 more to 1000 more)
										Moder	rate
										250 per 1000	550 more per 1000 (from 113 more to 1000 more)
Any side	effect	∟ (Risperidon	<b>e)</b> (assessed wi	th: Non-system	atic assessment	I or study-specific outco	me measu	ire)			

175 (2 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>	52/74 (70.3%)	79/101 (78.2%)	RR 1.17 (0.98 to	Study	population
6-8 weeks			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.076)	(10.270)	1.39)	703 per 1000	119 more per 1000 (from 14 fewer to 274 more)		
										Mode	rate
										697 per 1000	<b>118 more per 1000</b> (from 14 fewer to 272 more)
Discontii	nuation	due to adve	erse events	(Aripipraz	ole)) (assesse	d with: Study-specific r	eport)				
98 (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>	3/51 (5.9%)	5/47 (10.6%)	<b>RR 1.81</b> (0.46 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		5.9%) (10.6%)	7.16)	59 per 1000	48 more per 1000 (from 32 fewer to 362 more)
									Mode	rate	
										59 per 1000	<b>48 more per 1000</b> (from 32 fewer to 363 more)
Discontii	nuation	due to droc	ling (Aripip	o <b>razole)</b> (ass	essed 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	⊕⊝⊝ VERY LOW <sup>1,3,5</sup>	0/51 (0%)	3/165 (1.8%)	RR 2.19 (0.12 to	Study	population
8 weeks		Iniconcional			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0,0)	(1.070)	41.76)	0 per 1000	N/A
						publication blad				Mode	rate
										0 per 1000	N/A
Discontii	nuation	due to seda	tion (Aripi	razole) (ass	sessed with: Stud	dy-specific report)					

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>	0/51 (0%)	7/165 (4.2%)	RR 4.7 (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
						publication bias				Mode	rate
										0 per 1000	N/A
Disconti	nuation	due to trem	or (Aripipra	azole) (asses	sed with: Study-	specific report)					
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>	0/51 (0%)	4/165 (2.4%)	RR 2.82 (0.15 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		, ,	51.5)	0 per 1000	N/A
										Mode	rate
										0 per 1000	N/A
Clinically	y releva	ınt (>=7%) w	eight gain (	 (Aripiprazo	le) (assessed v	vith: Weight assessmer	nt)				
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	7/101 (6.9%)	56/212 (26.4%)	<b>RR 3.80</b> (1.79 to	Study	population
8 weeks		inconsistency	muncomess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.370)	(20.470)	8.05)	69 per 1000	<b>194 more per 1000</b> (from 55 more to 489 more)
										Mode	rate
										60 per 1000	168 more per 1000 (from 47 more to 423 more)
Weight g	jain (Ar	ipiprazole o	risperidon	(assessed	with: Non-system	atic assessment, study	-specific	outcome measure	or study-spe	ecific rep	port)
391 (3 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>	4/125 (3.2%)	18/266 (6.8%)	RR 2.43 (0.85 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias,			6.98)	32	46 more per 1000

						imprecision, publication bias				per 1000	(from 5 fewer to 191 more)
										Mode	rate
										26 per 1000	37 more per 1000 (from 4 fewer to 155 more)
Weight g	jain (Ar	ipiprazole) (a	assessed with: S	tudy-specific re	port)		<u> </u>				1
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%)	7/165 (4.2%)	RR 2.16 (0.27 to	Study	population
8 weeks		inconsistency	indirectiness.		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(270)	(4.270)	17.17)	20 per 1000	23 more per 1000 (from 14 fewer to 317 more)
										Mode	rate
										20 per 1000	23 more per 1000 (from 15 fewer to 323 more)
Weight g	⊥ jain (Ris	speridone) (a	assessed with: N	on-systematic a	I assessment or st	l udy-specific outcome r	neasure )	·			
175 (2 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>	3/74 (4.1%)	11/101 (10.9%)	RR 2.55 (0.75 to	Study	population
6-8 weeks		inconsistency	indirectriess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(4.176)	(10.976)	8.66)	41 per 1000	<b>63 more per 1000</b> (from 10 fewer to 311 more)
										Mode	rate
										41 per 1000	<b>64 more per 1000</b> (from 10 fewer to 314 more)
Weight g	jain (Ar	ipiprazole o	r risperidor	<b>1e)</b> (measured	with: Weight ass	essment (in kg); Better	r indicated	d by lower values)		1	
541 (6 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias strongly	⊕⊕⊖⊖ <b>LOW</b> <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 0.69 standard deviations higher (0.51 to 0.88 higher)
Weight g	ain (Ari	i <b>piprazole)</b> (n	neasured with: V	/eight 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>	⊕⊖⊖ <b>VERY LOW</b> <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 higher</b> (0.16 to 0.8 higher)
Weight g	ain (Ris	speridone) (n	neasured with: V	/eight 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>	⊕⊖⊖ <b>VERY LOW</b> <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	piprazole) (m	neasured with: B	MI change (kg/ı	m-squared); Bett	er indicated by lower va	alues)				
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>	⊕⊖⊖ <b>VERY LOW</b> <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	⊕⊖⊝ VERY LOW <sup>1,3,4</sup>	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			0.98)	50 per 1000	40 fewer per 1000 (from 1 fewer to 48 fewer)

										Moder	ate
										50 per 1000	41 fewer per 1000 (from 1 fewer to 48 fewer)
Prolactin	conce	ntration (ng	/ml) (Risper	ridone) (mea	sured with: Labo	ratory assessment; Be	etter indica	ated by lower values	s)	•	
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 1.8 standard deviations higher (1.38 to 2.22 higher)
Any treat	tment-e	emergent ex	trapyramida	al sympton	n (Aripipraz	ole) (assessed with:	Study-spe	ecific report of adve	rse event)		
313 (2 studies)	serious <sup>1</sup> no seri 2 studies) no seri	no serious no serious inconsistency indirectness		strongly	⊕⊝⊝ VERY LOW <sup>1,3,5</sup>	10/101 (9.9%)	44/212 (20.8%)	RR 1.89 (0.98 to	Study	population	
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(6.676)	(2010/0)	3.67)	99 per 1000	<b>88 more per 1000</b> (from 2 fewer to 264 more)
										Moder	ate
										99 per 1000	<b>88 more per 1000</b> (from 2 fewer to 264 more)
Extrapyr	amidal	symptoms (	Risperidon	<b>e)</b> (measured v	with: Abnormal In	voluntary Movements	Scale (Al	MS): Total; Better in	ndicated 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 LOW¹,3,6 due to risk of bias, imprecision, publication bias	34	58	-		The mean extrapyramidal symptoms (risperidone) in the intervention groups was <b>0.46 standard deviations</b> lower (0.89 to 0.03 lower)
Extrapyra	amidal	disorder (Ar	ripirazole) (a	assessed with: S	Study-specific rep	oort of adverse event)	1			1	

313 (2 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>	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	(2.2.)	(	51.91)	0 per 1000	N/A
						publication bias				Mode	rate
										0 per 1000	N/A
Fasting g	glucose	(mg/dL) cha	ange score	(Risperido	ne) (measured	with: Laboratory asses	ssment; E	Better indicated by lo	ower values	s)	
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>	⊕⊖⊖ <b>VERY LOW</b> <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 <b>0.02 standard deviations</b> higher (0.49 lower to 0.53 higher)
Fasting g	glucose	e (=>115 mg/	dL) - Aripip	razole (asse	ssed with: Labor	atory assessment)			1	1	
313 (2 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>	0/101 (0%)	2/212 (0.9%)	RR 1.57 (0.08 to	Study	population
8 weeks		inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(070)	(0.070)	32.11)	0 per 1000	N/A
						publication bias				Mode	rate
										0 per 1000	N/A
Fasting t	riglyce	rides (=>120	mg/dL for	females or	160 mg/dL	for males) (Arip	oiprazo	ole) (assessed wit	h: Laborato	ry asses	ssment)
313 (2 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>	7/101 (6.9%)	23/212	RR 1.8 (0.74 to	Study	population
8 weeks		inconsistency	munectness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.378)		4.35)	69 per 1000	<b>55 more per 1000</b> (from 18 fewer to 232 more)
										Mode	rate

										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 indicat	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>	⊕⊖⊖ <b>VERY LOW</b> <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 lower</b> (0.63 lower to 0.4 higher)
Leptin (n	ng/L) cl	nange score	(Risperido	<b>ne)</b> (measured	with: Laboratory	assessment; Better in	dicated	by lower values)			
104 (2 studies) 8-24 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>6</sup>	undetected	⊕⊕⊝ LOW¹.6 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  0.64 standard deviations higher  (0.24 to 1.04 higher)
Diastolic	blood	pressure (m	m Hg) char	nge scores	(Risperido	<b>ne)</b> (measured with: P	hysical o	exam; Better indicat	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 LOW¹,3,7 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 higher</b> (0.29 lower to 0.6 higher)
Systolic	blood p	ressure (mr	n Hg) chan	ge scores	(Risperidon	(measured with: Pr	ysical e	xam; Better indicate	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 LOW¹,3,7 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 (b	pm) cha	ange 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>	⊕⊖⊖ <b>VERY LOW</b> <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 higher</b> (0.24 to 1.15 higher)
Somnole study-specific			ripiprazole	or risperid	lone) (assesse	d with: Non-systematic	assessm	nent, study-specific o	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	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	14/226 (6.2%)	82/362 (22.7%)	RR 4.81 (2.85 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			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	ence/Dr	owsiness (A	ripiprazole	(assessed with	h: Study-specific	report of adverse even	nt)		l		
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	4/101 (4%)	22/212 (10.4%)	RR 2.98 (1.07 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	( - / - /	(1311)	8.31)	40 per 1000	<b>78 more per 1000</b> (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	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	10/125 (8%)	60/150 (40%)	RR 5.71 (3.08 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(673)	(1070)	10.6)	80 per 1000	377 more per 1000 (from 166 more to 768 more)
										Mode	rate
										77 per 1000	363 more per 1000 (from 160 more to 739 more)
Fatigue (	(Aripira	zole or rispe	eridone) (ass	essed with: No	n-systematic asse	essment, study-specifi	ic outcome	measure, stud	ly-specific repo	t or stud	ly-specific side effect
588 (5 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	17/226 (7.5%)	69/362 (19.1%)	RR 3.16 (1.95 to	Study	population
5 studies) -8 weeks	inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(**************************************	(,,	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-sp	pecific report of	f adverse event)	l			<u> </u>		1
313 (2 studies)	serious <sup>1</sup>	no serious	no serious	serious <sup>4</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	2/101 (2%)	35/212 (16.5%)	<b>RR 8.33</b> (2.11 to	Study	population
8 weeks	2 studies) incons	inconsistency indirectness		strongly suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(270)	(10.070)	32.9)	20 per 1000	145 more per 1000 (from 22 more to 632 more)	
										Mode	rate
									20 per	147 more per 1000 (from 22 more to 638 more)	

										1000		
Fatigue (	(Risperi	idone) (assesse	ed with: Non-sys	tematic assess	ment, study-spec	cific outcome measure	, or study-	specific side eff	fect checklist)	<u> </u>		
275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	15/125 (12%)	34/150 (22.7%)	RR 2.25 (1.38 to	Study	population	
6-8 weeks		inconsistency	mancounces		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(1270)	(22.170)	3.68)	120 per 1000	150 more per 1000 (from 46 more to 322 more)	
										Mode	rate	
										26 per 1000	32 more per 1000 (from 10 more to 70 more)	
Lethargy	/ (Aripip	orazole) (asses	ssed with: Study	-specific report	of adverse event	)		,	<b>I</b>	1		
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>	0/51 10/165 (0%) (6.1%)		RR 6.58 (0.39 to	Study	population	
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(6,0)	(6.1%)	(0.176)	110.35)	0 per 1000	N/A
						publication bias				Moderate		
										0 per 1000	N/A	
Sedation	⊣ n (Aripip	razole or ris	speridone)	(assessed with:	Non-systematic	assessment or study-s	specific re	port)		1		
409	serious <sup>1</sup>	no serious	no serious	serious <sup>4</sup>	reporting bias	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	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	4 (2.9%) (19.4%) oias,	4 (2.9%) (19.4%) pias,	(1.94 to 12.58)	29 per 1000	116 more per 1000 (from 28 more to 341 more)	
										Mode	rate	
										20 per	<b>79 more per 1000</b> (from 19 more to 232 more)	

										1000	
Sedation	n (Aripir	razole) (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	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	4/101 (4%)	44/212 (20.8%)	RR 4.25 (1.57 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(476)	(20.070)	11.51)	40 per 1000	<b>129 more per 1000</b> (from 23 more to 416 more
										Mode	rate
										39 per 1000	<b>127 more per 1000</b> (from 22 more to 410 more
Sedation	(Rispe	eridone) (asses	ssed with: Non-s	ystematic asses	ssment)	<del>!</del>		-			1
96 (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>	0/35 (0%)		RR 11.03 (0.66 to	Study	population
6 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	` , ` ,		183.98)	0 per 1000	N/A
						publication bias				Mode	rate
										0 per 1000	N/A
		ry tract infe		prazole or	risperidone	(assessed with: Non	n-systema	tic assessment, s	tudy-specific o	outcome	e measure, study-specific
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>	14/226 (6.2%)		<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	f bias, (6.2%) (8.3%)	of bias,	3.25)	62 per 1000	48 more per 1000 (from 2 fewer to 139 more)
										Mode	rate
										39 per	30 more per 1000

										1000	(from 1 fewer to 88 more)
Upper re	spirato	ry tract infe	ction (Aripi	<b>prazole)</b> (as	sessed with: Stu	dy-specific report of ac	dverse 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	⊕⊝⊝ VERY LOW <sup>1,2,3,5</sup>	5/101 (5%)	6/212 (2.8%)	RR 0.65 (0.16 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, inconsistency, imprecision, publication bias	(673)	(=1070)	2.58)	50 per 1000	17 fewer per 1000 (from 42 fewer to 78 more)
						publication bias				Mode	rate
										50 per 1000	18 fewer per 1000 (from 42 fewer to 79 more)
Upper re	spirato	ry tract infe	ction (Rispe	eridone) (as	sessed with: Nor	n-systematic assessme	ent, study-	specific outcome	e measure, or	study-s <sub> </sub>	pecific side effect checklist)
275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ L <b>OW</b> <sup>1,4</sup>	9/125 (7.2%)	24/150 (16%)	RR 2.45 (1.21 to	Study	population
6-8 weeks		in concionation by				due to risk of bias, imprecision	(1.270)	(1878)	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/	rhinorri	nea (Aripipra	azole or ris	peridone) (	assessed with: S	tudy-specific outcome	measure	or study-specific	report)		
295 (2 studies)	serious <sup>1</sup>	no serious	no serious	serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	5/90 (5.6%)	19/205 (9.3%)	RR 2.62 (1.02 to	Study	population
8 weeks		inconsistency	indirectriess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(3.0%)	(9.3%)	6.77)	56 per 1000	90 more per 1000 (from 1 more to 321 more)
										Mode	rate
										61	99 more per 1000

										per 1000	(from 1 more to 352 more)
Rhinitis/	rhinorrl	nea (Aripipra	azole) (assess	sed with: Study-	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	⊕⊝⊝⊝ VERY LOW <sup>1,3,5</sup>	1/51 (2%)	8/165 (4.8%)	RR 2.47 (0.32 to	Study	population
8 weeks		inconsistency	mancounces		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	<b>29 more per 1000</b> (from 14 fewer to 366 more)
Rhinitis/	rhinorrl	nea (Risperi	done) (assess	sed with: Study-	specific outcome	measure)			<u> </u>		1
79 (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>	4/39 (10.3%)	11/40	RR 2.68 (0.93 to	Study	population
8 weeks		inconsistency	indirectriess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.576)	(21.570)	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	ngestic	n (Aripirazo	le or risper	r <b>idone)</b> (asse	ssed with: Study	r-specific report or stud	dy-specific	side effect che	cklist)	!	1
413 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>5</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,5</sup>	22/152 (14.5%)		RR 1.42 (0.92 to	Study	population
8 weeks		inconsistency	munectress			due to risk of bias, imprecision	(14.570)	(1070)	2.19)	145 per 1000	61 more per 1000 (from 12 fewer to 172 more)
										Mode	rate

										20 per 1000	8 more per 1000 (from 2 fewer to 24 more)
Nasal co	ngestic	on (Aripipraz	zole) (assesse	d with: Study-sp	ecific report of a	dverse event)			<b>-</b>	I	,
313 (2 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>	2/101 (2%)	9/212 (4.2%)	RR 2.37 (0.52 to	Study	population
8 weeks		incomplete in the second of th			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(= /0)	(11270)	10.77)	20 per 1000	<b>27 more per 1000</b> (from 10 fewer to 193 more)
										Moder	rate
										20 per 1000	<b>27 more per 1000</b> (from 10 fewer to 195 more)
Nasal co	ngestic	n (Risperid	one) (assesse	d with: Study-sp	ecific side effect	checklist)					
100 serious <sup>1</sup> (1 study)	no serious	no serious no serious indirectness	,	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,5</sup>	20/51	25/49 (51%)	<b>RR 1.3</b> (0.84 to	Study	population	
8 weeks		inconsistency	maneomess			due to risk of bias, imprecision	(55.276)	, , ,	2.02)	392 per 1000	118 more per 1000 (from 63 fewer to 400 more)
										Moder	rate
										392 per 1000	118 more per 1000 (from 63 fewer to 400 more)
Nasopha	aryngitis	s (Aripipraz	ole or rispe	ridone) (ass	essed with: Non-	systematic assessmer	nt or study-	-specific report	)		
409 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>1,3,5</sup>	7/136 (5.1%)	24/273 (8.8%)	RR 1.65 (0.68 to	Study	population
6-8 weeks		inconsistency	muneciness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(5.1%)	(0.0%)	3.97)	51 per 1000	<b>33 more per 1000</b> (from 16 fewer to 153 more)
										Moder	rate

										57 per 1000	37 more per 1000 (from 18 fewer to 169 more)
Nasopha	aryngiti	s (Aripiprazo	ole) (assessed	with: Study-spe	cific report of adv	verse event)	1			•	
313 (2 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>	5/101 (5%)	18/212 (8.5%)	RR 1.61 (0.55 to	Study	population
(2 studies) 8 weeks		inconsistency	muneciness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(3%)	(6.5%)	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	aryngiti	s (Risperido	ne) (assessed	with: Non-syste	matic assessme	nt)				1	
96 (1 study)	serious <sup>1</sup>	no serious inconsistency	s no serious very serious reporting bias $\oplus \ominus \ominus \ominus$ 2/35 6/61 R	<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)	(5.570)	8.07)	57 per 1000	<b>41 more per 1000</b> (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	
312 (2 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>	0/86 (0%)	7/226 (3.1%)	RR 3.2 (0.4 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		. ,	25.77)	0 per 1000	N/A
						publication bias				l l	

										0 per 1000	N/A		
Nose ble		piprazole) (as	no serious	udy-specific rep	ort of adverse ev	rent)	0/51	5/165	RR 3.45	Study	population		
(1 study)	3011003	inconsistency	indirectness	very serious	strongly	VERY LOW <sup>1,3,5</sup>	(0%)	(3%)	(0.19 to				
3 weeks					suspected 3	due to risk of bias, imprecision, publication bias			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)								
96 (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>	0/35 (0%)	2/61 (3.3%)	<b>RR 2.9</b> (0.14 to	Study	population		
Sweeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			58.81)	0 per 1000	N/A		
						p uz nounon sido				Mode	rate		
										0 per 1000	N/A		
Coughin	g (Aripi	iprazole or r	isperidone)	(assessed with	: Non-systemation	c assessment, study-sp	pecific out	tcome measure or	study-specif	fic repor	t)		
391 (3 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>	6/125 (4.8%)	18/266 (6.8%)	RR 1.63 (0.65 to	Study	population		
i-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(,	) (6.8%)			4.12)	48 per 1000	<b>30 more per 1000</b> (from 17 fewer to 150 more)
										Mode	rate		
										39 per 1000	<b>25 more per 1000</b> (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	⊕⊝⊝⊝ VERY LOW <sup>1,3,5</sup>	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)	(1.1070)	8.01)	39 per 1000	33 more per 1000 (from 22 fewer to 275 more)
										Mode	rate
Coughing (Ris										39 per 1000	<b>33 more per 1000</b> (from 22 fewer to 273 more)
Coughin	ıg (Risp	eridone) (ass	essed with: Non	-systematic ass	essment or study	/-specific outcome me	asure)				
175 (2 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>	4/74 (5.4%)	6/101 (5.9%)	RR 1.46 (0.45 to	Study	population
(2 studies) 6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(6.176)	(6.676)	4.79)	54 per 1000	25 more per 1000 (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 risp	oeridone) (a	assessed with: No	on-systematic assessi	ment, stud	y-specific outco	ome measure, s	tudy-sp	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	⊕⊖⊝⊝ VERY LOW <sup>1,3,4</sup>	15/226 (6.6%)	64/362 (17.7%)	<b>RR 3.01</b> (1.73 to	Study	population
5 studies) 6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		,	5.24)	66 per 1000	133 more per 1000 (from 48 more to 281 more)
										Mode	rate
									57	115 more per 1000	

										1000		
Increase	d appe	tite (Aripipra	izole) (assess	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	⊕⊝⊝⊝ VERY LOW <sup>1,3,5</sup>	7/101 (6.9%)	27/212 (12.7%)	RR 2.11 (0.89 to	Study	population	
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(6.676)	(,,,)	5.01)	69 per 1000	77 more per 1000 (from 8 fewer to 278 more)	
										Mode	rate	
								easure, or study-		70 per 1000	78 more per 1000 (from 8 fewer to 281 more)	
Increase	d appe	tite (Risperio	done) (assess	ed with: Non-sy	stematic assessi	ment, study-specific ou	utcome me	easure, or study-s	specific side e	ffect ch	ecklist)	
275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	8/125 (6.4%)	37/150 (24.7%)	RR 3.83 (1.84 to	Study	population	
6-8 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(=,	(24.176)	,	8.01)	64 per 1000	<b>181 more per 1000</b> (from 54 more to 449 more
										Mode	rate	
										57 per 1000	161 more per 1000 (from 48 more to 400 more)	
Decrease	ed appe	etite (Aripipr	azole or ris	peridone)	(assessed with: \$	Study-specific report o	r study-sp	ecific side effect of	checklist)			
316 (2 studies)	serious <sup>1</sup>	serious <sup>2</sup>	no serious	very serious <sup>5</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2,5</sup>	6/102 (5.9%)	16/214 (7.5%)	RR 1.43 (0.5 to	Study	population	
2 studies) 3 weeks			indirectness			due to risk of bias, inconsistency, imprecision	(3.370)	(1.370)	4.13)	59 per 1000	<b>25 more per 1000</b> (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)			l	l	1
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%)	13/165 (7.9%)	RR 4.02 (0.54 to	Study	population
8 weeks		inconsistency	mancounces		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(270)	(1.070)	29.98)	20 per 1000	59 more per 1000 (from 9 fewer to 568 more)
										Mode	rate
										20 per 1000	60 more per 1000 (from 9 fewer to 580 more)
Decreas	ed appe	etite (Risperi	done) (asses	sed with: Study	-specific side effe	ect checklist)		Ť	<u> </u>	1	'
100 (1 study)	serious <sup>1</sup>	no serious inconsistency		very serious <sup>5</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,5</sup>	5/51 (9.8%)	3/49	<b>RR 0.62</b> (0.16 to	Study	population
8 weeks		inconsistency	indirectriess			due to risk of bias, imprecision	(3.076)		2.47)	98 per 1000	37 fewer per 1000 (from 82 fewer to 144 more)
										Mode	rate
										98 per 1000	37 fewer per 1000 (from 82 fewer to 144 more)
	-	/Stomachac	he (Aripipr	azole or ris	speridone) (	assessed with: Non-sy	stematic a	assessment, stu	dy-specific out	come m	easure, study-specific repor
491 (4 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,5</sup>	13/176 (7.4%)		RR 1.35	Study	population
6-8 weeks		inconsistency	munectress			due to risk of bias, imprecision	(1.470)	(1.370)	(0.69 to 2.64)	74 per 1000	26 more per 1000 (from 23 fewer to 121 more)
							1			Mode	<u>I</u>

										48 per 1000	17 more per 1000 (from 15 fewer to 79 more)
Abdomi	nal pain	/Stomachad	he (Aripipr	azole) (asses	sed with: Study-	specific report of adve	erse event)			1	<u>'</u>
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%)	7/165 (4.2%)	RR 2.16 (0.27 to	Study	population
8 weeks		incomplete in the second of th			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(278)	(270)	17.17)	20 per 1000	23 more per 1000 (from 14 fewer to 317 more)
										Moder	rate
									tcome measure, or st	20 per 1000	23 more per 1000 (from 15 fewer to 323 more)
Abdomi	nal pain	/Stomachad	he (Risperi	i <b>done)</b> (asses	ssed with: Non-sy	stematic assessment	, study-spe	ecific outcome	measure, or stud	dy-speci	ific side effect checklist)
275 (3 studies)	serious <sup>1</sup>	serious <sup>2</sup>	s <sup>2</sup> no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,2,5</sup>	12/125 (9.6%)	16/150 (10.7%)	<b>RR 1.25</b> (0.61 to	Study	population
6-8 weeks			muneciness			due to risk of bias, inconsistency, imprecision	(9.0%)	(10.7 76)	2.54)	96 per 1000	<b>24 more per 1000</b> (from 37 fewer to 148 more)
										Moder	rate
										77 per 1000	<b>19 more per 1000</b> (from 30 fewer to 119 more)
Abdomi	nal disc	omfort (Ris	peridone) (a	ssessed with: N	on-systematic as	ssessment)	1				
96 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊖⊖⊖ VERY LOW <sup>1,3,5</sup>	3/35	0/61	<b>RR 0.08</b> (0 to	Study	population
6 weeks		IIICOIISISTEIICY	mullectriess		suspected <sup>3</sup> due to impred	VERY LOW <sup>1,3,5</sup>	(8.6%) (0%)	1.56)	86 per 1000	79 fewer per 1000 (from 86 fewer to 48 more)	
										Moderate	

										86 per 1000	79 fewer per 1000 (from 86 fewer to 48 more)
Vomiting checklist)	(Aripip	prazole or ris	speridone)	(assessed with:	Non-systematic	assessment, study-spe	ecific outco	ome measure, stud	y-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%)		<b>RR 1.5</b> (0.97 to	Study	population
6-8 weeks		inconsistency	munconicss		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(11.370)	(13.270)	2.34)	115 per 1000	58 more per 1000 (from 3 fewer to 154 more)
										Mode	rate
										78 per 1000	39 more per 1000 (from 2 fewer to 105 more)
Vomiting	(Aripir	orazole) (asses	ssed with: Study	-specific report	of adverse event	)					
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>5</sup>	reporting bias strongly	⊕⊖⊝ VERY LOW <sup>1,3,5</sup>	6/101 (5.9%)	29/212 (13.7%)	RR 2.19 (0.95 to	Study	population
8 weeks		inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(6.676)	(13.176)	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	eridone) (asses	ssed with: Non-s	ystematic asses	ssment, study-sp	ecific outcome measur	e, or stud	y-specific side effec	ct checklist)		
275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>5</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,5</sup>	20/125 (16%)	26/150 (17.3%)	RR 1.23 (0.74 to	Study	population
6-8 weeks		,				due to risk of bias, imprecision		, ,	2.07)	160 per 1000	37 more per 1000 (from 42 fewer to 171 more)

										Mode	rate
										154 per 1000	35 more per 1000 (from 40 fewer to 165 more)
						sessment, study-speci					
412 (3 studies)	serious'	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,5</sup>	7/137 (5.1%)	15/275 (5.5%)	<b>RR 1.3</b> (0.51 to	Study	population
6-8 weeks						due to risk of bias, imprecision	(01170)	(0.070)	3.37)	51 per 1000	15 more per 1000 (from 25 fewer to 121 more)
										Mode	rate
										29 per 1000	9 more per 1000 (from 14 fewer to 69 more)
Nausea (	(Aripipr	azole) (assesso	I ed with: Study-sր	pecific 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	⊕⊝⊝ VERY LOW <sup>1,3,5</sup>	1/51 (2%)	8/165 (4.8%)	RR 2.47 (0.32 to	Study	population
8 weeks					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	<b>29 more per 1000</b> (from 14 fewer to 366 more)
Nausea (	(Risperi	i <b>done)</b> (assesse	ed with: Non-sys	tematic assessi	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	⊕⊝⊝ VERY LOW <sup>1,5</sup>	6/86 (7%)	7/110 (6.4%)	RR 1.02 (0.34 to	Study	population
6-8 weeks						due to risk of bias, imprecision	(, ,,,	(5. 170)	3)	70 per 1000	1 more per 1000 (from 46 fewer to 140 more)

										Mode	rate
										63 per 1000	1 more per 1000 (from 42 fewer to 126 more)
Gastroer	nteritis	viral (Aripipı	razole) (asses	ssed with: Study	r-specific report of	of adverse event)		•	1	1	
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>5</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,5</sup>	0/51 (0%)	5/165 (3%)	RR 3.45 (0.19 to	Study	population
8 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(3.13)		61.28)	0 per 1000	N/A
						publication bias				Mode	rate
										0 per 1000	N/A
Constipa	tion (R	isperidone)	(assessed with:	Non-systematic	assessment, stu	ı dy-specific outcome m	easure, c	or study-specific side	e effect che	cklist)	
275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1,4</sup>	8/125 (6.4%)	21/150 (14%)	RR 2.53 (1.19 to	Study	population
6-8 weeks		inconsistency				due to risk of bias, imprecision	(0.470)	(1470)	5.39)	64 per 1000	<b>98 more per 1000</b> (from 12 more to 281 more)
										Mode	rate
										29 per 1000	44 more per 1000 (from 6 more to 127 more)
Diarrhoe	a (Aripi	prazole or r	isperidone)	(assessed with	: Non-systemation	c assessment, study-sp	pecific rep	ort or study-specific	side effec	checkli	st)
293 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,5</sup>	17/136 (12.5%)	14/157 (8.9%)	RR 0.83 (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)

										Moder	rate
										64 per 1000	<b>11 fewer per 1000</b> (from 36 fewer to 38 more)
Diarrhoe	a (Aripi	prazole) (asse	essed with: Stud	y-specific repor	of adverse even	it)				•	
97 (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>	5/50 (10%)	4/47 (8.5%)	RR 0.85 (0.24 to	Study	population
8 weeks		inconsistency	munectness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10%)	(6.3%)	2.98)	100 per 1000	<b>15 fewer per 1000</b> (from 76 fewer to 198 more)
										Moder	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)				
196 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,5</sup>	12/86 (14%)	10/110 (9.1%)	RR 0.82 (0.39 to	Study	population
6-8 weeks		inconsistency	indirectiness			due to risk of bias, imprecision	(1470)	(5.170)	1.75)	140 per 1000	<b>25 fewer per 1000</b> (from 85 fewer to 105 more)
										Moder	rate
										29 per 1000	5 fewer per 1000 (from 18 fewer to 22 more)
Fever (A	ripipraz	ole or rispe	r <b>idone)</b> (asse	ssed with: Non-	systematic asses	I ssment, study-specific (	outcome	measure or study-s	pecific repo	ort)	
488 (4 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias	⊕⊖⊝ VERY LOW <sup>1,3,4</sup>	8/175 (4.6%)	29/313 (9.3%)	RR 2.25 (1.04 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		(/6)	4.87)	46 per 1000	<b>57 more per 1000</b> (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)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>5</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,3,5</sup>	1/101 (1%)	19/212 (9%)	RR 6.66 (1.13 to	Study	population
8 weeks		inconsistency	indirectiness.		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(170)	(576)	39.2)	10 per 1000	56 more per 1000 (from 1 more to 378 more)
										Mode	rate
										10 per 1000	<b>57 more per 1000</b> (from 1 more to 382 more)
Fever (R	isperid	one) (assessed	L with: Non-syster	natic assessme	I nt or study-speci	fic outcome measure)	_				
175 (2 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>	7/74 (9.5%)	10/101 (9.9%)	RR 1.26 (0.53 to	Study	population
6-8 weeks		inconsistency	indirectivess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(9.376)	(3.376)	3.02)	95 per 1000	25 more per 1000 (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	speridone)	(assessed with	: Study-specific	outcome measure)					
79 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>5</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>1,3,5</sup>	2/39 (5.1%)	4/40 (10%)	RR 1.95 (0.38 to	Study	population
8 weeks		inconsistency	indirectifess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.170)	(1070)	10.04)	51 per 1000	<b>49 more per 1000</b> (from 32 fewer to 464 more)

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										Mode	rate
										51 per 1000	48 more per 1000 (from 32 fewer to 461 more)
Insomnia checklist)	a (Aripi)	orazole or ri	speridone)	·	Non-systematic	assessment, study-spe	ecific outco	ome measure, stud	ly-specific	report or	study-specific side effect
372 (4 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊖⊖ LOW <sup>1,4</sup>	27/175 (15.4%)		<b>RR 0.59</b> (0.34 to	Study	population
6-8 weeks		inconsistency	maneciness			due to risk of bias, imprecision	(13.4%)	(0.176)	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	orazole) (asse	ssed with: Study	-specific report	of adverse even	t)					·
97 (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>		3/47 (6.4%)	<b>RR 0.8</b> (0.19 to	Study	population
8 weeks		inidensistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(070)	(0.476)	3.38)	80 per 1000	16 fewer per 1000 (from 65 fewer to 190 more)
										Mode	rate
										80 per 1000	16 fewer per 1000 (from 65 fewer to 190 more)
Insomnia	a (Rispe	eridone) (asse	ssed with: Non-s	systematic asse	ssment, study-sp	pecific outcome measur	re, or stud	y-specific side effec	ct checklist	)	
275 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1,4</sup>	23/125 (18.4%)		RR 0.56 (0.31 to	Study	population
6-8 weeks		, , , , , , , , , , , , , , , , , , , ,				due to risk of bias, imprecision	(121170)	(- ·)	1.03)	184 per	81 fewer per 1000 (from 127 fewer to 6 more)

										1000	
										Mode	rate
										154 per 1000	68 fewer per 1000 (from 106 fewer to 5 more)
Hyperso	mnia (A	Aripiprazole (	or risperido	ne) (assesse	d with: Non-syste	ematic assessment or s	study-spe	cific report)	1		
312 (2 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>	1/86 (1.2%)	7/226 (3.1%)	RR 2.01 (0.33 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			12.16)	12 per 1000	12 more per 1000 (from 8 fewer to 130 more)
										Mode	rate
										14 per 1000	<b>14 more per 1000</b> (from 9 fewer to 156 more)
Hyperso	⊥ mnia (A	⊥ Aripiprazole)	(assessed with:	Study-specific	L report of adverse	event)					
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>5</sup>	reporting bias	⊕⊖⊝⊝ VERY LOW <sup>1,3,5</sup>	0/51 (0%)	5/165 (3%)	<b>RR 3.45</b> (0.19 to	Study	population
8 weeks		in consistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0,0)	(670)	61.28)	0 per 1000	N/A
						publication bias				Mode	rate
										0 per 1000	N/A
Hyperso	mnia (R	Risperidone)	(assessed with:	Non-systematic	assessment)	1	+			1	,
96 (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>	1/35 (2.9%)	2/61 (3.3%)	RR 1.15 (0.11 to	Study	population
6 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision,		, ,	12.2)	29 per	4 more per 1000 (from 25 fewer to 320

						publication bias				1000	more)
										Moder	rate
										29 per 1000	4 more per 1000 (from 26 fewer to 325 more)
Sleep pr	oblems	(Risperidor	<b>1e)</b> (assessed w	vith: Study-spec	ific side effect ch	ecklist)	_				
100 (1 study) 8 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖ <b>VERY LOW</b> <sup>1,5</sup> due to risk of bias, imprecision	9/51 (17.6%)	11/49 (22.4%)	RR 1.27 (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)
	e (Arip	inrazole or r	ionoridono)			a accomment atudy of				1	
checklist)		ipiazoie oi i	isperidone)	(assessed with	n: Non-systemati	c assessment, study-s	pecific out	come measure, stu	dy-specific	report o	or study-specific side effect
588	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias	<b>0</b> 000	22/226	34/362	RR 1.1		population
,	serious <sup>1</sup>		T			1	22/226		T		
588 (5 studies)	serious <sup>1</sup>	no serious	no serious		reporting bias strongly	⊕⊖⊝⊖ VERY LOW¹,3,5 due to risk of bias, imprecision,	22/226	34/362	<b>RR 1.1</b> (0.65 to	Study 97 per	population  10 more per 1000 (from 34 fewer to 86 more)
588 (5 studies)	serious <sup>1</sup>	no serious	no serious		reporting bias strongly	⊕⊖⊝⊖ VERY LOW¹,3,5 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)
588 (5 studies) 6-8 weeks		no serious	no serious indirectness	very serious <sup>5</sup>	reporting bias strongly suspected <sup>3</sup>	⊕⊖⊝⊖ VERY LOW¹,3,5 due to risk of bias, imprecision, publication bias	22/226	34/362	<b>RR 1.1</b> (0.65 to	97 per 1000 Moder 114 per	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, publication bias	(9.9%)	(7.5%)	(0.35 to 2.07)	99 per 1000	15 fewer per 1000 (from 64 fewer to 106 more)
										Moderate	
										100 per 1000	<b>15 fewer per 1000</b> (from 65 fewer to 107 more)
Headach	e (Risp	eridone) (ass	essed with: Non-	systematic asse	essment, study-s	pecific outcome measu	ure, or stu	ıdy-specific side effe	ect checklis	t)	
275 (3 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	12/125 (9.6%)	18/150 (12%)	RR 1.31 (0.67 to 2.57)	Study population	
								(1270)		96 per 1000	30 more per 1000 (from 32 fewer to 151 more)
										Moderate	
										114 per 1000	35 more per 1000 (from 38 fewer to 179 more)
Dizzines	s (Risp	eridone) (asse	essed with: Study	/-specific side e	ffect checklist)					<u>I</u>	
100 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊖⊝ VERY LOW¹,5 due to risk of bias, imprecision	2/51 (3.9%)	8/49 (16.3%)	RR 4.16 (0.93 to 18.64)	Study population	
8 weeks								(10.070)		39 per 1000	124 more per 1000 (from 3 fewer to 692 more)
										Moderate	
										39 per 1000	<b>123 more per 1000</b> (from 3 fewer to 688 more)
Increase	d saliva	ation (Aripip	razole or ris	speridone)	(assessed with:	Study-specific outcome	e measur	e or study-specific r	eport)		
295	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	reporting bias	⊕⊖⊝⊖	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)
						publication bias				Mode	rate
										23 per 1000	60 more per 1000 (from 4 fewer to 341 more)
Increase	d saliva	ation (Aripip	razole) (asse	ssed with: Stud	y-specific report	of adverse event)		•	<b> </b>		1
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	(= /3)	(6.1. 76)	25.7)	20 per 1000	<b>47 more per 1000</b> (from 11 fewer to 484 more)
										Mode	rate
										20 per 1000	<b>48 more per 1000</b> (from 11 fewer to 494 more)
Increase	d saliva	ation (Risper	ridone) (asse	ssed with: Stud	y-specific outcon	ne measure)					
79 (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>	1/39 (2.6%)	4/40 (10%)	RR 3.9 (0.46 to	Study	population
8 weeks		linconsistency	muncomess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2.070)	(1070)	33.36)	26 per 1000	74 more per 1000 (from 14 fewer to 830 more)
										Mode	rate
										26	75 more per 1000
										per 1000	(from 14 fewer to 841 more)
Drooling	(Aripip	prazole or ris	speridone) (	assessed with:	Study-specific re	port or study-specific	side effect	checklist)			

(3 studies) 8 weeks		inconsistency	indirectness			LOW <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 of	of adverse event)		•		1		
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly	⊕⊖⊝ VERY LOW <sup>1,3,4</sup>	0/101 (0%)	19/212 (9%)	RR 9.65 (1.24 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(675)	(073)	74.91)	0 per 1000	N/A
										Mode	rate
										0 per 1000	N/A
Drooling	(Rispe	ridone) (asses	sed with: Study-	specific side eff	ect checklist)						
100 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1,4</sup>	3/51 (5.9%)	13/49 (26.5%)	RR 4.51 (1.37 to	Study	population
8 weeks		inconsistency	indirectiness.			due to risk of bias, imprecision	(0.370)	(20.070)	14.86)	59 per 1000	206 more per 1000 (from 22 more to 815 more)
										Mode	rate
										59 per 1000	207 more per 1000 (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	⊕⊝⊝ VERY LOW <sup>1,5</sup>	5/51 (9.8%)	9/49 (18.4%)	RR 1.87 (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	<b>85 more per 1000</b> (from 31 fewer to 412 more)
ncrease	d thirst	(Aripiprazo	e or risperi	i <b>done)</b> (asses	ssed with: Non-s	vstematic assessment,	study-sp	ecific report or stud	ly-specific s	de effe	ct checklist)
412 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,5</sup>	6/137 (4.4%)	13/275 (4.7%)	RR 1.46 (0.57 to	Study	population
6-8 weeks		inconsistency	manosinos			due to risk of bias, imprecision	(4.470)	(4.170)	3.74)	44 per 1000	20 more per 1000 (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>e)</b> (assessed w	rith: Study-speci	fic report of adve	erse 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%)	5/165 (3%)	RR 1.55 (0.18 to	Study	population
8 weeks		inconsistency	munectness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2 /6)	(376)	12.93)	20 per 1000	11 more per 1000 (from 16 fewer to 234 more)
										Mode	rate
										20 per 1000	11 more per 1000 (from 16 fewer to 239 more)
Increase	d thirst	(Risperidon	(assessed w	rith: Non-system	natic assessment	or study-specific side	effect che	ecklist)			
196 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>5</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,5</sup>	5/86 (5.8%)	8/110 (7.3%)	RR 1.44 (0.51 to	Study	population
6-8 weeks		inconsistency	indirectiness			due to risk of bias,	(0.070)	(1.070)	4.09)	58	26 more per 1000

						imprecision				per 1000	(from 28 fewer to 180 more)
										Moder	rate
										49 per 1000	22 more per 1000 (from 24 fewer to 151 more)
Tachyca	rdia (Ri	speridone) (a	assessed with: S	tudy-specific ou	itcome measure	or study-specific side	effect che	cklist)	•	ı	,
179 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1,4</sup>	1/90 (1.1%)	11/89 (12.4%)	RR 7.77 (1.45 to	Study	population
8 weeks						due to risk of bias, imprecision	(,6)	(-1.73)	41.72)	11 per 1000	<b>75 more per 1000</b> (from 5 more to 452 more)
										Moder	rate
										10 per 1000	<b>68 more per 1000</b> (from 5 more to 407 more)
Anorexia	(Rispe	eridone) (asses	ssed with: Study	-specific outcom	ne measure)			•		ļ	1
79 (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>	1/39 (2.6%)	4/40 (10%)	RR 3.9 (0.46 to	Study	population
8 weeks		iniconsistency	manosmoss		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2.070)	(10%)	33.36)	26 per 1000	<b>74 more per 1000</b> (from 14 fewer to 830 more)
										Moder	rate
										26 per 1000	<b>75 more per 1000</b> (from 14 fewer to 841 more)
Anxiety (	Risper	idone) (assess	ed with: Study-sp	pecific side effe	ct checklist)	1				1	'
100	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	undetected	⊕⊖⊝⊖	10/51	12/49	RR 1.25	Study	population

(1 study) 8 weeks		inconsistency	inconsistency 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	speridone) (as	ssessed with: No	n-systematic as	ssessment)						
96 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊖⊝ VERY LOW <sup>1,3,5</sup>	0/35 (0%)	2/61 (3.3%)	RR 2.9 (0.14 to	Study	population
6 weeks		indentification by			suspected <sup>3</sup>	due to risk of bias, imprecision,	(070)		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)						
79 (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>	0/39 (0%)	5/40 (12.5%)	<b>RR 10.73</b> (0.61 to	Study	population
8 weeks		inconsistency			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0 70)	(12.070)	187.79)	0 per 1000	N/A
						publication side				Mode	rate
										0 per 1000	N/A
Aggressi	ion (Ari	piprazole or	risperidon	<b>e)</b> (assessed w	vith: Non-system	atic assessment or stud	dy-specific	report)			1
193 (2 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>	6/85 (7.1%)	1/108 (0.9%)	RR 0.2 (0.04 to	Study	population
6-8 weeks		inconsistency	manconios		suspected <sup>3</sup>	due to risk of bias, imprecision,	(1.170)	(0.070)	1.11)	71 per	56 fewer per 1000 (from 68 fewer to 8 more)

						publication bias				1000	
										Mode	rate
										69 per 1000	55 fewer per 1000 (from 66 fewer to 8 more)
Aggress	ion (Ari	piprazole) (a	ssessed with: St	udy-specific rep	ort of adverse e	/ent)					
97 (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>	4/50 (8%)	1/47 (2.1%)	RR 0.27 (0.03 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(373)	(=::/0)	2.29)	80 per 1000	<b>58 fewer per 1000</b> (from 78 fewer to 103 more)
										Mode	rate
										80 per 1000	58 fewer per 1000 (from 78 fewer to 103 more)
Aggress	ion (Ris	s <b>peridone)</b> (a	ssessed with: No	on-systematic a	ssessment)						
96 (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>	2/35 (5.7%)	0/61 (0%)	RR 0.12 (0.01 to	Study	population
6 weeks		inconsistency	indirectiness		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(3.770)	(078)	2.35)	57 per 1000	<b>50 fewer per 1000</b> (from 57 fewer to 77 more)
										Mode	rate
										57 per 1000	50 fewer per 1000 (from 56 fewer to 77 more)
Agitation	n (Rispe	eridone) (asse	ssed with: Non-s	ystematic asse	ssment)				l .		1
96 (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>	2/35 (5.7%)	1/61 (1.6%)	RR 0.29 (0.03 to	Study	population
6 weeks					suspected 3	due to risk of bias,	(3.77)	(/0/	3.05)	57	41 fewer per 1000

						imprecision, publication bias				per 1000	(from 55 fewer to 117 more)
										Mode	rate
										57 per 1000	40 fewer per 1000 (from 55 fewer to 117 more)
Restless	ness ( <i>F</i>	Aripiprazole (	or risperido	ne) (assesse	d with: Non-syste	ematic assessment, stu	ıdy-speci	fic report or study-sp	ecific side	effect c	hecklist)
509 (4 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>	8/187 (4.3%)	8/322 (2.5%)	RR 0.63 (0.25 to	Study	population
6-8 weeks			man est nece		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(1.070)	(2.076)	1.57)	43 per 1000	16 fewer per 1000 (from 32 fewer to 24 more)
										Mode	rate
										44 per 1000	<b>16 fewer per 1000</b> (from 33 fewer to 25 more)
Restless	ness ( <i>F</i>	⊥ Aripiprazole)	(assessed with:	Study-specific	l report of adverse	e event)		•			1
313 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>5</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,5</sup>	4/101 (4%)	3/212 (1.4%)	RR 0.32 (0.08 to	Study	population
8 weeks		inconsistency	muncon ics		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(470)	(1.470)	1.32)	40 per 1000	27 fewer per 1000 (from 36 fewer to 13 more)
										Mode	rate
										39 per 1000	27 fewer per 1000 (from 36 fewer to 12 more)
Restless	ness (F	Risperidone)	(assessed with:	Non-systematic	c assessment or	study-specific side effe	ect checkl	list)			1
196	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	undetected	⊕⊖⊝⊝	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	3 more per 1000 (from 33 fewer to 136 more)
										Mode	rate
										44 per 1000	3 more per 1000 (from 31 fewer to 129 more)
Psychon	notor h	yperactivity	(Aripiprazo	le or rispe	ridone) (asse	ssed with: Non-system	natic asses	ssment or study-s	pecific report	)	
193 (2 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>	4/85 (4.7%)	3/108 (2.8%)	RR 0.56 (0.13 to	Study	population
6-8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	( /3)	(=1070)	2.47)	47 per 1000	21 fewer per 1000 (from 41 fewer to 69 more)
										Mode	rate
										49 per 1000	22 fewer per 1000 (from 43 fewer to 72 more)
Psychon	notor h	yperactivity	⊥ (Aripiprazo	le) (assessed	L with: Study-spec	ific report of adverse e	event)				
97 (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>	2/50 (4%)	1/47 (2.1%)	RR 0.53 (0.05 to	Study	population
( i Stady)		inioonidiaterioy	mancomoss				(470)	(2.170)			
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			5.67)	40 per 1000	19 fewer per 1000 (from 38 fewer to 187 more)
					suspected	imprecision,			5.67)	per	(from 38 fewer to 187 more)
					suspected *	imprecision,			5.67)	per 1000	(from 38 fewer to 187 more)
8 weeks	notor h	yperactivity	(Risperidor	<b>1e)</b> (assessed		imprecision,			5.67)	per 1000 Moder 40 per	(from 38 fewer to 187 more)  rate  19 fewer per 1000 (from 38 fewer to 187

(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	<b>25 fewer per 1000</b> (from 53 fewer to 166 more)
						publication side				Moder	rate
										57 per 1000	<b>25 fewer per 1000</b> (from 52 fewer to 165 more)
Tremor (	Aripipra	azole or risp	<b>eridone)</b> (as	sessed with: St	udy-specific outo	ome measure, study-s	pecific rep	oort or study-specifi	c side effec	t checkl	list)
492 (4 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly	⊕⊖⊝ VERY LOW <sup>1,3,4</sup>	1/191 (0.5%)	32/301 (10.6%)	RR 8.99 (2.4 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision,		, ,	33.64)	5 per 1000	<b>42 more per 1000</b> (from 7 more to 171 more)
						publication bias				Moder	rate
										0 per 1000	N/A
Tremor (	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	⊕⊖⊝⊝ VERY LOW <sup>1,3,4</sup>	0/101 (0%)	21/212 (9.9%)	RR 10.42 (1.33 to	Study	population
8 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(272)	(0.073)	81.48)	0 per 1000	N/A
						publication bias				Moder	rate
										0 per 1000	N/A
Tremor (	Risperi	done) (assesse	d with: Study-sp	ecific outcome	measure or stud	y-specific side effect ch	necklist)				1
179 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>5</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>1,5</sup>	1/90 (1.1%)	11/89 (12.4%)	RR 7.79 (1.46 to	Study	population
8 weeks		inconsistency	muneotness			due to risk of bias, imprecision	(1.170)	(12.470)	41.7)	11 per	<b>75 more per 1000</b> (from 5 more to 452 more)

										1000	
										Mode	rate
										10 per 1000	68 more per 1000 (from 5 more to 407 more)
Dyskines	sia/Hyp	erkinesia (A	ripiprazole	or risperid	one) (assesse	d with: Study-specific re	eport or s	study-specific side	effect check	ist)	
197 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊝ VERY LOW <sup>1,5</sup>	4/101 (4%)	6/96 (6.3%)	RR 1.51 (0.47 to	Study	population
8 weeks		inconsistency				due to risk of bias, imprecision	(470)	(0.070)	4.82)	40 per 1000	20 more per 1000 (from 21 fewer to 151 more)
				Mode	rate						
										39 per 1000	<b>20 more per 1000</b> (from 21 fewer to 149 more)
Dyskines	sia/Hyp	erkinesia (A	ripiprazole)	(assessed with	: Study-specific	report of adverse even	t)				
97 (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>	1/50 (2%)	0/47 (0%)	<b>RR 0.35</b> (0.01 to	Study	population
8 weeks		inconsistency	indirectriess		suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2 /6)	(076)	8.48)	20 per 1000	13 fewer per 1000 (from 20 fewer to 150 more)
										Mode	rate
										20 per 1000	13 fewer per 1000 (from 20 fewer to 150 more)
Dyskines	sia/Hyp	erkinesia (R	isperidone)	(assessed with	: Study-specific	side effect checklist)					
100 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,5</sup>	3/51 (5.9%)	6/49 (12.2%)	RR 2.08 (0.55 to	Study	population
8 weeks		in iconsistency	man collicss			due to risk of bias,	(3.370)	(12.2/0)	7.87)	59	64 more per 1000

						imprecision				per 1000	(from 26 fewer to 404 more)
										Mode	rate
										59 per 1000	<b>64 more per 1000</b> (from 27 fewer to 405 more)
Hypokin	esia (Aı	ripiprazole) (	assessed with: S	Study-specific re	port of adverse	event)				1	
97 (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>	0/50 (0%)	1/47 (2.1%)	RR 3.19 (0.13 to	Study	population
8 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2,2)	(=:://)	76.36)	0 per 1000	N/A
										Mode	rate
										0 per 1000	N/A
Muscle r	igidity (	⊥ (Aripiprazole	or risperio	d <b>one)</b> (assess	L sed with: Study-s	Lecific report or study-	specific s	side effect checkli	ist)		
197 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,5</sup>	1/101 (1%)	6/96 (6.3%)	RR 4.54 (0.79 to	Study	population
8 weeks		inconsistency	indirectriess			due to risk of bias, imprecision	(176)	(0.576)	26.12)	10 per 1000	35 more per 1000 (from 2 fewer to 249 more)
										Mode	rate
										10 per 1000	35 more per 1000 (from 2 fewer to 251 more)
Muscle r	igidity (	Aripiprazole	(assessed wit	h: Study-specifi	c report of adver	se event)			L		1
97	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>	0/50 (0%)	1/47 (2.1%)	RR 3.19 (0.13 to	Study	population
(1 study)											

						imprecision, publication bias				1000	
						publication bias				Moder	rate
										0 per 1000	N/A
Muscle r	igidity (	(Risperidone	(assessed wit	h: Study-specifi	c side effect che	cklist)				1	
100 (1 study)	serious <sup>1</sup>		no serious	very serious <sup>5</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,5</sup>	1/51 (2%)	5/49 (10.2%)	RR 5.2 (0.63 to	Study	population
8 weeks		inconsistency	indirectness			due to risk of bias, imprecision	(2%)	(10.2%)	42.96)	20 per 1000	<b>82 more per 1000</b> (from 7 fewer to 823 more)
										Moder	rate
										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)					
97 (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>	1/50 (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	(= 7 - 7)	(5.17)	8.48)	20 per 1000	13 fewer per 1000 (from 20 fewer to 150 more)
										Moder	rate
										20 per 1000	<b>13 fewer per 1000</b> (from 20 fewer to 150 more)
Enuresis	(Aripip	razole or ris	speridone) (	assessed with:	Non-systematic	assessment, study-spe	cific repo	rt or study-specific s	side effect of	checklist	t)
509 (4 studies)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>5</sup>	undetected	⊕⊖⊝ VERY LOW <sup>1,5</sup>	20/187 (10.7%)	26/322 (8.1%)	RR 1.14 (0.67 to	Study	population
6-8 weeks						due to risk of bias, imprecision	(121170)	(==)	1.93)	107 per	15 more per 1000

										1000	(from 35 fewer to 99 more)
										Mode	rate
										50 per 1000	7 more per 1000 (from 16 fewer to 46 more)
Enuresis	(Aripip	razole) (asses	sed with: Study-	-specific report	of adverse event	)			<u> </u>		1
313 2 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>	5/101 (5%)	7/212 (3.3%)	RR 0.92 (0.28 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		(4.0.0)	3.05)	50 per 1000	4 fewer per 1000 (from 36 fewer to 101 more)
										Mode	rate
										50 per 1000	4 fewer per 1000 (from 36 fewer to 102 more)
Enuresis	(Rispe	ridone) (asses	sed with: Non-s	ystematic asses	ssment or study-	specific side effect ched	cklist)				1
196 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>5</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,5</sup>	15/86	19/110 (17.3%)	RR 1.21 (0.68 to	Study	population
6-8 weeks		inconsistency	indirectiless			due to risk of bias, imprecision	(17.470)	(17.370)	2.18)	174 per 1000	<b>37 more per 1000</b> (from 56 fewer to 206 more)
										Mode	rate
										147 per 1000	31 more per 1000 (from 47 fewer to 173 more)
Skin irrita	ation/R	ash (Aripipr	azole or ris	peridone) (	assessed with: N	lon-systematic assessr	ment, stud	dy-specific report or	study-spec	cific side	e effect checklist)
412 (3 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,5</sup>	8/137 (5.8%)	17/275 (6.2%)	<b>RR 1.66</b> (0.76 to	Study	population
(3 studies) 6-8 weeks		inconsistency	muneciness			due to risk of bias,	(3.0%)	(0.270)	3.6)	58	39 more per 1000

						imprecision				per 1000	(from 14 fewer to 152 more)
										Moder	ate
										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	f adverse event)	•			ı	
216 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>1,3,5</sup>	1/51 (2%)	4/165 (2.4%)	RR 1.24 (0.14 to	Study	population
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(= 79)	(=1.73)	10.81)	20 per 1000	5 more per 1000 (from 17 fewer to 192 more)
										Moder	ate
										20 per 1000	<b>5 more per 1000</b> (from 17 fewer to 196 more)
Skin irrit	ation/R	ash (Risperi	done) (assess	sed with: Non-s	ystematic assess	ment or study-specific	side effe	ct checklist)	ļ.	!	
196 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,5</sup>	7/86 (8.1%)	13/110 (11.8%)	RR 1.74 (0.76 to	Study	population
6-8 weeks		inconcional income	indirectined			due to risk of bias, imprecision	(0.170)	(11.07.0)	4.01)	81 per 1000	<b>60 more per 1000</b> (from 20 fewer to 245 more)
										Moder	ate
										69 per 1000	<b>51 more per 1000</b> (from 17 fewer to 208 more)
Earache/	Ear info	ection (Risp	<b>eridone)</b> (ass	sessed with: No	n-systematic ass	essment or study-spec	cific side e	effect checklist)	l.	1	1
196	serious <sup>1</sup>	no serious	no serious	very serious <sup>5</sup>	undetected	⊕⊖⊝⊖	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: St	udy-specific side	e effect checklist	:)				1	
100 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>5</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,5</sup>	1/51 (2%)	5/49 (10.2%)	RR 5.2 (0.63 to	Study	population
8 weeks						due to risk of bias, imprecision	(=73)	(	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)

<sup>&</sup>lt;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

## Adverse events associated with low dose antipsychotics versus placebo

Quality assessment	Summary of Findings

<sup>&</sup>lt;sup>2</sup> I-squared value indicates moderate heterogeneity

Trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies

<sup>&</sup>lt;sup>5</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>6</sup> 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)</p>

<sup>8</sup> I-squared value indicates substantial heterogeneity

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 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% CI)
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	⊕⊝⊝ VERY LOW <sup>1,2,3,4</sup>	58/86 (67.4%)	58/82 (70.7%)	RR 1.03 (0.84 to	Study po	pulation
6-8 weeks				56.1645	suspected <sup>4</sup>	due to risk of bias, inconsistency, imprecision, publication bias	(6,11,76)	((3.1.74)	1.26)	674 per 1000	20 more per 1000 (from 108 fewer to 175 more)
						publication side				Moderate	
										663 per 1000	20 more per 1000 (from 106 fewer to 172 more)
Any side	effect	(Aripiprazo	ole 5mg/da	ay) (assesse	d with: study-sp	ecific report of advers	se event)	,	ı		1
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>5</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,4,5</sup>	37/51 (72.5%)	46/52 (88.5%)	RR 1.22 (1 to	Study po	pulation
8 weeks		,			suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias		(5.5.5.7)	1.48)	725 per 1000	160 more per 1000 (from 0 more to 348 more)
										Moderate	
										726 per 1000	160 more per 1000 (from 0 more to 348 more)
Any side	effect	(Risperido	ne 0.125-0	).175mg/d	day) (assesse	ed with: Non-systema	tic assess	sment)			
65	serious <sup>1</sup>	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)
						publication blac				Moderate	
										600 per 1000	198 fewer per 1000 (from 360 fewer to 72 more)
Discon	tinuatio	n due to se	edation (A	ripiprazo	le 5mg/day	(assessed with: St	udy-spe	cific report of adv	verse event)	1	
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊖⊝ VERY LOW <sup>1,3,4</sup>	0/51 (0%)	1/52 (1.9%)	<b>RR 2.94</b> (0.12 to	Study po	pulation
8 weeks					suspected 4	due to risk of bias, imprecision, publication bias			70.61)	0 per 1000	-
						publication bias				Moderate	)
										0 per 1000	-
Discon	tinuatio	n due to dr	ooling (Ar	ripiprazo	le 5mg/day	(assessed with: Sto	udy-spe	cific report of adv	rerse event)	1	\
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊖⊝ VERY LOW <sup>1,3,4</sup>	0/51 (0%)	1/52 (1.9%)	RR 2.94 (0.12 to	Study po	pulation
8 weeks					suspected 4	due to risk of bias, imprecision,		,	70.61)	0 per 1000	-
						publication bias				Moderate	
										moderate	•
										0 per 1000	-
Discon	tinuatio	n due to tre	emor (Arip	iprazole	5mg/day)	assessed with: Study	/-specific	c report of advers	se event)	0 per	-

(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,	(0%)	(3.8%)	(0.24 to 99.74)	0 per 1000	-
						publication bias				Moderate	
										0 per 1000	-
Any tre	atment-	emergent e	extrapyran	nidal sym	nptoms (A	ripiprazole 5n	ng/day	(assessed with: §	Study-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	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	6/51 (11.8%)	12/52 (23.1%)	RR 1.96 (0.8 to	Study po	pulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias			4.83)	118 per 1000	113 more per 1000 (from 24 fewer to 451 more)
										Moderate	1
										118 per 1000	113 more per 1000 (from 24 fewer to 452 more)
Extrapy	ramida	symptom	s (Risperio	done 0.12	25-0.175mg	g/day) (measured	with: Non	-systematic assessr	ment; Better	indicated b	by 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 LOW¹,4,6 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> lower (0.87 lower to 0.13 higher)
		l disorder (	Aripiprazo	ole 5mg/d	lay) (assessed	I with: Study-specific	report of a	adverse event)			<u>I</u>
Extrapy	/ramida	(									
Extrapy  103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊖⊝⊝ VERY LOW <sup>1,3,4</sup>	0/51 (0%)	2/52 (3.8%)	RR 4.91 (0.24 to	Study po	pulation

8 weeks					suspected 4	imprecision, publication bias			99.74)	1000	
										Moderate	
										0 per 1000	-
Tremor	(Aripip	razole 5mg	/day) (assess	sed with: Study	y-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	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	0/51 (0%)	4/52 (7.7%)	RR 8.83 (0.49 to	Study po	pulation
3 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias			159.93)	0 per 1000	-
						publication blue				Moderate	9
										0 per 1000	-
Clinical	ly relev	ant (>=7%)	weight ga	in (Aripi)	prazole 5m	ng/day) (assessed	d with: W	eight assessmen	t)		
103	ly relev	no serious	no serious	serious <sup>5</sup>	reporting bias	<b>0</b> 000	4/51	17/52	RR 4.17	Study po	pulation
103 (1 study)	_									Study po	pulation  249 more per 1000 (from 40 more to 827 more)
103 (1 study)	_	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	249 more per 1000 (from 40 more to 827 more)
Clinical  103 (1 study) 8 weeks	_	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	249 more per 1000 (from 40 more to 827 more)
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,	4/51 (7.8%)	17/52 (32.7%)	RR 4.17 (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) 8 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%)	RR 4.17 (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 4	imprecision, publication bias			9.51)	1000	(from 12 fewer to 297 more)
										Moderat	е
										38 per 1000	<b>58 more per 1000</b> (from 13 fewer to 323 more)
Veight	gain (A	ripiprazole	5mg/day)	(assessed with	th: Study-specific	c report of adverse ev	vent)				
03 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	1/51 (2%)	4/52 (7.7%)	RR 3.92 (0.45 to	Study po	opulation
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)
Veight	gain (R	isperidone	0.125-0.17	75mg/day	(assessed wit	th: Non-systematic as	sessmer	nt)			
5 I study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	2/35 (5.7%)	3/30 (10%)	RR 1.75 (0.31 to	Study po	opulation
weeks		inconsistency		School	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(0.770)	(1070)	9.79)	57 per 1000	43 more per 1000 (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 LOW¹,4,7 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 higher</b> (0.13 to 0.76 higher)
Weight	gain (in	kg) - Aripi	iprazole (5	mg/day)	(measured with:	Weight assessment;	Better i	ndicated by low	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 LOW¹,4,7  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 higher</b> (0.07 to 0.85 higher)
Weight	gain (in	kg) - Risp	eridone (0	0.125-0.1	75mg/day)	(measured with: Weig	ght asse	essment; Better	indicated by lower va	lues)
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 LOW¹,4,6  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 higher</b> (0.11 lower to 0.96 higher
BMI cha	ange (k	⊥ g/m-square	ed) - Aripip	orazole (	5mg/day) (m	easured with: Weigh	t assess	sment; Better in	dicated by lower valu	es)
103 (1 study)	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>	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	razole or	risperido	one) (assessed	with: Non-systemation	c assessr	ment or study-sp	ecific report of a	idverse ev	ent)
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>5</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,4,5</sup>	4/86 (4.7%)	15/82 (18.3%)	RR 3.95 (1.36 to	Study po	opulation
6-8 weeks		inconsistency	munectness		suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(4.770)	(10.576)	11.51)	47 per 1000	<b>137 more per 1000</b> (from 17 more to 489 more)
										Moderat	e
										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	serious <sup>5</sup>	reporting bias strongly	#⊕⊖⊖ VERY LOW <sup>1,4,5</sup>	2/51 (3.9%)	10/52 (19.2%)	<b>RR 4.9</b> (1.13 to	Study po	ppulation
8 weeks		·			suspected 4	due to risk of bias, imprecision, publication bias			21.29)	39 per 1000	<b>153 more per 1000</b> (from 5 more to 796 more)
						publication bias				Moderat	e
										39 per 1000	<b>152 more per 1000</b> (from 5 more to 791 more)
Increase	ed appe	etite (Rispe	ridone 0.1	25-0.175	mg/day) (as	sessed with: Non-sys	stematic a	assessment)	· · · · · ·		
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	2/35 (5.7%)	5/30 (16.7%)	RR 2.92 (0.61 to	Study po	ppulation
6 weeks		,			suspected <sup>4</sup>	due to risk of bias, imprecision,	(311 /3)	( 3.1.7.5)	13.96)	57 per 1000	110 more per 1000 (from 22 fewer to 741 more)

						publication bias				Moderate	
										57 per 1000	<b>109 more per 1000</b> (from 22 fewer to 739 more)
Decreas	sed app	etite (Aripi	prazole 5n	ng/day) (a	assessed with: S	tudy-specific report o	f advers	e event)	1	1	
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	1/51 (2%)	5/52 (9.6%)	RR 4.9 (0.59 to	Study po	oulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(270)	(0.070)	40.53)	20 per 1000	<b>76 more per 1000</b> (from 8 fewer to 775 more)
										Moderate	
										20 per 1000	<b>78 more per 1000</b> (from 8 fewer to 791 more)
Fasting lower values		se (mg/dL)	(Change S	core) - R	disperidon	e (0.125-0.175	mg/d	lay) (measured	with: Laborator	y assessme	nt; Better indicated by
45 (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	22	23	-		The mean fasting glucose (mg/dl) (change score) - risperidone (0.125-0.175mg/day) in the intervention groups was 0.03 standard deviations higher (0.55 lower to 0.62 higher
Fasting	glucos	e (=>115 m	ig/dL) - Ari	ipiprazol	e (5mg/day	(assessed with: La	aborator	y assessment)			
103 (1 study)						See comment	0/51 (0%)	0/52 (0%)	not pooled	See comment	See comment

103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	2/51 (3.9%)	6/52 (11.5%)	RR 2.94 (0.62 to	Study po	opulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias		,	13.9)	39 per 1000	<b>76 more per 1000</b> (from 15 fewer to 506 more)
										Moderat	е
										39 per 1000	<b>76 more per 1000</b> (from 15 fewer to 503 more)
	serious <sup>1</sup>	no serious	no serious	very	reporting bias	⊕⊖⊝⊖	22	21	-		The mean insulin
(1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>6</sup>	strongly	VERY LOW <sup>1,4,6</sup>	22	21	-		resistance (homa-ir)
(1 study)	serious <sup>1</sup>			,			22	21	-		resistance (homa-ir) (change score) - risperidone (0.125- 0.175mg/day) in the intervention groups was
1 study)	serious <sup>1</sup>			,	strongly	VERY LOW <sup>1,4,6</sup> due to risk of bias, imprecision,	22	21	-		resistance (homa-ir) (change score) - risperidone (0.125-
1 study) 3 weeks		inconsistency	indirectness	serious <sup>6</sup>	strongly suspected <sup>4</sup>	VERY LOW <sup>1,4,6</sup> due to risk of bias, imprecision,			-		resistance (homa-ir) (change score) - risperidone (0.125- 0.175mg/day) in the intervention groups was 0.3 standard deviation lower
1 study) 6 weeks  Aggres		inconsistency isperidone no serious	0.125-0.17	serious <sup>6</sup> 75mg/day	strongly suspected <sup>4</sup> (assessed with reporting bias	VERY LOW¹,4,6 due to risk of bias, imprecision, publication bias	sessment	0/30	RR 0.23	Study po	resistance (homa-ir) (change score) - risperidone (0.125- 0.175mg/day) in the intervention groups was 0.3 standard deviation lower
43 (1 study) 6 weeks  Aggres  65 (1 study) 6 weeks	sion (R	inconsistency	0.125-0.17	serious <sup>6</sup> 75mg/day	strongly suspected <sup>4</sup>	very Low <sup>1,4,6</sup> due to risk of bias, imprecision, publication bias	sessment	t)	RR 0.23 (0.01 to 4.66)	Study po 57 per 1000	resistance (homa-ir) (change score) - risperidone (0.125- 0.175mg/day) in the intervention groups wa- 0.3 standard deviation lower (0.9 lower to 0.3 higher

										57 per 1000	44 fewer per 1000 (from 56 fewer to 209 more)
Agitatic	on (Risp	eridone 0.1	l25-0.175n	ng/day) (a	ssessed with: No	on-systematic assess	sment)			l	
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	2/35 (5.7%)	0/30 (0%)	RR 0.23 (0.01 to	Study por	pulation
6 weeks		inconsistency	maneotress	School	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(0.770)	(676)	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)
•	sion (Ri	speridone	0.125-0.17	5mg/day	) (assessed with	n: Non-systematic ass		)			
65 (1 study) 6 weeks	1					See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
Abdom	inal disc	comfort (Ri	speridone	0.125-0.	175mg/day	<b>y)</b> (assessed with: N	on-syster	matic assessment)			
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	3/35 (8.6%)	0/30 (0%)	<b>RR 0.17</b> (0.01 to	Study por	pulation
6 weeks		moonsistency	muncomoso	Senous	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(0.070)	(076)	3.09)	86 per 1000	71 fewer per 1000 (from 85 fewer to 179 more)
										Moderate	
										86 per 1000	71 fewer per 1000 (from 85 fewer to 180 more)

68 2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	1/86 (1.2%)	3/82 (3.7%)	RR 2.44 (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	17 more per 1000 (from 7 fewer to 174 more)	
										Moderat	e	
										10 per 1000	14 more per 1000 (from 6 fewer to 150 more)	
Abdom	inal pai	n (upper) -	Aripiprazo	ole (5mg	/day) (assesse	ed with: Study-specific	report o	of adverse event)				
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	, , , , , ,	(2%) (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	te	
										20 per 1000	<b>19 more per 1000</b> (from 16 fewer to 399 more)	
								votomotic cocce	sment )		l	
Abdom	inal pai	n (upper) -	Risperido	ne (0.12	5-0.175mg/	day) (assessed wit	ih: Non-s	ystematic assess	Silioni )			
65	inal pai	no serious	no serious	very	reporting bias	<b>0</b> 000	0/35	1/30	RR 3.48	Study po	opulation	
Abdom  65 (1 study) 6 weeks		,	-	1			Ī			Study po 0 per 1000	opulation -	

										0 per 1000	-
Constip	ation (F	Risperidon	e 0.125-0.′	l75mg/da	<b>ay)</b> (assessed w	vith: Non-systematic a	assessme	ent)			
65	serious <sup>1</sup>	no serious	no serious	very	reporting bias	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	1/35	0/30	RR 0.39	Study po	pulation
(1 study) 6 weeks		inconsistency	indirectness	serious <sup>3</sup>	strongly suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(2.9%)	(0%)	(0.02 to 9.16)	29 per 1000	17 fewer per 1000 (from 28 fewer to 233 more)
										Moderate	9
										29 per 1000	18 fewer per 1000 (from 28 fewer to 237 more)
Nausea	(Aripip	T	isperidone	(assessed	with: Non-system	natic assessment or s	tudy-spe	cific report of adv	verse event)		
		no serious	no serious	very	reporting bias	$\oplus \ominus \ominus \ominus$	2/86	2/82	RR 1.07	Study population	
. ,	0011040	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	2/86 (2.3%)	2/82 (2.4%)	(0.15 to		-
. ,	School								_	23 per 1000	2 more per 1000 (from 20 fewer to 149 more)
. ,	Schloud				strongly	VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,			(0.15 to	23 per	2 more per 1000 (from 20 fewer to 149 more)
(2 studies) 6-8 weeks	SCHOOL				strongly	VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,			(0.15 to	23 per 1000	2 more per 1000 (from 20 fewer to 149 more) 2 more per 1000
6-8 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,			(0.15 to	23 per 1000 Moderate	2 more per 1000 (from 20 fewer to 149 more)  2 more per 1000 (from 20 fewer to 153
6-8 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			(0.15 to	23 per 1000 Moderate	2 more per 1000 (from 20 fewer to 149 more)  2 more per 1000 (from 20 fewer to 153 more)

						publication bias					more)
										Moderat	е
										20 per 1000	0 fewer per 1000 (from 19 fewer to 285 more)
Nausea	(Rispe	ridone 0.12	5-0.175mg	g/day) (ass	essed with: Non	-systematic assessme	ent)		· ·	1	
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>3</sup>	reporting bias	⊕⊖⊝ VERY LOW <sup>1,3,4</sup>	1/35 (2.9%)	1/30 (3.3%)	RR 1.17 (0.08 to	Study po	ppulation
6 weeks		inconcision of		Semode	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(2.070)	(0.070)	17.86)	29 per 1000	5 more per 1000 (from 26 fewer to 482 more)
										Moderate	
										29 per 1000	5 more per 1000 (from 27 fewer to 489 more)
											,
Vomitin	g (Aripi	iprazole or	risperido	1 <b>e)</b> (assesse	d with: Non-syst	ematic assessment o	r study-s	pecific report of a	dverse event)		,
168	g (Aripi	no serious	no serious	very	reporting bias	<b>1</b>	6/86	7/82	RR 1.21	Study po	ppulation
		-	· -	•		1	1	•		Study po 70 per 1000	,
168 (2 studies)		no serious	no serious	very	reporting bias strongly	⊕⊝⊖⊝ VERY LOW¹,3,4 due to risk of bias, imprecision,	6/86	7/82	RR 1.21 (0.42 to	70 per	15 more per 1000 (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	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	4/51 (7.8%)	5/52 (9.6%)	RR 1.23 (0.35 to	Study po	pulation
8 weeks				Somous	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(1.070)	(0.070)	4.31)	78 per 1000	18 more per 1000 (from 51 fewer to 260 more)
										Moderate	)
										78 per 1000	<b>18 more per 1000</b> (from 51 fewer to 258 more)
Vomitin	g (Risp	eridone 0.1	25-0.175n	ng/day) (a	ssessed with: No	on-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	⊕⊖⊖⊝ VERY LOW <sup>1,3,4</sup>	2/35 (5.7%)	2/30 (6.7%)	RR 1.17 (0.17 to	Study po	pulation
6 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias			7.79)	57 per 1000	10 more per 1000 (from 47 fewer to 388 more)
										Moderate	•
										57 per 1000	10 more per 1000 (from 47 fewer to 387 more)
Gastroe	enteritis	viral (Arip	iprazole 5	mg/day) (	assessed with: S	Study-specific report of	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	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	0/51 (0%)	1/52 (1.9%)	RR 2.94 (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	-
						publication bias				Moderate	)
										0 per 1000	-

5 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	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	е
										29 per 1000	5 more per 1000 (from 27 fewer to 489 more)
-		1	<u>-</u>	1		natic assessment or s	1			011	
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	0/86 (0%)	3/82 (3.7%)	<b>RR 6.87</b> (0.36 to		opulation
6-8 weeks					suspected 4	due to risk of bias, imprecision, publication bias			129.7)	0 per 1000	-
						'				Moderat	е
										0 per 1000	-
Pyrexia	(Aripip	razole 5mg	g/day) (asses	ssed with: Stu	dy-specific report	t of adverse event)	l		<u> </u>	1	
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	0/51 (0%)	3/52 (5.8%)	RR 6.87 (0.36 to	Study pe	opulation
8 weeks					suspected 4	due to risk of bias, imprecision, publication bias			129.7)	0 per 1000	-
						publication blac				Moderat	_
										woderat	е

Pyrexia	(Rispe	ridone 0.12	25-0.175mg	g/day) (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
Droolin	g (Aripi	prazole 5m	ng/day) (ass	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	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	0/51 (0%)	2/52 (3.8%)	RR 4.91 (0.24 to	Study pop	oulation
8 weeks					suspected 4	due to risk of bias, imprecision,			99.74)	0 per 1000	-
						publication bias				Moderate	
										0 per 1000	-
Increas	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	very serious <sup>3</sup>	reporting bias strongly	⊕⊖⊖⊝ VERY LOW <sup>1,3,4</sup>	1/51 (2%)	1/52 (1.9%)	RR 0.98 (0.06 to	Study po	oulation
8 weeks		inconsistency		Compac	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(270)	(1.676)	15.26)	20 per 1000	0 fewer per 1000 (from 18 fewer to 280 more)
										Moderate	Į.
										20 per 1000	0 fewer per 1000 (from 19 fewer to 285 more)
Thirst (	Aripipra	azole or ris	peridone)	(assessed with	n: Non-systemati	c assessment or stud	dy-specif	ic report of adverse e	event)	1	1
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	1/86 (1.2%)	3/82 (3.7%)	RR 2.94 (0.32 to	Study pop	oulation
,/						due to risk of bias,	,,	` ,	(	12 per	23 more per 1000

6-8 weeks					suspected 4	imprecision, publication bias			27.36)	1000	(from 8 fewer to 307 more)
										Moderate	
										10 per 1000	19 more per 1000 (from 7 fewer to 264 more)
Thirst (A	Aripipra	zole 5mg/d	lay) (assessed	d with: Study-s	pecific 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	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	1/51 (2%)	3/52 (5.8%)	RR 2.94 (0.32 to	Study population	
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	,	, ,	27.36)	20 per 1000	38 more per 1000 (from 13 fewer to 517 more)
										Moderate	ı
										20 per 1000	39 more per 1000 (from 14 fewer to 527 more)
Thirst (F	Risperio	done 0.125-	0.175mg/d	day) (assess	ed 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	) (assessed w	vith: Non-system	l natic assessment or s	L tudy-spe	cific report of adverse	e event)		
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊖⊝⊝ VERY LOW <sup>1,3,4</sup>	0/86 (0%)	2/82 (2.4%)	RR 4.91 (0.24 to	Study pop	oulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias			99.74)	0 per 1000	-
						paz.ioaioii biao				Moderate	

										0 per 1000	-
Fatigue	(Aripip	razole 5mg	g/day) (asses	sed with: Stu	dy-specific report	of adverse event)					
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 LOW¹,3,4 due to risk of bias, imprecision, publication bias	0/51 (0%)	2/52 (3.8%)	RR 4.91 (0.24 to 99.74)	Study por 0 per 1000	oulation
						publication bias				Moderate	
										0 per 1000	-
ratigue	(L/12he	1140116 0.12	:5-0. 1 <i>1</i> 5111(	<b>y/uay)</b> (ass	sessed with: Non-	-systematic assessme	ent)				
(1 study)	no serious risk of bias					See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
(1 study) 6 weeks	serious risk of bias	prazole 5n	ng/day) (ass	essed with: S	Study-specific repo	See comment  ort of adverse event)					See comment
(1 study) 6 weeks  Letharg	serious risk of bias	no serious	ng/day) (ass	essed with: S	reporting bias	ort of adverse event)  ⊕⊖⊖⊝	0/51	4/52	pooled		
(1 study) 6 weeks  Letharg  103 (1 study)	serious risk of bias y (Aripi	•	no serious	very		⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision,	(0%)	(0%)	pooled	comment	
65 (1 study) 6 weeks Letharg 103 (1 study) 8 weeks	serious risk of bias y (Aripi	no serious	no serious	very	reporting bias strongly	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias,	0/51	4/52	RR 8.83 (0.49 to	Study pol	oulation -

168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	3/86 (3.5%)	4/82 (4.9%)	<b>RR 1.32</b> (0.33 to	Study po	opulation
6-8 weeks				Concuc	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(0.070)	(1.670)	5.26)	35 per 1000	<b>11 more per 1000</b> (from 23 fewer to 149 more)
										Moderat	е
										34 per 1000	<b>11 more per 1000</b> (from 23 fewer to 145 more)
Somnol	lence (A	Aripiprazole	5mg/day	(assessed v	vith: Study-specif	ic report of adverse e	vent)				
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	2/51 (3.9%)	4/52 (7.7%)	RR 1.96 (0.38 to	Study po	opulation
8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(5 2 2 3 )	( ''')	10.24)	39 per 1000	38 more per 1000 (from 24 fewer to 362 more)
										Moderat	е
										39 per 1000	<b>37 more per 1000</b> (from 24 fewer to 360 more)
Somnol	lence (R	Risperidon	e 0.125-0.1	75mg/da	ay) (assessed w	I ith: Non-systematic a	ssessme	ent)			
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	1/35 (2.9%)	0/30 (0%)	<b>RR 0.39</b> (0.02 to	Study po	opulation
6 weeks		inconsistency	indirectrics:	School	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(2.576)	(070)	9.16)	29 per 1000	17 fewer per 1000 (from 28 fewer to 233 more)
										Moderat	е
										29 per 1000	<b>18 fewer per 1000</b> (from 28 fewer to 237

											more)
Sedatio	n (Aripi	prazole or	risperido	ne) (assesse	d with: Non-syste	ematic assessment o	r study-sp	pecific report of	adverse)		
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	3/86 (3.5%)	10/82 (12.2%)	<b>RR 3.01</b> (0.94 to	Study po	ppulation
6-8 weeks				66.1345	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(0.070)	(12.278)	9.62)	35 per 1000	70 more per 1000 (from 2 fewer to 301 more)
										Moderate	e
										29 per 1000	58 more per 1000 (from 2 fewer to 250 more)
Sedatio  103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias	ort of adverse event)  ⊕⊖⊖⊝ VERY LOW¹,3,4	3/51 (5.9%)	9/52 (17.3%)	RR 2.94 (0.84 to	Study po	ppulation
8 weeks		inconsistency	indirectriess	Serious	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(3.976)	(17.5%)	10.25)	59 per 1000	<b>114 more per 1000</b> (from 9 fewer to 544 more)
										Moderate	е
										59 per 1000	114 more per 1000 (from 9 fewer to 546 more)
Sedatio	n (Risp	eridone 0.1	25-0.175n	ng/day) (a	ssessed with: No	on-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	⊕⊖⊖⊝ VERY LOW <sup>1,3,4</sup>	0/35 (0%)	1/30 (3.3%)	RR 3.48 (0.15 to	Study po	ppulation
6 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision,	(-,-,	(= -2,-2)	82.48)	0 per 1000	-

						publication bias				Moderate	
										0 per 1000	-
leadac	he (Arip	oiprazole 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>	⊕⊖⊖⊖ VERY LOW <sup>1,3,4</sup> due to risk of bias, imprecision, publication bias	6/86 (7%)	5/82 (6.1%)	RR 0.9 (0.28 to 2.86)	Study population	
										70 per 1000	7 fewer per 1000 (from 50 fewer to 130 more)
										Moderate	
										77 per 1000	8 fewer per 1000 (from 55 fewer to 143 more)
											,
		piprazole 5	mg/day) (as	T		port of adverse event		3/52	RR 1.47	Study po	pulation
03 1 study)	he (Arip	-	· · · · · · · · · · · · · · · · · · ·	very serious <sup>3</sup>	Study-specific re reporting bias strongly suspected 4	port of adverse event  \[ \begin{align*} \top\colon \colon \\ \text{VERY LOW}^{1,3,4} \\ \text{due to risk of bias,} \\ \text{imprecision,} \\ \text{publication bias} \end{align*}	2/51 (3.9%)	3/52 (5.8%)	RR 1.47 (0.26 to 8.44)	Study po 39 per 1000	pulation  18 more per 1000 (from 29 fewer to 292 more)
03 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	18 more per 1000 (from 29 fewer to 292 more)
Headac 103 (1 study) 3 weeks		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)
03 1 study) 3 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 Moderate	18 more per 1000 (from 29 fewer to 292 more)  18 more per 1000 (from 29 fewer to 290
103 1 study) 3 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%)		(0.26 to	39 per 1000 Moderate	18 more per 1000 (from 29 fewer to 292 more)  18 more per 1000 (from 29 fewer to 290 more)

6 weeks					suspected <sup>4</sup>	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	Risperidone	0.125-0.1	75mg/da	<b>y)</b> (assessed w	rith: Non-systematic a	ssessme	ent)			
65 (1 study) 6 weeks						See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
Upper re	espirate	ory tract inf	fection (A	ripiprazol	le or rispe	ridone) (assesse	d with: No	on-systematic asses	sment or stu	ıdy-specific	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	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	1/86 (1.2%)	3/82 (3.7%)	RR 2.49 (0.36 to	Study por	oulation
6-8 weeks		inconsistency	indirectriess	School	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(1.270)	(6.1.70)	17.01)	12 per 1000	17 more per 1000 (from 7 fewer to 186 more)
										Moderate	
										14 per 1000	21 more per 1000 (from 9 fewer to 224 more)
		1	l.			\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \					
Upper re	espirat	ory tract inf	fection (Ar	ripiprazol	le 5mg/day	(assessed with: St	udy-spec	cific report of adverse	e event)		
103	espirate	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias	<b>0</b> 000	0/51	2/52	RR 4.91	Study por	oulation
	•	no serious	no serious	very			· · ·			Study pop 0 per 1000	oulation -

										0 per 1000	-
Upper r	espirate	ory tract in	fection (R	isperido	ne 0.125-0.	<b>175mg/day)</b> (a	ssessed	with: Non-system	atic assessme	nt)	
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	1/35 (2.9%)	1/30 (3.3%)	RR 1.17 (0.08 to	Study po	pulation
6 weeks		inconsistency	munectness	Serious	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(2.976)	(3.376)	17.86)	29 per 1000	5 more per 1000 (from 26 fewer to 482 more)
										Moderate	•
										29 per 1000	5 more per 1000 (from 27 fewer to 489 more)
Cough	(Aripira	zole or risp	peridone)	assessed with	n: Non-systemation	assessment or stud	y-specific	report of adverse	e event)		
168 (2 studies)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊖⊝ VERY LOW <sup>1,3,4</sup>	2/86 (2.3%)	8/82 (9.8%)	RR 3.92 (0.87 to	Study po	pulation
6-8 weeks		moonsistemey	man connects	Schous	suspected <sup>4</sup>	due to risk of bias, imprecision,	(2.070)	(5.575)	17.59)	23 per 1000	68 more per 1000
						publication bias					(from 3 fewer to 386 more)
						publication bias				Moderate	(from 3 fewer to 386 more)
						publication bias					(from 3 fewer to 386 more)
Cough (	(Aripipr	azole 5mg	<b>/day)</b> (assess	ed with: Study	y-specific report c					Moderate 20 per	(from 3 fewer to 386 more)  58 more per 1000 (from 3 fewer to 332
Cough (	(Aripipr	no serious inconsistency	/day) (assess	ed with: Study	y-specific report of reporting bias strongly		2/51 (3.9%)	8/52 (15.4%)	RR 3.92 (0.87 to	Moderate 20 per	(from 3 fewer to 386 more)  58 more per 1000 (from 3 fewer to 332 more)

						publication bias					more)
										Moderate	1
										39 per 1000	114 more per 1000 (from 5 fewer to 647 more)
ough	(Risper	idone 0.125	5-0.175mg	/day) (asse	essed with: Non-s	systematic assessme	nt)			1	
55 1 study) 5 weeks						See comment	0/35 (0%)	0/30 (0%)	not pooled	See	See comment
				(assessed with		report of adverse eve				l .	
03 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊖⊝⊝ VERY LOW <sup>1,3,4</sup>	1/51 (2%)	2/52 (3.8%)	RR 1.96 (0.18 to	Study population	
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)
										Moderate	)
										20 per 1000	19 more per 1000 (from 16 fewer to 399 more)
lasal c	ongesti	on (Aripipr	azole 5mg	g/day) (ass	essed with: Stud	ly-specific report of ac	dverse e	vent)	<u>'</u>		
03 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	1/51 (2%)	1/52 (1.9%)	RR 0.98 (0.06 to	Study po	pulation
weeks		inconsistency	munectiless	Sellous	suspected <sup>4</sup>	due to risk of bias, imprecision,	(2 /0)	(1.370)	15.26)	20 per 1000	0 fewer per 1000 (from 18 fewer to 280
weeks						publication bias					more)

										20 per 1000	<b>0 fewer per 1000</b> (from 19 fewer to 285 more)
Nasoph	aryngit	is (Aripipra	zole or ris	speridone	e) (assessed wit	h: Non-systematic as	ssessmer	nt or study-specific	c 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	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	4/86 (4.7%)	8/82 (9.8%)	RR 2.09 (0.65 to	Study po	opulation
6-8 weeks		inconsistency	munectiess	Serious	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(4.770)	(3.078)	6.79)	47 per 1000	51 more per 1000 (from 16 fewer to 269 more)
										Moderat	е
										48 per 1000	<b>52 more per 1000</b> (from 17 fewer to 278 more)
Nasoph  03 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	specific report of adv	2/51 (3.9%)	6/52 (11.5%)	RR 2.94 (0.62 to	Study po	ppulation
B weeks		inconsistency	munectiess	Serious	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(3.370)	(11.370)	13.9)	39 per 1000	76 more per 1000 (from 15 fewer to 506 more)
										Moderat	e
										39 per 1000	<b>76 more per 1000</b> (from 15 fewer to 503 more)
Nasoph	aryngit	is (Risperio	done 0.125	5-0.175mg	g/day) (asses	sed with: Non-syster	natic asse	essment)			
55 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊖⊝⊖ VERY LOW <sup>1,3,4</sup>	2/35 (5.7%)	2/30 (6.7%)	<b>RR 1.17</b> (0.17 to	Study po	opulation
6 weeks				3	suspected <sup>4</sup>	due to risk of bias, imprecision,	(3 73)	(==, /5)	7.79)	57 per	<b>10 more per 1000</b> (from 47 fewer to 388

						publication bias				1000	more)
										Moderate	
										57 per 1000	<b>10 more per 1000</b> (from 47 fewer to 387 more)
Nose blo	eed (Ar	ipiprazole d	or risperid	one) (asses	ssed with: Non-s	systematic assessme	nt or stud	y-specific report of a	dverse ever	nt)	<del>'</del>
168 (2 studies) 6-8 weeks						See comment	0/86 (0%)	0/82 (0%)	not pooled	See comment	See comment
Nose blo	eed (Ar	ipiprazole (	img/day) (a	assessed with	: Study-specific	report of adverse eve	ent)				
103 (1 study) 8 weeks						See comment	0/51 (0%)	0/52 (0%)	not pooled	See comment	See comment
Nose blo	eed (Ri	speridone (	).125-0.17	5mg/day)	(assessed with	l: Non-systematic ass	essment	)			
65 (1 study) 6 weeks						See comment	0/35 (0%)	0/30 (0%)	not pooled	See comment	See comment
Akathisi	ia (Arip	iprazole or	risperidor	1 <b>e)</b> (assesse	d with: Non-syst	ematic assessment c	or study-s	pecific 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	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	4/86 (4.7%)	1/82 (1.2%)	RR 0.35 (0.06 to	Study pop	pulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias		,	2.14)	47 per 1000	30 fewer per 1000 (from 44 fewer to 53 more)
										Moderate	

										44 per 1000	29 fewer per 1000 (from 41 fewer to 50 more)
Akathis	sia (Arip	iprazole 5r	ng/day) (ass	sessed with: S	tudy-specific rep	ort of adverse event)					
103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	3/51 (5.9%)	1/52 (1.9%)	RR 0.33 (0.04 to	Study po	pulation
8 weeks		inconsistency	mancomess	School	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(3.370)	(1.370)	3.04)	59 per 1000	39 fewer per 1000 (from 56 fewer to 120 more)
				Moderate	•						
										59 per 1000	40 fewer per 1000 (from 57 fewer to 120 more)
65	serious <sup>1</sup>	no serious	no serious	very	reporting bias	on-systematic assess	1/35	0/30	RR 0.39	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	(2.9%)	(0%)	(0.02 to 9.16)	29 per 1000	17 fewer per 1000 (from 28 fewer to 233 more)
										Moderate	9
										29 per 1000	18 fewer per 1000 (from 28 fewer to 237 more)
Insomn	ia (Risp	peridone 0.	125-0.175r	ng/day) (a	ssessed with: N	on-systematic assess	sment)				
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊖⊝⊝ VERY LOW <sup>1,3,4</sup>	2/35 (5.7%)	0/30 (0%)	RR 0.23 (0.01 to	Study po	pulation
6 weeks		inconsistency	in un ectiless	3611002	suspected <sup>4</sup>	due to risk of bias, imprecision,	(3.770)	(0 /0)	4.66)	57 per	<b>44 fewer per 1000</b> (from 57 fewer to 209

						publication bias				1000	more)
										Moderat	е
										57 per 1000	44 fewer per 1000 (from 56 fewer to 209 more)
Hyperso	omnia (	Aripiprazol	le or rispe	ridone) (a	assessed with: No	on-systematic assess	ment or s	study-specific re	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	⊕⊝⊝ VERY LOW <sup>1,3,4,8</sup>	1/86 (1.2%)	3/82 (3.7%)	RR 2.12 (0.38 to	Study po	ppulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, inconsistency, imprecision, publication bias		, ,	11.88)	12 per 1000	13 more per 1000 (from 7 fewer to 127 more)
						pasioanon siao				Moderat	e
										14 per 1000	16 more per 1000 (from 9 fewer to 152 more)
Hyperso	omnia (	Aripiprazol	le 5mg/day	<b>y)</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	⊕⊝⊝⊝ VERY LOW <sup>1,3,4</sup>	0/51 (0%)	3/52 (5.8%)	RR 6.87 (0.36 to	Study po	ppulation
B weeks					suspected <sup>4</sup>	due to risk of bias, imprecision,	(575)	(2.272)	129.7)	0 per 1000	-
o weeks						publication bias					
o weeks						publication bias				Moderat	e
o weeks						publication bias				Moderat 0 per 1000	e -
	omnia (	Risperidon	ne 0.125-0.	175mg/d	ay) (assessed	publication bias  with: Non-systematic	assessm	ent)		0 per	e -

(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	17 fewer per 1000 (from 28 fewer to 233 more)	
						publication blac				Moderat	e	
										29 per 1000	18 fewer per 1000 (from 28 fewer to 237 more)	
Psychor	motor h	yperactivi	ty (Risperi	done 0.1	25-0.175m	g/day) (assessed	with: No	n-systematic ass	sessment)	1		
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	2/35 (5.7%)	1/30 (3.3%)	RR 0.58 (0.06 to	Study po	opulation	
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)	
	` '	•	risperidor	1e) (assesse		ematic assessment of		·				
168 (2 studies)	serious <sup>1</sup>	serious <sup>8</sup>	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4,8</sup>	1/86 (1.2%)	2/82 (2.4%)	RR 1.61 (0.29 to	Study po	opulation	
6-8 weeks					suspected 4	due to risk of bias, inconsistency, imprecision,		,	9.04)	12 per 1000	7 more per 1000 (from 8 fewer to 93 more)	
						publication bias				Moderat	re e	
										10 per	6 more per 1000 (from 7 fewer to 80 more)	

103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	1/51 (2%)	0/52 (0%)	<b>RR 0.33</b> (0.01 to	Study po	pulation
8 weeks				00040	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(= /3)	(676)	7.85)	20 per 1000	13 fewer per 1000 (from 19 fewer to 134 more)
										Moderate	
										20 per 1000	13 fewer per 1000 (from 20 fewer to 137 more)
Enuresis	s (Risp	eridone 0.1	25-0.175m	ng/day) (as	ssessed with: No	on-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	⊕⊖⊖ VERY LOW <sup>1,3,4</sup>	0/35 (0%)	2/30 (6.7%)	RR 5.81 (0.29 to	Study po	pulation
6 weeks					suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias			116.41)	0 per 1000	-
						publication bias				Moderate	
										0 per 1000	-
Rash (A	ripipra	zole or risp	eridone) (a	ssessed with:	Non-systematic	assessment or study	-specific	report of adverse even	ent)		
168 (2 studies)	serious <sup>1</sup>	serious <sup>8</sup>	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝⊝ VERY LOW <sup>1,3,4,8</sup>	1/86 (1.2%)	2/82 (2.4%)	RR 1.61 (0.29 to	Study po	pulation
6-8 weeks					suspected <sup>4</sup>	due to risk of bias, inconsistency,		,	9.04)	12 per 1000	7 more per 1000 (from 8 fewer to 93 more)
						imprecision, publication bias				Moderate	)
										10 per 1000	6 more per 1000 (from 7 fewer to 80 more)
Rash (A	ı ripipraz	zole 5mg/da	ay) (assessed	l with: Study-sp	l pecific report of a	l adverse event)					

103 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	1/51 (2%)	0/52 (0%)	<b>RR 0.33</b> (0.01 to	Study po	ppulation
8 weeks				Somous	suspected <sup>4</sup>	due to risk of bias, imprecision, publication bias	(270)	(070)	7.85)	20 per 1000	13 fewer per 1000 (from 19 fewer to 134 more)
										Moderate	9
										20 per 1000	13 fewer per 1000 (from 20 fewer to 137 more)
Rash (R	isperid	one 0.125-	0.175mg/d	ay) (assesse	ed with: Non-sys	tematic assessment)	•			•	
65 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	0/35 (0%)	2/30 (6.7%)	RR 5.81 (0.29 to		pulation
6 weeks					suspected 4	due to risk of bias, imprecision, publication bias			116.41)	0 per 1000	-
										Moderate	9
										0 per 1000	-
adverse eve	-	no serious	no serious	very	reporting bias	<b>1</b>	2/51	0/52	RR 0.2		vith: Study-specific report of
(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%)	(0%)	(0.01 to 3.99)	39 per 1000	31 fewer per 1000 (from 39 fewer to 117 more)
										Moderate	е
										39 per 1000	31 fewer per 1000 (from 39 fewer to 117 more)

#### Adverse events associated with risperidone versus placebo

			Quality asses	ssment				S	ummary o	of Findir	ngs
(	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 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)		ergent extra	pyramidal	symptor	<b>ns</b> (measured w	vith: Chouinard Extra	apyramic	dal Symptoms Rating	Scale (ESF	RS): Sect	ion 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 0.83 standard deviations lower (1.61 to 0.05 lower)
Prolactin	n conc	entration (n	ng/ml) Cha	nge Scor	<b>es</b> (measured w	vith: Laboratory asse	essment;	Better indicated by I	ower values	5)	
28 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	reporting bias strongly	⊕⊝⊝ <b>VERY LOW</b> <sup>1,2,3</sup> due to risk of	15	13	-		The mean prolactin concentration (ng/ml) change scores in the

<sup>&</sup>lt;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>&</sup>lt;sup>2</sup> I-squared value indicates substantial to considerable heterogeneity

<sup>&</sup>lt;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>&</sup>lt;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>&</sup>lt;sup>5</sup> Events<300

<sup>&</sup>lt;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>&</sup>lt;sup>7</sup> N<400

<sup>8</sup> I-squared value indicates moderate heterogeneity

12 weeks					suspected <sup>3</sup>	bias, imprecision, publication bias				intervention groups was 1.01 standard deviations lower (1.80 to 0.22 lower)
Liver pr	oblems	s (change i	n alanine t	ransamin	ase [ALT])	(measured with: Lab	oratory	/ assessment; Bette	er indicated by low	er 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 problems (change in alanine transaminase [alt]) in the intervention groups was <b>0.83 standard deviations</b> lower (1.60 to 0.05 lower)
<sup>2</sup> N<400		bias as unclear if ed by the pharma		·		rve potential longer t	erm ad	verse effects		

<sup>1.33.6</sup> Adverse events associated with antivirals

Adverse events associated with amantadine hydrochloride versus placebo

			Quality asse	essment				Su	mmary of	Findings	5
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study 6		Relative effect	Anticipa	ted absolute effects
Follow up							With Control	With Adverse events associated with antivirals	(95% CI)	Risk with Control	Risk difference with Adverse events associated with antivirals (95% CI)
Any adve	erse ev	/ent (assessed w	vith: Study-specifi	c report of adv	rerse event)						
39	serious <sup>1</sup>	no serious	no serious	very	reporting bias	<b>0000</b>	14/20	14/19	RR 1.05	Study po	ppulation

(1 study) 5 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	(70%)	(73.7%)	(0.71 to 1.56)	700 per 1000	35 more per 1000 (from 203 fewer to 392 more)
						ľ				Moderat	е
										700 per 1000	35 more per 1000 (from 203 fewer to 392 more)
Insomn	ia (assess	ed with: Study-spe	ecific report of adv	verse event)			_1			-	
39 (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>	2/20 (10%)	4/19 (21.1%)	RR 2.11 (0.43 to	Study po	opulation
5 weeks		inconsistency	munectness	serious	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10%)	(21.176)	10.19)	100 per 1000	<b>111 more per 1000</b> (from 57 fewer to 919 more)
										Moderat	e
										100 per 1000	111 more per 1000 (from 57 fewer to 919 more)
Antisoc	ial beh	aviour (assess	 sed with: Study-sp	pecific report of	of adverse event)						
39 (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>	4/20 (20%)	2/19 (10.5%)	RR 0.53 (0.11 to	Study po	opulation
5 weeks		inconcional in the second of t	indirectines	Solidas	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2070)	(10.076)	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 more)
<sup>1</sup> Lliab riole o	f dataction I	hias as unclear if <sup>r</sup>	5 weeks is sufficie	nt follow-up o	furation to observe	longer-term adverse ev	ents and	reliability/valid	ity of measure is	s unclear	1

# 1.33.7 Adverse events associated with cognitive enhancers

Adverse events associated with piracetam and risperidone versus placebo and risperidone

		Q	uality assessr	ment				Sun	nmary of I	Findings	; 
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% CI)
40	serious <sup>1</sup>	no serious	no serious	very	ptom (asse	essed with: Extra  ⊕⊖⊖⊖ VERY LOW <sup>1,2</sup>	8/20	dal Symptoms Rating Scale	RR 0.75	Study p	opulation
(1 study) 10 weeks		inconsistency	indirectness	serious <sup>2</sup>		due to risk of bias, imprecision	(40%)	(30%)	(0.32 to 1.77)	400 per 1000	<b>100 fewer per 1000</b> (from 272 fewer to 308 more
						improdicion				Moderat	te
										400 per 1000	<b>100 fewer per 1000</b> (from 272 fewer to 308 more)
Constipa	ation (a	ssessed with: Stu	dy-specific side	effect checklist	t)		·				<del>-</del>
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	3/20 (15%)	4/20 (20%)	RR 1.33 (0.34 to	Study p	opulation
( ) 3.00)						due to risk of	(.070)	()	(3.3 . 13	150 per	50 more per 1000

<sup>&</sup>lt;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>&</sup>lt;sup>3</sup> Trial funded by pharmaceutical company

10 weeks						bias, imprecision			5.21)	1000	(from 99 fewer to 632 more)
						·				Moderat	te
										150 per 1000	<b>50 more per 1000</b> (from 99 fewer to 632 more)
Nervou	sness (a	assessed with: St	udy-specific side	effect checklis	st)	,	·		1		
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	2/20 (10%)	1/20 (5%)	<b>RR 0.5</b> (0.05 to	Study p	opulation
10 weeks				55.1545		due to risk of bias,	(1070)	(070)	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 tim	e drow	siness (asses	ssed with: Study-	specific side e	effect checklist)						l
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,2</sup>	9/20 (45%)	7/20 (35%)	RR 0.78 (0.36 to	Study p	opulation
10 weeks		inconsistency	indirectriess	Sellous		due to risk of bias, imprecision	(45 %)	(33%)	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	g drows	siness (asses	sed with: Study-s	specific side ef	fect checklist)	1	1				
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	8/20 (40%)	11/20 (55%)	<b>RR 1.38</b> (0.71 to	Study p	opulation
	1	Introducional	in an ecuiess	Jonious	1	VEIX I LOW	(40 /0)	(00/0)	2.68)		,

						imprecision				Moderat	te
										400 per 1000	<b>152 more per 1000</b> (from 116 fewer to 672 more)
Increas	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	⊕⊖⊝ VERY LOW <sup>1,2</sup>	6/20 (30%)	7/20 (35%)	RR 1.17 (0.48 to	Study p	opulation
10 weeks						due to risk of bias, imprecision	(2070)	(22,14)	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)
	_			•		*	•				
Loss of  40 (1 study)	appeti serious <sup>1</sup>	no serious inconsistency	h: Study-specific no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊖ VERY LOW <sup>1,2</sup>	1/20 (5%)	1/20 (5%)	RR 1 (0.07 to	Study p	opulation
40		no serious	no serious	very		VERY LOW <sup>1,2</sup> due to risk of bias,				Study po 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	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 bias,			(0.07 to	50 per 1000	0 fewer per 1000 (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	serious <sup>1</sup>	no serious inconsistency ssed with: Study-	no serious indirectness specific side effe	very serious <sup>2</sup>		VERY LOW <sup>1,2</sup> due to risk of bias, imprecision	3/20	4/20	(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	no serious indirectness	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	0 fewer per 1000 (from 47 fewer to 695 more) te 0 fewer per 1000 (from 47 fewer to 695 more)

											<b>50 more per 1000</b> (from 99 fewer to 632 more)
Fatigue	(assessed	with: Study-spec	ific side effect ch	ecklist)					,		
40 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	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)	-	<b>100 more per 1000</b> (from 81 fewer to 759 more)
						imprecision				Moderat	re
										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

		C	Quality assessn	nent				Sı	ımmary of	Findings	
<b>(</b>	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study ev	vent rates (%)	Relative effect	Anticipated	d 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	g (assess	sed with: Study-spe	cific report of adve	erse event)							
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,2</sup>	13/33 (39.4%)	6/30 (20%)	<b>RR 0.51</b> (0.22 to	Study pop	ulation
, ,,		,				due to risk of	, ,	,	`	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	ssessed with: Stu	dy-specific report	of adverse ev	ent)						
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖ VERY LOW <sup>1,2</sup>		7/30 23.3%)	RR 1.28 (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	1
										182 per 1000	<b>51 more per 1000</b> (from 93 fewer to 435 more)
Vomitin	g (assesse	ed with: Study-spe	cific report of adv	erse event)			I				
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>		7/30 23.3%)	RR 1.1 (0.44 to	Study po	pulation
12 weeks		inconsistency	indirectiness.	School		due to risk of bias, imprecision		20.070)	2.77)	212 per 1000	21 more per 1000 (from 119 fewer to 375 more)
										Moderate	) 
										212 per 1000	21 more per 1000 (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	⊕⊝⊝ VERY LOW <sup>1,2</sup>	6/33	5/30 (16.7%)	RR 0.92 (0.31 to	Study pop	ulation
12 weeks		inconsistency	munectiess	serious		due to risk of bias, imprecision	(10.276)	(10.7 %)	2.7)	182 per 1000	15 fewer per 1000 (from 125 fewer to 309 more)
										Moderate	
										182 per 1000	15 fewer per 1000 (from 126 fewer to 309 more)
Headac	he (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	⊕⊝⊝ VERY LOW <sup>1,2</sup>	2/33 (6.1%)	2/30 (6.7%)	<b>RR 1.1</b> (0.17 to	Study pop	ulation
12 weeks		inconsistency		Solicus		due to risk of bias, imprecision	(0.170)	(6.1. 76)	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	ssessed with	n: Study-specific re	eport of adverse ev	vent)		1					1
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖ VERY LOW <sup>1,2</sup>	3/33 (9.1%)	4/30 (13.3%)	RR 1.47 (0.36 to	Study pop	ulation
12 weeks		inconsistency	muncomoss.	Scrious		due to risk of bias, imprecision	(3.170)	(10.070)	6.03)	91 per 1000	43 more per 1000 (from 58 fewer to 457 more)
										Moderate	

										91 per 1000	43 more per 1000 (from 58 fewer to 458 more)
Somnol	lence (as	sessed with: Stud	y-specific report o	f adverse even	nt)	l					
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	5/33 (15.2%)	3/30 (10%)	<b>RR 0.66</b> (0.17 to	Study pop	oulation
12 weeks		inconsistency	munectiess	Serious		due to risk of bias, imprecision		(10%)	2.53)	152 per 1000	52 fewer per 1000 (from 126 fewer to 232 more)
										Moderate	
										152 per 1000	52 fewer per 1000 (from 126 fewer to 233 more)
Fatigue 63 (1 study)	serious <sup>1</sup>	no serious	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,2</sup>	6/33 (18.2%)	1/30 (3.3%)	RR 0.18 (0.02 to	Study pop	oulation
12 weeks		inconsistency	munectiess	Serious		due to risk of bias, imprecision		(3.370)	1.44)	182 per 1000	149 fewer per 1000 (from 178 fewer to 80 more)
										Moderate	
										182 per 1000	149 fewer per 1000 (from 178 fewer to 80 more)
Hypoth	ermia (a	ssessed with: Stud	ly-specific report c	of adverse ever	nt)	1	1		,	1	
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝ VERY LOW <sup>1,2</sup>	2/33 (6.1%)	1/30 (3.3%)	RR 0.55 (0.05 to	Study pop	oulation
12 weeks		The original of the state of th	ii iuii cott icss	Scrious		due to risk of	(0.170)	(0.070)	5.76)	61 per	<b>27 fewer per 1000</b> (from 58 fewer to 288

						bias, imprecision				1000	more)
										Moderate	
										61 per 1000	27 fewer per 1000 (from 58 fewer to 290 more)
Increase	ed activ	<b>/ity</b> (assessed wi	th: Study-specific	report of adve	rse event)						
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	3/33 (9.1%)	3/30 (10%)	RR 1.1 (0.24 to	Study pop	oulation
12 weeks				00000		due to risk of bias, imprecision	(61176)	(1070)	5.04)	91 per 1000	9 more per 1000 (from 69 fewer to 367 more)
										Moderate	
										91 per 1000	9 more per 1000 (from 69 fewer to 368 more)
Nausea	(assessed	with: Study-specifi	c report of adverse	e event)	!			,	1		
63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖⊝ VERY LOW <sup>1,2</sup>	2/33 (6.1%)	1/30 (3.3%)	RR 0.55 (0.05 to	Study pop	pulation
12 weeks		inconsistency	indirectiness	School		due to risk of bias, imprecision	(0.170)	(0.070)	5.76)	61 per 1000	27 fewer per 1000 (from 58 fewer to 288 more)
										Moderate	1
										61 per 1000	27 fewer per 1000 (from 58 fewer to 290 more)
Dizzines	SS (assess	L sed with: Study-spe	ecific report of adv	erse event)	1						1

63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	2/33 (6.1%)	0/30 (0%)	<b>RR 0.22</b> (0.01 to	Study pop	ulation
2 weeks				Somous		due to risk of bias, imprecision	`	(070)	4.39)	61 per 1000	47 fewer per 1000 (from 60 fewer to 205 more)
										Moderate	4
										61 per 1000	48 fewer per 1000 (from 60 fewer to 207 more)
Breathl	essnes	S (assessed with:	Study-specific re	port of adverse	e event)				•	•	
63 (1 study) 12 weeks						See comment	0/33 (0%)	0/30 (0%)	not pooled	See	See comment
Huna-o	⊣ ver feel	l <b>ing</b> (assessed w			1						
		iiig (assessed w	rith: Study-specifi	c report of adve	erse event)						
33	serious <sup>1</sup>	no serious	no serious	very	undetected	⊕⊖⊝⊖ VERY LOW <sup>1,2</sup>	0/33	1/30 (3.3%)	RR 3.29	Study pop	ulation
63 1 study)						⊕⊖⊖⊖ VERY LOW¹.² due to risk of bias, imprecision	(0%)	1/30 (3.3%)	RR 3.29 (0.14 to 77.82)	Study pop 0 per 1000	ulation
63 (1 study)		no serious	no serious	very		VERY LOW <sup>1,2</sup> due to risk of	(0%)		(0.14 to	0 per	ulation -
63 (1 study) 12 weeks		no serious	no serious	very		VERY LOW <sup>1,2</sup> due to risk of	(0%)		(0.14 to	0 per 1000	ulation -
53 (1 study) 12 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	(0%)		(0.14 to	0 per 1000 Moderate	ulation -
53 (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	(0%)		(0.14 to	0 per 1000 Moderate	- See comment

63 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,2</sup>	1/33 (3%)	0/30 (0%)	RR 0.37 (0.02 to	Study pop	ulation
12 weeks		,				due to risk of bias, imprecision		()	8.65)	30 per 1000	19 fewer per 1000 (from 30 fewer to 232 more)
										Moderate	
										30 per 1000	19 fewer per 1000 (from 29 fewer to 229 more)
Other (a	issessed wit	h: Study-specific r	enort of adverse	event)							
63	serious <sup>1</sup>	no serious	no serious	very	undetected	⊕⊖⊝⊖ VERY L OW <sup>1,2</sup>	20/33	15/30 (50%)	RR 0.82	Study pop	ulation
63 (1 study) 12 weeks		T			undetected	⊕⊖⊖ <b>VERY LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	20/33 (60.6%)	15/30 (50%)	RR 0.82 (0.53 to 1.3)	Study pop 606 per 1000	ulation  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			(0.53 to	606 per	109 fewer per 1000 (from 285 fewer to 182

# 1.33.9 Adverse events associated with opioid antagonists

Adverse events associated with naltrexone versus placebo

Quality assessment	Summary of Findings
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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% CI)
Any side	effect (	assessed with: St	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	⊕⊖⊝ VERY LOW <sup>1,2,3</sup>	7/18 (38.9%)	13/23 (56.5%)	RR 1.45 (0.74 to	Study po	opulation
6 weeks		inconsistency	munectness	Serious	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(30.378)	(30.370)	2.87)	389 per 1000	<b>175 more per 1000</b> (from 101 fewer to 727 more)
										Moderat	е
										389 per 1000	<b>175 more per 1000</b> (from 101 fewer to 727 more)
Aggressi	veness	(assessed with: \$	I 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	⊕⊖⊝ VERY LOW <sup>1,2,3</sup>	5/18	4/23 (17.4%)	RR 0.63 (0.2 to 2)	Study po	opulation
6 weeks			man seaness	Somous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(27.070)	(,	(0.2 to 2)	278 per 1000	103 fewer per 1000 (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	ehaviour (asse	essed with: Study	-specific side e	ffect checklist)		<u>.</u>				ı
41 (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>	2/18 (11.1%)	1/23 (4.3%)	RR 0.39 (0.04 to	Study po	pulation
6 weeks				3530	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(,3)	(	3.98)	111 per 1000	<b>68 fewer per 1000</b> (from 107 fewer to 331 more)

										Moderat	e
										111 per 1000	<b>68 fewer per 1000</b> (from 107 fewer to 331 more)
Hyperac	tivity (as	sessed with: Study	/-specific side eff	ect checklist)	•				<u> </u>	•	
41 (1. atudu)	serious <sup>1</sup>	no serious	no serious	very serious <sup>2</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>1,2,3</sup>		2/23	<b>RR 0.52</b> (0.1 to	Study po	ppulation
(1 study) 6 weeks		inconsistency	indirectness	serious	strongly suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(16.7%)	(8.1%)	2.8)	167 per 1000	<b>80 fewer per 1000</b> (from 150 fewer to 300 more)
										Moderat	e
										167 per 1000	<b>80 fewer per 1000</b> (from 150 fewer to 301 more)
Temper 1	tantrum	S (assessed with:	Study-specific si	de effect chec	klist)						
41 (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>		2/23 (8.7%)	RR 1.57 (0.15 to	Study po	ppulation
6 weeks		inconsistency	indirectivess	Serious	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(3.070)	(0.7 70)	15.92)	56 per 1000	<b>32 more per 1000</b> (from 47 fewer to 829 more)
										Moderat	e
										56 per 1000	<b>32 more per 1000</b> (from 48 fewer to 836 more)
Stereoty	pies (ass	essed with: Study	-specific side effe	ct checklist)		ļ					L
41 (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>	3/18 (16.7%)	2/23 (8.7%)	<b>RR 0.52</b> (0.1 to	Study po	ppulation
6 weeks		inconsistency	munoon ios	School	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.170)	(0 70)	2.8)	167 per 1000	<b>80 fewer per 1000</b> (from 150 fewer to 300 more)

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										Moderat	е
										167 per 1000	<b>80 fewer per 1000</b> (from 150 fewer to 301 more)
Irritabilit	<b>y</b> (assesse	d with: Study-spec	cific side effect ch	necklist)		1				1	1
41 (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>	2/18 (11.1%)	3/23 (13%)	RR 1.17 (0.22 to	Study po	opulation
6 weeks				33.1040	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(,,,	(1073)	6.3)	111 per 1000	<b>19 more per 1000</b> (from 87 fewer to 589 more)
										Moderat	e
										111 per 1000	<b>19 more per 1000</b> (from 87 fewer to 588 more)
Decrease	ed trans	ient verbal p	production (	assessed with	Study-specific sic	le effect checklist)	<b>I</b>				
41 (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>	0/18 (0%)	1/23 (4.3%)	RR 2.38 (0.1 to	Study po	opulation
6 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		,	55.06)	0 per 1000	-
						P 42.104.101.1 2.140				Moderat	e
										0 per 1000	-
Slight sle	eepines	<b>S</b> (assessed with:	Study-specific si	de effect chec	klist)					L	1
41 (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>	0/18 (0%)	1/23 (4.3%)	<b>RR 2.38</b> (0.1 to		opulation
6 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			55.06)	0 per 1000	-
										Moderat	е

										0 per 1000	-
Falling a	sleep (as	ssessed with: Stu	dy-specific side e	ffect checklist	)						
41 (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>	0/18 (0%)	2/23 (8.7%)	<b>RR 3.96</b> (0.2 to	Study p	oopulation
6 weeks					suspected 3	due to risk of bias, imprecision, publication bias			77.63)	0 per 1000	-
										Modera	nte
										0 per 1000	-
Decrease	ed appe	etite (assessed v	vith: Study-specifi	c side effect o	checklist)		•			•	
41 (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>	0/18 (0%)	2/23 (8.7%)	RR 3.96 (0.2 to	Study p	oopulation
6 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias			77.63)	0 per 1000	-
						publication blac				Modera	nte
										0 per 1000	-
Vomiting	(assessed	d with: Study-spec	ific side effect ch	ecklist)	•		1	·	<del>'</del>	-1	
41 (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>	0/18 (0%)	3/23 (13%)	<b>RR 5.54</b> (0.3 to	Study p	oopulation
6 weeks					suspected 3	due to risk of bias, imprecision, publication bias			100.86)	0 per 1000	-
						·				Modera	ite
										0 per 1000	-

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#### 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 e	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-specific	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	⊕⊝⊝ VERY LOW <sup>1,2,3</sup>	32/49 (65.3%)	39/48 (81.3%)	RR 1.24 (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)
										Modera	te
										653 per 1000	<b>157 more per 1000</b> (from 20 fewer to 385 more)
Discontin	uation	due to adve	rse events	l (assessed witl	n: Study-specific	I open-ended questic	onning for	adverse events)			
97 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious	very serious <sup>2</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,2,3</sup>	0/49 (0%)	1/48 (2.1%)	OR 3.13 (0.12 to	Study p	opulation
8 weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(===,		78.66)	0 per 1000	-
										Modera	te
										0 per	-

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<sup>&</sup>lt;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>&</sup>lt;sup>3</sup> Potential conflict of interest as drug and placebo were supplied by the manufacturer

										1000	
Abdomir	nal pain	(assessed with: S	Study-specific op	en-ended que	stionning for adve	erse events)	<u> </u>			I.	1
97 (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>	3/49 (6.1%)	4/48 (8.3%)	<b>RR 1.36</b> (0.32 to	Study p	opulation
3 weeks				30.1000	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(6.1.76)	(6.678)	5.76)	61 per 1000	<b>22 more per 1000</b> (from 42 fewer to 291 more)
										Modera	te
										61 per 1000	<b>22 more per 1000</b> (from 41 fewer to 290 more)
Jpper al	odomina	al pain (assess	ed with: Study-s	pecific open-e	nded questionnin	g for adverse event	s)	·			
7 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>	3/49 (6.1%)	9/48 (18.8%)	<b>RR 3.06</b> (0.88 to	Study p	opulation
weeks				30.1000	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(6.1.76)	(1010/3)	10.63)	61 per 1000	<b>126 more per 1000</b> (from 7 fewer to 590 more)
										Modera	te
										61 per 1000	126 more per 1000 (from 7 fewer to 587 more)
Diarrhoe	a (assesse	ed with: Study-spe	ecific open-ended	d questionning	for adverse ever	nts)					
7 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>	3/49 (6.1%)	1/48 (2.1%)	RR 0.34 (0.04 to	Study p	opulation
weeks		inconsistency	munectiess	Sellous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.178)	(2.170)	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	c open-ended qu	uestionning for	adverse events)						
97 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	reporting bias strongly	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	4/49 (8.2%)	14/48 (29.2%)	RR 3.57 (1.27 to	Study p	opulation
B weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(5.273)	(=0.=70)	10.08)	82 per 1000	210 more per 1000 (from 22 more to 741 more)
										Modera	te
										82 per 1000	<b>211 more per 1000</b> (from 22 more to 745 more)
/omiting	(assessed	d with: Study-spec	cific open-ended	questionning	for adverse event	s)	ļ				
7 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>	5/49 (10.2%)	7/48 (14.6%)	<b>RR 1.43</b> (0.49 to	Study p	opulation
weeks		and disconsistency		Somous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.270)	(111070)	4.19)	102 per 1000	44 more per 1000 (from 52 fewer to 326 more)
										Modera	te
										102 per 1000	44 more per 1000 (from 52 fewer to 325 more)
-atigue	assessed v	I vith: Study-specifi	c open-ended qu	Luestionning for	adverse events)						
7 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>	4/49 (8.2%)	11/48 (22.9%)	<b>RR 2.81</b> (0.96 to	Study p	opulation
weeks		inconsistency	indirectiness.	School	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.270)	(22.576)	8.21)	82 per 1000	148 more per 1000 (from 3 fewer to 589 more)
										Moderat	te

										82 per 1000	148 more per 1000 (from 3 fewer to 591 more)
Pyrexia (	assessed v	vith: Study-specifi	c open-ended qu	lestionning for	adverse events)		1		L		1
97	serious <sup>1</sup>	no serious	no serious	very serious <sup>2</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>1,2,3</sup>	3/49	0/48	RR 0.15	Study p	opulation
(1 study) 8 weeks		inconsistency	indirectness	serious	strongly suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(6.1%)	(0%)	(0.01 to 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)
influenza	a (assesse	I d with: Study-spec	cific open-ended	questionning	I for adverse event	ts)					
97 (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>	0/49 (0%)	3/48 (6.3%)	RR 7.14 (0.38 to	Study p	opulation
3 weeks		inconsistency	indirectricss	Schous	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(070)	(0.370)	134.69)	0 per 1000	-
						publication bias				Modera	te
										0 per 1000	-
Decease	d appet	: <b>ite</b> (assessed wi	th: Study-specifi	c open-ended	questionning for	adverse events)					
97	serious <sup>1</sup>	no serious	no serious	serious <sup>4</sup>	reporting bias	⊕⊝⊝ VERY LOW <sup>1,3,4</sup>	3/49	13/48	RR 4.42	Study p	opulation
1 study) 3 weeks		inconsistency	indirectness		strongly suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(6.1%)	(27.1%)	(1.34 to 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-specifi	c open-ended qu	uestionning for	r adverse events)		1			<u> </u>	1
17 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>	0/49 (0%)	3/48 (6.3%)	RR 7.14 (0.38 to	Study p	opulation
weeks		,			suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(2,2)		134.69)	0 per 1000	-
						publication bias				Modera	te
										0 per 1000	-
izzines	S (assesse	ed with: Study-spe	cific open-endec	I questionning	for adverse ever	its)	1			<u> </u>	1
7 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>	1/49 (2%)	3/48 (6.3%)	RR 3.06 (0.33 to	Study p	opulation
weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias		(* 211)	28.42)	20 per 1000	<b>42 more per 1000</b> (from 14 fewer to 560 more)
										Modera	te
										20 per 1000	41 more per 1000 (from 13 fewer to 548 more)
leadach	ie (assess	ed with: Study-spe	ecific open-ende	l d questionning	for adverse ever	nts)		,	_	ļ.	
7 I 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>	9/49 (18.4%)	12/48 (25%)	RR 1.36 (0.63 to	Study p	opulation
weeks				00.1040	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(101170)	(2070)	2.93)	184 per 1000	66 more per 1000 (from 68 fewer to 354 more)
										Modera	te
										184 per	<b>66 more per 1000</b> (from 68 fewer to 355

										1000	more)
Psychon	notor hy	peractivity (	assessed with: S	Study-specific	open-ended ques	stionning for adverse	e events)				1
97 (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>	4/49 (8.2%)	1/48 (2.1%)	RR 0.26 (0.03 to	Study p	opulation
8 weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(0.270)	(=)	2.2)	82 per 1000	60 fewer per 1000 (from 79 fewer to 98 more)
										Modera	te
										82 per 1000	61 fewer per 1000 (from 80 fewer to 98 more)
Aggress	ion (asse	ssed with: Study-s	specific open-end	ded questionni	ing for adverse ev	vents)		•			<del>'</del>
97 (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>	3/49 (6.1%)	2/48 (4.2%)	RR 0.68 (0.12 to	Study p	opulation
B weeks					suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(01170)	(/)		61 per 1000	20 fewer per 1000 (from 54 fewer to 177 more)
										Modera	te
										61 per 1000	20 fewer per 1000 (from 54 fewer to 176 more)
Early mo	orning a	wakening (as	sessed with: Stu	ıdy-specific op	en-ended questi	onning for adverse e	events)				
97 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>	0/49 (0%)	5/48 (10.4%)	RR 11.22 (0.64 to	Study p	opulation
3 weeks		inconsistency	indirectivess	Serious	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(078)	(10.470)	197.6)	0 per 1000	-
						p a should it should				Modera	te
										0 per	-

										1000	
Initial ins	somnia	(assessed with: S	tudy-specific ope	en-ended ques	stionning for adve	rse events)				•	
97 (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>	5/49 (10.2%)	3/48 (6.3%)	<b>RR 0.61</b> (0.15 to	Study po	opulation
8 weeks				Concac	suspected <sup>3</sup>	due to risk of bias, imprecision, publication bias	(10.270)	( · · /	2.42)	102 per 1000 Moderat	40 fewer per 1000 (from 87 fewer to 145 more)
										102 per 1000	40 fewer per 1000 (from 87 fewer to 145 more)

Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25)

### 1.34 ADVERSE 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					
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study e With Control		Relative effect (95% CI)	Risk with Control	Risk difference with Adverse events associated with hyperbaric oxygen treatment (HBOT) versus attention-placebo control (95% CI)	
Any adve	Any adverse event (assessed with: Study-specific daily treatment logbooks)											

Trial run and reported by pharmaceutical company

<sup>&</sup>lt;sup>4</sup> Events<300

62 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	, ,	reporting bias strongly suspected <sup>3</sup>		2/29 (6.9%)		(0.24 to 7.35)	Study population		
4 weeks										69 per 1000	<b>22 more per 1000</b> (from 52 fewer to 438 more)	
										Moderat	e	
										69 per 1000	<b>22 more per 1000</b> (from 52 fewer to 438 more)	
Minor-gra	ade ear	barotrauma	(assessed with	: Not reported)	)				1	1		
58 (1 study)	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>5</sup>	undetected	⊕⊕⊝⊝ <b>LOW</b> <sup>4,5</sup>	3/29 (10.3%)	11/29 (37.9%)	RR 3.67 (1.14 to	Study population		
4 weeks						due to risk of bias, imprecision	(101070)	(61.676)	11.79)	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)	

<sup>&</sup>lt;sup>1</sup> High risk of detection bias as unclear if 4 weeks sufficient follow-up duration to detect potential longer-term adverse events and adverse events were recorded by the intervention administrator who was non-blind to treatment assignment and to other potentially confounding factors

#### 1.34.2 Adverse events associated with nutritional interventions

Adverse events associated with multivitamin/mineral supplement versus placebo

<sup>&</sup>lt;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>&</sup>lt;sup>3</sup> Potential conflict of interest as study funded by the International Hyperbarics Association and authors profit from the use of hyperbaric treatment in their clinical practices

<sup>&</sup>lt;sup>4</sup> High risk of detection bias as unclear if 4 weeks was a sufficient follow-up duration to observe potential longer-term adverse events and outcome measure and outcome assessor/s not reported so blinding, and reliability and validity unclear

<sup>&</sup>lt;sup>5</sup> Events<300

Quality assessment							Summary of Findings					
Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative	Anticipated absolute effects		
(studies) Follow up							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)	
Discontin	nuation o	due to advers	se events (as	ssessed with: I	Number of part	icipants who disc	continue	d due to adverse events)	•			
141 (1 study)	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ LOW¹ due to imprecision	5/69 (7.2%)	3/72 (4.2%)	RR 0.57 (0.14 to	Study po	ppulation	
13 weeks	bias								2.31)	72 per 1000	31 fewer per 1000 (from 62 fewer to 95 more)	
										Moderate		
										73 per 1000	31 fewer per 1000 (from 63 fewer to 96 more)	
Discontin	nuation o	due to diarrh	oea (assessed	with: Number	of participants	who discontinue	d due to	diarrhoea)				
141 (1 study)	no serious risk of bias	s no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝ <b>LOW</b> <sup>1</sup> due to imprecision	3/69 (4.3%)	1/72 (1.4%)	RR 0.32 (0.03 to 3)	Study population		
13 weeks										43 per 1000	30 fewer per 1000 (from 42 fewer to 87 more)	
										Moderate		
										44 per 1000	30 fewer per 1000 (from 43 fewer to 88 more)	
Discontin	nuation o	due to increa	sed stimmi	ng (assessed	with: Number	of participants w	ho disco	ntinued due to increased	stimming)			
141 (1 study)	no serious risk of bias	sk of inconsistency in			undetected	⊕⊕⊖⊝ <b>LOW</b> <sup>1</sup>	1/69 (1.4%)	0/72 (0%)	RR 0.32 (0.01 to	Study population		
13 weeks					due to imprecision		, ()	7.72)	14 per 1000	10 fewer per 1000 (from 14 fewer to 97 more)		
										Moderat	e	

										15 per 1000	10 fewer per 1000 (from 15 fewer to 101 more)
Discontir	nuation o	due to behav	viour proble	ms (assesse	d with: Numbe	r of participants	who disco	ontinued due to b	pehaviour problems	)	
	no serious risk of	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	undetected	⊕⊕⊝⊝ LOW¹	1/69 (1.4%)	2/72 (2.8%)	<b>RR 1.92</b> (0.18 to	Study po	opulation
3 weeks	y) risk of	inconsistency	nancetress induced is			due to imprecision		,	20.66)	14 per 1000	13 more per 1000 (from 12 fewer to 285 more)
										Moderat	te
										15 per 1000	<b>14 more per 1000</b> (from 12 fewer to 295 more)

#### Adverse events associated with omega-3 fatty acids versus placebo

		Q	Quality assessr	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 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	rse eve	ent (assessed with	: Study-specific r	eport of advers	se event)			•			
27 (1 study)	serious <sup>1</sup>			very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	4/13 (30.8%)	5/14 (35.7%)	RR 1.16	Study po	ppulation
12 weeks		inconsistency	indirectiness	School		due to risk of bias, imprecision	(30.070)	(55.7 70)	(0.4 to 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	e event)			•				
27 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	0/13 (0%)	2/14 (14.3%)	<b>RR 4.67</b> (0.24 to	Study p	opulation
2 weeks			assassa	55.7545		due to risk of bias,	(0,0)	(1.11070)	88.96)	0 per 1000	-
						imprecision				Modera	te
										0 per 1000	-
Jpper re	spirato	ry infection (a	assessed with: St	udy-specific re	port of adverse	event)			<u> </u>		
27 (1 study)	serious <sup>1</sup>			very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	0/13 (0%)	1/14 (7.1%)	<b>RR 2.8</b> (0.12 to	Study p	opulation
2 weeks						due to risk of bias, imprecision			63.2)	0 per 1000	-
						Imprecision				Modera	te
										0 per 1000	-
Nose ble	eds (asse	essed with: Study-	specific report of	adverse event)	)						<u> </u>
27 1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	0/13 (0%)	1/14 (7.1%)	<b>RR 2.8</b> (0.12 to	Study p	opulation
2 weeks		,				due to risk of bias,		,	63.2)	0 per 1000	-
					imprecision		Modera	te			
										0 per 1000	-
GI symp	toms (as	sessed with: Study	/-specific report o	f adverse even	nt)	<u> </u>		<u> </u>			

27 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊖⊖ VERY LOW <sup>1,2</sup>	0/13 (0%)	1/14 (7.1%)	RR 2.8 (0.12 to	Study po	ppulation
12 weeks						due to risk of bias, imprecision		,	63.2)	0 per 1000	-
						Imprecision				Moderat	e
										0 per 1000	-
Hyperac	tivity (as:	sessed with: Study	-specific report of	f adverse eve	nt)						1
27 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,2</sup>	3/13 (23.1%)	0/14 (0%)	<b>RR 0.13</b> (0.01 to	Study po	ppulation
12 weeks				55.1545		due to risk of bias, imprecision	(20.176)	(073)	2.36)	231 per 1000	201 fewer per 1000 (from 228 fewer to 314 more)
										Moderate	   <b> </b>
										231 per 1000	<b>201 fewer per 1000</b> (from 229 fewer to 314 more)
Self-stim	nulatory	behaviour (a	ssessed with: Stu	ıdy-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	⊕⊝⊝ VERY LOW <sup>1,2</sup>	1/13 (7.7%)	0/14 (0%)	<b>RR 0.31</b> (0.01 to	Study po	ppulation
12 weeks						due to risk of bias, imprecision	(,9)	(0.13)	7.02)	77 per 1000	53 fewer per 1000 (from 76 fewer to 463 more)
										Moderate	e
										77 per 1000	53 fewer per 1000 (from 76 fewer to 464 more)
<sup>1</sup> High risk of <sup>2</sup> Events<30	f detection I 0 and 95%	L pias as unclear if 1 CI crosses both lir	2 weeks is sufficine of no effect and	ent follow-up of a	duration to obse appreciable ben	erve potential long efit or harm (RR 0	 er-term ad ).75/1.25)	lverse effects and	reliability/validity	of outcom	le measure is unclear

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#### Adverse events associated with immunoglobulin (dosages combined) versus placebo

		Qı	uality assessr	nent				Sum	nmary of F	indings	
Participants		Inconsistency	Indirectness	Imprecision	Publication	Overall	Study ev	vent rates (%)	Relative	Anticipa	ted 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% CI)
Any adve	rse eve	ent (assessed wit	h: 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	⊕⊕⊖⊝ <b>LOW</b> <sup>1,2</sup>	25/31 (80.6%)	71/94 (75.5%)	RR 0.94 (0.76 to	Study p	opulation
12 weeks						due to risk of bias, imprecision			1.15)	806 per 1000	48 fewer per 1000 (from 194 fewer to 121 more)
										Moderat	e
										807 per 1000	<b>48 fewer per 1000</b> (from 194 fewer to 121 more)
Discontin	nuation	due to adve	rse events	assessed with	: Study-specif	ic report of adve	rse event)				
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,3</sup>	1/31 (3.2%)	7/94 (7.4%)	RR 2.31 (0.3 to	Study p	opulation
12 weeks		in correlation by		Semedo		due to risk of bias, imprecision	(0.270)	(,0)	18.03)	32 per 1000	<b>42 more per 1000</b> (from 23 fewer to 549 more)
										Moderat	е
										32 per 1000	<b>42 more per 1000</b> (from 22 fewer to 545 more)
Infections	s/Infest	ations (assess	ed with: Study-sp	pecific report o	f adverse ever	nt)	•				
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊝⊝ VERY LOW <sup>1,3</sup>	16/31 (51.6%)	46/94 (48.9%)	RR 0.95 (0.64 to	Study po	opulation
12 weeks		,				due to risk of bias,	(311270)	(/ <del>-</del> /	1.41)	516 per	<b>26 fewer per 1000</b> (from 186 fewer to 212

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						imprecision				1000	more)
										Moderat	e
										516 per 1000	<b>26 fewer per 1000</b> (from 186 fewer to 212 more)
Gastroint	testinal	disorders (a	ssessed with: St	udy-specific re	port of adverse	e event)	·			,	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,3</sup>	9/31 (29%)	36/94 (38.3%)	RR 1.32 (0.72 to	Study po	opulation
12 weeks		, i				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)
Psychiatr	ric diso	rders (assesse	d 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	⊕⊝⊝⊝ VERY LOW <sup>1,3</sup>	6/31 (19.4%)	17/94 (18.1%)	<b>RR 0.93</b> (0.4 to	Study p	opulation
12 weeks				Consus		due to risk of bias, imprecision	(10.170)	(10.170)	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)
Respirato	ory/Tho	racic/Medias	stinal disor	ders (assess	sed with: Study	-specific report c	of adverse	event)	1	1	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,3</sup>	4/31 (12.9%)	15/94 (16%)	<b>RR 1.24</b> (0.44 to	Study pe	opulation
12 weeks		onblotonoy		School		due to risk of bias,	(12.570)	(1070)	3.45)	129 per 1000	<b>31 more per 1000</b> (from 72 fewer to 316 more)

						imprecision				Moderat	e
										129 per 1000	31 more per 1000 (from 72 fewer to 316 more)
Skin/Sub	ocutane	ous tissue c	lisorders (as	sessed with: S	tudy-specific re	eport of adverse	event)			*	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,3</sup>	3/31 (9.7%)	12/94 (12.8%)	RR 1.32 (0.4 to	Study po	opulation
12 weeks		in concionary	man counces			due to risk of bias, imprecision	(0.170)	(12.070)	4.37)	97 per 1000	31 more per 1000 (from 58 fewer to 326 more)
						Imprecision				Moderat	ee
										97 per 1000	<b>31 more per 1000</b> (from 58 fewer to 327 more)
General	disorde	rs/Administ	ration site o	onditions	(assessed wit	th: Study-specific	report of	f adverse event)			
125 (1 study)	serious <sup>1</sup>	no serious inconsistency				9/94 (9.6%)	RR 1.48 Study (0.34 to		population		
12 weeks			a souess			due to risk of bias, imprecision	(0.070)	(0.070)	6.5)	65 per 1000	<b>31 more per 1000</b> (from 43 fewer to 355 more)
						imprecision				Moderate	
										65 per 1000	31 more per 1000 (from 43 fewer to 357 more)
Nervous	system	disorders (	assessed with: S	tudy-specific re	eport of advers	se event)	ļ.				
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,3</sup>	0/31 (0%)	7/94 (7.4%)	RR 5.05 (0.3 to	Study po	opulation
12 weeks			a souess			due to risk of bias,	(0,70)	(,6)	86.01)	0 per 1000	-
						imprecision				Moderat	re
										0 per 1000	-

125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝⊝ VERY LOW <sup>1,3</sup>	1/31 (3.2%)	5/94 (5.3%)	<b>RR 1.65</b> (0.2 to	Study p	opulation
12 weeks		inconsistency	munectness	Sellous		due to risk of bias, imprecision	(3.2 /6)	(3.3%)	13.58)	32 per 1000	21 more per 1000 (from 26 fewer to 406 more
										Modera	te
										32 per 1000	21 more per 1000 (from 26 fewer to 403 more)
Investig	ations (a	assessed with: Stu	udy-specific repo	rt of adverse	event)	L					
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,3</sup>	1/31 (3.2%)	3/94 (3.2%)	<b>RR 0.99</b> (0.11 to	Study p	opulation
12 weeks				00.1000		due to risk of bias, imprecision	(0.270)	(0.270)	9.17)	32 per 1000	0 fewer per 1000 (from 29 fewer to 264 more)
						Impredicion				Modera	te
										32 per 1000	0 fewer per 1000 (from 28 fewer to 261 more)
Metabol	ism/Nut	rition disorc	ders (assessed	with: Study-s	pecific report of	f adverse event)				1	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊝ VERY LOW <sup>1,3</sup>	1/31 (3.2%)	3/94 (3.2%)	<b>RR 0.99</b> (0.11 to	Study p	opulation
12 weeks		indentification of	manosinoss	School		due to risk of bias, imprecision	(0.270)	(0.270)	9.17)	32 per 1000	0 fewer per 1000 (from 29 fewer to 264 more)
										Modera	te
										32 per 1000	0 fewer per 1000 (from 28 fewer to 261 more)
Eye disc	orders (a	ssessed with: Stu	ıdy-specific repo	rt of adverse e	event)					1	1
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊝ VERY LOW <sup>1,3</sup>	0/31 (0%)	3/94 (3.2%)	<b>RR 2.36</b> (0.13 to	Study p	opulation
12 weeks				2011040		due to risk of	(3,0)	(3.270)	44.42)	0 per	-

Autism: the management and support of children and young people on the autism spectrum (March 2013)

						bias, imprecision				1000	
						imprecision				Modera	ite
										0 per 1000	-
Blood/Ly	ymphati	c system dis	sorders (asse	ssed with: Stu	dy-specific rep	oort of adverse e	vent)			<del>'</del>	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,3</sup>	1/31 (3.2%)	1/94 (1.1%)	<b>RR 0.33</b> (0.02 to	Study p	oopulation
12 weeks		linconsistency	indirectriess	Serious		due to risk of bias, imprecision	(3.276)	(1.176)	5.12)	32 per 1000	22 fewer per 1000 (from 32 fewer to 133 more)
									Modera	ite	
										32 per 1000	21 fewer per 1000 (from 31 fewer to 132 more)
Renal/U	rinary d	isorders (asse	ssed with: Study	-specific repor	t of adverse e	vent)	Į.			1	
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,3</sup>	2/31 (6.5%)	0/94 (0%)	<b>RR 0.07</b> (0 to	Study p	oopulation
12 weeks		linconsistency	munectness	Serious		due to risk of bias, imprecision	(0.376)	(076)	1.37)	65 per 1000	60 fewer per 1000 (from 65 fewer to 24 more)
						Imprecision				Modera	nte
										65 per 1000	60 fewer per 1000 (from 65 fewer to 24 more)
Ear/Laby	rinth d	isorders (asse	ssed with: Study	-specific repor	t of adverse ev	vent)	<u> </u>				
125 (1 study)	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊝⊝ VERY LOW <sup>1,3</sup>	0/31 (0%)	1/94 (1.1%)	<b>RR 1.01</b> (0.04 to	Study p	oopulation
12 weeks		inconsistency	sistency indirectness serious			due to risk of bias, imprecision	(575)	(1175)	24.19)	0 per 1000	-
						F. 22.2.2.				Modera	ite

										0 per 1000	-
mmune	system	disorders (a	assessed with: St	udy-specific re	port of advers	e event)			·		
125 (1 study) 12 weeks	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	undetected	⊕⊖⊝ <b>VERY LOW</b> <sup>1,3</sup> due to risk of bias, imprecision	0/31 (0%)	1/94 (1.1%)	RR 1.01 (0.04 to 24.19)	O per 1000 Moderat	ee
Vascula 125		ers (assessed v	vith: Study-specif	very	verse event) undetected	⊕⊖⊖⊖	0/31	1/94	RR 1.01	Study p	opulation
-	serious <sup>1</sup>	no serious		3		VEDV L 014/1.3	(00/)	(4 40/)	(0.04+-		
(1 study)	serious	inconsistency	indirectness	serious <sup>3</sup>		VERY LOW <sup>1,3</sup> due to risk of bias,	(0%)	(1.1%)	(0.04 to 24.19)	0 per 1000	-
125 (1 study) 12 weeks	serious			serious <sup>3</sup>		due to risk of	(0%)	(1.1%)	`	0 per	-

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

		Qı	ality assessn	nent			Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	bias	Overall quality of evidence	Study e With Control	With Adverse events	(95% CI)	Anticip Risk with Control	Risk difference with Adverse events associated with combined ginkgo biloba and risperidone versus combined placebo and risperidone

								risperidone			(95% CI)
Daytime	drowsi	ness (assessed	with: Study-spe	cific side effec	t checklist)				<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>	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			2.26)	292 per 1000	32 fewer per 1000 (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	ness (assessed	d with: Study-spe	cific side effec	ct checklist)	1			<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>	0/24 (0%)	2/23 (8.7%)	<b>RR 5.21</b> (0.26 to	Study p	opulation
10 weeks						due to risk of bias,			102.98)	0 per 1000	-
						imprecision				Modera	te
										0 per 1000	-
Constipa	ation (ass	sessed with: Stud	y-specific side ef	fect checklist)			ļ.	•		<u> </u>	1
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>	3/24 (12.5%)	3/23 (13%)	<b>RR 1.04</b> (0.23 to	Study p	oopulation
10 weeks		inconsistency	indirectiness.	Schools		due to risk of bias, imprecision	(12.070)	(1070)	4.65)	125 per 1000	5 more per 1000 (from 96 fewer to 456 more)
						Imprecioion				Modera	te
										125 per 1000	5 more per 1000 (from 96 fewer to 456 more)
Dizzines	S (assesse	 ed with: Study-spe	Lecific side effect of	L checklist)	ļ	<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>	3/24 (12.5%)	1/23 (4.3%)	<b>RR 0.35</b> (0.04 to	Study p	opulation	
10 weeks						due to risk of bias, imprecision	(,	()	3.11)	125 per 1000	81 fewer per 1000 (from 120 fewer to 264 more)	
										Moderate		
										125 per 1000	81 fewer per 1000 (from 120 fewer to 264 more)	
Slow mo	vement	(assessed with:	Study-specific si	de effect checl	klist)		-		<del>-                                    </del>	+		
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>	1/24 (4.2%)	2/23 (8.7%)	RR 2.09 (0.2 to	Study p	opulation	
10 weeks				00.1000		due to risk of bias, imprecision	(= /3)	(6.1.76)	21.48)	42 per 1000	<b>45 more per 1000</b> (from 33 fewer to 853 more)	
										Modera	te	
										42 per 1000	46 more per 1000 (from 34 fewer to 860 more)	
Nervous	ness (as	sessed with: Stud	y-specific side e	ffect checklist)								
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>	1/24 (4.2%)	5/23 (21.7%)	RR 5.22 (0.66 to	Study p	opulation	
10 weeks		inconsistency	muncouries.	Solious		due to risk of bias, imprecision	(4.270)	(2 70)	41.32)	42 per 1000	<b>176 more per 1000</b> (from 14 fewer to 1000 more)	
										Modera	te	
										42 per 1000	177 more per 1000 (from 14 fewer to 1000 more)	
Restless	ness (as	L ssessed with: Stud	l dy-specific side e	ffect checklist	)	1				ļ		

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>	5/24 (20.8%)	3/23 (13%)	<b>RR 0.63</b> (0.17 to	Study p	opulation
10 weeks		inconsistency		Conocc		due to risk of bias, imprecision	(20.070)	(10%)	2.33)	208 per 1000	77 fewer per 1000 (from 173 fewer to 277 more)
					Moderate						
										208 per 1000	<b>77 fewer per 1000</b> (from 173 fewer to 277 more)
Increased	d appet	ite (assessed wi	th: Study-specifi	c side effect cl	hecklist)	<b>!</b>			1	· ·	<del>-</del>
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	ppetite	(assessed with:	L Study-specific si	de effect chec	klist)						
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>	4/24 (16.7%)	3/23 (13%)	RR 0.78 (0.2 to	Study p	opulation
10 weeks				00.1000		due to risk of bias, imprecision	(101170)	(1070)	3.12)	167 per 1000	<b>37 fewer per 1000</b> (from 133 fewer to 353 more)
										Modera	te
										167 per 1000	<b>37 fewer per 1000</b> (from 134 fewer to 354 more)
Fatigue (a	l assessed v	l vith: Study-specifi	I c side effect che	cklist)							

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>	2/24 (8.3%)		<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)
										Modera	te
										83 per 1000	<b>134 more per 1000</b> (from 37 fewer to 924 more)
Diarrhoe	<b>a</b> (assess	ed with: Study-spe	ecific side effect	checklist)		<b>'</b>	l		I	ı	
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>	3/24	3/23 6) (13%)	RR 1.04 (0.23 to	Study population	
10 weeks		inconsistency		School		due to risk of bias, imprecision	(12.070)	(10%)	4.65)	125 per 1000	5 more per 1000 (from 96 fewer to 456 more)
										Modera	te
										125 per 1000	5 more per 1000 (from 96 fewer to 456 more)
Twitches	(assesse	d with: Study-spec	cific side effect c	hecklist)	l		ı		I	l	
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>	0/24 (0%)	3/23 (13%)	RR 7.29 (0.4 to	Study p	opulation
10 weeks		inconsistency	indirectriess	Schous		due to risk of bias,	(070)	(1070)	133.82)	0 per 1000	-
						imprecision				Modera	te
										0 per 1000	-
Dry mou	th (assess	sed with: Study-sp	ecific side effect	checklist)	1	<u> </u>	1				
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>	1/24 (4.2%)	1/23 (4.3%)	RR 1.04 (0.07 to	Study p	opulation
10 weeks		,				due to risk of bias,	, ,	,	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 v	with: Study-spec	ific side effect	checklist)				<u> </u>		<del> </del>
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>	3/24 (12.5%)	1/23	RR 0.35 (0.04 to	Study p	opulation
10 weeks		inconsistency	indirectriess	Schous		due to risk of bias, imprecision	(12.370)	(4.570)	3.11)	125 per 1000	<b>81 fewer per 1000</b> (from 120 fewer to 264 more)
										Modera	te
										125 per 1000	<b>81 fewer per 1000</b> (from 120 fewer to 264 more)
Sore thr	oat/tong	J <b>ue</b> (assessed w	I ith: Study-specif	ic side effect c	hecklist)		<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>	5/24 (20.8%)	1/23	RR 0.21 (0.03 to	Study p	opulation
10 weeks		inconsistency		Solious		due to risk of bias, imprecision	(20.070)	(4.070)	1.65)	208 per 1000	<b>165 fewer per 1000</b> (from 202 fewer to 135 more)
										Modera	te
										208 per 1000	<b>164 fewer per 1000</b> (from 202 fewer to 135 more)
Abdomi	nal pain	(assessed with: S	L Study-specific sid	le effect check	l dist)	1	l				
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>	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)

			Moder	ate
			125 pe 1000	r 38 fewer per 1000 (from 109 fewer to 349 more)

<sup>&</sup>lt;sup>1</sup> Risk of detection bias is unclear/unknown for adverse event outcomes as it is unclear if 10 weeks is a sufficient follow-up duration to observe potential longer-term adverse events, the reliability and validity of the checklist used to record adverse events is unclear, and the checklist is based on parental report and parents will be non-blind to other potentially confounding factors

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

		Q	uality asses	sment			Summary of Findings						
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall quality of evidence	Study e	With With Adverse events		Control associated with gluten-		Anticipated a Risk with Control	Risk difference with Adverse events associated with gluten-free and casein-free diet (95% CI)
Any adve	rse e	vent (assessed	with: Outcome	e measure not	reported)				·				
72 (1 study) 35 weeks						See comment	0/34 (0%)	0/38 (0%)	not pooled	Effect size not estimable	Effect size not estimable		

<sup>&</sup>lt;sup>2</sup> Events<300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

### 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 (£)1	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>	Measure of outcome:     proportion of children     with clinically     meaningful     improvement expressed     by an ADOS-G score     improvement ≥ 4 points     Time horizon: 13 months     ICER and probabilistic     analysis based on     bootstrapping     techniques	£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).
- 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

<sup>2.2</sup> Clinical / economic question: antipsychotics versus placebo for the management of behaviour that challenges in children and young people with autism

Evide	vidence 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						

<sup>1.</sup> Costs expressed in 2012 UK pounds

<sup>2.</sup> Only intervention costs considered consisting of drug acquisition costs, efficacy data from 4 trials, PSA performed

<sup>3.</sup> 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>	Cost analysis     Time horizon: 18 years	-£99,039	NA	NA	Not estimated					

<sup>1.</sup> Costs converted and uplifted to 2012 UK pounds – converted using PPP exchange rates (<a href="http://www.oecd.org/std/ppp">http://www.oecd.org/std/ppp</a>) and UK PPS local authorities adults and children's services pay and prices inflation index (Curtis, 2012).

<sup>2.</sup> 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

<sup>3.</sup> 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>	Measure of outcome: number of dependency- free years     Time horizon: up to 65 years of age	-£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%)						

<sup>1.</sup> Costs converted and uplifted to 2012 UK pounds – converted using PPP exchange rates (<a href="http://www.oecd.org/std/ppp">http://www.oecd.org/std/ppp</a>) and UK PPS local authorities adults and children's services pay and prices inflation index (Curtis, 2012).

<sup>2.</sup> Economic model over lifetime, provincial government resource use estimates and prices, all relevant costs included, but efficacy estimates were judgements based on literature review

<sup>3.</sup> 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						

<sup>1.</sup> Costs converted and uplifted to 2012 UK pounds – converted using PPP exchange rates (<a href="http://www.oecd.org/std/ppp">http://www.oecd.org/std/ppp</a>) and UK PPS local authorities adults and children's services pay and prices inflation index (Curtis, 2012).

<sup>2.</sup> 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

<sup>3.</sup> 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 (£)1	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						

<sup>1.</sup> Costs expressed in 2012 UK pounds

<sup>2.</sup> Only intervention costs considered, resource use from RCTs included in guideline systematic review, efficacy data from 2 trials, PSA performed

<sup>3.</sup> NHS & PSS perspective, QALYs based on HUI3 (valuations elicited from Canadian population)