APPENDIX 14D: CLINICAL EVIDENCE –STUDY CHARACTERISTICS TABLES: INTERVENTIONS AIMED AT AIMED AT ASSOCIATED FEATURES OF AUTISM AND COEXISTING PROBLEMS OR DISORDERS

1.1 CHARACTERISTICS OF INCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT ADAPTIVE BEHAVIOUR

1.1.1 DAWSON2010

Study ID	DAWSON2010
Bibliographic reference	Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the early start denver model. Pediatrics. 2010;125:e17-e23.
Methods	**Allocation:** Randomised **Matching:** Stratified randomisation - participants stratified into two groups based on IQ (<55 and 55) and gender, and within each of these strata randomisation was conducted by using random permuted blocks of four **Blindness:** Outcomes were assessed by blind examiners. However, some of the outcomes relied on parent report and parents were not blind. Intervention administrators and child participants were also non-blind. **Setting:** Academic research (university) and home **Raters:** Clinicians and parent-report **Country:** USA
Participants	**Diagnosis:** Autistic disorder (on the ADI-R), autism or ASD (on the ADOS), and a clinical diagnosis based on DSM-IV; 81% had a diagnosis of autistic disorder and 19% had a diagnosis of PDD-NOS **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Clinical diagnosis based on all available information including ADI-R and ADOS scores **N:** 48 **Age:** 1.5-2.5 years (mean: 1.95 years) **Sex:** 29% female **Ethnicity:** 73% white **IQ:** Mean of 60.2 (based on Mullen Scales of Early Learning: Early-learning composite score) **Inclusion criteria:** Inclusion criteria included: age below 30 months at entry, meeting criteria for autistic disorder on the ADI-R, meeting criteria for autism or ASD on the ADOS, and a clinical diagnosis based on DSM-IV criteria using all available information; residing within 30 minutes of the University of Washington; and willingness to participate in a 2-year intervention **Exclusion criteria:** Exclusion criteria included: a neurodevelopmental disorder of known etiology (for example, fragile X syndrome); significant sensory or motor impairment; major physical problems such as a chronic serious health condition; seizures at time of entry; use of psychoactive medications; history of a serious head injury and/or neurologic disease; alcohol or drug exposure during the prenatal period; and ratio IQ below 35 as measured by mean age equivalence score/chronological age on the visual reception and fine motor subscales of the Mullen Scales of Early Learning
Interventions	**Experimental Intervention: Early Start Denver Model** - based on developmental and applied behavioral analytic principles. A detailed intervention manual and curriculum were used (Rogers & Dawson,

	2009).Teaching strategies were consistent with the principles of ABA, such as the use of operant conditioning, shaping, and chaining and each child's plan was individualized. **Delivery of intervention:** Delivered by trained therapists and parents **Format or method of administration:** Family format **Intensity:** 10 sessions/20 hours per week over 2 year period were offered and parents were encouraged to use strategies at home. The actual mean intensity of the intervention was 1581 hours with a trained therapist and parents reported spending 1695 hours using Early Start Denver Model strategies. **Duration of intervention:** 2 years **Total duration of follow-up:** 2 years
Outcomes	**Direct outcome:** **Coexisting problem or disorder: Adaptive behaviour** (as measured by VABS total score, VABS communication subscale, VABS socialization subscale and VABS Daily Living Skills subscale) **Indirect outcomes:** **Core autism feature: Overall autistic behaviours** (as measured by the Autism Diagnostic Observation Schedule [ADOS/ADOS-G] - Standardised severity score); Autism DSM-IV diagnosis (as measured by dichotomous rates of improvement in diagnosis from autistic disorder to PDD-NOS); **Restricted interests and rigid and repetitive behaviours** (as measured by the Repetitive Behavior Scale [RBS]) **Coexisting problems or disorders: Speech and language** (as measured by the MSEL - Receptive language and Expressive language subscales); **IQ** (as measured by the MSEL - Early-learning composite score); **fine and gross motor skills** (as measured by the Mullen Scales of Early Learning [MSEL] - Fine Motor subscale and the VABS - Motor Skills subscale)
Study Design	RCT
Source of funding	National Institute of Mental Health grant (U54MH066399 to Dr. Dawson)
Limitations	1. Risk of selection bias is unclear/unknown as unclear randomisation method and insufficient detail reported with regards to allocation concealment 2. High risk of response bias as participants were not blind to group assignment 3. High risk of performance bias as intervention administrators were not blind to group assignment 4. Risk of detection bias is different for different outcomes and is unclear/unknown for the Vineland Adaptive Behaviour Scale (VABS) as although there were blinded outcome assessor this outcome measure is based on interview with non-blind parent rather than direct behavioural observation, high risk for Repetitive Behavior Scale (RBS) as parent-completed and high risk for DSM-IV clinical diagnosis as blinding unclear
Notes	This trial is registered on ClinicalTrials.gov, Study NCT00090415. No outcomes reported for "observations of parent/child interaction" which was listed as primary outcome on ClinicalTrials.gov. However, Dawson contacted and reported that due to reductions in the budget for the NIH grant that supported this project, parent-child interactions were not measured for this study.

1.1.2 PAJAREYA2011

Study ID	PAJAREYA2011
Bibliographic reference	Pajareya K, Nopmaneejumruslers K. A pilot randomized controlled trial of DIR/Floortime parent training intervention for pre-school children with autistic spectrum disorders. Autism. 2011;15:563-577.
Methods	**Allocation:** Randomised **Matching:** Stratified randomisation based on age (24-47 months and 48-72 months) and autism severity (CARS scores 30-40 and 41-60) **Blindness:** Intervention administrator and parent participants non-blind. Clinician-rated outcome measures rated by a blind assessor **Setting:** Home **Raters:** Parent- and clinician-rated **Country:** Thailand
Participants	**Diagnosis:** DSM-IV-TR ASD (72% autism, 28% PDD-NOS) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis confirmed by a developmental paediatrician (no further detail reported) **N:** 32 **Age:** Range not reported but inclusion criteria 2-6 years (mean: 4.5 years) **Sex:** 13% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: met DSM-IV clinical criteria for ASD corroborated by a developmental paediatrician; were aged 2-6 years **Exclusion criteria:** Children were excluded if: they had any additional medical diagnosis (including genetic syndromes, seizures or diagnosed hearing or visual impairment); they would not able to attend follow-up visits due to geographical location; their parents were illiterate or had known chronic psychiatric or physical illness
Interventions	**Experimental Intervention: Developmental, Individual-Difference, Relationship-Based (DIR)/Floortime intervention.** Manualized intervention (Greenspan & Lewis, 2005) involving parent training (with no contact with the child) with parents receiving didactic instruction about the principles of the intervention and psychoeducation about ASD and one-on-one interactive home visits. During the home visits parents were trained to observe their child's cues and follow the child's lead. Techniques for training parents included modelling, observation of the parent implementing techniques and feedback. Parents were taught to implement the Floortime techniques appropriate to their child's current level of functional development as follows: If their child could not calm down or be warm and loving, parents encouraged to join their child in an activity their child enjoyed and maintain mutual attention and engagement (Floortime level 1); if their child could not engage in two-way gestural communication, did not express many subtle emotions or could not open and close many gestural communications in a row, parents were encouraged to use simple face-to-face communication (with an animated face) with increasing two-way communication (Floortime level 2); if their child could not engage in pretend play and/or use words to convey intentions or wishes, parents were encouraged to help their child to express needs, wishes and feelings through pretend play and using their ideas in daily conversation

	(Floortime level 3); and if the child could not connect thoughts logically and hold a conversation for a period of time, parents were encouraged to help their child become a logical and critical thinker (Floortime level 4) **Delivery of intervention:** Intervention delivered by the investigator (first author) **Format or method of administration:** Family-based (parent-child dyad) **Intensity:** Planned intensity of 260 hours (20 hours/week) with actual mean intensity of 197.6 hours (15.2 hours/week) **Duration of intervention:** 13 weeks **Total duration of follow-up:** 13 weeks
Outcomes	**Direct outcome** **Coexisting problem or disorder: Adaptive behaviour** (as measured by the Functional Emotional Developmental Questionnaires [FEDQ] and Functional Emotional Assessment Scale [FEAS]) **Indirect outcome** **Core autism feature: Overall autistic behaviours** (as measured by Childhood Autism Rating Scale [CARS] - Total score)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators non-blind 3. High risk of response bias as participants non-blind 4. Risk of detection bias is different for different outcomes but high risk for parent-rated FEDQ as no independent reliability and validity data for the Thai-version of this outcome measure and the questionnaire was parent-rated and parents were involved in the intervention so the outcome assessment was non-blind 5. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Contacted author regarding endpoint rather than change scores and the data requested was supplied

1.1.3 RICKARDS2007/2009

Study ID	RICKARDS2007/2009
Bibliographic reference	Rickards AL, Walstab JE, Wright-Rossi RA, Simpson J, Reddihough DS. A randomized, controlled trial of a home-based intervention program for children with autism and developmental delay. Journal of Developmental and Behavioral Pediatrics. 2007;28:308-316. Rickards AL, Walstab JE, Wright-Rossi RA, Simpson J, Reddihough DS. One-year follow-up of the outcome of a randomized controlled trial of a home-based intervention programme for children with autism and developmental delay and their families. Child: Care, Health and Development. 2009;35:593-602.
Methods	**Allocation:** Randomised

	Matching: Matched into pairs based on developmental quotient **Blindness:** Participants, parents and intervention administrators were non-blind. The outcome assessor was blinded (although some outcome measures relied on non-blind parental report) **Setting:** Early intervention centre and home-based **Raters:** Parent-report and blinded psychologist **Country:** Australia
Participants	**Diagnosis:** 66% of the sample (N=39) had a DSM-IV diagnosis of ASD **Coexisting conditions:** 15% had developmental delay, 19% had language delay, 2% had velocardiofacial syndrome, 2% had Fanconi anemia with hydrocephalus, 2% had Landau-Kleffner syndrome, 2% had Williams syndrome, 2% had Klinefelter syndrome, 2% were post-meningitis with hydrocephalus, and 2% had brain malformation **Qualifying Diagnostic Assessment:** Participants with ASD had been diagnosed by an autism assessment team according to DSM-IV criteria or more recently using the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Obseravtion Schedule (ADOS) **N:** 65 (N=65 were randomised, however, demographic and efficacy data were only reported for the completers, N=59) **Age:** 3-5 years (mean: 3.7 years) **Sex:** 20% female **Ethnicity:** Not reported **IQ:** Range not reported (mean: 60.4) **Inclusion criteria:** Children were included if they: were enrolled at an early intervention centre (Uncle Bob's Child Development Center or Westarc Early Intervention Center, Melbourne) for at least a year during the period May 2000 to December 2003, enrolment criteria for the early intervention centres were delays in two or more areas of development based on play observations, parental interview, and information supplied by the referring agency **Exclusion criteria:** Children were excluded if: they had cerebral palsy; their family had inadequate English-language skills to enable them to understand the home-based teacher and to complete the questionnaires
Interventions	**Experimental Intervention: Combined parent training and early intervention centre programme:** Both experimental and control group children participated in an early intervention centre programme that involved individualized programmes that covered all aspects of development. Training techniques used for the centre-based programmes included chaining, repetition, reward, play-based learning, communication systems (such as the picture exchange communication system), behavior modification techniques, speech and language and occupational therapy. The experimental group also received an additional home-based parent training intervention. Behavioural targets for the parent training intervention were jointly agreed between the family and intervention administrators and the home-based teacher worked with the child, discussed strategies (similar to those used in the centre) and helped the parents to understand the meaning of the child's challenging behaviour, demonstrated strategies to parents, and assisted parents in adapting the home environment for the needs of the child, for instance, the use of communication aids. **Control Intervention: Early intervention centre programme only** **Delivery of intervention:** Intervention administrators were specialist

	preschool teachers who had teaching degrees in early childhood education and postgraduate training in special education and experience in the field **Format or method of administration:** Individual and family-based **Intensity:** Actual intensity for the centre-based programme was not reported but planned intensity was 200 hours (5 hours/week). Actual number of sessions, rather than number of hours, was reported for the additional parent training intervention but number of hours was estimated as the paper reports that each session was 1-1.5 hours, thus estimated intensity for the additional parent training component was 26-60 hours (mean: 43.5), and total hours of intervention for the experimental group was 226-260 hours (mean: 243.5 hours; 6 hours/week) **Duration of intervention:** 40 weeks (over 12-month period) **Total duration of follow-up:** 108 weeks (12-month intervention, 13-month post-intervention assessment and post-intervention follow-up 12 months later)
Outcomes	**Direct outcome:** **Coexisting problem or disorder: Adaptive behaviour** (as measured by the Vineland Adaptive Behaviour Scale [VABS] - Total score, and the Bayley Behavior Rating Scale [BRS] -Total score) **Indirect outcomes:** **Behaviour that challenges** (as measured by the Behavior Screening Questionnaire [BSQ] - Total score, and the Preschool Behavior Checklist (PBCL) - Total score [ASD-only data available]) **Coexisting problem or disorder: IQ** (as measured by the Bayley Scales of Infant Development-Second Edition or Wechsler Preschool and Primary Scale of Intelligence-Revised [WPPSI-R] [ASD-only data available])
Study Design	RCT
Source of funding	Murdoch Children's Research Institute and the Jack Brockhoff Foundation
Limitations	1. High risk of performance bias as the intervention administrators were non-blind 2. High risk of response bias as the participants were non-blind 3. Risk of detection bias is unclear/unknown as although there was a blinded psychologist outcome assessor many of the outcome measures relied on non-blind parental report 4. High risk of selective reporting bias as data were not reported for the family outcome measures (the Questionnaire of Resources and Stress, QRS-F; the Family Empowerment Scale, FES; or the Family Support Scale (FSS) and authors did not respond to request for missing outcome data
Notes	This study was included as >50% of the sample had a diagnosis of autism, however, where possible data were extracted for the ASD-only group. The authors were contacted to request complete disaggregated data, however, there was no reply. Where disaggregated data could not be obtained the study was downgraded in GRADE on the basis of indirectness due to the population (as the sample included participants with developmental delay or language delay without autism). Also requested missing outcome data from the authors but no reply.

1.1.4 ROBERTS2011

Study ID	ROBERTS2011
Bibliographic reference	Roberts J, Williams K, Carter M, Evans D, Parmenter T, Silove N, et al. A randomised controlled trial of two early intervention programs for young children with autism: centre-based with parent program and home-based. Research in Autism Spectrum Disorders. 2011;5:1553-1566.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Outcome assessors were blinded but intervention administrators, participants and parents were non-blind and many of the outcome measures relied on parental interview **Setting:** Home-based versus centre-based **Raters:** Parent-reported (one child assessment measure but identity of outcome assessor not reported) **Country:** Australia
Participants	**Diagnosis:** DSM-IV ASD (according to ADOS 77% autistic disorder, 14% ASD and 9% non-ASD) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis made by referring clinician was corroborated using the Autism Diagnostic Observation Schedule (ADOS) **N:** 67 (N=67 randomised but demographic and outcome data only reported for completers N=57) **Age:** 2-5 years (mean: 3.5 years) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** Range not reported (mean: 61.8 as measured by the Griffiths Mental Development Scales - Extended Revised (GMDS): Developmental quotient) **Inclusion criteria:** Children were included if they: were of pre-school age; had a DSM-IV diagnosis of autistic disorder, Asperger's disorder or PDD-NOS made by the referring medical practitioner and/or psychologist; lived within a reasonable distance of a centre-based group; were judged by parents and staff to be ready for a centre-based programme **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Home-based Early Behavioural Intervention (EBI)** 'Building Blocks' programme. This intervention was individualized and delivered in the home to both the child and their parent/s. Intervention targets included behaviour management, functional communication skills, social development, attending and play skills, sensory processing issues, self-care skills, motor skills and academic skills. The intervention administrator trained parents to work effectively with their child using techniques including direct modelling of skills and constructive feedback to parents. **Control Intervention: Centre-based EBI.** This intervention involved group-based playgroup sessions for the children and concurrent group-based parent support and training groups. The playgroup programme was run according to a condensed preschool program manual which aimed to prepare children for integration into regular preschool settings by focusing on the development of social play skills, functional communication skills and participation in small group activities. The parent training and support groups were also run according to a manual and intended to provide parents with an opportunity to

	meet with other parents and professionals and to discuss a range of set topics (prioritised according to interest and need) including positive behaviour support, communication, self-care issues, school options, specialist services and sensory issues **Delivery of intervention:** Intervention administered by multidisciplinary team including teachers, speech pathologists, occupational therapists and psychologists. Centre-based intervention delivered in groups of 4-6. **Format or method of administration:** Family-based (1:1) for home-based intervention and group-based for centre-based intervention **Intensity:** Actual intensity not reported but planned intensity was 40 hours (2 hours/fortnightly) for the home-based intervention and 80 hours (2 hours/weekly) for the centre-based intervention **Duration of intervention:** 40 weeks **Total duration of follow-up:** 40 weeks
Outcomes	**Direct outcome:** **Coexisting problems or disorders: Adaptive behaviour** (as measured by the Vineland Adaptive Behaviour Scale [VABS] - Communication and Socialization subscales; and the Developmental Behaviour Checklist [DBC] - Total score) **Indirect outcomes:** **Coexisting problems or disorders: Speech and language** (as measured by the Reynell Developmental Language Scale - Comprehension and Expressive Language subscales; and the Pragmatics Profile - Total Q range) **Impact on the family**: Family quality of life (as measured by Beach Family Quality of Life Questionnaire - Total score and Family interaction, Parenting, Emotional wellbeing, Physical wellbeing and Disability support subscales); Parental coping skills (as measured by study-specific Parent Perception Questionnaire - Total score and Confidence, Coping, Knowledge, Understanding, Family issues and Planning subscales); Parental stress (as measured by the Parenting Stress Index [PSI] - Total score and Defensive responding, Parental distress, Parent-child dysfunctional interaction and Difficult child subscales)
Study Design	RCT
Source of funding	Australian Research Council Linkage Projects grant (No. LP0562663) in conjunction with Autism Spectrum Australia (Aspect)
Limitations	1. Risk of selection bias is unclear/unknown due to lack of comparability between groups at baseline. The experimental group had a higher proportion of children with a diagnosis of autistic disorder than the control group (87.5% relative to 69%) and the control group had a higher proportion of non-ASD diagnoses (17.2% relative to 0%). The experimental group also had a lower Griffiths developmental quotient score than the control group (57 relative to 66.5) 2. High risk of performance bias as intervention administrators were non-blind 3. High risk of response bias as participants and parents were non-blind 4. High risk of detection bias as, despite blinding outcome assessors, all but one of the outcome measures 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. There were also reliability and validity concerns for the Parent Perception Questionnaire as this was a study-specific, and non-standardized, measure

	5. Risk of selective reporting bias is unclear/unknown as the trial protocol was not registered on ClinicalTrials.gov or ISRCTN databases
Notes	The paper reports data fro three arms. However, data could not be extracted for the waitlist control group as allocation to this group was not randomised.

1.1.5 SMITH2000

Study ID	SMITH2000
Bibliographic reference	Smith T, Groen AD, Wynn JW. Randomized trial of intensive early intervention for children with pervasive developmental disorder. American Journal on Mental Retardation. 2000;105:269-285.
Methods	**Allocation:** Randomised **Matching:** Matched on IQ **Blindness:** Standardized tests were administered by doctoral students in clinical psychology who were blind to group assignment and treatment history. However, some of the outcome measures used parent or teacher report and parents and teachers were not blind. Intervention administrators and child participants were also non-blind. **Setting:** Experimental group had intervention administered in the home and then (after meeting a number of behavioural criteria) had intervention administered in group settings, such as classrooms. The setting for the control group was home-based. **Raters:** Clinician-rated standardized scales, parent interview and parent- and teacher-completed checklists **Country:** USA
Participants	**Diagnosis:** 50% diagnosed with autism and 50% diagnosed with PDD-NOS **Coexisting conditions:** 11% of participants had motor delays and 7% had medical conditions (skull fracture and tubercular meningitis) **Qualifying Diagnostic Assessment:** Diagnosis was made independently of the study by licensed psychologists at the California State Regional Centers (a state agency that coordinates services for individuals with developmental disabilities) **N:** 28 **Age:** Range not reported (mean age: 3 years) **Sex:** 18% female **Ethnicity:** 50% white **IQ:** Range not reported (mean: 51) **Inclusion criteria:** Child participants were required to: have a chronological age (CA) between 18 and 42 months at the time of referral; live within a one-hour drive of the research/treatment site (the UCLA Young Autism Project); have an IQ ratio between 35 and 75; and have a diagnosis of autism or pervasive developmental disorder NOS **Exclusion criteria:** Participants were excluded on the basis of major medical problems other than autism or mental retardation (e.g. cerebral plasy, blindness or deafness, known genetic disorders such as Down syndrome, or neurological conditions such as uncontrolled seizure disorders)
Interventions	**Experimental Intervention: Early Intensive Behavioural Intervention (EIBI).** Children received intervention based on Lovaas et al.'s (1981) manual and

	based on the principles of ABA. The intervention began with one-to-one, discrete trial, treatment delivered by a student therapist in the child's home and with parental involvement. Treatment progressed gradually from relatively simple tasks (for example, responding to basic requests made by an adult) to more complex tasks (such as conversing). Once the child had achieved certain behavioural criteria (speaking in short phrases; cooperating with verbal requests from others; playing appropriately with toys; and had acquired self-care skills such as dressing and toileting) the intervention was implemented away from the home and in group settings such as classrooms. This shift usually occurred approximately one year after onset of intervention but there was large variation across children. **Control intervention: Parent training.** Parent training was also based on Lovaas et al.'s (1981) manual. Parents were trained in the basic principles of discrimination learning, discrete trial formats and functional analyses of maladaptive behaviours and applied these techniques to help their children acquire parent-identified skills. **Delivery of intervention:** The intervention was delivered by teams of 4-6 student therapists **Format or method of administration:** The format was individual/parent **Intensity:** Experimental group: Intensive treatment was defined as 30 hours/week but the actual intervention intensity was 15 hours/week. The total intensity was 1141.5-5451.8 (mean: 2137.9) hours. Control group: Children's families received two sessions per week of parent training, totaling 5 hours per week. Range of intensity was 65-195 hours (but no mean reported) **Duration of intervention:** Experimental group: 145 weeks; Control group: 39 weeks **Total duration of follow-up:** Follow-up evaluations occurred when children were aged 7-8 years. Total length of follow-up was therefore up to 260 weeks
Outcomes	**Direct outcomes:** **Coexisting problems or disorders: Adaptive behaviour** (as measured by VABS - Adaptive behaviour composite, Communication, Socialization and Daily Living Skills subscales) **Indirect outcomes:** **Behaviour that challenges** (as measured by Achenbach Child Behavior Checklist [Parent- and teacher- report] - Aggression subscale) **Coexisting problems or disorders: Speech and language** (as measured by the Reynell Developmental Language Scale - Total score, Comprehension subscale and Expressive Language subscale); **IQ** (as measured by the Bayley Scales of Infant Development - Mental Development Index and Wechsler Individualized Achievement Test [WIAT]) **Impact on family** (as measured by Family Satisfaction Questionnaire - Overall Opinion subscale). However, an effect size can not be calculated from this data as a standard deviation value is reported as 0.
Study Design	RCT
Source of funding	Department of Education Grant No. H133G80103 (Intensive Early Intervention for Children with Mild to Moderate Mental Retardation) and UCLA Regents Account No. 4-444040-LS-60090
Limitations	1. High risk of response bias as participants were not blind to group assignment

	2. High risk of performance bias as intervention administrators were not blind to group assignment 3. Risk of detection bias different for different outcome measures: Unclear/unknown for the Vineland Adaptive Behaviour Scale (VABS) as although this outcome measure administered by doctoral students in clinical psychology who were blind to group assignment and treatment history, the outcome measure was based on interview with non-blind parent rather than direct behavioural observation. High risk of detection bias for Achenbach Child Behavior Checklist and Family Satisfaction Questionnaire as completed by non-blind parents or teachers and outcome measure either not validated in an autistic population or the psychometric properties of the outcome measure have not been tested. Risk of detection bias is also unclear/unknown for the Reynell Developmental Language Scale as although this outcome measure is commonly administered to children with autism it has not been validated in an autistic population and participants fall outside the age range for this test at endpoint. 4. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered
Notes	Not applicable

1.2 CHARACTERISTICS OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT ADAPTIVE BEHAVIOUR

1.2.1 DIGGLE2002

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.2 EIKESETH2002/2007

Reason for exclusion	Non-randomised group assignment

1.2.3 EIKESETH2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.4 ELDEVIK2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.5 ESCALONA2002

Reason for exclusion	Experimental rather than clinical effectiveness study

1.2.6 FAVA2011

Reason for exclusion	Non-randomised group assignment

1.2.7 FIELD2001

Reason for exclusion	Experimental rather than clinical effectiveness study

1.2.8 FREITAG2012

Reason for exclusion	No control group

1.2.9 GABRIELS2012

Reason for exclusion	Non-independent controls

1.2.10 HAGNER2012

Reason for exclusion	Efficacy data cannot be extracted

1.2.11 HEIMANN2006

Reason for exclusion	Experimental rather than clinical effectiveness study

1.2.12 INGERSOLL2010

Reason for exclusion	Outcomes reported are outside the scope

1.2.13 KAGOHARA2010

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.14 KAMPS1992

Reason for exclusion	Less than 50% of the sample had a diagnosis of autism

1.2.15 LUCKETT2007

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.16 MA2009

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.17 MATSON2012

Reason for exclusion	Non-systematic review

1.2.18 MCCONACHIE2007

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.19 MEYER1987

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.2.20 OSPINA2008

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.21 OZONOFF1998

Reason for exclusion	Non-randomised group assignment

1.2.22 PAJAREYA2012

Reason for exclusion	No control group data

1.2.23 PALMEN2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.24 PANERAI2002

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.2.25 PANERAI2009

Reason for exclusion	Non-randomised group assignment

1.2.26 PARSONS2011

Reason for exclusion	Systematic review and data could not be extracted as qualitative review

1.2.27 RAMDOSS2012B

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.28 REED2010

Reason for exclusion	Non-randomised group assignment

1.2.29 ROTHENBERG2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.30 SALLOWS2005

Reason for exclusion	The planned comparison of intensive versus non-intensive behavioural treatment was not carried out. Instead, data from the two groups were combined and a pre- to post-comparison made. The lack of a control group in this post-hoc design meant that efficacy data could not be extracted

1.2.31 SEIDA2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.32 SPRECKLEY2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.33 TAYLOR2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.34 TSANG2007

Reason for exclusion	Non-randomised group assignment

1.2.35 VANADEL2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.3 REFERENCES OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT ADAPTIVE BEHAVIOUR

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1.4 CHARACTERISTICS OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT ADAPTIVE BEHAVIOUR

1.4.1 ADAMS2004

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.4.2 MUNASINGHE2010

Reason for exclusion	Data cannot be extracted due to cross-over design and unavailability of first phase data

1.5 REFERENCES OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT ADAPTIVE BEHAVIOUR

Adams JB, Holloway C. Pilot study of a moderate dose multivitamin/mineral supplement for children with autistic spectrum disorder. Journal of Alternative and Complementary Medicine. 2004;10:1033-1039.

Munasinghe SA, Oliff C, Finn J, Wray JA. Digestive enzyme supplementation for autism spectrum disorders: a double-blind randomized controlled trial. Journal of Autism and Developmental Disorders. 2010;40:1131-1138.

1.6 CHARACTERISTICS OF INCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT SPEECH AND LANGUAGE

1.6.1 GATTINO2011

Study ID	GATTINO2011
Bibliographic reference	Gattino GS, Riesgo RDS, Longo D, Leite JCL, Faccini LS. Effects of relational music therapy on communication of children with autism: a randomized controlled study. Nordic Journal of Music Therapy. 2011;20:142-154.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants and intervention administrators non-blind but independent blinded outcome assessors **Setting:** Outpatient **Raters:** Blinded external investigators (no further detail reported) **Country:** Brazil

Participants	**Diagnosis:** DSM-IV-TR ASD (42% autistic disorder, 50% PDD-NOS, 8% Asperger's disorder) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Childhood Autism Rating Scale adapted for Brazil (CARS-BR) **N:** 24 **Age:** 6-12 years (mean: 9.8 years) **Sex:** 0% female **Ethnicity:** Not reported **IQ:** Not reported (but for N=22 27% LD as assessed using the Raven's Coloured Progressive Matrices for Children) **Inclusion criteria:** Children were included if they: had a DSM-IV-TR diagnosis of autistic disorder, PDD-NOS or Asperger's disorder (corroborated using the CARS); were male; were aged 7-12 years; lived in Porto Alegre or nearby cities; had not previously been treated with any music therapy intervention **Exclusion criteria:** Children were excluded if they: were currently receiving other music therapy; were intolerant to sounds or music or had profound hearing loss
Interventions	**Experimental Intervention: Relational Music Therapy (RMT).** This intervention is based on psychodynamic principles (free association, unconscious conflicts, drive component, transference and counter-transference) and aims to help participants through interactions with the music therapist based around music, for instance, singing, composing, improvising and playing musical games. The music therapist begins each session by providing various instruments on the floor or table and allows the participant to select one or several instruments and the focus is on the actions of the participant with the music therapist taking a non-directive role and prioritising participant initiatives and behavioural observation. The intervention also involves a parent component with parents being encouraged to attend some sessions so that the therapist can observe how the child interacts with his/her family through musical activities **Delivery of intervention:** Delivered by graduate music therapists **Format or method of administration:** Individual **Intensity:** Actual intensity not reported but planned intensity was 8 hours (16 weekly sessions; 0.5 hours/week) **Duration of intervention:** 30 weeks (due to school activities and vacations, the 16 sessions were completed over seven months) **Total duration of follow-up:** 30 weeks
Outcomes	**Direct outcome:** **Coexisting problem or disorder: Speech and language, including non-verbal** (as measured by the Childhood Autism Rating Scale [CARS] - Verbal communication and Non-verbal communication subscales) **Indirect outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by CARS - Social communication [composite score from imitation, verbal and non-verbal communication, consistency of intellectual responses and general impressions subscales])
Study Design	RCT
Source of funding	FIPE/HCPA (project no. 08006) and the Brazilian Research Council (CNPq)

Limitations	1. High risk of performance bias as intervention administrators non-blind 2. High risk of response bias as participants non-blind
Notes	Trial protocol registered on the Australian New Zealand Clinical Trials Registry (Study ID ACTRN12608000625370)

1.6.2 HOWLIN2007/GORDON2011

Study ID	HOWLIN2007/GORDON2011
Bibliographic reference	Howlin P, Gordon RK, Pasco G, Wade A, Charman T. The effectiveness of picture exchange communication system (PECS) training for teachers of children with autism: a pragmatic, group randomised controlled trial. Journal of Child Psychology and Psychiatry. 2007;48:473-481. Gordon K, Pasco G, McElduff F, Wade A, Howlin P, Charman T. A communication-based intervention for nonverbal children with autism: what changes? who benefits? Journal of Consulting and Clinical Psychology. 2011;79:447-457.
Methods	**Allocation:** Randomised (randomised in class groups, each including approximately 6 children and 2-3 staff) **Matching:** Stratified according to class size (>=6 children and <6 children) **Blindness:** Non-blind **Setting:** School (specialist education) **Raters:** Investigator-rated **Country:** UK
Participants	**Diagnosis:** ADOS-G autism (89%) or ASD (11%) **Coexisting conditions:** Children had little or no functional language (no more than single words/word approximations) **Qualifying Diagnostic Assessment:** Autism Diagnostic Observation Schedule-Generic (ADOS-G) Module 1 **N:** 88 children (18 classes across 15 schools) **Age:** 3-10 years (mean: 6.8 years) **Sex:** 13% female **Ethnicity:** Not reported **IQ:** Not reported (100% LD) **Inclusion criteria:** Children were included if they: had a formal diagnosis of autism corroborated by the ADOS-G Module 1; had little or no functional language (no more than single words/word approximations); were aged 4-11 years; were in a class with a minimum of 2 other children who also met the inclusion criteria **Exclusion criteria:** Children were excluded if they: showed evidence of sensory impairment; were using PECS beyond Phase 1 (i.e. able to exchange symbols only if prompted); were taught by a teacher who had previously received direct, in-class training/consultancy from PECS consultants
Interventions	**Experimental Intervention: Picture Exchange Communication System (PECS) training for teachers.** Two active arms in the trial (compared to no-treatment control): Immediate treatment (ITG) and delayed treatment (DTG) which differed only in the start point for training with the ITG receiving PECS training immediately after baseline assessment and the DTG receiving PECS

	training 2 terms after baseline assessment. PECS training began with a 2-day workshop (13 hours of training) to which 6 members of staff and 6 parents per class were invited. Training followed the PECS manual (Frost & Bondy, 2002). This workshop was followed (a week later) by the active training period involving 6 half-day consultation visits over the following 5 months to each class. These visits were intended to encourage teachers to facilitate children's use of PECS in various sessions during the school day and PECS consultants recommended and demonstrated strategies to teachers, monitored teachers' progress and provided feedback including written summaries, agreed action points and future goals. **Delivery of intervention:** Intervention was delivered to a mean of 5 children per class and intervention was delivered by expert consultants of Pyramid Educational Consultants UK **Format or method of administration:** Group-based **Intensity:** Actual intensity not reported but planned intensity was approximately calculated at 32.5 hours with an initial 2-day workshop (13 hours) followed by 6 half-day consultations over 5 months **Duration of intervention:** 24 weeks **Total duration of follow-up:** Mean interval between time 1 (baseline) and time 3 (follow-up for ITG and post-treatment for DTG) of: 78 weeks (for ITG); 63 weeks (for DTG); 65 weeks (for no treatment control)
Outcomes	*Direct outcome:* *Coexisting problem or disorder: Speech and language* (as measured by behavioural observations: Frequency (rate per minute) of spontaneous child communicative initiations using picture cards; Frequency (rate per minute) of spontaneous child communicative initiations using speech/vocalisation; Frequency (rate per minute) of spontaneous child communicative initiations using picture cards + speech/vocalisation; Frequency (rate per minute) of spontaneous child communicative initiations for requesting objects; and Frequency (rate per minute) of spontaneous child communicative initiations for requesting social routine or commenting; and British Picture Vocabulary test [BPVS] - Receptive language and Expressive One Word Picture Vocabulary Test [EOWPVT] - Expressive language) **Indirect outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Autism Diagnostic Observation Schedule-Generic (ADOS-G) - Communication and Social Interaction)
Study Design	RCT
Source of funding	The Three Guineas Trust
Limitations	1. Risk of selection bias is unclear/unknown as groups were not comparable at baseline (DTG children had a significantly higher ADOS language impairment score [mean=3.4] than those in the ITG [2.7] and NTG [2.5] and children in the ITG had a significantly higher nonverbal developmental quotient [25.9] than children in the DTG [22.7]) and insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators were non-blind 3. High risk of response bias as participants were non-blind 4. High risk of detection bias as outcome assessors were non-blind
Notes	Trial protocol registered on ISRCTN, study ID ISRCTN58763208.

	Due to baseline differences and the fact that the paper reports a statistical model which controls for these, the reported odds ratios (OR) were extracted from the paper and entered into analysis (using generic inverse variance method after converting to natural log scale). Data could not be extracted from GORDON2011 as rate ratios (rather than odds ratio, risk ratio or risk difference) reported

1.6.3 LIM20010

Study ID	LIM2010
Bibliographic reference	Lim HA. Effect of "developmental speech and language training through music" on speech production in children with autism spectrum disorders. Journal of Music Therapy. 2010;47:2-26.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants and intervention administrators non-blind but outcome assessors blinded **Setting:** Not reported **Raters:** Speech/language pathologists **Country:** USA
Participants	**Diagnosis:** ASD (diagnostic classification system not reported) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Previous diagnosis of ASD made by their own healthcare provider (level of functioning assessed using Chilhood Autism Rating Scale [CARS] or Autism Diagnostic Interview-Revised [ADI-R]) **N:** 50 **Age:** 3-5 years (mean: 4.7 years) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they had a previous diagnosis of ASD made by their own healthcare provider (level of functioning assessed using CARS or ADI-R) **Exclusion criteria:** Not reported (one participant was excluded due to a coexisting diagnosis of Down syndrome)
Interventions	**Experimental Intervention: Developmental Speech and Language Training through Music (DSLM).** 36 target words were included in six songs composed by the investigator which were presented to participants on video. Pictures from the Picture Exchange Communication System (PECS) for each of the 36 target words were also presented by the singer as she sang the congruent target word. Each song was presented two time consecutively in the music video **Speech therapy.** This active intervention comparison condition used exactly the same training stimuli and format as the DSLM condition with the exception that instead of six songs, the same texts were presented as six stories in the speech therapy condition **Delivery of intervention:** Intervention delivered in video format (actor in video was a music student)

	Format or method of administration: Video-based **Intensity:** 1.8 hours for music therapy and 1.1 hours for speech therapy (across 12 training sessions and 4 days) **Duration of intervention:** 0.6 weeks (4 days) **Total duration of follow-up:** 0.6 weeks (4 days)
Outcomes	**Direct outcome:** **Coexisting problem or disorder: Speech and language** (as measured by study-specific Verbal Production Evaluation Scale [VPES], a measure of expressive language and production of target words)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear, insufficient detail reported with regards to allocation concealment, and baseline comparability of groups is unclear 2. High risk of performance bias as intervention administrators non-blind 3. High risk of response bias as participants non-blind 4. Risk of selective reporting bias is unclear/unknown as trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Not applicable

1.6.4 WELTERLIN2012

Study ID	WELTERLIN2012
Bibliographic reference	Welterlin A, Turner-Brown LM, Harris S, Mesibov G, Delmolino L. The home TEACCHing program for toddlers with autism. Journal of Autism and Developmental Disorders. 2012;42:1827-1835.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, parents and intervention administrators were non-blind. Identity and blinding of outcome assessor/s unclear. **Setting:** Home-based **Raters:** Not reported **Country:** USA
Participants	**Diagnosis:** Autism **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Not reported **N:** 20 **Age:** 2-3.25 years (mean: 2.5 years) **Sex:** 10% female **Ethnicity:** 80% white **IQ:** 21-89 (mean: 55.4, as measured by the Mullen Scales of Early Learning [MSEL] - Developmental quotient) **Inclusion criteria:** Children were included if they were under 3.5 years of age and had a clinical diagnosis of autism **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Home TEACCH programme:** This intervention

	incorporated parent training in how to teach specific cognitive, fine motor, and language skills to their child. The intervention began with the clinician teaching the child the specific skills and modelling appropriate prompting behaviour and teaching environment set-up for the parents. Parents were also provided with education about autism and intervention strategies and assigned written homework and requested to practice applying new skills in between intervention sessions. From week 8 onwards, parents took over the active teaching of their child and the clinician provided coaching and feedback **Delivery of intervention:** The only description given of intervention administrator is 'clinician' **Format or method of administration:** Intervention delivered in clinician-parent-child triad **Intensity:** Actual intensity not reported but planned intensity was 18 hours (1.5 hour/week) **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct outcome:** **Coexisting problem or disorder: Speech and language** (as measured by the Mullen Scales of Early Learning [MSEL] - Receptive Language and Expressive Language subscales) **Indirect outcomes:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Scales of Independent Behavior-Revised (SIB) - Social interaction subscale) **Coexisting problem or disorder: IQ** (as measured by the Mullen Scales of Early Learning [MSEL] - Developmental quotient) **Impact on the family** (as measured by the Parenting Stress Index-3rd Edition [PSI] - Total score)
Study Design	RCT
Source of funding	Part of this project was the doctoral dissertation of the first author. Dr. Welterlin was supported, in part, by the Harris Fellowship Award and the 2007 Graduate Research Grants Program Award. Dr. Turner-Brown was supported by Division TEACCH, by the National Institutes of Child Health and Human Development T32-HD40127 and P30 HD03110, and by grant R40MC22648 through the U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Research Program
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear and insufficient detail is reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators were non-blind 3. High risk of response bias as participants were non-blind 4. Risk of detection bias is unclear/unknown as unclear if 12 weeks a sufficient follow-up duration to detect significant treatment effects. In addition (and more worryingly as it might lead to overestimation of treatment effects) the identity and blinding of outcome assessor/s are not reported 5. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov or ISCRTN
Notes	The Scales of Independent Behavior-Revised (SIB; Language comprehension

	and Language expression) were also used to measure the non-core feature of speech and language, however, data were not extracted for this outcome measure as the MSEL was the more widely used scale across studies. The study will be downgraded for indirectness in GRADE as any qualifying diagnostic assessment by a clinician was not reported

1.6.5 WHALEN2010

Study ID	WHALEN2010
Bibliographic reference	Whalen C, Moss D, Ilan AB, Vaupel M, Fielding P, Macdonald K, et al. Efficacy of TeachTown: Basics computer-assisted intervention for the Intensive Comprehensive Autism Program in Los Angeles unified school district. Autism. 2010;14:179-197.
Methods	**Allocation:** Randomised (by classroom) **Matching:** No matching **Blindness:** Participants and intervention administrators non-blind. Identity and blinding of outcome assessors not reported **Setting:** Educational (Intensive Comprehensive Autism Programs [ICAP]) **Raters:** Not reported **Country:** USA
Participants	**Diagnosis:** ASD (diagnostic classification system not reported) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Childhood Autism Rating Scale (CARS) completed by teachers and both experimental and control groups showed scores consistent with severe autism (mean: 42 for experimental and 43 for control) but the CARS does not appear to have been used as an inclusion criterion **N:** 8 classrooms (47 children) **Age:** 3-6 years (mean not reported) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they had autism and attended preschool or K-1 Intensive Comprehensive Autism Programs (ICAP) within the Los Angeles Unified School District and had parental consent to be in the study **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Combined computer-assisted educational intervention and intensive behavioural intervention (IBI) day class program (preschool or K-1).** Participants attended Intensive Comprehensive Autism Programs (ICAP) for 27-30 hours per week where children were taught in classes of no more than 8 with an adult to child ratio of 1:2 using an ABA approach (typically discrete trials) to target language/communication, sensory issues, and behaviour within a classroom organised according to TEACCH principles. In addition to this IBI intervention, participants in the experimental group also received computer-assisted instruction (using the 'Teachtown: Basics' program). This computer-assisted instruction intervention included computer lessons and off-computer natural environment activities to target

	additional skills and encourage generalization. The computer lessons incorporated the basic principles of ABA with teaching in a discrete trial format and reinforcement for correct responses, and for the off-computer activities techniques used followed the principles of pivotal response training. The computer lessons aimed to improve receptive language (including vocabulary, school readiness such as play and classroom vocabulary, semantics and community life such as body parts and environmental sounds), social understanding (including knowledge of eye gaze, joint attention, face matching and emotion recognition), life skills (including awareness and regulation, functional skills such as time telling and self-awareness such as food and clothing vocabulary), and academic/cognitive skills (including math, reading, categorization and problem solving). Off-computer activities additionally targeted expressive language, play, imitation, social interaction, motor skills and daily living skills. **Control intervention: IBI day class program-only (preschool or K-1)** **Delivery of intervention:** Intervention delivered by teachers and off-computer activities were delivered individually, in a small group or to the full class (<=8) **Format or method of administration:** Computer-based **Intensity:** 351 for IBI (of which 43.33 for computer-assisted intervention) for preschool and 390 for IBI (of which 43.33 for computer-assisted intervention) for K-1 **Duration of intervention:** 13 weeks **Total duration of follow-up:** 13 weeks
Outcomes	**Direct outcome:** **Coexisting problems or disorders: Speech and language** (as measured by Peabody Picture Vocabulary Test, 3rd Ed. [PPVT-III] - Total score, Expressive Vocabulary Test [EVT] - Total score, and the Brigance Inventory of Child Development - Receptive language and Expressive language subscales) **Indirect outcomes:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the Brigance Inventory of Child Development - Social skills subscale) **Coexisting problem or disorder: Sensory sensitivities** (as measured by the Brigance Inventory of Child Development - Auditory processing subscale)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear, insufficient detail reported with regards to allocation concealment and group comparability at baseline is unclear 2. High risk of performance bias as intervention administrators non-blind 3. High risk of response bias as participants non-blind 4. 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 5. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Contacted author regarding post-intervention mean and standard deviation

	data and requested information was provided

1.6.6 YODER2006B/2010

Study ID	YODER2006B/2010
Bibliographic reference	Yoder P, Stone WL. A randomized comparison of the effect of two prelinguistic communication interventions on the acquisition of spoken communication in preschoolers with ASD. Journal of Speech, Language, and Hearing Research. 200b6;49:698-711. Yoder PJ, Lieberman RG. Brief report: randomized test of the efficacy of picture exchange communication system on highly generalized picture exchanges in children with ASD. Journal of Autism and Developmental Disorders. 2010;40:629-632.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants and intervention administrators non-blind. Blinding of outcome assessors is unclear for most outcome measures (with the exception of the blinded outcome assessor for the Early Social Communication Scales-Abridged) **Setting:** University clinic **Raters:** Identity of raters not reported **Country:** USA
Participants	**Diagnosis:** ASD (92% autism and 8% PDD-NOS) **Coexisting conditions:** Participants were nonverbal or low verbal (as defined by using fewer than 20 different words across three communication samples) **Qualifying Diagnostic Assessment:** Prior clinical diagnosis was corroborated using the Autism Diagnostic Observation Schedule (ADOS) Module 1 **N:** 36 **Age:** 1-4 years (mean: 2.8 years) **Sex:** 14% female **Ethnicity:** 69% white **IQ:** 48-67 (mean: 51; as measured by the Mullen Scales of Early Learning [MSEL]) **Inclusion criteria:** Children were included if: they had a diagnosis of autistic disorder or PDD-NOS corroborated by the ADOS Module 1; were aged 1.5-5 years; showed evidence of being nonverbal or low verbal as defined by using fewer than 20 different words across three communication samples; their parents made a verbal commitment to bring them for three 20-min intervention sessions per week for 6 months **Exclusion criteria:** Children were excluded if: they demonstrated severe sensory or motor deficits (hearing screenings were obtained); the primary language spoken in the home was not English
Interventions	**Experimental Intervention: Picture Exchange Communication System (PECS) versus Responsive Education and Prelinguistic Milieu Teaching (RPMT)** **Picture Exchange Communication System (PECS).** Intervention based on the manual (Bondy & Frost, 1994) with the exception that training was

	implemented three times a week for 20 min rather than throughout the day. The PECS curriculum has six phases, beginning with the physically prompted exchange of a single picture without distractor pictures and ending with the exchange of a sentence strip in response to "What do you see?" Picture symbols were Mayer-Johnson line drawings closely resembling objects used during training sessions. The intervention also included a parent component involving demonstration and discussion of strategies to promote PECS use outside of treatment sessions **Responsive Education and Prelinguistic Milieu Teaching (RPMT).** Intervention was aimed at gestures, vocalizations and eye gaze and involved establishing highly engaging play routines and using the least intrusive prompting procedures to target specific prelinguistic communication behaviours. There was also a parent component which involved supporting parents in the use of responsive play and communication strategies (following Hanen centre curriculum [Sussman 2001]). The main differences between the two active interventions were in: Positioning (RPMT on floor and PECS mostly in chair); adult to child ratios (RPMT 1:1 and PECS 2:1 for phases 1, 2 & 4 and 1:1 for 3, 5 & 6); behaviours taught (gestures, gaze, vocalizations and words for RPMT and picture exchange and words for PECS); general teaching approach (incidental teaching for RPMT and discrete trial for PECS); relative consistency of linguistic mapping (moderate for RPMT and high for PECS); when word use was explicitly prompted (after meeting prelinguistic fluency criteria for RPMT and after phase 3 for PECS); types of prompts for spoken communication (mands and explicit imitation prompts for RPMT and fill-in-the-blank prompts for PECS); and consequences for word use (expansions, repetition and compliance for RPMT and repetition and compliance for PECS) **Delivery of intervention:** Each treatment team was composed of a master's degree level professional and a bachelor of arts (BA) degree level paraprofessional **Format or method of administration:** Individual **Intensity:** Actual mean intensity for children components of 20 hours (0.8 hours/week). Actual mean intensity for parent training: 10.6 hours for RPMT group and 7.9 hours for PECS group. **Duration of intervention:** 26 weeks **Total duration of follow-up:** 52 weeks (including 6-month post-intervention follow-up)
Outcomes	**Direct outcome:** **Coexisting problem or disorder: Speech and language, including non-verbal communication** (as measured by behavioural observations of frequency of nonimitative spoken acts and number of different nonimitative words; and the Early Social Communication Scales-Abridged [EScs-Abridged] - Number of picture exchanges)
Study Design	RCT
Source of funding	National Institute on Deafness and Other Communication Disorders (NICHD), the core grant support to the Vanderbilt University Kennedy Center and RGL supported by grant #T32HD07226 from the National Institute of Child Health and Human Development to Vanderbilt University
Limitations	1. Risk of selection bias is unclear/unknown as groups were not comparable at

	baseline and although some baseline differences were controlled for, such as baseline group differences in the Mullen expressive language score (higher for RPMT group than PECS group) and object-exchange turns (higher for PECS group than for RPMT group), correction was only performed where time 1 variables correlated with time 2 and 3 variables. Therefore, no covariate was entered to control for group differences on the ADOS social algorithm (higher in RPMT group) as this variable was not significantly correlated with the outcome variable in the YODER2010 paper, however, authors do not report correlations or corrections for this variable for the outcomes reported in YODER2006B paper. There was also insufficient detail reported with regards to allocation concealment, authors report that allocation was concealed but do not report the concealment method. 2. 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]) 3. High risk of response bias as participants were non-blind 4. Risk of detection bias is unclear for most outcomes (with the exception of the EScs-Abridged) as only 20% of behavioural observations were double-coded and no standardized coding instrument used so reliability and validity of outcome measures unclear and identity and blinding of outcome assessor also unclear 5. 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)
Notes	YODER2006A also part of the same trial but excluded as data cannot be extracted and author did not reply to request for missing outcome data

1.7 CHARACTERISTICS OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT SPEECH AND LANGUAGE

1.7.1 BALL2004

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.7.2 CARR2007A/2007B

Reason for exclusion	Non-randomised group assignment

1.7.3 FLIPPIN2010

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.7.4 GANZ2012

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.7.5 GLOGOWSKA2000

Reason for exclusion	Sample do not have diagnosis of ASD

1.7.6 GOLD2006

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.7.7 HOWLIN1981

Reason for exclusion	Non-randomised group assignment

1.7.8 KANE2010

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.7.9 KOEGEL1998

Reason for exclusion	Non-randomised group assignment

1.7.10 LANG2009

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.7.11 LAYTON1988

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.7.12 MCDUFFIE2012

Reason for exclusion	Outcomes reported are outside the scope

1.7.13 MILLAR2006

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.7.14 MOORE2000

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.7.15 MURDOCK2011

Reason for exclusion	Non-randomised group assignment

1.7.16 NEFDT2009

Reason for exclusion	Non-randomised group assignment (randomisation method based on order in which participant information was received)

1.7.17 OOSTERLING2010

Reason for exclusion	Non-randomised group assignment (although 35% of participants were randomised the majority of participants, the remaining 65%, were allocating according to where participants lived)

1.7.18 PRESTON2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.7.19 RAMDOSS2011A

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.7.20 RESCHKEHERNADEZ2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not

	appropriate to extract

1.7.21 SCHLOSSER2008

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.7.22 SIMPSON2011

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.7.23 STAHMER2001

Reason for exclusion	Non-randomised group assignment

1.7.24 SULZERAZAROFF2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.7.25 VANDERMEER2010

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.7.26 VAZQUEZ1994

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.7.27 VENKER2012

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.7.28 WHIPPLE2004

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.7.29 YODER1988

Reason for exclusion	No post-intervention outcome measure reported (assessment and intervention occurred simultaneously on an ongoing basis throughout trial and reported as single data point)

1.7.30 YODER2006A

Reason for exclusion	Efficacy data cannot be extracted

1.8 REFERENCES OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT SPEECH AND LANGUAGE

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1.9 CHARACTERISTICS OF EXCLUDED PHARMACOLOGICAL INTERVENTION STUDIES AIMED AT SPEECH AND LANGUAGE

1.9.1 FELDMAN1999

Reason for exclusion	Data cannot be extracted due to cross-over design and unavailability of either first phase data or results of paired-sample t-tests

1.10 REFERENCES OF EXCLUDED PHARMACOLOGICAL INTERVENTION STUDIES AIMED AT SPEECH AND LANGUAGE

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1.11 CHARACTERISTICS OF INCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT SPEECH AND LANGUAGE

1.11.1 ALLAM2008

Study ID	ALLAM2008
Bibliographic reference	Allam H, Eidine NG, Helmy G. Scalp acupuncture effect on language development in children with autism: a pilot study. Journal of Alternative and Complementary Medicine. 2008;14:109-114.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Participants were not blind to treatment allocation, care administrators were blind to treatment allocation. Details of outcome assessors are not reported, so blind is unclear. **Setting:** Academic **Raters:** Not reported **Country:** Egypt
Participants	**Diagnosis:** DSM-IV-TR Autism **Coexisting conditions:** All participants had delayed language development. Details of other co-exisiting conditions not reported. **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview Revised (ADI-R) **N:** 20

	Age: Range: 4-7 (Mean: not reported) **Sex:** 40% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if: they had delayed language development; they had a DSM-IV-T diagnosis of autism based on clinical observation; the diagnosis was further confirmed by the Autism Diagnostic Interview-Revised (ADI-R); they had a score of >30 on the Childhood Autism Rating Scale (CARS) **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Acupuncture and langauge therapy.** The intervention group only received acupuncture, applied to the scalp through 8 acupoints including the temples, cerebrum and aphasia points for 20 minutes at a time. **Control Intervention: Language therapy only.** Both the intervention group and the control group received language therapy conducted by a language therapist. The sessions were intended to improve attention while also stimulating verbal ability. Sessions were individualised to suit the children. **Delivery of intervention:** The intervention was delivered to both groups by the same language therapist. **Format or method of administration:** Not reported **Intensity:** Acupuncture was delivered to the intervention group twice a week, for 20 minutes for a total of 50 sessions (cycles of 2 months of acupuncture, followed by a 2 week rest for the duration of the treatment period). A total of 16.7 hours (40 minutes a week). Language therapy was delivered to both groups twice a week for the duration of the treatment period. No further intensity details are reported. **Duration of intervention:** 39 weeks **Total duration of follow-up:** 39 weeks
Outcomes	**Direct Outcome** **Coexisting problem or disorder: Speech and language** (as measured by the Arabic Language Test)
Study Design	RCT
Source of funding	Not reported
Limitations	1. High risk of performance bias: participants were not blind to treatment allocation 2. Unclear risk of detection bias: no validity or reliability information for any of the measures and no details of outcome assessor are reported 3. Unclear risk of selective reporting: the study is not registered
Notes	Not applicable

1.11.2 ZHOU2008/CHEUK2011

Study ID	ZHOU2008/CHEUK2011
Bibliographic reference	Zhou H, Zhang P. The effect of language therapy combined with point massage on communication disability in autism children. China Pratical Medical. 2008;3:24-26.

	Cheuk DKL, Wong V, Chen WX. Acupuncture for autism spectrum disorders (ASD)(Review). The Cochrane Database of Systematic Reviews. 2011;9:Art. No CD007849. Available from: DOI: 10.1002/14651858.CD007849.pub2.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** No blinding of participants, care administrators or outcomes assessors reported **Setting:** Not reported **Raters:** Not reported **Country:** Not reported
Participants	**Diagnosis:** Autism Spectrum Disorder (diagnostic classification not reported) **Coexisting conditions:** All participants had a coexsisting language delay. No further information reported. **Qualifying Diagnostic Assessment:** Aberrant Behvioural Checklist (ABC) **N:** 30 **Age:** Range: not reported (mean: 5.7 years) **Sex:** 27% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged between 2 and 10 years old; had a diagnosis if ASD confirmed by the Aberrant Behaviour Checklist (ABC); had a coexisting language delay diagnosed with the sign-significance relations scale (China Rehabilitation Research Centre). **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Acupressure and language therapy.** Acupressure was applied to three acupoints 100 times each using the thumb. Acupressure was then applied to 6 acupoints using the fingers. Finally, acupressure was applied to 5 further acupoints, 100 times each. In between the acupressure, areas of the face and head were massaged for several minutes. Each session lasted around 45 minutes. **Control Intervention: Language therapy only.** No details on language therapy reported. **Delivery of intervention:** Not reported **Format or method of administration:** Not reported **Intensity:** Children received 45 minutes of acupressure 5 days a week for 6-9 months. A total of 97.5-146.25 hours (3.75 hours a week). **Duration of intervention:** 26-39 weeks **Total duration of follow-up:** 39 weeks
Outcomes	**Direct Outcome** **Coexisting problem or disorder: Speech and language** (as measured by improvement China Rehabilitation Research Council (CRRC) sign-significance relations scale and basic development scale
Study Design	RCT
Source of funding	Not reported
Limitations	1. Unknown risk of selection bias: methods of randomisation or concealment of allocation not reported and treatment length varied for participants 2. High risk of performance bias: no blinding of participants or care administrators reported

	3. Unclear/unknown risk of detection bias: validity and reliability unclear on both measures. No blinding of outcome assessors reported. 4. Unclear risk of selective reporting: all outcomes are reported but study not registered
Notes	The original paper was a foreign paper and so was excluded on that basis. The study was then included in a systematic review and all information reported here is from that source.

1.12 CHARACTERISTICS OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT SPEECH AND LANGUAGE

1.12.1 CORBETT2008

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm) for analysis due to crossover design

1.13 REFERENCES OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT SPEECH AND LANGUAGE

Corbett BA, Shickman K, Ferrer E. Brief report: the effects of Tomatis sound therapy on language in children with autism. Journal of Autism and Developmental Disorders. 2008;38:562-566.

1.14 CHARACTERISTICS OF INCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT IQ AND ACADEMIC SKILLS

1.14.1 ROGERS2012

Study ID	ROGERS2012
Bibliographic reference	Rogers SJ, Estes A, Lord C, Vismara L, Winter J, Fitzpatrick A, et al. Effects of a brief Early Start Denver Model (ESDM)-based parent intervention on toddlers at risk for autism spectrum disorders: a randomized controlled trial. Journal of the American Academy of Child and Adolescent Psychiatry. 2012;51:1052-1065.
Methods	**Allocation:** Randomised **Matching:** Children were matched on age, gender and developmental quotient

	Blindness: No blinding reported in the study **Setting:** Three university clinics **Raters:** Parent-rated, laboratory personnel or raters not reported **Country:** USA
Participants	**Diagnosis:** Autism Spectrum Disorder (diagnostic classification not reported) **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** Autism Diagnostic Observation Scale for Toddlers (ADOS-T) **N:** 98 **Age:** Range: not reported (mean: 1.7 years) **Sex:** 31% female **Ethnicity:** 72% white **IQ:** Not reported (inclusion criteria DQ>35 as measured by MSEL) **Inclusion criteria:** Children were included if they: met the criteria of risk for ASD based on two screening questionnaires (Early Screening of Autistic Traits Questionnaire/Infant Toddler Checklist/Modified Checklist for Autism in Toddlers); met criteria for ASD based on the ADOS-T and clinical judgement of two independent clinicians; had developmental quotients of > 35; lived in a home where English was spoken daily; were able to crawl or walk **Exclusion criteria:** Children were excluded if: parents had suffered from significant mental illness (including substance misuse); children had coexisting significant medical conditions (e.g. Cerebral palsy); children had coexisting developmental disabilities relating to genetic disorders; children had developmental quotients of <35; gestational age was <35 weeks; children had previously been or were currently enrolled in >10 hours per week of intensive (1:1) autism intervention.
Interventions	**Experimental Intervention: The parent-delivered Early Start Denver Model (P-ESDM)** was delivered to parents via highly-structured sessions. Each session began with a 5-minute 'warm-up' where parents and children engaged in a play-based activity. The topic for the session was then explained to the parents (with written materials offered to support learning) and the required skill was demonstrated with the child. Parents then applied the skill themselves, with feedback and support from the therapist, before the skill was applied to a range of other activities. Parents were given written materials to take home to support the application of the new skill. The intervention focused on a range of skills including joint attention routines; developing non-verbal skills; encouraging speech; and conducting functional assessments of behaviour. **Delivery of intervention:** Qualified therapists delivered the intervention **Format or method of administration:** Parent-child dyads **Intensity:** Actual intensity of experimental intervention not reported but planned intensity of 12 hours (1 hour/week) and weekly mean intensity of all intervention was 1.48 hours **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct outcome:** **Coexisting problem or disorder: IQ** (as measured by the Mullen Scales of Early Learning [MSEL] - developmental quotient [DA/CAx100], verbal DQ and nonverbal DQ) **Indirect outcomes:**

	Core autism features: Impaired reciprocal social communication and interaction (as measured by the Autism Diagnostic Observation Scale for Toddlers [ADOS-T] - Social Affect domain; and Imitation tasks [Rogers et al., 2003] - Imitative sequences; Social engagement task [Dawson et al., 2004] - Orienting to social stimuli and Orienting to joint attention scores); **Restricted interests and rigid and repetitive behaviours** (as measured by ADOS-T - Restricted, Repetitive Behaviours domain) **Coexisting problems or disorders: Adaptive behaviour** (as measured by the Vineland Adaptive Behaviour Scale, Second Edition [VABS II] - Adaptive behaviour composite, and Communication; Daily living skills, and Socialisation subscales); **Speech and language** (as measured by the Macarthur Communication Developmental Inventories [CDI] - Phrases understood, Vocabularly comprehension, Vocabulary production, and Total gestures produced subscales)
Study Design	RCT
Source of funding	This research was funded by Autism Speaks grants and by the National Institute of Mental Health (NIMH) the National Institute of Child Health and Human Development (NICHD) grant MH R01 081757 (S.R.).
Limitations	1. Risk of selection bias is unclear/unknown as statistically significant group differences at baseline (children in the experimental group had a higher mean ADOS Social Affect score [mean 34.14] than children in the control group [mean 29.45] , and children in the control group had higher imitation and nonsocial orient scores [means 3.78 and 8 respectively] than children in the experimental group [means 2.53 and 7 respectively]) 2. High risk of performance bias as intervention administrators were non-blind and potential care confounds (significant differences in number of intervention hours received between groups with the control group receiving more weekly hours of intervention [mean=3.68] than the experimental group [mean=1.48]) 3. High risk of response bias as participants were non-blind 4. Risk of detection bias was different for different outcomes: Unclear/unknown for ADOS-T (outcome assessor reported as 'laboratory personnel' and blinding of outcome assessors not reported) and MSEL (identity and blinding of outcome assessors not reported) and high risk for CDI and VABS (parent-rated or based on parental report and parents were non-blind and involved in the intervention) and high risk for imitative sequences, orienting to social stimuli and orienting to joint attention measures (identity and blinding of outcome assessors not reported and reliability and validity of outcome measure unclear) 5. Risk of attrition bias is unclear/unknown as no information regarding drop-outs or unavailable data reported 6. High risk of other bias due to potential conflict of interest as three of the investigators receive royalties from sales of Early Start Denver Model materials
Notes	Data not extracted for the orienting to nonsocial stimuli task as outcome outside scope. Conflciting data reported in paper in table and text for pre-intervention differences in ADOS-T social affect scores (reported as favouring the control group in the table and the experimental group in the text), data were extracted from the table.

1.15 CHARACTERISTICS OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT IQ AND ACADEMIC SKILLS

1.15.1 BASSETT2000

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.2 BURROWS2004

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.3 CHIANG2007

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.4 COHEN2006

Reason for exclusion	Non-randomised group assignment

1.15.5 HOWLIN2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.6 HUME2012

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.15.7 KOZULIN2010

Reason for exclusion	Less than 50% of the sample had a diagnosis of autism

1.15.8 LEVY2006

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.9 LOVAAS1987/MCEACHIN1993

Reason for exclusion	Non-randomised group assignment

1.15.10 LUDWIG2001

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.11 MACHALICEK2008

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.15.12 MAKRYGIANNI2010

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.13 MCGAHAN2001

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.14 PETERSSCHEFFER2010

Reason for exclusion	Non-randomised group assignment

1.15.15 PETERSSCHEFFER2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.16 RAMDOSS2011B

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.17 REICHOW2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.18 SMITH1999

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.19 UNITEDHEALTHCARE2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.20 VIRTUESORTEGA2010

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.21 WARREN2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.15.22 WEINMANN2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.16 REFERENCES OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT IQ AND ACADEMIC SKILLS

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Peters-Scheffer N, Didden R, Mulders M, Korzilius H. Low intensity behavioral treatment supplementing preschool services for young children with autism spectrum disorders and severe to mild intellectual disability. Research in Developmental Disabilities. 2010;31:1678-1684.

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spectrum disorders: a systematic review. Research in Autism Spectrum Disorders. 2011b;5:1306-1318.

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Virtues-Ortega J. Applied behavior analytic intervention for autism in early childhood: meta-analysis, meta-regression and dose-response meta-analysis of multiple outcomes. Clinical Psychology Review. 2010;30:387-399.

Warren Z, McPheeters ML, Sathe N, Foss-Feig JH, Glasser A, Veenstra-VanderWeele J. A systematic review of early intensive intervention for autism spectrum disorders. Pediatrics. 2011;127:e1303-e1311.

Weinmann S, Schwarzbach C, Begemann M, Roll S, Vauth C, Willich SN, et al. Behavioural and skill-based early interventions in children with autism spectrum disorders. GMS Health Technology Assessment, 5, doc. 10; 2009. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3011283/pdf/HTA-05-10.pdf.

1.17 CHARACTERISTICS OF EXCLUDED PHARMACOLOGICAL INTERVENTION STUDIES AIMED AT IQ AND ACADEMIC SKILLS

1.17.1 HANDEN2011

Reason for exclusion	Outcomes outside scope

1.17.2 STERN1990

Reason for exclusion	Drug withdrawn from market due to significant safety concerns

1.18 REFERENCES OF EXCLUDED PHARMACOLOGICAL INTERVENTION STUDIES AIMED AT IQ AND ACADEMIC SKILLS

Handen BL, Johnson CR, McAuliffe-Bellin S, Murray PJ, Hardan AY. Safety and efficacy of donepezil in children and adolescents with autism: neuropsychological measures. Journal of Child and Adolescent Psychopharmacology. 2011;21:43-50.

Stern LM, Walker MK, Sawyer MG, Oades RD, Badcock NR, Spence JG. A controlled crossover trial of fenfluramine in autism. Journal of Child Psychology and Psychiatry. 1990;31:569-585.

1.19 CHARACTERISTICS OF INCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT IQ AND ACADEMIC SKILLS

1.19.1 WONG2010A

Study ID	WONG2010A
Bibliographic reference	Wong VC-N, Sun JG. Randomized controlled trial of acupuncture versus sham acupuncture in autism spectrum disorder. Journal of Alternative and Complementary Medicine. 2010a;16:545-553.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Care administrator was not blind. Participants, parents, teachers and assessors were all blind to treatment allocation. **Setting:** Not reported **Raters:** Not reported **Country:** China

Participants	**Diagnosis:** DSM-IV Autism **Coexisting conditions:** Associated neurological disorders and epilepsy were excluded. No further information of coexisiting conditions reported **Qualifying Diagnostic Assessment:** Observation and semi-structured interview; Autism Diagnostic Interview-Revised (ADI-R) **N:** 50 **Age:** Range 3-11 years (Mean: 6.1 years) **Sex:** 14% female **Ethnicity:** Not reported **IQ:** Range: not reported (Mean: 62.4), based on the general quotient of the Griffiths Mental Developmental Scale. **Inclusion criteria:** Inclusion criteria not explicitly reported. Children were included if they: received a DSM-IV diagnosis of autism from the first author, through observation assessment and a semi-structured interview with the parents (Autism Diagnostic Interview-Revised); a score > 30 in the Childhood Autism Rating Scale **Exclusion criteria:** Children were excluded if they: had associated neurological conditions; had epilepsy. No further details reported.
Interventions	**Experimental Intervention: Acupuncture** was applied to the tongue using an acupunture needle, via five acupoints; two on the surface of the tongue and three at the bottom of the tongue. The needle was inserted between 0.3 and 1 cm. The whole procedure lasted approx. 15 seconds. **Sham acupuncture** was applied to the tongue via the same five acupoints as the intervention group; two on the surface of the tongue and three at the bottom of the tongue. The acupuncturist touched the five points with the rough end of the needle rather than inserting the sharp end of the needle. The whole procedure lasted approx. 15 seconds. **Delivery of intervention:** A qualified acupuncturist delivered the intervention to children individually. **Format or method of administration:** Individual **Intensity:** 10 minutes - Acupuncture sessions lasted a total of 15 seconds, five days a week for 40 sessions (1.25 minutes per week). **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks
Outcomes	**Direct Outcome** **Coexisting problem or disorder: IQ** (as measured by the Griffiths Mental Developmental Scale - Mental age [m] and General quotient, and Locomotor, Personal-Social, Hearing & Speech, Eye & Hand Coordination, Performance, and Practical Reasoning subscales) **Indirect Outcome** **Core autism feature: Overall autistic behaviours** (as measured by Ritvo-Freeman Real Life Scale [RF-RLS] - Total score, and Motor, Social, Affective, Sensory, and Language subscales) **Coexisting problems or disorders: Adaptive behaviour** (as measured by the Functional Independence Measure for Children [WeeFIM] - Total score, and Self-care, Mobility, and Cognition subscales); **Speech and Language** (as measured by Reynell Language Developmental Scale [RLDS] - Comprehension score and Comprehension age [y], and Expression score and Expression age [y])
Study Design	RCT

Source of funding	Not reported
Limitations	1. High risk of performance bias as intervention administrators non-blind
Notes	Contacted author regarding endpoint rather than change scores, however, no reply so change scores inputted into meta-analysis

1.19.2WONG2010B

Study ID	WONG2010B
Bibliographic reference	Wong VC-N, Chen W-X, Liu W-L. Randomized controlled trial of electro-acupuncture for autism spectrum disorder. Alternative Medicine Review. 2010b;15:136-146.
Methods	**Allocation:** Randomised **Matching:** Participants were matched on age and severity of autism based on the Childhood Autism Rating Scale (CARS) **Blindness:** Participants and outcome assessors were blind to treatment allocation. The acupuncturist was not blind to the allocation of treatment. **Setting:** Hospital **Raters:** Parents and an unidentified assessor; both reported to be blind to treatment allocation **Country:** China
Participants	**Diagnosis:** DSM-IV Autism Spectrum Disorder **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Scale (ADOS) **N:** 59 **Age:** Range: not reported (mean: 9.3 years) **Sex:** 15% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 3-18 years; had a confirmed DSM-IV diagnosis of ASD based on the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Scale (ADOS), administered by the principle investigator **Exclusion criteria:** Children who had been on anti-epileptic drugs or who had received acupuncture within six months prior to starting the study.
Interventions	**Experimental Intervention: Electro-acupuncture** was delivered via 8 acupoints; Sishencong; Yintang; Neiguan; Shenmen; TaiChong; Ear naodian; Ear shenmen and Sanyinjiao. The acupuncture needles were connected to an electro-acupuncture machine which provided electrical spacing-density stimulation for 30 minutes. **Sham acupunture** was delivered with needles inserted to a superficial level. The acupuncture needles were connected to an electro-acupuncture machine which provided electrical spacing-density stimulation for 30 minutes. **Delivery of intervention:** The intervention was delivered to children individually by a qualified acupuncturist **Format or method of administration:** Individual **Intensity:** Children received 30 minutes of acupuncture three times a week for

	4 weeks. A total of 6 hours (1.5 hours a week). **Duration of intervention:** 4 weeks **Total duration of follow-up:** 4 weeks
Outcomes	**Direct Outcome** **Coexisting problem or disorder: IQ** (as measured by the Leiter International Performance Scale-Revised [LIPS-R] - FIQ and Attention and memory subscale) **Indirect Outcome** **Core autism feature: Overall autistic behaviours** (as measured by Ritvo-Freeman Real Life Scale [RF-RLS] - Total score and Motor, Social, Affective, Sensory, and Language subscales; Dichotomous measure of Positive treatment response ['much improvement [50% improvement]' and 'minimal improvement [25% improvement] on Clinical Global Impression-Improvement [CGI-I] scale]; Dichotomous measure of positive treatment response for social relatedness-social response, social initiation, eye contact, share, curiosity, patience [study-specific parent-reported 'better than before']; Dichotomous measure of positive treatment response for non-verbal and verbal communication-expressive language, receptive language, pointing, imitation [study-specific parent-reported 'better than before']; Dichotomous measure of positive treatment response for stereotypy interest and behaviour-temper, compulsive behaviour, adaptation to change [study-specific parent-reported 'better than before']; Dichotomous measure of positive treatment response for cognition-memory, learning ability [study-specific parent-reported 'better than before']; Dichotomous measure of positive treatment response for motor abnormalities-motor skill, coordination, drooling [study-specific parent-reported 'better than before']; and Dichotomous measure of positive treatment response for other parent-reported changes-appetite, attention span, sleeping pattern, "crafty" [study-specific parent-reported 'better than before']) **Behaviour that challenges** (as measured by Aberrant Behaviour Checklist [ABC] - Irritability, Lethargy, Stereotypy, Hyperactivity, and Inappropriate speech subscales) **Coexisting problems or disorders: Adaptive behaviour** (as measured by the Pediatric Evaluation Disability Inventory [PEDI] - self-care, mobility, social function, self-care caregiver assistant, mobility caregiver assistant, and social caregiver assistant subscales; Functional Independence Measure for Children [WeeFIM]-Total score and self-care, mobility, cognition, comprehension, expression, social interaction, problem solving, and memory subscales); **Speech and language** (as measured by the Reynell Developmental Language Scale [RDLS] - comprehension age [y] and expression age [y])
Study Design	RCT
Source of funding	A donation from the Board of Directors of the Tung Wah Group of Hospitals
Limitations	1. High risk of performance bias as intervention administrators non-blind 2. High risk of selective reporting: the study is registered online, but reports that follow-up measures will be taken. No follow-up outcomes have been published
Notes	Contacted author regarding endpoint rather than change scores and requested data supplied, however, change scores were inputted into most of the meta-analyses to maintain consistency with the other included study

1.20 CHARACTERISTICS OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT IQ AND ACADEMIC SKILLS

1.20.1 ORIEL2011

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.21 REFERENCES OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT IQ AND ACADEMIC SKILLS

Oriel KN, George CL, Peckus R, Semon A. The effects of aerobic exercise on academic engagement in young children with autism spectrum disorder. Pediatric Physical Therapy. 2011;23:187-193.

1.22 CHARACTERISTICS OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT SENSORY SENSITIVITIES

1.22.1 DUNN2012

Reason for exclusion	No control group

1.23 REFERENCES OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT SENSORY SENSITIVITIES

Dunn W, Cox J, Foster L, Mische-Lawson L, Tanquary J. Impact of a contextual intervention on child participation and parent competence among children with autism spectrum disorders: a pretest-posttest repeated-measures design. American Journal of Occupational Therapy. 2012;66:520-528.

1.24 CHARACTERISTICS OF INCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT SENSORY SENSITVITIES

1.24.1 BETTISON1996

Study ID	BETTISON1996
Bibliographic reference	Bettison S. The long-term effects of auditory training on children with autism. Journal of Autism and Developmental Disorders. 1996;26:361-374.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, parents and outcome assessors were blinded. Intervention administrators were non-blind **Setting:** Educational **Raters:** Parent-, teacher- and clinician-rated **Country:** Australia
Participants	**Diagnosis:** Autistic disorder, significant autistic symptoms, or Asperger syndrome (diagnostic classification system not reported) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** None reported **N:** 80 **Age:** 3-17 years (mean not reported) **Sex:** 18% female **Ethnicity:** Not reported **IQ:** FIQ not reported; PIQ range not reported (mean: 76, as assessed using the Leiter International Performance Scale [LIPS]) **Inclusion criteria:** Children were included if they: had a previous primary diagnosis (diagnostic classification system not reported) of autistic disorder, significant autistic symptoms, or Asperger syndrome (no corroborating diagnostic assessment for the study); showed no evidence of hearing loss (based on judgement of parents and diagnosticians); were midly to severely hypersensitive to sound (as indicated by the parent-reported Sound Sensitivity Questionnaire [SSQ]) **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Auditory integration training.** Intervention was based on method of Berard (1993). Participants listened to filtered and modulated music in two daily 30 minute listening sessions (which were separated by at least 4 hours) over 10 consecutive days. The music was specially modified for each participant based on their pretest audiogram **Control Intervention: Attention-placebo (structured listening) condition.** Participants in the control group listened to the same music for the same number of sessions as the experimental group, however, for the control group the music was unmodified **Delivery of intervention:** Identity of intervention administrator not reported **Format or method of administration:** Individual **Intensity:** 10 hours (7 hours/week) **Duration of intervention:** 1.4 weeks **Total duration of follow-up:** 52 weeks (follow-up assessments at 1 month, 3

	months, 6 months and 1 year)
Outcomes	**Direct outcome:** **Coexisting problem or disorder: Sensory sensitivities** (as measured by the Sound Sensitivity Questionnaire [SSQ] - Total score and Sound distress subscale; and the Sensory Problems Checklist [SP] - Total score) **Indirect outcomes:** **Core autism feature: Overall autistic behaviours** (as measured by the Autism Behaviour Checklist [ABC] - Total score) **Behaviour that challenges** (as measured by the parent- and teacher-completed Developmental Behaviour Checklist [DBC] - Total score) **Coexisting problem or disorder: Speech and language** (as measured by the Peabody Picture Vocabulary Test [PPVT] - Total score); and **IQ** (as measured by the Leiter International Performance Scale [LIPS] - Total score)
Study Design	RCT
Source of funding	Health, Housing and Community Services Research and Development Grant from the Commonwealth Department of Health, Housing and Community-Services, an Apex Trust for Autism Grant and the Autistic Association of New South Wales
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators non-blind 3. Risk of selective reporting bias is unclear/unknown as trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Not applicable

1.24.2FAZLIOGLU2008

Study ID	FAZLIOGLU2008
Bibliographic reference	Fazlioğlu Y, Baran G. A sensory integration therapy program on sensory problems for children with autism. Perceptual and Motor Skills. 2008;106:415-422.
Methods	**Allocation:** Randomised **Matching:** Matched on age, sex and level of functioning **Blindness:** Participants and intervention administrators were non-blind and blinding of outcome assessors unclear **Setting:** Educational (specialist) **Raters:** Not reported **Country:** Turkey
Participants	**Diagnosis:** DSM-IV Autism **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** None reported **N:** 30 **Age:** 7-11 years (mean not reported) **Sex:** 20% female **Ethnicity:** Not reported **IQ:** Not reported (all participants described as 'low functioning') **Inclusion criteria:** Children were included if they had a DSM-IV diagnosis of

	autism and were attending the Trakya University Training and Research Centre for Mentally and Physically Handicapped Children **Exclusion criteria:** Children were excluded if they had previously received any sensory integration intervention or had epileptic seizures
Interventions	**Experimental Intervention: Sensory integration therapy.** This intervention was based on "The Sensory Diet" (Chara, Chara & Chara, 2004). Participants were provided with a classroom programme of frequent and systematically applied somatosensory stimulation (brushing with a surgical brush and joint compression) followed by sensory-based activities designed to meet needs and integrated into the children's' daily routine. Targeted sensory behaviours included hearing, seeing, tasting, smelling, touching, balancing, moving (fine motor, gross motor, oral motor) and proprioception. Techniques included step-by-step activities, regular breaks (if children became overstimulated), prompt fading, modelling, extinction and reinforcement. Children learnt each skill to independence before moving on to the next skill. **Control Intervention: Treatment-as-usual.** Special education classes at the centre. **Delivery of intervention:** Intervention administrator not reported **Format or method of administration:** Individual **Intensity:** Actual intensity not reported but planned intensity was 18 hours (1.5 hour/week) **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct outcome:** **Coexisting problem or disorder: Sensory sensitivities** (as measured by Sensory Evaluation Form for Children with Autism - Total score)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators non-blind 3. High risk of response bias as participants non-blind 4. Risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported 5. Risk of selective reporting bias is unclear/unknown as trial protocol not registered on ClinicalTrials.gov or ISRCTN
Notes	Not applicable

1.24.3 SILVA2009

Study ID	SILVA2009
Bibliographic reference	Silva LMT, Schalock M, Ayres R, Bunse C, Budden S. Qigong massage treatment for sensory and self-regulation problems in young children with autism: a randomized controlled trial. American Journal of Occupational Therapy. 2009;63:423-432.
Methods	**Allocation:** Randomised **Matching:** No matching reported

	Blindness: No blinding of partipants, care administrators or outcome assessors reported **Setting:** Not reported **Raters:** Raters are not reported for some measures. Where it is reported, parents and teachers are the raters. **Country:** USA
Participants	**Diagnosis:** Autism (no diagnostic criteria reported) **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** Not reported **N:** 65 **Age:** Range: 2-9.75 years (mean: 5 years) **Sex:** 20% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were <6 years old; were eligible for early intervention for autism; had no additional, complicating medical diagnosis or chronic medication **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Qigong massage training**. Qigong massage is an intervention based in Chinese medicine. Trained therapists administered qigong massage treatment to the child, and trained parents how to administer the massage for daily massage at home **Delivery of intervention:** The intervention was delivered to children individually by trained therapists and parents **Format or method of administration:** Individual **Intensity:** Planned intensity: children were to be seen by the therapists 20 times during the 5-month intervention and parents were required to give children daily massages. No information regarding the duration of the the massages or actual intensity reported. **Duration of intervention:** 22 weeks **Total duration of follow-up:** 44 weeks
Outcomes	**Direct Outcome** **Coexisting problem or disorder: Sensory sensitivities** (as measured by the Pervasive Development Disorder Behavior Inventory [PDDBI] -Sensory subscale; and the Sense and Self-regulation Checklist [SSC]-Sense subscale) **Indirect Outcome** **Core autism feature: Overall autistic behaviours** (as measured by the Autism Behaviour Checklist [ABC]; and the PDDBI - Social, language and communication abilities and maladaptive behaviours subscales)
Study Design	RCT
Source of funding	A grant from the Curry Stone Foundation
Limitations	1. High risk of selection bias: 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. 2. High risk of performance bias: participants and care administrators are not

	blind to the treatment allocation 3. High risk of detection bias for some measures: All parent-rated PDDBI outcomes as parents were not blind to treatment allocation and were involved in delivering the intervention
Notes	There are discrepancies reported within the paper in relation to the age of the participants. The paper states that children aged 3-6 years were invited to participate in the study and that criteria for entry into the study was being aged less than 6 years. However, the age range reported for children included in the study was 2-9 years. There was a five-month follow-up for the intervention group, but as there are no follow-up scores for the control group, all outcomes reported are post-intervention. Data were not extracted for the systems score of the SSC as not clear what outcome this subscale was measuring

1.24.4 SILVA2011B

Study ID	SILVA2011B
Bibliographic reference	Silva LMT, Schalock M, Gabrielsen K. Early intervention for autism with a parent-delivered Qigong massage program: a randomized controlled trial. American Journal of Occupational Therapy. 2011b;65:550-559.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Participants and care administrators were not blind to allocation of treatment. Some outcomes were assessed by teachers, who were blind to allocation of treatment (none of which were included in this analysis due to the N for the intervention group being <10) and the rest were rated by parents, who were not blind. **Setting:** Home-based **Raters:** Teachers (who are not included in this analysis due to the N for the intervention group being <10) **Country:** USA
Participants	**Diagnosis:** Autism (diagnostic classification not reported) **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** Not reported **N:** 47 **Age:** Range: Not reported (Mean: 4.8 years) **Sex:** 30% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if: they were aged <6 years; had no additional complicating diagnosis; were not taking chronic medication; were not receiving active medical therapies (e.g. chelation); were already participating in early intervention treatment for ASD. **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Qigong massage training.** Qigong massage is an intervention based in Chinese medicine. Parents were trained in how to administer Qigong massage to their children at home. Throughout the study,

	parents delivered a daily protocol of 12 steps, including patting, pressing or shaking. Parents initially attended a 3-hr training session, which was followed by 7 weekly sessions lasting 30 minutes, where the trainer observed them using the technique and offered further support. Parents also received a training booklet and DVD to take home with them. **Delivery of intervention:** Massage was delivered to children individually, by their parents at home **Format or method of administration:** Individual **Intensity:** The intervention was delivered in daily sessions lasting approximately 15 minutes; a total of 29.75 hours (1.75 hours a week) **Duration of intervention:** 17 weeks **Total duration of follow-up:** 17 weeks
Outcomes	**Direct Outcome** **Coexisting problem or disorder: Sensory sensitivities** (as measured by Pervasive Developmental Disorder Behavior Inventory [PDDBI] - Sensory subscale; and the Sense and Self-Regulation Checklist [SSC]-Sense subscale) **Indirect Outcome** **Core autism feature: Overall autistic behaviours** (as measured by PDDBI - Autism Composite and Social, language and communication abilities, and Maladaptive behaviour subscales) **Impact on family** (as measured by Autism Parenting Stress Index [ASPI])
Study Design	RCT
Source of funding	Curry Stone Foundation and Northwest Health Foundation
Limitations	1. Unclear risk of selection bias: method of randomisation is clear, but concealment of allocation not reported 2. High risk of performance bias: participants and care administrators were not blind to treatment allocation 3. High risk of detection bias: all outcomes included in analysis were parent-rated and parents were not blind to treatment allocation on confounding factors 4. Unclear risk of selective reporting: All outcomes were reported but the study was not registered
Notes	Data were not extracted for the systems score of the SSC as not clear what outcome this subscale was measuring. Data could also not be extracted for the teacher-rated Autism Behaviour Checklist as N<10/arm

1.25 CHARACTERISTICS OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT SENSORY SENSITIVITIES

1.25.1 DUNBAR2012

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.25.2 LANG2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.25.3 PFEIFFER2011

Reason for exclusion	Efficacy data cannot be extracted and email sent to correspondence address to request data bounced back

1.25.4 SILVA2007

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.25.5 ZOLLWEG1997

Reason for exclusion	Less than 50% of the sample had a diagnosis of autism

1.26 REFERENCES OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT SENSORY SENSITIVITIES

Dunbar S, Carr-Hertel J, Lieberman H, Perez B, Ricks K. A pilot study comparison of sensory integration treatment and integrated preschool activities for children with autism. Internet Journal of Allied Health Sciences and Practice. 2012;10. Available from: http://ijahsp.nova.edu/articles/Vol10Num3/pdf/dunbar.pdf.

Lang R, O'Reilly M, Healy O, Rispoli M, Lydon H, Streusand W, et al. Sensory integration therapy for autism spectrum disorders: a systematic review. Research in Autism Spectrum Disorders. 2012;6:1004-1018.

Pfeiffer BA, Koenig K, Kinnealey M, Sheppard M, Henderson L. Effectiveness of sensory integration interventions in children with autism spectrum disorders: a pilot study. American Journal of Occupational Therapy. 2011;65:76-85.

Silva LMT, Cignolini A, Warren R, Budden S, Skowron-Gooch A. Improvement in sensory impairment and social interaction in young children with autism following treatment with an original Qigong massage methodology. American Journal of Chinese Medicine. 2007;35:393-406.

Zollweg W, Palm D, Vance V. The efficacy of auditory integration training: a double blind study. American Journal of Audiology. 1997;6:39-47.

1.27 CHARACTERISTICS OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT MOTOR SKILLS

1.27.1 WUANG2010

Reason for exclusion	Non-randomised group assignment

1.28 REFERENCES OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT MOTOR SKILLS

Wuang Y-P, Wang C-C, Huang M-H, Su C-Y. The effectiveness of simulated developmental horse-riding program in children with autism. Adapted Physical Activity Quarterly. 2010;27:113-126.

1.29 CHARACTERISTICS OF INCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

1.29.1 CHALFANT2007

Study ID	CHALFANT2007
Bibliographic reference	Chalfant AM, Rapee R, Carroll L. Treating anxiety disorders in children with high functioning autism spectrum disorders: a controlled trial. Journal of Autism and Developmental Disorders. 2007;37:1842-1857.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** No blinding of participants, care administrators and outcome assessors reported **Setting:** Clinical (no further information reported) **Raters:** Self-reports, parents and teachers **Country:** Australia
Participants	**Diagnosis:** Autism Spectrum Disorder (no diagnostic classification reported). 27.7% of participants had a diagnosis of 'High Functioning Autistic Disorder'

	and 72.3% had a diagnosis of 'Asperger's Disorder'. **Coexisting conditions:** All participants had a co-existing anxiety disorder (55.3% met the criteria for two anxiety disorders and 19.1% met the criteria for three anxiety disorders). Primary anxiety disorder diagnoses were Social Phobia (43%), Generalised Anxiety Disorder (29%), Separation Anxiety Disorder (17%), Specific Phobia (7%) and Panic Disorder (4%). 27.7% had a coexisting diagnosis of ADHD. **Qualifying Diagnostic Assessment:** Prior diagnosis of autism (made by a paediatrician, psychiatrist or clinical psychologist) was corroborated through accompanying documentation of diagnosis and clinical observations by the investigators during the pre-intervention assessment period. Diagnosis of anxiety disorder was assessed through the Anxiety Disorders Interview Schedule (ADIS). **N:** 51 participants were assigned to groups. Four participants dropped out of the intervention, so all demographic information and outcomes are based on 47 participants. **Age:** Range: 8-13 (Mean: 10.8) **Sex:** 26% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Participants were included if they: had a previous diagnosis of ASD from a paediatrician, psychiatrist or clinical psychologist; received confirmation of their diagnosis from investigators' clinical observations; and met the criteria for an anxiety disorder outside of the ASD symptoms (e.g. frequent, irrational **Exclusion criteria:** Children were excluded if they: had an intellectual delay; physical disability; were currently taking medication for anxiety or anti-depressants; presented with additional difficulties such as Conduct Disorder or Oppositional Defiant Disorder; had parents who were in the process of an acute marital breakdown
Interventions	**Experimental Intervention: The "Cool Kids" programme** (Lyneham et al., 2003) was adapted to meet the needs of children with autism and then applied to target components of anxiety. Topics included recognising the physical symptoms of anxiety, using coping skills such as 'self-talk', simple cognitive restructuring exercises and relapse prevention. Some sessions incorporated the families and involved planning weekly exposure tasks and families were also asked to keep a log of the outcome of these tasks. Parents were also offered sessions and provided with a manual to support their child's learning. Booster sessions were provided following completion of the programme. ASD-specific adaptations were made to the CBT programme including: extending the intervention over a longer period of time (6 months); using more visual aides and structured worksheets; devoting the most time to relaxation components (3 treatment sessions and 2 booster sessions) and exposure (4.5 treatment sessions and all booster sessions) because they involve more concrete exercises and place less emphasis on the children's communication skills; simplifying the information included in the cognitive therapy component (1.5 treatment sessions and 2 booster sessions) and providing children with large lists of possible alternative responses to assist them when required to generate their own helpful and unhelpful thoughts **Delivery of intervention:** Children received the intervention in groups of 6-8, delivered by two registered clinical psychologists.

	Format or method of administration: Group **Intensity:** The planned intensity was for children to attend twelve 2-hour sessions. A total of 24 hours (2 hours per week). No details on actual intensity are reported. **Duration of intervention:** 12 weeks. **Total duration of follow-up:** 12 weeks.
Outcomes	**Direct Outcome** **Coexisting problem or disorder: Anxiety** (as measured by the Revised Children's Manifest Anxiety Scale [RCMAS]; the Spence Children's Anxiety Scale [SCAS]: self-report and parent version; the Children's Automatic Thoughts Scale [CATS]; Strengths and Difficulties Questionnaire [SDQ]: Emotional: Parent and Teacher Versions) **Indirect Outcome** **Behaviour that challenges** (as measured by the Strengths and Difficulties Questionnaire [SDQ]: Externalising: Parent and Teacher Versions)
Study Design	RCT
Source of funding	Autism Spectrum Australia and the St George Foundation
Limitations	1. Unclear/unknown risk of selection bias as methods of randomisation and allocation concealment are not reported 2. High risk of performance bias as care for groups is not reported and participants and care administrators are not blind to treatment allocation 3. High risk of detection bias as outcome assessments are self-report, parent- and teacher-rated, so outcome assessors are not blind to treatment allocation and confounding factors. 4. Unclear risk of attrition bias, N=4 (12.5%) dropped out of experimental group and there was no dropout in control group
Notes	Not applicable

1.29.2 DRAHOTA2011/WOOD2009

Study ID	DRAHOTA2011/WOOD2009
Bibliographic reference	Drahota A, Wood JJ, Sze KM, Van Dyke M. Effects of cognitive behavioral therapy on daily living skills in children with high-functioning autism and concurrent anxiety disorders. Journal of Autism and Developmental Disorders. 2011;41:257-265. Wood JJ, Drahota A, Sze K, Har K, Chiu A, Langer DA. Cognitive behavioral therapy for anxiety in children with autism spectrum disorders: a randomized, controlled trial. Journal of Child Psychology and Psychiatry. 2009;50:224–234.
Methods	**Allocation:** Randomised **Matching:** Children were matched based on age and gender **Blindness:** Participants and care administrators were not blind to treatment allocation. Some outcome assessments were rated by independent graduate evaluators who were blind to treatment allocation. **Setting:** Research setting (no further details reported) **Raters:** Self-report, parents and independent graduate evaluators **Country:** USA

Participants	**Diagnosis:** Autism Spectrum Disorder (diagnostic classification criteria based on 'New System', Klin et al., 2005; 50% autistic disorder, 42.5% PDD-NOS and 7.5% Asperger syndrome) **Coexisting conditions:** All participants met the criteria for an anxiety disorder. 60% of participants had coexisting ADHD, 7% had a coexisting mood disorder (namely Dysthymia or Major Depressive Disorder) and 20% met the criteria for oppositional defiant disorder/conduct disorder. The number of DSM-IV diagnoses (including ASD and anxiety) range: 2-6 per child (mean: 4.28) **Qualifying Diagnostic Assessment:** Autism Diagnosis Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule-Module 3 (ADOS), a parent report checklist and a review of all previous assessments **N:** 40 **Age:** Range: 7-11 years (Mean: 9.2 years) **Sex:** 33% female **Ethnicity:** 48% white **IQ:** Not reported **Inclusion criteria:** Child participants met research criteria ('New System' diagnostic classification system based on Klin et al. 2005) for a diagnosis of autism, Asperger syndrome, or PDD-NOS (considered scores from ADI-R, ADOS-Module 3, a parent-report checklist about childrens' circumscribed interests and a review of all available previous assessment records); met DSM-IV diagnostic criteria for one of the following: separation anxiety disorder, social phobia, or obsessive compulsive disorder (corroborated using the Anxiety Disorders Interview Schedule for Children-Parent Version [ADIS-C/P]); were not taking any psychiatric medication at the baseline assessment, or were taking a stable dose of psychiatric medication (i.e., at least one month at the same dosage prior to the baseline assessment), and if medication was being used, children maintained the same dosage throughout the study. **Exclusion criteria:** Families were excluded if the child had a verbal IQ<70 (as assessed in previous testing, or, if there was any question about the child's verbal abilities noted by the independent evaluator at baseline, on the basis of the Wechsler Intelligence Scale for Children-IV administered by the independent evaluator); the child was currently in psychotherapy or social skills training, or was receiving behavioral interventions such as applied behavior analysis, the family was currently in family therapy or a parenting class, the child began taking psychiatric medication or changed his/her dosage during the intervention, or for any reason the child or parents appeared unable to participate in the intervention program
Interventions	**Experimental Intervention: Building Confidence CBT programme** (Wood and McLeod 2008) modified for use with children with ASD (Wood et al. 2007). Manualized intervention including coping skills training (e.g., affect recognition, cognitive restructuring, and the principle of exposure) followed by in vivo practice of the skills. The intervention also included a parent training component where parents were taught to support in vivo exposures and use positive reinforcement and communication skills to encourage their children's independence and autonomy. Autism-specific adaptations included the addition of some new modules to the manualized intervention which were aimed at social skills training for children with autism. For instance, additional intervention components included social coaching provided at school, home or in public immediately before the child attempted to join a social activity,

	reinforcement for positive social skills and a mentoring system at school. Other adaptations included an additional module which focused on building independence in self-care skills. In addition to adding new modules autism-specific adaptations were also made to general teaching approaches, for example, children's special interests were used as examples and rewards in teaching. **Delivery of intervention:** The intervention was delivered to individual families by two doctoral-level psychologists and 11 clinical or educational doctoral students **Format or method of administration:** Family **Intensity:** One 90-min session a week, for a duration of 16 weeks. A total of 24 hours. **Duration of intervention:** 16 weeks **Total duration of follow-up:** 29 weeks (16-week intervention followed by 3-month follow-up). Outcome data is for post-treatment only as there is no follow-up data for the control group
Outcomes	**Direct Outcome** **Coexisting problem or disorder: Anxiety** (as measured by the Anxiety Disorders Interview Schedule for Children - Clinical Severity Rating Scale [ADIS-CSR]; the Multidimensional Anxiety Scale for Children [MASC] and the Clinical Global Impression [CGI] - Improvement Scale) **Indirect Outcome** **Coexisting problem or disorder: Adaptive behaviour** (as measured by the Vineland Adaptive Behaviour Scales [VABS] - Daily living skills subscale) **Impact on family** (as measured by the Parent-Child Interaction Questionnaire [PCIQ] - Parent Intrusiveness subscale)
Study Design	RCT
Source of funding	National Institute of Mental Health grants F31-MH-73213 (PI: Amy Drahota) and R03-MH-075806 (PI: Jeffrey J. Wood), the Cure Autism Now Foundation (PI: Jeffrey J. Wood), and the UCLA Center for Autism Research and Training (PI: Jeffrey J. Wood)
Limitations	1. Unclear risk of selection bias: concealment of allocation method not reported and groups were not comparable at baseline 2. High risk of performance bias: participants and care administrators are not blind to treatment allocation 3. Detection bias is different for different outcomes: MASC and PCIQ has high risk of detection bias at the raters are parents and children and VABS has unclear risk of bias as based on interview with non-blind parents rather than direct behavioural observation High risk (direction unknown) of selective reporting bias: the study is registered, but a secondary outcome listed on ClinialTrials.gov is not reported
Notes	The daily living and impact on family outcomes are reported in Drahota et al., 2011 and are presented as part of the behaviour-focused psychological interventions. All anxiety outcomes are reported in Wood et al., 2009. Intention-to-treat analysis was available for impact on family and daily living skills outcomes and for dichotomous anxiety outcome measures, and where available this data was used. However, for continuous anxiety measures only available case data is reported.

1.29.3 REAVEN2012

Study ID	REAVEN2012
Bibliographic reference	Reaven J, Blakeley-Smith A, Culhane-Shelburne K, Hepburn S. Group cognitive behavior therapy for children with high-functioning autism spectrum disorders and anxiety: a randomized trial. Journal of Child Psychology and Psychiatry. 2012;53:410-419.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** No blinding of participants or care administrators reported. Outcome assessors were independent clinical evaluators who were blind to treatment allocation **Setting:** Not reported **Raters:** Independent clinical evaluators, but some measures were based on interviews with parents **Country:** USA
Participants	**Diagnosis:** DSM IV-TR ASD (Autism Spectrum Disorder) **Coexisting conditions:** All participants had a coexisting clinical anxiety disorder. The number of psychiatric diagnoses participants had in addition to ASD ranged from 1-8 (mean: 5) and the most common non-anxiety diagnostic categories were ADHD, disruptive disorders and mood disorders **Qualifying Diagnostic Assessment:** ADOS (Autism Diagnostic Observation Schedule) **N:** 50 **Age:** Range: 7.5-14 (Mean: 10.4) **Sex:** 4% female **Ethnicity:** 84% white **IQ:** Range 70-139 (Mean: 104.6) based on multiple IQ tests **Inclusion criteria:** Participants were included if they: were aged 7-14 years; had confirmation from one of the investigators of an ASD diagnosis based on a recent (within a year) ADOS and SCQ; were able to speak in full sentences (in order to complete the ADOS assessment); had symptoms of a clinical anxiety disorder based on three subscales of the Screen for Child Anxiety and Related Emotional Disorders assessment-parent version (SCARED): separation, social, generalised; had a VIQ of >70 (children with a VIQ <80 were assessed by clinicians to determine appropriateness for participation) **Exclusion criteria:** Children were excluded if: the independent clinical evaluator felt the childs primary psychiatric symptoms reflected another condition (e.g. depression or psychosis); if the child did not appear ready to participate in the group (for example, if they were able to separate from their parent without marked disruptive outbursts); if the parent could not commit to attending at least 80% of sessions
Interventions	**Experimental Intervention: Facing Your Fears.** The intervention involved multi-family group sessions and included large-group activities (children and parents together), small-group activities (children together; parents together), and dyadic work (parent/child pairs). CBT techniques were used throughout; emotion regulation, relaxation and graded exposure. Children were taught strategies to cope with anxiety and social skills. Parents attended sessions and played a coaching role for their child and were taught how parenting style can influence the child's anxiety. ASD-specific adaptations

	were made to the intervention including: consideration of the pacing of each session; use of a token reinforcement system to reward in-group behaviour; provision of visual structure and predictability of routine; use of multiple-choice worksheets and written examples of core concepts; inclusion of hands-on activities; focus on strengths and special interests; multiple opportunities for repetition and given time to practice new skills; encouraged to use video to consolidate learning of concepts and parents were given a detailed break-down of the intervention. **Delivery of intervention:** The intervention was delivered to children in groups of 3-6 by one clinical psychologist and two co-therapists who were clinical psychology trainees **Format or method of administration:** Group **Intensity:** The planned intensity was for children to attend 12 sessions that were 1.5 hours in duration. No information on actual intensity or number of weekly sessions was reported **Duration of intervention:** Range: 12-16 weeks (mean: not reported) **Total duration of follow-up:** 50 weeks (including 16 weeks of intervention, 2 weeks for pre-intervention measures to be obtained and 2-6 weeks following the sessions for the post-intervention measures to be collected, there was also a 3-month and 6-month post-intervention follow-up but data could not be extracted)
Outcomes	**Direct Outcome** **Coexisting problem or disorder: Anxiety** (as measured by the Anxiety Disorders Interview Schedule for Children - Parent version [ADIS-P] and the Clinical Global Impressions Scale - Improvement ratings [CGIS-I])
Study Design	RCT
Source of funding	Cure Autism Now, Autism Speaks, U.S Department of Health and Human Services (Grant #90DD0561)
Limitations	1. Unclear risk of selection bias: Randomisation was done through a computer-generated sequence, but method of concealment of allocation not reported 2. High risk of performance bias: No blinding of participants or care administrators reported 3. Unclear risk of detection bias for the ADIS-P: Outcome assessors were independent clinical evaluators, but this measure is based on a parent interview. Parents were not blind to treatment allocation and confounding factors. 4. High risk of selective reporting bias: No data reported for 3-month and 6-month post-intervention follow-up SCARED assessment 5. High risk of other bias: three of the investigators receive royalties from the intervention programme
Notes	Not applicable

1.29.4 SOFRONOFF2005

Study ID	SOFRONOFF2005
Bibliographic reference	Sofronoff K, Attwood T, Hinton S. A randomised controlled trial of a CBT intervention for anxiety in children with Asperger syndrome. Journal of Child

	Psychology and Psychiatry. 2005;46:1152-1160.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** No blinding of participants, care administrators or outcome assessors reported **Setting:** Not reported **Raters:** Parent-rated **Country:** Australia
Participants	**Diagnosis:** DSM-IV Asperger's Syndrome **Coexisting conditions:** 42% of participants had coexisting ADHD and 8% had coexisting depression **Qualifying Diagnostic Assessment:** Clinical interview conducted with parents (no further detail reported) and the Childhood Asperger Syndrome Test (CAST; cut-off 15) **N:** 76 (N=5 were assigned but did not meet CAST inclusion criteria; demographic and outcome data reported for N=71) **Age:** Range: 9-12 years (Mean: 10.6) **Sex:** 13% female **Ethnicity:** Not reported **IQ:** Range: 90-137 (Mean: 104.7) **Inclusion criteria:** Participants were included if: they had a primary diagnosis of Asperger Syndrome from a paediatrician and diagnosis was confirmed through a semi-structured clinical interview with the parent and the Childhood Asperger Syndrome Test (CAST cut-off >15); had symptoms of childhood anxiety based on parental report. **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: CBT for anxiety (child-only).** Using group discussion, practice opportunities, the concept of an 'emotional tool box' and social stories and homework assignments, participants explored positive emotions, feelings of anxiety, and strategies for 'fixing the feeling' including constructive methods to release the energy, expending energy in another way, relaxation, thinking about how other people can help and methods to weigh-up the probability of fears being realised. In the child-only intervention, parents were debriefed on how their child participated and given an outline of the between-session work. **CBT for anxiety (child and parent).** In the child and parent intervention, parents were trained as 'co-therapists' and were encouraged to coach their child throughout the different stages of the programme, as well as support with the between-session work. **Delivery of intervention:** The intervention was delivered to children in groups of 3, by post-graduate clinical psychology students **Format or method of administration:** Group **Intensity:** The planned intensity was for children to attend 6 sessions that were 2-hours in duration (1 a week) with a total of 12 hours intervention. No details of actual intensity reported **Duration of intervention:** 6-weeks **Total duration of follow-up:** 12 weeks; 6 weeks of intervention and 6-week follow-up
Outcomes	**Direct Outcome** **Coexisting problem or disorder: Anxiety** (as measured by the Spence Child

	Anxiety Scale - Parent version [SCAS-P])
Study Design	RCT
Source of funding	Not reported
Limitations	1. Unknown risk of selection bias: Methods of randomisation and allocation concealment not reported 2. High risk of performance bias: Participants and care administrators are not blind to allocation of treatment 3. High risk of detection bias: All outcomes are parent-rated and parents are not blind to allocation of treatment or confounding factors 4. High risk of selective reporting: Study has not been registered and not all outcomes reported
Notes	Efficacy data could not be extracted for two additional measures. The authors were contact for further information, but no response received. For analysis, significant differences were examined between the two active intervention arms (child-only and child + parent) and where there were no significant differences data from the two groups was combined and compared to waitlist control, where there were significant differences the intervention which was most similar to the other studies in the meta-analysis was selected

1.30 CHARACTERISTICS OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

1.30.1 DAVIS2012A

Reason for exclusion	Non-systematic review

1.30.2 LANG2010

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.30.3 REAVEN2009

Reason for exclusion	Non-randomised group assignment

1.30.4 SUNG2011

Reason for exclusion	Non-randomised group assignment

1.30.5 WHITE2004

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.31 REFERENCES OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

Davis NO, Kollins SH. Treatment for co-occurring attention deficit/hyperactivity disorder and autism spectrum disorder. Neurotherapeutics. 2012a;9:518-530.

Lang R, Regester A, Lauderdale S, Ashbaugh K, Haring A. Treatment of anxiety in autism spectrum disorders using cognitive behaviour therapy: a systematic review. Developmental Neurorehabilitation. 2010;13:53-63.

Reaven JA, Blakeley-Smith A, Nichols S, Dasari M, Flanigan E, Hepburn S. Cognitive-behavioral group treatment for anxiety symptoms in children with high-functioning autism spectrum disorders. a pilot study. Focus on Autism and Other Developmental Disabilities. 2009;24:27-37.

Sung M, Ooi YP, Goh TJ, Pathy P, Fung DSS, Ang RP, et al. Effects of cognitive-behavioral therapy on anxiety in children with autism spectrum disorders: a randomized controlled trial. Child Psychiatry and Human Development. 2011;42:634-649.

White AH. Cognitive behavioural therapy in children with autistic spectrum disorders. In: Bazian Ltd, ed. STEER: Succinct and Timely Evaluated Evidence Reviews. University of Southampton: Bazian Ltd and Wessex Institute for Health Research and Development;2004:volume 4 . Available from: http://www.signpoststeer.org/.

1.32 CHARACTERISTICS OF INCLUDED PHARMACOLOGICAL INTERVENTION STUDIES AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

1.32.1 ELILILLY2009/HARFTERKAMP2012

Study ID	ELILILLY2009/HARFTERKAMP2012
Bibliographic reference	Eli Lilly and Company. A Randomized, Double-blind Comparison of Atomoxetine Hydrochloride and Placebo for Symptoms of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents With Autism Spectrum Disorder. ClinicalTrials.gov NCT00380692. Available from: http://clinicaltrials.gov/ct2/show/NCT00380692. Harfterkamp M, van de Loo-Neus G, Minderaa RB, van der Gaag R-J, Escobar R, Schacht A, et al. A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. Journal of the American Academy of Child

	and Adolescent Psychiatry. 2012;51:733-741.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, parents, intervention administrators and outcome assessors were blind to group assignment **Setting:** Not reported **Raters:** Parent-, teacher- and clinician-rated **Country:** The Netherlands
Participants	**Diagnosis:** DSM-IV-TR autistic disorder (60%), Asperger's disorder (5%) or PDD-NOS (33%). NB: 2% had no ASD based on ADI-R **Coexisting conditions:** DSM-IV ADHD **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview-Revised (ADI-R) **N:** 97 **Age:** 6-17 years (mean: 9.9 years) **Sex:** 14% female **Ethnicity:** 98% white **IQ:** FIQ 61-138 (mean FIQ: 92.9; mean VIQ: 93.8; mean PIQ: 92.4) **Inclusion criteria:** Children were included if they: were aged 6-17 years old; had a diagnosis of autistic disorder, Asperger's disorder or PDD-NOS; meet DSM-IV criteria A-D for ADHD; score >=1.5 standard deviations above the norm for their diagnostic subtype using published norms for the ADHD Rating Scale-IV-Parent Version; IQ >60 **Exclusion criteria:** Children were excluded if they: weighed <20kg; met DSM-IV-TR criteria for Rett's disorder or childhood disintegrative disorder; had a history of bipolar I or II disorder, schizophrenia, another psychotic disorder, or substance abuse; were at serious suicidal risk; had a significant medical condition such as heart disease, hypertension, liver or renal failure, pulmonary disease, or seizure disorder (as indicated by history, physical exam or lab tests); had taken, or were currently taking, anticonvulsants for seizure control; present with a contraindication to the use of atomoxetine; are likely, according to the investigator's judgement, to need psychotropic medications during the study period or begin structured psychotherapy, or require hospitalisation or to be dismissed from in-patient treatment
Interventions	**Experimental Intervention: Atomoxetine** **Delivery of intervention:** Independent pharmacist **Format or method of administration:** Oral administration **Intensity:** Actual intensity not reported but planned intensity was a fixed final dose of 1.2mg/kg/day **Duration of intervention:** 8 weeks **Total duration of follow-up:** 28 weeks (8 week double-blind phase followed by 20 week open-label continuation phase, however, data only extracted for the double-blind phase as no control group data available for open-label continuation)
Outcomes	**Direct outcome:** **Coexisting problem or disorder: Hyperactivity/ADHD symptoms** (as measured by the DSM-IV ADHD Rating Scale-IV-Parent Version - Total score; the Clinical Global Impression Scale-ADHD-Improvement [CGI-ADHD-I]; the Conners' Teacher Rating Scale - Revised: Short Form [CTRS-R:S] - Oppositional, Hyperactivity, Cognitive/Attention and ADHD subscales; and

	the Aberrant Behaviour Checklist (ABC) - Hyperactivity & Noncompliance subscale) **Indirect outcomes:** **Core autism feature: Overall autistic behaviours** (as measured by Children's Social Behavior Questionnaire (CSBQ) - Total) Behaviour that challenges (as measured by the ABC - Irritability & Agitation, Lethargy & Social Withdrawal, Stereotypic Behaviour, Hyperactivity & Noncompliance, and Inappropriate Speech subscales) **Coexisting problem or disorder: Sleep problems** (as measured by Sleep Measure Scale - Time to fall asleep, Difficulty falling asleep, Total hours of sleep, Quality of sleep, and Functional outcome during day subscales) Impact on family: Parental distress (as measured by the General Health Questionnaire [GHQ-28] - Total score); and Parental stress (as measured by the Nijmeegse Ouderlijke Stress Index [NOSI] - Total score) **Adverse events** (as measured by dichotomous measures of: Any side effect; Discontinuation due to adverse events; Number of participants with abdominal pain during the trial; Number of participants with upper abdominal pain during the trial; Number of participants with diarrhoea during the trial; Number of participants with nausea during the trial; Number of participants with vomiting during the trial; Number of participants with fatigue during the trial; Number of participants with pyrexia during the trial; Number of participants with influenza during the trial; Number of participants with loss of appetite during the trial; Number of participants with myalgia during the trial; Number of participants with dizziness during the trial; Number of participants with headache during the trial; Number of participants with psychomotor hyperactivity during the trial; Number of participants with aggression during the trial; Number of participants with early morning awakening during the trial; and Number of participants with initial insomnia during the trial)
Study Design	RCT
Source of funding	Eli Lilly and Company
Limitations	1. Risk of detection bias is unclear/unknown as it is unclear if 8 weeks is a sufficient duration to detect significant treatment effects, particularly adverse events and most outcome measures are parent-reported or teacher-reported and as such are non-blind to other potentially confounding factors 2. High risk of other bias due to conflict of interest as study run and reported by pharmaceutical company
Notes	The ELILILLY2009 study results were posted on ClinicalTrials.gov, Study NCT00380692. Results for ABC hyperactivity included for both non-core feature of hyperactivity/ADHD symptoms and challenging behaviour meta-analyses. Data is not extracted for the Amsterdam Neurpsychological Tasks (ANT) or the Cytochrome P450 2D6 Genotype as the outcomes are outside the scope.

1.33 CHARACTERISTICS OF EXCLUDED PHARMACOLOGICAL INTERVENTION STUDIES AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

1.33.1 AMAN2000

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.33.2 CORTESE2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.33.3 RUPPMETHYLPHENIDATE2005

Reason for exclusion	High risk of carry-over given the cross-over design, short duration of each phase and lack of any washout in between treatment phases. Authors (Posey & Jahromi) were contacted requesting first period only data but one email bounced back (Posey) and no reply from other author (Jahromi)

1.34 REFERENCES OF EXCLUDED PHARMACOLOGICAL INTERVENTION STUDIES AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

Aman MG, Langworthy KS. Pharmacotherapy for hyperactivity in children with autism and other pervasive developmental disorders. Journal of Autism and Developmental Disorders. 2000;30:451-459.

Cortese S, Castelnau P, Morcillo C, Roux S, Bonnet-Brilhault F. Psychostimulants for ADHD-like symptoms in individuals with autism spectrum disorders. Expert Review of Neurotherapeutics. 2012;12:461-473.

Jahromi LB, Kasari CL, McCracken JT, Lee LS, Aman MG, McDougle CJ, et al. Positive effects of methylphenidate on social communication and self-regulation in children with pervasive developmental disorders and hyperactivity. Journal of Autism and Developmental Disorders. 2009;39:395-404.

Posey DJ, Aman MG, McCracken JT, Scahill L, Tierney E, Arnold LE, et al. Positive effects of methylphenidate on inattention and hyperactivity in pervasive developmental disorders: an analysis of secondary measures. Biological Psychiatry. 2007;61:538-544.

Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Archives of General Psychiatry. 2005;62:1266-1274.

1.35 CHARACTERISTICS OF INCLUDED PSYCHOSOCIAL AND PHARMACOLOGICAL INTERVENTION STUDIES AIMED AT COEXISTING MEDICAL OR FUNCTIONAL PROBLEMS

1.35.1 CORTESI2012

Study ID	CORTESI2012
Bibliographic reference	Cortesi F, Giannotti F, Sebastiani S, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomised placebo-controlled trial. Journal of Sleep Research. 2012;21:700-709.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Different blinding for different arms of the trial: For melatonin only and placebo groups, participants and researchers were blind to treatment allocation. No blinding is reported for combined treatment group and CBT-only group. **Setting:** Outpatient **Raters:** Parents were raters for one outcome measure; raters not reported for one outcome measure. **Country:** Italy
Participants	**Diagnosis:** DSM-IV-TR Disorders **Coexisting conditions:** All participants had mixed sleep onset and maintenance insomnia (characterised as sleep onset latency and/or wake after sleep onset of >30 mins, for 3 or more nights per week. **Qualifying Diagnostic Assessment:** ADI-R & ADOS/ADOS-G **N:** 160 **Age:** Range: not reported (mean: 6.7 years) **Sex:** 17% female **Ethnicity:** 99% white **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 4-10 years; had a diagnosis of autistic disorder based on DSM-IV-TR which was confirmed using the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G); suffered from mixed sleep onset and maintenance insomnia (sleep onset latency and waking from sleep for more than 30 minutes) occuring on three nights a week or more; no other neurological/ psychiatric/medical conditions. **Exclusion criteria:** Children were excluded if they: had not been drug free for 6 months prior to the start of the study and for the suration of the study; had any other psychiatric co-morbidities (indicated by a score of +/- 70 on the

	syndrome scales or composite scales of the Child Behaviour Checklist; were currently receiving psychotherapy or any other behavioural or family-based therapy.
Interventions	**Experimental Intervention: Melatonin** was administered to participants in tablet form and taken orally. High purity melatonin was administered. Doses included both fast-release melatonin and controlled-release melatonin, taking 6 hours following administration. Participants were required to attend a 15 minute meeting at the outpatient clinic, where they reported any adverse effects and collected their dose for the following 2 weeks. For participants in the melatonin-only group, no behavioural recommendations were made throughout the study. **CBT** comprising cognitive, behavioural and educational components was delivered to families, with the focus of reducing insomnia in children. The cognitive component focussed on addressing maladaptive beliefs/attitudes about sleep, while the behavioural and educational components included instructions around managing the child's sleep and methods of implementing healthy sleep behaviours to replace poor habits. Instructions included monitoring length and fequency of naps, encouraging children to remain in their own bed the whole night and engaging in fun pre-bedtime activities before the child was required to go to sleep. Following completion of the initial CBT course, maintenance sessions continued for the duration of the study to continue to consolidate treatment strategies. Participants received placebo made in the identical formulation to the melatonin medication. The active and inactive pills were identical in appearance, flavour and smell. The same protocal for melatonin administration was used for administration of the placebo. No behavioural recommendations were made to the placebo group throughout the study. **Delivery of intervention:** Melatonin and placebo were administered by parents at home. CBT was delivered to families individually, by experienced clinical psychologists.at the research setting. **Format or method of administration:** Oral / individual **Intensity:** Melatonin: Participants received 3mg of melatonin once a day in the evening for 12 weeks. Formulation included 1mg fast-release and 2mg slow-release melatonin. Placebo: Participants received 3mg of the placebo formulation, once a day in the evening for 12 weeks CBT: Families received four, weekly CBT sessions of 50 mins. A total of 3.3 hours. (Following the four sessions, families were also offered twice-monthly, 'individually tailored' sessions, but duration on these sessions was not reported). **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct Outcome** **Coexisting problem of sleep** (as measured by actigraphically derived data [total sleep time, sleep onset latency, wake after sleep onset, naptimes, sleep efficiency and bedtime] amd the Children's Sleep Habits Questionnaire [CSHQ])
Study Design	RCT
Source of funding	Study reports that no financial support was given

Limitations	1. Unclear risk of selection bias: Randomisation was done through a computerised random number generator, but concealment of allocation is not reported 2. Risk of performance bias is different for different arms of the trial: High risk for all comparisons involving CBT 3. Unclear risk of selective reporting: all outcomes are reported but the study is not registered 4. Risk of detection bias is different for different outcomes: Low risk for actigraph data (for all comparisons), high risk for CSHQ for comparisons involving CBT, low risk for CSHQ for melatonin and placebo comparison
Notes	Not applicable

1.35.2GRINGRAS2012

Study ID	GRINGRAS2012
Bibliographic reference	Gringras P, Gamble C, Jones AP, Wiggs L, Williamson PR, Sutcliffe A, et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. British Medical Journal. 2012;345:e6664.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Participants, care administrators and parents were blind to treatment allocation **Setting:** Outpatient **Raters:** Raters were parents for one measure and for one measure were not reported **Country:** UK
Participants	**Diagnosis:** Autism Spectrum Disorder (diagnostic classification not reported; data were taken from a wider sample of participants with neurodevelopmental disorders, but authors were contacted for disaggregated data for ASD sample). **Coexisting conditions:** All participants had a sleep disorder (characterised as sleep onset latency of more than 1 hour after lights-out and/or less than six hours sleep per night, for 3/5 nights). No other details of coexisting conditions reported **Qualifying Diagnostic Assessment:** Adaptive Behaviour Assessment System (inclusion based on score of ≥1.5 SD below the mean) **N:** 63 **Age:** Range 3.5-15.8years (Mean: 8.7 years) **Sex:** 29% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 3 years-15 years 8 months; had a neurodevelopmental disorder resulting in a score on the Adaptive Behaviour Assessment System of ≥1.5 SD below the mean; were reported by parents to have had a sleep disorder for at least the five months leading up to the study (characterised as sleep onset latency of more than 1 hour after lights-out and/or less than six hours sleep per night, for 3/5 nights).

	Exclusion criteria: Children were excluded if they: had used melatonin in the five months leading up to the study; were taking any other medications that could cause sleepiness
Interventions	**Experimental Intervention: Melatonin** was administered by parents in oral form where possible, or through a feeding tube if necessary, 45 minutes before bedtime. Children were given a small dose of 0.5mg at the start of the trial and this was increased every week for four weeks to a maximum of 12mg if: the child continued to meet the criteria for a sleep disorder; had experienced no serious adverse events; five of the previous seven doses (1 week) had been received. If adverse events were experienced, the dose was reduced. Participants received placebo made with an internal and external appearance identical to the intervention. **Delivery of intervention:** Melatonin and placebo were administered to children individually by their parents, within their home. **Format or method of administration:** Oral **Intensity:** Planned intensity: an initial dose of 0.5mg was received at randomisation. This dose was increased every week for four weeks (if necessary) in three dose increments; 2mg, 6mg to a maximum of 12mg. Actual intensity is not reported. **Duration of intervention:** Up to 12 weeks (mean duration not reported) **Total duration of follow-up:** Up to 12 weeks (mean follow-up not reported)
Outcomes	**Direct Outcome** **Coexisting problem of sleep** (as measured by parent-recorded sleep diaries) **Indirect Outcome** **Adverse events** (as measured by Treatment Emergent Signs and Symptoms [TESS])
Study Design	RCT
Source of funding	NIHR Health Technology Assessment programme (project number 05/14/02)
Limitations	Unclear risk of selective reporting: All outcomes are reported but study is not registered
Notes	Data were derived from a larger sample of children with neurodevelopmental disorders. Disaggregated data relating to children with autism were received from the authors upon request. Data were also collected from actigraph, but due to <10 participants in each arm, could not be extracted

1.36 CHARACTERISTICS OF EXCLUDED PSYCHOSOCIAL AND PHARMACOLOGICAL INTERVENTION STUDIES AIMED AT COEXISTING MEDICAL OR FUNCTIONAL PROBLEMS

1.36.1 GUENOLE2011

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.36.2 ROSSIGNOL2011

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.36.3 SCHRECK2001

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.36.4 VRIEND2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.36.5 WASDELL2008

Reason for exclusion	Less than 50% of the sample had a diagnosis of autism

1.36.6 WRIGHT2011

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.37 REFERENCES OF EXCLUDED PSYCHOSOCIAL AND PHARMACOLOGICAL INTERVENTION STUDIES AIMED AT COEXISTING MEDICAL OR FUNCTIONAL PROBLEMS

Guénolé F, Godbout R, Nicolas A, Franco P, Claustrat B, Baleyte J-M. Melatonin for disordered sleep in individuals with autism spectrum disorders: systematic review and discussion. Sleep Medicine Reviews. 2011;15:379-387.

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Schreck KA. Behavioral treatments for sleep problems in autism: empirically supported or just universally accepted? Behavioral Interventions. 2001;16:265-278.

Vriend JL, Corkum PV, Moon EC, Smith IM. Behavioral interventions for sleep problems in children with autism spectrum disorders: current findings and future directions. Journal of Pediatric Psychology. 2011;36:1017-1029.

Wasdell MB, Jan JE, Bomben MM, Freeman RD, Rietveld WJ, Tai J, et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. Journal of Pineal Research. 2008;44:57-64.

Wright B, Sims D, Smart S, Alwazeer A, Alderson-Day B, Allgar V, et al. Melatonin versus placebo in children with autism spectrum conditions and severe sleep problems not amenable to behaviour management strategies: a randomised controlled crossover trial. Journal of Autism and Developmental Disorders. 2011;41:175-184.

1.38 CHARACTERISTICS OF INCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT COEXISTING MEDICAL OR FUNCTIONAL PROBLEMS

1.38.1 HANDEN209

Study ID	HANDEN2009
Bibliographic reference	Handen BL, Melmed RD, Hansen RL, Aman MG, Burnham DL, Bruss JB, et al. A double-blind, placebo-controlled trial of oral human immunoglobulin for gastrointestinal dysfunction in children with autistic disorder. Journal of Autism and Developmental Disorders. 2009;39:796-805.
Methods	**Allocation:** Randomised **Matching:** Stratified by site and age (2-11 years and 12-17 years) **Blindness:** Participants are blinded and paper states 'double-blind' but it is unclear who else is blinded, for instance, the intervention administrators, parents, outcome assessors, and so on **Setting:** Not reported **Raters:** Parent-rated and clinician-rated, but for most outcome measures outcome assessors not reported **Country:** USA
Participants	**Diagnosis:** DSM-IV Autism **Coexisting conditions:** Gastrointestinal problems (a history of chronic and persistent gastrointesinal disturbance based on Rome II criteria for the

	diagnosis of irritable bowel syndrome corroborated during 2-week screening period using parent-rated daily GI symptoms data entered into a Palm Pilot) **Qualifying Diagnostic Assessment:** Diagnosis corroborated using the Autism Diagnostic Interview-Revised (ADI-R) **N:** 125 **Age:** 2-17 years (mean: 7.3 years) **Sex:** 14% female **Ethnicity:** 84% white **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 2-17 years; had a DSM-IV diagnosis of autism based on history and examination by clinicians experienced in the diagnosis of autism and corroborated by the ADI-R; a Clinical Global Impression-Severity (CGI-S) score of >=3 for autistic symptoms; a history of chronic and persistent gastrointestinal (GI) disturbance based on Rome II criteria for the diagnosis of irritable bowel syndrome corroborated during 2-week screening period using parent-rated daily GI symptoms data entered into a Palm Pilot (criteria included GI disturbance, of either constipation, diarrhoea or alternating periods of constipation and diarrhoea, for at least 6 weeks, but not necessarily consecutive weeks during the last 3 months and at least one of the following present, abnormal gaseousness, bloating or symptoms of moderate-to-severe abdominal pain or discomfort); had no elective changes in medication, diet intervention or behavioural therapy during the trial (based on carers agreement) **Exclusion criteria:** Children were excluded if they: showed evidence of a GI infection based on stool laboratory tests at baseline; had a known diagnosis of other GI pathology; were currently using antibiotics or antifungal medications, chelation therapy, medication affecting GI transit (stool softeners and bulking agents were permitted if constant doses were used for at least 30 days prior to the screening visit and no changes in dosing were planned during the trial); had any changes in diet intervention or alternative medical therapies (such as gluten-casein free diets, vitamin supplements) within 30 days prior to the screening visit; had any changes in psychotropic medication within 30 days prior to the screening visit (or 5 weeks for fluoxetine); had a DSM-IV diagnosis of a pervasive developmental disorder other than autism; showed evidence of a seizure disorder, Fragile x syndrome, Tuberous Sclerosis Complex, liver or pancreatic disease, cystic fibrosis, chronic infection, previous GI surgery (except fundoplication, appendectomy, gastrostomy, endoscopy, pyloromyotomy, or herniorraphy); were pregnant; had previously participated in another study within 60 days prior to the screening visit; had IgA deficiency (defined as serum IgA<5 mg/dl); had a history of severe hypersensitivity to human immunoglobulin; had received treatment with any human immunoglobulin and/or immunoglobulin products within 90 days prior to the screening visit; were receiving any concurrent medication that would compromise tolerance of drug or compliance with the protocol; had clinically significant abnormal laboratory test values at baseline; did not have data for at least 11 of the 14 days of daily parent-completed diary assessments or the weekly assessment during the screening period; had a GI symptoms score of <5 for week 2 and/or week 1 of the screening period; had a MGIS core of moderately or substantially improved during week 2 and/or week 1 of the screening period; had carers who were unable or unwilling to follow directions and use the electronic diary data entry system

Interventions	**Experimental Intervention: Human immunoglobulin** (IGOH; Oralgam) delivered in low dose (140mg/day), moderate dose (420mg/day) or high dose (840mg/day). The IGOH consisted of intravenous immunoglobulin (IVIG) in 60% sucrose (stablilizer) lyophilized into a white powder **Delivery of intervention:** Identity and blinding of intervention administrator not reported **Format or method of administration:** Oral administration **Intensity:** Actual intensity not reported but planned intensity was 140mg/day, 420mg/day or 840mg/day for low, moderate and high dose arms respectively **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct outcome:** **Coexisting problem or disorder: Gastrointestinal symptoms** (as measured by a dichotomous measure of positive treatment response [defined as 'moderately or substantially improved' on at least two of last 4 assessments or 'somewhat improved' for all of last 4 assessments of the Modified Global Improvement Scale [MGIS] for GI symptoms]) **Indirect outcomes:** **Behaviour that challenges** (as measured by a clinician-rated dichotomous measure of positive treatment response based upon the severity of behavioural problems [defined as 'much improved/very improved' on Clinical Global Impression-improvement, CGI-I]) and a parent-rated dichotomous measure of positive treatment response based upon the severity of behavioural problems [defined as 'much improved/very improved' on Parent Global Impression-improvement, PGI-I]) **Adverse events** (as measured by dichotomous measures of: Any side effect; Discontinuation due to adverse events; Number of participants with infections or infestations during the trial; Number of participants with gastrointestinal disorders during the trial; Number of participants with psychiatric disorders during the trial; Number of participants with respiratory, thoracic or mediastinal disorders during the trial; Number of participants with skin or subcutaneous tissue disorders during the trial; Number of participants with general disorders or administration site conditions during the trial; Number of participants with nervous system disorders during the trial; Number of participants with injury, poisoning or procedural complications during the trial; Number of participants with investigations during the trial; Number of participants with metabolism or nutrition disorders during the trial; Number of participants with eye disorders during the trial; Number of participants with blood or lymphatic system disorders during the trial; Number of participants with renal or urinary disorders during the trial; Number of participants with ear or labyrinth disorders during the trial; Number of participants with immune system disorders during the trial; Number of participants with vascular disorders during the trial)
Study Design	RCT
Source of funding	PediaMed Pharmaceuticals
Limitations	1. Risk of selection bias is unclear/unknown as insufficient detail reported with regards to allocation concealment and group comparability at baseline is unclear 2. Risk of performance bias is unclear/unknown as paper states 'double-blind' but gives no further detail with regards to who is blinded, i.e. parent,

	investigator, intervention administrator, outcome assessor 3. Risk of detection bias is unclear/unknown as paper states 'double-blind' but gives no further detail with regards to who is blinded so unclear if parent-rated and/or clinician-rated outcome assessors were blinded. Also the reliability and validity of some outcome measures is unclear, as the MGIS has not been validated in an autistic population and the outcome measure used to assess adverse events unclear 4. High risk of selective reporting bias as no data could be extracted for the ABC and continuous data could not be extracted for the MGIS scale, Daily GI Symptom Score, or Clinical Global Impression of Improvement (CGI-I) scale 5. High risk of other bias due to potential conflict of interest as study funded by pharmaceutical company
Notes	Trial protocol is registered on ClinicalTrials.gov, Study ID NCT00110708. Contacted author regarding missing outcome data but no reply. An initial comparison compared high and low dose arms. No significant differences were found between high and low dose arms for positive treatment effects or for adverse events and as a result all dose groups were combined and compared against placebo for meta-analysis. Subgroup analysis (by predominant bowel pattern and by age) performed for the primary outcome (gastrointestinal symptoms) but no significant subgroup differences.

1.39 CHARACTERISTICS OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT COEXISTING MEDICAL OR FUNCTIONAL PROBLEMS

1.39.1 HONOMICHL2002

Reason for exclusion	Data could not be extracted as N<10/arm due to cross-over and multisite design

1.39.1 PARRACHO2010

Reason for exclusion	Attrition was greater than 50% of the sample randomized and because much of this drop-out occurred either during the baseline period or in equal numbers by group before the end of the first crossover trial period, analysis of the dichotomous measure of drop-out was not considered informative

1.40 REFERENCES OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES AIMED AT COEXISTING MEDICAL OR FUNCTIONAL PROBLEMS

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Parracho HMRT, Gibson GR, Knott F, Bosscher D, Kleerebezem M, McCartney AL. A double-blind, placebo-controlled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum disorders. International Journal of Probiotics and Prebiotics. 2010;5:69-74.