APPENDIX 14F:

CLINICAL EVIDENCE – STUDY CHARACTERISTICS

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1.1 CHARACTERISTICS OF INCLUDED STUDIES

Study ID	**BELSITO2001**
Bibliographic reference	Belsito, K. M., Law, P. A., Kirk, K. S., *et al.* (2001) Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Autism and Developmental Disorders*, *31*, 175–181.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** not reported. **Raters:** caregiver report and clinician-rated. **Country:** US.
Participants	**Diagnosis:** ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** ADI-R. **N =** 35. **Age:** 3 to 11 years (mean 5.8 years). **Sex:** male 33, female 2. **Ethnicity:** Caucasian N = 22. **IQ:** not reported. **Inclusion criteria:** children with a primary diagnosis of ASD. **Exclusion criteria:** children with autistic disorder associated with comorbid medical aetiologies, such as Fragile X syndrome or metabolic disorders, were excluded. Children with severe or profound 'mental retardation' in whom a definitive diagnosis of autism could not be made were excluded. No participants were taking concurrent medications for at least 1 month before entering the trial.
Interventions	1. Lamotrigine (mean 5 mg per kg per day, administered twice daily) (N = 14). 2. Placebo (N = 14). ***Duration:*** **Intervention:** 12 weeks. **Follow-up:** 18 weeks.
Outcomes	Primary outcomes were autistic behaviours as measured by the ABC (Krug *et al.*, 1993), the Pre-Linguistic ADOS (DiLavore *et al.*, 1995) and the CARS (Schopler *et al.*, 1988). Other outcomes included challenging behaviour as measured by the Aberrant Behaviour Checklist (Aman *et al.*, 1985) and adaptive behaviour as measured by the VABS) (Sparrow *et al.*, 1984).
Study design	RCT
Source of funding	GlaxoWellcome
Limitations	Narrative reporting of results does not allow for extraction of data to calculate effect sizes.
Notes	The trial ended with a 4-week drug-free period, but data were not extracted for this. N = 7 participants dropped out, N = 5 from experimental group and N = 2 from placebo group. ITT analysis was not performed. The mean number of reported side effects for lamotrigine was 0.63 and for placebo 0.69; insomnia and

	hyperactivity were the most frequently reported side effects.

Study ID	**BUITELAAR1992**
Bibliographic reference	Buitelaar, J. K., van Engeland, H., de Kogel, K., *et al.* (1992) The adrenocorticotrophic hormone (4-9) analog ORG 2766 benefits autistic children: report on a second controlled clinical trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, *31*, 1149–1156.
Methods	**Allocation:** randomised. **Matching:** treatment order groups matched by IQ and age. **Blindness:** double-blind. **Setting:** outpatient. **Raters:** parent-, teacher- and clinician-rated scales. No details given about raters of behavioural observation. **Country:** Netherlands.
Participants	**Diagnosis:** DSM-II-R ASD (autistic disorder). **Coexisting conditions:** N = 2 convulsive disorder, N = 1 congenital thyroid aplasia. **Qualifying diagnostic assessment:** diagnosis made independently by two child psychiatrists on the basis of extensive diagnostic evaluations that included review of previous records, parent interview, child psychiatric observation and complete medical diagnostic workup. Subjects additionally characterised by scores on the CARS. **N =** 21. **Age:** 5 to 15 years (mean 10 years). **Sex:** male 17, female 4. **Ethnicity**: not reported. **IQ:** range and mean not reported (N = 4 in IQ range 22 to 40, N = 4 in IQ range 40 to 55, N = 3 in IQ range 55 to 70, N = 10 in IQ range 70 to 85). **Inclusion criteria:** not reported.
Interventions	1. ACTH (ORG 2766; oral tablets, 40 mg per day) (N = 21, but sample size halved for analysis because it because it was a crossover study). 2. Placebo (oral tablets) (N = 21, but sample size halved for analysis because it was a crossover study). ***Duration:*** **Intervention:** 8 weeks per intervention. **Follow-up:** 36 weeks.
Outcomes	Primary outcomes were challenging behaviour as measured by behaviour checklist ratings (Aberrant Behaviour Checklist [Aman *et al.*, 1985]; GAP designed for this study) and behaviour observation (playroom sessions), and symptom severity/improvement as measured by the CGI.
Study design	RCT (crossover)
Source of funding	ORG 2766 and placebos supplied by Organon International B.V.
Limitations	1. Small sample size. 2. Data could not be extracted for Aberrant Behaviour Checklist scales.

Notes	Data could not be extracted for Aberrant Behaviour Checklist – teacher ratings because data were only available for 15 subjects, hence sample size was less than ten per arm because this was a crossover study. N = 2 on antiepileptic medication (sodium valproate and ethosuximide), N = 1 received thyroid substitution therapy. The dosage remained fixed throughout the study.

Study ID	**BUITELAAR1996**
Bibliographic reference	Buitelaar, J. K., Dekker, M. E. M., van Ree, J. M., *et al.* (1996) A controlled trial with ORG 2766, an ACTH-(4-9) analog, in 50 relatively able children with autism. *European Neuropsychopharmacology*, *6*, 13–19.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** outpatient. **Raters:** parent-, teacher- and clinician-rated scales. Rater details not reported for the behaviour observation. **Country:** Netherlands.
Participants	**Diagnosis:** DSM-III-R ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** diagnosis made independently by two child psychiatrists on the basis of extensive diagnostic evaluations, which included review of previous records, a parent interview, a child psychiatric observation and a complete medical diagnostic workup. Subjects additionally characterised by scores on the CARS. **N =** 47. **Age:** 5 to 17 years (experimental group mean 9.7 years, control group mean 10.6 years). **Sex:** male 32, female 15. **Ethnicity:** not reported. **IQ:** range not reported (experimental group mean 79.9, control group mean 77.2). **Inclusion/exclusion criteria:** diagnosis of autistic disorder according to DSM-III-R criteria, PIQ >60 on WISC-R, aged 7 to 15 years; and no concurrent treatment with psychotropic medication.
Interventions	1. ACTH (ORG 2766; oral tablets, 40 mg once daily) (N = 29). 2. Placebo (oral tablets) (N = 18). ***Duration:*** **Intervention:** 6 weeks. **Follow-up:** 6 weeks.
Outcomes	Primary outcomes of interest, and for which data were available, were challenging behaviour as measured by the parent- and teacher-completed Aberrant Behaviour Checklist (Aman *et al.*, 1985), and symptom severity/improvement as measured by the investigator-rated CGI (NIMH, 1985).
Study design	RCT
Source of funding	ORG 2766 and placebos provided by Organon International B.V.

Limitations	1. There was a trend for participants in the experimental group to be younger and have higher CARS scores than subjects treated with placebo. 2. Randomisation methods unclear. Authors state, 'The subjects were in principle randomized'. 3. Uneven sample sizes.
Notes	• N = 50 children with ASD were included in the study, but N = 3 dropped out (N = 1 ORG 2766; N = 2 placebo) due to an increase in anxiety, nervousness and irritability after they taking the tablets. As demographic characteristics are only reported for the 47 completers, the number is given as 47 above. • Data could not be extracted for the playroom behaviour observation because more subjects dropped out in the placebo group resulting in a sample size of less than ten per arm and potential attrition bias. • There was no systematic difference in the number or distress of side effects. Side effects associated with ORG 2766 included headache (N = 2), increase in aggression and oppositional behaviour (N = 2), increase in anxiety (N = 1) and emotional lability (N = 1). Side effects associated with placebo were increase in anxiety (N = 3) and increase in stereotypies (N = 1). • Continuous data extracted for CGI, as reported. • Dichotomous data extracted for Aberrant Behaviour Checklist – Social Withdrawal subscale, with responders classified as participants showing reliable improvement on the Aberrant Behaviour Checklist – Social Withdrawal subscale either at home or at school or in both contexts (reliable change approach, Jacobson & Truax, 1991, used) and extracted as reported.

Study ID	CHEZ2000
Bibliographic reference	Chez, M. G., Buchanan, C. P., Bagan, B. T., *et al.* (2000) Secretin and autism: a two-part clinical investigation. *Journal of Autism and Developmental Disorders*, *30*, 87–94.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** not reported. **Raters:** parent-rated scale. **Country:** US.
participants	**Diagnosis:** ASD. **Coexisting conditions:** gastrointestinal problems (N = 9); past abnormal electroencephalograph (N = 10). **Qualifying diagnostic assessment:** not reported. **N =** 25. **Age:** range not reported (mean 6 years). **Sex:** male 22, female 3. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion criteria:** not reported.
Interventions	1. Secretin (intravenous injection, single dose 2 IU per kg) (N = 25, but sample size halved for analysis because this was a crossover study). 2. Placebo (normal saline, intravenous injection, single dose) (N = 25, but sample size halved for analysis because this was a crossover study). ***Duration:*** **Intervention:** single dose. **Follow-up:** 8 weeks.
Outcomes	Primary outcome was autistic behaviours as measured by a modified parent-completed version of the CARS.
Study design	RCT (crossover)
Source of funding	Not reported
Limitations	Small sample size
Notes	This double-blind placebo-controlled trial was preceded by an open-label trial of secretin; however, data were not extracted for that phase. One participant dropped out.

Study ID	CHEZ2002
Bibliographic reference	Chez, M. G., Buchanan, C. P., Aimonovitch, M. C., *et al.* (2002) Micronutrients versus standard medication management in autism: a naturalistic case-control study. *Journal of Child and Adolescent Psychopharmacology*, *17*, 833–837.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** not reported. **Raters:** parent-rated and clinician-rated scales. **Country:** US.
Participants	**Diagnosis:** DSM-IV-R ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** not reported. **N =** 31. **Age:** 3 to 12 years (mean 7.45 years). **Sex:** male 21, female 10. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion criteria:** children aged 3 to 12 years with a prior diagnosis of ASD (DSM-IV-R).
Interventions	1. L-Carnosine (powder to be mixed with food or drink, 400 mg twice daily) (N = 14). 2. Placebo (identical in powdered appearance) (N = 17). ***Duration:*** **Intervention:** 8 weeks. **Follow-up:** 8 weeks.
Outcomes	Primary outcome was autistic behaviours as measured by the CARS and the GARS. Secondary outcome was clinical global impression improvement scale.
Study design	RCT
Source of funding	Not reported
Limitations	Significant difference between groups in baseline scores on the Communication subscale of the GARS
Notes	Data not extracted for GARS scores due to baseline group differences.

Study ID	CHEZ2003
Bibliographic reference	Chez, M. G., Buchanan, T. M., Becker, M., *et al.* (2003) Donepezil hydrochloride: a double-blind study in autistic children. *Journal of Pediatric Neurology*, *1*, 83–88.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** not reported. **Raters:** parent-rated scale. **Country:** US.
Participants	**Diagnosis:** DSM-IV ASD (N = 13 autistic disorder; N = 27 PDD; N = 3 Landau-Kleffner syndrome). **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** diagnosis confirmed by a paediatric neurologist after completing a comprehensive neurological evaluation and also by a clinical interview with a clinical psychologist. **N =** 43. **Age:** 2 to 10 years (mean 6.8 years). **Sex:** male 35, female 8. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion criteria:** males or females aged 2 to 10 years with prior DSM-IV diagnosis of ASD. **Exclusion criteria:** concomitant neurological syndrome or disease in which neurological compromise is a feature (for example, neurofibromatosis).
Interventions	1. Donepezil hydrochloride (capsule sprinkle form for oral administration, 1.25 to 2.5 mg per day). 2. Placebo (identical in appearance capsule sprinkle form). ***Duration:*** **Intervention:** 6 weeks. **Follow-up:** 6 weeks.
Outcomes	Primary outcome was autistic behaviours as assessed by a modified parent-rating report version of the CARS.
Study design	RCT
Source of funding	Not reported
Limitations	Potential attrition bias
Notes	• The double-blind placebo-controlled phase was followed by a 6-week open-label extension. However, data for that phase were not extracted here. • Included patients with abnormal electroencephalograph. • Patients were maintained on the medications that they had initiated prior to study start: N = 32 anticonvulsants (divalproex sodium, valproic acid or lamotrigine); N = 6 corticosteroids (pulse-dose prednisone or prednisolone); N = 8 central nervous system stimulants (dextroamphetamine/amphetamine or methylphenidate); N = 7 antidepressants (fluoxetine hydrochloride or paroxetine); N = 4 antipsychotics (risperidone); and N = 9 alpha adrenergic blocking agents (clonidine). • N = 9 patients dropped out of the study: N = 6 from experimental

	and N = 3 from control. N = 2 on donepezil hydrochloride discontinued due to diarrhoea or stomach cramping and N = 4 due to increased irritability accompanied by increased screaming and vocalisations. In placebo group, N = 3 dropped out due to failure to attend post-test appointment.

Study ID	**CHEZ2007**
Bibliographic reference	Chez, M. G., Burton, Q., Dowling, T., *et al.* (2007) Memantine as adjunctive therapy in children diagnosed with autistic spectrum disorders: an observation of initial clinical response and maintenance tolerability. *Journal of Child Neurology*, *22*, 574–579.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** N/A – no control group. **Setting:** not reported. **Raters:** clinician-rated scale. **Country:** US.
Participants	**Diagnosis:** DSM-IV ASD (N = 105 autism; N = 46 PDD). **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** clinical observation by primary author. **N =** 151. **Age:** 2 to 26 years (mean 9.3 years). **Sex:** male 129, female 22. **Ethnicity:** not reported. **IQ:** not reported. **Exclusion criteria:** children excluded if any underlying genetic disorders such as Fragile X or Rett syndrome, and none had known brain malformations or known metabolic disorders such as aminoacidurias or degenerative diseases; concomitant lamotrigine not allowed as it may inhibit glutamate. Patients with active clinical seizures excluded.
Interventions	1. Memantine (once or twice daily taken whole or crushed, final dose 2.5 to 30 mg per day, mean 12.67 mg per day) (N = 151). ***Duration:*** **Intervention:** 1 to 20 months (mean 9.27 months). **Follow-up:** 1 to 20 months (mean 9.27 months).
Outcomes	Primary outcomes of interest were the core autistic symptoms of social communication difficulties and challenging behaviour. Both of these outcomes were measured with the CGI-I (CGI-I language was based on both receptive skills and expressive utterances and CGI-I behaviour was based on cognitive improvement as well as increased social interest or efforts).
Study design	Observational (before-and-after).
Source of funding	Not reported.
Limitations	Efficacy data could not be extracted.
Notes	• Participants with an abnormal baseline electroencephalograph were not excluded. • Concurrent medications included SSRIs (N = 20 fluoxetine; N = 11

	citalopram; N = 6 sertraline; N = 2 fluvoxamine; N = 6 escitalopram; N = 3 others); atypical antipsychotics (N = 31 risperidone; N = 5 aripiprazole; N = 17 quetiapine; N = 2 olanzapine; N = 3 ziprasidone); stimulants (N = 20 amphetamine salts; N = 22 methylphenidate products); atomoxetine (N = 5); alpha-adrenergic antagonists (N = 14 clonidine; N = 19 tizanidine; N = 4 guanfacine); lithium (N = 5); cholinesterase inhibitors (N = 15 donepezil; N = 9 rivastigmine; N = 2 galantamine); and antiepileptic drugs (N = 77 valproic acid; N = 1 topiramate; N = 1 levetiracetam). All patients on concurrent medication were kept as stable as possible and were not given memantine unless they were already stable on other medications for at least 8 weeks.

Study ID	**COOK1992**
Bibliographic reference	Cook, E. H. Jr., Rowlett, R., Jselskis, C., *et al.* (1992) Fluoxetine treatment of children and adults with autistic disorder and mental retardation. *Journal of the American Academy of Child and Adolescent Psychiatry*, *31*, 739–745.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** open-label. **Setting:** outpatient. **Raters:** treating clinician. **Country:** US.
Participants	**Diagnosis:** DSM-III-R ASD (autistic disorder). **Coexisting conditions:** learning disability (N = 3 profound, N = 7 severe, N = 3 moderate, N = 6 mild and N = 2 borderline); N = 3 OCD; N = 6 impulse control disorder not otherwise specified with self-injurious behaviour; N = 5 impulse control disorder not otherwise specified without self-injurious behaviour; N = 1 cyclothymia; N = 1 bipolar disorder not otherwise specified; N = 1 eating disorder. **Qualifying diagnostic assessment:** not reported. **N =** 23. **Age:** 7 to 28 years (mean 15.9 years). **Sex:** male 18, female 5. **Ethnicity:** not reported. **IQ:** not reported, but with a learning disability. **Inclusion criteria:** consecutive series of patients treated with fluoxetine by child and adolescent psychiatrists at the University of Chicago, IL, in an outpatient setting between 1988 and 1990.
Interventions	1. Fluoxetine (oral, ranged from 20 mg every other day to 80 mg per day). ***Duration:*** **Intervention:** 11 to 426 days (mean 189 days). **Follow-up:** 11 to 426 days (mean 189 days).
Outcomes	The primary outcome was symptom severity/improvement as assessed by the CGI. Two subscales were used. The first was an overall rating of severity of illness and therapeutic efficacy. The second was a rating limited to perseverations, compulsions, or rituals depending on the individual's particular difficulties.

Study design	Observational (before-and-after study).
Source of funding	Harris Center for Developmental Studies; NIMH Child and Adolescent Mental Health Academic Award MH00822
Limitations	1. Coexisting psychiatric conditions may threaten generalisability of findings. 2. No control group and efficacy data could not be extracted. 3. Small sample size. 4. Question of indirectness as adolescent sample.
Notes	• A group with learning disabilities and without autism were also studied; however, data were not extracted for this group. • Concomitant psychotropic medication included N = 8 neuroleptics; N = 1 carbamazepine; N = 2 lithium carbonate; N = 1 clonidine and alprazolam; and N = 1 methylphenidate. • Participants with side effects that significantly interfered with function or outweighed therapeutic effects were N = 6 out of N = 23. Side effects included hyperactivity, insomnia, elated affect, decreased appetite, behavioural problems and maculopapular rash.

Study ID	**DOSMAN2007**
Bibliographic reference	Dosman, C. F., Brian, J. A., Drmic, I. E., *et al.* (2007) Children with autism: effect of iron supplementation on sleep and ferritin. *Pediatric Neurology*, *36*, 152–158.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** open-label. **Setting:** not reported. **Raters:** parent-rated and clinician-rated scales. **Country:** Canada.
Participants	**Diagnosis:** ASD. **Coexisting conditions:** majority of sample had restless sleep (occurring on average once or twice per week). **Qualifying diagnostic assessment:** ADI-R, ADOS and clinical evaluation. **N =** 33. **Age:** 2 to 10 years (mean 6.5 years). **Sex:** male 27, female 6. **Ethnicity:** not reported. **IQ:** not reported. **Exclusion criteria:** currently receiving iron supplementation.
Interventions	1. Iron supplement (oral preparation 6 mg elemental iron per kg per day, N = 23; or if anticipated that oral preparations would not be accepted, sprinkles two sachets total of 60 mg per day, N = 10) (N = 33). ***Duration:*** **Intervention:** 8 weeks. **Follow-up:** 8 weeks.
Outcomes	Primary outcome was sleep patterns as assessed by two parent-report questionnaires (Sleep Disturbance Scale for Children, Bruni *et al.* 1996;

	and periodic leg movements during sleep scale of Chervin & Hedger, 2001). Secondary outcome was challenging behaviour as measured using the CGI-I.
Study design	Observational (before-and-after)
Source of funding	Trainee's Start-Up Fund, The Hospital for Sick Children, Toronto, Ontario, Canada
Limitations	High attrition rate
Notes	• N = 43 participants were originally enrolled in the study but data were not reported for participants who withdrew. N = 3 refused to take iron preparation; N = 2 refused venipuncture; N = 2 side effects; N = 3 unrelated to procedures. • Data reported for ferretin levels, but not extracted here.

Study ID	**DUNNGEIER2000**
Bibliographic reference	Dunn-Geier, J., Ho, H. H., Auersperg, E., *et al.* (2000) Effect of secretin on children with autism: a randomized controlled trial. *Developmental Medicine and Child Neurology*, *42*, 796–802.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** not reported. **Raters:** parent- and clinician-rated scales. **Country:** Canada.
Participants	**Diagnosis:** DSM-IV ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** CARS. **N =** 95. **Age:** 2 to 7 years (mean 5.1 years). **Sex:** male 88, female 7. **Ethnicity:** white N = 75. **IQ:** not reported. **Inclusion criteria:** a diagnosis of autism based on behavioural observation of the child and semistructured interview with the parent (defined as a score of ≥30 on the CARS; Schopler *et al.*, 1980), a score of ≥6 on the DSM-IV diagnostic criteria for autism, clinical judgement by a developmental paediatrician and registered psychologist experienced in the field of autism. **Exclusion criteria:** a recognisable neurological or genetic disorder (for example infantile spasms, Rett syndrome, Fragile X syndrome, Tourette's syndrome, tuberous sclerosis, phenylketonuria or neurofibromatosis), a pancreatic or liver disorder, or an allergy to lidocaine or prilocaine; also excluded if secretin had been used previously, if there had been any treatment initiated or changed within the 2 months immediately before enrolment or if any treatment was planned to begin within the 3 weeks after injection (including drugs, supplements, dietary changes and behavioural therapy).
Interventions	1. Secretin (single dose injection of 2 CU per kg to a maximum of 75 CU) (N = 47). 2. Placebo (single dose injection) (N = 48).

	Duration: **Intervention:** single dose. **Follow-up:** 3 weeks.
Outcomes	Primary outcomes were autistic behaviours (as measured by the CARS and the ABC; Krug *et al.*, 1993), core autistic symptom of communication (as measured by the PLS-3; Zimmerman *et al.*, 1992), and side effects (as measured by parent-completed gastrointestinal symptoms questionnaire and a treatment behaviour/side-effect rating scale designed for this study).
Study design	RCT
Source of funding	Financial contribution from Children at Risk, Ottawa, and grants from the Children's Hospital of Eastern Ontario Research Institute and the Woodward's Foundation
Limitations	1. Short duration of follow-up. 2. Data could not be extracted for CARS, ABC or side effect measures.
Notes	Treatment groups significantly different in baseline PLS-3 scores; however, this was controlled for in statistical analysis.

Study ID	**ERICKSON2007**
Bibliographic reference	Erickson, C. A., Posey, D. J., Stigler, K. A., *et al.* (2007) A retrospective study of memantine in children and adolescents with pervasive developmental disorders. *Psychopharmacology*, *191*, 141–147.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** N/A – no control group. **Setting:** outpatient. **Raters:** clinician-rated scale. **Country:** US.
Participants	**Diagnosis:** DSM-IV-TR ASD (N = 13 autistic disorder; N = 3 Asperger's disorder; N = 2 PDD). **Coexisting conditions:** N = 11(61%) comorbid 'mental retardation'. **Qualifying diagnostic assessment:** not reported. **N =** 18. **Age:** 6 to 19 years (mean 11.4 years). **Sex:** not reported. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion criteria:** all were patients meeting DSM-IV-TR criteria for a PDD who received treatment with memantine. In all cases, memantine was used targeting social impairment (including impaired social use of language) and/or inattention/hyperactivity.
Interventions	1. Memantine (2.5 to 20 mg per day; mean 10.1 mg per day) (N = 18). ***Duration:*** **Intervention:** 1.5 to 56 weeks (mean 19.3 weeks). **Follow-up:** 1.5 to 56 weeks (mean 19.3 weeks).
Outcomes	Primary outcome was symptom improvement/severity and as part of routine care the treating physician completed the CGI-S and CGI-I (Guy, 1976a).

Study design	Observational (case series)
Source of funding	NIMH (K23 MH68627), a Daniel X. Freedman Psychiatric Research Fellowship, and the Department of Housing and Urban Development (B-01-SP-IN-0200)
Limitations	1. Efficacy data could not be extracted. 2. Small sample size.
Notes	• N = 13 participants receiving concomitant medications had the doses of these medications held constant during the trial. • Challenging behaviour as assessed by the Aberrant Behaviour Checklist, but this was only for N = 6 and as such was not extracted because it does not meet the sample size eligibility criteria. • Target symptoms identified as the reason for prescribing memantine included N = 11 social withdrawal, N = 8 inattention, N = 10 communication impairment N = 5 and irritability. Most patients had more than one target symptom. • Overall, N = 8 were reported to have had adverse effects during treatment including N = 4 irritability, N = 1 rash, N = 1 emesis, N = 1 increased seizure frequency and N = 1 excessive sedation.

Study ID	EVANGELIOU2003
Bibliographic reference	Evangeliou, A., Vlachonikolis, I., Mihailidou, H., *et al.* (2003) Application of a ketogenic diet in children with autistic behavior: pilot study. *Journal of Child Neurology*, *18*, 113–118.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** N/A – no control group. **Setting:** not reported. **Raters:** clinician-rated scale. **Country:** Greece.
Participants	**Diagnosis:** ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** CARS. **N =** 30. **Age:** 4 to 10 years (median: 7 years). **Sex:** male 16, female 14. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion criteria:** not reported.
Interventions	1. Ketogenic diet (The recommended diet was the John Radcliffe diet, which distributes daily energy intake as follows: 30% of energy as medium-chain triglyceride oil, 30% as fresh cream, 11% as saturated fat, 19% as carbohydrates and 10% as protein. Participants also received vitamin and mineral supplements according to the recommended daily allowances for age) (N = 30). ***Duration:*** **Intervention:** 6 months (with continuous administration for 4 weeks at a time, interrupted by 2-week intervals that were diet-free). **Follow-up:** 6 months.
Outcomes	Primary outcome was autistic behaviour as measured by the CARS (Schopler *et al.*, 1980).
Study design	Observational (before-and-after)
Source of funding	Not reported
Limitations	High attrition rate; only 18 participants completed the diet for a 6-month period
Notes	All participants were concurrently treated with haloperidol. The participants were treated with haloperidol at least 6 months before the initiation of a ketogenic diet without having any changes in the CARS. During, and 6 months before and after, the diet no behavioural treatments were given.

Study ID	GAGIANO2005
Bibliographic reference	Gagiano, C., Read, S., Thorpe, L., *et al.* (2006) Short- and long-term efficacy and safety of risperidone in adults with disruptive behaviour disorders. *Psychopharmacology*, *179*, 629–636.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** not reported. **Raters:** clinician-rated. **Country:** Canada, South Africa and UK.
Participants	**Diagnosis:** DSM-IV intellectual disability. **Coexisting conditions:** N = 44 conduct disorder, N = 13 disruptive behaviour disorder, N = 11 intermittent explosive disorder, N = 5 oppositional defiant disorder and N = 4 antisocial personality disorder. **Qualifying diagnostic assessment:** IQ measured at screening using the WAIS or Stanford-Binet IQ tests. **N =** 77. **Age:** 18 to 59 years (mean not reported). **Sex:** male 47, female 30. **Ethnicity:** not reported. **IQ:** 35 to 83 (mean not reported). **Inclusion/exclusion criteria:** aged 18 to 65 years with a DSM-IV Axis I diagnosis of conduct disorder, oppositional defiant disorder, antisocial personality disorder, disruptive behaviour disorder or intermittent explosive disorder. Participants also had to have a DSM-IV Axis II diagnosis of borderline intellectual functioning, or mild or moderate 'mental retardation', which represents an IQ range of 35 to 84. Participants were excluded if they had a: diagnosis of schizophrenia and other psychotic disorders or PDD; head injury as a cause of mental impairment (except for birth trauma); seizure disorder requiring medication; clinically relevant abnormal laboratory values outside the normal range; serious or progressive illnesses (including but not restricted to liver or renal insufficiency, cardiac, vascular, gastrointestinal, pulmonary or endocrine disturbances; or human immunodeficiency virus infection); history of tardive dyskinesia or neuroleptic malignant syndrome; or a known hypersensitivity to antipsychotics. Participants who had previously received risperidone for conduct disorder for more than 3 weeks and those who had received risperidone for fewer than 3 weeks and did not respond were also excluded.
Interventions	1. Risperidone (oral tablets, 1 to 4 mg per day with a mean dose of 1.45 per day) (N = 39). 2. Placebo (oral tablets) (N = 38). ***Duration:*** **Intervention:** 4 weeks. **Follow-up:** 52 weeks (open-label continuation).
Outcomes	Primary outcome was symptom severity/improvement (as measured by the CGI (Guy, 1976a).
Study design	RCT
Source of funding	Johnson & Johnson Pharmaceutical Research and Development

Limitations	Data for challenging behaviour outcome (Aberrant Behaviour Checklist scores) could not be extracted.
Notes	• N = 4 in each group discontinued the study prematurely. No participant discontinued because of adverse events. N = 2 in the placebo group and N = 1 in the risperidone group withdrew because of insufficient response. • Allowable psychotropic medications other than risperidone included antidepressants, lithium, carbamazepine and valproic acid. Anticholinergic medication was discontinued at study entry. Limited use of sedative and hypnotic medication was allowed. Concomitant use of medications for medical disorders was also allowed. • N = 25 out of N = 38 in the placebo group, and N = 21 out of N = 39 in the risperidone group received concomitant medication. • After double-blind RCT, participants could enter open-label treatment with risperidone for 48 weeks.

Study ID	**HAESSLER2007**
Bibliographic reference	Haessler, F., Glaser, T., Beneke, M., *et al.* (2007) Zuclopenthixol in adults with intellectual disabilities and aggressive behaviours: discontinuation study. *British Journal of Psychiatry*, *190*, 447–448.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** predominantly residential. **Raters:** clinician-rated scale. **Country:** Germany.
Participants	**Diagnosis:** learning disability. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** not reported. **N =** 39. **Age:** 18 to 50 years (mean not reported). **Sex:** not reported. **Ethnicity:** not reported. **IQ:** 30 to 70 (mean not reported). **Inclusion/exclusion criteria:** all participants scored below 39 on the Disability Assessment Schedule (Holmes *et al.*, 1982). Exclusion criteria were the presence of a diagnosed neurological disorder (without epilepsy), psychotic disorder, infantile cerebral palsy, hypersensitivity to zuclopenthixol and cardiac abnormalities. Female participants who were sexually active and did not use an effective form of birth control were also excluded.
Interventions	1. Zuclopenthixol (2 to 20 mg per day, mean 11.4 mg per day) (N = 19). 2. Placebo (N = 20). ***Duration:*** **Intervention:** up to 12 weeks (discontinuation period). **Follow-up:** 18 weeks.
Outcomes	Primary outcome was the challenging behaviour, aggression (as measured by the MOAS (Yudofsky *et al.*, 1986). The outcome measure

	was dichotomous with participants rated as responders or non-responders. Patients with a deterioration of at least 3 points in MOAS sum scores at two subsequent visits when compared with their state at randomisation were designated as non-responders. All patients without deterioration were considered to be responders.
Study design	RCT
Source of funding	Study medication and placebos provided by Bayer Vital GmbH
Limitations	Low dosages of zuclopenthixol (6 to 18 mg, mean 11.4 mg) might be responsible for the relatively high relapse rates in the continuation (zuclopenthixol) subgroup. Small sample sizes.
Notes	• Concomitant use of other antipsychotics was not permitted throughout the study. Use of consistent doses of anticonvulsants as well as lithium, medication for extrapyramidal symptoms and benzodiazepines as an anti-epileptic escape medication was permitted. • Psychotropic adjunctive medications given after randomisation (N = 7) were equally distributed between the groups and involved the prescription of one benzodiazepine drug in each group. • This was a double-blind placebo controlled withdrawal study including responders from an open-label 6-week treatment with zuclopenthixol. • The psychopharmacological mechanism of zuclopenthixol differs slightly from the dopaminergic-serotonergic impact of risperidone. • The number of adverse events and possible symptoms of withdrawal, such as nausea, insomnia and diarrhoea, were recorded and did not differ between the groups.

Study ID	**HANDEN2006**
Bibliographic reference	Handen, B. L. & Hardan, A. Y. (2006) Open-label, prospective trial of olanzapine in adolescents with subaverage intelligence and disruptive behavioral disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, *45*, 928–935.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** open-label. **Setting:** outpatient. **Raters:** primary caregiver-report. **Country:** US.
Participants	**Diagnosis:** learning disability and disruptive behaviours. **Coexisting conditions:** N = 11 disruptive behaviour disorder, N = 12 ADHD, N = 2 oppositional defiant disorder, N = 1 stereotypic movement disorder, N = 1 anxiety disorder, N = 1 conduct disorder, N = 1 impulse control disorder. **Qualifying diagnostic assessment:** not reported. **N =** 16. **Age:** 13 to 17 years (mean 14.7 years). **Sex:** male 10, female 6.

	Ethnicity: not reported. **IQ:** 36 to 79 (mean 55) based on the most recently available test (typically conducted by the participant's school districts). **Inclusion/exclusion criteria:** inclusion criteria included a minimum score at or above the 85th percentile for age and gender on the irritability subscale of the Aberrant Behaviour Checklist. Axis I diagnoses included ADHD, oppositional defiant disorder, conduct disorder and disruptive behaviour disorder. Participants were excluded from the study if they had a diagnosis of schizophrenia or other psychotic disorder, autism, mood disorder, bipolar disorder or depressive disorder. Participants with an unstable seizure disorder (seizure within past 3 months), who were medically unstable or had significant medical or neurologic illness, were also excluded. Individuals who had been prescribed olanzapine for >3 weeks at >15 mg per day were also excluded. Participants were allowed to continue any concomitant therapies with the exception of typical and atypical antipsychotics. For participants prescribed concomitant medications, stable doses of these medications were required for a minimum of 4 weeks before entering the study. In addition, no changes in dosing of concomitant therapies were allowed during the course of the study.
Interventions	1. Olanzapine (2.5 to 20 mg per day; mean dose 13.7 mg per day) (N = 16). ***Duration:*** **Intervention:** 8 weeks. **Follow-up:** 8 weeks.
Outcomes	Primary outcomes were challenging behaviour (as measured by the Aberrant Behaviour Checklist; Aman *et al.*, 1985) and symptom severity/improvement CGI-S.
Study design	Observational
Source of funding	Not reported
Limitations	1. No control group. 2. Data could not be extracted to calculate effect sizes. 3. Small sample size. 4. Data could not be extracted for measures of adverse effects, for example weight gain.
Notes	• An ITT approach was used, with the last observation carried forward with missing data. • An adjusted Bonferroni level of significance was used ($p = 0.0024$). • N = 4 subjects were terminated from the study prematurely because of significant side effects (N = 2), worsening behaviour (N = 2) or refusal to take medication (N = 1).

Study ID	HARDAN2004
Bibliographic reference	Hardan, A. Y., Jou, R. J. & Handen, B. L. (2004) A retrospective assessment of topiramate in children and adolescents with pervasive developmental disorders. *Journal of Child and Adolescent Psychopharmacology*, *14*, 426–432.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** open-label. **Setting:** outpatient. **Raters:** clinician-rated and parent report. **Country:** US.
Participants	**Diagnosis:** DSM-IV ASD (N = 11 autistic disorder; N = 2 Asperger's disorder; N = 2 PDD). **Coexisting conditions:** Not reported **Qualifying diagnostic assessment:** all diagnoses made by board-certified child and adolescent psychiatrists with autism experience **N =** 15. **Age:** 8 to 18 years (mean 14.7 years). **Sex:** male 12, female 3. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion criteria:** participants treated with topiramate after their behavioural symptoms failed to respond to psychosocial interventions and at least two psychoactive agents. The study subjects were consecutive patients treated with topiramate. Participants taking other psychotropic medications were included only if their medications were unchanged. **Exclusion criteria:** none of the participants had serious medical or neurological disorders, including seizure disorder.
Interventions	1. Topiramate (mean dose: 235 mg ± 88 mg per day) (N = 15). ***Duration:*** **Intervention:** 8 to 56 weeks (mean 25 weeks). **Follow-up:** 8 to 56 weeks (mean 25 weeks).
Outcomes	Primary outcome was challenging behaviour as measured by the CPS (Goyette *et al.*, 1978) and symptom severity/improvement as measured by the CGI-I (Guy, 1976a).
Study design	Observational (case series)
Source of funding	NIMH grant MH 64027
Limitations	No control group and it was open-label, so could not get a rigorous and unbiased test of treatment efficacy
Notes	• N = 3 discontinued topiramate because of side effects, N = 2 cognitive difficulties such as disorientation and speech problems and N = 1 skin rash. • 8/15 participants were rated as treatment responders (based on CGI-GI).

Study ID	HELLINGS2005
Bibliographic reference	Hellings, J. A., Weckbaugh, M., Nickel, E. J., *et al.* (2005) A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. *Journal of Child and Adolescent Psychopharmacology*, *15*, 682–692.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** outpatient. **Raters:** parent report and clinician-rated. **Country:** US.
Participants	**Diagnosis:** ADI and ADOS ASD (N = 27 autistic disorder; N = 1 PDD; N = 2 Asperger's disorder) and aggression. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** ADI and ADOS. **N =** 30. **Age:** 6 to 20 years (mean 11.2 years). **Sex:** male 20, female 10. **Ethnicity:** Caucasian N = 27; African-American N = 2; Hispanic N = 1. **IQ:** 20 to 137 (mean 54). **Inclusion criteria:** age 6 to 20 years, significant aggression to self, others, or property at least three times per week, and the presence of a PDD. All comorbid DSM-IV Axis I diagnoses, except Tourette's disorder, were allowed. **Exclusion criteria:** previous adequate valproate trial for any indication or clinical seizures within the past year. Other exclusion criteria were a history of degenerative neurological changes or metabolic disorders, Tourette's disorder, a history of thrombocytopenia, hepatitis, pancreatitis, pregnancy or polycystic ovarian syndrome. Concomitant psychotropic or anti-seizure medications were not allowed. Stimulant medications were required to be stopped the day before placebo run-in commenced.
Interventions	1. Valproate (20 mg per kg per day) (N = 16). 2. Placebo (N = 14). ***Duration:*** **Intervention:** 8 weeks. **Follow-up:** 8 weeks.
Outcomes	Primary outcome was challenging behaviour as measured by the parent-rated Aberrant Behaviour Checklist – Community scale (Aman *et al.*, 1995a) and the MOAS (Yudofsky *et al.*, 1986). In addition symptom severity/improvement was measured with the CGI-I as rated by the principal investigator.
Study design	RCT
Source of funding	Grant from the NIMH (1K08MH01561-01), the National Institute of Child Health and Human Development (HD26927, HD02528) and an unrestricted $5,000 grant from Abbott Pharmaceuticals
Limitations	1. Small sample size. 2. Heterogeneity of sample with large differences in aggression frequency and severity for different weeks during the 8-week period, and large standard deviations reported for each of the measures. 3. Placebo-response problems.

Notes	• N = 3 in the experimental group and N = 2 in the control group dropped out. N = 1 discontinued due to skin rash. • An intent-to-treat analysis was performed. • Teacher-ratings were also collected, but only parent-ratings were used in the data analysis and reported. • Dichotomous data extracted for side effects with 'any side effect present during the trial' rated as event. • Multiple outcome measures, so data extracted were consistent with the previous literature with CARS scores extracted as a measure of autistic behaviours and Aberrant Behaviour Checklist–Irritability as a measure of challenging behaviour.

Study ID	**HELLINGS2006**
Bibliographic reference	Hellings, J. A., Zarcone, J. R., Reese, R. M., *et al.* (2006) A crossover study of risperidone in children, adolescents and adults with mental retardation. *Journal of Autism and Developmental Disorders*, *36*, 401–411.
Methods	**Allocation:** randomised. **Matching:** N/A – crossover study. **Blindness:** double-blind. **Setting:** community. **Raters:** caregiver report. **Country:** US.
Participants	**Diagnosis:** ASD (90%): learning disability (N = 40), DSM-IV autism (N = 28), PDD (N = 8). **Coexisting conditions:** N = 9 with epilepsy in remission for at least 1 year where dosages of antiseizure medications remained constant during the study. **Qualifying diagnostic assessment:** WAIS-R, WISC-III or Leiter International Performance Scale. **N =** 40. **Age:** 8 to 56 years (mean 22 years). **Sex:** male 23, female 17. **Ethnicity:** white N = 34, African-American N = 3, Hispanic N = 1, other N = 2. **IQ:** not reported; N = 11 mild 'mental retardation', N = 9 moderate 'mental retardation', N = 11 severe 'mental retardation' and N = 9 profound 'mental retardation'. **Inclusion/exclusion criteria:** aged 6 to 65 years, with a learning disability (IQ <70) and at least 6 months' history of aggression, property destruction or self-injury by caregiver report. In addition, baseline Irritability subscale scores rated on the Aberrant Behavior Checklist – Community rating scale (Aman *et al.*, 1985) were required to be above given norms for age, gender and setting as rated by the primary caregiver. Exclusion criteria were previous risperidone hypersensitivity, history of neuroleptic malignant syndrome, seizures within the past year, degenerative brain disease as assessed by history and a problematic living situation such as lack of reliable caregiving. Prior treatment with risperidone was not an exclusion criterion.
Interventions	1. Low dose risperidone (liquid 1 mg per day for children and adolescents; 2 mg per day for adults) (N = 39, but crossover so N = 18

	for analysis). 2. Placebo II (liquid) (N = 33, but crossover so N = 17 for analysis). High dose and Placebo I interventions were also reported but not analysed here as the study found no difference between high and low doses of risperidone in behavioural outcomes, but significantly more adverse effects of the high-dose intervention and Placebo I was used in the paper as a co-variate for analysis. ***Duration:*** **Intervention:** 3 to 5 weeks per intervention. **Follow-up:** 22 weeks (open-label continuation).
Outcomes	The primary outcome of interest was the challenging behaviour 'irritability', as measured by the Aberrant Behaviour Checklist.
Study design	RCT (crossover)
Source of funding	National Institute of Child Health and Human Development
Limitations	1. Rater blinding may have been compromised because participants received drug at predictable stages due to study design. 2. Broad age range. 3. IQ test was only performed if one had not been completed by participant in the last 3 years. 4. No qualifying diagnostic assessment used. 5. Adverse events such as increased appetite and weight gain were narratively described but not statistically quantified.
Notes	N = 12 participants did not complete the trial (N = 6 due to side effects, N = 3 due to insufficient response, N = 1 due to development of seizure reoccurrence, N = 2 were lost to follow-up).

Study ID	**HOLLANDER2010**
Bibliographic reference	Hollander, E., Chaplin, W., Soorya, L., *et al.* (2010) Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology*, *35*, 990–998.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** outpatient. **Raters:** blinded clinical psychologist. **Country:** US.
Participants	**Diagnosis:** DSM-IV-TR ASD (N = 23 autistic disorder; N = 4 Asperger's syndrome). **Coexisting conditions**: not reported. **Qualifying diagnostic assessment:** ADI-R and ADOS-G **N =** 27. **Age:** 5 to 15 years (mean 9.5 years). **Sex:** male 23, female 4. **Ethnicity:** white N = 8; Hispanic N = 6; black N = 6; Asian N = 3; other N = 2; more than one race N = 2. **IQ:** 30 to 126 (mean 63.3). **Inclusion criteria:** participants were children 5 to 17 years, outpatients, who met DSM-IV-TR diagnostic criteria for autistic disorder, full diagnostic criteria on the ADI-R and autism spectrum criteria on the

	ADOS-G. Participants had to be at least moderately ill (CGI-Severity score of at least 4) to justify exposure to this medication. The population was also stratified for significant irritability/aggression difficulties at baseline, such that children had an MOAS score of at least 13 or an Aberrant Behaviour Checklist – Irritability score of at least 18 (raw scores) to qualify. **Exclusion criteria:** excluded sexually active and pregnant females, and nursing mothers; subjects with overall adaptive behaviour scores below the age of 2 years on the VABS; participants with active or unstable epilepsy, other Axis I disorders, unstable medical illness, genetic syndromes, or congenital infections associated with autism-like syndromes, prematurity; participants treated within the previous 30 days with any drug known to have a well-defined potential for toxicity or with any psychotropic drugs; participants with clinically significant abnormalities in laboratory tests or physical examination; subjects with a history of hypersensitivity or severe side effects associated with the use of divalproex sodium or other ineffective previous therapeutic trial of divalproex sodium (serum levels within the range of 50 to 100 µg per ml for 6 weeks); and participants who had started any new non-medication treatments, such as diet, vitamins or psychosocial therapy, within the previous 3 months.
Interventions	1. Divalproex sodium (valproate) (N = 16). 2. Placebo (N = 11). ***Duration:*** **Intervention:** 12 weeks. **Follow-up:** 12 weeks.
Outcomes	Primary outcome measures were challenging behaviour as measured by the CGI scale focusing on irritability (CGI-I) and the irritability subscale of the Aberrant Behaviour Checklist. Secondary outcome measures of challenging behaviour included the MOAS. The core autistic symptom of repetitive behaviour was also assessed using the Child Yale-Brown Obsessive-Compulsive Scale (CY-BOCS).
Study design	RCT
Source of funding	NINDS R21 NS4 3979-01, E. Hollander, PI. Active medication and placebo provided by Abbott Laboratories. Also, Grant Number MO1-RR00071 from the National Center for Research Resources, a component of the National Institute of Health
Limitations	1. The placebo group had a significantly higher mean full-scale IQ than the experimental group. IQ was used as a covariate and results were unchanged. However, this difference was not controlled for in the data extracted. 2. Small sample size.
Notes	• N = 3 withdrew before week 12 (N = 2 on divalproex sodium, N = 1 on placebo). Only one participant in experimental group discontinued because of side effects. • Intent-to-treat approach to analysis used. • Dichotomous data extracted for CGI-Irritability with data extracted as reported for responders and non-responders. • No significant differences in weight gain between groups: placebo weight gain 2.95 lb (SD 3.37), experimental weight gain 3.02 lb (SD 6.41).

Study ID	IZMETH1988
Bibliographic reference	Izmeth, M. G. A., Khan, S. Y., Kumarajeewa, D. I. S. C., *et al.* (1988) Zuclopenthixol decanoate in the management of behavioural disorders in mentally handicapped patients. *Pharmatherapeutica*, *5*, 217–227.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** inpatient. **Raters:** clinicians. **Country:** UK.
Participants	**Diagnosis:** learning disability. **Coexisting conditions:** most patients had concurrent illness. The principal disorders were psychiatric (N = 24) and epilepsy (N = 29). The behavioural disorders ranged from antisocial behaviour to physical aggression. **Qualifying diagnostic assessment:** not reported. **N =** 113. **Age:** 18 to 56 years (experimental group mean 30 years; control group mean 32 years). **Sex:** male 67, female 45; not recorded 1. **Ethnicity:** not reported. **IQ:** 20 to 80 (experimental group mean 51, control group mean 48). **Inclusion/exclusion criteria:** 'mentally handicapped patients' with associated behavioural and/or psychiatric disorders, aged 18 to 60 years, and who had been receiving treatment with zuclopenthixol for at least 12 weeks were eligible for inclusion. Pregnancy or serious physical illness were exclusion criteria.
Interventions	1. Zuclopenthixol decanoate (intramuscular injection, mean dose 119 mg per week) (N = 57). 2. Placebo (oily base only, mean dose 129 mg per week) (N = 56). ***Duration:*** **Intervention:** 12 weeks. **Follow-up:** 12 weeks.
Outcomes	Primary outcomes were symptoms severity/improvement (as measured by the CGI, Guy, 1976a) and challenging behaviour (as measured by the NOISE-30 and the Specific Behaviour Rating Scale, which was designed for this study).
Study design	RCT
Source of funding	Not reported
Limitations	1. No data could be extracted for CGI or Specific Behaviour Rating Scale outcome measures as all reporting was narrative. The only quantitative value of treatment effects on final scores reported was for the irritability subscale of the NOISE-30 and even here only a significance level and not an exact *p* value was reported ($p < 0.05$). 2. Higher attrition rate in the placebo group.
Notes	• Prior to the 12-week double-blind period when participants were randomly allocated to zuclopenthixol or placebo all participants

	had received zuclopenthixol in a 4-week open-label phase. • No significant differences in sex, age, IQ, severity of 'handicap' or accommodation between groups. • N = 20 in the zuclopenthixol group received anti-Parkinsonian drugs. • N = 29 participants with co-existent epilepsy were receiving anticonvulsant drug treatment (carbamazepine, sodium valproate, phenytoin, sulthiame or phenobarbitone); N = 16 in zuclopenthixol group and N = 13 in placebo. • N = 18 participants were withdrawn because of behavioural deterioration: N = 4 in zuclopenthixol; N = 14 in placebo.

Study ID	**JAHROMI2009**
Bibliographic reference	Jahromi, L. B., Kasari, C. L., McCracken, J. T., *et al.* (2009) Positive effects of methylphenidate on social communication and self-regulation in children with pervasive developmental disorders and hyperactivity. *Journal of Autism and Developmental Disorders*, *39*, 395–404.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** outpatient. **Raters:** blind raters for behavioural observation measures. **Country:** US.
Participants	**Diagnosis:** DSM-IV ASD. **Coexisting conditions:** moderate to severe hyperactivity (Swanson, Nolan and Pelham version IV Questionnaire and CGI-S ratings). **Qualifying diagnostic assessment:** ADI-R. **N =** 33. **Age:** 5 to 13 years (mean 6.9 years). **Sex:** male 29, female 4. **Ethnicity:** Caucasian N = 23; African-American N = 7; Asian N = 2; Hispanic N = 1. **IQ:** not reported. **Inclusion/exclusion criteria:** see RUPP2005. This study had an additional inclusion criterion of a mental age of <9 years because the social behavioural constructs and measures used would not be developmentally appropriate for older children.
Interventions	1. Methylphenidate (oral capsules three times a day; given in low, medium and high dosage levels of 0.125, 0.250, and 0.500 mg per kg per dose, respectively) (N = 33, but sample size was halved for analysis because it was a crossover study and only data for the best dose were extracted). 2. Placebo (N = 33, but sample size was halved for analysis because it was a crossover study). ***Duration:*** **Intervention:** 4 weeks. **Follow-up:** 5 weeks (includes a 1 week test-dose phase prior to 4 week crossover trial).
Outcomes	Primary outcome was the core autistic symptom of social communication, assessed through observational ratings using a brief

	social communication measure, the JAMES and caregiver–child interactions including a competing demands task and a clean-up task.
Study design	RCT (crossover)
Source of funding	See RUPP2005
Limitations	1. Reduced sample size relative to RUPP2005 study. 2. Duration of each intervention. 3. Methylphenidate may help some of the core social and communication problems; however, this is not the target outcome of the drug and further research is needed as to whether methylphenidate helps these core problems enough to justify targeting them for treatment.
Notes	• Secondary analysis of subset of data from RUPP2005. • Data extracted for joint attention initiations (measured with the JAMES) only.

Study ID	**KARSTEN1981**
Bibliographic reference	Karsten, D., Kivimäki, T., Linna, S.-L., *et al.* (1981) Neuroleptic treatment of oligophrenic patients. A double-blind clinical multicentre trial of cis(Z)-clopenthixol and haloperidol. *Acta Psychiatrica Scandinavica Supplement*, *294*, 39–45.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** inpatient. **Raters:** psychiatrists and nursing staff. **Country:** Finland.
Participants	**Diagnosis:** learning disability. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** not reported. **N =** 100. **Age:** range not reported (mean age for cis(z)-clopenthixol group 25 years, mean age for haloperidol group 27 years). **Sex:** male 56, female 44. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion/exclusion criteria:** the study included individuals with a learning disability, with symptoms such as psychomotor excitation, agitation and violence, and who might benefit from the treatment of either cis(z)-clopenthixol or haloperidol. Participants were excluded if they had concomitant serious somatic illness or pathological laboratory findings as well as pregnant or epileptic participants.
Interventions	1. Cis(z)-clopenthixol (available as 5 mg and 25 mg tablets) (N = 49). 2. Haloperidol (available as 1 mg and 4 mg tablets) (N = 49). ***Duration:*** **Intervention:** 12 weeks. **Follow-up:** 12 weeks.
Outcomes	Primary outcomes were symptom severity/improvement (as measured by the CGI, McGlasham, 1973, psychiatrists and nurses scale) and side effects (assessed with CGI).

Study design	RCT
Source of funding	Not reported
Limitations	Range and mean for daily or final dosage not reported
Notes	• Identical placebo tablets were available as well. All participants were treated during the 12 weeks with both sets of tablets, only one set, however, contained active drug while the other was placebo. • Two patients were withdrawn from the trial, one from each treatment group. Reasons for withdrawal not reported. • The most frequently encountered single side effects were extrapyramidal (especially parkinsonism) and anticholinergic. • This study compared two antipsychotic drugs. For the statistical analysis of dichotomous data, cis(z)-clopenthixol was treated as the experimental condition and haloperidol as the control condition. • For data analysis for the symptom severity/improvement outcome, the dichotomous data were entered as reported with improved as 'event' and unchanged or deteriorated as 'no event'. For the side effects analysis, the data were calculated to produce dichotomous outcomes with no side effect rated as 'event' and all side effect categories (side effects interfering slightly with functioning, side effects interfering moderately with functioning and side effects interfering markedly with functioning) summed to produce 'no event' total score.

Study ID	**KING2001**
Bibliographic reference	King, B. H., Wright, D. M., Handen, B. L., *et al.* (2001) 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*, *40*, 658–665.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** not reported. **Raters:** parent-rated and clinician-rated scales. **Country:** not reported.
Participants	**Diagnosis:** DSM-IV and ICD-10 ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** ADI-R and ADOS-G. **N =** 39 (ITT sample). **Age:** 5 to 15 years (mean 7 years). **Sex:** male 34, female 5. **Ethnicity:** white: 75% in placebo and 79% in amantadine group. **IQ:** not reported. **Inclusion criteria:** diagnosis of autistic disorder according to DSM-IV and ICD-10 and the ADI-R and ADOS-G; composite age equivalent of >18 months on VABS; and Aberrant Behaviour Checklist – Community Version subscale scores for irritability and hyperactivity equal to or greater than age-adjusted 75th percentile. **Exclusion criteria:** IQ <35 as measured on the Mullen Scales of Early Learning or the Differential Ability Scale.

Interventions	1. Amantadine hydrochloride (Symmetrel syrup; 5 mg per kg per day) (N = 19). 2. Placebo (N = 20). ***Duration:*** **Intervention:** 4 weeks. **Follow-up:** 5 weeks (including 1 week placebo run-in).
Outcomes	Primary outcomes were challenging behaviour as measured by the parent-completed Aberrant Behaviour Checklist – Community Version (Aman *et al*., 1985 and 1995a) and symptom severity/improvement as measured by the CGI scale. Dichotomous outcome measures extracted for the Aberrant Behaviour Checklist – Community Version. Responders categorised on the basis of a reduction of at least 25% in subscale scores for the Aberrant Behaviour Checklist – Community Version for irritability and/or hyperactivity at the end of treatment.
Study design	RCT
Source of funding	Cerebrus Plc, Winnersh, UK
Limitations	Small sample size
Notes	• Some participants received psychopharmacological agents during the course of the study, or which SSRIs (for example, fluoxetine and fluvoxamine) were the largest category with N = 4 in experimental and N = 6 in control group. • Data could not be extracted for the CGI. • Similar numbers of patients in both active (N = 14) and placebo (N = 14) groups reported at least one side effect. The side effect reported most often was insomnia (N = 4 active and N = 2 placebo). N = 2 in amantadine group reported to have somnolence. N = 4 in placebo and N = 2 in amantadine group reported difficult or antisocial behaviours.

Study ID	KNIVSBERG2003
Bibliographic reference	Knivsberg, A-M., Reichelt, K-L., Høien, T., *et al.* (2003) Effect of dietary intervention on autistic behavior. *Focus on Autism and Other Developmental Disabilities*, *18*, 247–256.
Methods	**Allocation:** randomised. **Matching:** matched on age, cognitive level, and severity of autistic traits. **Blindness:** single-blind. **Setting:** not reported. **Raters:** parent-report and clinician-rated behavioural observation. **Country:** Norway.
Participants	**Diagnosis:** ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** not reported. **N =** 20. **Age:** range not reported (experimental group mean 7.5 years; control group mean 7.2 years). **Sex:** not reported. **Ethnicity:** not reported. **IQ:** range not reported (experimental group mean 81, control group mean 84.6, as measured by the Leiter International Performance Scale). **Inclusion criteria:** not reported.
Interventions	1. Gluten-free and casein-free diet group (a dietician visited the parents of the children in the diet group and gave the parents oral and written information about gluten-free and casein-free diets) (N = 10). 2. Control group (N = 10). ***Duration:*** **Intervention:** 1 year. **Follow-up:** 1 year.
Outcomes	Primary outcome was autistic behaviour as assessed by an observation scheme, the Diagnose of Psykotisk Adferd hos Børn (Diagnosis of Psychotic Behaviour in Children, Haracopos & Kelstrup, 1975) which included items evaluating social isolation and bizarre behaviour.
Study design	RCT
Source of funding	County Council of Rogaland, Sigval and Nanki Bergesen's public trust, and the Sein Family Foundation
Limitations	1. Small sample size. 2. No formal monitoring of dietary compliance.
Notes	–

Study ID	LEVY2003
Bibliographic reference	Levy, S. E., Souders, M. C., Wray, J., *et al.* (2003) Children with autistic spectrum disorders. I: comparison of placebo and single dose of human synthetic secretin. *Archives of Disease in Childhood*, *88*, 731–736.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** not reported. **Raters:** parent- or clinician-rated scales. **Country:** US.
Participants	**Diagnosis:** ASD. **Coexisting conditions:** >50% gastrointestinal symptoms. **Qualifying diagnostic assessment:** ADI-R. **N =** 62. **Age:** 3 to 8 years (mean 6 years). **Sex:** male 50, female 12. **Ethnicity:** Caucasian: 90.3%. **IQ:** not reported. **Inclusion criteria:** diagnosis of ASD. **Exclusion criteria:** significant hearing or vision loss; other neurological disorders, for example cerebral palsy, phenylketonuria, tuberous sclerosis, neurofibromatosis, seizure disorder; genetic disorder; prematurity (<32 weeks' gestation); diagnosis of coeliac disease or other gastrointestinal disease associated with malabsorption; previous treatment with secretin; anaemia and plumbism (lead poisoning).
Interventions	1. Secretin (human synthetic secretin, single intravenous dose; 2 CU per kg to a maximum dose of 75 CU) (N = 62, but N = 31 for analysis because it was a crossover study). 2. Placebo (N = 62, but N = 31 for analysis because it was a crossover study). ***Duration:*** **Intervention:** single dose. **Follow-up:** 8 weeks.
Outcomes	Primary outcome was autistic behaviours as measured by the Real Life Rating Scale (Freeman *et al.*, 1986). Other outcomes included the core autistic symptom of communication (as measured by the Communication and Symbolic Behaviour Scale and challenging behaviour (as measured by the GBRS developed for this study).
Study design	RCT (crossover)
Source of funding	Maternal and Child Health Bureau, Grant No. 2T73 MC 00035 09, the General Clinical Research Center of The Children's Hospital of Philadelphia, National Institute of Health Grant No. RR00240, and Mental Retardation and Development Disabilities Research Center National Institute of Health Grant No. 3P30 HD26979-04S2. ChiRhoClin Corporation donated the secretin
Limitations	There was a significant difference between the groups in the baseline CARS total score
Notes	Data not extracted for Teacher GBRS because Parent GBRS was selected as the measure for challenging behaviour.

Study ID	MARTINEAU1988
Bibliographic reference	Martineau, J., Barthelemy, C., Cheliakine, C., *et al.* (1988) Brief report: an open middle-term study of combined vitamin B6-magnesium in a subgroup of autistic children selected on their sensitivity to this treatment. *Journal of Autism and Developmental Disorders*, *18*, 435–447.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** N/A – no control group. **Setting:** not reported. **Raters:** nurse-rated scale. **Country:** France.
Participants	**Diagnosis:** DSM-III ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** not reported. **N =** 11. **Age:** 4 to 8 years (mean 5.8 years). **Sex:** male 5, female 6. **Ethnicity:** not reported. **IQ:** 30 to 80 (mean 50). **Inclusion/exclusion criteria:** all participants were in excellent physical health, audiologically intact, none had a history of gross neurological deficit, severe seizure disorder, endocrine or systematic disease.
Interventions	1. Vitamin B6-magnesium (oral medication twice daily; 30 mg per kg per day pyridoxine hydrochloride and 10 mg per kg per day magnesium lactate) (N = 11). ***Duration:*** **Intervention:** 8 weeks. **Follow-up:** 14 weeks.
Outcomes	Primary outcome was symptom severity/improvement as assessed by the BSE.
Study design	Observational (before-and-after)
Source of funding	Not reported
Limitations	1. Sample selected on basis of previous sensitivity to this treatment. 2. Small sample size.
Notes	No adverse reactions or side effects noted in any of the 11 participants during the study period.

Study ID	MCDOUGLE1996
Bibliographic reference	McDougle, C. J., Naylor, S. T., Cohen, D. J., *et al.* (1996) A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Archives of General Psychiatry*, *53*, 1001–1008.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** inpatient (N = 9) and outpatient (N = 21). **Raters:** clinician-rated scales. **Country:** US.
Participants	**Diagnosis:** DSM-III-R and ICD-10 ASD (autistic disorder). **Coexisting conditions:** N = 1 Fragile X syndrome, none of the other participants had a diagnosed genetic, metabolic or neurological cause for their syndrome. **Qualifying diagnostic assessment:** ADI and ADOS. **N =** 30. **Age:** 18 to 53 years (mean 30.1 years). **Sex:** male 27, female 3. **Ethnicity:** not reported. **IQ:** 25 to 115 (mean 79.9; as measured by WAIS-R for verbal and Leiter International Performance Scale for non-verbal participants). **Exclusion criteria:** participants were excluded if they met DSM-III-R criteria for schizophrenia or had psychotic symptoms, if they had abused illicit substances within the previous 6 months, or if a notable medical condition, including seizure disorder, was identified. Women with positive serum pregnancy test results were excluded.
Interventions	1. Fluvoxamine maleate (200 to 300 mg per day; mean dose 276.7 mg per day) (N = 15). 2. Placebo (200 to 300 mg per day; mean dose 283.3 mg per day) (N = 15). ***Duration:*** **Intervention:** 12 weeks. **Follow-up:** 12 weeks.
Outcomes	Primary outcomes included the core autistic symptom of repetitive behaviour as measured by the Y-BOCS; autistic behaviours as measured by the Real Life Rating Scale (Freeman *et al.*, 1986); challenging behaviour (aggression) as measured by the Brown Aggression Scale (Brown *et al.*, 1979); maladaptive behaviour as measured by the VABS; and symptom severity/improvement as measured by the CGI scale.
Study design	RCT
Source of funding	National Alliance for Research on Schizophrenia and Depression Young Investigator Award; the State of Connecticut Department of Mental Health and Addiction Services; The Korczak Foundation for Autism and Related Disorders; and grants M01 RR06022-33, P50 MH30929-18, HD 03008-27, and P01 MH25642 from the National Institutes of Health, Bethesda, MD. Fluvoxamine and financial support were provided by Solvay Pharmaceuticals, Marietta, GA
Limitations	1. Small sample size. 2. Y-BOCS scale was valid and reliable for assessing the severity of obsessive–compulsive symptoms in individuals with OCD, but its reliability and validity for assessing repetitive thoughts in autism is unknown.

Notes	All participants completed the trial. Fluvoxamine was well tolerated with no medically significant adverse events. N = 4 reported nausea (N = 3 in experimental and N = 1 in control group) during the first 2 weeks but they experienced tolerance and were able to continue. N = 3 experienced moderate sedation (N = 2 in experimental; N = 1 in control group), which also resolved.

Study ID	**MCDOUGLE1998A**
Bibliographic reference	McDougle, C. J., Holmes, J. P., Carlson, D. C., *et al.* (1998) A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Archives of General Psychiatry*, *55*, 633–641.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** Outpatient (N = 24), inpatient (N = 7). **Raters:** board-certified psychiatrists. **Country:** US.
Participants	**Diagnosis:** DSM-IV ASD: autism (N = 17), PDD (N = 14). **Coexisting conditions:** none reported. **Qualifying diagnostic assessment:** ADI and the ADOS. **N =** 31. **Age:** 18 to 43 years (mean 28.1 years). **Sex:** male 22, female 9. **Ethnicity:** white N = 24, African-American N = 6, Hispanic N = 1 **IQ:** Range not reported (mean 54.6 on WAIS-R or Leiter International Performance Scale). **Inclusion/exclusion criteria:** Y-BOCS compulsion subscale score of greater than 10, an SIB-Q score of 25 or greater or a Real Life Rating Scale (Freeman *et al.*, 1986) overall score of 0.20 or greater, no diagnosis of schizophrenia, psychotic symptoms or identified significant acute medical condition.
Interventions	1. Risperidone (oral capsules, mean dose 2.9 mg per day) (N = 15). 2. Placebo (oral capsules, mean dose 3.9 mg per day) (N = 16). ***Duration:*** **Intervention:** 12 weeks. **Follow-up:** 24 weeks (open-label continuation).
Outcomes	Primary outcomes were: autistic behaviours (as measured by Real Life Rating Scale, Freeman *et al.*, 1986); the core autistic symptom of repetitive behaviour (as measured by the Y-BOCS, Goodman *et al.*, 1989a); symptom severity/improvement (as measured by the CGI scale, Guy, 1976a); and the challenging behaviour, aggression (as measured by the SIB-Q).
Study design	RCT
Source of funding	Supported in part by grants from the Public Health Service, Young Investigator Award, Independent Investigator Award from the National Alliance for Research in Schizophrenia and Depression, Theodore and Vada Stanley Foundation Research Awards Program, State of Connecticut, Department of Mental Health and Addiction

	Services, NIMH, Rockville, MD
Limitations	Relatively short duration of intervention and no longer-term post-intervention follow-up
Notes	Subjects had not taken any psychotropic drugs for at least 4 weeks before the trial.

Study ID	**MCDOUGLE1998B**
Bibliographic reference	McDougle, C. J., Brodkin, E. S., Naylor, S. T., *et al.* (1998) Sertraline in adults with pervasive developmental disorders: a prospective open-label investigation. *Journal of Clinical Psychopharmacology*, *18*, 62–66.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** open-label. **Setting:** outpatient (N = 40) and inpatient (N = 2). **Raters:** clinician-rated scales. **Country:** US.
Participants	**Diagnosis:** DSM-IV ASD (N = 22 autistic disorder; N = 6 Asperger's disorder; N = 14 PDD). **Coexisting conditions:** participants did not meet criteria for any other DSM-IV Axis I or Axis II disorder other than 'mental retardation' (N = 28). **Qualifying diagnostic assessment:** ADI and ADOS used to aid diagnosis. **N =** 42. **Age:** 18 to 39 years (mean 26.1 years). **Sex:** male 27, female 15. **Ethnicity:** white N = 36; black N = 5; Hispanic N = 1. **IQ:** 25 to 114 (mean 60.5; as measured by the WAIS-R for verbal and the Leiter International Performance Scale for non-verbal participants). **Inclusion criteria:** symptom severity entry screening criteria: a Y-BOCS score of >15 (verbal patients) or >7 (non-verbal patients); an SIB-Q score of 25 or greater; a Real Life Rating Scale (Freeman *et al.*, 1986) overall score of 0.20 or greater; or a VABS Maladaptive part 1 score of 14 or greater; or a VABS Maladaptive part 2 score of 5 or greater. **Exclusion criteria:** participants were excluded if they met DSM-IV criteria for a psychotic disorder or bipolar disorder, or if a significant medical condition including seizure disorder was identified.
Interventions	1. Sertraline (50 to 200 mg per day) (N = 42). ***Duration:*** **Intervention:** 12 weeks. **Follow-up:** 12 weeks.
Outcomes	Primary outcomes included the core autistic symptom of repetitive behaviour as measured by the Y-BOCS; autistic behaviours as measured by the Real Life Rating Scale (Freeman *et al.*, 1986); maladaptive behaviour as measured by the VABS; and symptom severity/improvement as measured by the CGI-I score.
Study design	Observational (before-and-after study)
Source of funding	Educational grant from Pfizer Pharmaceuticals; MH-30929 from the NIMH; HD-03008 from the National Institute of Child Health and

	Human Development; an Independent Investigator Award from the National Alliance for Research on Schizophrenia and Depression; the Theodore and Vada Stanley Research Foundation; the State of Connecticut Department of Mental Health and Addiction Services; and a NIMH Research Unit on Pediatric Psychopharmacology grant to Indiana University.
Limitations	1. No control group and efficacy data could not be extracted. 2. Small sample size. 3. Y-BOCS scale valid and reliable for assessing severity of obsessive–compulsive symptoms in individuals with OCD but reliability and validity for assessing repetitive thoughts in autism is unknown.
Notes	• Participants were psychotropic drug-free for at least 4 weeks before the start of the trial. • Out of N = 42, N = 37 completed the trial and were included in the efficacy analysis. N = 3 dropped out because of increased anxiety/agitation; N = 1 because of a syncopal episode of undetermined cause; N = 1 because of noncompliance. • Side effects in the 37 completers included anorexia (N = 1); headache (N = 1); tinnitus (N = 1); alopecia (N = 1); weight gain (N = 3); sedation (N = 1); anxiety/agitation (N = 2). No adverse cardiovascular, extrapyramidal or proconvulsant effects were identified.

Study ID	MCKENZIE1966
Bibliographic reference	McKenzie, M. E. & Roswell-Harris, D. (1966) A controlled trial of prothipendyl (Tolnate) in mentally subnormal patients. *British Journal of Psychiatry*, *112*, 95–100.
Methods	**Allocation:** randomised. **Matching:** no matching and an IQ difference between groups.(experimental mean 34.4 and control mean 25.4). **Blindness:** blinding of investigators and outcome assessor. **Setting:** inpatient. **Raters:** medical officer. **Country:** UK.
Participants	**Diagnosis:** learning disability. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** not reported. **N =** 40. **Age:** 14 to 42 years (mean age for males: 20.5 years; mean age for females: 26.2 years). **Sex:** male 20, female 20. **Ethnicity:** not reported. **IQ:** 19 to 58 as measured by Goodenough Draw-a-Man test (experimental group mean 34.4; control group mean 25.4). **Inclusion/exclusion criteria:** each participant was given a complete physical examination to exclude intercurrent disease. All drugs except anticonvulsants were stopped for a month before commencement of the trial.
Interventions	1. Prothipendyl (oral tablets, 80 mg [one tablet] to 320 mg [four tablets] 6-hourly) (N = 20). 2. Placebo (oral tablets) (N = 19). ***Duration:*** **Intervention:** 16 weeks. **Follow-up:** 16 weeks.
Outcomes	Primary outcome was symptom severity/improvement as measured by clinical observation rating scale.
Study design	RCT
Source of funding	Smith Kline and French Laboratories Ltd supplied the drug and placebo
Limitations	Pre-trial differences between experimental and control groups in IQ
Notes	• In the first week of the trial, one participant was withdrawn at the request of her parents; the group to which she had been allocated was not explicitly reported. However, due to number discrepancies between groups the assumption was made that she had been allocated to the placebo group. • IQ scores based on the N = 29 who were testable. • Liver function was estimated in a random sample of N = 10; a raised serum alkaline phosphatase level was found in several participants and the start of the trial was postponed until the levels were within the normal range. • Calculated dichotomous outcome for the clinical assessment with participants showing slight improvement, good improvement, very good improvement or excellent improvement summed to

	provide 'event' score and participants showing no change or deterioration summed to provide 'no event' total score.

Study ID	**MEHLMADRONA2010**
Bibliographic reference	Mehl-Madrona, L., Leung, B., Kennedy, C., *et al.* (2010) Micronutrients versus standard medication management in autism: a naturalistic case-control study. *Journal of Child and Adolescent Psychopharmacology*, *20*, 95–103.
Methods	**Allocation:** non-randomised. **Matching:** matched on age (within a year), sex, parental education and income, IQ (by category), and symptom severity as measured on the CGI scale. **Blindness:** non-blind. **Setting:** not reported. **Raters:** parent-, teacher- and clinician-rated scales. **Country:** Hawaii.
Participants	**Diagnosis:** DSM-IV ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** clinical assessment based on interview, history and questionnaires. **N =** 88. **Age:** 2 to 28 years (experimental group mean 8.4 years; control group mean 9.4 years). **Sex:** male 68, female 20. **Ethnicity:** Caucasian >80%. **IQ:** range not reported (experimental group mean 88.8; control group mean 91.3). **Inclusion criteria:** presence of a complete set of outcome data for at least 3 months.
Interventions	1. Micronutrient management (EMPowerplus formula consists of all 14 of the known vitamins, 16 dietary minerals, three amino acids and three antioxidants) (N = 44). 2. Medication management (N = 44). ***Duration:*** **Intervention:** 3 to 98 months (experimental group mean 24 months; control group mean 18 months). **Follow-up:** 3 to 98 months (experimental group mean 24 months; control group mean 18 months).
Outcomes	Outcomes included autistic behaviours as measured by the CARS and the CPRS (Fish, 1985); challenging behaviour as measured by the Aberrant Behaviour Checklist and the Yale-Paris Self Injurious Behaviour Scale; and symptom severity/improvement as measured by CGI-S scale.
Study design	Observational (case-control)
Source of funding	Richmond Foundation of Santa Barbara, CA; Health Canada; Alberta Children's Hospital Foundation; and Janzen
Limitations	Not randomised
Notes	• Parents of N = 5 could not afford to purchase any supplements, so they were prescribed prenatal formulas (covered by their health

	insurance plan) in doses that approximated the micronutrient formula. • Data were extracted for the CARS rather than the CPRS as a measure of autistic behaviours because it is a more widely used measure. • Data were extracted for the irritability subscale of the Aberrant Behaviour Checklist because this is widely used as a measure of challenging behaviour. • Data could not be extracted for Yale-Paris SIB Scale. • The micronutrient group had 33 adverse events compared with 214 in the medication group. In no case was an adverse event reported more often in the micronutrient group. Furthermore, the average weight gain was significantly less in the micronutrient group compared to the medication group ($p < 0.0001$).

Study ID	**MOUSAINBOSC2006**
Bibliographic reference	Mousain-Bosc, M., Roche, M., Polge, A., *et al.* (2006) Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. II. Pervasive developmental disorder-autism. *Magnesium Research*, *19*, 53–62.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** N/A – no control group. **Setting:** not reported. **Raters:** physician rated. **Country:** France.
Participants	**Diagnosis:** DSM-IV ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** DSM-IV assessment. **N =** 33. **Age:** 1 to 10 years (mean 4 years). **Sex:** male 21, female 12. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion criteria:** not reported.
Interventions	1. Magnesium-vitamin B6 (6 mg per kg per day magnesium; 0.6 mg per kg per day vitamin B6). ***Duration:*** **Intervention:** mean 8 months. **Follow-up:** 24 months.
Outcomes	Primary outcomes were core autistic symptoms (social interactions, communication, and stereotyped restricted behaviour) as assessed by DSM-IV evaluation.
Study design	Observational (before-and-after)
Source of funding	Sanofi-Aventis
Limitations	1. No control group. 2. Exact *p* values not reported.
Notes	No other medical treatment was given before and during the magnesium-B6 treatment period.

Study ID	MUNASINGHE2010
Bibliographic reference	Munasinghe, S. A., Oliff, C., Finn, J., *et al.* (2010) Digestive enzyme supplementation for autism spectrum disorders: a double-blind randomized controlled trial. *Journal of Autism and Developmental Disorders*, *40*, 1131–1138.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** not reported. **Raters:** parent-report scales. **Country:** Australia.
Participants	**Diagnosis:** DSM-IV ASD (N = 38 autistic disorder; N = 5 PDD). **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** not reported. **N =** 43. **Age:** 2 to 8 years (mean 5.8 years). **Sex:** male 36, female 7. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion criteria:** children aged 3 to 8 years; resident of the Perth metropolitan area; have autistic disorder or PDD as established along the criteria of the American Psychological Association and outlined in the DSM-IV. **Exclusion criteria:** children should not have commenced on any new alternative therapy during the study period. Also excluded were: children with significant hearing or vision loss; comorbid neurological disorders including phenylketonuria, tuberous sclerosis, neurofibromatosis; other identifiable metabolic disorders, genetic abnormalities and intractable seizure disorders; coeliac disease; children who were to have any new medical/surgical intervention carried out in the next 6 months; children with a history of allergy to aspergillus enzyme proteins, papaya or any known allergy to fungal proteins (from which the enzymes in Peptizyde™ are derived); children with active stomach or duodenal ulcers, severe bowel inflammation (characterised by blood in stools; a history of haemophilia or other bleeding disorders; or within a week of scheduled surgery (contraindications as per manufacturer's guidelines).
Interventions	1. Proteolytic enzyme supplement (Peptizyde™; one half to nine capsules per day according to manufacturer's recommended dose) (N = 43, but it was a crossover study so the sample size was halved for analysis) 2. Placebo (N = 43, but it was a crossover study so the sample size was halved for analysis). ***Duration:*** **Intervention:** 3 months for each phase. **Follow-up:** 6 months.
Outcomes	Primary outcomes were the core autistic symptom of communication, as measured by the vocabulary subscale of the Language Development Survey (Rescorla, 1989); challenging behaviour as measured by the

	parent-rated GBRS; and the coexisting gastrointestinal symptoms as measured by the Additional Rating Scale, which required parents to rate gastrointestinal symptoms.
Study design	RCT (crossover)
Source of funding	Supplement and placebo supplied by Houston Nutraceuticals
Limitations	Small sample size
Notes	• Behavioural intervention and other ongoing medical therapy which a child had been engaged in for the previous 3 months or more was continued without interruption during the study period. • No serious adverse effects were noted by the investigating team during the 6 month study period. There was some suggestion of increased irritability and difficulties with engagement observed by parents and noted as reasons for discontinuation (N = 3 in experimental group; N = 1 in placebo group). However, the attrition rate was not high and for some of these participants problems continued post-cessation of the treatment.

Study ID	**NICOLSON2006**
Bibliographic reference	Nicolson, R., Craven-Thuss, B. & Smith, J. (2006) A prospective, open-label trial of galantamine in autistic disorder. *Journal of Child and Adolescent Psychopharmacology*, *16*, 621–629.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** N/A – no control group. **Setting:** not reported. **Raters:** parent-rated and clinician-rated scales. **Country:** Canada.
Participants	**Diagnosis:** DSM-IV ASD. **Coexisting conditions:** N = 7 coexisting mild or moderate learning disability. **Qualifying diagnostic assessment:** ADI-R and clinical observation. **N =** 13. **Age:** 4 to 17 years (mean 8.8 years). **Sex:** male 10, female 3. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion criteria:** participants were required to be off of all psychotropic medications for at least 4 weeks prior to the start of treatment with galantamine. **Exclusion criteria:** Individuals with a seizure disorder, a significant cardiac condition, or previous exposure to an acetylcholinesterase inhibitor were excluded from participating in this study.
Interventions	1. Galantamine (2 to 24 mg per day; mean final dose 18.4 mg per day) (N = 13). ***Duration:*** **Intervention:** 12 weeks. **Follow-up:** 12 weeks.
Outcomes	Primary outcomes were challenging behaviour as assessed by the

	Parent-completed Aberrant Behaviour Checklist – Irritability subscale and the long form of the CPS – Revised (Conners *et al.*, 1998). Other outcomes were autistic behaviours as measured by the CPRS (Fish, 1985) Autism factor, and symptom severity/improvement was assessed with the CGI – Severity scale (CGI-S).
Study design	Observational (before-and-after)
Source of funding	London Health Sciences Research, Inc.
Limitations	1. Efficacy data could not be extracted. 2. Small sample size.
Notes	• Data extracted for the Aberrant Behaviour Checklist rather than the Conners' Parent Rating Scale as a measure of challenging behaviour as this is the more widely used scale. • N = 3 participants dropped out of study: N = 2 after 8 weeks due to worsening of target symptoms, N = 1 withdrew 1 week before the end of the trial due to headaches.

Study ID	**OWLEY2006**
Bibliographic reference	Owley, T., Salt, J., Guter, S., *et al.* (2006) A prospective, open-label trial of memantine in the treatment of cognitive, behavioral, and memory dysfunction in pervasive developmental disorders. *Journal of Child and Adolescent Psychopharmacology*, *16*, 517–524.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** N/A – no control group. **Setting:** not reported. **Raters:** parent- and clinician-rated scales. **Country:** US.
Participants	**Diagnosis:** DSM-IV ASD (N = 10 autistic disorder; N = 2 Asperger's disorder; N = 2 PDD). **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** ADI-R and ADOS. **N =** 14. **Age:** 3 to 12 years (mean 7.8 years). **Sex:** male 14, female 0. **Ethnicity:** white N = 7; African-American N = 4; Hispanic N = 3. **IQ:** non-verbal IQ mean 96.8. **Exclusion criteria:** individuals were excluded if they had previously received memantine.
Interventions	1. Memantine (5 to 20 mg per day) (N = 14). ***Duration:*** **Intervention:** 8 weeks. **Follow-up:** 8 weeks.
Outcomes	Primary outcomes were challenging behaviour as assessed by the parent-completed Aberrant Behaviour Checklist – Community Version Irritability subscale, and symptom severity/improvement as measured by the CGI-S.
Study design	Observational (before-and-after)
Source of funding	The Autism Project of Illinois; National Institute of Health grant K01

	MH64539; NIMH grant U19 HD35482
Limitations	1. Efficacy data could not be extracted. 2. Small sample size.
Notes	• Participants could continue to take other medications, including psychotropic agents, but the doses of all medication were held stable throughout the study. N = 4 on additional psychotropic medications (risperidone, aripiprazole, guanfacine and melatonin). • N = 2 did not complete the study.

Study ID	**PAAVONEN2003**
Bibliographic reference	Paavonen, E. J., Nieminen-von Wendt, T., Vanhala, R., *et al.* (2003) Effectiveness of melatonin in the treatment of sleep disturbances in children with Asperger disorder. *Journal of Child and Adolescent Psychopharmacology*, *13*, 83–95.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** N/A – no control group. **Setting:** not reported. **Raters:** parent- and self-report. **Country:** Finland.
Participants	**Diagnosis:** DSM-IV ASD (Asperger's disorder). **Coexisting conditions:** N = 1 ADHD, N = 4 asthma, N = 3 overweight. **Qualifying diagnostic assessment:** not reported. **N =** 15. **Age:** 6 to 17 years (mean 10.3 years). **Sex:** male 13, female 2. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion criteria:** diagnosis of Asperger's disorder and all children had severe sleep problems during the previous 3 months. Severe insomnia was defined as continuous problems with sleep initiation or maintenance, disturbing either the child or the family, so that the child was constantly tired or had other symptoms that could be attributed to sleep deprivation. **Exclusion criteria:** children with ongoing psychotropic medication or major psychiatric comorbidity were excluded.
Interventions	1. Melatonin (3 mg per day, 30 minutes prior to bedtime) (N = 15). ***Duration:*** **Intervention:** 2 weeks. **Follow-up:** 5 weeks.
Outcomes	The primary outcome was sleep patterns as measured by an actigraph, which is a small piece of wrist-worn equipment used for collecting data relating to motor activity, a self-report sleep questionnaire (Children's Self Report Form for sleep problems; Owens *et al.*, 2000) and a parent-report questionnaire (Sleep Disturbance Scale for Children; Bruni *et al.*, 1996).
Study design	Observational (before-and-after)
Source of funding	Academy of Finland, The Finnish Medical Foundation, Research Funds of Helsinki University Central Hospital, the Foundation for Pediatric

	Research, the Foundation of Children's Castle Hospital and the Finnish Sleep Research Society
Limitations	Data could not be extracted for self-report and parent-report questionnaires.
Notes	Although no explicit criteria were used, all participants had sleep problems 'every night' or 'almost every night'.

Study ID	**POSEY2007**
Bibliographic reference	Posey, D. J., Aman, M. G., McCracken, J. T., *et al.* (2007) Positive effects of methylphenidate on inattention and hyperactivity in pervasive developmental disorders: an analysis of secondary measures. *Biological Psychiatry*, *61*, 538–544.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** outpatient. **Raters:** clinician-rated scale. **Country:** US.
Participants	**Diagnosis:** DSM-IV ASD (N = 47 autistic disorder; N = 5 Asperger's disorder; N = 14 PDD). **Coexisting conditions:** hyperactivity (CGI scale and Swanson, Nolan, and Pelham Questionnaire revised for DSM-IV ADHD scale, published online). **Qualifying diagnostic assessment:** ADI-R. **N =** 66. **Age:** 5 to 13 years (mean 7.5 years). **Sex:** male 59, female 7. **Ethnicity:** white N = 48; black or African-American N = 9; Asian N = 6; Hispanic or Latino N = 3. **IQ:** 16 to 135 (mean 62.6) as assessed with the Slosson Intelligence Test **Inclusion/exclusion criteria:** See RUPP2005.
Interventions	1. Methylphenidate (oral capsules three times a day; given in low, medium and high dosage levels of 0.125, 0.25 and 0.5 mg per kg per dose, respectively) (N = 66 but sample sizes differed by measure due to data availability; sample size was halved for analysis because it was a crossover study and only data for the best dose were extracted). 2. Placebo (N = 66 but sample sizes differed by measure due to data availability; sample size was halved for analysis because it was a crossover study). ***Duration:*** **Intervention:** 4 weeks. **Follow-up:** 5 weeks (includes a 1-week test-dose phase prior to 4-week crossover trial).
Outcomes	The main outcome of interest for this secondary analysis of the RUPP2005 data was the core autistic symptom of repetitive behaviour as assessed by the Children's Yale-Brown Obsessive Compulsive Scales-PDD (CY-BOCS-PDD).
Study design	RCT (crossover).
Source of funding	See RUPP2005.

Limitations	See RUPP2005.
Notes	Secondary analysis of the data from RUPP2005.

Study ID	**READ2007**
Bibliographic reference	Read, S. G. & Rendall, M. (2007) An open-label study of risperidone in the improvement of quality of life and treatment of symptoms of violent and self-injurious behaviour in adults with intellectual disability. *Journal of Applied Research in Intellectual Disabilities*, *20*, 256–264.
Methods	**Allocation:** N/A – no control group. **Matching:** N/A – no control group. **Blindness:** open-label. **Setting:** outpatient. **Raters:** research nurse independent of investigator with caregiver-report. **Country:** UK.
Participants	**Diagnosis:** learning disability. **Coexisting conditions:** N = 8 with ASD (33.3%); N = 13 with epilepsy (54.2%); and N = 11 with organic behaviour disorder (45.8%). **Qualifying diagnostic assessment:** not reported. **N =** 24. **Age:** 16 to 65 years (mean 27.4 years). **Sex:** male 19, female 5. **Ethnicity:** white N = 19; black N = 2; Asian N = 3. **IQ:** not reported; N = 18 (75%) with a severe or profound learning disability. **Inclusion/exclusion criteria:** not reported.
Interventions	1. Risperidone (oral tablet of 1 mg, 3 mg or 4 mg, or oral suspension of 1 mg per mL; final dose 0.5 to 6 mg per day, mean final dose 2.92 mg per day) (N = 24). ***Duration:*** **Intervention:** 4 to 103 days (mean duration of treatment 76.4 days). **Follow-up:** 76.4 days.
Outcomes	Primary outcome was challenging behaviour (as measured by the Aberrant Behaviour Checklist (Aman *et al.*, 1985). Secondary outcomes included symptom severity/improvement (as measured by the CGI-S) and quality of life (as measured by a modified version of the Composite Autonomic Symptom Scale).
Study design	Observational
Source of funding	Not reported
Limitations	1. No control group. 2. Data could not be extracted to calculate effect sizes.
Notes	• No antipsychotic treatments other than risperidone were allowed during the trial; use of these was stopped at trial entry and there was no wash-out period. • Doses of medication used to treat organic disorders were maintained constant. • The primary efficacy variable was the change from baseline to final visit (last observation carried forward). • N = 3 discontinued the study: N = 2 withdrew consent (at weeks

	4 and 6); N = 1 had abnormal electrocardiogram readings following screening and was therefore ineligible to continue. • Increases in body weight were modest (p = 0.061), and decreases in systolic (p = 0.191) and diastolic blood pressure (p = 0.031) were not clinically significant.

Study ID	**REMINGTON2001**
Bibliographic reference	Remington, G., Sloman, L., Konstantareas, M., *et al.* (2001) Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *Journal of Clinical Psychopharmacology*, *21*, 440–444.
Methods	**Allocation:** randomised. **Matching:** N/A – crossover study. **Blindness:** double-blind. **Setting:** outpatient. **Raters:** independently by two researchers. **Country:** Canada.
Participants	**Diagnosis:** DSM-IV ASD. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** diagnosis independently confirmed by two of the investigators who specialise in autistic disorder. **N =** 36. **Age:** 10 to 36 years (mean 16.3 years). **Sex:** male 30, female 6. **Ethnicity:** not reported. **IQ:** not reported. **Inclusion/exclusion criteria:** evidence that haloperidol or clomipramine had not been used previously or, if so, that an adequate therapeutic trial was not completed.
Interventions	1. Clomipramine (oral capsules, final dose 100 to 150 mg per day, mean 123 mg per day) (N = 36, but N = 18 for analysis because it was a crossover study) 2. Haloperidol (oral capsules, final dose 1 to 1.5 mg per day) (N = 36 but N = 18 for analysis because it was a crossover study). 3. Placebo (oral capsules) (N = 36, but N = 18 for analysis because it was a crossover study). ***Duration:*** **Intervention:** 6 weeks per intervention. **Follow-up:** 21 weeks.
Outcomes	Primary outcome measures were autistic behaviours (as measured by the CARS; Schopler *et al.*, 1980) and side effects (as measured by the DOTES as global measure of side effects, and Extrapyramidal Symptom Rating Scale to specifically evaluated drug-induced extrapyramidal symptoms).
Study design	RCT (crossover)
Source of funding	Ontario Mental Health Foundation
Limitations	1. Potential carryover effect due to crossover design and short duration of washout phase.

	2. Data reported did not allow calculation of effect size for Aberrant Behavior Checklist scores.
Notes	• N = 12 out of N = 32 participants completed the clomipramine trial; dropouts due to fatigue or lethargy (N = 4), tremors (N = 2), tachycardia (N = 1), insomnia (N = 1), diaphoresis (N = 1), nausea or vomiting (N = 1), decreased appetite (N = 1) and behavioural problems (N = 8). N = 1 categorised as side effects, but dropped out because of previous electrocardiogram results. • N = 23 out of N = 33 participants completed the haloperidol trial; dropouts due to fatigue (N = 5), dystonia (N = 1), depression (N = 1) and behavioural problems (N = 4). • N = 21 out of N = 32 participants completed the placebo trial; dropouts due to behavioural problems (N = 10) and nosebleeds (N = 1). • Benztropine (anti-Parkinsonian) could be used as required throughout the study.

Study ID	**RUPP2005**
Bibliographic reference	Research Units on Pediatric Psychopharmacology (RUPP) Autism Network (2005) Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Archives of General Psychiatry*, *62*, 1266–1274.
Methods	**Allocation:** randomised (with N = 2 exceptions, see notes). **Matching:** no matching. **Blindness:** double-blind. **Setting:** outpatient. **Raters:** parent-rated and teacher-rated. **Country:** US.
Participants	**Diagnosis:** DSM-IV ASD (N = 47 autistic disorder; N = 5 Asperger's disorder; N = 14 PDD). **Coexisting conditions:** hyperactivity (CGI scale and Swanson, Nolan, and Pelham Questionnaire revised for DSM-IV ADHD scale, published online). **Qualifying diagnostic assessment:** ADI-R. **N =** 66. **Age:** 5 to 13 years (mean 7.5 years). **Sex:** male 59, female 7. **Ethnicity:** white N = 48; black or African-American N = 9; Asian N = 6; Hispanic or Latino N = 3. **IQ:** 16 to 135 (mean 62.6) as assessed with the Slosson Intelligence Test. **Inclusion criteria:** boys and girls aged 5 to 14 years with a diagnosis of autistic disorder, Asperger's disorder, or PDD based on the criteria set forth in the DSM-IV. All of the subjects had to have interfering symptoms of hyperactivity and/or impulsiveness that were present for at least 6 months and began prior to the age of 7 years. The severity was confirmed by a CGI-S score of 4 or higher (rated 'moderately ill' taking into account all of the symptoms) and a total score of 27 or higher (item mean 1.5 on a 0 to 3 metric) on both a parent-rated and teacher-rated Swanson, Nolan, and Pelham version IV ADHD scale

	(items 1 to 18), with a score of at least 10 on the hyperactivity-impulsivity subscale; and mental age of at least 18 months as determined by IQ testing. **Exclusion criteria:** concurrent psychotropic medications for at least 1 to 3 weeks (1 week for stimulants and clonidine hydrochloride; 2 weeks for antidepressants except fluoxetine and citalopram hydrobromide; 3 weeks for fluoxetine, citalopram hydrobromide or antipsychotics) prior to baseline visit; other neuropsychiatric disorders that might require alternative medical management; for subjects with a tic disorder, tic severity had to be mild or less on a CGI-severity subscale rating pertaining to tics only; significant medical condition, such as heart or liver disease that could make treatment unsafe; for subjects with a seizure disorder, no seizures in the past 6 months and a stable anticonvulsant dose for at least 1 month; hypertension; treatment with an adequate trial of methylphenidate hydrochloride (0.4 mg per kg per dose given at least twice daily for a minimum of 2 weeks) within the past 2 years; and history of severe adverse response to methylphenidate.
Interventions	1. Methylphenidate (oral capsules three times a day; given in low, medium and high dosage levels of 0.125, 0.250 and 0.500 mg per kg per dose respectively) (N = 66, but sample sizes differed by measure due to data availability; sample size was halved for analysis because it was a crossover study and only data for the best dose were extracted). 2. Placebo (N = 66, but sample sizes differed by measure due to data availability; sample size was halved for analysis because it was a crossover study). ***Duration:*** **Intervention:** 4 weeks. **Follow-up:** 5 weeks (includes a 1 week test-dose phase prior to 4 week crossover trial).
Outcomes	The primary outcome was hyperactivity as measured by the hyperactivity subscale of the Aberrant Behaviour Checklist. A secondary outcome was symptom improvement as measured by the CGI-I.
Study design	RCT (crossover)
Source of funding	This study was supported by funds under contracts N01MH80011 (Dr Aman), N01MH70001 (Dr McDougle), N01MH70010 (Dr McCracken), and N01MH70009 (Dr Scahill) from the NIMH, Bethesda, MD; by grants M01 RR00750 for Indiana University, M01RR00052 for John Hopkins University, M01 RR00034 for Ohio State University, and M01 RR06022 for Yale University; from the General Clinical Research Centers, National Center for Research resources, National Institutes of Health, Bethesda, MD; by grants K23 MH068627 (Dr Posey) and K24 MH001805 (Dr McCracken) from the NIMH; and by the Korczak Foundation, Amsterdam (Dr Scahill)
Limitations	1. One week of treatment of each dose may not be long enough to determine efficacy. 2. High rate of discontinuation owing to adverse effects. 3. Rate of adverse events may be an underestimate relative to clinical settings because subjects who had had a previous adverse response to methylphenidate were excluded. 4. Possibility that test-dose phase could have influenced parent

	blinding.
Notes	• This study continues with an 8-week open-label phase. However, data were not extracted for this phase here. • N = 72 participated in the test-dose phase. N = 6 had intolerable side effects with more than one dosage level and dropped out. N = 16 of the remaining 66 subjects had intolerable adverse effects at the highest dose of methylphenidate and they were randomised to a modified crossover phase that omitted the highest dose. • N = 2 exceptions to completely randomised design: (1) subjects who could not tolerate the high dosage level received the medium dose twice; and (2) the high dose could not follow the placebo, so as to avoid an abrupt exposure to a high dose of methylphenidate that might cause adverse effects. • Parent- and teacher-rated Aberrant Behavior Checklist hyperactivity subscales were reported. However, only data from the parent-rated scale were extracted because this was the more consistently reported scale in the literature. • Data could not be extracted for the CGI-I or the overall response score that summed all the measures because results were not reported for best dose, which was selected as the intervention group of interest.

Study ID	**SINGH1992**
Bibliographic reference	Singh, I. & Owino, J. E. (1992) A double-blind comparison of zuclopenithixol tablets with placebo in the treatment of mentally handicapped in-patients with associated behavioural disorders. *Journal of Intellectual Disability Research*, *36*, 541–549.
Methods	**Allocation:** randomised. **Matching:** no matching, but no major differences in patient characteristics and no significant difference in the patient distribution according to the severity of 'mental handicap'. **Blindness:** double-blind. **Setting:** inpatient. **Raters:** clinicians. **Country:** UK.
Participants	**Diagnosis:** learning disability. **Coexisting conditions:** physical disorders (N = 21); epilepsy (N = 15); psychiatric disorders (N = 9). **Qualifying diagnostic assessment:** not reported. **N =** 52. **Age:** 33 to 60 years (34 and 38 years in experimental and control groups, respectively). **Sex:** male 28, female 24. **Ethnicity:** not reported. **IQ:** not reported; mild learning disability (N = 1); moderate learning disability (N = 17); severe learning disability (N = 34). **Inclusion/exclusion criteria:** participants had a learning disability, 16 to 65 years. Exclusion criteria were confirmed or possible pregnancy, severe concomitant diseases, or treatment with depot neuroleptics in

	the last 3 months.
Interventions	1. Zuclopenthixol (oral tablets, 10 to 150 mg per day, modal dose 20 mg per day) (N = 27). 2. Placebo (equivalent number of oral tablets) (N = 25). ***Duration:*** **Intervention:** 12 weeks (double-blind period), this followed on from 6-week open-label phase. **Follow-up:** 18 weeks.
Outcomes	Primary outcome measure was symptom severity/improvement (as measured by the CGA, which was derived from the CGI [Guy, 1976a]; the Behavioural Disorder Assessment; and a simplified Udvalg for Kliniske Undersøgelser Side-effect Rating Scale [Lingjaerde *et al.*, 1986]).
Study design	RCT
Source of funding	Not reported
Limitations	Higher attrition rate in placebo group
Notes	• This was a prospective study including a 6-week, open-label treatment phase in which all patients received zuclopenthixol dihydrochloride (10 mg tablets) followed by a 12-week, randomised, placebo-controlled, double-blind period using a parallel group design in which some participants discontinued active drug treatment and switched to placebo. • Participants could receive the hypnotics nitrazepam and temazepam, anticonvulsants and the anti-Parkinsonian drug procyclidine. Antibiotics and other medication for somatic diseases were permitted. • N = 41 were taking neuroleptic medication at trial entry; N = 12 in the zuclopenthixol group and N = 8 in the placebo group were receiving anti-Parkinsonian drugs at entry. • N = 9 were excluded from the efficacy analysis either due to protocol violation (for example, receiving unpermitted additional medication), withdrawal from the single-blind phase or receiving less than 2 weeks' treatment in the double-blind phase. • Of N = 43 (zuclopenthixol N = 24, placebo N = 19) who remained eligible for efficacy analysis, N = 5 (all receiving placebo) were withdrawn from the study resulting in outcome data for zuclopenthixol N = 24, placebo N = 14. • No data could be extracted for Behavioural Disorder Assessment or Udvalg for Kliniske Undersøgelser Side-effect Rating Scale outcome measures as narrative description of results. • Dichotomous data calculated for 'severity of behavioural disorder' on CGA with the number of participants causing fewer problems in management rated as 'events' and the number of participants remaining unchanged or causing more problems summed to create 'no events' total.

Study ID	TYRER2008
Bibliographic reference	Tyrer, P., Oliver-Africano, P. C., Ahmed, Z., *et al.* (2008) Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomised controlled trial. *The Lancet*, *371*, 57–63.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** community. **Raters:** keyworker report and independent researcher. **Country:** UK and Australia.
Participants	**Diagnosis:** learning disability. **Coexisting conditions:** N = 14 (16%) had autism. **Qualifying diagnostic assessment:** not reported. **N =** 86. **Age:** 26 to 51 years (placebo group mean age 43 years; risperidone group mean age 39 years; haloperidol mean age 37.5 years). **Sex:** male 53, female 33. **Ethnicity:** not reported. **IQ:** not reported; N = 1 borderline learning disability; N = 30 mild learning disability; N = 41 moderate learning disability; N = 14 severe (profound) learning disability. **Inclusion/exclusion criteria:** Individuals treated by services for learning disability (IQ <75) with all degrees of severity of learning disability, including those who had been given antipsychotic drugs in the past but no longer took them. Participants were required to have recent challenging behaviour and aggression (defined by at least two episodes of aggressive behaviour, with a total MOAS score of at least 4 in the past 7 days). Only those who had been previously diagnosed as having a psychosis were excluded. Possible autism was not an exclusion criteria, provided that a clinical diagnosis of psychosis was absent. Patients who had taken depot antipsychotic drugs or any other injected antipsychotic drug within the past 3 months or continuous oral antipsychotic drugs within the past week, or those under a section of the Mental Health Act 1983 (or the Queensland Mental Health Act 2000 in the Australian group) at the time of assessment were excluded.
Interventions	1. Risperidone (oral tablets, 1 to 2 mg per day) (N = 29). 2. Haloperidol (oral tablets, 2.5 to 5 mg per day) (N = 28). 3. Placebo (oral tablets) (N = 29). ***Duration:*** **Intervention:** 12 weeks. **Follow-up:** 26 weeks (optional continuation).
Outcomes	The primary outcome was challenging behaviour (as measured by the MOAS [Sorgi *et al.*, 1991] and the Aberrant Behaviour Checklist – Community Version [Aman *et al.*, 1985]). Secondary outcomes included effect on carers (as measured by the Uplift and Burden Scale, Pruchno, 1990), quality of life (as measured by the 40-item quality of life questionnaire; Schalock & Keith, 1993); side effects (as measured by the Udvalg for Kliniske Undersøgelser Scale, Lingjaerde *et al.*, 1987), and symptom severity/improvement (as measured by the CGI; Guy, 1976a).

Study design	RCT
Source of funding	National Coordinating Centre for Health Technology Assessment, Southampton, UK
Limitations	1. Results reported as median values and inter-quartile ranges, which may indicate skewed data. As a result, it was not possible to calculate effect sizes for this study. 2. The statistical analysis reported compares scores at week 4 rather than at the week-12 endpoint. 3. No data could be extracted for the Aberrant Behaviour Checklist – Community Version, the effect on carers, quality of life, or symptom severity/improvement. 4. No adjustment was made for multiple statistical comparisons.
Notes	• N = 11 dropouts by week 12 in the risperidone group, N = 6 dropouts in the haloperidol group and N = 8 dropouts in the placebo group. • Analysis was by ITT, inputting missing values by last observation carried forward. • Baseline differences in MOAS scores controlled for in statistical analysis.

Study ID	**VANDENBORRE1993**
Bibliographic reference	Vanden Borre, R., Vermote, R., Buttiëns, M., *et al.* (1993) Risperidone as add-on therapy in behavioural disturbances in mental retardation: a double-blind placebo-controlled cross-over study. *Acta Psychiatrica Scandinavica*, *87*, 167–171.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** inpatient. **Raters:** not reported. **Country:** Belgium.
Participants	**Diagnosis:** DSM-III-R intellectual disability. **Coexisting conditions:** not reported. **Qualifying diagnostic assessment:** not reported. **N =** 37. **Age:** 15 to 58 years (mean 30.5 years). **Sex:** not reported. **Ethnicity:** not reported. **IQ:** not reported; severe or profound learning disability. **Inclusion/exclusion criteria:** Individuals aged 15 to 65 years of either sex could be include in the study. A diagnosis of mild, moderate, severe, or profound 'mental retardation' (DSM-III-R) had to be established. Despite optimisation of current treatment, participants presented such persistent behavioural disturbances as hostility, aggressiveness, irritability, agitation, hyperactivity, automutilation and autism that required psychotropic medication. Participants with a severe organic disease affecting the absorption, distribution, metabolism or excretion of the test drug or from a mental disorder other than the target diagnosis were excluded. Participants with a history of alcohol or drug abuse were also excluded, as were women

	with pregnancy potential, pregnancy or lactation.
Interventions	1. Risperidone (oral solution, 4 to 12 mg per day, mean final dose 8.3 mg per day) (N = 37, but for analysis N = 19 because this was a crossover study). 2. Placebo (oral solution) (N = 37, but for analysis N = 19 because this was a crossover study). ***Duration:*** **Intervention:** 3 weeks per intervention (total of 8 weeks). **Follow-up:** 8 weeks.
Outcomes	Primary outcomes were symptoms severity/improvement (as measured by the CGI scale) and challenging behaviour (as measured by the Aberrant Behaviour Checklist).
Study design	RCT (crossover)
Source of funding	Not reported
Limitations	1. Results reported for primary outcomes do not allow for a calculation of effect sizes. 2. Results are indicative of group differences in adverse events. However, narrative description of results means data could not be extracted in order to quantify this finding.
Notes	• During the whole study period, the existing medication was to be continued unchanged. The consumption of concomitant medication was evenly distributed in both groups; butyrophenones, phenothiazines and benzodiazepines were the most frequently used concomitant medicines. • Both groups were comparable in sex distribution, target symptom and diagnosis (mostly severe or profound 'mental retardation'). • N = 2 dropped out under placebo: N = 1 after 7 days because of agitation and N = 1 after 9 days because of extrapyramidal symptoms. N = 5 dropped out under risperidone treatment: N = 1 because of an intercurrent event (respiratory infection) after 15 days; and N = 4 for adverse events, one for hypotension after 1 day, N = 1 for hypotension and sedation after 6 days, N = 1 for sedation after 7 days and N = 1 because of agitation after 15 days. • All participants were included in the efficacy analysis and in the safety analysis. • Adverse reactions were more numerous under risperidone treatment. Sedation was reported ten times and drowsiness six times as a treatment-emergent adverse event under risperidone treatment; these symptoms did not emerge under placebo. • There were no statistically significant changes in systolic or diastolic blood pressure, heart rate, electrocardiogram or body weight during this trial. No relevant alterations in haematology, blood biochemistry or urinalysis were detected.

Study ID	VANHEMERT1975
Bibliographic reference	van Hemert, J. C. J. (1975) Pipamperone (Dipiperon, R3345) in troublesome mental retardates: a double-blind placebo controlled cross-over study with long-term follow-up. *Acta Psychiatrica Scandinavica*, *52*, 237–245.
Methods	**Allocation:** randomised. **Matching:** no matching. **Blindness:** double-blind. **Setting:** inpatient. **Raters:** not reported. **Country:** Netherlands.
Participants	**Diagnosis:** DSM-II 'mental retardation'. **Coexisting conditions:** all participants presented strong aggressiveness or other troublesome behaviour, not induced by their environment (for example, agitation or aggressiveness towards the other patients). **Qualifying diagnostic assessment:** not reported. **N =** 20. **Age:** 22 to 42 years (median: 33 years). **Sex:** male 0, female 20. **Ethnicity:** not reported. **IQ:** not reported; N = 9 moderate learning disability, N = 10 severe learning disability and N = 1 profound learning disability. **Inclusion/exclusion criteria:** not reported.
Interventions	1. Pipamperone (oral tablets, 40 to 80 mg per day) (N = 20, but N = 10 for analysis because it was a crossover study). 2. Placebo (oral tablets) (N = 20, but N = 10 for analysis because it was a crossover study). ***Duration:*** **Intervention:** 3 weeks per intervention (total of 6 weeks). **Follow-up:** 4 months (open-label continuation).
Outcomes	Primary outcome was challenging behaviour (as measured by change scores on a ten-item scale).
Study design	RCT (crossover)
Source of funding	Janssen Pharmaceutica provided the medication
Limitations	Results reported for primary outcomes do not allow for calculation of effect sizes
Notes	• Other psychotropic drugs including hypnotics were not admitted. • Both groups comparable as to age, diagnosis and body weight at the onset of treatment. • Apart from drowsiness in N = 3 during pipamperone treatment, no side effects were reported or observed.

1.2 CHARACTERISTICS OF EXCLUDED STUDIES

ADAMS2004

Reason for exclusion	Sample size for analysis of completers was less than ten per arm.

ADAMS2011

Reason for exclusion	Data could not be extracted.

ADVOKAT2000

Reason for exclusion	Comorbid psychosis.

ALKAISI1974

Reason for exclusion	Comorbid epilepsy and the primary outcome was reduction of seizures.

AMMINGER2007

Reason for exclusion	Sample size was less than ten per arm.

AMORE2011

Reason for exclusion	Significant baseline differences between groups in primary outcome measure not controlled for in analysis.

ANAGNOSTOU2006

Reason for exclusion	Sample size was less than ten participants per arm.

ANDARI2010

Reason for exclusion	Sample size was less than ten per arm for analysis because this was a crossover study.

ANDERSEN2008

Reason for exclusion	Data could not be extracted due to narrative reporting of results.

BERTOGLIO2010

Reason for exclusion	Data could not be extracted.

BHAUMIK1997

Reason for exclusion	Comorbid epilepsy.

BOACHIE1997

Reason for exclusion	Comorbid psychosis.

BREUNING1982

Reason for exclusion	Data could not be extracted.

BRODKIN1997

Reason for exclusion	Data could not be extracted.

BUITELAAR1990

Reason for exclusion	Sample size was less than ten per arm for analysis because this was a crossover study.

BUITELAAR2000

Reason for exclusion	From a sift of learning disabilities studies but not a learning disabilities population, IQ >70.

CONIGLIO2001

Reason for exclusion	Data could not be extracted.

COPLAN2003

Reason for exclusion	Data could not be extracted.

COSKUN2009

Reason for exclusion	Mean age <15 years.

CRAFT1980

Reason for exclusion	Comorbid psychosis.

DANFORS2005

Reason for exclusion	Sample size was less than ten per arm.

DOLSKE1993

Reason for exclusion	Sample size was less than ten per arm.

DRMIC2008

Reason for exclusion	Data could not be extracted.

GHUMAN2009

Reason for exclusion	Sample size was than ten per arm.

GIANNOTTI2006

Reason for exclusion	Data could not be extracted.

GUASTELLA2010

Reason for exclusion	Sample size was less than ten per arm for analysis because this was a crossover study.

HANDEN2000

Reason for exclusion	Sample size was than ten per arm.

HELLINGS2010

Reason for exclusion	Data could not be extracted.

HENRY2006

Reason for exclusion	Mean age <15 years.

HENRY2009

Reason for exclusion	Mean age <15 years.

HOLLANDER2000

Reason for exclusion	Mean age <15 years.

HOLLANDER2003

Reason for exclusion	Sample size was less than ten per arm for analysis because this was a crossover study.

HOLLANDER2005

Reason for exclusion	Mean age <15 years.

HOLLANDER2007

Reason for exclusion	Sample size was less than ten per arm for analysis as this was a crossover study.

HONOMICHL2002

Reason for exclusion	Sample size was less than ten per arm.

JAMES2009

Reason for exclusion	Clinically relevant data could not be extracted.

JOHNSON2010

Reason for exclusion	Data could not be extracted. It was unclear if F-values reported were for main effects or interaction values.

JYONOUCHI2005

Reason for exclusion	Clinically relevant data could not be extracted.

KASTNER1993

Reason for exclusion	Comorbid epilepsy.

KERN2001

Reason for exclusion	Data could not be extracted.

KERN2002

Reason for exclusion	Sample size was less than ten per arm.

LELORD1981

Reason for exclusion	Data could not be extracted.

LIGHTDALE2001

Reason for exclusion	Data could not be extracted.

LONSDALE2002

Reason for exclusion	Clinically relevant data could not be extracted.

LOTT1996

Reason for exclusion	Data could not be extracted (narrative).

LYNCH1985

Reason for exclusion	Data could not be extracted.

MALT1995

Reason for exclusion	Comorbid psychosis.

MCDOUGLE1996

Reason for exclusion	Sample size for analysis of completers was less than ten per arm because this was a crossover study.

MEGUID2008

Reason for exclusion	Data could not be extracted. ANOVA reported change from baseline scores, but the variables and participants included were unclear.

MOFFATT1970

Reason for exclusion	Comorbid epilepsy.

MOLLOY2002

Reason for exclusion	Data could not be extracted.

NAZNI2008

Reason for exclusion	Data could not be extracted.

NICKELS2008

Reason for exclusion	Data could not be extracted.

OWLEY2001

Reason for exclusion	Data could not be extracted.

OWLEY2010

Reason for exclusion	Mean age <15 years.

POLITI2008

Reason for exclusion	Data could not be extracted.

QUINTANA1995

Reason for exclusion	Sample size was than ten per arm.

ROBERTS2001

Reason for exclusion	Data could not be extracted.

ROMEO2009

Reason for exclusion	Efficacy data duplicated from TYRER2008.

RUEDRICH1999

Reason for exclusion	Comorbid psychosis.

RUEDRICH2008

Reason for exclusion	Comorbid psychosis.

RUGINO2002

Reason for exclusion	Data could not be extracted.

STIGLER2004

Reason for exclusion	Data could not be extracted.

THALAYASINGAM2004

Reason for exclusion	Data could not be extracted.

TODA2006

Reason for exclusion	Data could not be extracted.

TROOST2005

Reason for exclusion	Mean age <15 years.

TYRER2009

Reason for exclusion	Data duplicated from TYRER2008.

UNIS2002

Reason for exclusion	Data could not be extracted.

VALICENTIMCDERM2006

Reason for exclusion	Mean age <15 years.

WASSERMAN2006

Reason for exclusion	Data could not be extracted. Time x group interaction data reported.

WEIR1968

Reason for exclusion	Data could not be extracted because the results from the comparison of interest are reported as not significant.

WHITELEY2010

Reason for exclusion	Data could not be extracted.

ZARCONE2001

Reason for exclusion	Sample size for analysis was less than ten per arm because it was a crossover study.

1.2.1 References of excluded studies

Adams, J. B. & Holloway, C. (2004) Pilot study of a moderate dose multivitamin/mineral supplement for children with autistic spectrum disorder. *Journal of Alternative and Complementary Medicine*, *10*, 1033–1039.

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