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CLINICAL PRACTICE GUIDELINES

Reducing pain in children with cancer: Methodology for the development of a clinical practice guideline

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Abstract

Although pain is one of the most prevalent and bothersome symptoms children with cancer experience, evidence-based guidance regarding assessment and management is lacking. With 44 international, multidisciplinary healthcare professionals and nine patient representatives, we aimed to develop a clinical practice guideline (following GRADE methodology), addressing assessment and pharmacological, psychological, and physical management of tumor-, treatment-, and

Abbreviations: AMED, Allied and Complementary Medicine Database; BMA, bone marrow aspiration; BMP, bone marrow puncture; CCC, Cochrane Childhood Cancer; CENTRAL, Cochrane Central Register of Controlled Trials; CI, confidence interval; CINAHL, Cumulative Index to Nursing and Allied Health Literature; COSMIN, COnsensus-based Standards for the selection of health status Measurement INstruments; CPG, Clinical Practice Guideline; EMBASE, Excerpta Medica dataBASE; EtD, evidence to decision; GDP, Guideline Development Panel; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HaPI, health and psychosocial instruments; ICMJE, International Committee of Medical Journal Editors; iPOG, International Pediatric Oncology Guidelines in Supportive Care Network; MA, meta-analysis; MEDLINE, Medical Literature Analysis and Retrieval System Online; MeSH, Medical Subject Heading; PICO, Patient Intervention Comparison Outcome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCCT, Randomized Controlled Crossover Trial; RCT, Randomized Controlled Trial; SR, systematic review; WG1, Working Group 1: Assessment of pain; WG2A, Working Group 2A: Pharmacological management of tumor-related pain; WG2B, Working Group 2B: Pharmacological management of treatment-related pain; WG2C, Working Group 2C: Pharmacological management of procedure-related pain; WG3A, Working Group 3A: Psychological and physical management of tumor and treatment-related pain; WG3B, Working Group 3B: Psychological and physical management of procedure-related pain.

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procedure-related pain in children with cancer. In this paper, we present our thorough methodology for this development, including the challenges we faced and how we approached these. This lays the foundation for our clinical practice guideline, for which there is a high clinical demand.

KEYWORDS
clinical practice guideline, evidence-based medicine, pain, pediatric oncology, supportive care

1 | INTRODUCTION

Pain in children with cancer has been well acknowledged and puts great burden on patients and their families.[1,2] For this reason, providing age-appropriate pain assessments and treatment strategies to reduce is a priority. Pain in children treated for cancer can have multiple origins, such as the tumor itself (e.g., pain associated with bone metastases), adverse effects of anticancer treatment (e.g., chemotherapy-induced neuropathic pain), or painful and distressing procedures that children with cancer undergo frequently (e.g., accessing a central venous access port).[3–5]

Even though reducing pain has been acknowledged as being of utmost importance, there is no uniform guideline that advises on assessment and management of pain in children with cancer. This is unfortunate, as high-quality evidence-based guidelines, also called clinical practice guidelines (CPGs), have been shown repeatedly to improve patient outcomes.[6,7] Clinical practice guidelines include a systematic review of evidence, thus providing clinicians with an overview of the current best available evidence.[8] Recommendations are then based upon the evidence and formulated by a representative multidisciplinary panel including professionals and patient representatives. Justifications and subgroup considerations are included to provide insight as to why specific treatments should or should not be provided and to which patients. In addition, by summarizing the available evidence research gaps are identified that help in composing and prioritizing a research agenda.

We know that children experience pain as one of the most bothersome symptoms of cancer and its treatment, and parents even designated pain as the most problematic are for their child undergoing cancer treatment.[9,10] With the current lack of evidence-based guidance in this area, and the existing large variations in daily practice, a CPG could be pivotal to improve pain outcomes and quality of life.[11]

We therefore initiated the development of a comprehensive CPG regarding pain in children with cancer. Our aim was to formulate recommendations for care for children with cancer regarding assessment and management of pain. In this article, we provide an overview of our methodology, and briefly present the identified evidence. Subsequent manuscripts will focus on the recommendations, reporting on (1) pain assessment, (2) management of procedure-related pain, and (3) management of tumor- and toxicity-related pain.

2 | METHODS

2.1 | Multidisciplinary guideline development panel

A full overview of the guideline development panel (GDP) can be found in Figure 1. The GDP was multidisciplinary and multinational, and consisted of 44 members, recruited through the International Pediatric Oncology Guidelines in Supportive Care Network (iPOG network) or solicited by other members.[12] All members provided a completed International Committee of Medical Journal Editors (ICMJE) form for disclosure of potential conflicts of interest.

The GDP consisted of a core group (CG) and six working groups (WGs), that focused on assessment and evaluation of pain (WG1), pharmacological management of tumor-related pain (WG2A), toxicity-related pain (WG2B), and procedure-related pain (WG2C), and psychological and physical management of tumor- and toxicity-related pain (WG3A) and procedure-related pain (WG3B).

Great value was placed on incorporating the perspective of the patient and the family. This was deemed important from a clinical viewpoint but also because we know from previous research how the involvement of patient representatives positively influenced CPG development.[13] Therefore, nine patient representatives (four cancer survivors and five parents) were solicited through childhood cancer patient/parent organizations and were involved in reviewing draft recommendations. Input was used to revise recommendations. The patient representatives attended a short training course covering the basics of evidence-based guideline development.

2.2 | Formulation of clinical questions

All WGs formulated clinical questions for topics deemed clinically relevant. Questions regarding pain assessment were developed in accordance with the COSMIN standards (COnsensus-based Standards for the selection of health status Measurement INstruments), defining the following: (1) target population, (2) domain, (3) determinant, and (4) relevant outcomes.[14] Questions regarding treatment strategies were developed according to the PICOS format, defining the following: (1) patient, (2) intervention, (3) comparison, (4) relevant outcomes, and (5) study design.

After finalization of the clinical questions, a simple nonweighted voting procedure using a 10-point scale was carried out to prioritize these questions for CPG development. For each WG, the clinical

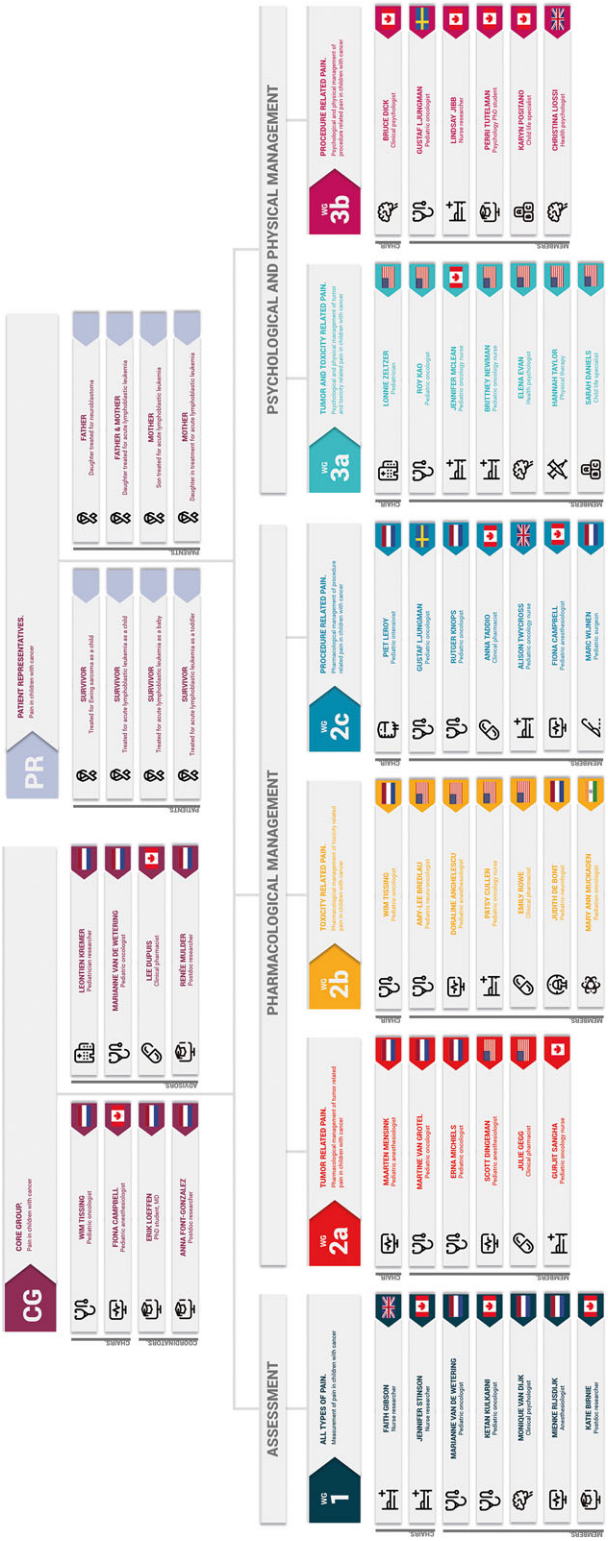

FIGURE 1 Overview of the guideline development panel

questions with the highest median score were included (maximum 5 per WG, to keep the work manageable).

2.3 | Rating importance of outcomes

In accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, we wanted to decide on important outcomes before commencing the literature search, as this would facilitate the discussion for recommendations later on in the process.[15] For all individual clinical questions, WG and CG members voted on the importance of outcomes on a 9-point scale. Outcomes were categorized according to median score: 1–3: "critical for decision making," 4–6: "important, but not critical for decision making," and 7–9: "low importance for decision making."[15]

2.4 | Systematic literature search

Together with a medical librarian, we designed two comprehensive search strategies. The first focused on identifying studies evaluating measurement properties of pain and distress measurement instruments used in children with cancer (WG1). The second on identifying randomized controlled trials (RCTs) on interventions to reduce pain in children with cancer (covering all clinical questions of WG2 and WG3, as we expected separate clinical question searches would lead to a lot of overlapping citations and thus double work).

Searches were compiled by combining several search filters. If available, we used search filters of Cochrane Childhood Cancer (CCC).[16] We combined four search strategies with the "AND" Boolean operator, focusing on (1) children, (2) childhood cancer, (3) pain, and (4) measurement properties (WG1) or RCTs (WG2-3). See Supporting Information Material S1 for complete search strategies.

Several electronic databases were searched, from inception until March 13, 2018 (initial search March 23, 2017, top-up search March 13, 2018): PubMed/MEDLINE, CINAHL, PsycINFO, HaPI, EMBASE, AMED, and CENTRAL. We limited results to English language publications. For identification of additional studies that were not included in the search, we performed forward and backward citation chasing of included studies and consulted experts for missing eligible studies.

2.5 | Eligibility criteria

Studies had to meet certain criteria, which differed somewhat per clinical question (see Supporting Information Material S2). Overarching inclusion criteria were as follows.

Patient criteria. Studies that encompassed children and/or adolescents with cancer, defined as: (1) all participants < 25 years old or a median or mean ≤ 16 years old and (2) at least 75% of participants diagnosed with cancer. For the WGs focused on procedure-related pain, participants had to undergo a relevant minor procedure (e.g., blood sampling, access to central venous access port), a lumbar puncture procedure, or a relevant major procedure (e.g., bone marrow aspiration, bone biopsy).

Intervention /instrument criteria. Studies that investigated a relevant intervention (pertinent to the clinical question, e.g., gabapentin for

neuropathic pain, hypnosis for procedural pain) or a relevant measurement instrument (e.g., visual analog scale for self-rated pain).

Comparison criteria. Only relevant for intervention studies. Comparators were active (e.g., placebo, another medication) or passive (e.g., standard care).

Outcome criteria. Relevant outcomes for measurement properties studies were defined in accordance with COSMIN (e.g., reliability, validity).[14] For RCTs on interventions, several outcomes were included for all clinical questions (e.g., pain intensity, adverse effects) and several outcomes differed per clinical question (e.g., ability to eat, duration of procedure).

Study criteria. Only primary studies with at least 10 participants were included. In accordance with COSMIN, measurement properties studies had to state that their aim was to evaluate the clinimetric properties of an existing measurement instrument or to develop a new measurement instrument.[14] For intervention studies, only RCTs (including crossover RCTs) were included. Studies had to be published in a peer-reviewed journal, with a full-text available in English.

2.6 | Selection of studies

As we anticipated retrieving a large number of citations, we opted for a three-step fan-out approach (see Figure 2). We began with a selection based on titles only as this process was recently found to be potentially more effective than screening on titles and abstracts.[17]

Title selection. Two independent reviewers (EL, WT/FC) performed this selection, which served to exclude studies that were obviously irrelevant (e.g., older adult population). A conservative approach for inclusion was used: all citations classified as "include" by at least one reviewer were included for the next selection round (irrespective of the other reviewer's classification, no discussion was held). This approach was applied only during title selection. In all other phases, discrepancies among two reviewers were discussed in detail and resolved by consensus (or if necessary by a third reviewer). Reviewers identified the specific WG(s) which the citation was relevant for, after which the included citations were fanned out to the relevant WGs.

To pilot the title selection process, three reviewers (EL, WT, and RM) appraised the first 250 citations. If absolute agreement was below 85%, selection criteria were optimized and the pilot was repeated for the subsequent 250 citations.

Abstract selection. Two independent reviewers (EL, members of relevant WG) performed the WG-wise selection based on title and abstract. Reviewers also flagged citations that were relevant for another WG.

Full-text selection. In the final selection round, the same two independent reviewers performed the WG-wise selection of full texts in a similar manner as the abstract selection.

2.7 | Data extraction

For the data extraction, a purpose-built data extraction form including manual was developed (see Supporting Information Material S3 and S4); this was pilot tested on three studies by two reviewers (EL and WT). Subsequently, the form was completed independently by two reviewers (same as in full-text selection) for each included study. The form differed slightly per clinical question, but for all questions covered: (1) general study information (e.g., title, year); (2) study design characteristics (e.g., setting, duration); (3) participant characteristics (e.g., sample size, diagnosis); (4) intervention/instrument characteristics (e.g., intervention, participants per arm); (5) outcome characteristics (e.g., included outcomes, values); (6) bias assessment (see next paragraph); and (7) additional information (at the discretion of the reviewer).

2.8 | Quality appraisal

For measurement properties studies, the COSMIN checklist for assessing methodological quality of such studies was used.[14,18] This resulted in a score per included outcome for each study, that could either be "excellent," "good," "fair," or "poor."

For RCTs on interventions, risk of bias of the included studies was determined according to the criteria used in the Cochrane Risk of Bias tool, comprising selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.[19] Per criteria risk of bias was judged as high, low, or unclear, as per the instructions in the Cochrane Handbook.[19]

After this, the quality of evidence for all outcomes was summarized using the GRADE system, where the primary focus is not on the individual studies, but on the body of evidence, i.e., all included studies per outcome combined.[20] The quality of evidence is classified as high, moderate, low, or very low. This classification is dependent on the design of the included studies (e.g., RCTs start as "high") and various specific factors, i.e., the quality is downgraded for study limitations, inconsistency, indirectness, imprecision or publication bias, or upgraded for dose response effect or large magnitude of effect.[21] The GRADE appraisal was performed independently by two reviewers.

2.9 | Data analysis

For intervention studies, the relative intervention effects for each outcome were calculated, using relative risks including 95% confidence intervals (CIs) for dichotomous outcomes, and standardized mean differences including 95% CIs for continuous outcomes. Meta-analyses were performed when multiple studies were included that had an equal study design and similar patient characteristics. Heterogeneity was assessed using forest plots and the I^2 statistic (cutoff for substantial heterogeneity ≥50%).[19] If there was no substantial heterogeneity, we estimated treatment effects using a fixed-effect model. If substantial heterogeneity was present, we explored possible causes and used a random-effect model to estimate treatment effects. Meta-analyses were performed in Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). All other statistical analyses were performed in SPSS version 23.0 (IBM corp., Armonk, NY, USA). For all statistical tests, a P value of <0.05 was considered statistically significant.

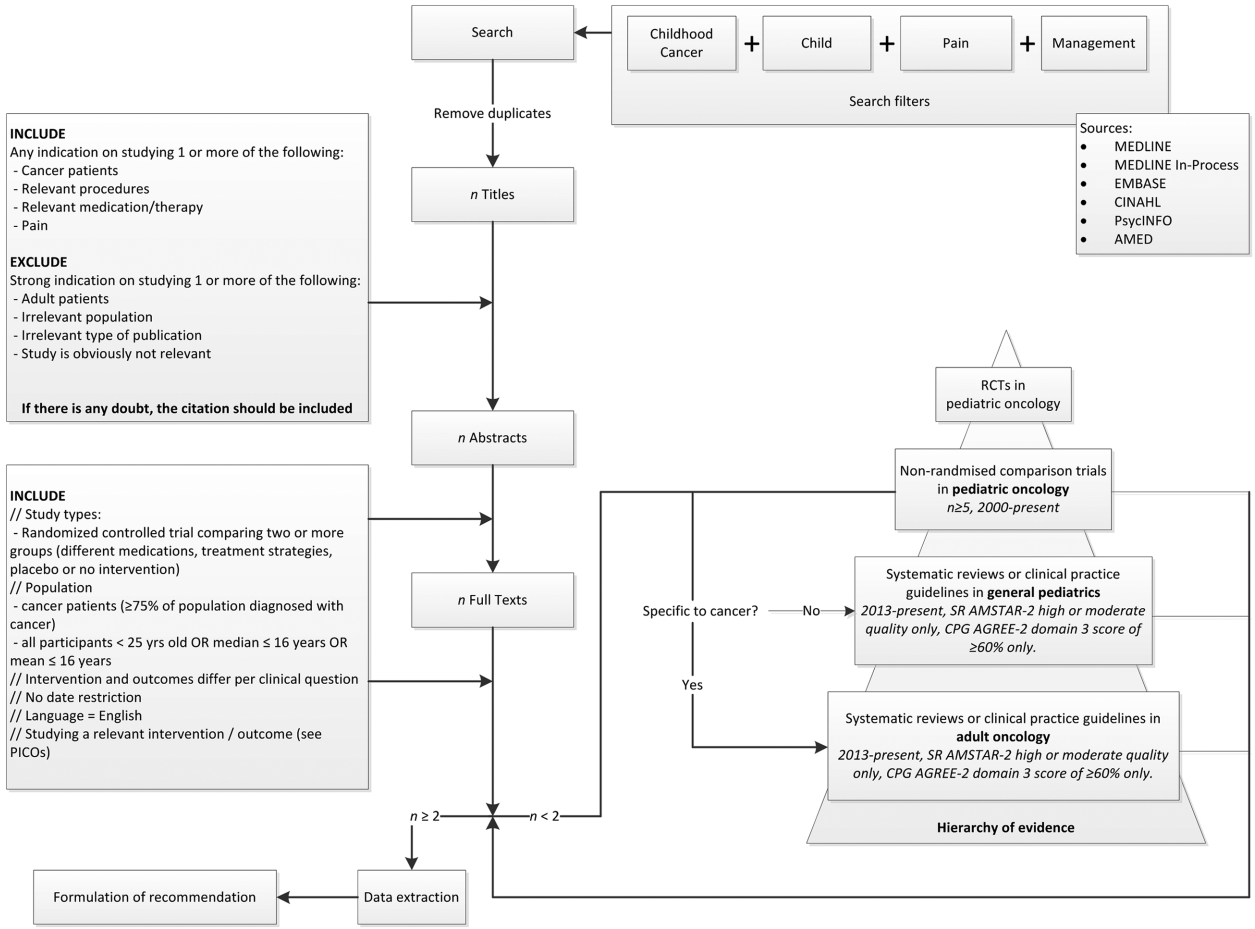

FIGURE 2 Flowchart of the study search and selection regarding clinical questions on the management of pain in children with cancer

2.10 | Synthesis of results

We prepared a narrative synthesis discussing our findings per clinical question. Tables with characteristics of included studies were prepared and contained information regarding study design, sample, intervention/instrument, where applicable comparison, and outcomes of the included studies.

For questions regarding measurement properties studies, we prepared a summary of findings tables per construct (e.g., self-reported pain intensity). To provide a comprehensive overview, we also developed a quality matrix including information on purpose, number of studies, age group, and COSMIN quality score.

For questions regarding intervention studies we prepared a summary of findings table per clinical question, with information for each included outcome on number of studies, number of participants, description of intervention, definition of outcome (unit), statistical method, effect size, and quality of evidence.

2.11 | Project group meeting in Amsterdam

All project members were invited to a two-day in-person consensus conference in Amsterdam (NL) in February 2018. Of 44 members, 36 attended (82%). The majority of the meeting proceedings consisted of discussing included studies, evidence summaries and formulating recommendations in small WGs setting. In addition, total group meetings were held to discuss the draft recommendations and to devise the way forward. Decisions were made through group discussion and consensus. In all steps, except the formulation of final recommendations, a voting procedure was performed (majority voting system) in case of absence of unanimity. Final recommendations had to be supported unanimously by all WG members.

2.12 | Formulation of recommendations; evidence-to-decision table

For each clinical question, the WGs completed an evidence-to-decision (EtD) framework. Recently, GRADE published the EtD-framework, which is a systematic and transparent approach to formulating healthcare recommendations.[22] This framework consists of 11 questions in six domains and facilitates taking both the evidence and the represented expert knowledge into account. After an EtD framework was completed, we formulated an overall conclusion in which the benefits and harms are weighed. On the basis of these conclusions, recommendations for clinical care were formulated. These EtD frameworks and accompanying recommendations were also discussed in a separate meeting with the patient representatives, to explore their values and preferences and so validate and/or expand decision-making. If the latter led to alterations in the recommendations, these were discussed

again in the relevant WG. Final recommendations had also to be supported unanimously by the patient representatives panel.

2.13 | Additional evidence searches

For some of the included clinical questions on pain management, the literature review yielded very few or no eligible studies, leading to insufficient evidence upon which to base a recommendation. For these questions, the CG proposed a flowchart with steps to follow that the project group subsequently agreed with (see Figure 2).

For clinical questions regarding assessment of pain with insufficient evidence, we searched for systematic reviews (SRs), meta-analyses (MAs), and CPGs concerning pain measurement instruments in all child populations (indirect evidence). For all treatment questions with insufficient evidence we searched for lower quality evidence (i.e., nonrandomized comparison trials) in children with cancer, and for most questions we also searched for SRs, MAs, and CPGs in other child populations (e.g., for distraction techniques during procedures). For questions with a pathophysiology specific to cancer (e.g., chemotherapy-induced mucositis), we did not search for literature from other child populations, but only for adult oncology CPGs.

The systematic searches for these questions were more focused than the initial searches (see Supporting Information Material S1). For the non-RCTs, we included all primary studies with a comparison design (parallel, crossover, pre-post), a minimum of 10 participants, and published since 2000. For the SRs, MAs, and CPGs, we included only studies that complied with minimal quality criteria, and were published since 2013 (see Figure 2).

After the selection of studies and extraction of data, the retrieved information was added to the relevant evidence summary, which was subsequently used to complete the updated EtD framework. Formulation of recommendations then commenced in a similar manner as in the previous phase.

2.14 | Funding source

The project "Towards evidence-based guidelines for supportive care in childhood oncology" is supported by the Alpe d'HuZes foundation/Dutch Cancer Society (RUG 2013-6345). The funding source had no role in the study design, in the collection, analysis, and interpretation of the data, in the preparation of the manuscript, or in the decision to submit the manuscript for publication.

3 | RESULTS

3.1 | Clinical questions

The WGs formulated 89 clinical questions (see Supporting Information Material S2). After the voting rounds, 22 clinical questions were included (Table 1). Prioritized outcomes differed per clinical question; however, for the questions on pain management strategies, self-rated pain intensity was consistently prioritized as the most critical outcome.

3.2 | Systematic review

See Figure 3 for a PRISMA flow diagram of the selection process.[23] See Supporting Information Material S5 for a list of excluded studies that were read in full text. In the title selection process pilot, agreement was excellent (231 of 250 citations [92.4%] had identical scores by all three reviewers).

The literature search for clinical questions regarding assessment of pain yielded 2,857 citations. Of these, 79 articles were read in full text, of which 13 studies were included: two on self-rating of pain intensity using numbers, six on behavioral distress assessment, two on neuropathic pain, and three on multidimensional instruments.[24–36] Unfortunately for self-rating of pain intensity using numerical rating scales and for "simple" proxy ratings, no studies were eligible for inclusion.

For clinical questions on pain management strategies, the literature search yielded 11 159 citations, of which 194 articles were read in full text and eventually 55 RCTs were included. Regarding pharmacological management of tumor-related pain, no RCTs were eligible for inclusion. With regard to pharmacological management of treatment-related pain, seven RCTs were included: five on mucositis, one on neuropathic pain, and one on phantom limb pain.[37–42] Only one RCT was included regarding psychological and physical management of tumor- and treatment-related pain, concerning physical therapy.[43] Regarding pain during procedures, there were 33 RCTs included on pharmacological management: seven on minor procedures, eight on lumbar punctures, and 13 on major procedures.[44-76] For psychological and physical management of pain during procedures, 15 RCTs were included: six on hypnosis, five on active distraction, two on passive distraction, and two on combining treatment modalities.[69,71,77–89]

4 | DISCUSSION

The primary focus in children with cancer has initially, understandably, been on improving survival, supportive care has long been a relatively unexplored niche. However, with current survival rates and the high burden of cancer and its treatment on patients and their families, improving supportive care is increasingly acknowledged as an area that deserves attention.[90,91] To improve care, we initiated a project to develop childhood cancer supportive care CPGs, of which the development of a CPG regarding pain in children with cancer is one of the initial foci.[11] We executed this project in a very rigorous manner and described our methods in this article to promote transparency and to inspire and educate others on the verge of initiating a supportive care CPG project. Currently, we are developing recommendations, which will be published in a three-part series: (1) assessment of pain, (2) pharmacological, psychological, and physical management of tumor- and treatment-related pain, and (3) pharmacological, psychological, and physical management of procedure-related pain.

One of the strengths of this project is also an important challenge. Because we aspired to develop as comprehensive a CPG as possible, we included many clinical questions. When all these questions are answered, the emerging clinical and/or research recommendations will help healthcare professionals greatly in their daily work. However,

TABLE 1 Included clinical questions

	Patient	Instrument		Critical outcomes (as prioritized)
	Children with cancer	Pain intensity: self-rating (numbers, pictures)		Reliability, validity, clinical utility, responsiveness, interpretability
	Children with cancer	"Simple" rating by proxy		Reliability,, validity, clinical utility, interpretability
	Children with cancer	Behavioral distress assessment instruments		Reliability, validity, clinical utility, responsiveness, interpretability
	Children with cancer	Neuropathic pain		Reliability, validity, clinical utility, interpretability
	Children with cancer	Multidimensional instruments		Reliability, validity, clinical utility, interpretability
	Patient	**Intervention**	**Control**	**Critical outcomes (as prioritized)**
2A	Children with cancer	Pharmacological therapies to manage nociceptive pain	Any	Pain intensity (self-rated), distress (self-rated), quality of life (self-reported), adverse effects, distress ("simple" proxy rating), behavioral distress, changes in physical functioning, changes in general functioning
2A	Children with cancer	Pharmacological therapies to manage bone pain	Any	Pain intensity (self-rated), distress (self-rated), quality of life (self-reported), adverse effects, distress ("simple" proxy rating), behavioral distress, changes in physical functioning, changes in general functioning
2A	Children with cancer	Pharmacological therapies to manage tumor-related neuropathic pain	Any	Pain intensity (self-rated), distress (self-rated), quality of life (self-reported), adverse effects, distress ("simple" proxy rating), behavioral distress, changes in physical functioning, changes in general functioning, sleep
2A	Children with cancer	Opioid-sparing	Any	Pain intensity (self-rated), distress (self-rated), quality of life (self-reported), adverse effects, changes in physical functioning, changes in general functioning
2A	Children with cancer	Role of invasive procedures	Any	NA
2B	Children with cancer	Pharmacological therapies to manage chemotherapy-induced neuropathic pain	Any	Pain intensity (self-rated), distress (self-rated), quality of life (self-reported), adverse effects, distress ("simple" proxy rating), behavioral distress, changes in physical functioning, changes in general functioning, quality of life (reported by proxy), global judgement of satisfaction with treatment
2B	Children with cancer	Pharmacological therapies to manage pain from mucositis	Any	Pain intensity (self-rated), distress (self-rated), quality of life (self-reported), adverse effects, distress ("simple" proxy rating), behavioral distress,, quality of life (reported by proxy), duration of therapeutic effect, global judgement of satisfaction with treatment, oral intake, ability to eat
2B	Children with cancer	Pharmacological therapies to manage pain from constipation due to opioids	Any	Pain intensity (self-rated), adverse effects, distress (self-rated), distress ("simple" proxy rating), change in dose of opioids
2B	Children with cancer	Pharmacological therapies to manage phantom limb pain	Any	Pain intensity (self-rated), distress (self-rated), quality of life (self-reported), adverse effects, distress ("simple" proxy rating), behavioral distress, changes in physical functioning, changes in general functioning, quality of life (reported by proxy), duration of therapeutic effects, global judgement of satisfaction with treatment, need for "classic" (nociceptive) pain interventions
2B	Children with cancer	Pharmacological therapies to manage anti-gd2 antibody infusion-related pain	Any	Pain intensity (self-rated), distress (self-rated), adverse effects, distress ("simple" proxy rating), behavioral distress, quality of life (self-reported), changes in physical functioning, sleep

(Continues)

TABLE 1 (Continued)

	Patient	Instrument		Critical outcomes (as prioritized)
2C	Children with cancer undergoing a minor procedure	Pharmacological therapies to reduce procedure-related pain and distress	Any	Pain intensity (self-rated), distress (self-rated), behavioral distress, adverse effects
2C	Children with cancer undergoing a lumbar puncture	Pharmacological therapies to reduce procedure-related pain and distress	Any	Pain intensity (self-rated), distress (self-rated), adverse effects, distress ("simple" proxy rating), behavioral distress, procedure success
2C	Children with cancer undergoing a major procedure	Pharmacological therapies to reduce procedure-related pain and distress	Any	Pain intensity (self-rated), distress (self-rated), adverse effects, distress ("simple" proxy rating), behavioral distress
3A	Children with cancer	Physical therapy	Any	Pain intensity (self-rated), distress (self-rated), quality of life (self-reported), changes in general functioning, changes in physical functioning, adverse effects
3A	Children with cancer	Active distraction	Any	Pain intensity (self-rated), quality of life (self-reported), distress (self-rated), changes in general functioning, global judgement of satisfaction with treatment, adverse effects
3A	Children with cancer	Passive distraction	Any	Pain intensity (self-rated), quality of life (self-reported), distress (self-rated), changes in general functioning, global judgement of satisfaction with treatment, adverse effects
3A	Children with cancer	Meditation/mindfulness	Any	Pain intensity (self-rated), distress (self-rated), quality of life (self-reported), global judgement of satisfaction with treatment, adverse effects
3A	Children with cancer	Guided imagery	Any	Pain intensity (self-rated), quality of life (self-reported), distress (self-rated), changes in general functioning, global judgement of satisfaction with treatment, adverse effects
3B	Children with cancer undergoing a painful procedure	Active distraction	Any	Pain intensity (self-rated), distress (self-rated), distress ("simple" proxy rating), behavioral distress, fear for future medical procedures, adverse effects
3B	Children with cancer undergoing a painful procedure	Combination of modalities	Any	Pain intensity (self-rated), distress (self-rated), distress ("simple" proxy rating), behavioral distress, global judgement of satisfaction with treatment, fear for future medical procedures, adverse effects
3B	Children with cancer undergoing a painful procedure	Hypnosis	Any	Pain intensity (self-rated), distress (self-rated), distress ("simple" proxy rating), behavioral distress, fear for future medical procedures, adverse effects
3B	Children with cancer undergoing a painful procedure	Passive distraction	Any	Pain intensity (self-rated), distress (self-rated), distress ("simple" proxy rating), behavioral distress, fear for future medical procedures, adverse effects
3B	Children with cancer undergoing a painful procedure	Parent coaching	Any	Pain intensity (self-rated), distress (self-rated), distress ("simple" proxy rating), behavioral distress, fear for future medical procedures, adverse effects

the obvious drawback of including multiple clinical questions is that it might lead to almost unmanageable amounts of work. We have, however, made efforts to reduce this without compromising quality, i.e., by combining search strategies.

The biggest challenge in the development of this CPG was handling situations in which there was either very little or very low quality evidence. As previously mentioned, research in supportive care in childhood cancer is a relatively new area of investigation, thus the evidence base is small. Nevertheless, we were still disappointed by the scarcity of high-quality studies conducted in this important field of cancer care. This left us with several suboptimal options: omitting the clinical question, basing a recommendation upon expert consensus, or searching for lower quality and/or more indirect evidence. In a recent paper from the GRADE guidelines series, the GRADE working group acknowledged that clinicians can be frustrated when a guideline does not actually provide guidance.[92] Guideline panels are therefore encouraged to make

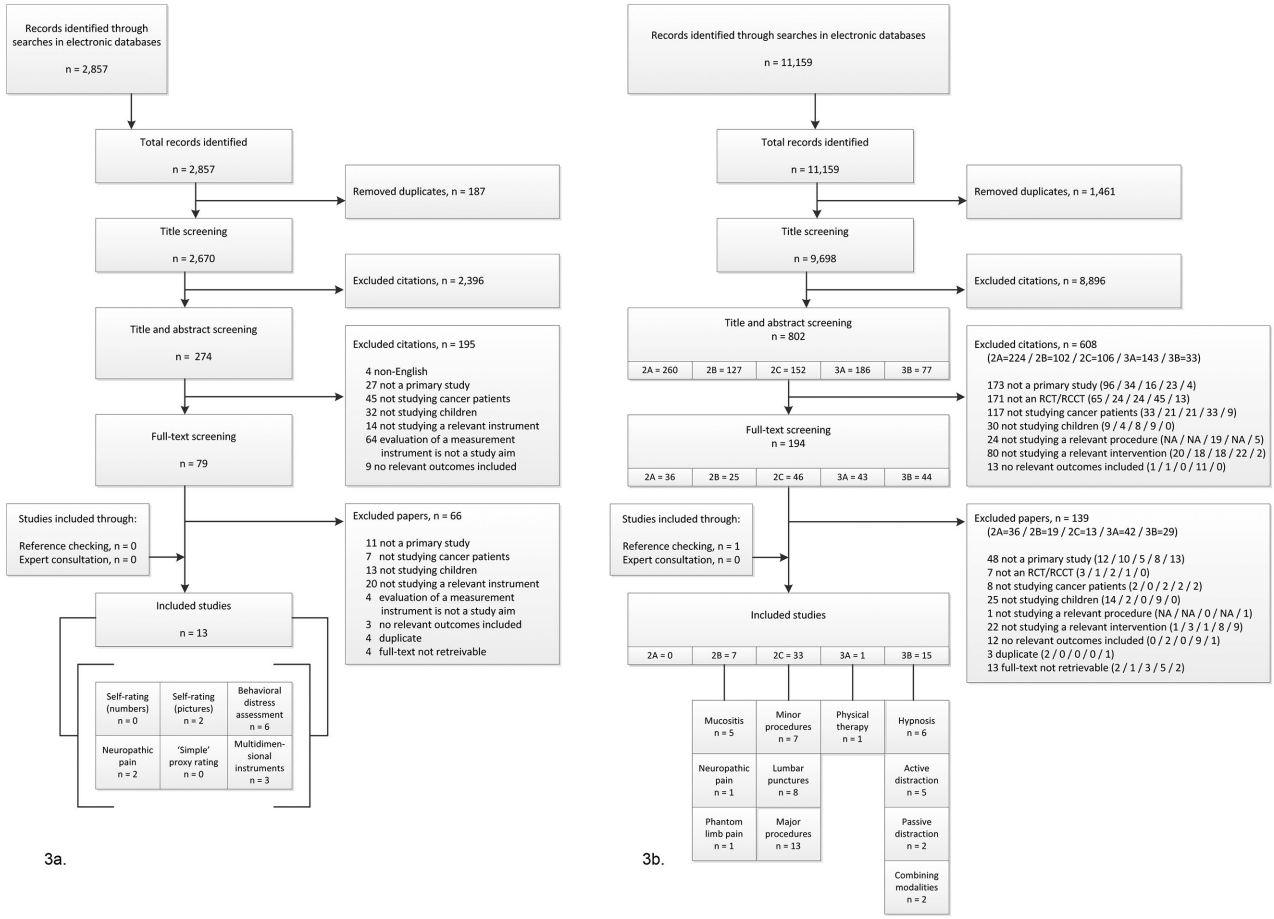

FIGURE 3 A, Flowchart of the citation screening and selection, working group 1. B, Flowchart of the citation screening and selection, working groups 2A, 2B, 2C, 3A, 3B

an effort to provide recommendations, even when evidence is scarce or of low quality. Our guideline panel fully endorsed this aim; nevertheless, the panel also did not want to base a recommendation solely on expert opinion. Therefore, we devised a method to identify additional evidence (be it either of lower quality or more indirect) upon which to base our recommendations.

In addition, we encouraged patient representatives to share their values and preferences as so to contribute to formulating the recommendations. Working together closely with patient representatives, and providing them with training in evidence-based guideline development, will facilitate a CPG in which the patient perspective is interweaved.

The lack of identified high-quality studies also emphasizes the importance of undertaking studies focusing on effective pain measurement and management, as pain has been acknowledged repeatedly as one of the most important adverse effects of childhood cancer and its therapy.[1] Large randomized studies are needed, and as patient numbers are relatively small we encourage these to be multicentered and international in scope. In our upcoming CPGs, detailed research recommendations will be included which can serve to inform the research agenda for the coming decade.

In conclusion, with the improving cure rates of childhood cancer, it is of the utmost importance to develop high-quality evidence-based guidelines for supportive care, to reduce variabilities in care and improve patient outcomes. In this project, we took the first steps toward a comprehensive CPG regarding assessment and pharmacological, psychological, and physical management of tumor-, treatment-, and procedure-related pain in children with cancer.

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AUTHOR CONTRIBUTIONS

EL, LK, MD, RM, AF, and WT contributed to the conception of the study. EL, LK, MD, RM, AF, LD, FC, and WT contributed to the design of the study. EL, LK, MD, RM, AF, LD, FC, WT and all members of the Pain in Children with Cancer Guideline Development Panel (PCCGDP) contributed to the search strategy, data extraction, quality appraisal,

and the interpretation of the data. EL, LK, MD, FC, and WT drafted the manuscript which was subsequently critically revised by RM, AF, LD, and all members of the (PCCGDP). All authors approved the final version.

CONFLICTS OF INTEREST

The authors have no conflicts of interest or financial relationships relevant to this article to disclose.

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REFERENCES

1. Hedén L, Pöder U, von Essen L, Ljungman G. Parents' perceptions of their child's symptom burden during and after cancer treatment. *J Pain Symptom Manage*. 2013;46(3):366-375.
2. Tenniglo LJA, Loeffen EAH, Kremer LCM, et al. Patients' and parents' views regarding supportive care in childhood cancer. *Support Care Cancer*. 2017;25(10):3151-3160.
3. Westhoff PG, Verdam MGE, Oort FJ, et al. Course of quality of life after radiation therapy for painful bone metastases: a detailed analysis from the Dutch Bone Metastasis Study. *Int J Radiat Oncol*. 2016;95(5):1391-1398.
4. Friedrichsdorf SJ, Nugent AP. Management of neuropathic pain in children with cancer. *Curr Opin Support Palliat Care*. 2013;7:131-138.
5. Hockenberry MJ, McCarthy K, Taylor O, et al. Managing painful procedures in children with cancer. *J Pediatr Hematol Oncol*. 2011;33(2):119-127.
6. Greenfield S. Variations in resource utilization among medical specialties and systems of care. *JAMA*. 1992;267(12):1624.
7. Lugtenberg M, Burgers JS, Westert GP. Effects of evidence-based clinical practice guidelines on quality of care: a systematic review. *Qual Saf Health Care*. 2009;18(5):385-392.
8. Graham R, Mancher M, Wolman DM. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press; 2011.
9. Ljungman G, Gordh T, Sorensen S, Kreuger A. Pain in paediatric oncology: interviews with children, adolescents and their parents. *Acta Paediatr*. 1999;88(6):623-630.
10. Pöder U, Ljungman G, Von Essen L. Parents' perceptions of their children's cancer-related symptoms during treatment: a prospective, longitudinal study. *J Pain Symptom Manage*. 2010;40(5):661-670.
11. Loeffen EAH, Mulder RL, Van De Wetering MD, et al. Current variations in childhood cancer supportive care in the Netherlands. *Cancer*. 2016;122(4):642-650.
12. International Pediatric Oncology Guidelines in Supportive Care Network (iPOG Network). [database online]. http://www.sickkids.ca/Research/iPOG/. Accessed August 14, 2018
13. Armstrong MJ, Mullins CD, Gronseth GS, Gagliardi AR. Impact of patient involvement on clinical practice guideline development: a parallel group study. *Implement Sci*. 2018;13(1):1-13.
14. Mokkink LB, Terwee CB, Knol DL, et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. *BMC Med Res Methodol*. 2010;10:22.
15. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64(4):395-400.
16. Kremer L, Leclercq E, Noorman J, Jellema P, van Dalen E. Cochrane Childhood Cancer Group. *About Cochrane Collab (Cochrane Rev Groups)*. 2017(3), Art. No.: CHILDCA.
17. Mateen FJ, Oh J, Tergas AI, Bhayani NH, Kamdar BB. Titles versus titles and abstracts for initial screening of articles for systematic reviews. *Clin Epidemiol*. 2013;5:89-95.
18. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res*. 2010;19(4):539-549.
19. Higgins JPT, Green S. eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. [updated March 2011]. The Cochrane Collaboration; 2011. www.handbook.cochrane.org Accessed August 14, 2018.
20. Guyatt GH, Oxman AD, Vist GE, et al. GRADE : an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(April):924-926.
21. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406.
22. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. *BMJ*. 2016;353(11):i2089.
23. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
24. Mahon P, Holsti L, Siden H, Strahlendorf C, Turnham L, Giaschi D. Using colors to assess pain in toddlers: validation of "The Rainbow Pain Scale"—A proof-of-principle study. *J Pediatr Oncol Nurs*. 2015;32(1):40-46.
25. West N, Oakes L, Hinds PS, et al. Measuring pain in pediatric oncology ICU patients. *J Pediatr Oncol Nurs*. 1994;11(2):64-70.
26. Gauvain-Piquard A, Rodary C, Rezvani A, Lemerle J. Pain in children aged 2–6 years: a new observational rating scale elaborated in a pediatric oncology unit: preliminary report. *Pain*. 1987;31(2):177-188.
27. Gauvain-Piquard A, Rodary C, Rezvani A, Serbouti S. The development of the DEGRR: a scale to assess pain in young children with cancer. *Eur J Pain*. 1999;3(2):165-176.
28. Marec-Berard P, Gomez F, Combet S, Thibault P, Moine PL, Bergeron C. HEDEN pain scale: a shortened behavioral scale for assessment of prolonged cancer or postsurgical pain in children aged 2 to 6 years. *Pediatr Hematol Oncol*. 2015;32(5):291-303.
29. Gilchrist LS, Tanner L. The pediatric-modified total neuropathy score: a reliable and valid measure of chemotherapy-induced peripheral neuropathy in children with non-CNS cancers. *Support Care Cancer*. 2013;21(3):847-856.
30. Lavoie Smith EM, Li L, Hutchinson RJ, et al. Measuring vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. *Cancer Nurs*. 2013;36(5):E49-60.
31. Elliott CH, Jay SM, Woody P. An observation scale for measuring children's distress during medical procedures. *J Pediatr Psychol*. 1987;12(4):543-551.
32. Katz ER, Kellerman J, Siegel SE. Behavioral distress in children with cancer undergoing medical procedures: developmental considerations. *J Consult Clin Psychol*. 1980;48(3):356-365.
33. LeBaron S, Zeltzer L. Assessment of acute pain and anxiety in children and adolescents by self-reports, observer reports, and a behavior checklist. *J Consult Clin Psychol*. 1984;52(5):729-738.
34. Collins JJ, Byrnes ME, Dunkel IJ, et al. The measurement of symptoms in children with cancer. *J Pain Symptom Manag*. 2000;19(5):363-377.

35. Collins JJ, Devine TD, Dick GS, et al. The measurement of symptoms in young children with cancer: the validation of the Memorial Symptom Assessment Scale in children aged 7–12. *J Pain Symptom Manag*. 2002;23(1):10-16.

36. Stinson JN, Jibb LA, Nguyen C, et al. Construct validity and reliability of a real-time multidimensional smartphone app to assess pain in children and adolescents with cancer. *Pain*. 2015;156(12):2607-2615.

37. Bardellini E, Amadori F, Schumacher RF, D'Ippolito C, Porta F, Majorana A. Efficacy of a solution composed by verbascoside, polyvinylpyrrolidone (PVP) and sodium hyaluronate in the treatment of chemotherapy-induced oral mucositis in children with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2016;38(7):559-562.

38. Cheng KKF, Chang AM. Palliation of oral mucositis symptoms in pediatric patients treated with cancer chemotherapy. *Cancer Nurs*. 2003;26(6):476-484.

39. Collins JJ, Grier HE, Sethna NF, Wilder RT, Berde CB. Regional anesthesia for pain associated with terminal pediatric malignancy. *Pain*. 1996;65(1):63-69.

40. Oudot C, Laplanche A, Orbach D, et al. PCA analgesia for children with chemotherapy-related mucositis: a double-blind randomized comparison of morphine and pethidine. *Bull Cancer*. 2011;98(2):E11-E18.

41. Raphael MF, Den Boer AM, Abbink FCH, et al. Caphosol, a therapeutic option in case of cancer therapy-induced oral mucositis in children? Results from a prospective multicenter double blind randomized controlled trial. *Support Care Cancer*. 2013;21:S158-S159.

42. Wang X, Yi Y, Tang D, et al. Gabapentin as an adjuvant therapy for prevention of acute phantom-limb pain in pediatric patients undergoing amputation for malignant bone tumors: a prospective double-blind randomized controlled trial. *J Pain Symptom Manage*. 2018;55(3):721-727.

43. Speyer E, Herbinet A, Vuillemin A, Briançon S, Chastagner P. Effect of adapted physical activity sessions in the hospital on health-related quality of life for children with cancer: a cross-over randomized trial. *Pediatr Blood Cancer*. 2010;55(6):1160-1166.

44. Bishai R, Taddio A, Bar-oz B, Freedman MH, Koren G, Background A. Relative efficacy of amethocaine gel and lidocaine–prilocaine cream for Port-a-Cath puncture in children. *Pediatrics*. 1999;104:e31.

45. Hedén L, von Essen L, Frykholm P, Ljungman G. Low-dose oral midazolam reduces fear and distress during needle procedures in children with cancer. *Pediatr Blood Cancer*. 2009;53(7):1200-1204.

46. Hedén LE, von Essen L, Ljungman G. Effect of morphine in needle procedures in children with cancer. *Eur J Pain*. 2011;15(10):1056-1060.

47. Heden L, von Essen L, Ljungman G. Effect of high-dose paracetamol on needle procedures in children with cancer–an RCT. *Acta Paediatr*. 2014;103(3):314-319.

48. Ljungman G, Kreuger A, Andréasson S, Gordh T, Sörensen S. Midazolam nasal spray reduces procedural anxiety in children. *Pediatrics*. 2000;105(1):73-78.

49. Lullmann B, Leonhardt J, Metzelder M, et al. Pain reduction in children during port-a-cath catheter puncture using local anaesthesia with EMLATM. *Eur J Pediatr*. 2010;169(12):1465-1469.

50. Miser AW, Goh TS, Dose AM, et al. Trial of a topically administered local anesthetic (EMLA cream) for pain relief during central venous port accesses in children with cancer. *J Pain Symptom Manag*. 1994;9(4):259-264.

51. Calamandrei M, Messeri A, Busoni P, Bernini G, Lippi A, Tucci F. Comparison of two application techniques of EMLA and pain assessment in pediatric oncology patients. *Reg Anesth*. 1996;21(6):557-560.

52. Ellis J, McCarthy P, Gosselin P, Splinter W. Intravenous sedation for control of distress during lumbar punctures for pediatric cancer patients. *Pain Res Manag*. 2000;5(2):141-147.

53. Glaisyer HR, Sury MRJ. Recovery after anesthesia for short pediatric oncology procedures: propofol and remifentanil compared with propofol, nitrous oxide, and sevoflurane. *Anesth Analg*. 2005;100(4):959-963.

54. Juarez Gimenez JC, Oliveras M, Hidalgo E, et al. Anesthetic efficacy of eutectic prilocaine-lidocaine cream in pediatric oncology patients undergoing lumbar puncture. *Ann Pharmacother*. 1996;30(11):1235-1237.

55. Kapelushnik J, Koren G, Solh H, Greenberg M, DeVeber L. Evaluating the efficacy of EMLA in alleviating pain associated with lumbar puncture; comparison of open and double-blinded protocols in children. *Pain*. 1990;42(1):31-34.

56. Ljungman G, Gordh T, Sorensen S, Kreuger A. Lumbar puncture in pediatric oncology: conscious sedation vs. general anesthesia. *Med Pediatr Oncol*. 2001;36(3):372-379.

57. Whitlow PG, Saboda K, Roe DJ, Bazzell S, Wilson C. Topical analgesia treats pain and decreases propofol use during lumbar punctures in a randomized pediatric leukemia trial. *Pediatr Blood Cancer*. 2015;62(1):85-90.

58. Yang C-H, Tian X, Yin H-B, Gao X-H, Li N. Sedation and analgesia with fentanyl and etomidate for intrathecal injection in childhood leukemia patients. *Medicine (Baltimore)*. 2015;94(1):e361-e361.

59. Abdolkarimi B, Zareifar S, Golestani Eraghi M, Saleh F. Comparison effect of intravenous ketamine with pethidine for analgesia and sedation during bone marrow procedures in oncologic children: a randomized, double-blinded, crossover trial. *Int J Hematol Oncol Stem Cell Res*. 2016;10(4):206-211.

60. Anghelescu DL, Burgoyne LL, Faughnan LG, Hankins GM, Smeltzer MP, Pui CH. Prospective randomized crossover evaluation of three anesthetic regimens for painful procedures in children with cancer. *J Pediatr*. 2013;162(1):137-141.

61. Aouad MT, Moussa AR, Dagher CM, et al. Addition of ketamine to propofol for initiation of procedural anesthesia in children reduces propofol consumption and preserves hemodynamic stability. *Acta Anaesthesiol Scand*. 2008;52(4):561-565.

62. Belen FB, Kocak U, Kayilioglu H, et al. Use of low dose oral midazolam during invasive procedures in pediatric hematology patients. *Gazi Med J*. 2015;26(4):177-179.

63. Bhatnagar S, Mishra S, Gupta M, Srikanti M, Mondol A, Diwedi A. Efficacy and safety of a mixture of ketamine, midazolam and atropine for procedural sedation in paediatric oncology: a randomised study of oral versus intramuscular route. *J Paediatr Child Heal*. 2008;44(4):201-204.

64. Chiaretti A, Ruggiero A, Barbi E, et al. Comparison of propofol versus propofol-ketamine combination in pediatric oncologic procedures performed by non-anesthesiologists. *Pediatr Blood Cancer*. 2011;57(7):1163-1167.

65. Friedman AG, Mulhern RK, Fairclough D, et al. Midazolam premedication for pediatric bone marrow aspiration and lumbar puncture. *Med Pediatr Oncol*. 1991;19(6):499-504.

66. Ghadami Yazdi A, Ayatollahi V, Hashemi A, Behdad S, Ghadami Yazdi E. Effect of two different concentrations of propofol and ketamine combinations (Ketofol) in pediatric patients under lumbar puncture or bone marrow aspiration. *Iran J Pediatr Hematol Oncol*. 2013;3(1):187-192.

67. Iannalfi A, Bernini G, Caprilli S, Lippi A, Tucci F, Messeri A. Painful procedures in children with cancer: comparison of moderate sedation and general anesthesia for lumbar puncture and bone marrow aspiration. *Pediatr Blood Cancer*. 2005;45(7):933-938.

68. Jay SM, Elliott CH, Katz E, Siegel SE. Cognitive-behavioral and pharmacologic interventions for childrens' distress during painful medical procedures. *J Consult Clin Psychol*. 1987;55(6):860-865.
69. Jay SM, Elliott CH, Woody PD, Siegel S. An investigation of cognitive-behavior therapy combined with oral valium for children undergoing painful medical procedures. *Health Psychol*. 1991;10(5):317-322.
70. Jay S, Elliott CH, Fitzgibbons I, Woody P, Siegel S. A comparative study of cognitive behavior therapy versus general anesthesia for painful medical procedures in children. *Pain*. 1995;62(1):3-9.
71. Kazak AE, Penati B, Boyer BA, et al. A randomized controlled prospective outcome study of a psychological and pharmacological intervention protocol for procedural distress in pediatric leukemia. *J Pediatr Psychol*. 1996;21(5):615-631.
72. Marx CM, Stein J, Tyler MK, et al. Ketamine-midazolam versus meperidine-midazolam for painful procedures in pediatric oncology patients. *J Clin Oncol*. 1997;15(1):94-102.
73. Nagel K, Willan AR, Lappan J, Korz L, Buckley N, Barr RD. Pediatric oncology sedation trial (POST): a double-blind randomized study. *Pediatr Blood Cancer*. 2008;51(5):634-638.
74. Sandler ES, Weyman C, Connor K. Midazolam versus fentanyl as premedication for painful procedures in children with cancer. *Pediatrics*. 1992;89(4 Pt 1):631-634.
75. Schechter NL, Weisman SJ, Rosenblum M, Bernstein B, Conard PL. The use of oral transmucosal fentanyl citrate for painful procedures in children. *Pediatrics*. 1995;95(3):335-339.
76. Tamminga RYJ, Noordhoek M, Kroon J, Faber-Nijholt R. Ketamine anesthesia with or without diazepam premedication for bone marrow punctures in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol*. 2000;17(5):383-388.
77. Dahlquist LM, Pendley JS, Landthrip DS, Jones CL, Steuber CP. Distraction intervention for preschoolers undergoing intramuscular injections and subcutaneous port access. *Heal Psychol*. 2002;21(1):94-99.
78. Gershon J, Zimand E, Pickering M, Rothbaum BO, Hodges L. A pilot and feasibility study of virtual reality as a distraction for children with cancer. *J Am Acad Child Adolesc Psychiatry*. 2004;43(10):1243-1249.
79. Heden L, L VONE, Ljungman G, Hedén L, Von Essen L, Ljungman G. Randomized interventions for needle procedures in children with cancer. *Eur J Cancer Care (Engl)*. 2009;18(4):358-363.
80. Windich-Biermeier A, Sjoberg I, Dale JC, Eshelman D, Guzzetta CE. Effects of distraction on pain, fear, and distress during venous port access and venipuncture in children and adolescents with cancer. *J Pediatr Oncol Nurs*. 2007;24(1):8-19.
81. Wolitzky K, Fivush R, Zimand E, Hodges L, Rothbaum BO. Effectiveness of virtual reality distraction during a painful medical procedure in pediatric oncology patients. *Psychol Health*. 2005;20(6):817-824.
82. Nguyen TN, Nilsson S, Hellstrom AL, Bengtson A. Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial. *J Pediatr Oncol Nurs*. 2010;27(3):146-155.
83. Wint SS, Eshelman D, Steele J, Guzzetta CE. Effects of distraction using virtual reality glasses during lumbar punctures in adolescents with cancer. *Oncol Nurs Forum*. 2002;29:E8-15.
84. Liossi C, Hatira P. Clinical hypnosis versus cognitive behavioral training for pain management with pediatric cancer patients undergoing bone marrow aspirations. *Int J Clin Exp Hypn*. 1999;47(2):104-116.
85. Liossi C, Hatira P. Clinical hypnosis in the alleviation of procedure-related pain in pediatric oncology patients. *Int J Clin Exp Hypn*. 2003;51(1):4-28.
86. Liossi C, White P, Hatira P. Randomized clinical trial of local anesthetic versus a combination of local anesthetic with self-hypnosis in the management of pediatric procedure-related pain. *Heal Psychol*. 2006;25(3):307-315.
87. Liossi C, White P, Hatira P. A randomized clinical trial of a brief hypnosis intervention to control venepuncture-related pain of paediatric cancer patients. *Pain*. 2009;142(3):255-263.
88. Wall VJ, Womack W. Hypnotic versus active cognitive strategies for alleviation of procedural distress in pediatric oncology patients. *Am J Clin Hypn*. 1989;31(3):181-191.
89. Zeltzer L, LeBaron S. Hypnosis and nonhypnotic techniques for reduction of pain and anxiety during painful procedures in children and adolescents with cancer. *J Pediatr*. 1982;101(6):1032-1035.
90. Sung L. Priorities for quality care in pediatric oncology supportive care. *J Oncol Pract*. 2015;11(3):187-189.
91. Loeffen EAH, Kremer LCM, Mulder RL, et al. The importance of evidence-based supportive care practice guidelines in childhood cancer—a plea for their development and implementation. *Support Care Cancer*. 2017;25(4):1121-1125.
92. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66(7):719-725.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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