Reducing pain and distress related to needle procedures in children with cancer

Loeffen, Erik A. H.; Mulder, Renee L.; Font-Gonzalez, Anna; Leroy, Piet L. J. M.; Dick, Bruce D.; Taddio, Anna; Ljungman, Gustaf; Jibb, Lindsay A.; Tutelman, Perri R.; Liossi, Christina

Published in:
European Journal of Cancer

DOI:
10.1016/j.ejca.2020.02.039

European Journal of Cancer 131 (2020) 53–67

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Reducing pain and distress related to needle procedures in children with cancer: A clinical practice guideline

Erik A.H. Loeffen [a,*], Renée L. Mulder [b,c], Anna Font-Gonzalez [b,c], Piet L.J.M. Leroy [d], Bruce D. Dick [e], Anna Taddio [f,g], Gustaf Ljungman [h], Lindsay A. Jibb [i], Perri R. Tutelman [j], Christina Liossi [k], Alison Twycross [l], Karyn Positano [m], Rutger R. Knops [c], Marc Wijnen [c], Marianne D. van de Wetering [c], Leontien C.M. Kremer [b,c], L. Lee Dupuis [f,g], Fiona Campbell [n,1], Wim J.E. Tissing [a,c,1]

[a] *University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatric Oncology/Hematology, Groningen, the Netherlands*
[b] *Department of Pediatric Oncology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands*
[c] *Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands*
[d] *Department of Pediatrics, Maastricht University Medical Centre, Maastricht, the Netherlands*
[e] *Departments of Anesthesiology and Pain Medicine, Psychiatry &Pediatrics, University of Alberta, Edmonton, AB, Canada*
[f] *Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada*
[g] *Department of Pharmacy and Research Institute, The Hospital for Sick Children, Toronto, Canada*
[h] *Department of Women's and Children's Health, Pediatric Oncology, Uppsala University, Uppsala, Sweden*
[i] *School of Nursing, Faculty of Health Sciences, University of Ottawa, Ottawa, Canada*
[j] *Centre for Pediatric Pain Research, IWK Health Centre Halifax, NS, Canada*
[k] *Pediatric Psychology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom*
[l] *School of Health and Social Care, London South Bank University, London, United Kingdom*
[m] *University of Toronto, Toronto, ON, Canada*
[n] *Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, Toronto, ON, Canada*

Received 5 December 2019; received in revised form 13 February 2020; accepted 17 February 2020
Available online 14 April 2020

KEYWORDS
Pediatric oncology;
Procedural pain;

Abstract ***Background:*** Children with cancer often undergo long treatment trajectories involving repeated needle procedures that potentially cause pain and distress. As part of a comprehensive effort to develop clinical practice guidelines (CPGs) to address pain prevention and management in children with cancer, we aimed to provide recommendations on the

* *Corresponding author*: Department of Pediatric Oncology/Hematology,Beatrix Children's Hospital PO Box 30.001 9700 RB Groningen University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.. Fax: +31 50 36 14 235.
E-mail address: eah.loeffen@umcg.nl (E.A.H. Loeffen).
[1] F.C. Campbell and W.J.E. Tissing contributed equally to this work.

https://doi.org/10.1016/j.ejca.2020.02.039

Supportive care;
Guideline

pharmacological and psychological management of procedure-related pain and distress.
Methods: Of the international inter-disciplinary CPG development panel (44 individuals), two working groups including 13 healthcare professionals focused on procedural pain and distress. Grading of Recommendations Assessment, Development and Evaluation methodology was used, including the use of systematic literature reviews to inform recommendations and the use of evidence to decision frameworks. At an in-person meeting in February 2018, the guideline panel discussed these frameworks and formulated recommendations which were then discussed with a patient-parent panel consisting of 4 survivors and 5 parents.
Results: The systematic reviews led to the inclusion of 48 randomised controlled trials (total number of participants = 2271). Quality of evidence supporting the recommendations ranged from very low to moderate. Strong recommendations were made for the use of topical anesthetics in all needle procedures, for offering deep sedation (DS)/general anesthesia (GA) to all children undergoing lumbar puncture, for the use of DS/ GA in major procedures in children of all ages, for the use of hypnosis in all needle procedures and for the use of active distraction in all needle procedures.
Conclusion: In this CPG, an evidence-based approach to manage procedure-related pain and distress in children with cancer is presented. As children with cancer often undergo repeated needle procedures during treatment, prevention and alleviation of procedure-related pain and distress is of the utmost importance to increase quality of life in these children and their families.

1. Introduction

With the introduction of intensive treatment protocols, survival rates for childhood cancer in developed countries have now increased from 40% in the 1970s to over 80% [1,2]. The drawback of these intensive and prolonged treatments is that they are often associated with significant morbidity. Of these side-effects, pain is a key area for which healthcare professionals seek guidance [3].

In contrast to adult patients with cancer, in whom pain is mostly tumor related, pain in children with cancer is mostly related to treatment or procedures [4]. Children with cancer undergo various potentially painful and/or distressing needle procedures, such as accessing the central venous access port or bone marrow punctures. It is increasingly acknowledged that children are at risk of long-term sequelae from inadequate pain management during needle procedures, for example, increased levels of anxiety and non-compliance with care [5]. Pain should be measured and managed, bearing in mind that children require a developmentally appropriate approach [6].

Guidance is urgently needed for procedural pain in children with cancer. Major practice variations have been documented across centers [7]. A recent study showed that only 10% of institutions had standards for pediatric bone marrow aspiration pain management [8]. The lack of attention to pain management practices may negatively influence health outcomes for children with cancer.

In this clinical practice guideline (CPG), we provide recommendations regarding pharmacological and psychological interventions for reducing pain and distress related to needle procedures in children with cancer. This CPG is targeted to healthcare professionals who care for children with cancer undergoing painful medical procedures, including pediatric oncologists, nurses, anesthesiologists and child life specialists. This CPG is the first of a series of CPGs focusing on pain in children and adolescents with cancer.

2. Methods

The full methodology for this guideline development project has been published separately [9]. A brief summary is provided here.

2.1. CPG development panel

The CPG development panel comprised 44 international panel members and was divided into six working groups. Two working groups focused on pharmacological and psychological interventions to reduce pain related to needle procedures and included three pediatric oncologists, two pediatric oncology nurses, two clinical psychologists and a pediatric anesthesiologist, academic pharmacist, pediatric intensivist, child life specialist, pediatric oncology researcher and pediatric surgeon. A core group of eight individuals with experience in CPG development supervised the process and provided methodological expertise.

2.2. Scope, definitions and clinical questions

For the purposes of this CPG, needle procedures were categorised as minor procedures (blood sampling,

peripheral intravenous access and access to central venous access port), lumbar puncture procedures (LPs) and major procedures (bone marrow aspiration (BMA), bone marrow puncture (BMP), combined LP with BMA/BMP, bone biopsy, organ biopsy and echo-/radiographically guided punctures). Levels of sedation were defined according to the American Society of Anesthesiologists: no sedation, minimal sedation, moderate sedation, deep sedation (DS) and general anesthesia (GA) [10].

Refer Table 1 for a full list of clinical questions that were included. Clinical outcomes for these questions were prioritised using a simple voting procedure, in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [11].

2.3. Systematic literature review

For 22 clinical questions, systematic literature searches were performed (last update March 13th 2018). Randomised controlled trials (RCTs) studying children and adolescents with cancer were eligible for inclusion. Study selection, quality appraisal (Cochrane risk of bias tool and GRADE) and data extraction were performed independently by two reviewers [12–14].

2.4. Formulation of recommendations

When formulating recommendations, the CPG development panel prioritised the perspective of the patient and his/her family as most important when formulating recommendations. Evidence summaries were disseminated and used to complete evidence to decision (EtD) frameworks [15]. These frameworks facilitate formulation of recommendations in a systematic and transparent manner by considering the balance between benefits and harms of an intervention and also other factors such as costs, feasibility and acceptability. In February 2018, the results of the systematic review and the EtD frameworks were discussed during an in-person guideline panel meeting in Amsterdam attended by 36 members (80%) including 11 of the 13 members (85%) of the procedural pain working groups. Decisions were made through group discussion and consensus; final recommendations had to be supported unanimously. For questions where the evidence was deemed insufficient to formulate a recommendation, an approach to

Table 1
Included clinical questions and hierarchy of outcomes.

Clinical question number	Patient, intervention, and comparison			Prioritised clinical outcomes
1	In children with cancer undergoing a relevant minor procedure, what is the effect of a **topical anesthetic** vs. *any active or passive comparator* on:			8 - Pain intensity, self-rated 8 - Distress, self-rated 8 - Adverse effects 7 - Behavioral distress
2	In children with cancer undergoing a relevant minor procedure, what is the effect of oral analgesics vs. any active or passive comparator on:			Identical to #1
3	In children with cancer undergoing a relevant minor procedure, what is the effect of	**Sedatives**	Any active or passive comparator	Identical to #1
4	In children with cancer undergoing a lumbar puncture procedure, what is the effect of	**Level of sedation**	Any active (mainly other level of sedation) or passive comparator	8 - Pain intensity, self-rated 8 - Distress, self-rated 7 - Behavioral distress 7 - Adverse effects 7 - Success of procedure
5	In children with cancer undergoing a relevant major procedure, what is the effect of	**Level of sedation**	Any active (mainly other level of sedation) or passive comparator	8 - Pain intensity, self-rated 8 - Distress, self-rated 7 - Behavioral distress 7 - Adverse effects
6	In children with cancer undergoing a relevant procedure, what is the effectof	**Hypnosis**	Any active or passive comparator	8 - Pain intensity, self-rated 8 - Distress, self-rated 7 - Distress, rated by proxy 7 - Behavioral distress 7 - Global judgment of satisfaction with treatment 7 - Fear of future medical procedures 7 - Adverse effects
7	In children with cancer undergoing a relevant procedure, what is the effect of	**Distraction**	Any active or passive comparator	Identical to #6
8	In children with cancer undergoing a relevant procedure, what is the effect of	**Combination of modalities**	Any single modality	Identical to #6

identify non-RCT and indirect evidence including evidence syntheses was established. Draft recommendations were refined and finalised using repeated group conversations through email and telephone.

In accordance with GRADE methodology, good practice statements were formulated to address practice points for which studies were not possible or feasible but that according to the panel underpin a comprehensive guideline. Good practice statements were 'ungraded' because no formal grading of evidence can be performed [16].

2.5. Patient and parent review

The draft recommendations were reviewed in an in-person group meeting by a patient-parent panel (four survivors, five parents) to consider the values and preferences of children and families. Participants received a short training session on CPG development and contributed to the decisions regarding the direction and strength of recommendations and to implementation considerations (refer Supplemental Material S1).

2.6. CPG update cycle

This CPG will be updated in five years (March 2024) or earlier should novel studies or insights warrant an earlier update.

3. Results

We retrieved 11.159 citations. Refer Fig.1 for a flowchart of the selection process. In all, 48 primary studies were included (total number of participants = 2.271); 33 studies (n = 1.602) and 15 studies (n = 669) focused on pharmacological or psychological interventions, respectively.

In Table 2, the conclusions of included studies are presented. The formulated recommendations (arranged per type) and the ungraded good practice statements are presented in Tables 3 and 4, respectively. Refer Supplemental Materials S2 and S3 for the full evidence summaries and Supplemental Materials S4 and S5 for the EtD frameworks. For a flowchart to guide clinical care, refer Fig.2.

3.1. Pharmacological interventions

The clinical questions regarding the use of pharmacological interventions are presented in Table 1. Critical outcomes for all these questions included self-rated pain intensity, self-rated distress, adverse effects and behavioral distress. For clinical questions regarding LPs, success of the procedure was also a critical outcome.

3.1.1. Topical anesthetics

We recommend the use of a topical anesthetic for all needle procedures (strong recommendation, low quality of evidence).

3.1.1.1. Evidence. A total of six studies (minor procedures: 3 studies (n = 173); LPs: 3 studies (n = 46)) informed this recommendation [17–22]. All studies compared lidocaine-prilocaine 5% (Eutectic Mixture of Local Anesthetics; EMLA®) cream to either a placebo or another topical anesthetic each with a 60 min application time in needle insertion into a subcutaneous intravenous port. Lidocaine-prilocaine 5% reduced self-rated pain intensity in four studies (no significant difference in 2 studies) and reduced proxy-rated distress in 3 studies (no significant difference in three studies). Adverse effects were addressed in two studies; there were no significant differences between groups. Given the low number of included RCTs, additional evidence was sought and two general pediatrics evidence syntheses (dermal laceration repair, vaccine injection pain) were included [23,24]. Both syntheses concluded that topical anesthetics are effective in reducing pain.

3.1.1.2. Evidence to decision. The panel concluded that the desirable consequences of topical anesthetics clearly outweigh the undesirable consequences (i.e. possible erythema, itchiness). Required resources are small relative to the benefits, and topical anesthetics are acceptable to key stakeholders and feasible to implement.

3.1.1.3. Implementation considerations. Topical anesthetics used in included studies were lidocaine-prilocaine 5% cream or patch (e.g. EMLA®) and amethocaine 4% gel (e.g. Ametop™). The required application time relative to the procedure (e.g. for lidocaine-prilocaine 5% at least 60 min before procedure) is feasible in pediatric oncology as most procedures are planned procedures. Healthcare providers, patients and parents should be educated regarding application timing (e.g. when leaving for the hospital or coming early to apply) and patch removal technique to minimise distress. Topical anesthetics should be introduced as early in the treatment trajectory as possible.

3.1.2. Sedation in major procedures

We recommend the use of DS or anesthesia for major procedures (strong recommendation, very low quality evidence).

3.1.2.1. Evidence. Twelve studies evaluating a wide spectrum of sedative drugs were included. Of these, two compared different sedation levels [25,26]. GA reduced behavioral distress compared with no sedation, with

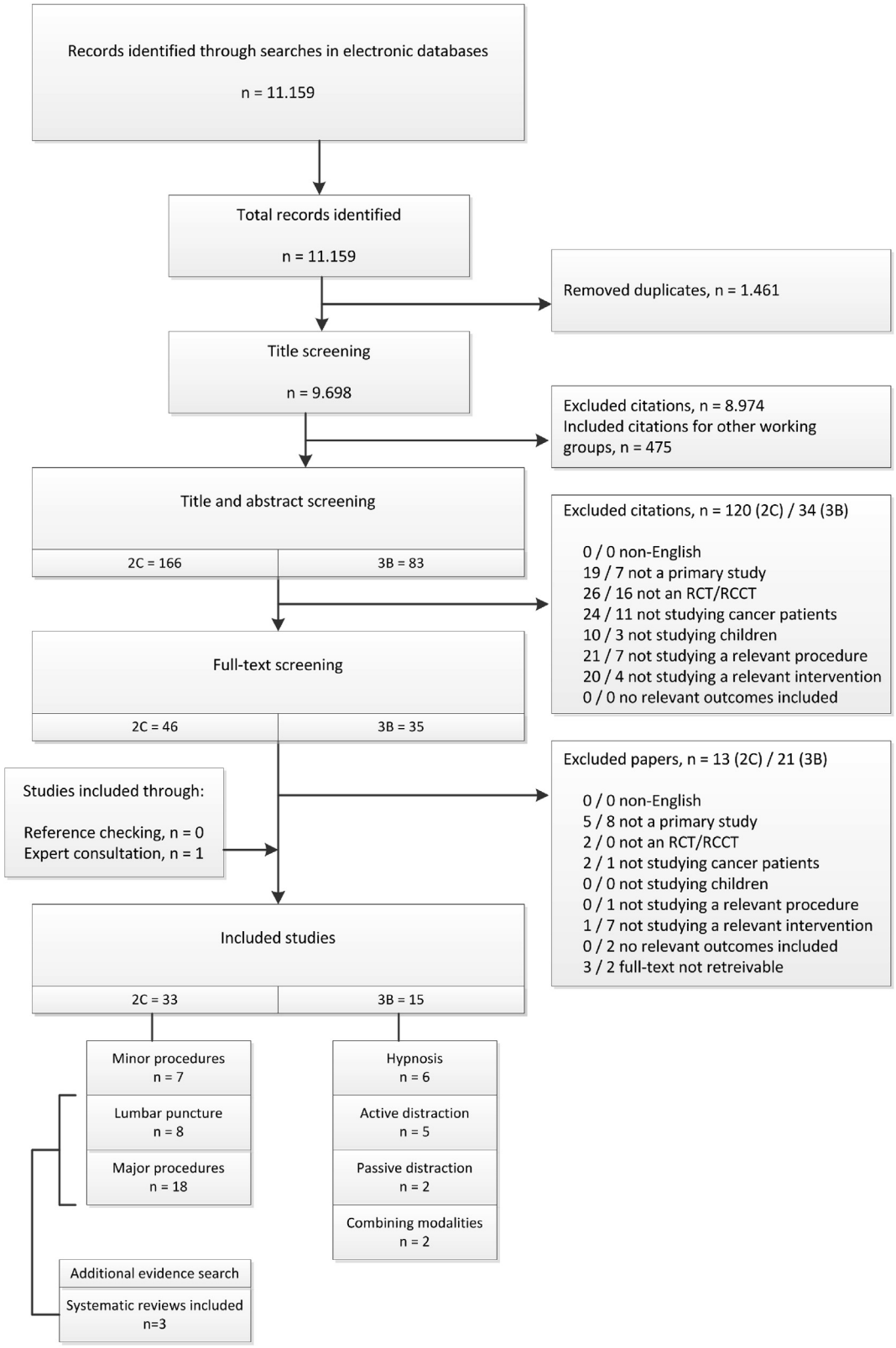

Fig. 1. Flowchart of the selection process. Working groups are indicated using their working group number; 2C for pharmacological management of procedure-related pain, 3B for psychological management of procedure related pain.

Table 2
Conclusions of evidence.

Topical anesthetics	
Minor procedures	Quality of evidence
Reduced self-rated pain intensity with lidocaine-prilocaine 5% (60 min) vs. placebo	⊕⊕◯◯ LOW(18)
Reduced proxy-rated distress with lidocaine-prilocaine 5% (60 min) vs. placebo	⊕⊕◯◯ LOW(18)
No significant difference in adverse effects with lidocaine-prilocaine 5% (60 min) vs. placebo	⊕⊕◯◯ LOW(18)
Reduced self-rated pain intensity with lidocaine-prilocaine 5% (60 min) vs. lidocaine-prilocaine 5% (40 min)	⊕⊕◯◯ LOW(17)
No significant difference in proxy-rated distress with lidocaine-prilocaine 5% (60 min) vs. lidocaine-prilocaine 5% (40 min)	⊕⊕◯◯ LOW(17)
No significant difference in self-rated pain intensity with lidocaine-prilocaine 5% (60 min) vs amethocaine gel (30 min)	⊕◯◯◯ VERY LOW(19)
No significant difference in proxy-rated distress with lidocaine-prilocaine 5% (60 min) vs amethocaine gel (30 min)	⊕◯◯◯ VERY LOW(19)
No significant difference in adverse effects with lidocaine-prilocaine 5% (60 min) vs amethocaine gel (30 min)	⊕◯◯◯ VERY LOW(19)
No significant difference in success of procedure with lidocaine-prilocaine 5% (60 min) vs amethocaine gel (30 min)	⊕◯◯◯ VERY LOW(19)
Lumbar puncture procedures	Quality of evidence
Varying results (benefit in 2 studies, no significant difference in 1 study) with lidocaine-prilocaine 5% vs. placebo	⊕⊕◯◯ LOW(20–22)
Reduced proxy rated distress with lidocaine-prilocaine 5% vs. placebo	⊕⊕◯◯ LOW(20–22)
No significant difference in success of procedure with lidocaine-prilocaine 5% vs. placebo	⊕⊕◯◯ LOW(20–22)
Oral analgesics	
Minor procedures	Quality of evidence
No significant difference in self-rated pain intensity with paracetamol vs. placebo	⊕⊕⊕◯ MODERATE (36)
Reduced self-rated distress with paracetamol vs. placebo	⊕⊕⊕◯ MODERATE (36)
Reduced behavioral distress with paracetamol vs. placebo	⊕⊕⊕◯ MODERATE (36)
No significant difference in self-rated pain intensity with morphine vs. placebo	⊕⊕⊕◯ MODERATE (35)
Increased self-rated distress with morphine vs. placebo	⊕⊕⊕◯ MODERATE (35)
Use of sedation	
Minor procedures	Quality of evidence
No significant difference in self-rated pain intensity with midazolam vs. placebo	⊕⊕◯◯ LOW(33.34)
No significant difference in self-rated distress (distress, needle discomfort) with midazolam vs. placebo	⊕⊕◯◯ LOW(33.34)
Reduced self-rated distress (fear) with midazolam vs. placebo	⊕⊕◯◯ LOW(33)
Reduced behavioral distress with midazolam vs. placebo	⊕⊕◯◯ LOW(33)
Increased adverse effects with midazolam vs. placebo	⊕⊕◯◯ LOW(33)
Lumbar puncture procedures	Quality of evidence
No significant difference in self-rated distress with general anesthesia vs. deep sedation	⊕⊕◯◯ LOW(30)
No significant difference in adverse effects with general anesthesia vs. deep sedation	⊕⊕◯◯ LOW(30)
No significant difference in success of procedure with general anesthesia vs. deep sedation	⊕⊕◯◯ LOW(30)
No significant difference in duration of procedure with general anesthesia vs. deep sedation	⊕⊕◯◯ LOW(30)
Major procedures	Quality of evidence
No significant difference in self-rated pain intensity with general anesthesia vs. no sedation	⊕◯◯◯ VERY LOW(25)
No significant difference in self-rated distress with general anesthesia vs. no sedation	⊕◯◯◯ VERY LOW(25)
Reduced behavioral distress with general anesthesia vs. no sedation	⊕◯◯◯ VERY LOW(25)
No significant difference in self-rated pain intensity with general anesthesia vs. deep sedation	⊕⊕◯◯ LOW(26)
No significant difference in self-rated distress with general anesthesia vs. deep sedation	⊕⊕◯◯ LOW(26)
No significant difference in behavioral distress with general anesthesia vs. deep sedation	⊕⊕◯◯ LOW(26)
No significant difference in adverse effects with general anesthesia vs. deep sedation	⊕⊕◯◯ LOW(26)
Hypnosis	
Minor procedures	Quality of evidence
Reduced self-rated pain intensity with hypnosis vs. standard care	⊕⊕⊕◯ MODERATE (38–41)
Reduced self-rated distress with hypnosis vs. standard care	⊕⊕⊕◯ MODERATE (38–41)
Reduced behavioral distress with hypnosis vs. standard care	⊕⊕⊕◯ MODERATE (38–41)
Reduced fear of future medical procedures with hypnosis vs. standard care	⊕⊕⊕◯ MODERATE (40.41)
Reduced self-reported distress in parents with hypnosis vs. standard care	⊕⊕⊕◯ MODERATE (41)
Active distraction	
Minor procedures	Quality of evidence
No significant difference in self-rated pain intensity with active distraction vs. standard care	⊕⊕◯◯ LOW(44.45)
No significant difference in self-rated distress with active distraction vs. standard care	⊕⊕◯◯ LOW(44.45)
Reduced behavioral distress with hypnosis vs. standard care	⊕⊕◯◯ LOW(45)
No significant difference in proxy-rated distress with active distraction vs. standard care	⊕⊕◯◯ LOW(43.45)
Passive distraction	
Lumbar puncture procedures	Quality of evidence
Reduced self-rated pain intensity during and after procedure with passive distraction vs. standard care	⊕⊕◯◯ LOW(47)
No significant difference in self-rated pain intensity before procedure with passive distraction vs. standard care	⊕⊕◯◯ LOW(47)
No significant difference in self-rated pain intensity with passive distraction vs.	⊕◯◯◯ VERY LOW(48)

Table 2 (*continued*)

standard care	
Reduced self-rated distress with passive distraction vs. standard care	⊕⊕◯◯ LOW(47)
Combining modalities	
Major procedures	Quality of evidence
Reduced self-rated pain intensity post-intervention with combining strategies vs. single procedure	⊕⊕◯◯ LOW(49)
No significant difference in self-rated pain intensity pre-intervention with combining strategies vs. single procedure	⊕⊕◯◯ LOW(49)
Reduced self-rated distress pre-intervention with combining strategies vs. single procedure	⊕⊕◯◯ LOW(49)
No significant difference in self-rated distress post-intervention with combining strategies vs. single procedure	⊕⊕◯◯ LOW(49)
Varying results (with no formal testing) with hypnosis vs. non-hypnotic attention techniques	⊕◯◯◯ VERY LOW(50)
Reduced behavioral distress post-intervention with combining strategies vs. single procedure	⊕⊕◯◯ LOW(49)
No significant difference behavioral distress pre-intervention with combining strategies vs. single procedure	⊕⊕◯◯ LOW(49)

no significant differences in self-rated pain intensity and distress (1 study, n = 18)[25]. Compared with DS, GA showed no significant differences between groups (one study, n = 31) [26].

3.1.2.2. Evidence to decision. The panel concluded that the desirable consequences of DS or GA probably outweigh the undesirable consequences. The panel judged that the vast majority of patients would want to undergo a major procedure with DS or GA. Also the panel judged that clinicians would prefer to perform these procedures with DS or GA. The patient-parent panel supported this recommendation unanimously. In fact, patients who had not receive DS or GA for major procedures stated explicitly that they would have wanted so had they had the choice. Although the required resources are substantial, the panel deemed the option feasible to implement and acceptable for institutions caring for children with cancer.

3.1.2.3. Implementation considerations. We realise the stratification of the sedation spectrum established by the ASA is relatively artificial [27]. Therefore this recommendation should be seen in the light of the overarching aim of this CPG: optimal patient comfort, absence of restraint and successful performance of the procedure.

The CPG panel recognised that some of the agents evaluated in the studies informing this recommendation differ from modern practice with respect to the provision of DS and GA. The CPG panel therefore directs users of this CPG to current evidence-based guidance on this topic such as the American Academy of Pediatrics guideline on using sedation for diagnostic and therapeutic procedures in pediatric patients [28].

To safely implement this recommendation, the facilities to provide DS/GA should be readily available, including the presence of an expert to administer the anesthetic drugs and monitor the patient. At minimum, patient monitoring requirements should comply with local laws and regulations or the American Academy of Pediatrics guideline on monitoring of sedation in children may be consulted [27].

3.1.3. Sedation in lumbar punctures

We recommend that the use of DS or GA be offered to all children undergoing lumbar punctures.

3.1.3.1. Evidence. Eight studies were included. Two compared different sedation levels: one did not present data in an extractable manner [29] and the other study (n = 22) observed no differences between GA and DS with respect to self-rated distress, success of procedure or adverse effects [30].

3.1.3.2. Evidence to decision. Overall the panel concluded that the desirable consequences probably outweigh the undesirable consequences and that the option is feasible to implement. Furthermore, the panel took into account the need for motion control in LPs and the body of evidence for major procedures (several studies focused on combined BMAs/LPs) that favored higher levels of sedation.

Motion control is critical to the successful performance of LPs and is often difficult to achieve without sedation, especially in younger children. However, both the guideline development panel and the patient-parent panel acknowledged that there are children who may prefer not to receive DS or GA for lumbar puncture, and for whom no, minimal or moderate sedation and/or psychological interventions will suffice to establish a successful and comfortable LP [31,32]. A strong recommendation was made to emphasise (1) the need to determine each patient's needs and preferences and (2) the requirement that all levels of sedation be readily accessible and available to all patients. When the success

Table 3
List of recommendations, presented per type of procedure.

#	GRADE Recommendation text*	Strength‡	Quality of evidence
	Minor procedures†		
1	We recommend the use of a topical anesthetic for all needle procedures	Strong	Low
4	We suggest that sedatives **not** be used routinely for minor procedures	Weak	Low
5	We suggest that oral analgesics **not** be used for minor procedures	Weak	Low
6	We recommend the use of hypnosis for all needle procedures	Strong	Moderate
7	We recommend the use of active distraction for all needle procedures	Strong	Low
8	We suggest the use of passive distraction for all needle procedures	Weak	Very low
10	We recommend combining psychological interventions with pharmacological interventions during all needle procedures	Strong	Very low
	Lumbar puncture procedures†		
1	We recommend the use of a topical anesthetic for all needle procedures	Strong	Low
3	We recommend that the use of deep sedation or general anesthesia be offered to all children undergoing lumbar punctures**	Strong	Very low
6	We recommend the use of hypnosis for all needle procedures	Strong	Moderate
7	We recommend the use of active distraction for all needle procedures	Strong	Low
8	We suggest the use of passive distraction for all needle procedures	Weak	Very low
10	We recommend combining psychological interventions with pharmacological interventions during all needle procedures	Strong	Very low
	Major procedures†		
1	We recommend the use of a topical anesthetic for all needle procedures	Strong	Low
2	We recommend the use of deep sedation or anesthesia for major procedures	Strong	Very low
6	We recommend the use of hypnosis for all needle procedures	Strong	Moderate
7	We recommend the use of active distraction for all needle procedures	Strong	Low
8	We suggest the use of passive distraction for all needle procedures	Weak	Very low
10	We recommend combining psychological interventions with pharmacological interventions during all needle procedures	Strong	Very low

* Selection of approach should be based on the developmental stage and preferences of the patient, availability of resources and the patient's prior experience with the interventions and the procedure. Pharmacological interventions should be dosed appropriately. All interventions should be administered by appropriate, qualified providers according to local legislation and medical regulations.

** The panel acknowledges that there are children who may prefer not to receive deep sedation or general anesthesia for lumbar puncture, but instead prefer to receive no, minimal or moderate sedation and/or psychological interventions [31,32]. A strong recommendation was made to emphasize 1) the need to determine each patient's needs and preferences and 2) the requirement that all levels of sedation be readily accessible and available to all patients. When the success of the procedure is not likely to be compromised, patients preferences should be honored.

† Definitions: minor procedures = blood sampling, peripheral intravenous access, and access to central venous access port. Lumbar puncture procedures = lumbar puncture procedures only (not combined procedures). Major procedures = bone marrow aspiration (BMA), bone marrow puncture (BMP), combined LP with BMA/BMP, bone biopsy, organ biopsy, and echo-/radiographically guided puncture.

‡ Strong and weak recommendations have different implications. A strong recommendation implies that most patients in that situation would want the recommended course of action and only a small proportion would not. For clinicians this implies that most patients should receive the recommended course of action (which however does not omit the need for discussing options). A weak recommendation (sometimes called conditional, discretionary, or qualified) implies that most patients in that situation would want the recommended course of action, but many would not. For clinicians this implies that they should recognize that different choices will be appropriate for different patients and that one must help each patient to arrive at a management decision consistent with her or his values and preferences [15].

of the procedure is not likely to be compromised, the patient preferences should be honored.

3.1.3.3. Implementation considerations. Refer implementation considerations presented for the use of DS or GA for major procedures.

3.1.4. Sedation for minor procedures

We suggest that sedatives not be used routinely for minor procedures (weak recommendation, low quality evidence).

3.1.4.1. Evidence. Two studies (n = 93) compared midazolam to placebo in needle insertion into a subcutaneous intravenous port [33,34]. No differences between groups were found for self-rated outcomes (pain intensity and distress), except for reduced self-rated fear in one study [33,34]. In one study, midazolam reduced behavioral distress but was also associated with adverse effects (e.g. anger, over-sedation) [33].

3.1.4.2. Evidence to decision. Appraising the limited evidence, the panel concluded that the desirable consequences of the use of sedatives probably do not outweigh the undesirable consequences. In addition, the panel judged that sedative use is not acceptable to key

Table 4
List of good practice statements.

Ungraded good practice statements
Prior to all needle procedures, healthcare providers, children and parents should be educated and prepared regarding needle procedures and interventions to reduce pain and distress.
The child and his/her family should always be consulted in determining the appropriate management strategy to reduce procedure-related pain and distress.
Healthcare professionals should offer parents the option to be present during their child's needle procedures if the child wishes to.
Throughout the course of treatment, children should have ongoing assessments and re-assessments of pain and distress and the appropriateness of interventions should be re-assessed to determine the continued effectiveness of strategies to reduce procedural pain and distress.

stakeholders nor is it feasible to implement. Information regarding other sedatives was lacking.

3.1.4.3. Implementation considerations. There may be a subset of children who are extremely anxious before and/or during minor procedures for whom sedation might be beneficial [28].

3.1.5. Oral analgesics in minor procedures

We suggest that oral analgesics not be used for minor procedures (weak recommendation, low quality evidence).

3.1.5.1. Evidence. Two placebo-controlled studies (n = 101) were included, one focusing on oral acetaminophen (paracetamol) and one on oral morphine. Both found no significant differences in self-rated pain intensity [35,36]. Acetaminophen reduced self-rated distress and behavioral distress [36]. Morphine increased self-rated distress [35].

In the systematic search for general pediatrics evidence syntheses, one vaccine pain CPG was included. This CPG recommended against acetaminophen use due to a lack of evidence [37].

3.1.5.2. Evidence to decision. In formulating this recommendation, the CPG panel considered both the included evidence and the wide between-patient variability of analgesic bioavailability and time to maximum effect. Thus, coordinating the procedure with the peak analgesic effect would be logistically difficult. Overall, the panel concluded that the undesirable consequences of analgesics outweigh their uncertain desirable effects.

3.2. Psychological interventions

The included clinical questions on psychological interventions focused on hypnosis, active distraction and passive distraction (reer Table 1). Critical outcomes for all these questions were self-rated pain intensity, self-rated distress, proxy-rated distress, behavioral distress, fear of future medical procedures, adverse effects and, for the questions on distraction, global judgement of satisfaction with treatment.

Hypnosis was defined as a trance-like state awareness, where a child is highly focused on (suggested or self-created) images or ideas. Active distraction was defined as distraction in which a child actively participates, for example, completing a puzzle or playing a computer game. Passive distraction was defined as distraction in which a child does not actively participate, for example, listening to music or watching a movie.

It should be noted that in procedures where DS or GA is used, the use of psychological interventions is limited to the preparation phase.

3.2.1. Hypnosis

We recommend the use of hypnosis for all needle procedures (strong recommendation, moderate quality evidence).

3.2.1.1. Evidence. Four studies (n = 120), all from one study group, compared the use of hypnosis to standard care during minor procedures, LPs and major procedures [38–41]. In all studies, hypnosis reduced self-rated pain intensity, self-rated distress and behavioral distress; in two studies, hypnosis reduced fear of future medical procedures.

3.2.1.2. Evidence to decision. The panel concluded that the desirable consequences of hypnosis clearly outweigh the undesirable consequences. In addition, hypnosis is feasible to implement (although formal training is required) and acceptable to stakeholders. Thus, the CPG panel made a strong recommendation based on the consistent demonstration of benefit of hypnosis and the low likelihood of harm. This recommendation was unanimously supported by the patient-parent panel.

3.2.1.3. Implementation considerations. The patient-parent panel emphasised the need to eliminate misconceptions about hypnosis through education. To implement hypnosis, professionals need to be trained to use this

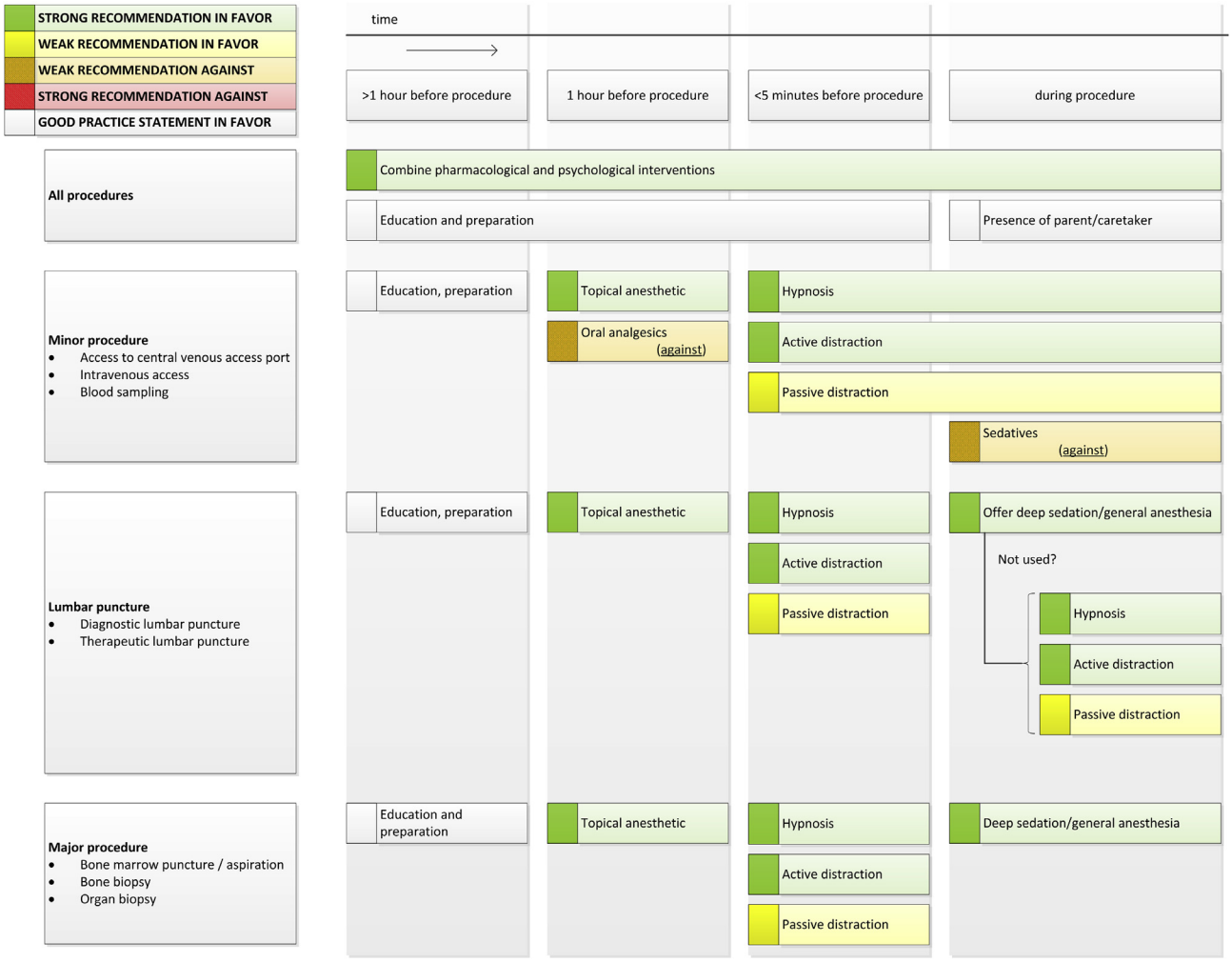

Fig. 2. Flowchart summarizing the recommendations to reduce procedural pain and distress, for use in clinical practice.

technique. They could then perform hypnosis or train patients to perform self-hypnosis.

3.2.2. Active distraction

We recommend the use of active distraction for all needle procedures (strong recommendation, low quality evidence).

3.2.2.1. Evidence. Five studies (n = 171) evaluated the use of active distraction compared with standard care during minor procedures [42–45]. Although several critical outcomes were not reported in sufficient detail to extract data, active distraction reduced behavioral distress (one study), with no significant differences for self-rated pain intensity (one study), and self- and proxy-rated distress (two studies).

3.2.2.2. Evidence to decision. As there is a low likelihood that distraction causes harm, even small benefits can be of value, and the panel thus concluded that the desirable consequences probably outweigh the undesirable consequences (if any). Distraction interventions can be of low cost and therefore accessible in nearly all settings. The parent-patient panel unanimously underlined the strong recommendation.

3.2.2.3. Implementation considerations. The parent-patient panel emphasised the need to take the time, together with the child, to select the preferred distraction. In addition, from the literature (and from the experience of our patient-parent panel), we know that there are people who benefit from knowing and seeing what is going on and therefore prefer not to be distracted [46].

3.2.3. Passive distraction

We suggest the use of passive distraction for all needle procedures (weak recommendation, very low quality evidence).

3.2.3.1. Evidence. Two studies (n = 70) evaluated the use of passive distraction compared with standard care during LPs [47,48]. In one study, passive distraction reduced self-rated anxiety and self-rated pain intensity during and after (but not before) the procedure [47].

In one study, there was no significant difference for self-rated pain intensity [48].

3.2.3.2. Evidence to decision. The panel concluded that the desirable consequences probably outweigh the undesirable consequences, with the option being feasible and acceptable. However, given the very low overall quality of the evidence and the focus of the included studies on LPs only, the panel preferred active distraction over passive distraction and thus categorised this recommendation as weak.

3.2.3.3. Implementation considerations. Refer the implementation considerations paragraph of active distraction. As no person is needed to interact with the child, passive distraction might be more simple to implement than active distraction.

3.3. Combining intervention modalities

We recommend combining psychological interventions with pharmacological interventions during all needle procedures (strong recommendation, very low quality evidence).

3.3.1. Evidence

Two studies (n = 175) compared combined interventions (valium and cognitive behavioral therapy in one study, midazolam/morphine and play/guided imagery in the other) to single interventions in major procedures [49,50]. In one study, combining intervention modalities reduced self-rated pain intensity post-intervention (but not pre-intervention), self-rated distress pre-intervention (but not post-intervention) and behavioral distress post-intervention (but not pre-intervention) [49].

3.3.2. Evidence to decision

Given the available evidence and the previous strong recommendations for several single interventions among different modalities, the panel judged a strong recommendation for combining appropriate interventions as justifiable. Combining psychological and pharmacological interventions is generally feasible and acceptable to key stakeholders. This recommendation was also based on the included studies on psychological interventions that included pharmacological interventions as part of standard care.

3.3.3. Implementation considerations

Other than situations where combining modalities is not applicable (e.g. during DS), the panel judged that clinicians should always strive to combine recommended pharmacological interventions (e.g. topical anesthetics) with recommended psychological interventions (e.g. active distraction) to optimise pain/distress management.

3.4. Ungraded good practice statements

3.4.1. Education and preparation

Before all needle procedures, healthcare providers, children and parents should be educated and prepared regarding needle procedures and interventions to reduce pain and distress (ungraded good practice statement).

Both the CPG panel and the patient-parent panel deemed education and preparation (starting as early as possible in the treatment process) to be critical to the provision of high-quality, patient-centered care of children undergoing procedures. This might be partly covered in the process of gaining informed consent. Children and parents should be informed about the meaning and process of each procedure and about what measures can be taken to reduce pain and distress. This can effectively decrease distress and increase coping and compliance during a variety of medical procedures [51]. In addition, healthcare providers need to be trained on effective procedural pain and distress management strategies.

3.4.2. Empowerment

The child and his/her family should always be consulted in determining the appropriate management strategy to reduce procedure-related pain and distress (ungraded good practice statement).

Healthcare providers should always engage a child and their parents in the selection of effective interventions to reduce procedural pain and distress. Developmental age, personality, gender and cultural factors may all play a role in the success of an intervention. An informed decision on the preferred strategy should be made together. The patient-parent panel emphasised the autonomy of the child by saying: put the child in charge. Several projects are being undertaken that contribute to this aim, for instance, the Comfort, Ask, Relax, Distract (CARD) project in which patient empowerment is combined with education, for patients as well as healthcare providers [55].

3.4.3. Presence of parents

Healthcare professionals should offer parents the option to be present during their child's needle procedures if the child wishes to (ungraded good practice statement).

Parental presence might facilitate patient distraction and/or comfort and if desired the parents can act as a coach for their child. During preparation and education, parents should be informed about what behaviors and techniques are helpful to decrease distress and increase coping.

3.4.4. Ongoing pain assessments

Throughout the course of treatment, children should have ongoing assessments and re-assessments of pain and distress and the appropriateness of interventions should be re-assessed to determine the continued

effectiveness of strategies to reduce procedural pain and distress (ungraded good practice statement).

Intervention effectiveness may vary over the course of a child's cancer treatment, and their preferences and capabilities might change. A child's willingness to accept certain interventions is among other things influenced by the pain and distress experienced during past procedures. This may not have a linear trajectory. For instance, a negative procedure experience (e.g. more distressing, multiple attempts before success) can provoke increased levels of fear, which may call for a different approach with regard to managing procedural pain and distress in the future.

3.5. Recommendations for research

The panel identified several evidence gaps (refer Supplemental Materials S4 and S5). Overall, the panel calls for large, multicenter RCTs that evaluate the critical outcomes defined in this guideline. In particular, head-to-head intervention comparison trials and cost-effectiveness trials for sedation drugs, use of nitrous oxide, virtual reality for distraction and trials in which different combinations of treatment modalities are compared are needed. Developing specific guidance for children with developmental disorders would also be of interest.

Future studies should take into account the long treatment trajectories with repeated procedures that children with cancer often undergo. Most current studies focus on one procedure. However, an intervention can be effective for one procedure but ineffective over time due to increases in pain and/or distress. Therefore, longitudinal design studies taking into account pain and distress over multiple procedures and other relevant outcomes such as psychological sequelae, compliance behavior and quality of life are needed.

The patient-parent panel emphasised that attention should be placed on identifying optimal ways to put the child in charge of their own procedure experience. Children should be fully and optimally facilitated to explore possibilities and formulate their own approach to pharmacological and psychological management of procedure-related pain and distress, within the boundaries of what is clinically possible and appropriate.

4. Discussion

Throughout the course of treatment, children with cancer undergo frequent, repeated procedures that are associated with high levels of pain and distress [4]. In this CPG, we have formulated recommendations to reduce pain and distress during these procedures to improve health-related quality of life for children with cancer and their families.

This CPG endeavor benefited from an international and interprofessional CPG development panel. We believe this contributed significantly to the international applicability of the recommendations. However, we included only one healthcare professional from a non–high-income country. Although some of the recommendations are feasible in lower income settings (e.g. use of distraction), this may not be the case for all recommendations. We have provided detailed evidence summaries, accompanying EtD frameworks, transparent reports of the justification for each recommendation and implementation considerations to facilitate local adaptation of the recommendations.

Use of the rigorous methodology of the GRADE working group increases the credibility of our recommendations [14]. Inclusion of patients and parents in the recommendation formulation process and integrating their perspective increased the applicability and usefulness of our recommendations. The panel placed high value on using a patient-centered approach, as is also increasingly promoted [52,53].

This CPG is limited by the scarcity of direct evidence available to address our clinical questions. Few high-quality studies have been performed that focus on alleviating procedural pain in children with cancer. The GRADE group acknowledges the frustration of clinicians when a CPG does not succeed in providing guidance, and therefore encourages guideline developers to attempt to formulate recommendations even when confidence in the effect estimate is low [54]. The scarcity of direct evidence calls for high-quality RCTs to be conducted in this field.

In addition, there might be subgroups of patients for whom these recommendations might not be applicable and who could benefit from recommendations tailored to their specific situation. For example, this might be true for children with severe procedural distress/needle phobia.

Pain and distress from repeated procedures is often a great burden for children with cancer and their families. Our group has formulated recommendations to guide healthcare professionals in daily practice, aimed at reducing this suffering. It is critical that clinicians recognise the great between-patient variability in the severity of procedural pain and distress. Therefore, tailoring our recommendations to the individual child is of utmost importance. This approach will result in improved care for children with cancer undergoing painful procedures, thereby reducing suffering and potentially enhancing health-related quality of life.

Disclaimer

The views expressed in the submitted article are those of the authors and might not reflect the official position of their institution or the funding source.

Funding source

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

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Conflict of interest statement

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

Acknowledgements

The authors thank the Dutch pediatric oncology patient and parent association 'VerenigingOuders, Kinderen en Kanker' for playing an active role in the recruitment of parent representatives. In addition, the authors thank Edith Leclercq (passed away in 2018) and Cochrane Childhood Cancer for assistance in designing and commencing the literature searches. Lastly, the authors thank the iPOG network for helping in member recruitment and providing the international network to learn and benefit from one another in developing and implementing childhood cancer supportive care guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.02.039.

References

[1] Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev [Internet] 2010 Jun;36(4):277–85. cited 2014 Nov 20, http://www.sciencedirect.com/science/article/pii/S030573721000023X.

[2] Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. Lancet oncol [Internet]. Elsevier 2014 Jan 1;vol. 15(1):35–47. http://www.thelancet.com/article/S1470204513705485/fulltext. [Accessed 15 April 2015].

[3] Loeffen EAH, Mulder RL, Kremer LCM, Michiels EMC, Abbink FCH, Ball LM, et al. Development of clinical practice guidelines for supportive care in childhood cancer—prioritization of topics using a Delphi approach [cited 2017 Mar 14] Support Care Cancer [Internet] 2015 Jul 18;23(7):1987–95. http://www.ncbi.nlm.nih.gov/pubmed/25516211.

[4] van de Wetering MD, Schouten-van Meeteren NYN. Supportive care for children withcancer. Semin Oncol [Internet] 2011 Jun; 38(3):374–9. cited 2017 May 15, http://www.ncbi.nlm.nih.gov/pubmed/21600366.

[5] McMurtry CM, Pillai Riddell R, Taddio A, Racine N, Asmundson GJG, Noel M, et al. Far from "just a poke": common painful needle procedures and the development of needle fear. wolterskluwer health Clin J Pain [internet] 2015 Oct;vol. 31(10): S3–11. cited 2018 Oct 8, http://www.ncbi.nlm.nih.gov/pubmed/26352920.

[6] Association AM. Module 6 pain Management : pediatric pain management, vol. 7; 2012.

[7] Loeffen EAH, Mulder RL, Van De Wetering MD, Font-Gonzalez A, Floor, et al. Current variations in childhood cancer supportive care in The Netherlands. 2015.

[8] Kato Y, Maeda M, Aoki Y, Ishii E, Ishida Y, Kiyotani C, et al. Pain management during bone marrow aspiration and biopsy in pediatric cancer patients. Pediatr Int 2014;56(3):354–9.

[9] Loeffen EA, Kremer LC, Van De Wetering MD, Mulder RL, Font-Gonzalez A, Dupuis LL, et al. Reducing pain in children with cancer: methodology for the development of a clinical practice guideline. Pediatr Blood Canc 2019;66(6).

[10] Continuum of depth of sedation: definition of general anesthesia and levels of sedation/analgesia. 2014.

[11] Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J ClinEpidemiol 2011;64(4):395–400.

[12] Higgins JPTGS, editor. Cochrane handbook for systematic reviews of interventions Version 5.1.0[Internet]; 2011 [updated M. The Cochrane Collaboration, www.handbook.cochrane.org.

[13] Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64(4):401–6.

[14] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(4): 383–94.

[15] Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ [Internet] 2016;353(11):i2089. http://www.ncbi.nlm.nih.gov/pubmed/27365494.

[16] Guyatt GH, Alonso-Coello P, Schünemann HJ, Djulbegovic B, Nothacker M, Lange S, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J ClinEpidemiol 2016;80:3–7.

[17] Lullmann B, Leonhardt J, Metzelder M, Hoy L, Gerr H, Linderkamp C, et al. Pain reduction in children during port-a-cath catheter puncture using local anaesthesia with EMLA. Eur J Pediatr 2010;169(12):1465–9.

[18] Miser AW, Goh TS, Dose AM, O'Fallon JR, Niedringhaus RD, Betcher DL, 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 [internet] 1994;9(4):259–64. New york, New York: elsevier science, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=107392867&lang=nl&site=ehost-live&scope=site.

[19] Bishai R, Taddio A, Bar-oz B, Freedman MH, Koren G, Background A. Relative efficacy of amethocainegel and lidocaine–prilocainecream for port-a-cathpuncture in children, vol. 104; 1999. September.

[20] Juarez Gimenez JC, Oliveras M, Hidalgo E, Cabanas MJ, Barroso C, Moraga FA, et al. Anesthetic efficacy of eutectic prilocaine-lidocaine cream in pediatric oncology patients undergoing lumbar puncture. Ann Pharmacother 1996;30(11):1235–7.

[21] 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 [Internet] 1990;42(1):31–4. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed5&AN=20231774.

[22] Whitlow PG, Saboda K, Roe DJ, Bazzell S, Wilson C. Topical analgesia treats pain and decreases propofoluse during lumbar punctures in a randomized pediatric leukemia trial. Pediatr Blood Canc 2015;62:85–90.

[23] Tayeb BO, Eidelman A, Eidelman CL, Mcnicol ED, Carr DB. Topical anaesthetics for pain control during repair of dermal laceration. Cochrane Database Syst Rev 2017;2017(2).

[24] Shah V, Taddio A, McMurtry CM, Halperin SA, Noel M, Riddell RP, et al. Pharmacological and combined interventions to reduce vaccine injection pain in children and adults systematic review and meta-analysis. Clin J Pain 2015;31(10):S38–63.

[25] 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 [internet] 1995;62(1):3–9. Baltimore, Maryland: Lippincott Williams & Wilkins, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=104779280&lang=nl&site=ehost-live&scope=site.

[26] 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 Canc 2005;45(7):933–8.

[27] Cote CJ, Wilson S. Guidelines for monitoring and management of pediatricpatients before, during, and after sedation for diagnostic and therapeutic procedures: update 2016. e20161212–e20161212 Pediatrics [Internet] 2016;138(1). http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2016-1212.

[28] Coté CJ, Wilson S, American Academy of Pediatrics; American Academy of Pediatric Dentirstry. Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures. Pediatrics 2019 Jun;143(6):e20191000. https://doi.org/10.1542/peds.2019-1000.

[29] Yang C-HH, Tian X, Yin H-BB, Gao X-HH, Li N. Sedation and analgesia with fentanyl and etomidate for intrathecal injection in childhood leukemia patients. Medicine (baltimore) [internet] 2015;94(1):e361. Baltimore, Maryland: Lippincott Williams & Wilkins, http://journals.lww.com/md-journal.

[30] Ljungman G, Gordh T, Sorensen S, Kreuger A. Lumbar puncture in pediatric oncology: conscious sedation vs. general anesthesia. Med PediatrOncol 2001;36(3):372–9.

[31] Livingston M, Lawell M, McAllister N. Successful use of nitrous oxide during lumbar punctures: a call for nitrous oxide in pediatric oncology clinics. Pediatr Blood Canc 2017;64(11).

[32] Maslak K, Favara-Scacco C, Barchitta M, Agodi A, Astuto M, Scalisi R, et al. General anesthesia, conscious sedation, or nothing: decision-making by children during painful procedures. Pediatr Blood Canc 2019 May;66(5):e27600.

[33] Hedén L, von Essen L, Frykholm P, Ljungman G. Low-dose oral midazolam reduces fear and distress during needle procedures in children with cancer. Pediatrblood cancer [internet] 2009;53(7):1200–4. Hoboken, New Jersey: John Wiley &Sons, Inc. http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=105329866&lang=nl&site=ehost-live&scope=site.

[34] Ljungman G, Kreuger A, Andréasson S, Gordh T, Sörensen S. Midazolam nasal spray reduces procedural anxiety in children. Pediatrics [internet] 2000;105(1):73–8. Chicago, Illinois: American Academy of Pediatrics, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=107101020&lang=nl&site=ehost-live&scope=site.

[35] Hedén LE, von Essen L, Ljungman G. Effect of morphine in needle procedures in children with cancer. Eur J pain [internet] 2011;15(10):1056–60. Malden, Massachusetts: Wiley-blackwell, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=104594801&lang=nl&site=ehost-live&scope=site.

[36] Heden L, von Essen L, Ljungman G. Effect of high-dose paracetamol on needle procedures in children with cancer–an RCT. ActaPaediatr 2014;103(3):314–9.

[37] Taddio A, McMurtry M, Shah V, PilaiRiddel R, Chambers CT, Noel M, et al. Reducing pain during vaccine injections: clinical practice guideline. Cmaj 2015;187(13):975–82.

[38] Liossi C, Hatira P. Clinical hypnosis versus cognitive behavioral training for pain management with pediatric cancer patients undergoing bone marrow aspirations. Int J ClinExpHypn [Internet] 1999;47(2):104–16. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed7&AN=29152914.

[39] Liossi C, Hatira P. Clinical hypnosis in the alleviation of procedure-related pain in pediatric oncology patients. Int J clinexphypn [internet] 2003;51(1):4–28. Oxfordshire, <Blank>: routledge, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=106783790&lang=nl&site=ehost-live&scope=site.

[40] 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 [internet] 2006;25(3):307–15. Washington, District of Columbia: American psychological association, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=106315381&lang=nl&site=ehost-live&scope=site.

[41] 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 [internet] 2009;142(3):255–63. Baltimore, Maryland: Lippincott Williams & Wilkins, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=105477597&lang=nl&site=ehost-live&scope=site.

[42] Dahlquist LM, Pendley JS, Landthrip DS, Jones CL, Steuber CP. Distraction intervention for preschoolers undergoing intramuscular injections and subcutaneous port access. Heal Psychol [Internet] 2002;21(1):94–9. Washington, District of Columbia: American psychological association, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=106974921&lang=nl&site=ehost-live&scope=site.

[43] Heden L, Vone L, Ljungman G, Hedén L, Von Essen L, Ljungman G. Randomized interventions for needle procedures in children with cancer. Eur J Cancer Care (Engl) [Internet] 2009;18(4):358–63. 2008/12/02.Malden, Massachusetts: Wiley-Blackwell, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=105376653&lang=nl&site=ehost-live&scope=site.

[44] 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 Pediatroncolnurs [Internet] 2007;vol. 24(1):8–19. Thousand oaks, California: sage publications inc. http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=106242887&lang=nl&site=ehost-live&scope=site.

[45] Wolitzky K, Fivush R, Zimand E, Hodges L, Rothbaum BO. Effectiveness of virtual reality distraction during a painful medical procedure in pediatric oncology patients. Psycholhealth [Internet] 2005;20(6):817–24. Oxfordshire, <Blank>: Routledge, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=106393820&lang=nl&site=ehost-live&scope=site.

[46] Mithal P, Simmons P, Cornelissen T, Wong H, Riddell RP, Mcmurtry CM, et al. To look or not to look during vaccination : a pilot randomized trial, vol. 527; 2018. January.

[47] 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):146–55.

[48] Wint SS, Eshelman D, Steele J, Guzzetta CE. Effects of distraction using virtual reality glasses during lumbar punctures in adolescents with cancer. Oncol Nursforum [Internet] 2002;29: E8–15. Pittsburgh, Pennsylvania: oncology nursing society, http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=106906796&lang=nl&site=ehost-live&scope=site.

[49] 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 [Internet] 1991;vol. 10(5):317–22. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed5&AN=21872635.

[50] Kazak AE, Penati B, Boyer BA, Himelstein B, Brophy P, Waibel MK, 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):615–31.

[51] Flowers SR, Birnie KA. Procedural Preparation and Support as a Standard of Care in Pediatric Oncology. Wiley-Blackwell Pediatr Blood Cancer [Internet] 2015 Dec 1;62(S5):S694–723. https://doi.org/10.1002/pbc.25813. cited 2018 Oct 9.

[52] Williams MR, Ward DS, Carlson D, Cravero J, Dexter F, Lightdale JR, et al. Evaluating patient-centered outcomes in clinical trials of procedural sedation, Part 1 efficacy: sedation consortium on endpoints and procedures for treatment, education, and research recommendations. Anesth Analg 2017;124(3):821–30.

[53] Cravero JP, Coté CJ. Raising the bar for pediatric sedation studies and trials. PaediatrAnaesth 2015;25(1):2–4.

[54] Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J ClinEpidemiol 2013;66(7):719–25.

[55] Taddio A, Alderman L, Freedman T, McDowall T, McMurtry CM, MacDonald N, et al. The CARD^{TM} System for improving the vaccination experience at school: Results of a small-scale implementation project on program delivery. Paediatr Child Health 2019 Apr;24(Suppl 1):S54–67. https://doi.org/10.1093/pch/pxz021. Epub 2019 Mar 29.