Guidelines on the management of chronic pain in children

WEB ANNEXES A to K

World Health Organization

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WEB ANNEXES A TO K

WEB ANNEX A

PROCESSES AND METHODS FOR GUIDELINE DEVELOPMENT

1. INTRODUCTION

This Web Annex provides detailed information on the processes, procedures and methods for developing *Guidelines on the management of chronic pain in children*. These guidelines were developed according to World Health Organization (WHO) guidance on guideline development: *WHO handbook for guideline development* (2nd edition, 2014).1 The main steps for developing WHO guidelines include: 1) establishment of the general scope of the guideline and development of the key questions; 2) identification of contributors to the guideline process: 3) performance of systematic reviews of the evidence to address the key questions; 4) assessment of the quality (certainty) of the body of evidence for important and critical outcomes; 5) formulation of recommendations and drafting of the guideline document; 6) review and approval by the Guideline Development Group (GDG); 7) external peer review; 7) review and approval by WHO's internal quality assurance processes; and 8) publication and dissemination.

2. SCOPE AND KEY QUESTIONS

a) Drafting of the key question

In response to Member States' needs, the WHO Steering Group initially proposed a draft scope for these guidelines, focused on nonpharmacological, pharmacological and combination therapy for the management of chronic pain associated with a medical illness or condition (i.e. secondary pain) in children. In order to further focus the content of the guidelines and to guide the systematic reviews of the evidence, the WHO Steering Group drafted a single key question in PICO (population, intervention, comparator, outcome) format:

> Among children with chronic pain associated with a medical illness or condition ("secondary chronic pain"), would giving nonpharmacological, pharmacological or a combination of management interventions compared to placebo produce significant pain reduction and other critical outcomes?

b) Public comment and stakeholder input

This key question and the planned scope of the guidelines were posted for public comment on the WHO website from 20 December 2019 to 13 January 2020. Interested persons and entities could provide written comments and also read them at a public hearing held via video conference on 16 January 2020. In addition to the public posting, United Nations Member States, governmental and nongovernmental organizations, research and academic institutions, philanthropic foundations, and private sector entities with an interest or stake in the management of chronic pain in children were invited to provide comments and participate in the hearing. Advanced registration was required in order to optimally manage the forum and ensure wide participation. Registrants were invited to deliver a two-minute statement and submit a written template-based statement with a 200-word limit. There was no opportunity for discussion or debate.

There were 93 registrants for the public hearing, including 16 journalists or students who requested to listen but did not make comments. Of the remaining 77 registrants, 49 provided oral and written statements on the scope and/or key question. The hearing lasted approximately three hours.

c) Finalization of the scope and key questions

The GDG met on 24 January 2020 to discuss the statements from the public hearing. Upon review and discussion of the statements, the GDG revised the scope and key question by: 1) expanding the population to include children with primary chronic pain; 2) redefining the subgroups of the population by age, use of palliative care and intellectual disability; 3) defining the nonpharmacological interventions as psychological and physical management of pain; and 4) adding outcomes to the key question for further consideration.

The GDG agreed upon the following key question:

> Among children with chronic pain, would giving pharmacological, psychological, physical interventions or a combination of these, compared to placebo or active comparators, produce significant improvement in the pain experience and other critical outcomes?

d) Prioritization of outcomes

In order to identify those outcomes most important for decision-making, the GDG prioritized a list of potentially important outcomes. In this exercise, administered by the delegated WHO responsible technical officers, GDG members scored ten outcomes in terms of their importance from 1 to 9 (where 7–9 indicated that the outcome was critical for a decision, 4–6 indicated that it was important and 1–3 indicated that it was not important). All mean scores were tallied and ranked. From this exercise, seven critical and three important outcomes were identified. Any adverse event reported in primary studies was considered to be a critical outcome.

Details of the finalized key question and outcomes are presented in Table 1.

TABLE 1. DETAILS OF THE FINAL KEY QUESTION

Population
■ **Children (0-19 years) with chronic pain (pain that persists or recurs for longer than 3 months)**
This population will include children with chronic primary pain and those with any medical illness or condition where pain is a symptom or where pain is related to an illness or the treatment of an illness (i.e. chronic secondary pain).
Subgroups
■ By age: infant, child, adolescent
■ By type of care: palliative care versus not palliative care[1]
■ By presence or absence of intellectual disability[2]
Interventions
■ Pharmacological interventions such as acetaminophen (paracetamol), non-steroidal anti-inflammatory drugs, antidepressants, anti-epileptic drugs, opioids, ketamine and other anaesthetics
■ Psychological interventions such as cognitive behavioural therapy, acceptance and commitment therapy, relaxation, biofeedback and parent and social interventions
■ Physical interventions such as physiotherapy, occupational therapy
■ Combinations of above interventions
Comparator
■ Active or placebo comparators
Comparison may include different combinations of management options, pharmacological versus non-pharmacological management, or within drug class comparisons and between drug comparisons.
Outcomes
Critical outcomes
■ Pain experience (reduction in pain intensity, continuous pain intensity)
■ Health-related quality of life (physical, emotional, social and school functioning, e.g. Paediatric Quality of Life Inventory)
■ Functional disability (physical functioning and disability, e.g. Functional Disability Inventory)
■ Role functioning (e.g. school attendance)
■ Patient or family reported outcomes (e.g. goal setting outcomes)
■ Emotional functioning, depression, happiness
■ Sleep (e.g. duration and quality)
■ Adverse events
Important outcomes
■ Activity participation (e.g. playing, sports)
■ Global judgment of satisfaction with treatment or global impression of change
■ Fatigue

[1] This is an approach to care for persons, families and caregivers who are facing a life-limiting illness or where a person is near the end of life. The goal of palliative care is to improve the quality of life of patients and their families. This approach focuses on the prevention and relief of suffering by means of early identification, assessment and treatment of pain as well as by addressing the physical, psychosocial and spiritual needs of the individual and their family and caregivers.

[2] Intellectual disability is characterized by impairment of skills across multiple developmental areas such as cognitive functioning and adaptive behaviour. WHO. Mental disorders, 28 November 2019 [webpage] (https://www.who.int/news-room/fact-sheets/detail/mental-disorders, accessed 5 December 2020).

3. CONTRIBUTORS

A broad range of contributors helped to develop this guideline: each type of contributor had a well-defined role and was subject to specific WHO policies and procedures. This approach helps to ensure the effectiveness and objectivity of all contributors, while bringing together a pool of contributors with diverse experiences, expertise and perspectives. A summary of each type of contributor and their roles and assessment process is provided in Table 2.

a) WHO Steering Group

The WHO Steering Group managed the administrative aspects of the guideline development process and provided technical and procedural support for the GDG throughout the process. The Steering Group comprised WHO staff from the Departments of Maternal, Newborn, Child, Adolescent Health and Ageing; Noncommunicable Diseases; Mental Health and Substance Abuse; and Access to Medicines and Health Products. Members were selected by the director of each relevant technical unit. For each of the six WHO regional offices, advisors with a focus on maternal, newborn, child and adolescent health and ageing were asked to participate or to nominate a focal person to be part of the steering group. The African Region made a nomination. The members of the Steering Group are listed in Web Annex A of the guideline.

The Steering Group drafted the scope and key questions of the guideline, identified and approved the members of the GDG, collected and assessed the declarations of interest of external contributors (with support from the Office of Compliance, Risk Management and Ethics), and finalized the planning proposal. The Steering Group also oversaw the process for selecting contractors for performing the evidence reviews, drafted the null recommendations, finalized the draft guidelines for review by the GDG and External Review Group (ERG) and managed the guideline publication and dissemination processes. In addition, the Steering Group is responsible for monitoring new information after the guideline is published, assessing the need for updating, and for responding to end-user feedback and requests.

b) Guideline Development Group

The GDG was composed of 22 external experts with a range of technical skills, experiences and perspectives, and with wide geographic representation and gender balance. The GDG consisted of technical experts in pain management in children and various other stakeholders whose expertise included human rights law, bioethics, social policy, care in humanitarian settings, lived experiences with chronic pain and guideline methods. Each GDG member represented themselves as individuals: they did not represent any Member State, governmental or nongovernmental entity, or institution. The importance of this fact was made clear to each GDG member at the start of their participation, and reiterated at the beginning of each GDG meeting.

The GDG was responsible for formulating the recommendations in the guideline and for the final guideline content. Specifically, the GDG worked with the WHO Steering Group to define the scope and key questions and prioritize the outcomes, reviewed the systematic reviews, formulated the recommendations and corresponding rationale statements, and reviewed and approved the final guideline document.

GDG members were identified and selected via a clearly defined and transparent process. A list of potential members was identified from a "Call for experts" for both the pain management guideline and a concurrently planned document entitled Access to Controlled Medicines. This call was published on the WHO website from 29 August to 24 October 2019, and was also shared through other WHO public web pages (e.g. the Maternal Newborn Child and Adolescent Health website), social media (Twitter and LinkedIn) and emailed to various palliative care associations, childhood cancer communities and paediatric and anaesthesiology societies across the globe. No members of the GDG for the 2012 WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses participated in developing this guideline.

There were 108 eligible individuals from the call for experts (there was one ineligible submission from a WHO staff member). Of these submissions, 40 were primarily interested in joining the GDG for the guideline on the management of pain in children, while an additional 13 individuals requested to work on either this guideline or the Access to Controlled Medicines document, but preferred this guideline.

Of the 53 individuals who indicated an interest in the guideline on the management of chronic pain in children, 49 were technical experts in the field of clinical treatment of chronic pain in children, or academic researchers in this area or in addiction research. One applicant anticipated being an end-user of the guideline, and three others had technical expertise in related areas (health economics, bioethics, equity or human rights). The vast majority of the submissions worked in the WHO Region of the Americas (19), the European Region (14) and the African Region (12).

In order to include additional perspectives, particularly from regions and with expertise that were lacking or underrepresented in the responses to the open call, the WHO Steering Group sought the names of additional individuals from staff in relevant WHO departments and from WHO expert advisory panels. An additional nine GDG members were identified using this approach.

The GDG held two virtual meetings: the first on 24 January 2020, when the group finalized and approved the general scope, key questions including outcomes and target audience of the guideline. In a subsequent survey, the GDG members prioritized the potential outcomes of interest. The GDG met for a second time on 14–18 September 2020 when members examined the Grading of Recommendation Assessment, Development and Evaluation (GRADE) evidence profiles; interpreted the evidence on benefits and harms and other considerations; and formulated recommendations, guiding principles, best practice statements and a list of research gaps.

c) Guideline methodologist

A guideline methodologist was hired as a consultant to support the WHO Steering Group and the GDG throughout the development process. The methodologist is an expert in the processes and methods for evidence synthesis and critical appraisal, GRADE and in the formulation of evidence-based recommendations.

d) Systematic review teams

Two systematic review teams were contracted by the WHO Steering Group to provide input into the key questions, perform systematic reviews, develop GRADE evidence

profiles including an assessment of the quality (certainty) of the body of evidence, and to present the review findings to the GDG. The teams contracted to perform these reviews were identified through an open bidding process after WHO issued a request for proposals on the United Nations Global Marketplace (https://www.ungm.org/). Proposals were assessed by a panel of WHO staff based on a weighted set of technical and cost criteria. The first review focused on effectiveness and safety of physical, psychological and pharmacological interventions for the management of chronic pain in children. The second review was a qualitative evidence synthesis of the sociocultural acceptability of the included interventions and the values and preferences of patients, caregivers, and providers in relation to these interventions.

e) Other technical experts

The responsible WHO technical officers hired a consultant economist to perform a rapid systematic review of existing economic evaluations of the interventions examined in this guideline, and to provide cost data on the various treatments in diverse settings.

f) External review group

The ERG provided input into the final content and presentation of the guidelines. These individuals have an interest and expertise in the management of chronic pain in children. They were identified by the delegated WHO technical officers with input from the Steering Group as persons who could provide varied perspectives and expertise to complement those of the GDG. Their specific role was to review the draft final guideline and provide comments, particularly related to errors or missing data, and clarification on issues related to implementation, dissemination, ethics, regulation and monitoring. ERG members attended the September 2020 GDG meeting at which recommendations were formulated and were encouraged to participate in the discussions. They did not, however, have a direct role in formulating or approving the recommendations.

g) Meeting observers

Representatives of several paediatric, anaesthesiology, palliative care and pain groups or organizations were invited to attend the September 2020 GDG meeting as observers. These organizations were potential end-users and implementers of the guidelines, or represented various target audiences. Only one invitee accepted. Their role at the meeting was to observe, and to speak only at the explicit request of the meeting co-chairs. They did not participate in the formulation of recommendations.

h) Funders

This guideline was funded by WHO; there were no external sources of funding.

4. MANAGEMENT OF CONTRIBUTORS

a) Declaration of interests

All potential contributors to the development of the guideline, including both individuals external to the Organization and employees of WHO, completed a standard WHO declaration of interests form.[3]

b) Assessment and management of conflicts of interest

Assessment of the declarations of interest and other information gathered on potential contributors was made according to the principles, processes and procedures laid out in the WHO Guidelines for Declaration of Interests (WHO Experts).[3] Each type of contributor was subject to specific rules and procedures (Table 2).

Guideline Development Group

Prior to issuing an invitation to join the GDG, potential members were vetted according to WHO's standard policies and procedures for collaborations with external experts.[3] In addition to the standard declaration of interests (DOI) form for external experts,[3] potential members submitted a detailed curriculum vitae.

In the interests of transparency and to identify any additional relevant information or conflicts of interest, each prospective GDG member provided a brief biography which was published for public notice and comment from 24 December 2019 to 10 February 2020 on the website of the Department of Maternal, Newborn, Child, Adolescent Health and Ageing. No comments were received.

The WHO Steering Group performed an internet search for additional information on prospective members, including sources of research funding, published declarations of interests, board membership and other affiliations, and publications, including public statements, commentaries and opinion pieces related to the management of pain in children.

All information gathered on each potential GDG member was carefully examined by the delegated technical officers, in consultation with the Steering Group, the Director of the Department of Maternal, Newborn, Child, Adolescent Health and Ageing, and WHO's Office of Compliance, Risk Management and Ethics. Financial, intellectual and other interests disclosed by and identified about potential GDG members were assessed for any potential or perceived risk that they might impinge on the potential member's impartiality.

The standards applied and process followed in this assessment are described in the WHO *Guidelines for Declaration of Interests (WHO Experts)*.[3] Interests were assessed as insignificant or minimal if they were considered unlikely to affect or reasonably be perceived to affect the individual's judgement on the management of chronic pain in children. If an interest was deemed to be potentially significant, the following management options were considered: 1) conditional participation of the individual in the guideline development process; 2) partial exclusion; or 3) total exclusion.

Following satisfactory assessments in line with this vetting process, the WHO Steering Group offered formal invitations to individuals to join the GDG in January 2020. Four members were added in February 2020 to provide expertise in specific areas. At the time of the invitation, each member was asked to update their declaration of interests if there were any changes, and to sign the WHO *Confidentiality undertaking.*[3] None of the identified potential GDG members was assessed as having a significant conflict of interest. All appointed members were therefore permitted to participate fully in the guideline development process. The list of GDG members and a summary of their declarations of interest are found in Annex A of the main guideline document.

At the beginning of the two GDG meetings, all attendees including GDG members verbally declared any relevant interests, highlighting any updates.

External Review Group

Potential members of the ERG underwent an evaluation process identical to that of the GDG. Their biographies were posted for public comment from 20 May to 17 June 2020. No comments were received and no conflicts of interest identified.

Contractors

All contractors who contributed to the guideline completed the WHO declaration of interests (DOI) form. Any disclosed interests were assessed according to the WHO policy for conflicts of interest.[3] Contractors were not permitted to have any financial interests relevant to the subject of this guideline.

Meeting observers

The single meeting observer completed the standard WHO declaration of interest form and was deemed to have no conflicts of interest. The observer identified her affiliation at the beginning of the GDG meeting.

WHO staff

WHO staff are subject to the WHO Code of Ethics and Professional Conduct.[4] Senior technical staff, including the delegated technical officers and WHO Steering Group members, provide declarations of interests annually to the Office of Compliance, Risk Management and Ethics, which assesses and provides instructions for any necessary management plan. Other staff members working on guidelines completed the declaration of interest form at the beginning of the guideline development process. The delegated technical officers and members of the Steering Group did not disclose interests which were relevant to these guidelines.

c) Leadership of the Guideline Development Group

Members of the GDG nominated and confirmed two co-chairs at the first GDG meeting on 24 January 2020. These individuals were selected for their experience in managing group processes, interpreting evidence and chairing WHO meetings that require building consensus among participants with diverse views. The role of the co-chairs was to serve as a liaison between the GDG and WHO Steering Group throughout the development process, to facilitate the presentation and sharing of information and discussions, and to guide the GDG in the consensus process to develop recommendations. While they were permitted to express their opinions at the meetings, their primary role was to facilitate consensus-building in the group. If consensus could not be reached and voting was necessary to finalize the recommendations, they had the right to vote but could not exercise veto or any other exceptional powers in the decision-making process.

d) Group processes and decision-making

The principles and general procedures for decision-making for WHO guidelines are set out in the WHO Handbook for Guideline Development (2nd edition, 2014).[1] All meeting attendees had clearly defined roles and the meeting co-chairs were responsible for

seeing that these roles were adhered to. GDG members were solely responsible for finalizing and approving the recommendations and rationale statements, and had voting rights when consensus could not be achieved. The delegated WHO responsible technical officers helped to guide the meeting process, ensure that WHO policies and procedures were followed, and provided administrative support, as well as technical support upon request. ERG members and external technical experts could participate in the discussions on recommendations but could not participate in the consensus process when recommendations were finalized, and could not vote. The guideline methodologist guided the co-chairs and GDG in interpreting the evidence, understanding GRADE certainty-of-evidence assessments, translating evidence into recommendations and in optimal guideline processes and procedures.

WHO guideline recommendations are formulated by means of a process which is designed to achieve consensus among GDG members. Consensus is defined as the situation in which all GDG members can agree to, or "live with" the recommendation as formulated, including its general wording, direction and strength (strong or conditional). Consensus is still considered to have been achieved where there are minor disagreements concerning the wording of a recommendation or its rationale statement.

Specific rules for agreeing on recommendations and other decisions were established at the beginning of the September 2020 GDG meeting. In order for a recommendation to be finalized, at least two-thirds of the full complement of the GDG had to be in attendance. Deliberations among GDG members took place until consensus was reached, meaning that all members agreed to the final wording. If consensus could not be achieved, a vote was held. Voting was anonymized, took place online, and was organized and collated by the delegated WHO responsible technical officers. A decision threshold of 80% was set apriori for approval of any recommendation requiring a vote.

e) Confidentiality

All persons who were not WHO employees and attended one or both GDG meetings signed the WHO standard Confidentiality Undertaking3 prior to the first meeting. The purpose of this form is to ensure that participants in the guideline development process uphold WHO's efforts to speak with a single voice when providing clear, evidence-based recommendations. Importantly, a pledge of confidentiality also helps to ensure that each GDG member and any other participant can speak freely at meetings. WHO staff are subject to confidentiality rules according to the WHO Code of Ethics and Professional Conduct.[4]

5. SYSTEMATIC REVIEWS AND EVIDENCE ASSESSMENT

a) Scoping review

At the beginning of the guideline development process, the responsible technical officers performed a scoping review to identify existing systematic reviews addressing the key question. The following databases were searched: PROSPERO, Cochrane Library, Epistemonikos and Campbell Collaboration. None of the identified reviews was deemed to be sufficiently comprehensive or up to date to be used as the basis for formulating recommendations in these guidelines.

b) Commissioned systematic reviews

WHO commissioned a Cochrane Task Force composed of members of the Cochrane Pain, Palliative and Supportive Care Group (PaPas), Cochrane Qualitative Implementation Methods Group (QIMG) and Cochrane Response to perform systematic reviews on the effectiveness, harms and acceptability of physical, psychological and pharmacological therapies for chronic pain in children.

WHO commissioned the Cochrane QIMG to perform a qualitative evidence synthesis of experiences with and sociocultural acceptability of physical, psychological and pharmacological interventions for the management of chronic pain in children, and the relative values placed on the benefits and harms of these interventions. This review examined the perspectives of patients, parents and caregivers, healthcare providers and other key stakeholders with respect to: 1) safety and efficacy of interventions used to manage pain in children; 2) dependence and misuse potential; and 3) the public health benefits and risks of different strategies to ensure appropriate access. Particular attention was given in this review to capturing a diversity of viewpoints relating to socioeconomic status, ethnicity, sociocultural factors, gender, religion and geographical region of residence.

All commissioned reviews adhered to Cochrane methods and standards as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (2nd edition).[5] The specific approaches and methods used are described in each systematic review.[6,7]

c) Assessment of the certainty of the body of evidence for each outcome

The GRADE system was used to assess the certainty (quality) of the body of quantitative evidence for each critical and important outcome. The certainty of evidence for each outcome was rated as high, moderate, low or very low, based on a set of criteria including study limitations, inconsistency, imprecision, indirectness and publication bias.[8] The findings of the qualitative reviews were appraised using the GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach.[9] Overall confidence in the evidence from reviews of qualitative research was based on methodological limitations of the individual studies, adequacy of the data, coherence of the evidence and relevance of the individual studies to the review finding. These assessments of quantitative and qualitative evidence were presented in GRADE evidence profiles to the GDG for discussion and formulation of recommendations.

6. FORMULATING RECOMMENDATIONS

a) Evidence-to-decision frameworks

The GDG formulated recommendations at a virtual meeting on 15–18 September 2020. Facilitated by the two GDG co-chairs and assisted by the WHO Steering Group and the guideline methodologist, the GDG used a structured framework for decision-making. This was the GRADE evidence-to-decision (EtD) framework for public health interventions,[10] which includes the following considerations: priority of the problem, the balance of the benefit-s and harms of the intervention, certainty of evidence, value placed on outcomes by those impacted by recommendations, intervention impact on equity, resource implications, and intervention acceptability and feasibility.

b) Process for formulating recommendations

The WHO Steering Group developed a set of "null recommendations", which included both "for" and against" options as a neutral starting point for GDG discussions at the 15-18 September 2020 meeting. The systematic review teams, working with the guideline methodologist and the WHO Steering Group, populated the EtD framework with data from the reviews and other sources. Systematic reviews, GRADE evidence profiles, populated EtD frameworks and the null recommendations were presented to the GDG prior to the meeting, and formed the basis for its discussions.

c) Recommendations

The GDG formulated either a strong or conditional recommendation, for or against each intervention or group of interventions discussed on the basis of the evidence on benefits, harms and other considerations according to the EtD framework. A strong recommendation means the GDG was confident that the desirable effects of adherence to a recommendation outweighed the undesirable effects. Most informed patients would choose the recommended intervention and for policy-makers the recommendation could be adopted as a policy in most situations. On the other hand, a conditional recommendation means that the GDG concluded that the desirable effects of adherence to a recommendation probably outweighed the undesirable effects, but to a lesser degree of confidence. Patients' choices will then vary according to their values and preferences and shared-decision-making with their provider may be needed. Policy-makers may require substantial debate and the involvement of many stakeholders to reach a decision.11

In addition to recommendations on interventions for the management of chronic pain in children, these guidelines present a set of *guiding principles*. These principles, composed and approved by the GDG, underpin all aspects of the management of chronic pain in children. Since these statements are based on human rights and ethics principles, they do not require a systematic review of research evidence on benefits and harms.

Another type of statement contained in this guideline is referred to as best practice statements. Likewise, being based on good clinical or public health practice and experience, these statements do not require a systematic review of the benefits and harms of an intervention. Best practice statements are generally not contested because not carrying them out would be either nonsensical or illogical.

7. REVIEW AND APPROVAL

After the GDG meeting, the writer drafted the guidelines: once approved by the delegated WHO technical officers, the draft was circulated to the GDG for review and approval. The draft final guideline was also sent for peer review by the ERG. The role of peer review is to provide technical feedback, identify errors of fact, comment on clarity of language and provide considerations related to implementation, adaptation and contextual issues. Its role is not to change the recommendations already agreed by the GDG. However, if the peer reviewers identify major concerns, these can be referred back to the GDG for consideration. In the present case, this situation did not arise.

WHO has an internal approval and quality assurance process to ensure that all WHO publications, including guidelines, meet the highest international standards for quality,

reporting and presentation. These guidelines were reviewed and approved by the WHO Guidelines Review Committee (GRC) and by the Deputy Director-General and Acting Executive Director, Universal Health Coverage/Life Course and the Chief Scientist.

8. UPDATING

The WHO Secretariat will continue to follow research development in pharmacological, physical and psychological management of chronic pain in children, particularly for questions in which the certainty (quality) of evidence was found to be low or very low. If new evidence emerges or other important considerations arise which may impact the current recommendations, the Department of Maternal, Newborn, Child, Adolescent and Ageing will coordinate an update of these guidelines, following the procedures outlined in the WHO *handbook for guideline development* (2nd edition).[1]

Unless new evidence necessitates an earlier review, at five years from publication of these guidelines, the Department of Maternal, Newborn, Child and Adolescent Health and Ageing at the WHO headquarters in Geneva, Switzerland, along with its internal partners, will conduct systematic reviews of the relevant evidence and appraise the need for updating or revalidating the current guidelines. WHO will seek stakeholder input on the scope of the updated guideline, as new interventions and considerations emerge.

TABLE 2. CONTRIBUTORS TO THE GUIDELINE: SELECTION PROCESS AND ROLE

Contributor	Internal or external to WHO	Role	Who selected the contributor or how selected	Criteria for selection	DOI, COI	Confidentiality undertaking agreement	Whom represented
WHO Steering Group (SG)	Internal	Support administration of the guideline development process	WHO senior management	Representation from relevant WHO departments	Collected, managed; subject to WHO staff regulations	Subject to WHO staff regulations	WHO
Guideline Development Group (GDG)	External	Define the scope of the guideline, review the evidence, formulate recommendations	Open call for members	Assessment of DOI/COI, diversity of expertise and geography, gender balance	Collected, managed	Signed	Themselves as individuals
External Review Group (ERG)	External	Contribute to discussions at the GDG meeting, provide critical review of the draft final guideline	Responsible technical officers and WHO SG	Suggested by the SG to diversify GDG expertise and perspectives, and selected from open call for GDG members	Collected, managed	Signed	Themselves as individuals
Methodologist	External	Oversee the guideline processes and methods	Responsible technical officers	Pre-defined criteria with assessment by the SG	Collected, managed	Signed	Contractor
Systematic review teams	External	Draft and finalize the systematic reviews; draft evidence-to-decision tables	Competitive bidding process	Pre-defined criteria with assessment by a WHO selection panel	Collected, managed	Signed	Contractor, Cochrane
Specialized technical advisors	External	Economist consultant	Responsible technical officers	Pre-defined criteria with assessment by the SG	Collected, managed	Signed	Contractor
Guideline writer	External	Writer	Competitive bidding process	Pre-defined criteria with assessment by a WHO selection panel	Collected, managed	Signed	Contractor
Observers	External	Observe the GDG meeting; able to express an opinion if invited by the meeting co-chairs	Stakeholders suggested by the SG	Stakeholder interest	Collected; represented an organization	Signed	Affiliated organization
Funder	Internal	Funded external contracts	NA	NA	NA	NA	NA

Abbreviations: COI, conflict of interest; DOI, declaration of interests; GDG, Guideline Development Group; NA, not applicable; SG, WHO Steering Group

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WEB ANNEX B.

SYSTEMATIC REVIEW OF EFFECTIVENESS AND QUALITATIVE EVIDENCE: SUMMARY OF THE METHODS

Characteristic	Effectiveness of physical interventions	Effectiveness of psychological interventions	Effectiveness of pharmacological interventions	Qualitative review
Study designs, included	RCTs; prospective non-randomized, comparative trials	RCTs	RCTs; prospective non-randomized, comparative trials; including cross-over studies, cluster-RCTs; superiority and equivalence design trials	Studies containing qualitative or mixed-methods data
Study designs, excluded	Studies without a comparison group. Superiority and equivalence design trials	Studies without a comparison group.	Studies without a comparison group.	Studies with exclusively quantitative data
Interventions	Any interventions that involves bodily movement and energy expenditure; e.g. physiotherapy, muscle strengthening, sports, condition; excluded passive interventions (e.g. massage)	Intervention has recognizable psychological content	Analgesic medicines, including (but not exclusively) antidepressants, acetaminophen/paracetamol, opioids, NSAIDs, anticonvulsant drugs, antiepileptic drugs, ketamine; opioids. Drugs via any route	Physical interventions, psychological interventions, pharmacological agents
Comparators	Any active intervention, placebo or waiting list			
Use of existing systematic reviews	None: de novo review	Update of three prior Cochrane reviews[3], addition of cancer patients as de novo review	De novo review; search identified several existing reviews which were examined for relevant studies	None: de novo review
Databases searched	Cochrane Central Register of Controlled Trials, Medline, Embase	Cochrane Central Register of Controlled Trials, Medline, Embase, PsycINFO	Cochrane Central Register of Controlled Trials, Medline, Embase	CINAHL, EMBASE, MEDLINE, BIREME PsycINFO, ASSIA, Scopus; AJOL (African Journals Online); Global Health Library (includes regional indexes for Africa (AIM), the Americas (LILACS), Eastern Mediterranean (IMEMR), South-East Asia (IMSEAR), Western Pacific (WPRIM), SciELO)
Dates searched	Database inception to April 2020	Update of prior reviews and cancer review to March 2020	Database inception to April 2020	Inception of the database to March-May 2020 (varied with the specific database)
Languages	No exclusions			English only
Risk of bias tools	RCTs: Cochrane risk of bias tool Non-randomized studies with a control group: ROBINS-I			Critical Appraisal Skills Profile tool
Assessment of the quality/confidence in the findings	GRADE			GRADE CERQual

[3] 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(4).
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(9).
Law E, Fisher E, Eccleston C, Palermo TM. Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database Syst Rev. 2019;3:Cd009660.

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development and Evaluation; CERQual, Confidence in the Evidence from Reviews of Qualitative research; RCTs, randomized controlled trials

WEB ANNEX C.

SYSTEMATIC REVIEW OF EFFECTIVENESS: CHARACTERISTICS OF THE EVIDENCE

Characteristic	Physical interventions	Psychological interventions	Pharmacological therapy
No. studies/no. participants	25/1470 (24 published studies, 1 from trial registry with results)	63/5025	34/4091
No. of studies by design	24 RCTS: 22 parallel-group RCTs, 2 cluster-RCTs 1 NRS	63 RCTs: 61 parallel-group RCTs; 1 stepped-wedge cluster design; 1 cross-over RCT	29 RCTs: 17 parallel-group RCTs, 12 cross-over RCTs 5 NRS
No. ongoing trials	12	16	5
Funders	NR: 7 No funding: 1 Government, charities, hospitals, academia: 16 Pharmaceutical company: 1	Government or research foundations: 48 No funding: 2 NR: 13	NR: 18 Government or academia: 4 Pharmaceutical company: 8 Research foundation and pharma: 2 NR but authors/acknowledgements included pharma: 2
Conflict of interest	NR: 4 Reported "no COI": 19 COI reported: 2	NR: 34 Reported "no COI": 27 COI reported: 2	NR: 23 Reported "no COI": 5 COI reported: 6
Country of origin	US (4), UK (4), Turkey (3), Canada (2), Sweden (2), Australia (1), Brazil (1), Chile (1), Denmark (1), India (1), Iran (1), Israel (1), Netherlands (1), Portugal (1), Saudi Arabia (1)	North America (34), Sweden (11), Netherlands (6), Germany (6), Australia (2), Brazil (1), China (1), Italy (1), Spain (1)	US (11), UK (5), Italy (3), Iran (3), South Africa (2), Germany (2), Argentina (1), Brazil (1), Canada (1), Czech Republic (1), Pakistan (1), Turkey (1), multi-country (1)
Type of pain/ population	Primary MSS disorder (8), secondary MMS pain (8), primary visceral pain (3), secondary visceral pain (1), chronic widespread pain (2), CRPS (1), mixed pain (1), headache (1)	Primary visceral pain (12), widespread pain (2), headache (5), secondary MSS pain (2), secondary visceral pain (3), chronic widespread pain (2), secondary headache (2), mixed conditions (14), headache - not primary (23)	Primary visceral pain (7), MSS pain (12), non-chronic headache (7), primary headache or orofacial pain (2), widespread pain (2), secondary visceral pain (1), mixed pain (1), CRPS (1)
Mean age (years) % female	13.0 73	12.9 67	12.3 74

Intervention and comparators	No intervention or waiting list control (4), standard care or other active control (7), no intervention, active (non-PT) control (1) (includes one 4-arm trial with PT arms also) RCTs comparing two types of PT (12): ■ Physiotherapy, exercise and self-training vs self-training ■ Task-oriented activity training video-based game vs task-oriented activity training in daily living conditions ■ Strengthening exercises vs proprioceptive-balance exercises ■ Resistive underwater exercises vs stand physical therapy ■ Land physiotherapy vs combined hydrotherapy and land physiotherapy ■ Generalised physiotherapy vs targeted exercise group ■ 1 vs 3 sessions of physiotherapy/week ■ Conventional exercise vs Pilates ■ Hypermobile range group vs neutral control group ■ Hydrotherapy vs watsu ■ Qigong vs aerobics · Supervised vs unsupervised home exercise programme In addition, one NRS compared physical therapy + home exercise + group exercise vs physical therapy + home exercise	Intervention arms: CBT: 43 Relaxation: 15 Behavioural therapy: 7 Hypnosis: 3 Problem-solving therapy: 2 Acceptance commitment therapy: 1 Comparison arms: Active control: 36 Standard/usual care: 16 Waiting list: 17 Note: 13 studies included more than 2 arms.	Interventions: paracetamol/ acetaminophen, anticonvulsants, antidepressants, leukotriene receptor antagonists, NSAIDs, progestin, triptan Comparators: 1. Placebo or non-pharma intervention (e.g. behavioural intervention, acupressure or fennel): 16 (including 1 study with both placebo and active arms) 2. Another pharmaceutical agent: 18

Numbers represent number of studies, unless otherwise indicated.

Abbreviations: CBT, cognitive behavioural therapy; COI, conflict of interests; CRPS, Chronic Regional Pain Syndrome, MSS musculoskeletal system; no., number; NR, not reported; NRS, non-randomized study/studies; NSAID, non-steroidal anti-inflammatory drug; PT, physical therapy; vs versus

More detailed information is available in Appendix B.1-3 (study characteristics) and C.1-3 (forest plots and GRADE analyses).

WEB ANNEX D.

SYSTEMATIC REVIEW OF EFFECTIVENESS: RESULTS, PHYSICAL THERAPY

Intervention: any physical therapy intervention
Comparator: any standard care, wait-listed for the intervention, or non-physical therapy control
N=12 studies in total.

Outcome	Studies	Effect estimate	Certainty
Pain			
Intensity, post-treatment	6 studies, N=374	Favours intervention SMD -0.6 (-1.15 to -0.04)	Very low
Intensity, follow-up	3 studies, N=187	No difference SMD -0.13 (-0.74 to 0.48)	Very low
30% pain reduction	No studies	-	-
50% pain reduction	No studies	-	-
Health-related quality of life			
Post-treatment	2 studies, N=133	No difference SMD -0.64 (-1.91 to 0.63)	Very low
Follow-up	No studies	-	-
Functional disability			
Post-treatment	4 studies, N=174	Favours intervention SMD -0.64 (-0.95 to -0.34)	Very low
Follow-up	1 study, N=36	No difference SMD -0.38 (-1.04 to 0.28)	Very low
Role functioning			
Post-treatment	2 studies, N=93	No difference (Narrative results only)	Very low
Follow-up	1 study, N=39	No difference No differences between groups in role functioning	Very low
Emotional functioning			
Depression, post-treatment	3 studies, N=93	No difference SMD -0.25 (-0.66 to 0.16)	Very low
Depression, follow-up	1 study, N=36	No difference SMD -0.22 (-0.88 to 0.44)	Very low

Anxiety, post-treatment	2 studies, N=57	No difference SMD 0.06 (-1.39 to 1.51)	Very low
Anxiety, follow-up	No studies	-	-
Sleep			
Post-treatment and follow up	No studies	-	-
Adverse events			
Treatment-related serious adverse events	No studies	-	-
Treatment-related adverse events	4 studies, N=161	No difference RD 0.01 (-0.04 to 0.05)	Very low
Other adverse events	No studies	-	-
Activity participation			
Post-treatment	1 study, N=54	Favours intervention Fewer activity participation absences were reported in the treatment group compared to control group.	Very low
Follow-up	No studies	-	-
Patient global judgement*			
Satisfaction with treatment, post-treatment	No studies	-	-
Satisfaction with treatment, follow-up	No studies	-	-
Impression of change, post-treatment	1 study, N=42	Favours intervention 18/21 reported "slight but noticeable change" and 10/21 reported "definite improvement" in the treatment group. 1/22 reported "slight but noticeable" or "definite improvement" in the control group.	Very low
Impression of change, follow-up	No studies	-	-
Fatigue*			
Post-treatment	No studies	-	-
Follow-up	No studies	-	-

(*) Important outcomes; all other outcomes were assessed as critical.

Abbreviations: N, total number of study participants; RD, risk difference; SMD, standardized mean difference

Effect sizes are presented as standardized mean difference (95% confidence interval) unless otherwise indicated.

WEB ANNEX E.

SYSTEMATIC REVIEW OF EFFECTIVENESS: RESULTS, PSYCHOLOGICAL THERAPY

Intervention: Any psychological intervention.

Comparator: Standard care, wait-listed or active (non-psychological intervention) controls.

Effect sizes in [ ] are for the subset of psychological therapy studies where the intervention involved cognitive behavioural therapy, behavioural therapy, acceptance and commitment therapy, or relaxation training versus any control.

Additional stratified analyses are found in Web Annexes F and G of the systematic review.

Outcome	Studies (all interventions combined)	Effect estimate: all interventions combined [CBT, TB, ACT, RT only]	Certainty**	Face-to-face delivery (CBT, BT, ACT, RT only)	Remote Delivery (CBT, TB, ACT, RT only)
Pain					
Intensity, post-treatment	38 studies, N=3025	Favours intervention SMD -0.29 (-0.43 to -0.16) [SMD -0.25 (-0.38 to -0.12)]	Low	Favours intervention SMD -030 (-0.51 to -0.10)	Favours intervention SMD-0.19 (-0.35 to -0.04)
Intensity, follow-up	21 studies, N=1881	No difference SMD -0.14 (-0.30 to 0.02) [SMD -0.15 (-0.32 to 0.02)]	Low	No difference SMD -0.17 (-0.39 to 0.05)	No difference SMD -0.13 (-0.39 to 0.13)
30% pain reduction, post-treatment	1 study, N=104	No difference SMD 1.13 (0.64 to 2.02) [SMD 1.13 (0.64 to 2.02)]	Very low	No difference RR 1.13 (0.64 to 2.02)	--
30% pain reduction, follow-up	1 study, N=104	No difference SMD 1.07 (0.77 to 1.49) [same]	Very low	No difference RR 1.07 (0.77 to 1.49)	--
50% pain reduction, post-treatment	22 studies, N=1140	Favours intervention SMD 2.11 (1.61 to 2.77) [same]	Low	Favours intervention RR 2.27 (1.48 to 3.49)	Favours intervention RR 1.91 (1.38 to 2.66)
50% pain reduction, follow-up	9 studies, N=445	Favours intervention SMD 2.09 (1.29 to 3.38) [SMD 2.46 (1.41 to 4.29)]	Very low	Favours intervention RR 3.42 (1.86 to 6.28)	Favours intervention RR 1.76 (0.88 to 3.52)
Health-related quality of life					
Post-treatment	12 studies, N=1268	No difference SMD -0.07 (-0.23 to 0.08) [same]	Moderate	No difference SMD -0.12 (-0.36 to 0.11)	No difference SMD -0.06 (-0.23 to 0.12)
Follow-up	6 studies, N=766	No difference SMD 0.01 (-0.13 to 0.16) [same]	Moderate	No difference SMD 0.04 (-0.30 to 0.38)	No difference SMD 0.01 (-0.15 to 0.17)
Functional disability					
Post-treatment	24 studies, N=2358	Favours intervention SMD -0.25 (-0.39 to -0.11) [SMD -0.24 (-0.38 to -0.10)]	Low	Favours intervention SMD -0.31 (-0.47 to -0.14)	No difference SMD -0.14 (-0.33 to 0.06)

Follow-up	14 studies, N=1755	Favours intervention SMD -0.23 (-0.38 to -0.08) [S MD -0.24 (-0.40 to -0.07)]	Moderate	Favours intervention SMD -0.35 (-0.59 to -0.10)	No difference SMD -0.12 (-0.26 to 0.03)
Role functioning					
Post-treatment	9 studies, N=856	No difference SMD -0.21 (-0.52 to 0.10) [SMD -0.22 (-0.55 to 0.12)]	Very low	No difference SMD -0.26 (-0.94 to 0.42)	No difference SMD -0.16 (-0.34 to 0.02)
Follow-up	4 studies, N=476	No difference SMD 0.14 (-0.32 to 0.60) [same]	Very low	No difference SMD 0.29 (-0.35 to 0.93)	No difference SMD - 0.22 (-0.49 to 0.06)
Emotional functioning					
Depression, post-treatment	19 studies, N=1781	No difference SMD -0.02 (-0.11 to 0.08) [SMD -0.02 (-0.12 to 0.02)]	High	No difference SMD -0.06 (-0.24 to 0.13)	No difference SMD -0.01 (-0.13 to 0.12)
Depression, follow-up	12 studies, N=1375	No difference SMD 0.06 (-0.05 to 0.16) [SMD -0.02 (-0.09 to 0.13)]	High	No difference SMD 0.03 (-0.16 to 0.22)	No difference SMD 0.05 (-0.10 to 0.20)
Anxiety, post-treatment	19 studies, N=2031	No difference SMD -0.08 (-0.21, 0.04) [SMD -0.07 (-0.20, 0.06)]	Moderate	No difference SMD -0.03 (-0.19 to 0.14)	No difference SMD -0.14 (-0.34 to 0.06)
Anxiety, follow-up	13 studies, N=1515	No difference SMD -0.07 (-0.17 to 0.03) [SMD -0.08 (-0.19 to 0.02)]	High	No difference SMD -0.09 (-0.25 to 0.06)	No difference SMD -0.09 (-0.24 to 0.06)
Sleep					
Post-treatment	3 studies, N=426	No difference SMD 0.08 (-0.11 to 0.27) [same]	Low	--	--
Follow up	1 study, N=269	No difference SMD 0.00 (-0.24 to 0.24) [same]	Very low	--	No difference SMD 0.0 (-0.24 to 0.24)
Adverse events					
Treatment-related serious adverse events	No studies	--	--	--	--
Treatment-related adverse events	7 studies, N=702	5 studies reported no AEs of any type in any trial arm. One study reported more AEs in the control arm (education + amitriptyline) compared to treatment arm (most attributed to amitriptyline). One study reported mild headache in the treatment arm when listening to CDs.	Very low	--	--
Other adverse events	No studies	--	-	--	--
Activity participation					
Post-treatment	No studies	--	-	--	--
Follow-up	1 study, N=44	**Favours intervention** SMD -0.99 (-1.62 to -0.36) [same]	Very low	**Favours intervention** SMD -0.99 (-1.62 to -0.36)	--

Patient global judgement*					
Satisfaction with treatment, post-treatment	6 studies, N=535	Favours intervention SMD -0.43 (-0.60 to -0.26) [same]	Moderate	Favours intervention SMD -0.57 (-0.93 to -0.21)	Favours intervention SMD -0.39 (-0.58 to -0.19)
Satisfaction with treatment, follow-up	1 study, N=269	Favours intervention SMD -2.20 (-3.50 to -0.90) [same]	Very low	--	Favours intervention MD -2.20 (-3.50 to -0.90)
Impression of change, post-treatment	1 study, N=143	Favours intervention SMD -0.55 (-0.89 to -0.22) [same]	Very low	--	Favours intervention SMD -0.55 (-0.89 to -0.22)
Impression of change, follow-up	1 study, N=143	Favours intervention SMD -0.43 (-0.76 to -0.10) [same]	Very low	--	Favours intervention SMD -0.43 (-0.76 to -0.10)
Fatigue*					
Post-treatment and follow-up	No studies	--		--	--

(*) Important outcomes; all other outcomes were assessed as critical.

(**) Certainty of evidence applies to all studies combined; certainty was not assessed for the subgroup which combined CBT, ACT, BT and RT.

Abbreviations: ACT, acceptance commitment therapy; BT, behavioural therapy; CBT, cognitive behavioural therapy; MD, mean difference; N, total number of study participants; RD, risk difference; RR, risk ratio; RT, relaxation therapy; SMD, standardized mean difference

Effect sizes are presented as standardized mean difference (95% confidence interval) unless otherwise indicated.

WEB ANNEX F.

SYSTEMATIC REVIEW OF EFFECTIVENESS: RESULTS, PHARMACOLOGICAL THERAPY

Outcome	Studies	Effect estimate	Certainty
Pain			
Intensity, post-treatment	5 studies, N=623	Favours intervention SMD -0.19 (-0.35 to -0.03)	Low
Anticonvulsants vs placebo (pregabalin)	1 study, N=107	Favours intervention SMD -0.39 (-0.77 to 0.00)	Very low
Antidepressants vs placebo (amitriptyline, citalopram, duloxetine)	3 studies, N=300	No difference SMD -0.16 (-0.39 to 0.08)	Low
NSAID vs other (Ibuprofen vs acupressure or sham acupressure)	1 study, N=216	No difference SMD -0.14 (-0.43 to 0.14)	Very low
Intensity, follow-up			
Antidepressants vs placebo (amitriptyline, citalopram)	2 studies, N=148	No difference SMD -0.22 (-0.54 to 0.10)	Very low
30% pain reduction, post-treatment	2 studies, N=286	No difference RR 1.33 (1.00 to 1.77)	Very low
Anticonvulsant vs placebo (pregabalin)	1 study, N=105	No difference RR 1.06 (0.61 to 1.85)	Very low
Antidepressant vs placebo (duloxetine)	1 study, N=181	Favours intervention RR 1.44 (1.03 to 2.02)	Very low
30% pain reduction, follow-up	No studies	--	--
50% pain reduction post-treatment	2 studies, N=286	Favours intervention RR 1.71 (1.13 to 2.58)	Very low
Anticonvulsant vs placebo (pregabalin)	1 study, N=105	No difference RR 2.13 (0.70 to 6.47)	Very low
Antidepressant vs placebo (duloxetine)	1 study, N=181	Favours intervention RR 1.65 (1.06 to 2.58)	Very low
50% pain reduction, follow-up			
Triptan vs NSAID vs placebo	1 study, N=29	One crossover trial reported 28/29 (triptan group - zolmitriptan), 28/29 (NSAID group – ibuprofen) and 25/29 (placebo group) reached 50% pain reduction.	Very low
Health-related quality of life			
Post-treatment: Antidepressant vs placebo (amitriptyline)	1 study, N=33	One study reported the treatment group was more likely to improve quality of life from baseline, compared to placebo.	Very low
Follow-up: Antidepressant vs placebo (amitriptyline)	1 study, N=33	One study reported the antidepressant group was more likely to improve quality of life from baseline, compared to placebo.	Very low

Functional disability			
Post-treatment: Antidepressant vs placebo (duloxetine)	1 study, N=184	No difference SMD 0.10 (-0.19 to 0.39)	Very low
Follow-up	No studies		
Role functioning			
Post-treatment: ASA vs placebo	1 study, N=29	One cross-over trial (29 participants) reported fewer school absences compared to baseline in the ASA (acetyl salicylic acid) group compared to the placebo group.	Very low
Follow-up	No studies		
Emotional functioning			
Depression, post-treatment: Antidepressant vs placebo(citalopram, amitriptyline, duloxetine)	3 studies, N=389	No difference SMD -0.06 (-0.25 to 0.14)	Low
Depression, follow-up: Antidepressant vs placebo (citalopram)	1 study, N=115	No difference SMD -0.26 (-0.63 to 0.11)	Very low
Anxiety, post-treatment: Antidepressant vs placebo (citalopram, duloxetine)	2 studies, N=299	No difference SMD -0.07 (-0.30, 0.16)	Low
Anxiety, follow-up: Antidepressant vs placebo (citalopram)	1 study, N=115	No difference SMD 0.03 (-0.34 to 0.39)	Very low
Sleep			
Post-treatment: Anticonvulsants vs placebo (pregabalin)	1 study, N=104	No difference SMD -0.09 (-0.47 to 0.30)	Very low
Follow up	No studies		
Adverse events			
Treatment-related serious adverse events	4 studies, N=1128	No difference RD 0.00 (-0.01 to 0.01)	Very low
Anticonvulsant vs placebo (pregabalin)	1 study, N=107	No difference RD 0.02 (-0.03 to 0.07)	Very low
Antidepressants vs placebo (duloxetine)	1 study, N=184	No difference RD 0.02 (-0.01 to 0.06)	Very low
NSAID + other vs placebo (sumatriptan and naproxen)	2 studies, N=837	No difference RD 0.00 (-0.01 to 0.01)	Very low
Treatment-related adverse events	3 studies, N=781	No difference RD 0.09 (-0.02 to 0.21)	Very low

Anticonvulsant vs placebo (pregabalin)	1 study, N=107	No difference RD 0.06 (-0.12 to 0.24)	Very low
Antidepressants vs placebo (duloxetine)	1 study, N=184	Favours control RD 0.20 (0.07 to 0.33)	Very low
NSAID + other vs placebo (sumatriptan and naproxen)	1 study, N=490	No difference RD 0.03 (-0.02 to 0.09)	Very low
Other adverse events	No studies		
Activity participation*			
Post-treatment	1 study, N=110	One non-randomized study reported no differences between citalopram and placebo groups on activity participation, post-treatment.	Very low
Follow-up	No studies	--	-
Patient global judgement*			
Satisfaction with treatment, post-treatment	3 studies, N=695	One study reported a higher percentage of subjects treated with sumatriptan and naproxen versus placebo reported being satisfied/very satisfied for "how effective the medication is overall" and "overall satisfaction with medication" at 2 and 24 hours post-dose (unadjusted P ≤ .014). Two further studies comparing antidepressants (citalopram and amitriptyline) to placebo did not note any differences between groups in the ITT analyses.	Low
Satisfaction with treatment, follow-up	1 study, N=115	One study reported no differences between children receiving antidepressants (citalopram) to placebo in the ITT analyses at follow-up (p = 0.491).	Very low
Impression of change, post-treatment	1 study, N=104	One study reported patient global impression of change response was significantly improved with pregabalin versus placebo (p = 0.013), with 53.1% of subjects much improved or very much improved at endpoint with pregabalin, compared with 29.5% with placebo.	Very low
Impression of change, follow up	No studies		
Fatigue*			
Post-treatment	No studies		
Follow up	No studies		

(*) These outcomes were prioritized as "important outcomes"; the remainder were considered "critical outcomes".

Abbreviations: AE, treatment-related adverse event; N, number of studies; RD difference; SMD, standardized mean difference; ITT, intention to treat

WEB ANNEX G.

SYSTEMATIC REVIEW OF QUALITATIVE EVIDENCE: STUDY CHARACTERISTICS

Characteristic	Findings, total body of evidence
No. studies/no. participants	Fulfilled inclusion criteria: 74 Reviewed in detail: 33
Linkage to effectiveness review	Linked to studies in quantitative review: 12 Examined an included intervention but not linked to a study in the effectiveness review: 6 Not linked to effectiveness review: 15*
Funders	Not stated: 22 (30%) Charitable foundation: 13 (18%) Government grant: 17 (23%) Pharma company: 3 (4%) Other (e.g. academic institution, hospital): 21 (28%) No funding: 4 (5%) (Note: some studies listed multiple funders.)
Conflict of interest	Declared no conflicts of interest: 29 (39%) No information provided: 43 (58%) Declared a conflict: 2 (3%) (not included in the detailed analysis of 33 studies)
Country income	HIC: 60 (81%) MIC: 14 (19%) LIC: 1 (1%)
Country of origin	HIC: USA (22), Canada (9), United Kingdom (9), Sweden (8), Norway (3), Spain (2), Australia (3), France (1), Germany (1), The Netherlands (1), Portugal (1), Taiwan (1) MIC: Brazil (3), South Africa (3), Thailand (3), Jordan (1), Zambia (1), Morocco (1), Cameroon (1), Indonesia (1), Tanzania (1) LIC: 0 studies (Note: two studies encompassed two countries.)
Type of pain/population	Palliative care: 9 (12%) Included children with an intellectual disability:4 (5%) Abdominal pain: 4 (5%) Arthritis: 10- (14%) Cancer: 10 (14%) Sickle cell disease: 5 (7%) MSS pain: 4 (5%), Unspecified type: 6 (8%) Mixed diagnoses/types of pain: 14 (19%) Other pain conditions: 15 (20%)
Participants	Children: 54% Family members: 50% Health care providers: 31%

Age (years)	<1 year: 2 1–9: 3 10–19: 35 Mixed: 34 Not specified: 2
Interventions	Of the 18 studies with link to a specific intervention of interest: Psychological: 9 Physical therapy: 5 Mixed psychological, physical and/or pharmacological interventions: 4 Pharmacological: 0

(*) Studies included since the setting was LMIC and relevant aspects of chronic pain management in children were examined, although without focus on a specific intervention.

Categories of low-, middle- and high-income countries are based on World Bank List of Economies, June 2020 (https://www.ilae.org/files/dmfile/World-Bank-list-of-economies-2020_09.pdf).

Numbers represent number of studies, unless otherwise indicated.

Abbreviations: CBT, cognitive behavioural therapy; COI, conflict of interests; CRPS, Chronic Regional Pain Syndrome; HIC, high-income country; LIC, low-income country; MIC, middle-income country; MSS musculoskeletal system; no., number; NR, not reported; NRS, non-randomized study/studies; NSAID, non-steroidal anti-inflammatory drug; PT, physical therapy

More detailed information is available from the systematic review.

WEB ANNEX H.

SUMMARY OF THE KEY FINDINGS OF THE SYSTEMATIC REVIEW OF QUALITATIVE RESEARCH

Finding	Interventions	Countries (references)	Confidence
Psychological therapies			
1. For ACT aimed at parents and their adolescent child, some parents accepted their role in addressing their own behaviour and thoughts, whereas others rejected this.	ACT	Sweden (31)	Low
2. Some adolescent children did not see the relevance of ACT for addressing pain and wanted a medical cure for their pain, not to live well with pain.	ACT	Sweden (31)	Low
3. For some parents and adolescent children, ACT was viewed as a last resort treatment, only to be pursued when a biomedical approach to explaining and treating pain had been unsuccessful.	ACT	Sweden (31)	Moderate
4. Having a choice of different tasks to suit personal preferences and clarity of purpose of tasks in ACT and CBT interventions were important factors in their acceptability for adolescent children. Another important factor in the Web-MAP psychological intervention was giving adolescents alternative strategies to use if one did not work.	ACT, CBT, WebMAP	Sweden, USA, Canada (31, 34, 35)	High
5. Online psychological interventions, with or without an exercise component, for children aged 9 years and over with abdominal pain or cancer had low adherence caused by boredom from the lengthy and/or repetitive content.	DARWeb, Pain Squad+ smartphone app	Spain, Canada (38, 39)	High
6. When adolescent children found the psychological techniques to have positive outcomes, they used them in daily life. Parents stated that it took evidence from personal experience that the practice would be effective in managing pain to motivate their adolescent children to complete it.	WebMAP, CBT	USA, Canada (34, 35)	Moderate
7. Some children aged 9 years and over and parents were put off the interventions if the intervention content did not seem to apply to them or meet their needs. Conversely, they were encouraged to use it when they identified with the content.	CBT (WebMAP), DARWeb	USA, Canada, Spain (35, 38)	Moderate
8. Adolescent females indicated that group sessions could diminish communication as they did not like speaking about personal issues in front of others or did not identify with the other members of the group: this led to reduced participation.	ACT, FIT Teens	Sweden, USA (31, 40)	Moderate
9. Children aged 10–19 years with abdominal pain and childhood-onset systemic lupus erythematosus expressed reluctance to use skills learned in the interventions, such as coping skills, in front of their peers. This meant these skills were not practiced regularly in daily life.	CBT (AIM & TEACH)	USA (32, 33)	Low
13. For both PT and psychological interventions, the characteristics and behaviour of the person delivering the intervention, e.g. being warm, open, caring and empathetic, were important to gain the child's trust and develop rapport, and thus help them feel that the person/therapist understood their pain.	Psychological interventions – MBSR, TEACH	Sweden, USA (23, 32, 42)	Moderate
14. PT and psychological interventions were more acceptable when they were tailored to the individual child and their developmental and information processing needs and physical abilities. Aspects requiring tailoring include the format (visual, auditory), language sophistication, task complexity and appropriateness of metaphors used for pain management and difficulty of physical exercises. In an LMIC, treatments for palliative care were more acceptable to children when they were tailored to the individual child.	Psychological interventions - MBSR, TEACH, CBT	Sweden, USA, UK, Australia, Zambia (24, 25, 31, 32, 34, 40, 42, 43)	High
23. Children aged 9 years and older and their parents found skills learned in psychological interventions were transferable and also improved factors such as sleep problems, anxiety and/or mood and quality of life.	CBT, PSST, DARWeb, pain neuroscience education, AIM/ ADAPT, TEACH	USA, Spain, Portugal (21, 32-34, 36-38)	Moderate
25. Children aged 9 years and older perceived that psychological interventions or those with psychological components alleviated pain levels experienced for neck pain, abdominal pain, lupus and headaches/migraine.	TEACH, DARWeb & CBT	USA, Spain, Portugal (21, 32, 34, 38)	Low
24. A group format for physical and psychological intervention delivery normalized chronic pain for children and allowed sharing of experiences: this was perceived as supportive. However, some children participating in an ACT intervention with group sessions for children with various types of chronic pain felt guilty that they were not as severely ill as other intervention group participants and considered themselves imposters. Group dynamics could also be a negative experience for some children if negative attitudes and prejudices among group members were not addressed by the group facilitator.	Psychological intervention – ACT, MBSR	USA, Canada, Australia, Sweden (22, 23, 25, 31)	High
33. It was sometimes burdensome for families to have to travel to repeated face-to-face intervention sessions and a barrier to participation in PT and psychological interventions. Children had to rely on their parents to take them to these intervention sessions.	Psychological intervention – TEACH	USA, Canada, Australia (22, 25, 32)	Moderate

34. For psychological interventions using CBT, a child's schooling, homework and after-school commitments were sometimes in competition with time for practising skills learned in the intervention. For online interventions where components had to be completed at specific times (DARweb) the same commitments could pose a barrier to their timely completion.	CBT (TEACH, CBT-HA), DARWeb	USA, Spain (32, 34, 38)	Moderate
35. Parents and children aged 9 years and over needed reminders to practise the psychological and PT interventions at home.	Psychological interventions –TEACH, CBT-HA, WebMAP, DARWeb, Pain Squad+	USA, Canada, Australia, Spain (22, 32, 34, 35, 38, 39)	High
Physical therapies			
36. Social support helped adherence to PT interventions. For example, if a child had assistance from school staff to conduct their exercise programme then their adherence was better than that of children and families with no help at school. Parents of children undertaking the WebMAP psychological intervention also expressed a desire/need for social support from other families of children with headache and ongoing booster session support from the intervention delivery team once the programme had ended.	Psychological intervention -WebMAP	USA, Canada, Australia (25, 35)	Moderate
10. PT interventions prescribing repetitive exercises for children aged 7 years and over with JIA led to child and parental boredom resulting in adherence problems and family conflict. Children preferred activities over exercises or, when specific exercises were required for them to be better incorporated into existing family lifestyle/school routines or community group activities.	PT exercise interventions	UK, Australia (24-26)	High
11. For an exercise intervention for children aged 7–13 years with JIA, the desired aim/outcome of families did not meld with the intervention aims: they wanted better psychosocial outcomes and not physical outcomes.	PT exercise intervention	UK (24)	Very low
12. For a physical exercise intervention, parents of children over 8 years with JIA felt their children were reluctant to be different from their peers; this meant they were less likely to take part in suggested physical exercise and thus reduced the opportunities for exercise and joint movement.	PT exercise intervention	Australia (26)	Low
26. Both parents and instructors noticed improved physical fitness in children with JIA and teenagers with fibromyalgia themselves noticed their improved fitness. This occurred for both group interventions and home-based exercises. Teenagers with fibromyalgia in the FIT Teens group program reported decreased pain flares, increased strength, stamina and physical functioning due to the intervention.	PT interventions incl. FIT Teens	USA, Canada, Australia, Sweden (22, 26, 40, 42)	High
27. For PT interventions for JIA and lower back pain, children's improved physical fitness was perceived to have improved other aspects of children's lives, e.g. improved balance leading to a perceived reduction in falls after one intervention and increased confidence in physical abilities giving children more confidence in being able to cope with new situations. Some young people resumed physical activities they had previously abandoned.	PT interventions	Sweden, Canada (22, 42)	Moderate
28. In both psychological and PT interventions, children aged over 9 years perceived that reducing their focus on pain, e.g. by using distraction techniques, resulted in reduced pain intensity. Teenagers with fibromyalgia in the FIT Teens PT program reported decreased pain flares due to the intervention.	PT interventions incl. FIT Teens & MBSR	USA, Sweden (23, 40, 42)	Low
29. Female children with JIA or fibromyalgia aged between 7 and 19 years of age and parents felt that PT interventions could exacerbate pain leading to non-adherence, and cause parental distress and conflict between parent and child which affected the whole family. A fear of worsening pain was also a barrier to adherence in children with musculoskeletal pain. Some children with fibromyalgia reported being sore for two days, exhausted after sessions and that the physical exercises hurt while they were doing them.	PT exercise interventions – FIT Teens	USA, Canada, UK, Australia, Sweden (22, 24, 26, 40, 42)	High
30. Exercise interventions for children aged 7 years and over with JIA requiring a significant time commitment and a boring regimen worsened negative impacts on psychosocial outcomes of some families: overburdening children and their families caused psychological distress, parent-child conflict, parent-parent conflict, and allowed parents less time for their other children and for paid work.	PT exercise interventions	UK, Australia (24, 26)	Moderate
33. It was sometimes burdensome for families to have to travel to repeated face-to-face intervention sessions and a barrier to participation in PT and psychological interventions. Children had to rely on their parents to take them to these intervention sessions.	PT interventions	USA, Canada, Australia (22, 25, 32)	Moderate
35. Parents and children aged 9 years and over needed reminders to practise the psychological and PT interventions at home.	PT interventions – Pain Squad +	USA, Canada, Australia, Spain (22, 32, 34, 35, 38, 39)	High

36. Social support helped adherence. For example, if a child had assistance from school staff to conduct their exercise programme then their adherence was better than that of children and families with no help at school. Parents of children undertaking the WebMAP psychological intervention also expressed a desire/need for social support from other families of children with headache and ongoing booster session support from the intervention delivery team once the programme had ended.	PT interventions, WebMAP psychological intervention	USA, Canada, Australia (25, 35)	Moderate
37. The length of time required to complete the prescribed exercise programme was difficult to fit around the child's existing school, homework and social commitments; exercises completed within school time and those which took less than half-an-hour to complete or did not involve travelling to a venue such as a gym were more likely to be adhered to. Access to an intervention in community centres was easier for children with JIA and their families than access to hospitals.	PT interventions/ PT components in mixed-type interventions	Canada, USA, UK, Australia (22, 24-26, 40)	High
38. In order to keep children and families involved in home exercise programmes, parents of children with JIA recommended peer-accepted lifestyle activities of less than 30 minutes, mechanisms to identify improvements and adaptation of exercises according to the child's current health status. Children preferred activities over exercises or exercises which fitted into their routines and existing activities: this helped their adherence to the intervention.	PT exercise Interventions	UK, Australia (24, 26)	Moderate
39. Healthcare professionals and children felt fear of pain could be overcome during the PT intervention if children could learn about the difference between conditional pain caused by fibromyalgia or JIA, and exercise-induced muscle soreness.	PT exercise intervention	USA, Canada (22, 40)	Low
Pharmacological therapies			
31. Some HCPs including doctors and nurses expressed the fear that children might get addicted to opioids and fake reports of pain to receive opioids, and that opioids were more dangerous than the pain itself: this meant that pain went untreated and children suffered.	None specific – opioids	Thailand, Morocco (44, 48)	Low
21. For children with cancer, parents demonstrated or stated their acceptance of opioid treatment: some Jordanian parents stated that their child's pain could and should be managed, including with analgesics such as opioids. Similarly, Cameroonian children aged 9–14 with cancer receiving palliative care in rural communities and their families welcomed provision of adequate pain medication, including opioids (oral morphine), which was provided for free. In Indonesia, parents administered opioids (morphine) to their child with cancer pain for palliative care under doctor's advice. In contrast, some HCPs in Morocco and Thailand believed that parents feared their children would become addicted to morphine and were likely to refuse it.	None specific – opioids	Jordan, Cameroon, Indonesia, Morocco, Thailand (46, 49-52)	Moderate
Therapies in general			
40. In some cultures, it may not be acceptable for children to express their pain – HCPs need to take into account children's values and beliefs in order to improve the quality of pain management and care.	None	Thailand, Morocco (48, 58)	Moderate
17. Some cultural beliefs were impediments or barriers to pain management. Physicians in Morocco believed that, for some families, illness-related pain was perceived as inevitable and had to be endured, especially by boys; while nurses in Zambia reported that traditional beliefs that attributed sickness to witchcraft made it difficult for some patients to cooperate with pain management, whether pharmacological or nonpharmacological. The cultural preference/norm that patients should hide their pain in Thailand and Tanzania contributed to inadequate pain management for cancer pain and other pain conditions.	None	Morocco, Zambia, Thailand, Tanzania (29, 43, 44, 48)	Moderate
20. When assessing pain in Morocco, some HCPs recognized that they needed more training in assessing and managing children's pain and wanted tools/scales to measure pain for themselves and children. In some situations in Jordan, Morocco and Brazil, a crying child was identified as the most common pain cue/primary pain manifestation recognized by parents and HCPs. In Thailand and Brazil, HCPs stated that parents played a key role in communicating their child's pain to them, especially when a child had cognitive impairments, and that parents were often better at judging pain than HCPs because they know their own child. However, parents in Indonesia reported finding it difficult to judge if their child with cancer was in pain and the level of pain, unless the child told them. Some Jordanian parents believed that children with cancer should be responsible and express their pain, rather than be asked about their pain.	None	Jordan, Morocco, Brazil, Thailand (44, 47-50)	Low

Abbreviations: ACT, acceptance and commitment therapy; CBT, cognitive behavioural therapy; HCP, health care providers; JIA, juvenile idiopathic arthritis; LMIC, low- and middle-income countries; PT, physical therapy, WebMAP , Web-based Management of Adolescent Pain;FIT , Fibromyalgia Integrative Training;

Note: Some included studies examined more than one type of intervention (physical, psychological or pharmacological): these studies are categorized by the main intervention type.

The numbers preceding each finding refer to findings in the systematic review. For the complete findings, see the systematic review (Cochrane Pain, Palliative and Supportive Care, France E et al. A qualitative evidence synthesis of the management of chronic pain in children. Cochrane; September 2020).

WEB ANNEX I.

SYSTEMATIC REVIEW OF ECONOMIC STUDIES: METHODS

Characteristic	Effectiveness of pharmacotherapy
Study designs, included	All types of comparative economic evaluations including cost-utility, cost-effectiveness, cost-benefit or cost-consequence analyses assessing both costs and outcomes associated with interventions of interest.
Study designs, excluded	Cost-of-illness studies, studies with effectiveness data based only on assumptions
Interventions	As for the effectiveness and qualitative reviews: medicines, including antidepressants, acetaminophen/paracetamol, opioids, NSAIDs, anticonvulsant drugs, antiepileptic drugs, ketamine; drugs via any route
Comparators	As for the effectiveness review
Use of existing systematic reviews	None: de novo review
Databases searched	EMBASE, MEDLINE, MEDLINE in-Process, Cochrane Controlled Trials Register, NHS EED
Dates searched	2010 to 23 August 2020
Languages	English only
Risk of bias tools	Risk of bias not assessed.
Assessment of the quality/ confidence in the body of evidence	Studies were examined at the individual level only.

WEB ANNEX J.

SYSTEMATIC REVIEW OF ECONOMIC EVALUATION STUDIES: STUDY CHARACTERISTICS

Characteristic	Findings, total body of evidence
No. studies/no. participants	3 studies/ Evans 512, Lalouni 100, Law 228
Funders	NR: Evans Mixed: Lalouni US National Institutes of Health: law
Conflict of interest	No conflict of interest: Evans, Law, Lalouni
Country of origin	USA: Evans, Law Sweden: Lalouni
Type of pain/population	Mixed: Evans, Law Functional abdominal pain disorders: Lalouni
Age in years (SD); % female	Evans: 15.2 (2.6); 76% Laloui: I: 10.1 (1.2); C: 10.4 (1.5); I 61%, C: 77% Law: I: 14.5 (1.7), C: 14.9 (1.6); I: 77%, C: 73%
Interventions and comparators	Interdisciplinary pain rehabilitation programme (no comparator) (Evans) CBT delivered online vs usual care (Lalouni) Adjunctive internet CBT vs adjunctive internet education (Law)
Type of economic analysis	Cost-effectiveness analysis: Evans Cost-utility analysis: Lalouni Comparative cost analysis: Law

Abbreviations: C, comparison group; CBT, cognitive behavioural therapy; I, intervention group; no., number; SD, standard deviation

Included studies:

Evans JR, Benore E, Banez GA. The Cost-Effectiveness of Intensive Interdisciplinary Pediatric Chronic Pain Rehabilitation. J Pediatr Psychol. 2016;41(8):849-856.

Lalouni M, Ljótsson B, Bonnert M et al. Clinical and Cost Effectiveness of Online Cognitive Behavioural Therapy in Children With Functional Abdominal Pain Disorders. Clin Gastroenterol Hepatol. 2019;17(11):2236-2244.e2211.

Law EF, Groenewald CB, Zhou C, Palermo TM. Effect on Health Care Costs for Adolescents Receiving Adjunctive Internet-Delivered Cognitive-Behavioural Therapy: Results of a Randomized Controlled Trial. J Pain. 2018;19(8):910-919.

WEB ANNEX K.

EVIDENCE-TO-DECISION TABLES

The Guideline Development Group discussed each of the listed considerations and made a judgement in each case (highlighted). This process facilitated the formulation of the recommendations.

A. PHYSICAL THERAPY

Question	Judgement
1. Is the problem a priority?	No, Yes, Varies, Uncertain
2. How substantial are the benefits?	Large, Moderate, Small, Trivial, Varies, Uncertain
3. How substantial are the harms?	Large, Moderate, Small, Trivial, Varies, Uncertain
4. What is the overall certainty of the evidence?	High, Moderate, Low, Very Low
5. What is the balance between benefits and harms?	Favours intervention, Against intervention: probably favours physical therapy
6. Do people value the intervention?	Degree of Variability or Uncertainty: possibly important uncertainty or variability
7. How large are the resource requirements (costs)?	Large, Moderate, Negligible costs or savings: varies
8. What is the certainty of the evidence for the costs?	High, Moderate, Low, Very Low: no data
9. Is the intervention cost-effective?	Favours intervention, Against intervention: probably favours physical therapy
10. What would the impact be on health equity?	Reduced, Increased, Varies, Uncertain: probably increased

B. PSYCHOLOGICAL THERAPY

Question	Judgement
1. Is the problem a priority?	No, Yes, Varies, Uncertain
2. How substantial are the benefits?	Large, Moderate, Small, Trivial, Varies, Uncertain
3. How substantial are the harms?	Large, Moderate, Small, Trivial, Varies, Uncertain
4. What is the overall certainty of the evidence?	High, Moderate, Low, Very Low
5. What is the balance between benefits and harms?	Favours intervention, Against intervention: favours/probably favours psychological therapy
6. Do people value the intervention?	Degree of Variability or Uncertainty: no or probably no important uncertainty or variability
7. How large are the resource requirements (costs)?	Large, Moderate, Negligible costs or savings: varies
8. What is the certainty of the evidence for the costs?	High, Moderate, Low, Very Low: no data
9. Is the intervention cost-effective?	Favours intervention, Against intervention: probably favours psychological therapy, varies
10. What would the impact be on health equity?	Reduced, Increased, Varies, Uncertain: probably increased
11. Is the intervention acceptable to all stakeholders?	No, Yes, Varies, Uncertain: probably yes
12. Is the intervention feasible to implement?	No, Yes, Varies, Uncertain: probably yes

C. PHARMACOLOGICAL THERAPY

Question	Judgement
1. Is the problem a priority?	No, Yes, Varies, Uncertain
2. How substantial are the benefits?	Large, Moderate, Small, Trivial, Varies, Uncertain
3. How substantial are the harms?	Large, Moderate, Small, Trivial, Varies, Uncertain
4. What is the overall certainty of the evidence?	High, Moderate, Low, Very Low
5. What is the balance between benefits and harms?	Favours intervention, Against intervention: probably favours pharmacotherapy/varies
6. Do people value the intervention?	Degree of Variability or Uncertainty: possibly important uncertainty or variability/probably no important uncertainty or variability
7. How large are the resource requirements (costs)?	Large, Moderate, Negligible costs or savings: varies
8. What is the certainty of the evidence for the costs?	High, Moderate, Low, Very Low: no data
9. Is the intervention cost-effective?	Favours intervention, Against intervention: probably favours pharmacotherapy, varies
10. What would the impact be on health equity?	Reduced, Increased, Varies, Uncertain: probably increased
11. Is the intervention acceptable to all stakeholders?	No, Yes, Varies, Uncertain: probably yes
12. Is the intervention feasible to implement?	No, Yes, Varies, Uncertain: probably yes


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