APPENDIX 14C: CLINICAL EVIDENCE –STUDY CHARACTERISTICS TABLES: INTERVENTIONS AIMED AT BEHAVIOUR THAT CHALLENGES

1.1 CHARACTERISTICS OF INCLUDED PSYCHOSOCIAL INTERVENTION STUDIES

1.1.1 AMAN2009/ARNOLD2012/SCAHILL2012

Study ID	AMAN2009/ARNOLD2012/SCAHILL2012
Bibliographic reference	Aman MG, McDougle CJ, Scahill L, Handen B, Arnold LE, Johnson C, et al. Medication and parent training in children with pervasive developmental disorders and serious behavior problems: results from a randomized clinical trial. Journal of the American Academy of Child and Adolescent Psychiatry. 2009;48:1143-1154. Arnold LE, Aman MG, Li X, Butter E, Humphries K, Scahill L, et al. Research Units of Pediatric Psychopharmacology (RUPP) autism network randomized clinical trial of parent training and medication: one-year follow-up. Journal of the American Academy of Child and Adolescent Psychiatry. 2012;51:1173-1184. Scahill L, McDougle CJ, Aman MG, Johnson C, Handen B, Bearss K, et al. Effects of risperidone and parent training on adaptive functioning in children with pervasive developmental disorders and serious behavioral problems. Journal of American Academy of Child and Adolescent Psychiatry. 2012;51:136-146.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Investigators, care administrators, outcome assessors (given all outcome measures relied on parent-report), participants and parents were non-blind **Setting:** Not reported **Raters:** Clinician-rated interview and parent-report **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR pervasive developmental disorder (65% autistic disorder, 28% PDD-NOS, and 6% Asperger's disorder) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis was corroborated using the Autism Diagnostic Interview-Revised (ADI-R) **N:** 124 **Age:** Range not reported (mean: 7.4 years) **Sex:** Not reported **Ethnicity:** 75% white **IQ:** Not reported (19% mild LD; 24% moderate LD) **Inclusion criteria:** Children were included if they: had a diagnosis of ASD (autism, PDD-NOS, Asperger's disorder) established by DSM-IV-TR clinical criteria and corroborated by the Autism Diagnostic Interview-Revised (ADI-R); were aged 4-14 years; had serious behavioural problems as defined by a score of >18 on the Irritability subscale of the parent-rated ABC and a score of >=4 on the CGI-Severity scale; had been medication free for 2 weeks for most

	psychotropic drugs and for 4 weeks for fluoxetine and/or depot neuroleptics; had an IQ of >=35 or a mental age of >= 18 months as measured by the Stanford-Binet 5, Leiter International Performance Scale, or Mullen Scales of Early Learning. **Exclusion criteria:** Children were excluded if they: had a positive beta human chorionic gonadotropin pregnancy test for girls; had a previous adequate trial of risperidone; had a diagnosis of other PDD (i.e., Rett's disorder, childhood disintegrative disorder); had a lifetime diagnosis of schizophrenia, other psychotic disorder, bipolar disorder, or current diagnosis of major depression, obsessive-compulsive disorder, or substance abuse; had a significant medical condition (e.g., heart, liver, renal, pulmonary disease); had an unstable seizure disorder (had not been seizure-free for at least 6 months or anticonvulsant treatment had not been stable for at least 4 weeks); had significant abnormality on routine laboratory test.
Interventions	**Experimental Intervention: Combined risperidone (or aripiprazole if risperidone was ineffective) and parent training** based on the RUPP manual (Scahill et al., 2009). Parent training involved 7-9 weekly 60-90 minute sessions where parents were taught to use preventative approaches (e.g. visual schedules), effective use of positive reinforcement, and teaching compliance, functional communication skills and specific adaptive skills. Parent training teaching techniques included direct instruction, use of video vignettes, practice activities, behaviour rehearsal with feedback, role-playing, and individualized homework assignments. **Control intervention: Risperidone (or aripiprazole if risperidone was ineffective)** **Delivery of intervention:** Delivery of antipsychotics not reported. Parent training was delivered by one therapist per parent or couple. **Format or method of administration:** Not reported for antipsychotics, individual/family for parent training **Intensity:** Experimental intervention: Risperidone (or aripiprazole) 0.5-3.5mg/day (mean: 2mg/day) and 10.8 60-90 min sessions for parent training Control intervention: Risperidone (or aripiprazole) 0.5-3.5mg/day (mean: 2.3mg/day) **Duration of intervention:** 24 weeks **Total duration of follow-up:** 54-162.5 weeks (mean: 80 weeks; including one-year post-intervention follow-up)
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by the Home Situations Questionnaire [HSQ] - Severity score; the Aberrant Behavior Checklist [ABC] - Irritability, Lethargy, Stereotypy, Hyperactivity and Inappropriate Speech subscales; and the Noncompliance Index [based on Vineland Daily Living Skills domain]) **Indirect outcomes:** **Core autism feature: Restricted interests and rigid and repetitive behaviours** (as measured by the Children's Yale-Brown Obsessive Compulsive Scales-PDD [CYBOCS-PDD] - Compulsions subscale) **Coexisting problem or disorder: Adaptive behaviour** (as measured by the

	Vineland Adaptive Behavior Scales [VABS] - Daily living skills, Socialization, and Communication subscales, and Adaptive Composite score)
Study Design	RCT
Source of funding	National Institute of Mental Health RUPP grants: Ohio State University (U10MH66768); Indiana University (U10MH66766); and Yale University (U10MH66764)
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method was unclear and insufficient detail reported with regards to allocation concealment and there were significant differences between groups at baseline (the control group had significantly higher scores on ABC-Stereotypy and lower scores on Vineland Adaptive Behavior Scale subscales and fewer participants with average IQ than the experimental group at baseline) 2. High risk of performance bias as care administrators were not blind to group assignment 3. High risk of response bias as participants and parents were not blind to group assignment 4. High risk of detection bias as outcome measures were based on non-blind parent-report and there were reliability and validity concerns with regards to the primary outcome measure (the Home Situations Questionnaire [HSQ]) 5. High risk of attrition bias due to higher dropout rates in the experimental (combined risperidone and parent training) group (N=20; 27% attrition) than the control (risperidone only) group (N=9; 18% attrition) 6. High risk of selective reporting bias as efficacy data was not reported for the secondary outcome of Clinical Global Impression (CGI)-Improvement as listed on ClinicialTrials.gov 7. High risk of other bias due to conflict of interest as the study authors were consultants to pharmaceutical companies and the study drug was provided by Johnson&Johnson
Notes	This trial is registered on ClinicalTrials.gov, Study NCT00080145. Contacted author regarding missing outcome data and no reply. Behaviour that challenges outcomes and the CYBOCS-PDD are reported in AMAN2009. The adaptive behaviour outcomes are reported in SCAHILL2012. Follow-up data for behaviour that challenges outcomes are reported in ARNOLD2012.

1.1.2 CARR2006

Study ID	CARR2006
Bibliographic reference	Carr EG, Blakeley-Smith A. Classroom intervention for illness-related problem behavior in children with developmental disabilities. Behavior Modification. 2006;30:901-924.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Non-blind **Setting:** Educational (school)

	Raters: Teaching assistants **Country:** USA
Participants	**Diagnosis:** DSM-IV ASD or mental retardation (76.2% autism; 9.5% PDD; 14.3% learning disabilities) **Coexisting conditions:** 81% with learning disabilities; 5% with seizure disorder **Qualifying Diagnostic Assessment:** Clinical interview with school psychologist **N:** 22 (N=1 dropped out post-randomisation as changed school districts) **Age:** 3-11 years (mean: 7.3 years) **Sex:** 14% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Participants were selected on the basis of nomination by both teachers and parents as students who appeared to experience problem behaviour when ill. The first 22 children whom both teachers and parents confirmed as showing an association between problem behaviour and illness were selected for inclusion. **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Behavioural intervention and medical intervention.** The behavioural intervention aimed at addressing the problem of escape motivated problem behaviour associated with illness. Strategies included: behavioural momentum (Mace et al., 1988; defined as beginning an academic session with a mastered task and then interspersing 2-4 non-mastered tasks between successive presentations of the mastered tasks); increased choice of and access to reinforcement (Dyer et al., 1990; defined as presenting the student with 4-6 reinforcers to choose from rather than a single one as was typical and reducing the number of correct responses required to access reinforcement by 30% to 50%); and escape extinction and prompts (Carr et al., 1980; defined as maintaining the presentation of academic demands even after the occurrence of problem behaviour and not allowing the student to escape from completing the task and providing an imitative, gestural or physical prompt to ensure correct responding). **Control Intervention: Medical intervention.** Consistent with the school protocol for illness, children in both the experimental and control groups were taken to the school nurse to received medical treatment for discomfort or pain **Delivery of intervention:** Behavioural intervention was delivered in an individual format by teaching assistants in the classroom. Control and experimental participants were always placed in different classrooms. **Format or method of administration:** Individual **Intensity:** Intensity was variable as intervention was delivered in response to illness-related problem behaviour **Duration of intervention:** 43 weeks **Total duration of follow-up:** 43 weeks (follow-up for waitlist control group was 56 weeks as the intervention was delivered in the post-treatment period).
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by a study-specific problem behaviour questionnaire. Data was extracted for the Likert rating of the child's

	most serious problem behaviours)
Study Design	RCT
Source of funding	National Institute on Disability and Rehabilitation Research, U.S. Department of Education (Grant H133B98005)
Limitations	1. Risk of selection bias is unclear/unknown due to 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. High risk of detection bias as outcome was assessed by the same individuals who delivered the intervention and outcome assessment was not blind to group assignment and the outcome measure was designed specifically for the study and as such lacks formal assessments of reliability and validity 5. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered
Notes	Not applicable

1.1.3 SOFRONOFF2004

Study ID	SOFRONOFF2004
Bibliographic reference	Sofronoff K, Leslie A, Brown W. Parent management training and Asperger syndrome: a randomized controlled trial to evaluate a parent based intervention. Autism. 2004;8:301-317.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Non-blind **Setting:** University clinic **Raters:** Parent-report **Country:** Australia
Participants	**Diagnosis:** Asperger syndrome **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Recent diagnosis of Asperger syndrome by consultant paediatrician at the Mater Children's Hospital, Queensland, Australia **N:** 51 **Age:** 6-12 years (mean: 9.3 years) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Not reported **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Parent training:** This three-armed trial included two active intervention arms that involved the same intervention content but

	in one group the parent training was delivered in a one-day group workshop (parent training one-day workshop group) and in the other arm the same parent training content was delivered in individual therapist-parent sessions over 6 weeks (parent training individual sessions group). The parent training consisted of six components (and in the individual sessions group these were delivered in a one component/week format): Psychoeducation (through video demonstration and discussion the nature of Asperger syndrome, the heterogeneity of the disorder and the importance of considering the child's perspective in problem situations were outlined and parents were encouraged to give examples of aspects of the disorder affecting their own child); Comic Strip Conversations (parents were presented with a technique devised by Gray, 1994a, which involves using simple drawings to illustrate a conversation between two people and to emphasize what the people may be thinking); Social Stories (parents were presented with another technique devised by Carol Gray [Gray, 1994b] which involves creating a short story specifically for a target child in order to illustrate a particular situation including social cues, anticipated actions and information on what is occurring and why); Management of problem behaviours (parents were introduced to common problem behaviours for children with Asperger syndrome, including interrupting, temper tantrums, anger, non-compliance and bedtime problems, and techniques for dealing with these problems were outlined); Management of rigid behaviours and special interests (the focus of this component was to emphasize the importance of parents understanding the rigid or repetitive behaviour from their child's perspective in order to understand why their child has a need for routines and also as a potential way of using a special interest of their child as a reward to facilitate other activities); and Management of anxiety (parents were taught that problem behaviours were often the result of anxiety and the importance for parents to recognise and address their child's anxiety were emphasised as a means of not just treating but also preventing anxiety-inducing situations) **Delivery of intervention:** Group size of 18 for the one-day workshop group. The individual/s administering the one-day group workshop not reported but for the individual sessions the intervention administrator was a graduate student **Format or method of administration:** Group-based for the one-day workshop group and individual for the parent training individual sessions group **Intensity:** Actual intensity not reported but planned intensity was one day (6 hours) for the workshop group and 6 hours over 6 weeks (1 hour/week) for the individual sessions group **Duration of intervention:** 1 day for workshop group and 6 weeks for individual sessions group **Total duration of follow-up:** 19 weeks (including intervention ranging from 1 day to 6 weeks, followed by a 4-week post-intervention assessment and a 3-month follow-up)
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by the Eyberg Child Behaviour Inventory [ECBI] - Number of problem behaviours and Intensity of problem behaviours subscales) **Indirect outcome:**

	Core autism feature: Impaired reciprocal social communication and interaction (as measured by the Social Skills Questionnaire [Spence, 1995] - Total score)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear, the paper simply states that participants were randomised as questionnaires were returned. There was also insufficient detail reported with regards to group comparability at baseline and 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 measures were parent-reported and parents were the participants in the intervention and were non-blind 5. Risk of attrition bias is unclear/unknown as the timing of assessments is not entirely clear from the paper but post-intervention assessments are described as occurring at 1-month and 3-months post-intervention, and if this is accurate (namely that the follow-up periods were calculated from the end of intervention) then the follow-up durations are different for the two active interventions, and unclear for the waitlist control group, as the workshop intervention duration is only one day compared to the six week individual sessions intervention 6. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	The two active intervention arms were initially compared and where there were no significant differences the groups were combined and entered into meta-analysis. Where there was a significant difference between active intervention arms the data from each active intervention arm (relative to treatment-as-usual) was entered into the meta-analysis as subgroups (with the subtotal function disabled).

1.1.4 SOFRONOFF2007

Study ID	SOFRONOFF2007
Bibliographic reference	Sofronoff K, Attwood T, Hinton S, Levin I. A randomized controlled trial of a cognitive behavioural intervention for anger management in children diagnosed with Asperger syndrome. Journal of Autism and Developmental Disorders. 2007;37:1203-1214.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** No blinding of participants, individuals responsible for administering care or outcome assessors reported **Setting:** Not reported **Raters:** Parents **Country:** Australia
Participants	**Diagnosis:** DSM-IV diagnosis of Asperger Syndrome

	Coexisting conditions: Co-exsisting conditions were not excluded from the study. 45% had an additional diagnosis of ADHD. No further information reported **Qualifying Diagnostic Assessment:** CAST (Childhood Asperger Syndrome Test) and clinical interview conducted with parents (no further detail reported) **N:** 52 **Age:** Range: 9.8-13.6 years (Mean: 10.8 years) **Sex:** 4% female **Ethnicity:** Not reported **IQ:** Range 95-132 (Mean: 106.9) WISC-III Short-form **Inclusion criteria:** Children were included if they had a primary diagnosis of Asperger syndrome from a pediatrician which was corroborated by a semi-structured interview based on DSM-IV criteria conducted with parents and the Childhood Asperger Syndrome Test (CAST) **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: CBT for anger management.** Using group discussion, practice opportunities, the concept of an 'emotional tool box' and social stories and homework assignments, participants explored positive emotions, feelings of anger, and strategies for 'fixing the feeling' for anger management including taking a break, expending energy in another way, relaxation, thinking about how other people can help and thinking through the consequences of anger. Intervention also included 'parent groups' where parents were taken through what their children were learning in the intervention and were encouraged to help their child with homework assignments. **Delivery of intervention:** The intervention was delivered to children in pairs, supported by two therapists. Therapists were post-graduate clinical psychology students **Format or method of administration:** Group **Intensity:** Children were required to attend a 2-hour session, once a week for six weeks. A total of 12 hours (2 hours per week). **Duration of intervention:** 6 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct outcome** **Behaviour that challenges** (as measured by the parent rated instances of anger and parent rated confidence in their child's ability to manage their own anger)
Study Design	RCT
Source of funding	Apex Autism Trust Foundation
Limitations	1. Unknown risk of selection bias: Methods of randomisation and concealment of allocation have not been reported 2. High risk of performance bias: Care confounds for the control group have not been reported. Participants and individuals responsible for administering care are not blind to allocation of treatment 3. High risk of detection bias: All measures were parent reported and parents were not blind to the allocation of treatment or possible confounding factors. 4. Unknown risk of attrition bias: Following randomisation, five families

	withdrew from the study, but no details of group allocation are reported for these families. 5. High risk of selective reporting: Efficacy data could not be extracted for the ChIA-P as standard deviations (or other measure of variability) not reported. Efficacy data could also not be extracted for the self-rated 'Dylan is being Teased' measure as neither means nor standard deviations reported
Notes	The author was contacting requesting missing outcome data but no reply was received

1.2 CHARACTERISTICS OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES

1.2.1 BANDA2008

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

1.2.2 BROOKMANFRAZEE2006

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

1.2.3 CANNELLA2006

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

1.2.4 CEBULA2012

Reason for exclusion	Non-randomised group assignment

1.2.5 KOEGEL1992

Reason for exclusion	Non-randomised group assignment

1.2.6 LANQUETOT1989

Reason for exclusion	Data cannot be extracted

1.2.7 LAW2009

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

1.2.8 LEQUIA2012

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

1.2.9 LUNDQVIST2009

Reason for exclusion	Mean age of the sample was over 19 years of age

1.2.10 MACHALICEK2007

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

1.2.11 MATSON1996

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

1.2.12 MCINTYRE2008

Reason for exclusion	Non-randomised group assignment (randomisation method based on alternate assignment)

1.2.13 NEEF1995

Reason for exclusion	Non-randomised group assignment

1.2.14 SCHULTZ2011

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

1.2.15 SOFRONOFF2002

Reason for exclusion	Non-randomised group assignment

1.2.16 SOFRONOFF2011

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

1.2.17 SOLOMON2008

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

1.2.18 VONDEREMBSE2011

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

1.2.19 WHITTINGHAM2009

Reason for exclusion	Non-randomised group assignment (participants names were drawn by lots and allocated alternatively to experimental and control group)

1.3 REFERENCES OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES

Banda DR, Grimmett E. Enhancing social and transition behaviors of persons with autism through activity schedules: a review. Education and Training in Developmental Disabilities. 2008;43:324-333.

Brookman-Frazee L, Stahmer A, Baker-Ericzen MJ, Tsai K. Parenting interventions for children with autism spectrum and disruptive behavior disorders: opportunities for cross-fertilization. Clinical Child and Family Psychology Review. 2006;9:181-200.

Cannella HI, O'Reilly MF, Lancioni GE. Treatment of hand mouthing in individuals with severe to profound developmental disabilities: a review of the literature. Research in Developmental Disabilities. 2006;27:529-544.

Cebula KR. Applied behavior analysis programs for autism: sibling psychosocial adjustment during and following intervention use. Journal of Autism and Developmental Disorders. 2012;42:847-862.

Koegel RL, Koegel LK, Surratt A. Language intervention and disruptive behavior in preschool children with autism. Journal of Autism and Developmental Disorders. 1992;22:141-153.

Lanquetot R. The effectiveness of peer modeling with autistic children. Journal of the Multihandicapped Person. 1989;2:25-34.

Law J, Plunkett C, Taylor J, Gunning M. Developing policy in the provision of parenting programmes: Integrating a review of reviews with the perspectives of both parents and professionals. Child: Care, Health and Development. 2009;35:302-312.

Lequia J, Machalicek W, Rispoli MJ. Effects of activity schedules on challenging behavior exhibited in children with autism spectrum disorders: a systematic review. Research in Autism Spectrum Disorders. 2012;6:480-492.

Lundqvist L-O, Andersson G, Viding J. Effects of vibroacoustic music on challenging behaviors in individuals with autism and developmental disabilities. Research in Autism Spectrum Disorders. 2009;3:390-400.

Machalicek W, O'Reilly MF, Beretvas N, Sigafoos J, Lancioni GE. A review of interventions to reduce challenging behavior in school settings for students with autism spectrum disorders. Research in Autism Spectrum Disorders. 2007;1:229-246.

Matson JL, Benavidez DA, Compton LS, Paclawskyj T, Baglio C. Behavioral treatment of autistic persons: a review of research from 1980 to the present. Research in Developmental Disabilities. 1996;17:433-465.

McIntyre LL. Parent training for young children with developmental disabilities: randomized controlled trial. American Journal on Mental Retardation. 2008;113:356-368.

Neef NA. Pyramidal parent training by peers. Journal of Applied Behavior Analysis. 1995;28:333-337.

Schultz TR, Schmidt CT, Stichter JP. A review of parent education programs for parents of children with autism spectrum disorders. Focus on Autism and Other Developmental Disabilities. 2011;26:96-104.

Sofronoff K, Farbotko M. The effectiveness of parent management training to increase self-efficacy in parents of children with Asperger syndrome. Autism. 2002;6:271-286.

Sofronoff K, Jahnel D, Sanders M. Stepping Stones Triple P seminars for parents of a child with a disability: a randomized controlled trial. Research in Developmental Disabilities. 2011;32:2253-2262.

Solomon M, Ono M, Timmer S, Goodlin-Jones B. The effectiveness of parent-child interaction therapy for families of children on the autism spectrum. Journal of Autism and Developmental Disorders. 2008;38:1767-1776.

von der Embse N, Brown A, Fortain J. Facilitating inclusion by reducing problem behaviors for students with autism spectrum disorders. Intervention in School and Clinic. 2011;47:22-30.

Whittingham K, Sofronoff K, Sheffield J, Sanders MR. Stepping Stones Triple P: an RCT of a parenting program with parents of a child diagnosed with an autism spectrum disorder. Journal of Abnormal Child Psychology. 2009;37:469-480.

1.4 CHARACTERISTICS OF INCLUDED PHARMACOLOGICAL INTERVENTION STUDIES

1.4.1 AKHONDZADEH2004

Study ID	AKHONZADEH2004
Bibliographic reference	Akhondzadeh S, Erfani S, Mohammadi MR, Tehrani-Doost M, Amini H, Gudarzi SS, et al. Cyproheptadine in the treatment of autistic disorder: a double-blind placebo-controlled trial. Journal of Clinical Pharmacy and Therapeutics. 2004;29:145-150.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, parents, intervention administrators and outcome assessors were blind to treatment assignment. However, where outcomes were parent-reported they would be non-blind to other potentially confounding factors and the blinding of the clinician for other factors is unclear. **Setting:** Outpatient **Raters:** Parent- and clinician-rated **Country:** Iran
Participants	**Diagnosis:** DSM-IV autism **Coexisting conditions:** Severely disruptive symptoms **Qualifying Diagnostic Assessment:** Diagnosis of autism was confirmed by two child psychiatrists **N:** 40 **Age:** 3-11 years (mean: 6.7 years) **Sex:** 40% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were outpatients at a speciality clinic for children at Roozbeth Psychiatric Teaching Hospital; had a DSM-IV diagnosis of autism corroborated by two psychiatrists; presented with a chief complaint of severely disruptive symptoms related to autistic disorder **Exclusion criteria:** Children were excluded if they: had previously received neuroleptics; had received any psychotropic drug treatment within 6 months prior to recruitment; had a significant active medical problem such as epilepsy
Interventions	**Experimental Intervention: Combined cyproheptadine and haloperidol.** Biperiden (0.04 mg/kg/day) was also administered to all participants as a prophylaxis against extrapyramidal symptoms compared to combined haloperidol and placebo **Delivery of intervention:** Individual delivering intervention not reported **Format or method of administration:** Not reported **Intensity:** Actual intensity not reported but planned intensity was final dose of 0.05 mg/kg/day for haloperidol, 0.2mg/kg/day for cyproheptadine and dose of placebo not reported **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks

Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by Aberrant Behaviour Checklist [ABC] - Total Change Score) **Indirect outcomes:** **Core autism feature: Overall autistic behaviour** (as measured by Childhood Autism Rating Scale [CARS] - Total Change Score) **Adverse events** (as measured by dichotomous measures of: Any treatment-emergent EPS; Number of participants with trouble swallowing during the trial; Number of participants with stiffness during the trial; Number of participants with constipation during the trial; Number of participants with diarrhoea during the trial; Number of participants with day time drowsiness during the trial; Number of participants with slow movement during the trial; Number of participants with restlessness during the trial; Number of participants with morning drowsiness during the trial; Number of participants with increased appetite during the trial; and Number of participants with fatigue during the trial)
Study Design	RCT
Source of funding	This study formed part of Dr Erfani's postgraduate thesis.
Limitations	1. Risk of detection bias is unclear/unknown as the ABC and CARS outcome measures were parent-rated and so non-blind to other potentially confounding factors, the blinding of the clinician rating adverse events in terms of other factors (aside from treatment assignment) is unclear, and it is unclear if 8 weeks is a sufficient follow-up duration to observe adverse events 2. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Author contacted requesting endpoint rather than change scores but no reply

1.4.2 AKHONDZADEH2008

Study ID	AKHONDZADEH2008
Bibliographic reference	Akhondzadeh S, Tajdar H, Mohammadi M-R, Mohammadi M, Nouroozinejad G-H, Shabstari OL, et al. A double-blind placebo controlled trial of piracetam added to risperidone in patients with autistic disorder. Child Psychiatry and Human Development. 2008;39:237-245.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, intervention administrators and outcome assessors were blinded **Setting:** Outpatient **Raters:** Third-year resident of psychiatry (and study author) **Country:** Iran
Participants	**Diagnosis:** DSM-IV autism **Coexisting conditions:** Severe challenging behaviour **Qualifying Diagnostic Assessment:** Diagnosis confirmed by a child psychiatrist (and study author) based on behavioural observation of the child

	and semistructured interview with the parent, a score >=6 on the DSM-IV diagnosis criteria for autism and clinical judgement **N:** 40 **Age:** 3-11 years (mean: 6.8 years) **Sex:** 25% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 3-11 years old; had a DSM-IV clinical diagnosis of autism that was confirmed by the study psychiatrist; were outpatients at a speciality clinic for children at Roozbeth Psychiatric Teaching Hospital; had significant problems with challenging behaviour **Exclusion criteria:** Children were excluded if: a definitive diagnosis of autism could not be made due to severe or profound learning disabilities; they had received neuroleptics or any psychotropic drug treatment within the 6 months prior to recruitment or during the trial; they had received any psychosocial intervention during the trial; they had a significant and active medical problem
Interventions	**Experimental Intervention: Combined piracetam and risperidone** (compared with combined placebo and risperidone) **Delivery of intervention:** Delivered by investigational drug pharmacist **Format or method of administration:** Oral administration **Intensity:** Fixed final dose of risperidone 2mg/day (for children weighing 10-40kg) and 3mg/day (for children weighing >40kg) and fixed final dose of piracetam of 800mg/day **Duration of intervention:** 10 weeks **Total duration of follow-up:** 10 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by the Aberrant Behaviour Checklist [ABC] -Total [Change Score]) **Indirect outcome:** **Adverse events** (as measured by dichotomous measure of any treatment-emergent EPS; and number of participants with the following adverse events during the trial: constipation; nervousness; day time drowsiness; morning drowsiness; increased appetite; dry mouth; fatigue; or loss of appetite)
Study Design	RCT
Source of funding	This study was Dr. Hamid Tajdar's postgraduate thesis and was supported by a grant from Tehran University of Medical Sciences
Limitations	1. Risk of selective reporting bias is unclear/unknown as trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Author contacted regarding endpoint rather than change score data but no reply so change scores entered into meta-analysis.

1.4.3 AKHONDZADEH2010

Study ID	AKHONDZADEH2010
Bibliographic reference	Akhondzadeh S, Fallah J, Mohammadi M-R, Imani R, Mohammadi M, Salehi B, et al. Double-blind placebo-controlled trial of pentoxifylline added to risperidone: effects on aberrant behavior in children with autism. Progress in Neuro -Psychopharmacology and Biological Psychiatry. 2010;34:32-36.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, intervention administrators and outcome assessors were blinded. However, some of the outcome measures relied on parental report and parents would have been non-blind to other potentially confounding factors. **Setting:** Outpatient **Raters:** Clinician-rated and parental report. Independent raters for positive treatment outcomes and adverse events **Country:** Iran
Participants	**Diagnosis:** DSM-IV-TR Autism **Coexisting conditions:** Severely disruptive symptoms **Qualifying Diagnostic Assessment:** Diagnosis was confirmed by a child psychiatrist (investigator) based on behavioural observation of the child and semi-structured interview with the parent, a score >=6 on the DSM-IV-TR diagnosis criteria for autism and clinical judgement **N:** 40 **Age:** 4-12 years (mean: 7.7 years) **Sex:** 28% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 4-12 years of age; met DSM-IV-TR criteria for autism (score of >=6) as assessed through behavioural observation of the child, semi-structured interview with the parent and clinical judgement; presented with a chief complaint of severely disruptive symptoms related to autistic disorder **Exclusion criteria:** Children were excluded if they had: concomitant schizophrenia or psychotic disorder; a history of drug or alcohol abuse or tardive dyskinesia; severe or profound learning disabilities and a definitive diagnosis of autism could not be made; a significant active medical problem such as epilepsy; received neuroleptics or any psychotropic drug treatment within the 6 months prior to recruitment
Interventions	**Experimental Intervention: Combined pentoxifylline and risperidone** compared against combined risperidone and placebo **Delivery of intervention:** Intervention delivered by pharmacist **Format or method of administration:** Oral administration **Intensity:** Actual intensity not reported but planned intensity was final dose of 2mg/day (for children weighing 10-40kg) or 3mg/day (for children weighing >40kg) of risperidone, and 400mg/day (for children weighing 10-40kg) or 600mg/day (for children weighing >40kg) of pentoxifylline **Duration of intervention:** 10 weeks

	Total duration of follow-up: 10 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by Aberrant Behaviour Checklist [ABC] - Irritability & Agitation, Lethargy & Social Withdrawal, Stereotypic Behaviour, Hyperactivity & Noncompliance, and Inappropriate Speech subscales) **Indirect outcome:** **Adverse events** (as measured by dichotomous measures of: Number of participants with constipation during the trial; Number of participants with restlessness during the trial; Number of participants with day time drowsiness during the trial; Number of participants with gassing; Number of participants with increased appetite during the trial; Number of participants with weight gain; Number of participants with dry mouth during the trial; Number of participants with fatigue during the trial; Number of participants with loss of appetite during the trial and Number of participants with extrapyramidal symptoms which was assessed using the Extrapyramidal Symptoms Rating Scale [ESRS])
Study Design	RCT
Source of funding	This study was supported by a grant from Tehran University of Medical Sciences to Prof. Shahin Akhondzadeh (Grant no: 5401)
Limitations	1. Risk of detection bias is unclear/unknown as although there was a blind outcome rater (and independent outcome rater for positive treatment outcomes and side effects) the ABC was completed based on parental report and parents will be non-blind to other potentially confounding factors and for adverse events it is unclear if 10 weeks is a sufficient follow-up duration to observe potential longer-term side effects
Notes	Not applicable

1.4.4 CAMPBELL1993

Study ID	CAMPBELL1993
Bibliographic reference	Campbell M, Anderson LT, Small AM, Adams P, Gonzalez NM, Ernst M. Naltrexone in autistic children: behavioral symptoms and attentional learning. Journal of the American Academy of Child and Adolescent Psychiatry. 1993;32:1283-1291.
Methods	**Allocation:** Randomised **Matching:** No blinding **Blindness:** Participants blinded and outcome assessor of positive treatment response outcome blinded to treatment allocation. However, blinding of intervention administrators and outcome assessor of adverse event outcomes unclear **Setting:** Inpatient **Raters:** Clinician-rated **Country:** USA

Participants	**Diagnosis:** DSM-III-R Autistic disorder (infantile onset) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis corroborated by three independent psychiatrists (no further detail reported) **N:** Paper does not report number randomly assigned. Only reports number completed (N=45) and demographics and data is only reported for those participants who provided data that could be analysed (N=41) **Age:** 2-7 years (mean: 4.9 years) **Sex:** 17% female **Ethnicity:** 7% white **IQ:** FIQ not reported. For N=37: 22% severe LD; 24% moderate LD; 38% mild LD; 13% borderline; 3% normal IQ. For N=38 adaptive and language developmental quotients (as measured by Gesell Developmental Schedules) were reported as 51.5 for adaptive behaviour and 28.7 for language. **Inclusion criteria:** Children were included in the study if they: were inpatients at the Bellevue Hospital Psychiatric Nursery, Children's Inpatient Service; were aged 2-7 years; had a diagnosis of DSM-III-R autistic disorder (infantile onset, <36 months) confirmed by three independent psychiatrists; received no medication (including antibiotics, psychoactive drugs and aspirin) during the two-week placebo washout period (at least 2 weeks before baseline evaluations) **Exclusion criteria:** Children were excluded if they: had identifiable causes of autism (such as congenital rubella or inborn errors of metabolism); had tardive or withdrawal dyskinesia or other associated movement disorders (such as Tourette's syndrome or chorea); had systemic disease (such as renal or vascular); had a history of, or clinical evidence of, cardiac disease or nephrosis; had a history of, or had current, seizure disorder; had a history of, or clinical evidence of, hyperthyroidism or hypothyroidism; were concurrently receiving any psychoactive medication; had a hypersensitivity to naltrexone; were dependent on opioids
Interventions	**Experimental Intervention: Naltrexone** (Trexan) tablets **Delivery of intervention:** Intervention administrator not reported **Format or method of administration:** Oral administration **Intensity:** Optimal dose of 1mg/kg/day **Duration of intervention:** 3 weeks **Total duration of follow-up:** 6 weeks (includes 2-week placebo washout period at beginning of trial and 1-week post-treatment placebo period)
Outcomes	**Direct outcome:** **Behaviour that challenges:** Positive treatment response (as measured by dichotomous measure of 'much improved/very improved' on Clinical Global Impression-Improvement [CGI-I] scale) **Indirect outcomes:** **Adverse events** (as measured by dichotomous measures of: Number of participants experiencing any adverse event during the trial; number of participants with increased aggressiveness during the trial; number of participants with increased self-injurious behaviour during the trial; number of participants with increased hyperactivity during the trial; number of participants with worsening of temper tantrums during the trial; number of

	participants with increased stereotypies during the trial; number of participants with increased irritability during the trial; number of participants with decreased verbal production [transient] during the trial; number of participants with slight sleepiness during the trial; number of participants falling asleep during the trial; number of participants with decreased appetite during the trial; and number of participants with vomiting during the trial)
Study Design	RCT
Source of funding	Supported in part by USPHS Grants MH-32212 (MC) and MH-18915 (MC, ME, NMG) from the NIMH, the Hirschell and Deanna E. Levine Foundation, and the Marion O. and Maximillian E. Hoffman Foundation, Inc. Drug and placebo tablets were supplied by the New York Health and Hospitals Corporation and IE du Pont de Nemours and Company
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method was unclear, insufficient detail was reported with regards to allocation concealment, and groups were not comparable at baseline (there was a significant group difference at baseline [t=2.41, p=0.02] in mean adaptive developmental quotients, as measured by the Gesell Developmental Schedules, with significantly higher mean DQ in the experimental group [mean: 56.8] relative to the control group [mean: 44.9]) 2. Risk of performance bias was unclear as blinding of intervention administrators was unclear 3. High risk of detection bias for adverse event outcomes as unclear if 6 weeks is a sufficient follow-up duration to observe potential longer-term adverse events, the outcome measure was designed by an author specifically for the study with no independent reliability or validity ratings, and the identity and blinding of the outcome assessor is unclear 4. Risk of attrition bias is unclear as number of people assigned and dropout is not reported 5. High risk of other bias due to potential conflict of interest as drug and placebo were supplied by the manufacturer
Notes	Outcomes reported for attention and discrimination learning are not extracted as these are outside the scope

1.4.5 HARDAN2012

Study ID	HARDAN2012
Bibliographic reference	Hardan AY, Fung LK, Libove RA, Obukhanych TV, Nair S, Herzenberg LA, et al. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. Biological Psychiatry. 2012;71:956-961.
Methods	**Allocation:** Randomised **Matching:** Matched on age (above and below 7.5 years) and gender **Blindness:** Participants, intervention administrators, parents and outcome assessors were blinded to group assignment. Blinding to other potentially confounding factors was unclear **Setting:** Outpatient

	Raters: Clinician- and parent-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR Autism **Coexisting conditions:** Coexisting irritability (Clinical Global Impressions-Severity [CGI-S] for irritability score => 4) **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview-Revised (ADI-R) and/or Autism Diagnostic Observation Schedule (ADOS) **N:** 33 **Age:** 3-10 years (mean not reported for N=33 but for N=29 participants with data mean: 7.1 years) **Sex:** 6% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were outpatients of the Autism and Developmental Disabilities Clinic at Stanford University; were aged 3-12 years; were physically healthy; had a DSM-IV-TR diagnosis of autism based on ADI-R and/or ADOS and expert clinical evaluation; had a score of =>4 on Clinical Global Impression-Severity (CGI-S) scale for irritability; had a carer who interacted with them on a regular basis and could reliably bring the child to clinic visits and provide trustworthy ratings; had not had any changes made to any concomitant medications or biomedical interventions within the 2 weeks prior to enrolment; had no changes planned for psychosocial interventions during the trial **Exclusion criteria:** Children were excluded if they: had a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or psychotic disorder not otherwise specified; had received a prior adequate trial of N-acetylcysteine; had active medical problems including unstable seizures or significant physical illness; were pregnant or sexually active female participants; were receiving antioxidant agents or GSH prodrugs in the 4 weeks prior to the start of the trial
Interventions	**Experimental Intervention: N-acetylcysteine (NAC)** **Delivery of intervention:** Delivered by parent **Format or method of administration:** Oral administration **Intensity:** Final dose of 2700mg/day (3 doses of 900mg) **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by Aberrant Behaviour Checklist [ABC] - Irritability & Agitation, Lethargy & Social Withdrawal, Stereotypic Behaviour, Hyperactivity & Noncompliance, and Inappropriate Speech subscales; Clinical Global Impression-Severity [CGI-S] scale; and Clinical Global Impression-Improvement [CGI-I] scale) **Indirect outcomes:** **Core autism features: Impaired reciprocal social communication and interaction** (as measured by Social Responsiveness Scale [SRS] - Total score and Social Awareness, Social Cognition, Social Communication, Social Motivation, and Autistic Mannerisms subscales); **Restricted interests and rigid and repetitive behaviours** (as measured by Repetitive Behavior Scale

	[RBS] - Stereotypies, Self-injurious behaviour, Compulsions, Rituals, Sameness, and Restricted subscales) **Adverse events** (as measured by dichotomous measures of: Number of participants experiencing any gastrointestinal side effect; Number of participants with constipation during the trial; Number of participants with nausea during the trial; Number of participants with diarrhoea during the trial; Number of participants with increased appetite during the trial; Number of participants with loss of appetite during the trial; Number of participants with akathisia during the trial; Number of participants with excitement/agitation during the trial; Number of participants with increased motor activity during the trial; Number of participants with tremor during the trial; Number of participants with dizziness during the trial; Number of participants with depressed affect during the trial; Number of participants with nasal congestion during the trial; Number of participants with increased salivation during the trial; and Number of participants with sweating during the trial)
Study Design	RCT
Source of funding	Escher Family Fund at the Silicon Valley Community Foundation to AYH
Limitations	1. High risk of other bias due to potential conflict of interest as study drugs were provided by BioAdvantex Pharma Inc., investigators were consultants to pharmaceutical companies and two of the investigators are listed as inventors on two patents covering the use of N-acetylcysteine in cystic fibrosis
Notes	Trial protocol is registered on ClinicalTrials.gov, study ID NCT00627705

1.4.6 HELLINGS2005

Study ID	HELLINGS2005
Bibliographic reference	Hellings JA, Weckbaugh M, Nickel EJ, Cain SE, Zarcone JR, Reese M, et al. A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. Journal of Child and Adolescent Psychopharmacology. 2005;15:682-692.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Investigators, parents and participants were blinded **Setting:** Outpatient **Raters:** Clinician- and parent-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV ASD (90% Autistic disorder, 3% PDD-NOS and 7% Asperger's disorder) **Coexisting conditions:** Aggressive behaviour **Qualifying Diagnostic Assessment:** DSM-IV clinical diagnosis informed by the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) **N:** 36 (N=36 began 1-week placebo run-in but full demographic and data analysis reported for N=30)

	Age: 6-20 years (mean: 11.2 years) **Sex:** 33% female **Ethnicity:** 90% white **IQ:** 20-137 (mean: 54; 87% ID) **Inclusion criteria:** Children were included if they: were aged 6-20 years old; had a DSM-IV diagnosis of pervasive developmental disorder (including individuals with any coexisting condition with the exception of Tourette's Disorder); showed significant aggression to self, others or property at least 3 times a week **Exclusion criteria:** Children were excluded if they: had had a previous adequate valproate trial for any indication or clinical seizures within the past year; had a history of degenerative neurological changes, metabolic disorders, Tourette's Disorder, thrombocytopenia, hepatitis, pancreatitis, pregnancy or polycystic ovarian syndrome; were currently taking any psychotropic or anti-seizure medication
Interventions	**Experimental Intervention: Valproate** liquid (250mg/5ml) **Delivery of intervention:** Parents delivered intervention and clinician adjusted dose **Format or method of administration:** Oral administration **Intensity:** Final intended dosage was 20mg/kg/day (mean VPA through blood levels were 77.8 mcg/mL at week 8) **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by the parent-rated Aberrant Behaviour Checklist [ABC] - Irritability & Agitation subscale and the Overt Aggression Scale [OAS] - Total score; and the clinician-rated Clinical Global Impression Scale [CGI] - Severity and Improvement scales) **Indirect outcome:** **Adverse events** (as measured by dichotomous measures of any side effect and discontinuation due to adverse events, and weight gain [in kg])
Study Design	RCT
Source of funding	National Institute of Mental Health (1K08MH01561-01), the National Institute of Child Health and Human Development (HD26927, HD02528), and an unrestricted $5,000 grant from Abbott Pharmaceuticals
Limitations	1. Risk of selective reporting bias is unclear/unknown as randomisation method is unclear 2. High risk of selective reporting bias as results for the teacher-rated ABC-Irritability and OAS are not reported. Data is also not reported for the ABC-C hyperactivity subscale or Self-Injurious Behavior Questionnaire (SIB-Q) which are listed as outcome on ClinicalTrials.gov 3. High risk of other bias due to potential conflict of interest as the study was partially funded by Abbott Pharmaceuticals
Notes	This trial is listed on ClinicalTrials.gov, Study NCT00065884. Authors contacted regarding missing outcome data but no reply. The sample included both adults and children but only N=1 >19 years (the age cut-off for this guideline) so quality was not downgraded.

1.4.7 HOLLANDER2010

Study ID	HOLLANDER2010
Bibliographic reference	Hollander E, Chaplin W, Soorya L, Wasserman S, Novotny S, Rusoff J, et al. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. Neuropsychopharmacology. 2010;35:990-998.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Investiagtors, participants and outcome assessors were blinded **Setting:** Outpatient **Raters:** Clinician- and parent-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR Autistic disorder (85% Autistic disorder and 15% Asperger's syndrome) **Coexisting conditions:** Significant irritability or aggression problems **Qualifying Diagnostic Assessment:** Participants mer DSM-IV-TR diagnostic criteria for autistic disorder, full diagnostic criteria on the Autism Diagnostic Interview-Revised (ADI-R) and autism spectrum criteria on the Autism Diagnostic Observation Schedule-Generic (ADOS-G) **N:** 27 **Age:** 4-14 years (mean: 9.5 years) **Sex:** 16% female **Ethnicity:** 30% white **IQ:** 30-126 (mean: 63.3; as measured by Leiter international performance scale-revised [Leiter-R]) **Inclusion criteria:** Children were included if they: were aged 5-17 years old; met DSM-IV criteria for autistic disorder, full diagnostic criteria on the ADI-R and autism spectrum criteria on the ADOS-G; scored >=4 on the Clinical Global Impression-Severity scale (CGI-S); had significant irritability or aggression problems as defined by a score of >=18 on the Aberrant Behavior Checklist-Irritabilty subscale (ABC-I) or >=13 on the Overt Aggression Scale-Modified (OAS-M) **Exclusion criteria:** Children were excluded if they: were sexually active or pregnant or nursing mothers; had an overall adaptive behavior score <2 years on the Vineland Adaptive Behavior Scales (VABS); had active or unstable epilepsy; had another Axis I disorder; had an unstable medical illness; had a genetic syndrome or congenital infection associated with autism-like symptoms; were born premature; had been treated within the previous 30 days with any psychotropic drugs (or drugs known to have a well-defined potential for toxicity); had clinically significant abnormalities in laboratory tests or physical examinations; had a history of hypersensitivity or severe side effects to divalproex sodium; had had a previous ineffective trial of divalproex sodium; had begun any new nonmedication treatment within the previous 3 months

Interventions	**Experimental Intervention: Divalproex sodium** **Delivery of intervention:** Study physicians **Format or method of administration:** Not reported **Intensity:** Not reported **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by a dichotomous measure of positive treatment response ['much improved/very improved' on CGI-improvement focused on irritability]; Aberrant Behaviour Checklist [ABC] - Irritability & Agitation subscale) **Indirect outcomes:** **Core autism feature: Overall autistic behaviours** (as measured by dichotomous measure of positive treatment response ['much improved/very improved' on CGI-I-autism focusing on all symptoms including core symptom domains) **Adverse events** (as measured by dichotomous measures of discontinuation due to adverse events and number of participants with more than one side effect; and weight gain [in lbs])
Study Design	RCT
Source of funding	NINDS R21 NS4 3979-01, E Hollander, PI. Active medication and matching placebo were provided by Abbott Laboratories. In addition, this publication was made possible by Grant Number MO1-RR00071 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH)
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and there is insufficient detail reported with regards to allocation concealment. There was also a statistically significant (p=0.017) group difference in baseline IQ with the placebo group having a significantly higher IQ (76.1) than the experimental group (52.9) 2. High risk of selective reporting bias as data could not be extracted for the secondary outcome measures of the Child-Yale-Brown Obsessive Compulsive Scale (CYBOCS), the Vineland Adaptive Behavior Scale (VABS) or the Young Mania Rating Scale (YMRS). 3. High risk of other bias due to potential conflict of interest as study drugs were provided by Abbott Laboratories and authors are consultants to pharmaceutical companies
Notes	This trial is registered on ClinicalTrials.gov, Study NCT00211757. Authors contacted regarding missing outcome data but no reply. Data not extracted for Overt Aggression Scale-Modified (OAS-M) - Irritability subscale as the irritability subscale of the ABC is the more commonly used measure.

1.4.8 JOHNSON&JOHNSON2011/KENT2012

Study ID	JOHNSON&JOHNSON2011/KENT2012

Bibliographic reference	Johnson & Johnson Pharmaceutical Research & Development, L. L. C. Risperidone in the Treatment of Children and Adolescents With Autistic Disorder: A Double-Blind, Placebo-Controlled Study of Efficacy and Safety, Followed by an Open-Label Extension Study of Safety. ClinicalTrials.gov NCT00576732; 2011. Avaialble from: http://clinicaltrials.gov/ct2/show/results/NCT00576732. Kent JM, Kushner S, Ning X, Karcher K, Ness S, Aman M, et al. Riseridone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. Journal of Autism and Developmental Disorders. 2012; Epub available ahead of print. Available from: http://link.springer.com/article/10.1007%2Fs10803-012-1723-5.
Methods	**Allocation:** Randomised **Matching:** Blocked randomisation, stratified by site and baseline weight (20 to <45 kg or =>45 kg) **Blindness:** Participants and investigators were blind **Setting:** Not reported **Raters:** Clinician-rated for some outcome measures. However, rater for Aberrant Behavior Checklist (ABC) is not reported **Country:** USA
Participants	**Diagnosis:** DSM-IV Autistic Disorder **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview - Revised (ADI-R) **N:** 96 **Age:** Range not reported (mean: 9.3 years) **Sex:** 13% female **Ethnicity:** 70% white **IQ:** Not reported (but inclusion criteria was mental age>18 months assessed using LIPS-R or other standardized IQ test) **Inclusion criteria:** Children were included if they: were aged 5-17 years; had DSM-IV diagnosis of Autistic Disorder corroborated using ADI-R; a score of >18 on Aberrant Behavior Checklist - Irritability subscale (ABC-I); a score of >4 on Clinical Global Impressions-Severity scale (CGI-S); had mental age >18 months; had body weight >20kg; seizure-free for at least 6 months and if on anticonvulsants the dosage stable for at least 4 weeks; were medication-free for at least 1 week before the start of the study for all psychotropic drugs, with the exception of fluoxetine or injectable medications where a 4 or 8 week, respectively, medication-free period is required; had normal fasting glucose and creatinine, and liver function test levels less than 1.5 times the upper limit of normal; (for female participants) were premenarchal or sexually abstinent or, if heterosexually active, must practice an effective method of birth control **Exclusion criteria:** History of prior or current DSM-IV diagnosis of a psychotic disorder (for example, schizophrenia, bipolar disorder, other psychosis), PDD-NOS, Asperger's syndrome or Rett's disorder; any history of hypersensitivity

	to risperidone or other known drug allergy; participants who received risperidone within the 3-month period prior to screening; participants who did not demonstrate sufficient clinical response to an adequate trial of risperidone in the past (an adequate trial is defined as a period of at least 4 weeks at an adequate dose); Neurologic disorder (for example, Neuroleptic Malignant Syndrome, seizure disorders that are unstable, seizure activity within the past 6 months); history of alcohol or substance dependence in the 3-month period prior to screening; female participant who is pregnant (positive beta-HCG) or breat feeding; participants with existing moderate or severe extrapyramidal symptoms or history of tardive dyskinesia; participants who have received an experimental drug or used an experimental medical devise in the 3-month period prior to planned start of treatment
Interventions	**Experimental Intervention: Risperidone in high and low doses** compared with placebo **Delivery of intervention:** Not reported **Format or method of administration:** Oral solution **Intensity:** Low dose risperidone: 0.125mg (if <45 kg) or 0.175mg (if >=45kg); High dose risperidone: 1.25mg (if <45 kg) or 1.75mg (if >=45kg) **Duration of intervention:** 6 weeks **Total duration of follow-up:** 26 weeks (includes open-label phase, however, data cannot be extracted for follow-up as all participants received risperidone resulting in no control group for 6 month outcome measures)
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by change scores on the Aberrant Behavior Checklist-Irritability subscale [ABC-I] and a dichotomous measure of positive treatment response [>25% improvement on ABC-I]; and global state as measured by change scores on the Clinical Global Impressions-Severity Scale [CGI-S] and a dichotomous measure of positive treatment response ['much improved/very improved' on CGI-improvement [CGI-I]) **Indirect outcome:** **Adverse events:** Fasting Glucose (as measured by change in fasting Glucose [mg/dL]); and Insulin Resistance (as measured by change in Insulin Resistance [HOMA-IR])
Study Design	RCT
Source of funding	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Limitations	1. Risk of selection bias is unclear/unknown due to unclear randomisation method and insufficient detail reported with regards to allocation concealment 2. The risk of detection bias is unclear/unknown as although investigators were blind, the rater of the ABC is not reported and if parent-completed it will be non-blind to other important confounding and prognostic factors 3. Risk of detection bias is different for different outcomes but is unclear/unknown for adverse event outcomes as unclear if 6 weeks is sufficient follow-up duration to observe potential longer-term adverse events 4. High risk of other bias due to conflict of interest as the study was funded and run by the pharmaceutical company that manufactured the drug tested
Notes	This trial is registered on ClinicalTrials.gov, Study NCT00576732.

	Data was extracted from results posted on ClinicalTrials.gov, Aman contacted regarding endpoint scores and missing outcome data and data was provided, and from published paper (KENT2012) Data for low and high dose groups combined and entered into meta-analysis as even high dose consistent with other trials. However, additional comparisons examined the effects of low dose against placebo. More than 90% of participants were naive to antipsychotic drugs.

1.4.9 KING2001

Study ID	KING2001
Bibliorgraphic reference	King BH, Wright M, Handen BL, Sikich L, Zimmerman AW, McMahon W, et al. Double-blind, placebo-controlled study of amantadine hydrochloride in the treatment of children with autistic disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2001;40:658-665.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants and intervention administrators (parents/carers) were blinded. Blinding of investigators for investigator-rated outcome measures is not reported **Setting:** Outpatient **Raters:** Parent- and investigator-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV/ICD-10 Autistic disorder **Coexisting conditions:** None reported. 26% of participants were taking concomitant SSRIs. **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) **N:** 39 **Age:** 5-15 years (mean: 7 years) **Sex:** 13% female **Ethnicity:** 77% white **IQ:** Not reported **Inclusion criteria:** Children were included if they: had a diagnosis of autistic disorder according to DSM-IV and ICD-10 criteria and corroborated by the ADI-R and ADOS-G; had a composite age equivalent >18 months on the Vineland Adaptive Behavior Scales (VABS); scored equal to or greater than the age-adjusted 75th percentile on the Aberrant Behavior Checklist (ABC) Irritability and Hyperactivity subscales **Exclusion criteria:** Children were excluded if they: had an IQ (ratio, nonverbal) score <35 (as measured by the Mullen Scales of Early Learning or the Differential Ability Scale); had a diagnosis of fragile X syndrome or tuberous sclerosis complex; were receiving neuroleptic, anticonvulsant, or stimulant medication; were taking selective serotonin reuptake inhibitors only if the dose had not been stable for at least 1 month prior to entry or if the dose changed during the study period; showed evidence of having any clinically

	important medical illness
Interventions	**Experimental Intervention: Amantadine hydrochloride** (Symmetrel® syrup) compared to taste and colour-matched placebo **Delivery of intervention:** Treatment was delivered by a parent or carer **Format or method of administration:** Oral administration (syrup) **Intensity:** Actual intensity not reported but planned intensity was 2.5 mg/kg (single dose) per day for first week of treatment period and 5 mg/kg (two doses) per day for remaining three weeks of treatment **Duration of intervention:** 4 weeks **Total duration of follow-up:** 5 weeks (4-week double-blind treatment period was preceded by a 1-week single-blind placebo run-in phase [single dose of 2.5 mg/kg per day])
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by dichotomous measures of positive treatment response for irritability or hyperactivity defined as >25% improvement on ABC-Irritability and/or hyperactivity; and positive clinician-rated treatment response defined as 'moderate or marked improvement' on CGI-improvement) **Indirect outcome:** **Adverse events** (as measured by dichotomous measures of: at least one side effect; number of participants with insomnia during the trial; number of participants with antisocial behaviour the trial)
Study Design	RCT
Source of funding	Cerebrus plc, Winnersh, U.K.
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. Risk of detection bias is unclear for behaviour that challenges outcomes either because the outcome assessor is the parent who will be non-blind to other potentially confounding factors or the blinding for the investigator-rated outcome measures is unclear. High risk of detection bias for adverse event outcomes as 5 weeks may not be a sufficient follow-up duration to observe adverse events and identity and blinding of outcome assessors is not reported. 3. High risk of selective reporting bias as only the number of responders is available and not means (sd) for continuous scales 4. High risk of other bias due to potential conflict of interest as the trial is funded by a pharmaceutical company
Notes	Contacted author to request continuous outcome data but no reply

1.4.10 MARCUS2009/VARNI2012

Study ID	MARCUS2009/VARNI2012
Bibliographic reference	Marcus RN, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. Journal of the

	American Academy of Child and Adolescent Psychiatry. 2009;48:1110-1119. Varni JW, Handen BL, Corey-Lisle PK, Guo Z, Manos G, Ammerman DK, et al. Effect of aripiprazole 2 to 15 mg/d on health-related quality of life in the treatment of irritability associated with autistic disorder in children: a post-hoc analysis of two controlled trials. Clinical Therapeutics. 2012;34:980-992.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. participant, parent, investigator, intervention administrator, outcome assessor **Setting:** Research setting **Raters:** Clinician- and parent-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR Autistic Disorder **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis was corroborated using the Autism Diagnostic Interview-Revised (ADI-R) **N:** 218 **Age:** Range not reported (mean: 9.7 years) **Sex:** 11% female **Ethnicity:** 71% white **IQ:** Not reported **Inclusion criteria:** Participants were 6 to 17 years of age, met DSM-IV-TR criteria for autistic disorder, and demonstrated behaviours such as irritability, agitation, self-injurious behavior, or a combination of these symptoms (Clinical Global Impressions-Severity [CGI-S] score>=4 and Aberrant Behavior Checklist [ABC]-Irritability subscale score>=18). **Exclusion criteria:** Included: a current diagnosis of bipolar disorder, psychosis, schizophrenia or major depression, fragile X syndrome, PDD-not otherwise specified, Asperger's disorder, Rett disorder, or childhood disintegrative disorder; history of neuroleptic malignant syndrome; a significant risk for committing suicide determined by the investigator based on history or routine psychiatric status examination; seizure in the past year; history of severe head trauma or stroke; history or current evidence of any unstable medical conditions; or an abnormal laboratory test result, considered clinically significant vital sign result, or electrocardiogram (ECG) finding considered clinically significant. The subjects considered treatment resistant to neuroleptic medication or with a known allergy or hypersensitivity to aripiprazole were also excluded. All of the subjects were required to weigh 15 kg or greater.
Interventions	**Experimental Intervention: Aripiprazole (in 5mg, 10mg, or 15mg fixed doses)** versus placebo **Delivery of intervention:** Not reported **Format or method of administration:** Not reported **Intensity:** Fixed doses of 5mg/day or 10mg/day or 15mg/day (3 active treatment arms) **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks

Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by a dichotomous measure of positive treatment response [>25% improvement on Aberrant Behavior Checklist-Irritability subscale & 'much improved/very improved' on Clinical Global Impression-improvement]; and change scores on ABC-Lethargy, Stereotypy, Hyperactivity, and Inappropriate Speech subscales; and global state as measured by change scores on Clinical Global Impression Scale [CGI-S] - Severity) **Indirect outcomes:** **Core autism feature: Restricted interests and rigid and repetitive behaviours** (as measured by change score on the Children's Yale-Brown Obsessive Compulsive Scale [CYBOCS] - Compulsions subscale) **Coexisting problem or disorder: Adaptive behaviour** (as measured by the PedsQL 4.0 Generic Core Scales [change scores] - Total score, and Emotional functioning [feeling afraid/scared; feeling sad/blue; feeling angry; trouble sleeping; worrying about what will happen], Social functioning [getting along with peers; peers not wanting to be friends; getting teased; not being able to do things peers can do; keeping up with peers] and Cognitive functioning [difficulty keeping attention on things; difficulty remembering what people tell him/her; difficulty remembering what he/she just heard; difficulty thinking quickly; trouble remembering what he/she thinking; trouble remembering >1 think at a time] subscales) **Adverse events** (as measured by dichotomous measures of any side effect; discontinuation due to sedation; discontinuation due to drooling; discontinuation due to tremor; any treatment-emergent EPS; and clinically relevant [>=7%] weight gain; and continuous measures of weight gain [kg] and BMI change [kg/m-squared])
Study Design	RCT
Source of funding	Bristol-Myers Squibb (Princeton, NJ) and Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan).
Limitations	1. High risk of selection bias due to unclear randomisation method and insufficient detail reported with regards to allocation concealment. There were also no baseline statistical comparisons between groups reported. 2. The risk of performance bias is unclear/unknown as the paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. participant, investigator, intervention administrator 3. The risk of detection bias is unclear/unknown as the paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. parent, outcome assessor. It is also unclear if follow-up duration of 8 weeks is sufficient to detect significant treatment effects, in particular, adverse events 4. High risk of selective reporting bias as mean and standard deviation data was not reported for the Caregiver Strain Questionnaire (CGSQ) 5. High risk of other bias due to conflict of interest as the study was funded and run by the pharmaceutical company that manufactured the drug tested
Notes	Contacted author regarding endpoint scores and missing outcome data but email bounced back. Fixed dose groups combined for meta-analysis but individual comparisons

	also conducted to examine potential dose mediators. Post-hoc analysis reported in VARNI2012 for adaptive behaviour outcomes. Standard errors reported in VARNI2012 which were converted into standard deviations for meta-analysis.

1.4.11 OWEN2009/AMAN2010/VARNI2012

Study ID	OWEN2009/AMAN2010/VARNI2012
Bibliographic reference	Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. Pediatrics. 2009;124:1533-1540. Aman MG, Kasper W, Manos G, Mathew S, Marcus R, Owen R, et al. Line-item analysis of the aberrant behavior checklist: results from two studies of aripiprazole in the treatment of irritability associated with autistic disorder. Journal of Child and Adolescent Psychopharmacology. 2010;20:415-422. Varni JW, Handen BL, Corey-Lisle PK, Guo Z, Manos G, Ammerman DK, et al. Effect of aripiprazole 2 to 15 mg/d on health-related quality of life in the treatment of irritability associated with autistic disorder in children: a post-hoc analysis of two controlled trials. Clinical Therapeutics. 2012;34:980-992.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. participant, parent, investigator, intervention administrator, outcome assessor **Setting:** Not reported **Raters:** Clinician- and parent-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR Autistic Disorder **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis corroborated by Autism Diagnostic Interview-Revised (ADI-R) **N:** 98 **Age:** Range not reported (mean: 9.3 years) **Sex:** 12% female **Ethnicity:** 74% white **IQ:** Not reported **Inclusion criteria:** Participants were 6 to 17 years of age; met DSM-IV-TR criteria for autistic disorder; and demonstrated behaviours such as tantrums, aggression, self-injurious behavior, or a combination of these (Clinical Global Impression–Severity [CGI-S] score >= 4 and Aberrant Behavior Checklist [ABC] irritability subscale score of >= 18 at screening and baseline) **Exclusion criteria:** A current diagnosis of bipolar disorder, psychosis, schizophrenia or major depression, or fragile X syndrome or a diagnosis of pervasive developmental disorder–not otherwise specified, Asperger

	syndrome, Rett syndrome, or childhood disintegrative disorder; history of neuroleptic malignant syndrome; a significant risk for committing suicide; seizure in the past year; history of severe head trauma or stroke; history or current evidence of any unstable medical conditions; or a laboratory test, vital sign, or electrocardiogram (ECG) result considered clinically significant; participants who were considered to be treatment resistant to antipsychotic medication or had a known allergy or hypersensitivity to aripiprazole; weight >=15 kg
Interventions	**Experimental Intervention: Aripiprazole (flexible dose)** versus placebo **Delivery of intervention:** Not reported **Format or method of administration:** Not reported **Intensity:** 2-15mg/day **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by a dichotomous measure of positive treatment response [>25% improvement on ABC-Irritability & 'much improved/very improved' on CGI-improvement]; and continuous measures of change scores for Aberrant Behavior Checklist [ABC] - Irritability, Lethargy, Stereotypy, Hyperactivity, and Inappropriate Speech subscales) **Indirect outcomes:** **Coexisting problem or disorder: Adaptive behaviour** (as measured by the PedsQL 4.0 Generic Core Scales [change scores] - Total score, and Emotional functioning [feeling afraid/scared; feeling sad/blue; feeling angry; trouble sleeping; worrying about what will happen], Social functioning [getting along with peers; peers not wanting to be friends; getting teased; not being able to do things peers can do; keeping up with peers] and Cognitive functioning [difficulty keeping attention on things; difficulty remembering what people tell him/her; difficulty remembering what he/she just heard; difficulty thinking quickly; trouble remembering what he/she thinking; trouble remembering >1 think at a time] subscales) **Adverse events** (as measured by dichotomous measures of: any side effect; discontinuation due to adverse event/s; any treatment-emergent extrapyramidal symptoms; clinically relevant prolactin elevation [above upper limit of normal for age & gender]; and clinically relevant [>=7%] weight gain)
Study Design	RCT
Source of funding	Bristol-Myers Squibb (Princeton, NJ) and Otsuka Pharmaceutical Co, Ltd (Tokyo, Japan)
Limitations	1. The risk of performance bias is unclear/unknown as the paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. participant, investigator, intervention administrator 2. The risk of detection bias is unclear/unknown as the paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. parent, outcome assessor. It is also unclear if follow-up duration of 8 weeks is sufficient to detect significant treatment effects, in particular, adverse events 3. High risk of selective reporting bias as data could not be extracted for the following outcome measures as no measure of variability was reported:

	Clinical Global Impressions-Severity and Improvement scales; CY-BOCS (compulsions scale); Caregiver Strain Questionnaire (CGSQ); or BMI 4. High risk of other bias due to conflict of interest as the study was funded and run by the pharmaceutical company that manufactured the drug tested
Notes	AMAN2010 does not report primary data. However, variability measures for the ABC outcome measures are not reported in OWEN2009 so are extracted from AMAN2010 This trial is registered on ClinicalTrials.gov, Study NCT00332241. Contacted author regarding endpoint scores and missing outcome data but email bounced back. Post-hoc analysis reported in VARNI2012 for adaptive behaviour outcomes. Standard errors reported in VARNI2012 which were converted into standard deviations for meta-analysis.

1.4.12 REZAEI2010

Study ID	REZAEI2010
Bibliographic reference	Rezaei V, Mohammadi M-R, Ghanizadeh A, Sahraian A, Tabrizi M, Rezazadeh S-A, et al. Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2010;34:1269-1272.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Intervention administrators, participants and outcome assessors were blind to group assignment **Setting:** Outpatient **Raters:** Clinician-rated (with input from parents) **Country:** Iran
Participants	**Diagnosis:** DSM-IV-TR autism **Coexisting conditions:** Severely disruptive behaviours **Qualifying Diagnostic Assessment:** Diagnosis confirmed by a study psychiatrist through behavioural observation of the child and administration of the Autism Diagnostic Interview-Revised (ADI-R) **N:** 40 **Age:** 4-12 years (mean: 8.0 years) **Sex:** 33% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 3-12 years old; had a DSM-IV-TR diagnosis of autism (>=6 on criteria for autism) as confirmed and corroborated by a psychiatrist using behavioral observation, semi-structured interview with the parent and the ADI-R; presented with a chief complaint of disruptive symptoms and scored >=12 on the Aberrant Behavior Checlist-Community (ABC-C) Irritability subscale **Exclusion criteria:** Children were excluded if they: had schizophrenia, psychotic disorders or epilepsy; had a history of drug or alcohol abuse or

	tardive dyskinesia; had previously received neuroleptics or any psychotropic drug treatment 6 months prior to recruitment; had a significant active medical condition; had severe or profound intellectual disabilities what meant a definitive diagnosis of autism could not be made
Interventions	**Experimental Intervention: Topiramate + risperidone tablets** (versus placebo + risperidone tablets) **Delivery of intervention:** Drugs dispensed by investigational pharmacist **Format or method of administration:** Oral administration **Intensity:** Dosage titrated up to 2-3mg/day of risperidone (based on weight, 10-40kg and >40kg respectively) and 200mg/day of topiramate **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by the Aberrant Behavior Checklist [ABC] - Irritability & Agitation, Lethargy & Social Withdrawal, Stereotypic Behaviour, Hyperactivity & Noncompliance, and Inappropriate Speech subscales)
Study Design	RCT
Source of funding	Grant from Tehran University of Medical Sciences to Prof. Shahin Akhondzadeh (Grant No: 6550)
Limitations	1. High risk of selective reporting bias as data cannot be extracted for adverse events
Notes	This trial was registered on the Iranian Clinical Trials Registry, Study IRCT138901141556N9

1.4.13 RUPPRISPERIDONE

Study ID	RUPPRISPERIDONE2001
Bibliographic reference	Aman MG, Holloway JA, McDougle CJ, Scahill L, Tierney E, McCracken JT, et al. Cognitive effects of risperidone in children with autism and irritable behavior. Journal of Child and Adolescent Psychopharmacology. 2008;18:227-236. Anderson GM, Scahill L, McCracken JT, McDougle CJ, Aman MG, Tierney E, et al. Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. Biological Psychiatry. 2007;61:545-550. Arnold LE, Vitiello B, McDougle C, Scahill L, Shah B, Gonzalez NM, et al. Parent-defined target symptoms respond to risperidone in RUPP autism study: customer approach to clinical trials. Journal of the American Academy of Child and Adolescent Psychiatry. 2003;42:1443-1450. Arnold LE, Farmer C, Kraemer HC, Davies M, Witwer A, Chuang S, et al. Moderators, mediators, and other predictors of risperidone response in children with autistic disorder and irritability. Journal of Child and Adolescent

	Psychopharmacology. 2010;20:83-93. McDougle CJ, Scahill L, Aman MG, McCracken JT, Tierney E, Davies M, et al. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. American Journal of Psychiatry. 2005;162:1142-1148. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. New England Journal of Medicine. 2002;347:314-321. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefit and blinded discontinuation after 6 months. American Journal of Psychiatry. 2005;162:1361-1369. Scahill L, McCracken J, McDougle CJ, Aman M, Arnold LE, Tierney E, et al. Methodological issues in designing a multisite trial of risperidone in children and adolescents with autism. Journal of Child and Adolescent Psychopharmacology. 2001;11:377-388.
Methods	**Allocation:** Randomised **Matching:** Randomisation was balanced within site by pubertal status (Tanner stages I and II for prepubertal status and Tanner III or higher for postpubertal status), gender, and anticonvulsant use **Blindness:** Participants, care administrators and outcome assessors were blind. Two blinded clinicians followed each participant, one who focused on clinical ratings and one who evaluated side effects and adjusted the medication dose, in an attempt to prevent the emergence of obvious side effects breaking the blind. **Setting:** The study was conducted across five university sites **Raters:** Parent-completed and clinician-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV Autistic disorder **Coexisting conditions:** Not reported (4% on anticonvulsants for seizure disorder) **Qualifying Diagnostic Assessment:** Diagnosis of autism was based on a clinical evaluation that included a DSM-IV interview with a parent and direct observation of the participants. The clinical diagnosis was corroborated by the Autism Diagnostic Interview-revised (ADI-R). **N:** 101 (data only available for N=38 in AMAN2008 and N=94 in ARNOLD2003) **Age:** 5-17 years (mean: 8.8 years) **Sex:** 19% female **Ethnicity:** 66% white **IQ:** Not reported **Inclusion criteria:** Males and females between the ages of 5 years and 17 years 2 months; DSM-IV diagnosis of autistic disorder (established by clinical assessment, corroborated by the Autism Diagnostic Interview); Inpatients or

	outpatients; Medication free for at least 2 weeks for all psychotropic medications (4 weeks for fluoxetine or depot neuroleptics); Anticonvulsants used for the treatment of a seizure disorder were permitted if the dosage had been stable for 4 weeks and the patient had been seizure free for at least 6 months; Clinical Global Impressions severity score of at least 4 (moderately ill) at baseline rated by the blinded rater; A score of 18 or greater on the Irritability subscale of the Aberrant Behavior Checklist at baseline (on the parent-rated and/or clinician-rated version); and a mental age of at least 18 months as measured by the age-appropriate form of the Wechsler Intelligence Test, by the revised Leiter, or by the Mullen **Exclusion criteria:** Females with a positive Beta human chorionic gonadotropin (HCG) pregnancy test; Evidence of a prior adequate trial with risperidone (defined as duration of 2 weeks or more at a dose of at least 1 mg/day); Evidence of hypersensitivity to risperidone (defined as allergic response [e.g. skin rash] or potentially serious adverse effect [e.g. significant tachycardia]); Past history of neuroleptic malignant syndrome; DSM-IV diagnosis of schizophrenia, another psychotic disorder, or substance abuse; A significant medical condition such as heart disease, hypertension, liver or renal failure, or pulmonary disease identified by history, physical examination, or laboratory tests; and weight less than 15kg
Interventions	**Experimental Intervention: Risperidone** or placebo **Delivery of intervention:** Not reported **Format or method of administration:** Oral tablet (matched risperidone and placebo) **Intensity:** Final daily dose of risperidone 0.5-3.5 mg (mean: 1.8 mg); final daily dose of placebo 1-3.5 mg (mean: 2.4 mg) **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks (an open-label 16-week extension is reported in AMAN2005 and 95-week open-label follow-up phase in ANDERSON2007 but efficacy or safety data is not extractable for this follow-up)
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by dichotomous measures of positive treatment response as defined by a primary outcome algorithm [>25% improvement on ABC-Irritability & 'much improved/very improved' on CGI-improvement] and a parent-defined target symptom rating [<3 "definitely improved" or better]; dichotomous measure of relapse [as defined by >=25% increase on ABC-Irritability and a CGI-Improvement rating of 'much worse' or 'very much worse']; and the Aberrant Behavior Checklist [ABC] - Irritability & Agitation, Lethargy & Social Withdrawal, Stereotypic Behaviour, Hyperactivity & Noncompliance, and Inappropriate Speech subscales; Vineland Adaptive Behaviour Scale (VABS) - Maladaptive Behaviour Index; and improvement as measured on a 9-point scale for parent-defined target symptoms [which fall into 7 categories of aggression, self-injury, property destruction, tantrums, yelling/screaming, stereotypy, hyperactive/impulsive/agitated]). Potential moderators and mediators of treatment effects on ABC-Irritability change scores are also considered (ARNOLD2010)

	Indirect outcomes: **Core autism features: Overall autistic behaviours** (as measured by Ritvo-Freeman Real-life Rating Scale (RLRS) - Total score and Motor, Social, Affective, Sensory and Language subscales); **Restricted interests and rigid and repetitive behaviours** (as measured by Children's Yale-Brown Obsessive Compulsive Scale [CYBOCS] - Compulsions subscale) **Coexisting problem or disorder: Academic skills** (as measured by Classroom Analogue Task - Total number of maths problems correctly calculated) **Adverse events**: Weight gain (as measured in kg); Prolactin concentration (as measured in ng/ml); Leptin concentration (mg/L) Change Score
Study Design	RCT
Source of funding	National Institute of Mental Health (N01MH70009, to Dr. Scahill; N01MH70010, to Dr. McCracken; N01MH70001, to Dr. McDougle; and N01MH80011, to Dr. Aman), General Clinical Research Center grants from the National Institutes of Health (M01 RR00750, to Indiana University; M01 RR00052, to Johns Hopkins University; M01 RR00034, to Ohio State University; and M01 RR06022, to Yale University), and a grant from the Korczak Foundation (to Dr. Scahill).
Limitations	1. Risk of selection bias is unclear/unknown as randomisation is balanced but stratification methods are unclear, the groups are not comparable at baseline (with significantly greater scores on ABC Inappropriate speech subscale [p=0.03] in the control group and a trend for significantly lower scores on VABS Daily Living subscale [p=0.07] and ABC Stereotypy [p=0.09] in the control group [RUPP2002]), and insufficient detail reported with regards to allocation concealment 2. Risk of detection bias is unclear/unknown for adverse event outcomes as it is unclear if the follow-up duration of 8 weeks is sufficient to detect significant adverse events (for instance, 6-month follow-up in 43 participants followed longitudinally [ANDERSON2007] showed weight gain increased from 2.7kg at 8 weeks to 5.6kg at 6 months). 3. High risk of selective reporting bias as some adverse event outcomes of the trial (reported in AMAN2005) are not reported in sufficient detail to be entered into a meta-analysis 4. Conflict of interest in terms of funding is unclear as study medications were donated by Janssen Pharmaceutica. Note: There are some additional methodological concerns with the discontinuation trial reported in RUPP2005, including a high risk of detection bias as all participants were responders and time-points were different for risperidone and placebo arms.
Notes	Data extracted from Aman et al. (2008), Anderson et al. (2007), Arnold et al. (2003), Arnold et al. (2010), McDougle et al. (2005), RUPP (2002), RUPP (2005) and Scahill et al. (2001). This trial is registered on ClinicalTrials.gov, Study NCT00005014. Unpublished data requested for AMAN2005 but not provided.

1.4.14 SHEA2004/PANDINA2007

Study ID	SHEA2004/PANDINA2007
Bibliographic reference	Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics. 2004;114:e634-e641. Pandina GJ, Bossie CA, Youssef E, Zhu Y, Dunbar F. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. Journal of Autism and Developmental Disorders. 2007;37:367-373.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. participant, parent, investigator, intervention administrator, outcome assessor **Setting:** Outpatient **Raters:** Clinician- and parent-rated **Country:** Canada
Participants	**Diagnosis:** DSM-IV Pervasive Developmental Disorders (70% Autistic disorder; 15% Asperger's disorder; 1% Childhood disintegrative disorder; 14% PDD-NOS) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Not reported **N:** 80 in SHEA2004 (however, N=1 in the experimental group did not receive any study drug and had no baseline assessments so for demographic and intention-to-treat analysis N=79); N=55 in PANDINA2007 **Age:** 5-12 years (means: 7.5 years in SHEA2004 and 7.2 years in PANDINA2007) **Sex:** 23% female in SHEA2004 and 22% female in PANDINA2007 **Ethnicity:** 70% white in SHEA2004 and 62% white in PANDINA2007 **IQ:** Not reported in SHEA2004 and mean FIQ of 55.5 in PANDINA2007 **Inclusion criteria:** Physically healthy male and female outpatients who were aged 5 to 12 years inclusive were eligible to participate in this study provided that they had a DSM-IV Axis I diagnosis of PDD (with or without learning disabilities) and a total score>=30 on the Childhood Autism Rating Scale (CARS) **Exclusion criteria:** Participants were excluded if they: had schizophrenia, other psychotic disorders, clinically relevant nonneurologic disease, clinically significant laboratory abnormalities, or a seizure disorder for which they were receiving >1 anticonvulsant or if they had had a seizure in the last 3 months; had a history of hypersensitivity to neuroleptics, tardive dyskinesia, neuroleptic malignant syndrome, drug or alcohol abuse, or HIV; had used risperidone in the last 3 months, had been previously unresponsive or intolerant to risperidone, or were using a prohibited medication (including antipsychotics [other than the study medication], antidepressants, lithium, α2-antagonists, clonidine, guanfacine, cholinesterase inhibitors, psychostimulants, and naltrexone).

Interventions	**Experimental Intervention: Risperidone** versus placebo **Delivery of intervention:** Not reported **Format or method of administration:** Oral solution **Intensity:** 0.01mg/kg/day-0.06mg/kg/day (mean: 1.48mg/day [0.05mg/kg/day]) **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by Aberrant Behavior Checklist [ABC] - Irritability, Hyperactivity, Inappropriate Speech, Lethargy, and Stereotypy subscales; and Nisonger Child Behavior Rating Form (N-CBRF) Parent Version-Conduct problem, Hyperactive, Self-isolated/ritualistic, Insecure/anxious, Overly sensitive, and Self-injurious/stereotypic subscales; and Visual Analog Scale for the most troublesome symptom (VAS-MS) Change Score [for which data only extractable from SHEA2004]; and global state as measured by dichotomous measure of positive treatment response ['much improved/very improved' on CGI-improvement] and only reported in SHEA2004) **Indirect outcomes:** **Adverse events** (as measured by dichotomous measure of any side effect; weight gain [in kg]; and only in SHEA2004 additional measures of pulse (bpm) change score, and diastolic and systolic blood pressure (mm Hg) change scores)
Study Design	RCT
Source of funding	Janssen-Ortho Inc, Canada, and Johnson & Johnson Pharmaceutical Research and Development
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. Risk of performance bias is unclear/unknown as the paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. participant, parent, investigator, intervention administrator, outcome assessor. Also it is not clear that groups received the same care apart from the intervention studied as more participants in the experimental group received concomitant medications for other medical conditions (N=36; 90%) than participants in the placebo group (N=26; 66.7%) 3. Risk of detection bias is unclear/unknown as the paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. participant, parent, investigator, intervention administrator, outcome assessor and unclear if follow-up duration of 8 weeks sufficient to detect significant treatment effects, in particular, adverse events. 4. High risk of other bias due to conflict of interest as the study was funded and run by the pharmaceutical company that manufactured the drug tested
Notes	PANDINA2007 reports on a subgroup of participants with autistic disorder from the original SHEA2004 trial. A sensitivity analysis was conducted to see if substituting the autistic disorder population for the ASD population changed results and as it did not, the data for the larger N for the ASD

	population in SHEA2004 was used for meta-analysis. This trial is registered on ClinicalTrials.gov, Study NCT00261508. Contacted author regarding endpoint scores and missing outcome data and requested information was provided. Data was extracted for the ABC rather than the N-CBRF scale for challenging behaviour as the former is the more widely used rating scale.

1.4.15 TROOST2005

Study ID	TROOST2005
Bibliographic reference	Troost PW, Lahuis BE, Steenhuis M-P, Ketelaars CEJ, Buitelaar JK, van Engeland H, et al. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. Journal of American Academy of Child and Adolescent Psychiatry. 2005;44:1137-1144.
Methods	**Allocation:** Randomised (discontinuation study following open-label treatment) **Matching:** Stratified by investigational site **Blindness:** Participants, parents and outcome assessors were blind. It is not clear whether investigators and intervention administrators were blind. **Setting:** Not reported **Raters:** Parent- and clinician-rated **Country:** The Netherlands
Participants	**Diagnosis:** DSM-IV-TR Pervasive Developmental Disorder (25% Autistic disorder; 8% Asperger disorder; and 67% PDD-NOS) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnoses made using Autism Diagnostic Interview-Revised (ADI-R) and clinical judgement **N:** 24 (from N=36 who started open-label treatment and N=26 who were identified as short-term responders) **Age:** Range not reported (mean: 9.1 years) **Sex:** 8% female **Ethnicity:** 92% white **IQ:** Not reported **Inclusion criteria:** All participants were required to: meet DSM-IV-TR criteria for a pervasive developmental disorder; demonstrate clinically significant tantrums, aggression, self-injurious behavior, or a combination of these problems, defined as a rating of moderate or higher on the Clinical Global Impressions of Severity Scale (CGI-S) and a score <=18 on the Irritability Scale of the Aberrant Behavior Checklist (ABC); be aged 5 to 17 years; weigh >15 kg; have a mental age of >18 months; and be short-term responders to risperidone as defined by >=25% ABC Irritability score reduction and a rating of "much improved" or "very improved" on the CGI-S. **Exclusion criteria:** Children on effective psychotropic drug treatment for disruptive behavior were excluded
Interventions	**Experimental Intervention: Randomised discontinuation study to continued risperidone** or placebo

	Delivery of intervention: Not reported **Format or method of administration:** Oral capsules **Intensity:** Range not reported (mean: 1.81mg/day) **Duration of intervention:** 8 weeks for discontinuation phase **Total duration of follow-up:** 32 weeks (including open-label treatment and discontinuation phases)
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by a dichotomous measure of relapse [defined as Clinical Global Impression Scale of Symptom Change [CGI-SC score of 'much worse' or 'very much worse' for at least 2 consecutive weeks when compared with baseline of the discontinuation phase and >=25% increase in ABC-Irritability]; time to relapse [in weeks]; and Aberrant Behavior Checklist [ABC] - Irritability & Agitation, Lethargy & Social Withdrawal, Stereotypic Behaviour, Hyperactivity & Noncompliance, and Inappropriate Speech subscales)
Study Design	RCT (discontinuation study)
Source of funding	Korczak Foundation.
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear and although the randomisation sequence was generated externally, it is not clear if allocation was concealed from investigators. 2. Risk of performance bias is unclear/unknown as although the paper states that drugs were supplied by the pharmacist as matching capsules in identical packages it is not clear who the pharmacist was supplying to, i.e. investigators, participants, parents, and thus it is not clear whether the intervention administrator was blinded 3. High risk of other bias due to conflict of interest as drugs were donated by Janssen Cilag BV and three of the authors are paid consultants to or have received support from pharmaceutical companies
Notes	Study medications were donated by Janssen Cilag BV. Dr. Buitelaar is a paid consultant to or has received support from Janssen Cilag BV, Abbott, VCB, Shire, Medice, and Eli Lilly; Dr. Minderaa is a paid consultant to Eli Lilly and Janssen Cilag BV; and Dr. Scahill is a paid consultant to Janssen Pharmaceutica Inc., Bristol-Myers Squibb, and Pfizer

1.5 CHARACTERISTICS OF EXCLUDED PHARMACOLOGICAL INTERVENTION STUDIES

1.5.1 ANDERSON1984

Reason for exclusion	Efficacy data cannot be extracted

1.5.2 ANDERSON1989

Reason for exclusion	Efficacy data cannot be extracted

1.5.3 BARNARD2002

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

1.5.4 BROADSTOCK2003

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

1.5.5 BROADSTOCK2007

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

1.5.6 BOUVARD1995

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

1.5.7 CAMPBELL1982

Reason for exclusion	Efficacy data cannot be extracted

1.5.8 CAMPBELL1988

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

1.5.9 CHAVEZ2006

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

1.5.10 CHENGSHANNON2004

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

1.5.11 CHING2012

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

1.5.12 CURRAN2011

Reason for exclusion	Not primary data and no additional extractable outcomes reported

1.5.13 DINCA2005

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

1.5.14 EKMAN1989

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

1.5.15 ELBE2012

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

1.5.16 ELCHAAR2006

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

1.5.17 FOUNTOULAKIS2004

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

1.5.18 GONZALEZ1994

Reason for exclusion	Data cannot be extracted as results are not reported for the control group

1.5.19 HASPEL1995

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

1.5.20 HELLINGS2006

Reason for exclusion	Sample included children and adults and mean age of the sample was over 19 years

1.5.21 HUBAND2010

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

1.5.22 JENSEN2007

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

1.5.23 JESNER2007

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

1.5.24 KAVIRAJAN2009

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

1.5.25 KOLMEN1997

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

1.5.26 LEBOYER1992

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

1.5.27 MARCUS2011

Reason for exclusion	No placebo or active control group

1.5.28 MCADAM2002

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

1.5.29 NIEDERHOFER2002

Reason for exclusion	Insufficient trial detail reported (letter to editor) for data to be extracted and no reply to request to author for full trial report

1.5.30 PARIKH2008

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

1.5.31 PERRY1989

Reason for exclusion	Data cannot be extracted

1.5.32 RIDDLE1999

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

1.5.33 RITVO1986

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

1.5.34 RUPPRISPERIDONE2001 (TIERNEY2007)

Reason for exclusion	Data cannot be extracted

1.5.35 RUPPRISPERIDONE2001 (VITIELLO2005)

Reason for exclusion	Outcomes reported are outside the scope

1.5.36 SHARMA2012

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

1.5.37 STACHNIK2007

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

1.5.38 SUNG2010

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

1.5.39 TROOST2006

Reason for exclusion	Outcomes reported are outside the scope

1.5.40 WASSERMAN2006

Reason for exclusion	Data could not be extracted

1.5.41 WILLEMSENSWINKELS1995/1996

Reason for exclusion	Sample size for analysis was less than ten participants per arm (N<10/arm) due to cross-over design and available-case data reporting

1.5.42 WILLEMSENSWINKELS1999

Reason for exclusion	Non-randomised group assignment

1.5.43 YARBROUGH1987

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

1.5.44 ZARCONE2001

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

1.5.45 ZUDDAS2011

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

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1.7 CHARACTERISTICS OF INCLUDED BIOMEDICAL INTERVENTION STUDIES

1.7.1 BENT2011

Study ID	BENT2011
Bibliographic reference	Bent S, Bertoglio K, Ashwood P, Bostrom A, Hendren RL. A pilot randomized controlled trial of omega-3 fatty acids for autism spectrum disorder. Journal of Autism and Developmental Disorders. 2011;41:545-554.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, parents (who were intervention administrators) and outcome assessors were blinded **Setting:** Outpatient **Raters:** Parent-rated or identity of outcome assessor not reported (but study reports that all outcome assessment blinded) **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR ASD **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** Diagnosis corroborated using the Autism Diagnostic Observation Scale (ADOS), the Social Communication Questionnaire (SCQ) and by clinical review by an expert clinician (investigator) **N:** 27 **Age:** Range not reported but inclusion criteria 3-8 years (mean: 5.8 years) **Sex:** 11% female **Ethnicity:** Not reported **IQ:** Range not reported (mean: 77.5 as assessed by the Stanford-Binet Intelligence Scales) **Inclusion criteria:** Children were included if they: were aged 3-8 years; had a DSM-IV-TR diagnosis of autism corroborated using the ADOS, the SCQ and by clinical review by investigator; had a non-verbal IQ =>50; were on a stable medical regimen; had a clinician rating of at least moderate severity of autistic symptoms (Clinical Global Impression Severity [CGI-S] =>4) **Exclusion criteria:** Children were excluded if they: had a history of allergy to fish or nuts, diabetes, a bleeding disorder, a seizure disorder, cancer, perinatal brain injury, other serious medical illness; were currently or had previously used omega-3 fatty acids
Interventions	**Experimental Intervention: Omega-3 fatty acid supplement.** The supplement was provided as an orange-flavoured pudding packet (Coromega®, Vista, CA) **Control intervention: Placebo pudding packets** had the same orange flavour with an identical appearance and taste, but included safflower oil which has a similar texture to omega-3 fatty acids and is comprised of non-omega-3 fatty acids **Delivery of intervention:** Intervention delivered by parents (compliance reported to be perfect or nearly perfect for 69% of participants in analysis for

	the experimental group and for 75% of the placebo group) **Format or method of administration:** Oral administration **Intensity:** 1.3g of omega-3 fatty acids per day (with 1.1g of eicosapentanoic acid [EPA] and docosahexanoic acid [DHA]) administered as two daily doses (with 650mg of omega-3 fatty acids, 350mg of EPA and 230mg of DHA per dose) **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges, in particular hyperactivity** (as measured by the Aberrant Behaviour Checklist [ABC] - Hyperactivity & Noncompliance, Inappropriate Speech, Irritability & Agitation, Lethargy & Social Withdrawal, and Stereotypic Behaviour subscales; and the Behavior Assessment System for Children [BASC] - Hyperactivity, Externalizing, and Behavioral symptoms subscales) **Indirect outcomes:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the Social Responsiveness Scale [SRS] - Total score) **Coexisting problems or disorders: Adaptive behaviour** (as measured by the BASC - Adaptive skill subscale); **speech and language** (as measured by the Peabody Picture Vocabulary Test [PPVT] - Total score and the Expressive Vocabulary Test [EVT] - Total score); and **anxiety** (as measured by the BASC - Internalizing subscale) **Adverse events** (as measured by dichotomous measures of: Any side effect; Number of participants with rashes during the trial; Number of participants with upper respiratory infection during the trial; Number of participants with nose bleeds during the trial; Number of participants with increased GI symptoms during the trial; Number of participants with increased hyperactivity during the trial; and Number of participants with increased self-stimulatory behaviour during the trial)
Study Design	RCT
Source of funding	Autism Speaks, the Higgins Family Foundation, The Emch Foundation, The Taube Foundation, NIH/NCRR UCSF-CTSI Grant Number UL1 RR024131 (Dr. Bent) and the MIND Institute (Dr. Hendren)
Limitations	1. Risk of selection bias is unclear/unknown as insufficient detail reported with regards to allocation concealment and groups were not comparable at baseline (significant baseline group difference [p=0.03] for Clinical Global Impression-Severity [CGI-S] scores with greater severity in the experimental group [mean=4.6] than in the control group [mean=4.2])
Notes	Paper tested adequacy of blinding by asking carers at the end of the study: "do you think your child was taking omega-3 fatty acids or placebo?" and no statistically significant group differences were found in the percentage of carers who believed their child had been receiving omega-3 (40% in the omega-3 group and 64% in the placebo group, p=0.39). Contacted author regarding endpoint rather than change scores and data provided.

	Trial protocol registered on ClinicalTrials.gov, Study ID NCT00786799

1.7.2 HASANZADEH2012

Study ID	HASANZADEH2012
Bibliographic reference	Hasanzadeh E, Mohammadi M-R, Ghanizadeh A, Rezazadeh S-A, Tabrizi M, Rezaei F, et al. A double-blind placebo controlled trial of ginkgo biloba added to risperidone in patients with autistic disorders. Child Psychiatry and Human Development. 2012;43:674–682.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, intervention administrators, outcome assessors and parents blinded to treatment assignment **Setting:** Outpatient **Raters:** Clinician-rated **Country:** Iran
Participants	**Diagnosis:** DSM-IV-TR Autism **Coexisting conditions:** Children presented with a chief complaint of severely disruptive symptoms related to autistic disorder and scored >=12 on the Irritability subscale of the Aberrant Behavior Checklist-Community (ABC-C) **Qualifying Diagnostic Assessment:** DSM-IV-TR criteria for autism (score of >=6) as assessed by an experienced child psychiatrist through behavioural observation of the child, administration of the ADI-R and clinical judgement **N:** 47 **Age:** 4-11 years (mean: 6.4 years) **Sex:** 17% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 4-12 years of age; met DSM-IV-TR criteria for autism (score of >=6) as assessed by an experienced child psychiatrist through behavioural observation of the child, administration of the ADI-R and clinical judgement; presented with a chief complaint of severely disruptive symptoms related to autistic disorder and scored >=12 on the Irritability subscale of the Aberrant Behavior Checklist-Community (ABC-C) **Exclusion criteria:** Children were excluded if they: had a diagnosis of schizophrenia or psychotic disorder; had a history of drug or alcohol abuse or tardive dyskinesia; had received neuroleptics or any psychotropic drug treatments in the 6 months prior to enrolment in the trial; had a significant active medical problem; had a history of coagulopathy with bleeding tendency, proven aneurysms or hematoma; had severe learning disabilities (on the basis that this makes the diagnosis of autism uncertain)
Interventions	**Experimental Intervention: Combined ginkgo biloba and risperidone** **Control Intervention: Combined placebo and risperidone** **Delivery of intervention:** Intervention administered by investigational drug pharmacist

	Format or method of administration: Oral administration **Intensity:** Actual intensity not reported but planned intensity was final dose of 2 or 3mg/day of risperidone (for children weighing 10-30kg and >30kg respectively) and 80 or 120mg/day of ginkgo biloba (for children weighing <30kg and >30kg respectively) **Duration of intervention:** 10 weeks **Total duration of follow-up:** 10 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by the Aberrant Behaviour Checklist [ABC] - Irritability & Agitation, Lethargy & Social Withdrawal, Stereotypic Behaviour, Hyperactivity & Noncompliance, and Inappropriate Speech subscales) **Indirect outcome:** **Adverse events** (as measured by dichotomous measures of: Number of participants with day time drowsiness during the trial; Number of participants with morning drowsiness during the trial; Number of participants with constipation during the trial; Number of participants with dizziness during the trial; Number of participants with slow movement during the trial; Number of participants with nervousness during the trial; Number of participants with restlessness during the trial; Number of participants with increased appetite during the trial; Number of participants with loss of appetite during the trial; Number of participants with fatigue during the trial; Number of participants with diarrhoea during the trial; Number of participants with twitches during the trial; Number of participants with dry mouth during the trial; Number of participants with trouble swallowing during the trial; Number of participants with sore throat/tongue during the trial; and Number of participants with abdominal pain during the trial)
Study Design	RCT
Source of funding	Grant from Tehran University of Medical Sciences to Prof. Shahin Akhondzadeh (Grant No: 9500)
Limitations	1. Risk of detection bias is different for different outcomes but is unclear/unknown for adverse event outcomes as it is unclear if 10 weeks is a sufficient follow-up duration to observe potential longer-term adverse events, the reliability and validity of the checklist used to record adverse events is unclear, and the checklist is based on parental report and parents will be non-blind to other potentially confounding factors
Notes	Trial protocol registered on the Iranian Clinical Trials Registry, Study ID IRCT201012031556N19

1.7.3 JOHNSON2010

Study ID	JOHNSON2010
Bibliographic reference	Johnson CR, Handen BL, Zimmer M, Sacco K. Polyunsaturated fatty acid supplementation in young children with autism. Journal of Developmental and Physical Disabilities. 2010;22:1-10.

Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Non-blind (with the exception of the behavioural observation outcome measure) **Setting:** Outpatient **Raters:** Not reported **Country:** USA
Participants	**Diagnosis:** DSM-IV ASD (74% autistic disorder, 26% PDD-NOS) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis corroborated using the Autism Diagnostic Observation Schedule (ADOS) **N:** 23 **Age:** 2-4 years (mean: 3.4 years) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: had a DSM-IV diagnosis of ASD corroborated using the ADOS **Exclusion criteria:** Children were excluded if they: were taking any prescription medications; had identifiable genetic or metabolic conditions to explain their autistic symptoms; had seizures; had a history of low platelet count; had a bleeding disorder
Interventions	**Experimental Intervention: Omega-3 fatty acid supplement.** The supplement was Docoahexaonic Acid (DHA; Martek Biosciences product) capsules. **Control Intervention: Healthy diet control group.** Parents were provided with standard written materials and counselled on adhering to a healthy diet based on the food guide pyramid for young children **Delivery of intervention:** Parents delivered intervention **Format or method of administration:** Oral administration **Intensity:** Actual intensity not reported but planned intensity was 400mg/day (in two doses) **Duration of intervention:** 13 weeks **Total duration of follow-up:** 13 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by the Child Behavior Checklist 1.5 - 5 [CBCL/1.5-5] - Total problem score and Emotion regulation, Withdrawn, Attention problems, Aggressive behaviours, Externalizing, and ODD subscales) **Indirect outcomes:** **Core autism features: Overall autistic behaviours** (as measured by CBCL/1.5-5 - PDD subscale); **Impaired reciprocal social communication and interaction** (as measured by behavioural observation of: Frequency of positive vocalizations; and Frequency of social initiations) **Coexisting problems or disorders: Adaptive behaviour** (as measured by behavioural observation of frequency of attending to task/activity); **Speech and language** (as measured by Mullen Scales of Early Learning [MSEL] - Receptive Language and Expressive Language subscales); **Fine and gross motor skills** (as measured by MSEL - Fine motor subscale); **ADHD symptoms**

	(as measured by CBCL/1.5-5 - ADHD subscale); **Anxiety** (as measured by CBCL/1.5-5 - Anxious/Depressed, Internalizing, Affective, and Anxiety subscales); **Sleep problems** (as measured by CBCL/1.5-5 - Sleep problems subscale); and **Somatic complaints** (as measured by CBCL/1.5-5 - Somatic complaints subscale)
Study Design	RCT
Source of funding	John F. & Nancy A. Emmerling Fund/The Pittsburgh Foundation
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 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 different for different outcomes and is low risk for behavioural observation outcome measures as outcome assessors blinded but high risk for all other outcome measures (CBCL/1.5-5 and MSEL) as outcome assessment non-blind 5. High risk of selective reporting bias as data could not be extracted for adverse event outcomes 6. High risk of other bias die to potential conflict of interest as one of the authors consultant to pharmaceutical companies
Notes	Mean total adherence for the experimental group was 85.3% (range 0-100). Adherence for the control group was not reported.

1.7.4 KERN2001

Study ID	KERN2001
Bibliographic reference	Kern JK, Miller VS, Cauller L, Kendall R, Mehta J, Dodd M. Effectiveness of N,N-dimethylglycine in autism and pervasive development disorder. Journal of Child Neurology. 2001;16:169-173.
Methods	**Allocation:** Randomised **Matching:** Matched on age and gender **Blindness:** Parents and outcome assessors blinded but blinding of participants and intervention administrators unclear **Setting:** Not reported **Raters:** Parent-rated and clinician-rated (data could only be extracted for parent-rated outcome) **Country:** USA
Participants	**Diagnosis:** DSM-IV ASD **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis corroborated independently by study investigators (no further detail reported) **N:** 39 **Age:** 3-11 years (mean not reported) **Sex:** Not reported **Ethnicity:** Not reported

	IQ: Not reported **Inclusion criteria:** Children were included if they had a DSM-IV diagnosis of ASD corroborated by study investigators (no further detail reported) **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Dimethylglycine supplement.** Tablets were foil-wrapped. **Control Intervention: Placebo** (manitol) tablets identical in appearance **Delivery of intervention:** Identity and blinding of intervention administrator unclear **Format or method of administration:** Oral administration **Intensity:** Actual intensity not reported but planned intensity was 125-625mg/day dependent on weight (125mg/day for children weighing < 40 lbs; 250mg/day for children weighing 41-70 lbs; 375mg/day for children weighing 71-100 lbs; 500mg/day for children weighing 101-130 lbs; and 625mg/day for children weighing > 131 lbs) **Duration of intervention:** 4 weeks **Total duration of follow-up:** 4 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by parental report of positive treatment response)
Study Design	RCT
Source of funding	Foodscience Corporation, Essex Junction, VT.
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and groups were not comparable at baseline (statistically significant [p=0.0003] baseline group differences for the Lethargy subscale of the Aberrant Behavior Checklist [ABC] with the experimental group showing greater severity than the control group) 2. Risk of performance bias is unclear/unknown as identity and blinding of intervention administrator unclear 3. Risk of response bias is unclear/unknown as insufficient detail reported with regards to participant blinding 4. Risk of detection bias is unclear/unknown as the outcome measure was under-specified and not standardized, and although parents were blind to treatment assignment they would be non-blind to other potentially confounding factors 5. High risk of selective reporting bias as data could not be extracted for the Aberrant Behavior Checklist (Irritability, Lethargy/Social Withdrawal, Stereotypic Behavior, Hyperactivity and Inappropriate Speech subscales) or the Maladaptive Behavior Domain of the Vineland Adaptive Behavior Scale 6. High risk of other bias due to potential conflict of interest as trial funded by manufacturer of supplement
Notes	18% of participants receiving concurrent medication (clonidine, thioridazine, paroxetine, imipramine, methylphenidate, and fluoxetine) but at a stable dosage for trial duration. Contacted author regarding missing outcome data and author replied and confirmed that she no longer had access to this data.

1.7.5 PIRAVEJ2009

Study ID	PIRAVEJ2009
Bibliographic reference	Piravej K, Tangtrongchitr P, Chandarasiri P, Paothong L, Sukprasong S. Effects of Thai traditional massage on autistic children's behavior. Journal of Alternative and Complementary Medicine. 2009;15:1355-1361.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Participants, parents and the masseuse were not blind to treatment allocation. The sensory integration teacher was blind to treatment allocation. **Setting:** Not reported **Raters:** Parents and sensory integration teacher **Country:** Thailand
Participants	**Diagnosis:** DSM-IV autistic disorder **Coexisting conditions:** No details on coexisiting conditions reported **Qualifying Diagnostic Assessment:** Not reported **N:** 60 **Age:** Range: 3-10 years (Mean: 4.7 years) **Sex:** 18% **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included in the study if they had a DSM-IV diagnosis of autistic disorder from a psychiatrist. No further information reported. **Exclusion criteria:** Children were excluded if: they had any conditions that are not suitable for massage (e.g. Arthritis, joint dislocation); they were unable to attend at least 80% of the programme and at least 13 massage sessions; their parents were not cooperative.
Interventions	**Experimental Intervention: Combined Thai massage and sensory integration therapy.** A standardised Thai massage was delivered to all the children in the intervention group by the same masseuse. The masseuse built a rapport with the child before starting the massage, to reduce any anxieties. Massage was then applied to the whole body (feet, legs, arms, hands, fingers, back, neck, shoulders and ears) using moderate pressure. **Control Intervention: Sensory integration therapy only.** Sensory integration therapy was delivered to children in the experimental and control groups by the same occupational therapist, and creative and playful activities that included use of all the senses (including vestibular, tactile and proprioception) were used to encourage the children to develop new skills and abilities. **Delivery of intervention:** The sensory integration was delivered by an occupational therapist and the Thai massage was delivered by a masseuse. Both interventions were delivered to children individually. **Format or method of administration:** Individual **Intensity:** Sensory integration therapy: 16 hour-long sessions, with 2 sessions per week. A total of 16 hours.

	Thai massage: No details on intensity reported, but the exclusion criteria states that children had to attend a minimum of 13 sessions in order to be included in the study. **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks
Outcomes	**Direct Outcome** **Behaviour that challenges** (as measured by the Connors Parent Rating Scale [CPRS], the Connors Teacher Rating Scale [CTRS] and sleep problems measured using a parent-reported sleep diary)
Study Design	RCT
Source of funding	Asia Research Centre
Limitations	1. Unknown risk of selection bias - Method of concealment of allocation not reported and groups were not comparable at baseline. The massage and sensory integration group had lower scores of hyperactivity, hyperactivity index, and sleep-related problems 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 was different for different outcomes - Low risk for CTRS as teachers blinded to treatment allocation, and high risk for CPRS and SD as parents were non-blind
Notes	Not applicable

1.7.6 ROSSIGNOL2009

Study ID	ROSSIGNOL2009
Bibliographic reference	Rossignol DA, Rossignol LW, Smith S, Schneider C, Logerquist S, Usman A, et al. Hyperbaric treatment for children with autism: a multicenter, randomized, double-blind, controlled trial. BMC Pediatrics. 2009;9:21.
Methods	**Allocation:** Randomised **Matching:** Stratified by study site **Blindness:** Investigators, participants, carers and outcome assessors were blinded. Intervention administrator was non-blind **Setting:** Not reported **Raters:** Parent- and clinician-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV Autistic disorder **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis corroborated by psychologists using the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) **N:** 62 **Age:** Range not reported but inclusion criteria 2-7 years (mean: 4.9 years) **Sex:** 16% female **Ethnicity:** Not reported

	IQ: Not reported **Inclusion criteria:** Children were included if they: had a DSM-IV diagnosis of autistic disorder corroborated by psychologists using the ADI-R and ADOS; were aged 2-7 years; had never received Hyperbaric Oxygen Therapy (HBOT) **Exclusion criteria:** Children were excluded if they: had a DSM-IV diagnosis of Pervasive Developmental Disorder other than Autistic Disorder (including PDD-NOS and Asperger's Disorder); had seizure disorder; had fragile X syndrome; had a current ear infection; had uncontrolled asthma; were unable to equalize ear pressure; were currently receiving chelation medication
Interventions	**Experimental Intervention: Hyperbaric oxygen treatment (HBOT).** Participants were delivered 1.3 atmosphere (atm) and 24% oxygen in a monoplace hyperbaric chamber. Oxygen flowing at 10 litres per minute from an oxygen concentrator was mixed with room air and pumped into the chamber following the protocol described in Rossignol et al. (2007) **Control Intervention: Attention-placebo condition.** Control treatment involved slightly pressurised room air (1.03 atm and 21% oxygen) in a monoplace hyperbaric chamber **Delivery of intervention:** Intervention delivered by a hyperbaric technician **Format or method of administration:** Individual **Intensity:** Actual intensity not reported but planned intensity was 40 hours (10 hours/week) **Duration of intervention:** 4 weeks **Total duration of follow-up:** 4 weeks
Outcomes	**Direct outcome:** **Behaviour that challenges** (as measured by the Aberrant Behaviour Checklist [ABC] - Total [change score] and Irritability [change score], Lethargy [change score], Stereotypy [change score], Hyperactivity [change score] and Inappropriate Speech [change score] subscales) **Indirect outcomes:** **Core autism features: Overall autistic behaviours** (as measured by the Autism Treatment Evaluation Checklist [ATEC] - Total, and Speech/Language/Communication, Sociability, Sensory/Cognitive Awareness, and Health/Physical/Behavior subscales [change scores]) **Coexisting problems or disorders: Adaptive behaviour** (as measured by dichotomous measure of clinician-rated positive treatment response [defined as 'much improved/very improved' on Clinical Global Impression-Improvement [CGI-I] for change in overall functioning]; dichotomous measure of parent-rated positive treatment response [defined as 'much improved/very improved' on Parent Global Impression-Improvement [PGI-I] for change in overall functioning]) **Adverse events** (as measured by dichotomous measure of number of participants experiencing any adverse event during the trial)
Study Design	RCT
Source of funding	International Hyperbarics Association (IHA)
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear and insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrator non-blind

	3. Risk of detection bias is different for different outcomes and is low risk for most outcomes apart from adverse events where there is a high risk of detection bias as it is unclear if 4 weeks is a sufficient follow-up duration to detect potential longer-term adverse events and adverse events were recorded by the intervention administrator who was non-blind to treatment assignment and to other potentially confounding factors 4. High risk of other bias due to potential conflict of interest as study funded by the International Hyperbarics Association and authors profit from the use of hyperbaric treatment in their clinical practices
Notes	Trial protocol is registered on ClinicalTrials.gov, Study ID NCT00335790. Contacted author regarding endpoint ADOS scores and data provided

1.8 CHARACTERISTICS OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES

1.8.1 BENT2009

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

1.8.2 BUITELAAR1992

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

1.8.3 BUITELAAR1996

Reason for exclusion	Non-randomised group assignment

1.8.4 CAMPBELL1978

Reason for exclusion	Data cannot be extracted

1.8.5 CLAYTON2007

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

1.8.6 ESCALONA2001

Reason for exclusion	Efficacy data cannot be extracted and authors did not respond to data request

1.8.7 FIELD1997

Reason for exclusion	Efficacy data cannot be extracted and authors did not respond to data request

1.8.8 GOREN2011

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

1.8.9 HARTSHORN2001

Reason for exclusion	Non-randomised group assignment

1.8.10 JAMES2011

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

1.8.11 JOHNSON2011

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

1.8.12 KERN2002

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

1.8.13 KOENIG2012

Reason for exclusion	Non-randomised group assignment

1.8.14 LANG2010

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

1.8.15 LEVY2003

Reason for exclusion	Efficacy data cannot be extracted and authors did not respond to data request

1.8.16 MULLOY2010

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

1.8.17 SILVA2011A

Reason for exclusion	Not primary data and no additional extractable outcomes reported

1.8.18 SINHA2006

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

1.8.19 SINHA2011

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

1.8.20 SOWA2012

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

1.9 REFERENCES OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES

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