ClinicalEvidence

Autism

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ABSTRACT

INTRODUCTION: Evidence for the efficacy of treatments for autism has improved in recent years. In this systematic review the evidence for both drug and non-drug treatments is appraised and clinical guidance is provided for their use. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of early intensive multidisciplinary intervention programmes in children with autism? What are the effects of dietary interventions in children with autism? What are the effects of drug treatments in children with autism? What are the effects of non-drug treatments in children with autism? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2009 (Clinical evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 30 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: applied behavioural analysis; auditory integration training; Autism Preschool Programme; casein-free diet; chelation; Child's Talk programme; cognitive behavioural therapy; digestive enzymes; EarlyBird programme; facilitated communication; Floortime therapy; gluten-free diet; immunoglobulins; melatonin; memantine; methylphenidate; More Than Words programme; music therapy; olanzapine; omega-3 fish oil; picture exchange communication system; Portage scheme; probiotics; relationship development interventions; risperidone; secretin; selective serotonin reuptake inhibitors (SSRIs); sensory integration training; social stories; social skills training; Son-Rise programme; TEACCH; vitamin A; vitamin B6 (pyridoxine) plus magnesium; and vitamin C.

QUESTIONS

INTERVENTIONS

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To be covered in future updates

Art therapy

Footnote

*In the absence of robust RCT evidence in children with autism, categorisation is based on observational evidence and strong consensus belief that these interventions are likely to be beneficial.

Key points

- Autism is one of a group of pervasive developmental disorders, and is characterised by qualitative impairments in communication and social interaction, and by repetitive and stereotyped behaviours and interests.

  Abnormal development is present before the age of 3 years. A quarter of affected children show developmental regression, with loss of previously acquired skills.

  One third of children with autism have epilepsy, and three quarters have mental retardation. Only 15% of adults with autism will lead independent lives.

  Twin and family studies suggest that most cases of autism occur because of a combination of genetic factors. Autism is not caused by perinatal factors or by the MMR vaccine.
- It may be difficult to apply the results of research in practice, as improvements in outcomes assessed in RCTs using standardised assessment tools may not correlate with improvements in function in a particular child with autism.
- Some interventions are administered by (or in conjunction with) parents, and may be carried out in the home. Consideration of the direct financial costs, indirect costs (through possible lost earnings), and the impact on relationships within the family (to siblings or spouse) must be balanced against likely and possible improvements in outcome for the child with autism.
- There is a lack of good-quality evidence on the effectiveness of early multidisciplinary intervention programmes, or for other treatments for children with autism.

  There is consensus, supported by a systematic review, that early intensive behavioural interventions are likely to be beneficial in children with autism.

  Attendance at a "More Than Words" training course for parents may improve communication between parents and children, as may participation in Child's Talk.

  There is consensus that the Autism Preschool Programme and TEACCH may be effective, although no RCTs or cohort studies evaluating these interventions have been found.

  We don't know whether early intervention using the EarlyBird programme, the Portage scheme, Relationship-Development Intervention, Social stories, music therapy, CBT, facilitated communication or Son-Rise are beneficial in children with autism.
- Methylphenidate may reduce hyperactivity in children with autism.

  Methylphenidate may increase social withdrawal and irritability. Growth and blood pressure monitoring are required.
- Risperidone may improve behaviour in children with autism compared with placebo, but its use is limited by adverse effects such as weight gain, drowsiness, prolactinaemia, and tremors.
- There is consensus that selective serotonin reuptake inhibitors (SSRIs) improve symptoms in children with autism, although no RCTs have been found. The adverse effects of SSRIs, including possible increases in agitation, hostility, and suicidal ideation, are well documented.
- We don't know whether auditory integration training, sensory integration training, chelation, a gluten- and casein-free diet, digestive enzymes, omega-3 fish oil, secretin, vitamin A, vitamin B6 plus magnesium, melatonin, olanzapine, or vitamin C are beneficial for treating children with autism, as few studies have been found.

DEFINITION

Autism is one of the pervasive developmental disorders (PDD), a group of conditions that also includes Asperger syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS), Rett syndrome, and childhood disintegrative disorder. Collectively, autism, Asperger syndrome, and PDD-NOS are often referred to as "autistic spectrum disorders" (ASDs). However, Rett syndrome and childhood disintegrative disorder fall outside the autistic spectrum. Autism is characterised by qualitative impairments in communication and social interaction, and by restricted, repetitive, and stereotyped patterns of behaviours and interests. Abnormal development is present before the age of 3 years. The clinical features required for a diagnosis of autism to be made are set out in *International classification of diseases* (ICD-10) [1] and *Diagnostic and statistical manual of mental disorders 4th ed* (DSM-IV). [2] For ICD-10 criteria see table 1, p 18 . Individuals with autism have a history of language delay (single word or phrase speech delay), and a quarter lose previously acquired skills (regression), most commonly in the second year of life. [3] A third of individuals develop epilepsy, [4] and three quarters have mental retardation. [5] Males are affected more com-

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monly than females (3.5–4.0:1). [6] The findings of this review apply to children and adolescents with autism, and results may not be generalisable to children with other ASDs. **Diagnosis:** The generally accepted "gold standard" assessment tools for autism are the Autism Diagnostic Interview-Revised (ADI-R), [7] a semistructured, interviewer-based schedule administered to the primary caregiver, and the Autism Diagnostic Observational Schedule, [8] a semistructured assessment carried out with the individuals themselves. Although these schedules are informative for the clinician, autism remains a clinical diagnosis.

INCIDENCE/ PREVALENCE

The detected prevalence of autism has increased in recent years, and a recent high-quality UK study found 40/10,000 children to have childhood autism. [9] The prevalence of autism for studies published between 1977 and 1991 was 4.4/10,000, whereas that for the studies published during the period 1992 to 2001 was 12.7/10,000. [10] When considering all autism spectrum disorders, findings suggest the prevalence rises to 120/10,000; many of these people have PDD-NOS. [9]

AETIOLOGY/ RISK FACTORS

Evidence from twin and family studies suggests that most cases of autism arise because of a combination of genetic factors. [11] Family studies indicate that the rate of autism in siblings of autistic individuals is about 2.2%, [12] and the sibling recurrence rate for all PDDs is 5% to 6% [13] — significantly greater than that of the general population. Monozygotic twin studies show 60% to 91% concordance for autism, and therefore it is likely that most cases arise on the basis of multiple susceptibility genes, with influence from environmental or other factors. [14] A minority of cases of autism can be attributed to genetic disorders, including chromosomal abnormalities, fragile X syndrome, tuberose sclerosis, neurofibromatosis type 1, and a variety of other medical conditions. [14] Although perinatal factors have been implicated, it is unlikely that they have a causal role. [15] Research evidence suggests that autism is not caused by the MMR vaccine, or by thimerosal (mercury) in vaccines (see review on measles, mumps, and rubella: prevention). [15] There is strong evidence supporting a neurobiological basis of autism. [16] Ongoing research into the relationship between neurophysiology, neuroanatomy, neurochemistry, and genetic factors is likely to increase our understanding, and represents the best chance of unravelling the complex aetiology of ASD. The presence of phenotypic and genetic heterogeneity may have significant implications for studies of interventions/treatments for autism, as efficacy may vary with phenotype.

PROGNOSIS

Autism is a lifelong condition with a highly variable clinical course throughout childhood and adolescence. [17] Many adults with autism require lifelong full-time care. About 15% of adults with autism will live independent lives, whereas 15% to 20% will live alone with community support. [17] Verbal and overall cognitive capacity seem the most important predictors of ability to live independently as an adult. [18]

AIMS OF INTERVENTION

To improve social function, communication, cognitive ability, and reduce the repetitive, obsessional, and comorbid behaviours seen in autism, with minimal adverse effects of treatment.

OUTCOMES

Social function; behavioural function; cognitive function; communication; repetitive behaviour; global function; self care; family function; and adverse effects of treatment.

METHODS

Clinical Evidence search and appraisal May 2009. For this review various sources were used for the identification of studies: Medline 1986 to May 2009, Embase 1986 to April 2009, and The Cochrane Library, Issue 2, 2009. Additional searches were carried out on the NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE) websites. Abstracts of studies retrieved in the search were assessed independently by two information specialists. Predetermined criteria were used to identify relevant studies. Study design criteria included: systematic reviews; RCTs; quasi-randomised trials; controlled clinical trials; and prospective and retrospective cohort studies. Prospective and retrospective cohort studies were included only for interventions for which we could find no RCTs. We included studies with at least 20 participants. There was no minimum level or length of follow-up. We included open-label studies for interventions that could not be blinded. We only included studies of children or adolescents with autism; if studies included individuals with other ASDs, those which provided a subgroup analysis of at least 20 individuals with autism were included. **Limitations of the research:** The guidance included in this review is applicable to children with autism rather than other ASDs. Many excluded studies have included small numbers of participants, with a range of ASD diagnoses and therefore a range of abilities; combining data on the outcome of individuals with autism and those individuals with other PDDs is unlikely to be either scientifically valid or clinically useful. In addition, participants in studies have frequently been diagnosed using clinical criteria, without standardised assessment tools, and outcomes have been assessed using a variety of measures, often after a short follow-up period. Much of the research is observational and few RCTs were found. Only by conducting well-designed RCTs in large samples of people characterised

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as having autism using standardised assessment tools, and by measuring outcomes using standardised measures after an acceptable time period, will the effect of interventions be robustly proved. **Applying the evidence in practice:** For clinicians and parents, various factors require consideration when deciding whether an intervention or treatment may be of benefit to a child with autism. As described, the limitations of the research have led to weaknesses in the evidence base for many established interventions. Some studies have appropriately measured outcome using standardised assessment tools; however, improvements in scale scores on such assessments do not necessarily translate into obvious functional improvements in the everyday life of a child with autism. Longitudinal studies and data on long-term outcome after interventions are lacking; for some children, improvements in outcome may be moderate, and there is at present no way of ascertaining whether a particular group of children may benefit from a specific intervention. In addition to considering the possible adverse effects of treatment, the wider cost of interventions should be considered. Many interventions are expensive, and costs may not necessarily be covered by state funding. Some interventions are administered by (or in conjunction with) parents and may be carried out in the home. Consideration of the direct financial costs, indirect costs (through possible lost earnings), and the impact on relationships within the family (to siblings or spouse) must be balanced against likely and possible improvements in outcome for the individual with autism. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 19).

QUESTION **What are the effects of early intensive multidisciplinary intervention programmes in children with autism?**

OPTION **EARLY INTENSIVE BEHAVIOURAL INTERVENTIONS**

Cognitive function
Compared with other therapy Early intensive behavioural interventions may improve IQ and comprehension (very low-quality evidence).

Behavioural function
Compared with other therapy Early intensive behavioural interventions may improve adaptive behaviour (very low-quality evidence).

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found one systematic review (search date 2009; 11 studies, 397 children [1 RCT, 23 children]) comparing early intensive behavioural interventions (interventions based on applied behavioural analysis that begin in the preschool years, including home based, school based, multisite, or community based treatment) versus other types of therapy (including less intensive therapy, minimum therapy, standard schooling, parent training, eclectic education, parent-directed early intensive behavioural intervention, and autism-specific education/nursery or generic special education) for young children with autism over a mean duration of 27 months. [19] The review reported that data were not available for individual participants, so their analyses was based on comparisons of the published group means. The review found that early intensive behavioural interventions significantly improved mean scores for IQ (range –5.0 to +31.5; mean change: 18.3 with early intensive behavioural interventions *v* 5.4 with other therapy; P <0.05), Vineland adaptive behaviour scale mean score (range –2.0 to +2.0; mean change: +5.1 with early intensive behavioural interventions *v* –2.4 with other therapy; P <0.01) and mean comprehension scores (range 7.0 to 24.0; mean change: 15.7 with early intensive behavioural interventions *v* 4.5 with other therapy; P <0.05) compared with other therapies. [19]

Harms: The review gave no information on adverse effects. [19]

Comment: **Clinical guide:**
The review concluded that early intensive behavioural interventions resulted in improved outcomes between groups, but for individuals there was considerable variability in outcomes. It concluded that early intensive behavioural interventions are effective in some, but not all, preschool children

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with autism. [19] Despite the lack of robust RCT evidence, there is also consensus based on clinical experience that early intensive behavioural interventions are likely to be beneficial.

OPTION AUTISM PRESCHOOL PROGRAMME

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of the Autism Preschool Programme compared with no active treatment or with other treatments in children with autism.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found one systematic review (search date 2002) identifying no RCTs meeting our inclusion criteria (see comment). [20] We found no subsequent RCTs or cohort studies comparing the Autism Preschool Programme versus no treatment or usual care.

Harms: We found no studies that met our inclusion criteria.

Comment: **Clinical guide:**
Large, well-designed RCTs with comparable control groups and long-term follow-up are required to assess the effectiveness of the Autism Preschool Programme.

OPTION CHILD'S TALK

Social function
Compared with standard care The Child's Talk programme may result in improvements in social interaction and language outcomes compared with existing care alone (moderate-quality evidence).

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found one pilot RCT (28 children with autism diagnosed with the Autism Diagnostic Interview) comparing Child's Talk versus existing care alone. [21] It found that Child's Talk significantly improved social interaction compared with existing care alone (as measured by change in Autism Diagnostic Observational Schedule [ADOS] score: –4.3 points with Child's Talk *v* 0 points with existing care alone; P = 0.01; lower ADOS score indicates less impairment). Analysis of the ADOS subdomains suggested that improvements were mostly accounted for by the reciprocal social interaction sub-domain (post-intervention scores: 7.7 with Child's Talk *v* 10.7 with existing care alone; P = 0.004). It also found that Child's Talk significantly improved expressive language (measured with the MacArthur Inventory scores: 199.4 with Child's Talk *v* 33.1 with existing care alone; P <0.001; higher score indicates less impairment). Parent–child interaction was also scored from videotapes of interactions before and after intervention. The RCT found that, compared with existing care alone, Child's Talk significantly increased child communication acts (37.6 with Child's Talk *v* 27.5 with existing care alone; P = 0.041), parent synchrony (65.1 with Child's Talk *v* 49.5 with existing care alone; P = 0.016), and significantly reduced parent asynchrony (32.6 with Child's Talk *v* 50.5 with existing care alone; P = 0.009). [21]

Harms: The RCT gave no information on adverse effects. [21]

Comment: **Clinical guide:**
Following the results of this pilot study, a large, multicentre RCT assessing the effects of a similar intervention (Preschool Autism Communication Trial [PACT]) has been completed in the UK; data will be available in 2010 (Parr J, 2009, personal communication).

OPTION MORE THAN WORDS

Social function
Compared with delayed treatment Children with autism and their parents who had undertaken a "More Than Words" training course may have improved communication outcomes compared with parents and children who had delayed access to the course (very low-quality evidence).

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found one quasi-randomised trial (parents of 29 children with autism) comparing immediate (parents of 17 children) versus delayed (parents of 12 children) access to a More Than Words course. [22] Communication outcomes were measured before and after immediate group intervention (before the delayed group entered the programme). The RCT found that parents of children who had received More Than Words had more facilitative communication strategies (measured with

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the unpublished "Joy and Fun" Assessment; maximum scale score 36) compared with parents who had not; but the difference between groups did not quite reach significance (mean difference between scores 3.6 points; P = 0.05). Considering children's outcomes, when before and after immediate intervention and control group outcomes were compared, children in the intervention group used significantly more words than control children (measured with the MacArthur Communicative Developmental Index: mean 50 more words used by children receiving More Than Words *v* no intervention; P = 0.019).

Harms: The RCT gave no information on adverse effects. [22]

Comment: **Clinical guide:**
There is consensus based on clinical experience that More Than Words is likely to be beneficial in children with autism.

OPTION PICTURE EXCHANGE COMMUNICATION SYSTEM

Social function
Compared with other treatment or no treatment We don't know whether the picture exchange communication system (PECS) is more effective than other treatment (prelinguistic milieu teaching) or no treatment at increasing the frequency of speech, or standardised communication/language scores. However, there is consensus that PECS is beneficial in the treatment of children with autism (very low-quality evidence).

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found two RCTs (reported in 3 publications) that examined the effects of the PECS on symptoms of autism in children. [23] [24] [25]

The first RCT (33 children with autism, 3 children with autistic spectrum disorder (ASD); average age 2.5–3 years) compared PECS versus responsive education and prelinguistic milieu teaching in three 20-minute sessions per week over 6 months. Outcomes were initially reported after the sixth month of treatment then followed up 6 months post treatment to evaluate whether any improvements were maintained. [23] [24] The RCT found that PECS significantly improved the frequency of non-imitative speech immediately after 6 months of treatment (mean speech frequency in 15-minute semistructured play with examiner: 3.6 with PECS *v* 0.6 with prelinguistic milieu teaching; P = 0.03) and the number of non-imitative words (number of words in 15-minute semistructured play with examiner: 2.4 with PECS *v* 0.6 with prelinguistic milieu teaching; P = 0.04). [23] [24] However, these treatment effects were not maintained; the RCT reported similar mean speech frequency (P = 0.96) and number of word scores (P = 0.93) between groups at 6-month follow-up (absolute data not reported). [23] [24]

The second RCT (75 children who met the Autism Diagnostic Observational Schedule [ADOS]-G criteria for autism, 9 children who met criteria for ASD; mean age 6.8 years) was a group RCT with school classroom as the randomised unit. [25] This three-armed trial compared three interventions: immediate treatment (receiving PECS training immediately after baseline assessment), delayed treatment (receiving PECS training two terms after initial baseline assessment), and no treatment (receiving no PECS training, but monitored during the baseline intervention period, simulating a watchful waiting condition). There was no subgroup analysis for children with autism. The RCT found that PECS training significantly increased the rate of initiations immediately post treatment. Children who had received PECS training (immediate and delayed) were 2.73 times more likely (95% CI 1.22 to 6.08; P <0.05) to be in a higher initiation group than children who had received no training. The RCT also found PECS training significantly increased PECS use. Children who received PECS training (immediate or delayed) were 3.90 times more likely (95% CI 1.75 to 8.68; P <0.001) to be in a higher PECS-use category compared with children who received no treatment immediately post intervention. However, there was no significant difference between groups in rate of speech (OR 1.10, 95% CI 0.46 to 2.62; P = 0.83) immediately post treatment. [25] The RCT also found no significant difference for PECS training immediately following treatment for communication scores (ADOS-G domain scores: OR 0.52, 95% CI 0.24 to 1.12; P = 0.10; ADOS-G RSI domain scores: OR 0.55, 95% CI 0.25 to 1.19; P = 0.13), or on scores on standardised language tests (Expressive One Word Picture Vocabulary Test [EOWPVT]; OR 1.01, 95% CI 0.89 to 1.15; P = 0.87; British Picture Vocabulary Scales [BPVS]; OR 1.54, 95% CI 0.52 to 4.54; P = 0.44). [25]

Harms: The RCTs gave no information on adverse effects.

Comment: **Clinical guide:**
There is consensus that PECS is likely to be beneficial in children with autism who have little speech, allowing them to express themselves; clinical experience suggests this usually relates to their needs, rather than spontaneous communication about other topics.

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OPTION TEACCH

Cognitive function
Compared with usual care TEACCH may improve psychoeducational scores in children with autism (very low-quality evidence).

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review or RCTs that met our inclusion criteria. One quasi-randomised trial (22 children with autism; aged 2–6 years) compared 10 sessions of TEACCH versus usual care. [26] The first 11 families to respond to the study announcement were allocated to TEACCH, and the next 11 were allocated to control. The results of the trial should be interpreted with caution because children were not randomly allocated to treatment, and there may have been important differences between groups in severity of autism at baseline; the significance of the difference between groups in baseline scores on the Psychoeducational Profile−Revised was not assessed by the trial, and concomitant interventions may also have differed between groups; we therefore report only limited data from the trial. The trial found that, compared with usual care, TEACCH significantly improved overall Psychoeducational Profile−Revised scores as well as improving the subsets of imitation, fine and gross motor skills, and non-verbal conceptual skills (P <0.05 for all outcomes). [26] We found no cohort studies.

Harms: We found no RCTs that met our inclusion criteria. The quasi-randomised trial gave no information on adverse effects. [26] We found no cohort studies.

Comment: **Clinical guide:**
There is consensus among clinicians that TEACCH is likely to be beneficial in children with autism. Large, well-designed RCTs with comparable control groups and long-term follow-up are required to assess whether early intervention with TEACCH is effective.

OPTION EARLYBIRD PROGRAMME

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of EarlyBird programmes on symptoms of autism in children.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies of sufficient quality that examined the effects of EarlyBird programmes on symptoms of autism in children.

Harms: We found no studies.

Comment: **Clinical guide:**
The EarlyBird programme provides parents with information about the diagnosis of autism, how to socially engage and communicate with children, and how to manage challenging behaviours. Although there are no published data showing that EarlyBird leads to better outcomes in children of parents who attend a course, there is observational evidence that many parents find the course educational and helpful.

OPTION FLOORTIME

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of Floortime on symptoms of autism in children.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies of sufficient quality that examined the effects of Floortime on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

OPTION PORTAGE SCHEME

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of the Portage scheme on symptoms of autism in children.

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For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of the Portage scheme on symptoms of autism in children.

Harms: We found no studies.

Comment: **Clinical guide:**
Portage workers support parents and teach social and communication techniques with which to engage children; there is no evidence as to whether such an unstructured intervention improves outcome.

OPTION RELATIONSHIP-DEVELOPMENT INTERVENTION

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of relationship-development intervention on symptoms of autism in children.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of relationship-development intervention on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

OPTION SOCIAL SKILLS TRAINING

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of social skills training on symptoms of autism in children.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of social skills training on symptoms of autism in children.

Harms: We found no studies.

Comment: **Clinical guide:**
In moderate- and high-functioning individuals with autism, social skills training may be helpful, as it teaches children and adolescents how to make appropriate social overtures and responses, which can be used in common social situations.

OPTION SOCIAL STORIES

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of social stories on symptoms of autism in children.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of social stories on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

OPTION SON-RISE

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of the Son-Rise programme on symptoms of autism in children.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of the Son-Rise programme on symptoms of autism in children.

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Harms: We found no studies.

Comment: None.

OPTION MUSIC THERAPY New

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of music therapy on the symptoms of autism in children.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found one systematic review (search date 2004), which found no studies that met our inclusion criteria. [27]

Harms: We found no studies.

Comment: None.

OPTION COGNITIVE BEHAVIOURAL THERAPY New

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of CBT on the on symptoms of autism in children.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of CBT on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

OPTION FACILITATED COMMUNICATION New

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of facilitated communication on the on symptoms of autism in children.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found no systematic reviews, RCTs, or cohort studies that examined the effects of facilitated communication on symptoms of autism.

Harms: We found no studies.

Comment: None.

QUESTION What are the effects of dietary interventions in children with autism?

OPTION DIGESTIVE ENZYMES

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of digestive enzymes on symptoms of autism in children.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of digestive enzymes on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

OPTION GLUTEN AND CASEIN EXCLUSION DIET

Global improvement

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Compared with no dietary advice Advice to follow a gluten- and casein-free diet may improve an autistic trait score in children (low-quality evidence).

Note
We found no clinically important results about the effects of a gluten-free diet alone, or a casein-free diet alone, in children with autism.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits:

Gluten- or casein-free diet versus normal diet:
We found no systematic review or RCTs.

Combination gluten- and casein-free diet versus normal diet:
We found one systematic review (search date 2007; 2 RCTs). [28] One of the RCTs included in the review did not meet inclusion criteria for this review so will not be discussed further. The other RCT identified by the review (20 children with autism and abnormal urinary peptides; average age 7 years) compared advice to parents to provide the child with a gluten- and casein-free diet versus no advice. It found that a casein- and gluten-free diet significantly improved total autistic trait score (measured using the Diagnosis of Psychotic Behavior in Children [DIPAB] questionnaire, a standardised Danish scale that measures several traits, each assessed on a scale from 0 to 4 [higher score indicates greater severity]) compared with the control group after 1 year (difference in DIPAB score from baseline to follow-up: 6.9 with casein- and gluten-free diet *v* 0.3 with control; P = 0.001). [29] Owing to the small size of the RCT comparing combination gluten- and casein-free diet versus normal diet, groups were not balanced for confounding at baseline, and results must be interpreted with caution. [29]

Harms: The RCT gave no information on adverse effects. [29]

Comment:

Clinical guide:
Restricted diets are often inconvenient for families, and can be expensive. Until the results of large RCTs of dietary interventions are available, healthy, balanced diets are recommended for children with autism.

OPTION OMEGA-3 FISH OIL

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of omega-3 fish oil in children with autism.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of omega-3 fish oil on children with autism.

Harms: We found no studies.

Comment: None.

OPTION PROBIOTICS

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of probiotics on symptoms of autism in children.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of probiotics on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

OPTION VITAMIN A

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of vitamin A as a treatment for autism in children.

For GRADE evaluation of interventions for autism, see table, p 19 .

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Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of vitamin A on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

OPTION VITAMIN B6 (PYRIDOXINE) PLUS MAGNESIUM

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of vitamin B6 plus magnesium in children with autism.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found one systematic review (search date 2005), which identified no RCTs of sufficient quality. [30]

Harms: We found no studies.

Comment: None.

OPTION VITAMIN C

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of vitamin C in children with autism.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of vitamin C on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

OPTION MELATONIN New

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of melatonin on the symptoms of autism in children.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of melatonin on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

QUESTION What are the effects of drug treatments in children with autism?

OPTION METHYLPHENIDATE HYDROCHLORIDE

Behavioural function
Compared with placebo Methylphenidate hydrochloride may slightly reduce hyperactivity in children with autism (low-quality evidence).

Adverse effects
Methylphenidate is associated with adverse effects such as reduced appetite, difficulty sleeping, abdominal discomfort, and irritability.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found no systematic review, but found one crossover RCT (66 children with pervasive developmental disorders, 47 children with autism, all of whom had tolerated test doses of methylphenidate) comparing methylphenidate versus placebo for 4 weeks. [31] Low, medium, and high doses of

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methylphenidate were given three times daily (0.125, 0.250, and 0.500 mg/kg/dose). The RCT found that, in children with autism, methylphenidate at any dose improved hyperactivity at 4 weeks after crossover compared with placebo (response rate: 13/47 [28%] with methylphenidate 0.125 mg/kg/dose *v* 15/47 [32%] with methylphenidate 0.250 mg/kg/dose *v* 12/47 [26%] with methylphenidate 0.500 mg/kg/dose *v* 6/47 [13%] with placebo; P <0.01 for any dose *v* placebo). Response was assessed by combining parent and physician assessment of changes in hyperactivity, and the Clinical Global Impression-1 subscales of the Aberrant Behaviour Checklist. Relatively low response rates were seen with all doses of methylphenidate, therefore it is unclear whether methylphenidate results in clinically important improvements in symptoms. Data from the 8-week open-label continuation phase was not reported separately for children with autism.

Harms: The RCT found that 18% of children who either received the methylphenidate test dose or participated in the trial withdrew because of adverse effects, including reduced appetite, difficulty sleeping, abdominal discomfort, and irritability. [31]

Comment: **Clinical guide:**
In the RCT, response rates to methylphenidate in children with autism and hyperactivity were lower than those seen in children with ADHD alone; pharmacogenetic factors are likely to underlie this difference in efficacy of methylphenidate in the two disorders. Growth parameters and blood pressure should be monitored in children treated with methylphenidate.

OPTION RISPERIDONE

Behavioural function
Compared with placebo Risperidone is more effective at improving behaviour such as irritability, social withdrawal, stereotypy, hyperactivity, and inappropriate speech at 8 weeks in children with autism (moderate-quality evidence).

Adverse effects
Risperidone is associated with adverse effects such as weight gain, tremors, and drowsiness, and an increase in serum prolactin.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found one systematic review (search date 2006; 3 RCTs, 208 people with ASD) comparing risperidone. [32] The review found that risperidone significantly improved clinical global impression scores (3 RCTs; 66/102 [65%] with risperidone *v* 13/106 [12%] with placebo; RR 4.83, 95% CI 2.21 to 10.59; P = 0.000082) compared with placebo. The review also reported that risperidone significantly improved aberrant behaviours such as irritability (2 RCTs, 178 people; aberrant behaviour checklist [58 items, subdivided between 5 scales]; mean difference: −8.09, 95% CI −12.99 to −3.19; P = 0.0012; absolute numbers not reported), social withdrawal (2 RCTs, 178 people; aberrant behaviour checklist [58 items, subdivided between 5 scales]; mean difference: −3.00, 95% CI −5.03 to −0.97; P = 0.0038; absolute numbers not reported), hyperactivity (2 RCTs, 178 people; aberrant behaviour checklist [58 items, subdivided between 5 scales]; mean difference: −8.98, 95% CI −12.01 to −5.94; P <0.0001; absolute numbers not reported), stereotypy (2 RCTs, 178 people; aberrant behaviour checklist [58 items, subdivided between 5 scales]; mean difference: −1.71, 95% CI −2.97 to −0.45; P = 0.0080; absolute numbers not reported), and inappropriate speech (2 RCTs, 178 people; aberrant behaviour checklist [58 items, subdivided between 5 scales]; mean difference: −1.93, 95% CI −3.79 to −0.07; P = 0.042; absolute numbers not reported) compared with placebo. [32]

Harms: The review reported that risperidone significantly increased the risk of weight gain (mean difference: 1.78, 95% CI 1.15 to 2.41; P <0.0001) compared with placebo. [32] One additional RCT (101 children with autism; aged 5−17 years) assessed the effects of long-term risperidone treatment versus placebo for 8 weeks initially, then 63 children took part in a 4-month open-label follow-up. [33] The RCT found that risperidone significantly increased serum prolactin levels at 8 weeks (P <0.0001), 6 months (P <0.001), and 22 months (P <0.0001) compared with placebo. [33] Treatment with risperidone was associated with two- to four-fold increase in serum prolactin levels; the long-term consequences of this are unclear. [33]

Comment: **Clinical guide**:
Risperidone may be useful for behavioural symptoms of autism, but its adverse effects limit its use in children. Further long-term studies are needed to monitor possible adverse effects, including weight gain, increased blood pressure, and extrapyramidal effects. Also, prolactin levels should be regularly measured in children receiving risperidone before and during treatment.

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OPTION IMMUNOGLOBULINS

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of immunoglobulins on symptoms of autism in children.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of immunoglobulins on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

OPTION MEMANTINE

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of memantine on symptoms of autism in children.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of memantine on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

OPTION SELECTIVE SEROTONIN-REUPTAKE INHIBITORS

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of SSRIs in children with autism.

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: **SSRIs versus placebo:**
We found one systematic review (search date 2005), which identified no RCTs or cohort studies that met our inclusion criteria. [34]

Harms: We found no studies that met our inclusion criteria. The adverse effects of SSRIs, including possible increases in agitation, hostility, and suicidal ideation, are well documented (see review on depression in children and adolescent).

Comment: **Clinical guide:**
There is clinical consensus that SSRIs are of benefit to children with autism; however, robust RCTs are needed to assess their effectiveness and safety. [35]

OPTION SECRETIN

Global improvement
Compared with placebo Secretin does not seem more effective in treating any of the symptoms of autism in children (moderate-quality evidence).

For GRADE evaluation of interventions for autism, **see table, p 19 .**

Benefits: We found one systematic review (search date 2005), which identified six RCTs (242 children) solely in children with autism. [36] The review could not perform any meta-analyses as the RCTs assessed a wide variety of outcomes in heterogeneous populations. Three of the RCTs (including children with autism) described in the review found no significant difference in symptoms of autism after administration of secretin or placebo (measured by the Childhood Autism Rating Scale in 2 RCTs and the Gilliam Autism Rating Scale in the other; standardised mean differences not significant). [36] The lack of efficacy of secretin was supported by the other RCTs, all of which found no evidence that single or multiple doses of secretin were effective.

Harms: RCTs identified by the review found that children taking both secretin and placebo had a variety of minor adverse effects, including irritability, hyperactivity, and vomiting. [36]

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Comment: None.

OPTION OLANZAPINE New

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of olanzapine on the symptoms of autism in children.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of olanzapine on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

QUESTION What are the effects of non-drug treatments in children with autism?

OPTION AUDITORY INTEGRATION TRAINING

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of auditory integration training in children with autism.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found one systematic review (search date 2002), which identified no RCTs meeting our inclusion criteria. [37] We found no subsequent RCTs or cohort studies comparing auditory integration training versus usual care or other treatments.

Harms: We found no studies that met our inclusion criteria. There have been concerns about potential hearing loss with auditory integration training, because treatment involves listening to audio output. [38]

Comment: **Clinical guide:**
The American Academy of Pediatrics (1998) has suggested that auditory integration training should be used for research purposes only. [39] Treatment with auditory integration training may involve high costs to the family.

OPTION CHELATION

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of chelation on symptoms of autism in children.

Adverse effects
After recent deaths of children who received edetate disodium, and the lack of evidence for the efficacy of this treatment, its use is currently under careful review.

For GRADE evaluation of interventions for autism, see table, p 19 .

Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of chelation on symptoms of autism in children.

Harms: We found no studies (see comment).

Comment: **Clinical guide**:
After recent deaths of children who received edetate disodium, and the lack of evidence for the efficacy of this treatment, its use is currently under careful review. [40] [41]

OPTION SENSORY INTEGRATION TRAINING

We found no clinically important results from RCTs, quasi-randomised trials, or cohort studies about the effects of sensory integration training on symptoms of autism in children.

For GRADE evaluation of interventions for autism, see table, p 19 .

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Benefits: We found no systematic review, RCTs, or cohort studies that examined the effects of sensory integration training on symptoms of autism in children.

Harms: We found no studies.

Comment: None.

GLOSSARY

TEACCH (Treatment and Education of Autistic and related Communication handicapped Children) This structured developmental teaching programme provides continuity in the classroom setting, thus aiming to improve developmental skills in order to enable children to learn. Parents are trained in TEACCH methods and schooling at home, and this is supplemented by day therapy or special schooling, given by professionals.

Auditory integration training This is based on the hypothesis that individuals have insensitivity or abnormal sensitivity to various frequencies of sound waves, and that behavioural and learning difficulties are a result of this. It is hypothesised that auditory integration training addresses sound sensitivity and "re-educates" hearing, thus improving associated symptoms. Treatment with auditory integration training involves listening to electronically modified music, heard through headphones, for two daily 30-minute sessions over 10 days.

Autism Preschool Programme This programme offers parents and carers support in behavioural and language development methods that are then carried out at home or during day care.

Chelation therapy This involves the use of a compound that binds to heavy metals such as lead and mercury. Chelation agents are introduced to the body by iv infusion, bind to heavy metals, and are then excreted in the urine. Chelation therapy has been used in children with autism as some individuals believe that autism results from high levels of toxic heavy metals that cause damage to the brain.

Child's Talk This programme uses video feedback in order to promote facilitative strategies that lead to closer interpersonal interaction between the child and their parents. Parents are then able to identify which strategies are successful and lead to their child becoming more engaged, thus aiding communication.

EarlyBird programme This is a 3-month programme combining group training sessions for parents of children with autism with individual home visits. Video feedback is used to help parents use what they learn to engage and communicate with their child.

Floortime This is a series of 20–30 minute periods during which parents interact and play with their child on the floor. The aim of the interaction is to promote social and communicative abilities.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

More Than Words (Hanen programme) This is designed to help parents of children under the age of 6 years who are experiencing difficulties in social interaction and communication. Parents learn several strategies that may help to improve their child's communication and social interaction.

Picture exchange communication system (PECS) This was developed to help young children with autism learn to initiate requests and communicate their needs. PECS uses a behaviourally based programme to teach the child to exchange a picture card for something the child likes and wants. Objects, pictures, or symbols may be used, according to the developmental level of the child. The six phases of PECS are structured to enable a child to: learn the picture exchange; actively find a person to give a symbol to as a request; discriminate between several symbols; use a portable communication book; and construct simple sentences, requests, and comments.

Portage This is a home-based teaching support service for pre-school children with special educational needs and their families. Portage offers weekly visits to families by specialist teachers to help plan and support "play-based" programmes, which parents/carers carry out with their children.

Probiotics These have recently been suggested as a treatment for autism as some individuals believe that autism is related to the effects of GI tract bacteria.

Relationship-development intervention This is a parent-based programme for individuals with autism spectrum and other relationship-based disorders. The goal of the programme is to help people to systematically build up the motivation and strategies in order to successfully interact in social relationships. Relationship-development intervention focuses on improving behaviours such as referencing and enabling individuals to share emotions.

Sensory integration training This aims to treat the sensory behaviours of children with autism by exposing them to various sensory stimuli.

Social skills training In moderate- and high-functioning individuals with autism, social skills training teaches children and adolescents how to make appropriate social overtures and responses that can be used in common social situations.

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Social stories This method presents appropriate social behaviours in the form of a story, and aims to enable individuals with autism to interact appropriately with others.

Son-Rise This is an intensive home-based, parent-run intervention aimed at children with autism. Son-Rise involves intensive one-to-one contact with the child in a specially designed play room.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Music therapy: New option for which we found no studies. Categorised as Unknown effectiveness.

Cognitive behavioural therapy: New option for which we found no studies. Categorised as Unknown effectiveness.

Facilitated communication: New option for which we found no studies. Categorised as Unknown effectiveness.

Melatonin: New option for which we found no studies. Categorised as Unknown effectiveness.

Olanzapine: New option for which we found no studies. Categorised as Unknown effectiveness.

Early intensive behavioural interventions: One systematic review added comparing early intensive behavioural interventions versus other therapy. [19] The review found that early intensive behavioural interventions improved group mean scores for IQ, comprehension, and adaptive behaviour. However individual outcomes were varied. [19] Categorisation unchanged (Likely to be beneficial).

Picture exchange communication system: Two RCTs added comparing the picture exchange communication system (PECS) versus prelinguistic milieu teaching, delayed PECS training, or control. [23] [24] [25] The first RCT found that PECS improved the frequency of non-imitative speech and words compared with prelinguistic milieu teaching. [23] [24] The second RCT found that PECS improved the rate of initiations and the PECS use compared with no treatment, but it found no differences between groups on scores of speech frequency, communication, or language. [25] Categorisation unchanged (Likely to be beneficial).

Risperidone: One systematic review added comparing risperidone versus placebo. [32] The review found that risperidone improved global function, irritability, social withdrawal, hyperactivity, stereotypy, and inappropriate speech compared with placebo. However, the review also reported that risperidone increased the risk of weight gain. One additional RCT added to the harms section reported that risperidone increased serum prolactin levels at 8 weeks, 6 months, and 22 months compared with placebo. [33] Categorisation unchanged (Trade-off between benefits and harms).

SSRIs: One systematic review added [34] including no RCTs or cohort studies that met our criteria. Categorisation unchanged (Trade-off between benefits and harms).

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TABLE 1 **Diagnostic criteria for childhood autism − International Classification of Diseases (ICD-10) issued by the WHO** [1]

Qualitative impairments in reciprocal social interaction, as manifested by at least 3 of the following 5:

- Failure to adequately use eye-to-eye gaze, facial expression, body posture, and gesture to regulate social interaction
- Failure to develop peer relationships
- Rarely seeking and using other people for comfort and affection at times of stress or distress, offering comfort and affection to others when they are showing distress or unhappiness, or both
- Lack of shared enjoyment in terms of vicarious pleasure in other people's happiness, spontaneous seeking to share their own enjoyment through joint involvement with others, or both
- Lack of socioemotional reciprocity

Qualitative impairments in communication:

- Lack of social usage of whatever language skills are present
- Impairment in make believe and social imitation play
- Poor synchrony and lack of reciprocity in conversational language
- Poor flexibility in language expression and a relative lack of creativity and fantasy in thought processes
- Lack of emotional response to other people's verbal and non-verbal overtures
- Impaired use of variations in cadence or emphasis to reflect communicative modulation
- Lack of accompanying gesture to provide emphasis or aid meaning in spoken communication

Restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities, as manifested by at least 2 of the following 6:

- Encompassing preoccupation with stereotyped and restricted patterns of interest
- Specific attachments to unusual objects
- Apparently compulsive adherence to specific, non-functional routines or rituals
- Stereotyped and repetitive motor mannerisms
- Preoccupations with part-objects or non-functional details of the environment
- Distress over changes in small, non-functional details of the environment

Developmental abnormalities must have been present in the first 3 years for the diagnosis to be made

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TABLE **GRADE evaluation of interventions for autism.**

Important outcomes	Global improvement, social function, behavioural function, cognitive function, and adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of early intensive multidisciplinary intervention programmes in children with autism?									
11 (397) [19]	Cognitive function (communication and IQ scores)	Early intensive behavioural interventions v other therapy	2	−2	−1	0	0	Very low	Quality points deducted for uncertain follow-up and for comparison of means. Consistency point deducted for different comparisons
11 (397) [19]	Behavioural function	Early intensive behavioural interventions v other therapy	2	−2	−1	0	0	Very low	Quality points deducted for uncertain follow-up and for comparison of means. Consistency point deducted for different comparisons
1 (28) [21]	Social function	Child's Talk *v* existing care	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (29) [22]	Social function	More Than Words *v* delayed access to programme	2	–1	0	0	0	Very low	Quasi-randomised RCT. Quality point deducted for sparse data
2 (118) [25] [23] [24]	Social function	PECS *v* other treatment or no treatment	4	−3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting, and no subgroup for autism.
1 (22) [26]	Cognitive function	TEACCH *v* usual care	2	–2	0	0	0	Very low	Quasi-randomised study. Quality points deducted for sparse data and baseline differences
What are the effects of dietary interventions in children with autism?									
1 (20) [29]	Global improvement	Advice to follow gluten and casein free diet *v* no dietary advice	4	–2	0	0	0	Low	Quality points deducted for sparse data and baseline differences
What are the effects of drug treatments in children with autism?									
1 (66) [31]	Behavioural function	Methylphenidate *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and uncertainty about clinical relevance of improvement
3 (208) [32]	Behavioural function	Risperidone *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting
6 (242) [36]	Global improvement	Secretin *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for heterogeneous population
What are the effects of non-drug treatments in children with autism?									
No studies found									

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes.

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