Non-pharmacological interventions for autism spectrum disorder in children: an overview of systematic reviews

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Abstract

Objective To assess the effectiveness of non-pharmacological interventions for the treatment of autism spectrum disorder (ASD) in children.

Design Overview of systematic reviews (SRs).

Participants Children aged 12 years and under with ASD.

Search methods In October 2021, we searched Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PsycINFO and Epistemonikos placing no restrictions on language or date of publication.

Interventions 17 non-pharmacological interventions compared with placebo, no-treatment (including waiting list) or other interventions (ie, usual care, as defined by the authors of each study).

Data collection and analysis We rated the methodological quality of the included SRs using A Measurement Tool to Assess Systematic Reviews (AMSTAR 2). We reported the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) certainty of the evidence (CoE) according to the analysis conducted by the authors of the included SRs.

Main outcome measures A multidisciplinary group of experts agreed on analysing nine critical outcomes evolving core and non-core ASD symptoms.

Public and patient involvement statement Organisations of parents of children with ASD participated in external revision of the final version of the report.

Results We identified 52 reports that were within our scope, of which 48 were excluded for various reasons. After excluding less reliable SRs, we included four SRs. Non-pharmacological interventions (ie, Early Intensive Behavioural Intervention, Applied Behaviour Analysis, Picture Exchange Communication System and Naturalistic Developmental Behavioural Interventions) may have favourable effects on some core outcomes including language, social and functioning, play or daily living skills in children with ASD (with either no GRADE assessment, very low or low CoE). In addition, we identified a lack of report for other key outcomes in the included SRs (ie, restricted, repetitive behaviour; play and sensory processing).

Conclusions Synthesised evidence regarding the efficacy of non-pharmacological interventions for children with ASD is scarce. High-quality SRs addressing the variety of both non-pharmacological interventions and relevant outcomes are needed.

PROSPERO registration number CRD42020206535.

Summary box

What is already known about this subject?

- Non-pharmacological interventions are a promising alternative to treat associated and core symptoms of autism spectrum disorder (ASD) in children.

What are the new findings?

- Most systematic reviews (SRs) on this topic were of critical low confidence, according to A Measurement Tool to Assess Systematic Reviews 2.
- Non-pharmacological interventions (ie, Early Intensive Behavioural Intervention, Applied Behaviour Analysis, Picture Exchange Communication System and Naturalistic Developmental Behavioural Interventions) may have favourable effects on some core outcomes including language, social and functioning, play or daily living skills in children with ASD (with either no Grading of Recommendations, Assessment, Development and Evaluation assessment, very low or low certainty of the evidence).
- We identified a lack of report for other key outcomes in the included SRs (ie, restricted, repetitive behaviour; play and sensory processing).

Summary box

How might it impact clinical practice in the foreseeable future?

- Reliable and high-quality synthethised evidence regarding the efficacy of non-pharmacological interventions for children with ASD is scarce.
- In order to inform guidelines, clinicians, parents, policymakers, and other stakeholders, high-quality SRs addressing the variety of both non-pharmacological interventions and relevant outcomes are needed.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterised by an impairment in social communication, and restrictive and repetitive behaviour.[1] In 2016, the Centers for Disease Control and Prevention reported that ASD prevalence was 18.5 per 1000 in children aged 8 years.[2] Recently, the current global prevalence of ASD has been reported at 1%.[3] Beyond the core features of ASD, other behavioural symptoms such as irritability, aggression and self-aggression and impulsivity may be observable throughout life in patients with ASD.[4] Comorbidities are also common, ranging from other neurodevelopmental disorders (eg, attention deficit hyperactivity disorder) to insomnia, mood disorders and anxiety disorders.[3]

Aripiprazole and risperidone are the only two drugs approved by the United States Food and Drug Administration[5 6] for children with ASD, specifically to treat irritability. However, their limited efficacy, rates of adverse events and lack of benefits for core symptoms of ASD[7 8] raise non-pharmacological interventions as a promising alternative with a broader potential.

Non-pharmacological therapies for ASD in children may include educational, behavioural or communication strategies (used alone or in combination) as part of an individualised plan to enhance learning and community participation.[7] Many non-pharmacological interventions have been developed based on theoretical assumptions about the underlying mechanisms at play in the core symptoms of ASD.[9 10] At the same time, a variety of taxonomies has been developed to conceptualise the different non-pharmacological therapies, but no consensus has been achieved so far.[11–13] These interventions aim to improve communication, social skills, daily living skills, play, leisure skills, academic achievement, maladaptive behaviours, among others.[14] Nevertheless, non-pharmacological approaches require the involvement of both family and community support, which are dependent on specific cultural and socioeconomic factors, with additional challenges when implemented in low-income and middle-income countries.[15 16]

Besides the importance of the clinical short-term outcomes during childhood, concerns exist regarding adult life outcomes for ASD.[17] Magiati *et al* has reported unfavourable outcomes for social integration and independence in a large proportion of adult patients with ASD,[18] which highlights the importance of early interventions.[19–21] Indeed, a systematic review found that higher levels of cognitive status in childhood and the presence of early language skills may predict better long-term outcomes in patients with ASD.[18]

Although several systematic reviews (SRs) assessing non-pharmacological interventions have been conducted, they present methodological issues (such as heterogeneity among primary studies) that have not been sufficiently addressed.[11 20 22 23] At the same time, as the body of evidence of both randomised and non-randomised primary studies is growing, an exhaustive assessment of the emerging SRs addressing this topic is needed. Considering also the range of possible interventions for ASD and their potential benefits and limitations, we aim to assess the effectiveness of non-pharmacological interventions for the treatment of ASD in children using the evidence from high-quality SRs.

Methods

This overview of SRs was carried out following a common prospectively registered protocol for both pharmacological and non-pharmacological interventions for children with ASD (PROSPERO CRD42020206535). We followed the updated 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines[24] (see online supplemental appendix 1).

This overview is part of a broader research requested by the Chilean Ministry of Health (see 'Funding statement' section), to exhaustively search for—and quickly provide—evidence from high-quality reviews regarding the effect of some pharmacological and non-pharmacological interventions on critical outcomes (see 'Eligibility criteria' section). In this part, we include our findings on non-pharmacological interventions.

Eligibility criteria

Study design

We included SR as defined by their authors, with a minimum requirement that they followed a method for retrieving and synthesising evidence involving randomised controlled trials relevant to a focused review question, setting eligibility criteria and conducting a systematic search of the literature.

Patient population

We included SRs involving children aged 12 years and under with ASD. We considered the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,[1] International Classification of Diseases, 10th revision[25] or any well-established diagnostic criteria, including Asperger's syndrome, pervasive developmental disorder-not otherwise specified and autistic disorder.

Interventions

Between 26 August 2020 and 11 January 2021, we conducted 11 rounds of consultations with a multidisciplinary group of experts with experience in ASD (including paediatric neurologists, child and adolescent psychiatrists, occupational therapists, psychologists and phonoaudiologists) and with representatives of the Chilean Ministry of Health (further details are available in https://osf.io/9vwdz/). By simple consensus, the experts agreed that 17 interventions were relevant, considering their applicability at a local setting:

- Applied Behaviour Analysis (ABA)
- Early Intensive Behavioural Intervention (EIBI)
- Developmental, Individual Difference, Relationship-based model (floortime)
- Relationship Development Intervention
- Focused Playtime Intervention (FPI)
- Play and Language for Autistic Youngsters
- Improving Parents as Communication Teachers
- Pivotal Response Treatment (PRT)
- Early Start Denver Model (ESDM)
- Joint Attention, Symbolic Play Engagement and Regulation (JASPER)
- Caregiver Skills Training programme

- Video-feedback Intervention to promote Positive Parenting adapted to Autism
- Cognitive Behavioural Therapy
- Prompts for Restructuring Oral Muscular Phonetic Targets
- Picture Exchange Communication System (PECS)
- Treatment and Education of Autistic and Communication-Handicapped Children Autism Programme
- Sensory Integration Interventions

In order to avoid overlapping classes and to disambiguate definitions (eg, between ABA and EIBI), we classified the non-pharmacological interventions considering the SRs' authors definitions and the conceptualisation provided by our advisory board.

Comparison groups included

Placebo, no-treatment (including waiting list) or other interventions (ie, usual care, as defined by the authors of each study).

Outcomes included

The multidisciplinary group of experts agreed on analysing the following critical outcomes (as measured by validated and widely used instruments):

- Autism symptom severity, as measured by validated and widely used scales (ie, Autism Diagnostic Interview-Revised (ADI-R) scale,[26] the Autism Diagnostic Observation Schedule (ADOS),[27] Childhood Autism Rating Scale[28] or the Autism Screening Questionnaire (ASQ)[29]).
- Restricted, repetitive behaviour, as measured by scales such as ADI-R repetitive behaviour domain[26] or ADOS stereotyped behaviour/restricted interests domain.[27]
- Sensory processing, as measured by scales such as the Autism Screening Instrument for Educational Planning.[30]
- Language, as measured by instruments such as the Communication and Symbolic Behaviour Scales Developmental Profile (Caregiver Questionnaire).[31]
- Social communication, as measured by scales such as the Social Communication Assessment for Toddlers with Autism.[32]
- Social functioning, as measured by scales such as ADI-R social domain.[26]
- Play, as measured by instruments such as the Test of Pretend Play.[33]
- Behaviour problems, as measured by scales such as the Child Behaviour Scale,[34] or the Nisonger Child Behaviour Rating Scales.[35]
- Daily living skills, as measured by instruments such as the Vineland Adaptive Behaviour Scales (VABS).[36]

To identify the correspondence of these outcomes with the different scales and measurement instruments used in previous studies, we relied on a UK National Health Service report obtained through the Core Outcome Measures in Effectiveness Trials (COMET) initiative platform for Core Outcomes Sets as a framework.[37] Nevertheless, we considered other scales or instruments for these outcomes if reported in any included SR.

Excluded studies

We excluded primary studies (with observational, experimental or pseudo-experimental designs) and non-SRs of the literature (scoping reviews, narrative reviews, among others), as well as SRs with critically low confidence as assessed by A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2).[38] SRs rated higher than critically low according to AMSTAR 2 were excluded if we identified another more reliable SR addressing the same clinical question. We did not include SRs which did not provide outcome data regarding the population and interventions of interest (neither in the main analysis or subgroup analyses).

We placed no restrictions on language or publication date.

Search strategy for identification of studies

We searched the following databases from inception with no restrictions on date, language or publication status:

1. Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online, searched 22 October 2021.
2. Medline (Ovid MEDLINE), searched from 1946 to 22 October 2021.
3. Embase (Elsevier.com), searched from 1947 to 22 October 2021.
4. PsycINFO (Ebsco), searched on 22 October 2021.
5. Epistemonikos, searched on 22 October 2021.

For our search in Medline (Ovid), we used a high-sensitivity filter developed by Cochrane that allows us to identify randomised clinical trials while maximising sensitivity and precision[39] and a filter to retrieve SR and meta-analysis developed by the Health Information Research Unit of McMaster University for Medline (Ovid) and Embase (Elsevier.com) databases.[40] The filter for clinical trials was adapted for use with Embase (Elsevier.com) and PsycINFO (Ebsco). Each search strategy, together with its corresponding filter, is detailed in online supplemental appendix 2.

Selection of studies

Two authors independently screened the results of the electronic search by title and abstract. We obtained the full-text versions of the reviews that were deemed appropriate and applied the selection criteria to determine final inclusion. We resolved any disagreements between review authors through discussion. Where resolution was not achieved, a third overview author considered the review in question, and we made a majority decision. This step was carried out on the Rayyan platform.[41]

Data collection

We entered the selected studies into a data extraction form (elaborated in Google Sheets, Google). For this stage, we carried out a pilot test on a random sample of 175 records (randomly retrieved from results of electronic searches described above), in which the authors discussed the adoption of agreed criteria.

The data extracted from the included SRs were: (1) participants: age (range); (2) intervention and comparison; (3) outcomes: outcomes of interest, scales or instruments used for measurements; (4) study characteristics: first author, year of publication and number of primary studies included.

We extracted the effect sizes from meta-analyses or, if not available, of single studies included in SRs reporting an effect measure (either in the main analysis or a subgroup analysis) for each non-pharmacological intervention and outcome of interest.

We collected dichotomous effect measures such as risk ratios or ORs and continuous measures of treatment effect such as mean differences (MD) or standardised MD (SMD)—in case of an SR included different scales or instruments for measuring a given result (with a consistent direction of effect, according to each scale). We considered the corresponding 95% CIs for each effect estimation, as well.

Summary of results and appraisal of systematic reviews

Two authors independently rated the methodological quality of the included SRs using AMSTAR 2.[38] In the event of discrepancies, the final assessment was resolved by a third author.

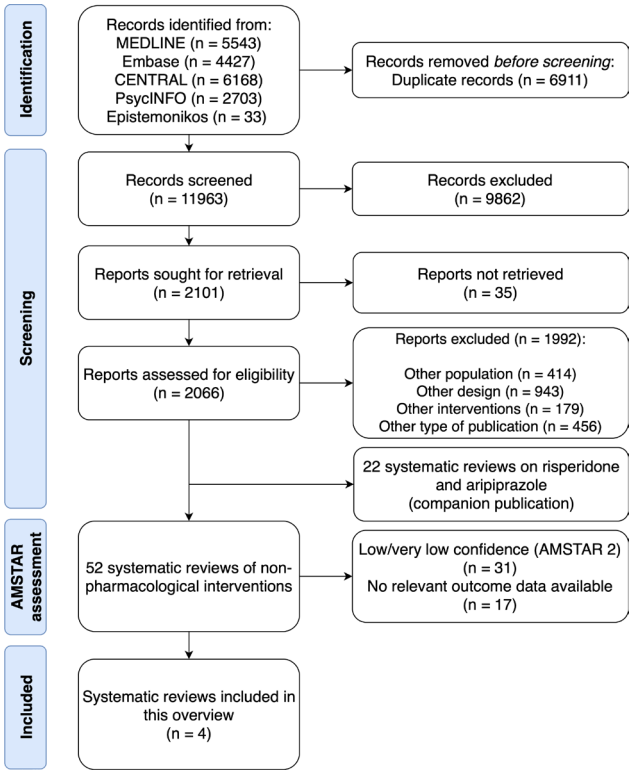

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of identification, screening and inclusion processes. AMSTAR 2, A Measurement Tool to Assess Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials.

We extracted the findings in summary tables based on population characteristics, intervention, comparison, critical outcomes and effect measures. As mentioned above, we prioritised data from the most reliable SRs for each clinical question, according to AMSTAR 2.

If available, the certainty of the evidence (CoE) was reported for each outcome as per the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[42] analysis conducted by the authors of the included SRs.

We did not map the studies within the included SRs nor analyse overlap among primary studies because we included the highest quality SR for each intervention. If we had found two high-quality SRs for a single intervention, we would have mapped and analysed overlap.

Results

We retrieved a total of 18 874 articles (figure 1). After deduplication, we screened 11 963, of which 2066 were assessed by reading the full text. We identified 52 reports that were within the scope of this overview.

Of these, we excluded 17 reviews for problems related to outcome data. Ten studies did not report disaggregated data of interest to our review due to pooling of different study designs (three SRs), populations (two SRs), interventions (five SRs) or outcomes (two SRs). Moreover, some reviews did not report any quantitative data (two SRs) or focused on outcomes unrelated to our review question (three SRs), such as the role of oxytocin, intellectual quotient and adaptive behaviour. We also excluded 31 SRs that were rated as being of critically low confidence according to AMSTAR 2 (see table 1).

Confidence in the results of the included systematic reviews

Of the five SRs that did not rate as critically low according to AMSTAR 2 (see table 1), we included one SR analysing the effects of ABA,[43] and another assessing PECS and FPI.[44] Of two SRs evaluating the effects of EIBI,[45 46] we included Reichow *et al* (rated as high confidence)[45] instead of Makrygianni and Reed (rated as low confidence).[46] We also decided to include one SR[47] gathering PRT, ESDM and JASPER (in addition to Learning Experiences and Alternate Model, and Joint Attention/Imitation, among others) into the Naturalistic Developmental Behavioural Interventions (NDBI) category. Table 2 shows the main characteristics of the included SRs.

The online supplemental appendixonline supplemental appendix presents details about excluded studies (https://osf.io/9vwdz/).

Figure 1 presents the PRISMA flow chart showing the details of the selection process.

Main results of each non-pharmacological intervention

Early Intensive Behavioural Intervention

The results below are based on the findings of a high confidence SR.[45]

EIBI may cause little to no difference in the severity of autism symptoms compared with control at 24 months follow-up, but we are very uncertain (SMD −0.34, 95% CI −0.79 to 0.11, 2 studies, 81 participants, very low CoE). The instruments used to measure this outcome included ADI-R and ASQ.

EIBI may improve language (ie, expressive language) compared with control at 24 to 36 months follow-up (SMD 0.51, 95% CI 0.12 to 0.90, 4 studies, 165 patients, low CoE). The instruments used to measure this outcome included the Expressive Vocabulary Test[48] and Developmental Profile.[49]

EIBI may increase social functioning compared with control, after 24–35 months (MD 6.56 points, 95% CI 1.52 to 11.61, 5 studies, 201 patients, CoE not available). The measurement instrument used was VABS socialisation subscale.[36]

EIBI may cause little to no difference in behaviour problems compared with control at 24–36 months (SMD −0.58 SD, 95% CI −1.24 to 0.07, 2 primary studies, 67 patients, very low CoE). The instruments used were: the Child Behaviour Checklist[50] and the Developmental Behaviour Checklist.[50 51]

EIBI may improve daily living skills compared with control at 24–36 months (MD 9.58 points, 95% CI 5.57 to 13.60, 5 studies, 201 participants, CoE not available). The measurement instrument used was VABS daily living skills subscale.[36]

No data were found for repetitive or restrictive behaviour, sensory processing, social communication or play.

Applied Behaviour Analysis

The following results are based on data extracted from Virués-Ortega (a low confidence SR).[43]

ABA may improve expressive language (SMD 1.47, 95% CI 0.85 to 2.08, 10 studies, 164 participants, follow-up and CoE not available). The scales used included the British Picture Language Scale[52] and the Clinical Evaluation of Language Fundamentals.[53]

ABA may also improve social communication (MD 1.45, 95% CI 0.02 to 1.88, CoE not available) and social functioning (MD 0.95, 95% CI 0.53 to 1.37, follow-up and CoE not available). Moreover, ABA may improve daily living skills (MD 0.62 95% CI 0.3 to 0.93, follow-up and CoE not available). This was based on 11 studies with 301 participants assessed with the VABS communication, socialisation and daily living skills subscales.[36]

Table 1 Quality assessments of the potentially eligible systematic reviews, according to the AMSTAR 2 tool

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Overall certainty
Baril 2017[67]	N	N	N	PY	N	N	PY	PY	N	Y	–	–	N	N	–	N	Critically low
Bassett 2001[68]	Y	PY	N	PY	Y	N	N	Y	Y	N	–	–	N	N	–	N	Critically low
Binns 2019[69]	N	N	N	N	Y	Y	PY	PY	N	N	–	–	N	Y	–	Y	Critically low
Bradshaw 2014[70]	N	N	N	PY	Y	Y	N	PY	N	N	–	–	N	N	–	N	Critically low
Brignell 2018[44]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	–	–	Y	Y	–	Y	High
Caron 2017[71]	N	N	N	PY	N	N	N	PY	N	N	–		N	N	–	N	Critically low
Carruthers 2020[72]	Y	N	N	PY	Y	N	N	PY	N	N	–	–	N	N	–	Y	Critically low
Eldevik 2009[73]	N	N	N	N	Y	Y	PY	N	N	N	Y	Y	N	N	N	N	Critically low
Factor 2019[74]	N	N	N	N	N	Y	PY	Y	N	N	–	–	N	Y	–	Y	Critically low
Lima Antão 2018[75]	Y	N	N	N	N	N	PY	PY	N	N	–	–	N	N	–	Y	Critically low
Flippin 2010[76]	Y	N	N	N	Y	N	N	PY	N	N	–	–	N	N	–	N	Critically low
Forbes 2020[77]	Y	N	Y	N	N	Y	N	N	N	N	–	–	N	N	–	Y	Critically low
French 2017[78]	Y	N	N	N	N	N	PY	N	Y	N	–	–	Y	Y	–	Y	Critically low
Fuller 2020[79]	Y	N	N	N	N	Y	N	N	PY	Y	N	N	N	N	N	Y	Critically low
Gwin 2018[80]	N	N	N	N	N	N	N	N	N	N	–	–	N	N	–	N	Critically low
Lake 2020[81]	Y	N	Y	N	Y	N	N	PY	PY	Y	–	–	N	N	–	Y	Critically low
Lang 2010[82]	N	PY	N	N	Y	Y	N	N	PY	N	–	–	N	N	–	Y	Critically low
Magiati 2013[83]	N	N	N	N	N	N	N	N	N	N	–	–	N	N	–	Y	Critically low
Makrygianni 2010[46]	Y	PY	Y	N	N	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N	Low
Fernandes 2013[84]	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Critically low
Ospina 2008[85]	N	Y	N	N	Y	Y	N	PY	Y	Y	Y	N	N	N	N	Y	Critically low
Perihan 2020[86]	Y	N	N	N	N	Y	N	PY	N	N	N	N	N	N	N	Y	Critically low
Reichow 2018[45]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Rodgers 2020[87]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Critically low
Ryberg 2015[88]	Y	N	N	N	N	N	N	PY	N	N	–	–	N	N	–	Y	Critically low
Sandbank 2020[89]	Y	N	N	PY	N	N	N	N	PY	N	N	Y	Y	Y	Y	N	Critically low
Schoen 2019[90]	N	N	N	N	Y	Y	Y	PY	N	N	–	–	N	N	–	Y	Critically low
Shalev 2019[91]	N	N	N	N	Y	Y	PY	PY	N	N	–	–	N	Y	–	Y	Critically low
Shi 2021[92]	Y	PY	Y	N	Y	Y	N	Y	PY	N	N	Y	Y	Y	Y	Y	Critically low
Spreckley 2008[23]	Y	N	N	PY	N	N	N	PY	PY	N	N	N	N	N	N	Y	Critically low
Sukhodolsky 2013[93]	Y	PY	N	N	Y	Y	N	PY	PY	N	Y	N	N	Y	Y	Y	Critically low
Tiede 2019[47]	Y	PY	Y	N	Y	Y	Y	PY	PY	N	Y	Y	Y	Y	Y	Y	Low
Virués-Ortega 2010[43]	Y	N	Y	PY	Y	N	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	Low
Wang 2020[94]	Y	N	Y	N	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Warren 2011a[95]	Y	N	N	N	Y	Y	Y	Y	PY	Y	–	–	Y	N	–	Y	Critically low
Warren 2011b[96]	N	PY	Y	N	Y	Y	N	N	Y	N	–	–	Y	N	–	Y	Critically low

1. Did the research questions and inclusion criteria for the review include the components of PICO? 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? 3. Did the review authors explain their selection of the study designs for inclusion in the review? 4. Did the review authors use a comprehensive literature search strategy? 5. Did the review authors perform study selection in duplicate? 6. Did the review authors perform data extraction in duplicate? 7. Did the review authors provide a list of excluded studies and justify the exclusions? 8. Did the review authors describe the included studies in adequate detail? 9. Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review? 10. Did the review authors report on the sources of funding for the studies included in the review? 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? 13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? 15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? We use '–' in case an AMSTAR 2 question does not apply.

AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2; N, no; PN, probably no; PY, probably yes; RoB, risk of bias; Y, yes.

No information was found on severity of autism symptoms, restrictive or repetitive behaviour, sensory processing, play or behaviour problems.

No information was found regarding severity of autism symptoms, repetitive or restrictive behaviour, sensory processing, daily living skills, play, social functioning or behaviour problems.

Picture Exchange Communication System

The following results are based on the findings of Brignell *et al* (a high confidence SR).[44]

In language (expressive), participants in the PECS group may initiate verbal and non-verbal communication 2.73 more times per minute compared with control after 7.5–10.7 months (OR 2.73, 95% CI 1.22 to 6.08, 1 study, 84 participants, very low CoE).

In social communication, PECS may result in little to no difference in reciprocal social interaction events considered as any change in the communication or reciprocal social interaction subscales of the ADOS-Generic,[27 44] at 7.5–10.7 months (OR 0.55, 95% CI 0.25 to 1.19, 1 study, 84 participants, very low CoE).

Naturalistic interventions: Naturalistic Developmental Behavioural Interventions

The following results are based on the findings reported by Tiede and Walton (a low confidence SR).[47]

NDBI interventions may reduce the severity of autism symptoms compared with control (SMD –0.38, 95% CI –0.71 to –0.04, nine studies, number of participants and CoE not available). The measurements used included the ADOS Calibrated Severity Score[27 44] and the Social Responsiveness Scale.[54]

NDBI may improve expressive language (SMD 0.32, 95% CI 0.07 to 0.56, twelve studies, number of participants and CoE not available). The scales used to measure this outcome included the

Table 2 Main characteristics of the included systematic reviews

Study	Primary studies (n)	Patients' age	Interventions	Comparison	Outcomes assessed	GRADE CoE
Tiede G 2019 [47]	29	≤6 years	Naturalistic Developmental Behavioural Interventions: JASPER, ImPACT, RIT spectrum support programme, ESDM, PRT, among others	Usual care	Autism symptoms severity; language; social communication; play; daily living skills	Not assessed
Brignell *A 2018* [44]	2	≤12 years	Picture Exchange Communication System, Focused Playtime Intervention	Usual care	Language	Assessed
Reichow B 2018[45]	5	≤6 years	Early Intensive Behavioural Intervention	Usual care	Autism symptoms severity; language; social functioning; behaviour problems; daily living skills	Assessed
Virués-Ortega J 2010 [43]	22	26–49 months	ABA	Eclectic intervention*	Language; social communication; daily living skills	Not assessed

*Citation from Virués-Ortega[43]: '…eclectic intervention or a combination of standard interventions including Treatment and Education of Autistic Children and related Communication Handicapped Children special education classes and sensory integration therapy; public school special education group; regular school; low-intensity ABA intervention; any specific intervention'.

ABA, Applied Behaviour Assessment; CoE, certainty of evidence; ESDM, Early Start Denver Model; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; ImPACT, Improving Parents as Communication Teachers; JASPER, Joint Attention, Symbolic Play Engagement and Regulation; PRT, Pivotal Response Treatment; RIT, Rochester Institute of Technology.

ADOS 6-point scale derived from total language items (ADOS language)[27 44] and the Communication and Symbolic Behaviour Scales.[55]

NDBI may also have a favourable effect on social communication (SMD 0.65, 95% CI 0.37 to 0.93, number of participants and CoE not available). The scales used to measure this outcome included parent child interaction joint engagement[56] and teacher child interaction joint engagement.[57] Moreover, NDBI also improved play skills (SMD 0.23, 95% CI 0.04 to 0.41, number of participants and CoE not available) measured with instruments including the Structured Play Assessment[58] and Short Play and Communication Evaluation.[59]

NDBI may result in little to no difference in daily living skills (SMD 0.09, 95% CI −0.24 to 0.42, five studies) VABS daily living skills subscale.[36] Neither the number of participants nor CoE was reported.

No information was found on social functioning, behaviour problems, sensory processing or repetitive, restrictive behaviour.

Focused Playtime Intervention

Results for FPI are based on the findings of Brignell *et al*(a high confidence SR).[44]

FPI may cause little to no difference in expressive language compared with control at 20–21 weeks (p=0.23, 1 study, 70 participants, GRADE CoE very low). The Mullen Scales of Early Learning-Expressive Language Index[60] was used.

No information was found regarding severity of autism symptoms, repetitive or restrictive behaviour, sensory processing, social communication, social functioning, behaviour problems, play or daily living skills.

We synthesise these results in table 3.

Discussion

We included four SRs that met our criteria regarding confidence according to AMSTAR 2: one assessed EIBI,[45] one assessed NDBI,[47] another analysed ABA[43] and one addressed both PECS and FPI.[44] No SRs regarding other interventions met our criteria to be included in this overview.

Starting a new intervention implies costs for both child and caregiver—whether they be emotional, financial, in terms of time spent or others. The intense marketing directed at families and patients' organisations generates further confusion,[61] so it is of the utmost importance that we provide and promote information to help families and clinicians make an informed therapeutic decision.[62] SRs may inform clinicians, patients, families and other stakeholders' decision-making providing aggregated and critically appraised evidence from randomised clinical trials or other clinical study designs.[63] Nevertheless, interventions for ASD offered by health systems are not always evidence-based.[64]

In our overview of SRs, only EIBI and NDBI showed a possible improvement in the severity of symptoms of autism, while language may be improved by EIBI, ABA, PECS and NDBI. Social functioning may be improved by using ABA and EIBI, and behaviour problems may be improved only by using EIBI, but these judgements reached low or very low CoE. We found no data for effects on repetitive behaviours or sensory processing. Both social communication and play may improve using EIBI, NDBI and ABA, but we are not certain. EIBI and ABA may increase daily living skills, but again, we are uncertain. Only the SRs evaluating EIBI,[45] FPI[43] and PECS[43] conducted GRADE assessments.

Our results are partially consistent with a preprint by Trembath *et al*,[65] who found EIBI, PECS and NDBI to have a favourable effect on expressive language (with low or moderate quality), and EIBI to have a favourable effect on daily living skills (low quality). However, Trembath *et al*[65] considered a different range of outcomes and non-pharmacological interventions. Furthermore, they did not conduct GRADE assessments, and they used a modified version of a Joanna Briggs Institute tool for quality appraisal (instead of AMSTAR 2), thus establishing several differences with our report.

One possible limitation of this overview is that since our search and screening was limited to SRs, we were unable to retrieve any possible methodologically rigorous clinical trials not included in SRs. At the same time, we did not consider single-case designs, which may constitute an important source of evidence on interventions for ASD.[66] Additionally, there were many interventions for which no reliable SR existed. We had minor deviations from our protocol: we initially drafted a set of outcomes, but after consultation with the multidisciplinary group of experts and with representatives of the Chilean Ministry of Health, we modified four of these to fit the needs of the stakeholders. Furthermore, we aimed to extract long-term data

Table 3 Summary of main results of non-pharmacological interventions

Intervention Study (AMSTAR 2 confidence)	Effect (GRADE CoE)								
	Severity of autism symptoms	Restricted, repetitive behaviour	Sensory processing	Language	Social communication	Social functioning	Play	Behaviour problems	Daily living skills
EIBI Reichow *et al*[45] (high confidence)	No effect (very low CoE)	–	–	Favours EIBI (low CoE)	–	Favours EIBI (no GRADE assessment)	–	No effect (very low CoE)	Favours EIBI (no GRADE assessment)
ABA Virués-Ortega[43] (low confidence)	–	–	–	Favours ABA (no GRADE assessment)	Favours ABA (no GRADE assessment)	Favours ABA (no GRADE assessment)	–	–	Favours ABA (no GRADE assessment)
PECS Brignell *et al*[44] (high confidence)	–	–	–	Favours PECS (very low CoE)	No effect (very low CoE)	–	–	–	–
NDBI Tiede and Walton[47] (low confidence)	Favours NDBI (no GRADE assessment)	–	–	Favours NDBI (no GRADE assessment)	Favours NDBI (no GRADE assessment)	–	Favours NDBI (no GRADE assessment)	–	No effect (no GRADE assessment)
FPI Brignell *et al*[44] (high confidence)	–	–	–	No effect (very low CoE)	–	–	–	–	–

We used '–' in case data were not reported.

ABA, Applied Behaviour Analysis; AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2; CoE, certainty of evidence; EIBI, Early Intensive Behavioural Intervention; FPI, Focused Playtime Intervention; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; NDBI, Naturalistic Developmental Behavioural Interventions; PECS, Picture Exchange Communication System.

and disaggregated data by age, but we were limited by the scarcity of the available evidence. We found that most of the retrieved SRs were of low quality, as rated using AMSTAR 2, and many of them did not comply with PRISMA guidelines either.

A major deviation from our protocol is that we did not include pharmacological interventions in this overview: we drafted a common protocol for two overviews (this one, and other comprehending pharmacological interventions), part of a broader project commissioned by the Chilean Ministry of Health (see 'Funding statement' section). Another deviation from the protocol is that we mentioned that we will include randomised clinical trials (and searched CENTRAL), which was modified because of subsequent requirements of the ministerial counterpart to focus only on SRs.

The main strengths of this overview are the comprehensive nature of the search and the assessment of the included SRs in terms of quality using a widely accepted tool (ie, AMSTAR 2), which provides a very complete report on each decision. Other strengths include: the prospective record of the protocol in PROSPERO for greater transparency, our compliance with the PRISMA statement and our extensive and sensitive search using a consensus algorithm. Yet another strength is the inclusion of nationwide experts for the definition of the core outcomes and interventions of interest, and the inclusion of patients (see 'Public and patient involvement statement' section). Furthermore, patient organisations approved the final version of our evidence synthesis with no further comments.

Findings regarding four non-pharmacological interventions (EIBI, ABA, PECS and NDBI), with favourable effects in some outcomes, with low or very low CoE, remain challenging. Additional high-quality randomised clinical trials are needed to contribute to reliable updated and rigorous synthesised evidence to inform decision makers and other stakeholders. Despite the reported benefits, clinicians, parents and caregivers need to monitor the harms and benefits of all the therapies on offer to manage ASD over time.

Synthesised evidence regarding the efficacy of non-pharmacological interventions for children with ASD is limited. High-quality SRs addressing the variety of both non-pharmacological interventions and relevant outcomes are needed. Prior, an exhaustive scoping review may be required to clarify (and to disambiguate) and schematise the different non-pharmacological interventions, their approaches and their classes or subclasses.

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