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Systematic review of autistic representation in the treatment literature for pediatric chronic pain

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ABSTRACT

Chronic pain disproportionately affects autistic children and young people, yet they are underrepresented in pain research. Research on psychological, physical, and pharmacological therapies for other conditions suggests modifications are required to ensure treatment accessibility and efficacy for autistic individuals. However, no such evidence base has been synthesized in pediatric pain. The aim of this review was to (1) review existing "gold-standard" treatment literature for pediatric chronic pain to determine the representation of autistic participants, and (2) review literature on treatment of chronic pain specifically in autistic children and young people to describe the current evidence landscape and identify next directions for research. 16.7% (12/72) of randomized controlled trials included in Cochrane reviews of interventions for pediatric chronic pain explicitly excluded youth with a developmental delay/disability, of which only 8.3% specifically named autism. However, 52.8% of Cochrane-included trials had criteria or protocols which may have disproportionately impacted autistic participants, such as excluding intellectual disability, psychiatric conditions, medical conditions, and/or requiring participants to communicate verbally. Twenty-nine studies of treating chronic pain in autistic children and young people were identified, of which the majority were case reports (k = 27, 93%) with large variation in pain condition, intervention applied, and outcomes measured. Given the high prevalence of chronic pain in autistic children and young people, there is an ethical imperative to ensure their representation in intervention trials, co-develop interventions that address the specific needs of autistic individuals who live with pediatric chronic pain, and to increase accessibility in chronic pain research more broadly.

Registration: PROSPERO: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=491423 registered March 19 2024.

Open Science Framework: https://osf.io/8na64/ registered December 18, 2023

Perspective: Autistic children and young people (CYP) are not represented in reviews of chronic pain treatments, and the literature on treating chronic pain specifically in this population is so variable no clear conclusions can be drawn. Efforts to increase accessibility of chronic pain interventions and research for autistic CYP is needed.

Introduction

Chronic pain refers to pain that lasts over 3 months and is a large-scale health issue in children and young people (CYP). The highest standard of evidence, meta-analysis of randomized controlled trials (RCTs), supports the use of psychological, physical, and pharmacological approaches to treating pediatric chronic pain. However, as pain is affected by social, biological, and psychological factors, appropriate treatment must be unique to each person.

Chronic pain disproportionately affects autistic CYP. In the general population, rates of chronic pain are higher in autistic (15.6%) compared to nonautistic CYP (8.2%).[1] Compared to the general

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population prevalence of 1–2% with an autism diagnosis,[2] patients receiving services at tertiary pain care centers are reported to have higher rates of autism diagnoses (9%) as well as more autistic traits (14–21%).[3,4] The diagnostic criteria for autism refer to differences in social communication that may impact communication between the CYP and their caregivers/healthcare team for assessment and treatment, and differences in sensory experiences and behaviours that may include hyper- or hypo-responsivity to pain and increased pain-related anxiety.[5–7] Autistic CYP have unique experiences of pain that may inform their need for tailored treatment approaches, such as sensory processing challenges, differences in coping (e.g., engaging in routine and ritualistic behaviours), or isolation and difficulty relating to nonautistic youth with chronic pain.[4,8] Autistic CYP may also exhibit unique strengths in managing their pain, if provided an affirming environment in which to harness such attributes (e.g., incorporation of treatment into a routine, special interests in understanding their condition). Despite their unique needs and overrepresentation in pain samples, autistic CYP have been historically underrepresented in chronic pain research, particularly with respect to treatment.

Research on the use of psychological, physical, and pharmacological therapies for treating other conditions in autistic populations suggests that modifications are required to maximize treatment accessibility and efficacy in these populations. Such modifications include slower pacing of sessions, reducing uncertainty, increasing provider knowledge of autism, adapting communication, environmental sensory adaptations, understanding differences in body perception and embodied movement, using instructional-based learning for physical activity, and considering the role of polypharmacy.[9–13]

A recent scoping review identified key intervention elements for the management of procedural pain and anxiety in autistic CYP.[14]These include preprocedural preparation through habituation and coping skills, direct pain management (e.g., distraction, relaxation, positive reinforcement, anesthetics or sedation, ice, vibration), organizational interventions (e.g., adapting the sensory environment of the care setting), in the context of a collaborative relationship between autistic CYP, parents, and health care providers. Notably, only 30 articles were identified, including grey literature, and spanned a variety of designs, settings, and sample characteristics. The authors were unable to comment on intervention effectiveness, or risk of bias in research.[14] No such evidence base has been synthesized specific to the treatment of pediatric chronic pain. While rigorous reviews have been conducted examining the efficacy in autistic populations of many treatments also used for chronic pain (e.g., anti-depressants, cognitive-behavioural therapy),[15–17] or to examine the treatment of related experiences (i.e., irritability),[18] pain has not been examined as an outcome.

The aim of the present study is to (1) review the existing "gold-standard" treatment literature for pediatric chronic pain to determine the representation of autistic children and youth, and (2) review the available literature on treatment of chronic pain specifically in populations of autistic children and youth to describe the current evidence base and next directions for research.

Methods

The study team included people with living experience as an autistic individual, caregiving experience of an autistic child, living experience of other forms of neurodivergence and chronic illness, and research and clinical experience in autism, developmental pediatrics, clinical psychology, physiotherapy, rehabilitation, and pain medicine.

This review's protocol was registered on the PROSPERO register of systematic reviews (#491423) and OSF. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline[19] for reporting.

Search strategy

The search strategy was developed in collaboration with a Research Librarian and the larger research team. See Supplemental File 1 or on searchRxiv (https://doi.org/10.1079/searchRxiv.2024.00611) for all the search strategies used in the review.

For Part 1 of the review, the research team searched the Cochrane Library on October 28, 2023 for existing Cochrane reviews focusing on the treatment of pediatric chronic pain. All RCTs found in these reviews were included, except for non-English publications,[20] as the team did not have the resources to pursue translation.

For Part 2, a search was conducted of the following: MEDLINE (Ovid), Embase (Ovid), PsycINFO (EBSCO), CINAHL (EBSCO), Scopus, PEDro and Google Scholar on December 18, 2023. Grey literature was sought from the WHO International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, Proquest Dissertations & Theses Global, Networked Digital Library of Theses and Dissertations (NDLTD), Papers First (OCLC FirstSearch) and Proceedings (OCLC FirstSearch). The search was not limited by language or by publication date. The search strategy used a modified pediatric search filter to narrow to the pediatric and young adult population.[21] References of the relevant reviews were searched, and the team used Scopus to search the references and citing articles of all included studies.

Eligibility criteria and screening

For Part 1, the eligibility criteria for included RCTs were predetermined by the Cochrane reviews.

For Part 2, the eligibility criteria set included primary studies of any design that assessed outcomes related to the treatment of chronic or recurrent pain (pain that persists or recurs for at least 3 months). The mean age of participants had to be within 0 and 25 years, at least a subset of participants (no a priori threshold specified) must have a diagnosis of autism spectrum disorder[1] and chronic pain (inclusive of conditions with pain as a primary feature), intervention targets the management/reduction of pain or pain-related functioning, the manuscript presents original data and is available in English. Before screening, the study inclusion/exclusion criteria were piloted by a study author (K.E.B.). All references from the search were uploaded to Covidence software and duplicates were removed. The titles and abstracts of all references were screened by 2 independent reviewers (K.E.B., C.P., K. L., B.D.). The full texts of the references were then uploaded into Covidence and were reviewed by 2 independent reviewers (C.P., K.E.B., K. L., A.H.). Any conflicts at both stages were resolved through consensus.

Data extraction

In Part 1, data extraction was conducted by 2 coauthors (K.E.B. and A.H.) using an author-developed data extraction tool on Covidence. The tool collected data focusing on the exclusion of autistic communities in the included articles and was piloted by a study author (K.E.B.) on one RCT from each of the Cochrane reviews prior to extraction. The data extraction tool collected: (a) explicit exclusion criteria (i.e., where the authors specifically stated that they excluded young people with a developmental delay, autism, or similar diagnostic label) and terminology used in the article, (b) implicit exclusion criteria and the terminology used, and (c) the sample size of autistic participants if applicable.

[1] This manuscript preferentially uses identity-first language and the term 'autistic' to describe the sample after considering the research in this area[85] and the preferences of team members with lived experience. However, for the purpose of clarifying the population of interest (specifically children and young people who had received a formal diagnosis of autism) the diagnostic term is used where necessary to differentiate from participants who self-identified without a diagnosis or were reported to have autistic traits.

Implicit exclusion was defined as any criteria that may disproportionately impact autistic CYP (i.e., they may be more likely to be represented in these criteria than nonautistic CYP), such as presence of an intellectual disability, co-occurring conditions, requiring verbal communication, etc.[2,22–25] RCTs were screened and extracted by 2 independent reviewers (K.E.B. and A.H.), with conflicts resolved through discussion and a third reviewer if necessary. Risk of bias was not assessed for the included RCTs, as they previously went through risk of bias assessments in their relevant Cochrane reviews. In a deviation from protocol, the team did not contact authors to obtain data specific to autistic CYP as none of the articles indicated that this was measured or might be available.

In Part 2, a data extraction tool was developed by an author (K.E.B.) for usage on Covidence and was piloted on studies identified during development of the search strategy. This tool collected the following data: (a) study design (type of study, publication venue, if the study would meet the criteria for Cochrane review inclusion, if the study specifically looked at autistic populations/needs, exclusion criteria); (b) study setting (country/region of study setting, type of setting); (c) participant characteristics of the autistic sample (sample size, age, sex, gender, race, ethnicity, pain-related diagnoses, co-occurring conditions); (d) intervention characteristics (name, classification, description of intervention, description of control/placebo/comparator, duration of intervention, accessibility/autism-related modifications of the protocol), and (e) efficacy domains (outcomes measured, who is reporting, time points of measurement, narrative summary of efficacy outcomes and effect sizes, adverse effects). Using this tool, reviewers (K.E.B., A.H., C.P.) independently read and extracted data from the papers included. Consensus was needed from 2 reviewers, and conflicts were discussed, and a third reviewer consulted if necessary.

Critical appraisal was conducted using the Mixed Methods Appraisal Tool (MMAT) version 18, to assess risk of bias in the present review. This tool was selected as it allows for the same measure to be used across mixed study types. Each study was evaluated against the MMAT criteria; however, each type of study included unique criteria (e.g., RCTs have different criteria than qualitative, quantitative descriptive, or quantitative non-randomized trials). The MMAT was scored by two independent reviewers (K.E.B., A.H., C.P.), with disagreements resolved through discussion or including a third reviewer if needed. Scoring consisted of "yes", "no", and "can't tell" answers to study-specific questions about analysis, sampling, methods, etc. As the use of an overall score in the MMAT to summarize and/or exclude studies is discouraged, instead the ratings for each criterion is presented for each study to provide an overall description of the methodological quality of the included studies.

Data synthesis

In Part 1, explicit and implicit exclusion were categorized based on the reasons identified in the papers.

For Part 2, the team conducted a narrative synthesis of findings. Insufficient data and significant heterogeneity meant the team was unable to separate by co-occurring intellectual disability, painful condition type, intervention type, and study focus. The state of the literature over time was summarized by publication date. Pain-related outcomes were grouped using the Pediatric Chronic Pain Clinical Trials core outcomes.[26] Given that the intention was to demonstrate the diversity of methods used in examining treatment of chronic pain in autistic CYP, the research team did not prioritize any specific results, but rather reported the MMAT scores for each criterion for each study. Informal methods were used to investigate heterogeneity, such as ordering tables by participant characteristics and intervention characteristics.

Results

Part 1: representation of autistic participants in Cochrane reviews of pediatric chronic pain treatments

Search results

For Part 1, the search retrieved 41 Cochrane reviews. 33 reviews were excluded as they did not focus on the treatment of chronic pain in youth, leaving 8 reviews[27–34] included in this review. Of the 8 Cochrane reviews, 74 RCTs were extracted, of which one was a duplicate. Of the 73 RCTs, one was excluded as it was not reported in English, which left 72 RCTs. See Fig. 1 for a PRISMA flow chart of the review and study inclusion process.

Representation of autistic participants

None of the RCTs in Part 1 reported having any autistic CYP represented in the study sample.

Explicit exclusion of autistic participants

In Part 1, 12 (17%) RCTs included explicit exclusion criteria towards autistic CYP. Of those with explicit exclusion criteria, only one specifically mentioned autism; the rest excluded based on developmental delay or impairment. The RCTs containing explicit exclusion criteria were all from the Cochrane reviews focused on psychotherapy (75% from the review on face-to-face psychotherapy[29] (k = 9), and 25% from the review on remotely delivered psychotherapy[28] (k = 3)).

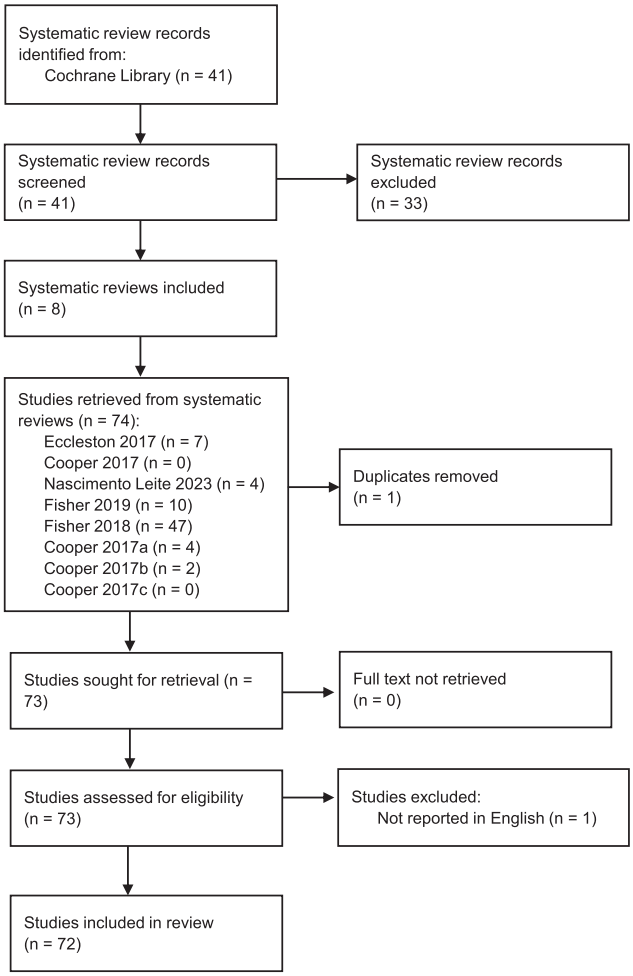

Fig. 1. PRISMA flow diagram for Part 1.

Implicit exclusion of autistic participants

38 (53%) of RCTs did not have *explicit* exclusion criteria but did have *implicit* exclusion criteria. Reasons for implicit exclusion were as follows: requiring participants to be "otherwise healthy" or have no co-occurring conditions (k = 31, 43% of total sample), requiring participants be "English-speaking" or equivalent (k = 9, 13%), excluding those with cognitive impairments (k = 5, 7%), requiring verbal communication (k = 7, 10%), excluding those with conditions that would impact participation (k = 4, 6%), requiring participants adhere to protocol (k = 3, 4%), and requiring scores below clinical threshold on the Child Behaviour Checklist (k = 1, 1%).

Of the 38 RCTs with implicit but no explicit exclusion, 23 were from RCTs of in-person psychotherapy (61%), 6 from RCTs of remotely delivered psychotherapy (16%), 3 from RCTs of non-steroidal anti-inflammatories (NSAIDs; 8%), 1 from an RCT of anti-epileptic medications (3%), 3 from RCTs of anti-depressant medications (8%), and 2 from RCTs of physical therapy and education (5%).

See Supplemental File 2 for a description of implicit and explicit exclusion by RCT. Refer to Fig. 2 for a visual representation of exclusion criteria represented in RCTs over time.

Part 2: Available literature on the treatment of pediatric chronic pain in autistic children and young people

Search results

For Part 2, the search retrieved 3953 records after duplicates were removed and a further 46 records were identified through citation searching. The team excluded 3703 of the records during title and abstract screening. 296 full text were sought for retrieval and 8 could not be retrieved. 288 reports were assessed for eligibility and 259 were excluded for not meeting eligibility criteria. This left 29 studies for final synthesis. See Fig. 3 for the PRISMA flow chart of the study inclusion process, and https://osf.io/hnu8y for all records excluded during the title and abstract and full text review process.

Study and participant characteristics

In Part 2, 29 studies from 2003 to 2023 were included (see trend over time in Fig. 4) representing data from 178 participants. Of note, most studies had a single case/participant (k = 24, 83%). 19 studies focused specifically on autistic populations/needs (k = 19, 66%) and 11 did not (k = 10, 34%). The majority were case reports (k = 27, 93%), and most were based in the USA (k = 14, 48%) or Europe (k = 10, 34%). Participants spanned ages 4 to 21. The demographics of the study participants were reported based on gender, sex, ethnicity, and race: 10 studies reported sex (based on whether the study identified measuring sex assigned at birth and/or used sex terminology of male and female; 34%), 18 studies reported gender (based on the study identifying having measured gender identity and/or used gender terminology of boys, girls, men, women, gender-diverse; 62%), including one study that reported both sex and gender, and two studies reported neither (7%). Studies that reported sex included 8 males and 5 females. Studies that reported gender included 12 men/boys and 129 girls; which included one study[35] that focused on menstrual pain including 124 girls. 4 studies reported racial makeup of their sample (14%), and 1 reported ethnicity (3%). Of those that reported race, 100% had "Caucasian"/white majority samples (k = 4), and Hamilton 2011[35] was the only study that reported inclusion of other racial backgrounds: "89% were white, 4% were Asian, and 3% were Black".

Pain-related diagnoses and co-occurring conditions were collected; studies focused mainly on gastrointestinal (GI) conditions (k = 6, 21%), headaches or migraines (k = 7, 24%), vitamin deficiencies (k = 5, 17%), and red ear syndrome (k = 2, 7%). Many participants had co-occurring conditions (k = 18, 62%): most common being attention deficit hyperactivity disorders (k = 3, 17%), seizures/epilepsy (k = 3, 17%), self-harm/injurious behaviour (k = 3, 17%), gastrointestinal conditions (k = 4, 14%), and mental health conditions including depression, anxiety, and bipolar disorder (k = 4, 14%). See Supplemental File 3 for an in-depth representation of the study characteristics.

Interventions

Over half of the interventions were pharmacological (k = 15, 52%), 4 studies had psychological interventions (14%), 5 were surgical (17%), 4 had multidisciplinary interventions (14%), 4 were nutraceutical (14%), 1 was probiotic (3%) and 1 was not reported (3%). Of the pharmacological studies, 3 studies included interventions[2] also described in the Cochrane reviews of Part 1 (10%): Courtney et al., 2022[36] used indomethacin (a NSAID) and amitriptyline (an anti-depressant), Hamilton et al., 2011[35] included ibuprofen (a NSAID), O'Doherty et al., 2020[37] included Gabapentin (an anti-epileptic) and amitriptyline (an anti-depressant). In addition to the pharmacological interventions, 4 nutraceutical interventions consisted of vitamin supplements. Psychological interventions represented include token economy and escape extinction,[38] acceptance and commitment therapy,[39] and psychoeducational modules.[40] Surgical techniques were endoscopy and colonoscopy,[41] arthroscopic techniques for knee repair,[42,43] and pneumatic endoscopic dilatation.[44,45] The probiotic intervention consisted of fecal microbiota transplantation.[46] Notably, several key established treatments for pediatric chronic pain (e.g., cognitive-behavioural therapy, physiotherapy, intensive interdisciplinary pain rehabilitation) were minimally or not at all represented.[27–29,47]

Modifications/Adaptations to interventions

Few studies (21%, k = 6) reported modifications related to accessibility/autism, which included collaborating with the patient in protocol development,[38] electing for a less invasive intervention to avoid hospitalization,[45] and using non-verbal communication methods.[48] Study methodology precluded the ability to evaluate the efficacy of these adaptations.

Outcomes

Outcomes were categorized according to the core outcome set recommendations for pediatric pain trials [26]; see Fig. 5 for a visual overview and detailed information regarding interventions and outcomes in Supplemental Files 4 and 5, respectively.

Over half of the studies included outcomes relating to pain severity (k = 17, 58%), 13 studies included outcomes relating to overall well-being (45%), 9 studies had outcomes connected to physical functioning (31%), 6 reported behavioural outcomes such as independence, social behaviour, self-injurious behaviour, etc. (21%), 5 reported emotional functioning outcomes (17%), 4 reported healthcare use (14%), 2 reported pain interference with daily living (7%), 1 reported sleep (3%) and 1 reported biomarkers (3%). In total, the 29 studies yielded 73 outcomes, which were reported by parents, healthcare providers/researchers, and patients/participants: 18 outcomes were self-reported (25%), 12 were reported by the parents/caregivers (16%), 3 were reported by the child and parent/caregiver together (4%), 1 by health professional (1%), and 39 outcomes did not describe who reported them (53%). Individually, 5 studies included outcomes reported by the child and their parent (17%), 3 studies included outcomes reported only by parents/caregivers (10%), 2 studies only included outcomes reported by the patient (7%), and 1 study included outcomes from both the patient and healthcare providers (3%). Most studies found that their interventions were effective towards improving pain and pain-related outcomes, such as sleep, emotional functioning, and behaviour.

[2] The terminology used here to classify the interventions was derived, where possible, from the original Cochrane reviews. The label (e.g., anti-depressant, anti-epileptic) does not necessarily reflect the target etiology for which it is used, as many of the listed medications are commonly used to treat chronic pain.

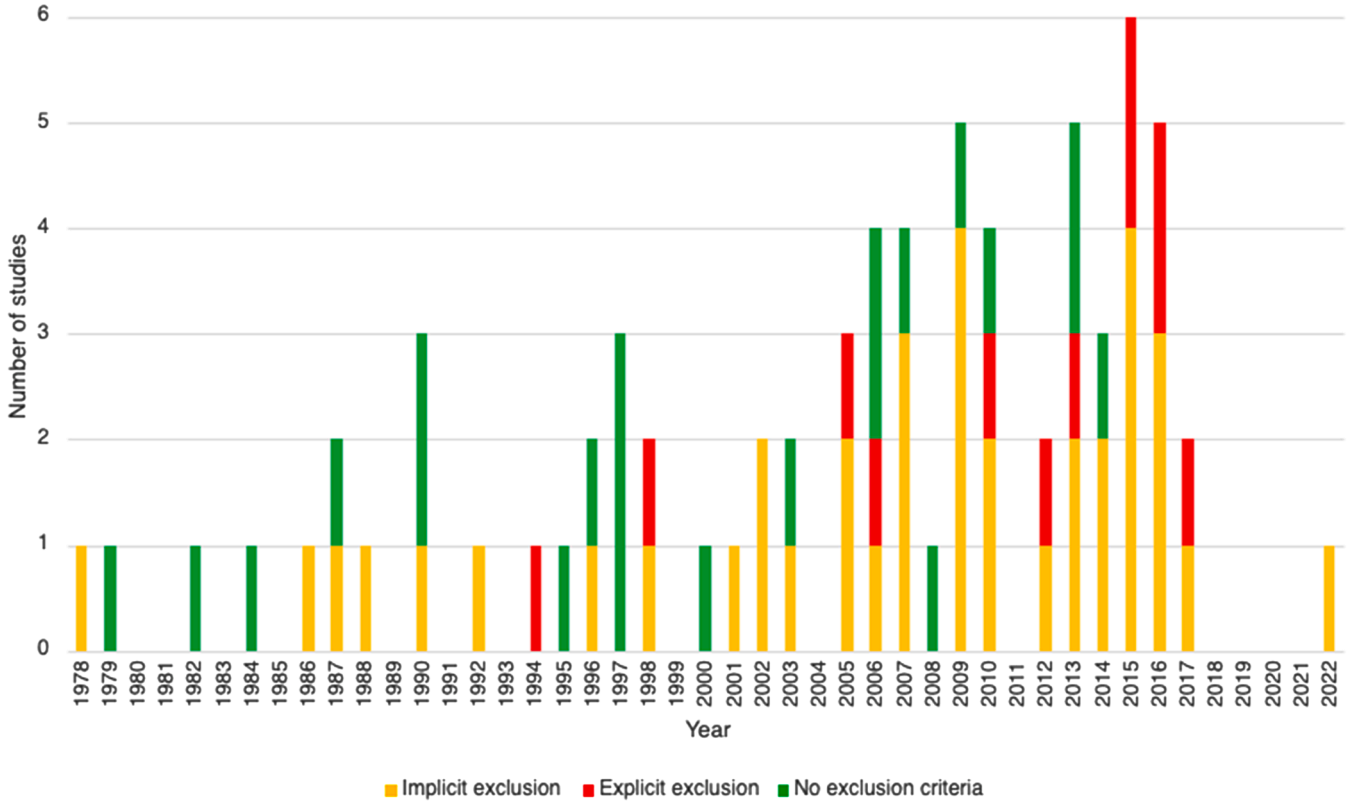

Fig. 2. Explicit and implicit exclusion criteria against autistic children and young people in RCTs of chronic pain treatments by year of publication. Studies are categorized based on the most specific form of exclusion, therefore some of the studies that are categorized as "explicit exclusion" may have also included implicit exclusion criteria. None of these RCTs reported having autistic CYP participate.

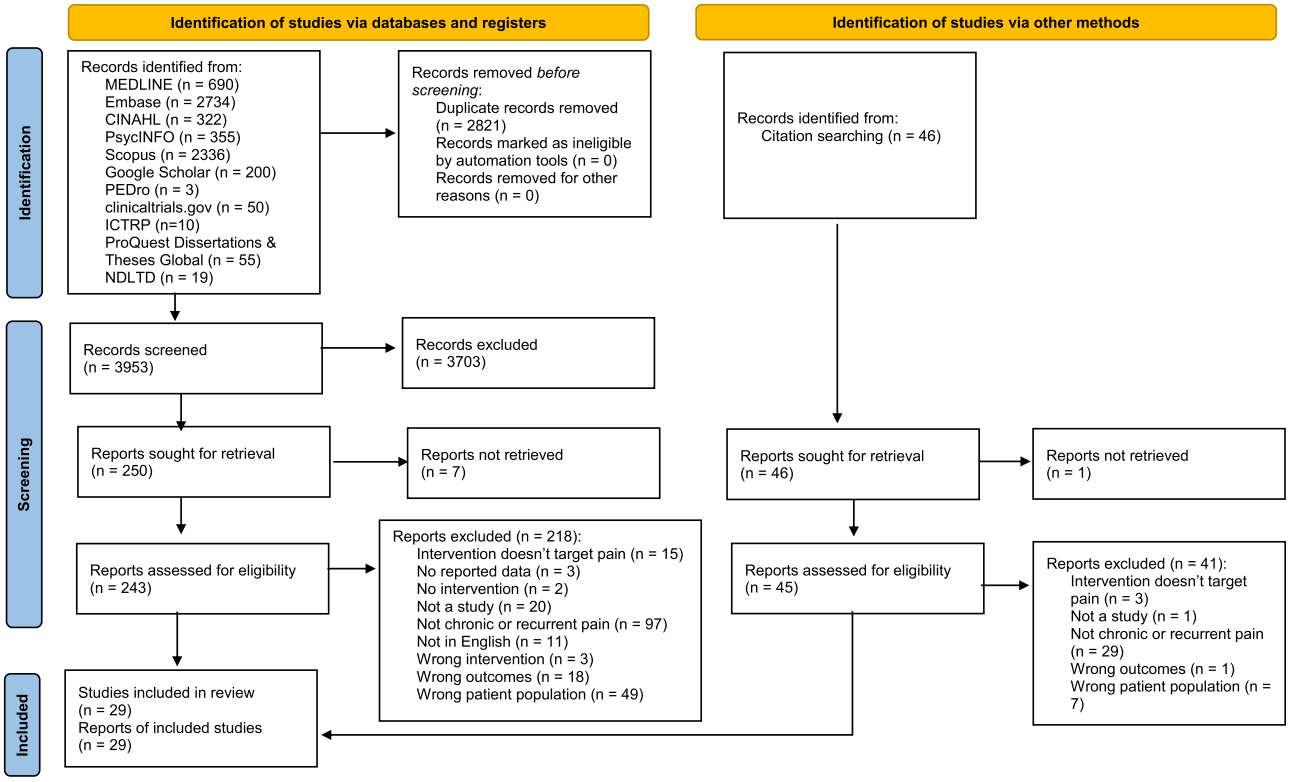

Fig. 3. PRISMA flow diagram for Part 2.

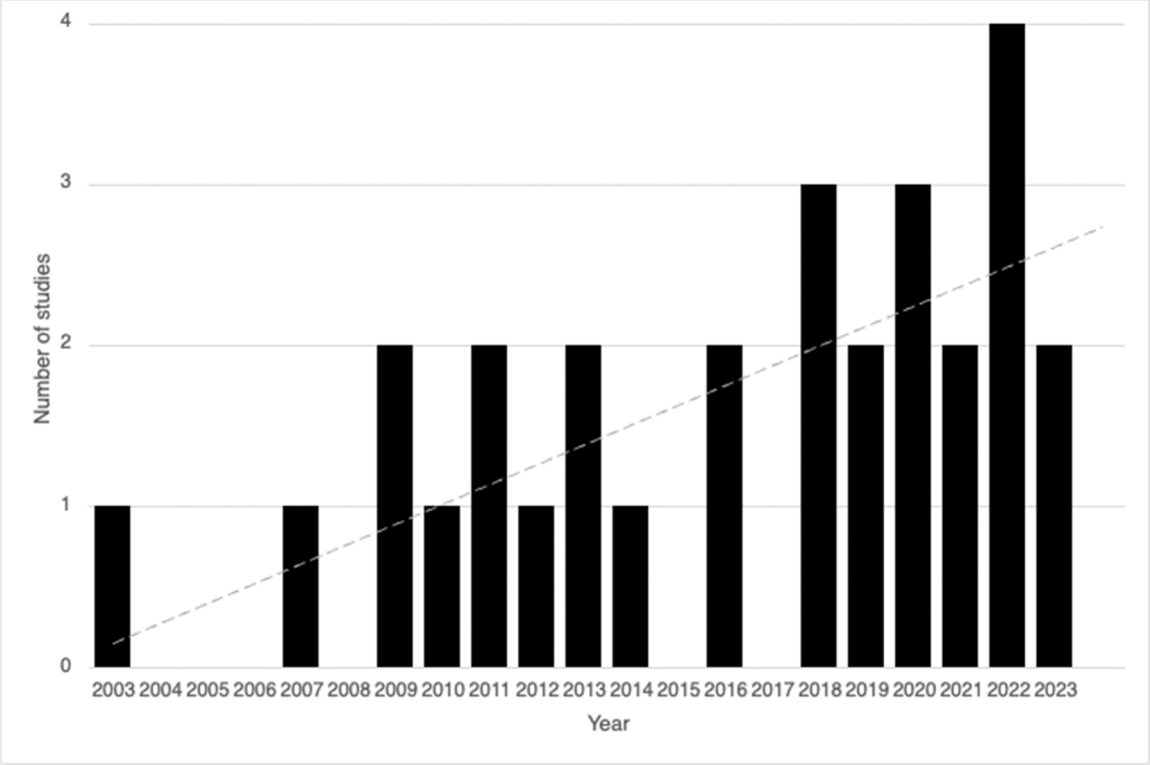

Fig. 4. Primary research studies on the treatment of chronic pain in autistic CYP by year of publication, with trendline illustrating a modest increase over time.

Quality assessment

As recommended by the Mixed Methods Appraisal Tool,[49] the detailed assessment is displayed in Supplemental File 6, without summarizing a quantitative score. As the studies were mainly case reports, the quality of evidence was low; however, the methods, analysis, and sampling were often appropriate in the context of the case report format (e.g., non-probability sampling, descriptive statistics, etc.) though generally little information was provided regarding the appropriateness of the outcome measures with respect to validity, reliability, and autism-specific accommodations.

Discussion

This review took two approaches to characterizing the literature (or lack thereof) on the treatment of chronic pain in autistic CYP. First, RCTs included in the highest standard meta-analyses for pediatric chronic pain were reviewed to determine the representation of autistic CYP, none of which reported having autistic participants represented in their sample. Various layers of exclusion were observed, from explicitly excluding neurodevelopmental populations, to implicit restriction based on co-occurring conditions, methods of communication, or other factors that disproportionately impact autistic CYP. These findings are congruent with a recent scoping review which described that 59% of clinical trials including children and related to the leading causes of global disability-adjusted life years had at least one explicit or implicit exclusion criterion against children with disabilities.[50] The rigor associated with clinical trial methodology offers few opportunities for developmental adaptations or flexibility, raising the question of whether RCTs are the most appropriate methodology for examining the efficacy of pain treatments in autistic CYP. However, none of the 72 RCTs reviewed described the prevalence/inclusion of autistic participants, making it impossible to even conduct a subgroup analysis of the needs of these youth.

Findings from Part 1 illustrated that all the RCTs that explicitly excluded autistic CYP were psychotherapy trials. This may be related to requirements for verbal engagement and/or lack of flexibility in delivering a manualized intervention, though no study explicitly stated why this criterion was in place beyond referring to ability to communicate and "participate" (whether this refers to study participation or intervention participation is unknown).[28,29] Psychotherapy trials were also the most likely to implicitly exclude autistic CYP. This may reflect better equality among pharmacological and physical therapy trials, but not improved equity or justice, as none of the RCTs of any modality described having autistic participants or accessibility options.

The second part of this review examined the available literature on treatment of chronic pain specifically in populations of autistic CYP without restriction based on study design. Perhaps unsurprisingly, given the heterogeneity inherent within autistic populations and associated needs for treatment adaptations, most included primary studies were case reports. However, given the high representation of autistic CYP in pediatric chronic pain clinics, even small trials should be possible, perhaps with the use of adaptive designs,[51] such as sequential multiple assignment randomized trials, previously used to test personalized interventions in autistic populations.[52]

Many of the included primary studies did not solely aim to examine chronic pain treatment in autistic youth. Often chronic pain was related to a rare/unusual presentation of a medical condition, treatments were addressing multiple co-occurring diagnoses, and the fact that the child had an autism diagnosis was sometimes ancillary to the focus of the case report. Many of the case reports focused more on a diagnostic process, with minimal data on treatment and outcomes, though by design all primary studies in Part 2 had to describe outcomes of an intervention that targeted management/reduction of pain or pain-related functioning. This reliance on small, heterogeneous, post-hoc interpretations of data collected for other purposes demonstrates a clear need for studies specifically designed to address the treatment needs of autistic CYP with chronic pain conditions. There is also existing research (though often also involving single studies with small samples or consensus statements) on improving pain-related communication in autistic children,[53] pain interventions in adults with intellectual disability,[54] and pain in

Study	Intervention	Sample size	Pain severity and pain interference with daily living	Physical functioning	Emotional functioning	Behavioural measures	Overall well-being
Surgical							
Alenchery 2021[41]	Foreign body removal	n = 1	●	●	○	○	○
Andreozzi 2019[42]*	Arthroscopic surgery to excise cyst	n = 1	○	●	○	○	○
Betalli 2013[44]	Pneumatic dilation; laparoscopic myotomy, partial antireflux fundoplication	n = 3	○	○	○	○	●
George 2003[43]	Posterior horn repair with inside-to-outside arthroscopic technique	n = 1	●	●	○	○	○
Grandi 2011[45]	Pneumatic endoscopic dilatation	n = 2	○	●	○	○	●
Psychological							
Allen 2012[40]*	Unified Protocol for the Treatment of Emotions in Youth With Pain (UP-YP)	n = 1	●	○	●	○	●
Arvans 2009[38]*	Token Economy and Escape Extinction	n = 1	●	○	○	●	●
WiweLipsker 2018[39]*	Acceptance and Commitment Therapy	n = 1	●	○	●	○	○
Probiotic							
Huang 2022[46]*	Fecal Microbiota Transplantation	n = 1	○	○	●	○	●
Pharmacological							
Benke 2018[155]	Biotin, acetazolamide	n = 1	○	○	○	●	●
Courtney 2022[36]	Indomethacin, amitriptyline	n = 1	●	●	○	○	○
Hamilton 2011[35]	Hormonal contraception, ibuprofen/acetaminophen	n = 124	○	○	○	○	●
Kadouh 2022[156]*	Lidocaine transitioned to mexiletine	n = 1	●	●	○	○	●
Karian 2020[157]	Botox injection	n = 1	○	○	○	●	●
Kasahara 2023[158]*	Methylphenidate, atomoxetine, guanfacine	n = 1	●	○	●	●	●
McKinley 2014[159]	Rituximab	n = 1	●	○	○	○	●
McVige 2020[160]*	Medical cannabis	n = 20 +	●	○	○	○	●
O'Doherty 2020[37]*	Diclofenac, Morphine, Carbamazepin, Indometacin, Paracetamol, Amitriptyline, Gabapentin, Oxcarbazepin	n = 1	●	○	○	○	○
Palcevski 2010[161]	Antibiotics, mesalazine, proton pump inhibitor	n = 1	●	○	○	○	○
Ramirez 2013[162]*	Metronidazole, ketoconazole	n = 1	●	●	○	●	○
Nutraceutical							
Duggan 2007[163]	Vitamin C, multivitamin	n = 1	○	●	○	○	●
Jimenez 2023[164]	Vitamin C	n = 1	●	○	○	○	●
McLellan 2018[165]	Vitamin C	n = 1	○	○	○	○	●
Weig 2009[166]	Vitamin D	n = 1	●	●	○	○	○
Multidisciplinary							
Chadehumbe 2022[167]*	Nerve block, migraine prevention therapies	n =5	○	○	○	●	○
Cravero 2016[48]	Tramadol hydrochloride, massage, laxatives and gastrointestinal treatment, selective serotonin reuptake inhibitors, morphine	n =1	○	○	○	○	●
D'Amico 2021[168]	Magnesium supplement, symptom tracking	n = 1	●	○	○	○	○
Shah 2016[169]	Vitamin D, ferrous sulfate; physical/occupational/speech therapy, neuropsychology	n =1	○	○	○	○	●
Other							
Gowai 2019[170]*	"Treatment protocol" for non-Hodgkin's lymphoma	n = 1	○	○	○	○	●

● Treatment reported as effective for this outcome for at least one time point (based on narrative description in included studies, not necessarily statistically or clinically significant
● Treatment reported as not effective for this outcome
○ Outcome not measured

Fig. 5. Visual summary of findings by outcome domain. * These studies had multiple outcomes of the same type, this table summarizes and presents them under one score. + This study included 14 participants with pain and 6 with epilepsy. The pain outcome is specific to the pain sample; however the overall well-being outcomes apply to both.

CYP with cerebral palsy,[55] intellectual disability,[56] and severe neurologic impairment[57] that could inform future directions. The authors offer recommendations in Table 1 based on the current review that may support the growth of literature on treatment of chronic pain in autistic CYP.

Primary studies represented a range of interventions, primarily pharmacological. There was insufficient data to conduct meta-analysis due to the wide range of interventions and outcomes measured. Few studies reported modifications to make the intervention more accessible to autistic CYP, however, many case reports describe an individualized intervention.

Approximately half of the primary studies had an outcome measure related to pain. It was encouraging to note that measures of other pain-related variables, such as behavioural/emotional functioning and sleep, were commonly included.[26] Engagement of autistic CYP is needed to determine whether the core outcomes represent the needs of this population, and research to validate such measures in autistic CYP.[58–60] Exploration of methods to adapt pain-related communication for autistic CYP[53] and account for the dynamic nature of pain[61,62] may offer richer outcome information beyond standardized measurements.

None of the included RCTs (Part 1) and primary studies (Part 2) described having involved autistic CYP or their parents in designing interventions. Feedback from autistic CYP and their caregivers is needed to develop a collaborative approach that supports the autonomy of the autistic CYP, as well as supporting their caregiver in advocating and scaffolding the young person. Family-centered care is considered best practice in providing health care services to children with developmental disabilities.[63,64]

Evidence suggests that having a co-occurring developmental condition (e.g., epilepsy, intellectual disability, cerebral palsy) puts autistic CYP at even higher risk of developing chronic pain.[1] Treatment of chronic pain in autistic CYP must consider intersections with other diagnoses, social positions, and identity factors that may modulate the pain and treatment experience. With increasing calls for intersectional, anti-racist, anti-ableist, gender-inclusive practices in developmental and pain science, this is clearly necessary for a path forward.[65–68] Within Part 2 primary studies, racial/ethnic data was poorly reported and samples were predominantly White, similar to other treatment literature for autistic CYP.[69] While the sex ratio mirrored the general population of autistic youth with a higher proportion of boys, this is the opposite of what has been reported in chronic pain settings.[3,4] Diverse gender identities were not represented despite higher representation in autistic samples and unique intersections with chronic pain.[4,70]

Limitations

Reviewing such diverse literature required pragmatic decision-making, with benefits and limitations to the present review. In Part 1, the team reviewed literature from Cochrane reviews available at the time of the search and did not search for new studies that may have been published since those meta-analyses. As such, more recent clinical trials may not have been captured, however, if such trials were available and had representation of autistic CYP, they should have been captured in the primary literature search in Part 2.

Part 1 involved examining inclusion/exclusion criteria, but it is possible that other aspects of study participation may not have been inclusive/accessible (e.g., methods of pain assessment or other requirements of study participation). This approach may also have not captured autistic CYP who declined to participate or dropped out of treatment due to inaccessibility of the treatment protocol. Some studies[71,72] did account for tailoring study materials to a variety of developmental levels, but this generally referred to adapting for a wide study age range, rather than autism-specific modifications. A third of the studies had a criterion related to requiring participants to be "English speaking" (or other language equivalent), which was categorized as representing implicit exclusion. While this was chosen to attempt to distinguish studies that may exclude non-verbal participants, that this phrasing is often used to denote whether the family has proficiency in a language and does not necessarily reflect a requirement to "speak". This finding should be interpreted with caution but also represents an important consideration regarding the broader accessibility of clinical trials research.

In Part 2, only examining individuals with a diagnosis of autism spectrum disorder/condition meant that studies of CYP with high autistic traits or a suspected diagnosis of autism[73,74] were not captured and may result in a sex/gender bias, due to the tendency of girls and individuals assigned female to receive an autism diagnosis later.[75] Additionally, those from racialized communities are more likely to be previously misdiagnosed or diagnosed late with autism.[76] A more inclusive definition of pain (e.g., including self-injurious behaviour or irritability) could have been helpful to address potential heterogeneity in how pain is expressed and communicated in autistic CYP.[60] Much of the literature reviewed focused on dietary interventions, probiotics, and fecal microbiota transplantation[77] aiming to reduce gastrointestinal

Table 1
Recommendations for the inclusion and representation of autistic children and young people in clinical research for the treatment of pediatric chronic pain.

Recommendations for all pain trials
Engage people with living experience of autism and their families in the design of clinical trials. Ensure this includes representation of varying levels of abilities.
Consider the validity of common core outcomes measures in pain trials for autistic populations.
Request additional funding to support the availability of inclusive practices.
Collect and report data on the number of autistic participants, any autism-specific adaptations, and conduct sub-analyses where possible. Where not possible, make data available for meta-analysis.
Consider how "typical" generic exclusion criteria may disproportionately impact autistic CYP, and use this as an opportunity to develop more inclusive protocols.
Report exclusion criteria with more detail and transparency, including clarifying when "English speaking" requires English proficiency and/or verbal communication. This may be appropriately communicated in a supplementary document if needed for space restrictions.
Consider how practices inherent to a study or treatment may systematically bias against autistic CYP, in ways that are not captured in exclusion/inclusion criteria (e.g., the social communication required for a consent discussion or engagement in psychotherapy, the stopping of current medications or restriction of polypharmacy, the requirement to attend study visits in a healthcare setting).
When conducting research on pain conditions that more commonly occur in autistic CYP, ensure that autism diagnosis and autistic traits are being considered and measured.
Recommendations for pain ttrials specifically examining autistic CYP
Consider using validated, standard outcome measures to allow for meta-analysis/pooling of data.
Reflect on what data can be collected to reflect the heterogeneity of autism and clarify the generalizability of findings (e.g., presence/absence of intellectual disability).
Explore opportunities for engagement of families and other caregivers/support persons in the design and deliver of interventions.
Design trials and interpret data from an intersectional framework that appreciates that young people autistic CYP have multiple intersecting aspects to their identities that may be critical for understanding their experience of and response to pain treatment.
Consider how biases in the diagnostic pipeline for autism may impact who has a diagnosis vs. identified autistic traits, and account for this in research (e.g., by including screening or measures of autistic traits, in addition to asking about existing diagnoses).
Conduct research specifically focused on pain conditions that more commonly co-occur in autistic CYP (e.g., hypermobility syndromes, migraine), the role of specific autistic experiences in pain treatment (e.g., masking, sensory sensitivities, self-injurious behaviour), and how specific experiences of participating in a clinical trial (e.g., receiving a placebo intervention, agreeing to randomization) may differ in autistic populations.

symptoms/abdominal pain in a general population of autistic CYP, but they were not included if it was unclear whether the participants would meet criteria for chronic pain.[78] Finally, case reports that described a treatment for autistic CYP who have co-occurring chronic pain, but where the treatment was not described as specifically addressing pain, were not included but may have held relevant information regarding mitigation of risk factors for pain.[79]

Conclusions

The literature on characterizing pain experiences in autistic CYP is emerging, but the treatment literature has barely begun. An increasing number of papers excluding autistic young people may reflect a move towards increasing standards of rigor and reproducibility,[80] at the expense of inclusion and accessibility. While there has been a modest increase in publications reporting on the treatment of chronic pain in autistic CYP, these were not conducted with sufficient rigor to meet criteria for inclusion in clinical guidelines.

Available literature on treating pain in autistic CYP is highly heterogeneous. This review adds to the growing literature on disparities in representation in clinical trials. [69,81–83] There is a clear need for interventions developed in collaboration with lived experience engagement to address the specific needs of autistic CYP who live with chronic pain, to bridge the gap between efficacy and effectiveness,[84] and to address the lack of accessibility in chronic pain trials in general.

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Authorship contributions

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2025.105390.

Data availability

Data is available from the authors on reasonable request.

References

1. Whitney DG, Shapiro DN. National prevalence of pain among children and adolescents with autism spectrum disorders. *JAMA Pediatr*. 2019;173(12):1203–1205. https://doi.org/10.1001/JAMAPEDIATRICS.2019.3826.
2. Zeidan J, Fombonne E, Scorah J, et al. Global prevalence of autism: a systematic review update. *Autism Res*. 2022;15(5):778–790. https://doi.org/10.1002/aur.2696.
3. Wiwe Lipsker C, Bölte S, Hirvikoski T, Lekander M, Holmström L, Wicksell RK. Prevalence of autism traits and attention-deficit hyperactivity disorder symptoms in a clinical sample of children and adolescents with chronic pain. *J Pain Res*. 2018;11:2827–2836. https://doi.org/10.2147/JPR.S177534.
4. Han GT, Heavner HS, Rains TR, Hoang AH, Stone AL. Chronic pain in autistic youth: clinical prevalence and reflections on tailoring evidence-based interventions from an interdisciplinary treatment team. *Children*. 2024;11(3):312. https://doi.org/10.3390/children11030312.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed..,. American Psychiatric Publishing,; 2013.
6. Garcia-Villamisar D, Moore D, Garcia-Martínez M. Internalizing symptoms mediate the relation between acute pain and autism in adults. *J Autism Dev Disord*. 2019;49(1):270–278. https://doi.org/10.1007/S10803-018-3765-9.
7. Failla MD, Gerdes MB, Williams ZJ, Moore DJ, Cascio CJ. Increased pain sensitivity and pain-related anxiety in individuals with autism. *Pain Rep*. 2020;5(6), E861. https://doi.org/10.1097/PR9.0000000000000861.
8. Jordan A, Parchment A, Gauntlett-Gilbert J, et al. Understanding the impacts of chronic pain on autistic adolescents and effective pain management: a reflexive thematic analysis adolescent–maternal dyadic study. *J Pediatr Psychol*. 2024;49:185–194. https://doi.org/10.1093/JPEPSY/JSAE004.
9. Hynes J, Block M. Effects of physical activity on social, behavioral, and cognitive skills in children and young adults with autism spectrum disorder: a systematic review of the literature. *Rev J Autism Dev Disord*. 2023;10(4):749–770. https://doi.org/10.1007/s40489-022-00319-5.
10. Bertilsson I, Gard G, Sjödahl Hammarlund C. Physiotherapists' experiences of the meaning of movement quality in autism: a descriptive phenomenological study. *Physiother Theory Pract*. 2022;38(2):299–308. https://doi.org/10.1080/09593985.2020.1759166.
11. Petty S, Bergenheim ML, Mahoney G, Chamberlain L. Adapting services for autism: recommendations from a specialist multidisciplinary perspective using freelisting. *Current Psychology*. 2023;42(9):7489–7500. https://doi.org/10.1007/s12144-021-02061-3.
12. Pemovska T, Loizou S, Appleton R, et al. Approaches to improving mental health care for autistic children and young people: a systematic review and meta-analysis. *Psychol Med*. 2024;54:2313–2343. https://doi.org/10.1017/S0033291724001089.
13. Ritter C, Hewitt K, McMorris CA. Psychotropic polypharmacy among children and youth with autism: a systematic review. *J Child Adolesc Psychopharmacol*. 2021;31(4):244–258. https://doi.org/10.1089/cap.2020.0110.
14. Leblanc L, Genest C, Villemaire J, Dodin P, Gauvin-Lepage J. Management of procedural pain and anxiety in youth with autism spectrum disorder: a scoping review. *Pain Management Nursing*. 2024;25(3):265–284. https://doi.org/10.1016/j.pmn.2024.02.004.
15. Hurwitz R, Blackmore R, Hazell P, Williams K, Woolfenden S. Tricyclic antidepressants for autism spectrum disorders (ASD) in children and adolescents. Published online March 14 *Cochrane Database Syst Rev*. 2012. https://doi.org/10.1002/14651858.CD008372.pub2. Published online March 14.
16. James AC, Reardon T, Soler A, James G, Creswell C. Cognitive behavioural therapy for anxiety disorders in children and adolescents. *Cochrane Database Syst Rev*. 2020;2020(11). https://doi.org/10.1002/14651858.CD013162.pub2.
17. Williams K, Brignell A, Randall M, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2013;8:CD004677. https://doi.org/10.1002/14651858.CD004677.pub3.
18. Iffland M, Livingstone N, Jorgensen M, Hazell P, Gillies D. Pharmacological intervention for irritability, aggression, and self-injury in autism spectrum disorder (ASD). *Cochrane Database Syst Rev*. 2023;2023(10). https://doi.org/10.1002/14651858.CD011769.pub2.
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
20. Chen YZ, Li N, Zhou KY. [Preventive effect of behavioral therapy plus flunarizine in children with migraine]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2014;16(11):1105–1108.
21. Tjosvold L., Campbell S., Dorgan M. Filter to Retrieve Pediatric Articles in the OVID Medline Database. Geoffrey & Robyn Sperber Health Sciences Library, University of Alberta. September 14, 2020. Accessed June 23, 2024. ⟨https://era.library.ualberta.ca/items/3079719f-03e2–4093-8238–49dfa1cfe97d/view/87db983a-e621–41bd-9d70–03ac37999262/Filter-20to-20Retrieve-20Pediatrics-20Articles-20in-20OVID-20EMBASE.pdf⟩.
22. Mutluer T, Aslan Genç H, Özcan Morey A, et al. Population-based psychiatric comorbidity in children and adolescents with autism spectrum disorder: a meta-analysis. *Front Psychiatry*. 2022:13. https://doi.org/10.3389/fpsyt.2022.856208.
23. Van Naarden Braun K, Christensen D, Doernberg N, et al. Trends in the prevalence of autism spectrum disorder, cerebral palsy, hearing loss, intellectual disability, and vision impairment, Metropolitan Atlanta, 1991–2010. *PLoS One*. 2015;10(4), e0124120. https://doi.org/10.1371/journal.pone.0124120.
24. Al-Beltagi M. Autism medical comorbidities. *World J Clin Pediatr*. 2021;10(3):15–28. https://doi.org/10.5409/wjcp.v10.i3.15.
25. Rose V, Trembath D, Keen D, Paynter J. The proportion of minimally verbal children with autism spectrum disorder in a community-based early intervention

programme. *J Intel Disabil Res*. 2016;60(5):464–477. https://doi.org/10.1111/jir.12284.
26. Palermo TM, Walco GA, Paladhi UR, et al. Core outcome set for pediatric chronic pain clinical trials: results from a Delphi poll and consensus meeting. *Pain*. 2021;162(10):2539–2547. https://doi.org/10.1097/j.pain.0000000000002241.
27. Nascimento Leite M, Kamper SJ, O'Connell NE, et al. Physical activity and education about physical activity for chronic musculoskeletal pain in children and adolescents. *Cochrane Database Syst Rev*. 2023;(7). https://doi.org/10.1002/14651858.CD013527.pub2.
28. Fisher E, Law E, Dudeney J, Eccleston C, Palermo TM. Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev*. 2019;2019(4). https://doi.org/10.1002/14651858.CD011118.pub3.
29. Fisher E, Law E, Dudeney J, Palermo TM, Stewart G, Eccleston C. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev*. 2018;2018(9). https://doi.org/10.1002/14651858.CD003968.pub5.
30. Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NM. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev*. 2017;8(8):CD012537. https://doi.org/10.1002/14651858.CD012537.pub2.
31. Cooper TE, Wiffen PJ, Heathcote LC, et al. Antiepileptic drugs for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev*. 2017;8(8):CD012536. https://doi.org/10.1002/14651858.CD012536.pub2.
32. Cooper TE, Fisher E, Gray AL, et al. Opioids for chronic non-cancer pain in children and adolescents. *Cochrane Database of Syst Rev*. 2017;7:CD012538. https://doi.org/10.1002/14651858.CD012538.pub2.
33. Cooper TE, Fisher E, Anderson B, Wilkinson NM, Williams DG, Eccleston C. Paracetamol (acetaminophen) for chronic non-cancer pain in children and adolescents. *Cochrane Database of Systematic Reviews*. 2017;2019(10). https://doi.org/10.1002/14651858.cd012539.pub2.
34. Cooper TE, Heathcote LC, Clinch J, et al. Antidepressants for chronic non-cancer pain in children and adolescents. *Cochrane Database of Systematic Reviews*. 2017;8:CD012535. https://doi.org/10.1002/14651858.CD012535.pub2.
35. Hamilton A, Marshal MP, Murray PJ. Autism spectrum disorders and menstruation. *J Adolesc Health*. 2011;49(4):443–445. https://doi.org/10.1016/j.jadohealth.2011.01.015.
36. Courtney A, Holmes Z, Weston S. If your ears are burning we must be talking about Red Ear Syndrome: a case report. *Australasian J Dermatol*. 2022;63(1):121–122. https://doi.org/10.1111/ajd.13_13832.
37. O'Doherty E, Morton M, Blazys V, Cordeiro NJV. Chronic paroxysmal hemicrania presenting as facial pain in a child with autism and bipolar disorder: diagnostic challenges. *Dev Med Child Neurol*. 2020;62(ement 1):61–62. https://doi.org/10.1111/dmcn.14411.
38. Arvans RK, LeBlanc LA. Functional assessment and treatment of migraine reports and school absences in an adolescent with Asperger's disorder. *Educ Treat Children*. 2009;32(1):151–166. https://doi.org/10.1353/etc.0.0046.
39. Wiwe Lipsker C, von Heijne M, Bolte S, Wicksell RK. A case report and literature review of autism and attention deficit hyperactivity disorder in paediatric chronic pain. *Acta Paediatr*. 2018;107(5):753–758. https://doi.org/10.1111/apa.14220.
40. Allen LB, Tsao JCI, Seidman LC, Ehrenreich-May J, Zeltzer LK. A unified, transdiagnostic treatment for adolescents with chronic pain and comorbid anxiety and depression. *Cogn Behav Pract*. 2012;19(1):56–67. https://doi.org/10.1016/j.cbpra.2011.04.007.
41. Alenchery AJ, Chen CB, Mahajan L. Unusual foreign body found on colonoscopy in an adolescent female (SUPPL):S1503- *Am J Gastroenterol*. 2021;116. https://doi.org/10.14309/01.ajg.0000788252.34177.bd.
42. Andreozzi V, Monaco E, Conteduca F, et al. Diagnosis and treatment of a symptomatic posterior cruciate ganglion cyst in a child with autism. *Case Rep Orthop*. 2019;2019(101591806):9192347. https://doi.org/10.1155/2019/9192347.
43. George M, Wall EJ. Locked knee caused by meniscal subluxation: magnetic resonance imaging and arthroscopic verification. *Arthroscopy - J Arthroscopic Related Surgery*. 2003;19(8):885–888. https://doi.org/10.1016/S0749-8063%2803%2900749-7.
44. Betalli P, Carretto E, Cananzi M, et al. Autism and esophageal achalasia in childhood: a possible correlation? Report on three cases. *Dis Esophagus*. 2013;26(3):237–240. https://doi.org/10.1111/j.1442-2050.2012.01358.x.
45. Grandi F, Carretto E, Betalli P, et al. Autism and esophageal achalasia in childhood: a possible correlation. Report on two cases. *Digest Liver Dis*. 2011;43(. 5). S414-.
46. Huang HL, Xu HM, Liu YD, et al. First application of fecal microbiota transplantation in adult asperger syndrome with digestive symptoms-a case report. *Front Psychiatry*. 2022;13, 695481. https://doi.org/10.3389/fpsyt.2022.695481.
47. Hechler T, Kanstrup M, Holley AL, et al. Systematic review on intensive interdisciplinary pain treatment of children with chronic pain. *Pediatrics*. 2015;136(1):115–127. https://doi.org/10.1542/peds.2014-3319.
48. Cravero C, Guinchat V, Barete S, Consoli A. Cornelia de Lange and Ehlers-Danlos: comorbidity of two rare syndromes. *BMJ Case Rep*. 2016;2016(101526291). https://doi.org/10.1136/bcr-2015-210925.
49. Hong Q., Pluye P., Fàbregues S., et al. Mixed Methods Appraisal Tool (MMAT) Version 2018. Canadian Intellectual Property Office.
50. Camanni G, Ciccone O, Lepri A, Tinarelli C, Bedetti C, Elisei S. How much do children with disabilities participate in Clinical Trials? A Scoping review. *Psychiatr Danub*. 2023;35(3):11–16.
51. Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med*. 2018;16(1):29. https://doi.org/10.1186/s12916-018-1017-7.
52. Kasari C, Sturm A, Shih W. SMARTer approach to personalizing intervention for children with autism spectrum disorder. *J Speech Lang Hear Res*. 2018;61(11):2629–2640. https://doi.org/10.1044/2018_JSLHR-L-RSAUT-18-0029.
53. Fitzpatrick R, McGuire BE, Lydon HK. Improving pain-related communication in children with autism spectrum disorder and intellectual disability. *Paediatric Neonatal Pain*. 2022;4(1):23–33. https://doi.org/10.1002/pne2.12076.
54. Lonchampt S, Gerber F, Aubry J, Desmeules J, Kosel M, Besson M. Pain interventions in adults with intellectual disability: a scoping review and pharmacological considerations. *European J Pain*. 2020;24(5):875–885. https://doi.org/10.1002/ejp.1547.
55. Ostojic K, Paget SP, Morrow AM. Management of pain in children and adolescents with cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2019;61(3):315–321. https://doi.org/10.1111/dmcn.14088.
56. Barney CC, Andersen RD, Defrin R, Genik LM, McGuire BE, Symons FJ. Challenges in pain assessment and management among individuals with intellectual and developmental disabilities. *Pain Rep*. 2020;5(4), e821. https://doi.org/10.1097/PR9.0000000000000822.
57. Hauer J, Houtrow AJ, Feudtner C, et al. Pain assessment and treatment in children with significant impairment of the central nervous system. *Pediatrics*. 2017;139(6):29. https://doi.org/10.1542/peds.2017-1002.
58. Noyek S, Jessa JS, Faulkner V, et al. A systematic review of self and observer assessment of pain and related functioning in youth with brain-based developmental disabilities. *Pain*. 2024;165(3):523–536. https://doi.org/10.1097/j.pain.0000000000003066.
59. Ely E, Chen-Lim ML, Carpenter KM, Wallhauser E, Friedlaender E. Pain assessment of children with autism spectrum disorders. *J Develop Behav Pediatrics*. 2016;37(1):53–61. https://doi.org/10.1097/DBP.0000000000000240.
60. Johnson E, van Zijl K, Kuyler A. Pain communication in children with autism spectrum disorder: a scoping review. *Paediatric Neonatal Pain*. 2023;5(4):127–141. https://doi.org/10.1002/pne2.12115.
61. Boerner KE, Pearl-Dowler L, Holsti L, Wharton MN, Siden H, Oberlander TF. Family perspectives on in-home multimodal longitudinal data collection for children who function across the developmental spectrum. *J Develop Behav Pediatrics*. 2023;44(4):e284–e291. https://doi.org/10.1097/DBP.0000000000001183.
62. Kichline T, Cushing CC, Connelly M, et al. Microtemporal relationships in the fear avoidance model. *Clin J Pain*. 2022;38(9):562–567. https://doi.org/10.1097/AJP.0000000000001058.
63. Mas JM, Dunst CJ, Balcells-Balcells A, Garcia-Ventura S, Giné C, Cañadas M. Family-centered practices and the parental well-being of young children with disabilities and developmental delay. *Res Dev Disabil*. 2019;94, 103495. https://doi.org/10.1016/j.ridd.2019.103495.
64. Carrington L, Hale L, Freeman C, Qureshi A, Perry M. Family-centred care for children with biopsychosocial support needs: a scoping review. *Disabilities*. 2021;1(4):301–330. https://doi.org/10.3390/disabilities1040022.
65. Iruka IU, Gardner-Neblett N, Telfer NA, et al. Effects of racism on child development: advancing antiracist developmental science. *Annu Rev Develop Psychol Annu Rev Dev Psychol*. 2022;2022:109–141. https://doi.org/10.1146/annurev-devpsych-121020.
66. Letzen JE, Mathur VA, Janevic MR, et al. Confronting racism in all forms of pain research: reframing study designs. *J Pain*. 2022;23(6):893–912. https://doi.org/10.1016/j.jpain.2022.01.010.
67. Boerner KE, Keogh E, Inkster AM, Nahman-Averbuch H, Oberlander TF. A developmental framework for understanding the influence of sex and gender on health: pediatric pain as an exemplar. *Neurosci Biobehav Rev*. 2024;158, 105546. https://doi.org/10.1016/j.neubiorev.2024.105546.
68. Bottema-Beutel K, Kapp SK, Sasson N, Gernsbacher MA, Natri H, Botha M. Anti-ableism and scientific accuracy in autism research: a false dichotomy. *Front Psychiatry*. 2023;14:1244451. https://doi.org/10.3389/fpsyt.2023.1244451.
69. Pickard K, Reyes N, Reaven J. Examining the inclusion of diverse participants in cognitive behavior therapy research for youth with autism spectrum disorder and anxiety. *Autism*. 2018;23(4):1057–1064. https://doi.org/10.1177/1362361318795678.
70. Boerner KE, Harrison LE, Battison EAJ, Murphy C, Wilson AC. Topical review: acute and chronic pain experiences in transgender and gender-diverse youth. *J Pediatr Psychol*. 2023;48(12):984–991. https://doi.org/10.1093/jpepsy/jsad075.
71. Vlieger AM, Menko-Frankenhuis C, Wolfkamp SCS, Tromp E, Benninga MA. Hypnotherapy for children with functional abdominal pain or irritable bowel syndrome: a randomized controlled trial. *Gastroenterology*. 2007;133(5):1430–1436. https://doi.org/10.1053/j.gastro.2007.08.072.
72. van Tilburg MAL, Chitkara DK, Palsson OS, et al. Audio-recorded guided imagery treatment reduces functional abdominal pain in children: a pilot study. *Pediatrics*. 2009;124(5):e890–e897. https://doi.org/10.1542/peds.2009-0028.
73. Balter LJT, Wiwe Lipsker C, Wicksell RK, Lekander M. Neuropsychiatric symptoms in pediatric chronic pain and outcome of acceptance and commitment therapy. *Front Psychol*. 2021;12, 576943. https://doi.org/10.3389/fpsyg.2021.576943.
74. Bursch B, Ingman K, Vitti L, Hyman P, Zeltzer LK. Chronic pain in individuals with previously undiagnosed autistic spectrum disorders. *J Pain*. 2004;5(5):290–295. https://doi.org/10.1016/j.jpain.2004.04.004.
75. McDonnell CG, DeLucia EA, Hayden EP, et al. Sex differences in age of diagnosis and first concern among children with autism spectrum disorder. *Journal of Clinical Child & Adolescent Psychology*. 2021;50(5):645–655. https://doi.org/10.1080/15374416.2020.1823850.
76. Mandell DS, Ittenbach RF, Levy SE, Pinto-Martin JA. Disparities in diagnoses received prior to a diagnosis of autism spectrum disorder. *J Autism Dev Disord*. 2007;37(9):1795–1802. https://doi.org/10.1007/s10803-006-0314-8.

77. Yang J, Fu X, Liao X, Li Y. Effects of gut microbial-based treatments on gut microbiota, behavioral symptoms, and gastrointestinal symptoms in children with autism spectrum disorder: a systematic review. *Psychiatry Res.* 2020;293, 113471. https://doi.org/10.1016/j.psychres.2020.113471.
78. Barke A, Korwisi B, Jakob R, Konstanjsek N, Rief W, Treede RD. Classification of chronic pain for the International Classification of Diseases (ICD-11): results of the 2017 international World Health Organization field testing. *Pain.* 2022;163(2): e310–e318. https://doi.org/10.1097/j.pain.0000000000002287.
79. Loades ME. Evidence-Based Practice in the Face of Complexity and Comorbidity: A Case Study of an Adolescent With Asperger's Syndrome, Anxiety, Depression, and Chronic Pain. *J Child Adolescent Psychiatric Nursing.* 2015;28(2):73–83. https://doi.org/10.1111/jcap.12108.
80. Gewandter JS, Dworkin RH, Turk DC, et al. Improving study conduct and data quality in clinical trials of chronic pain treatments: Immpact recommendations. *J Pain.* 2020;21(9-10):931–942. https://doi.org/10.1016/j.jpain.2019.12.003.
81. Jiang TE, Edwards KA, Dildine TC, et al. Trends in patient representation in low back pain pharmacological randomized clinical trials, 2011 to 2020: a systematic review. *J Pain.* 2024;25(6), 104456. https://doi.org/10.1016/j.jpain.2023.12.013.
82. Boyd T, Chibueze J, Pester BD, et al. Age, race, ethnicity, and sex of participants in clinical trials focused on chronic pain. *J Pain.* 2024;25(8), 104511. https://doi.org/10.1016/j.jpain.2024.03.007.
83. Salmasi V, Lii TR, Humphreys K, Reddy V, Mackey SC. A literature review of the impact of exclusion criteria on generalizability of clinical trial findings to patients with chronic pain. *Pain Rep.* 2022;7(6), e1050. https://doi.org/10.1097/PR9.0000000000001050.
84. Lake JK, Tablon Modica P, Chan V, Weiss JA. Considering efficacy and effectiveness trials of cognitive behavioral therapy among youth with autism: a systematic review. *Autism.* 2020;24(7):1590–1606. https://doi.org/10.1177/1362361320918754.
85. Bottema-Beutel K, Kapp SK, Lester JN, Sasson NJ, Hand BN. Avoiding Ableist Language: Suggestions for Autism Researchers. *Autism Adulthood.* 2021;3(1):18–29. https://doi.org/10.1089/aut.2020.0014.