Clinical Practice Guideline for Pain Management in Children with Cancer

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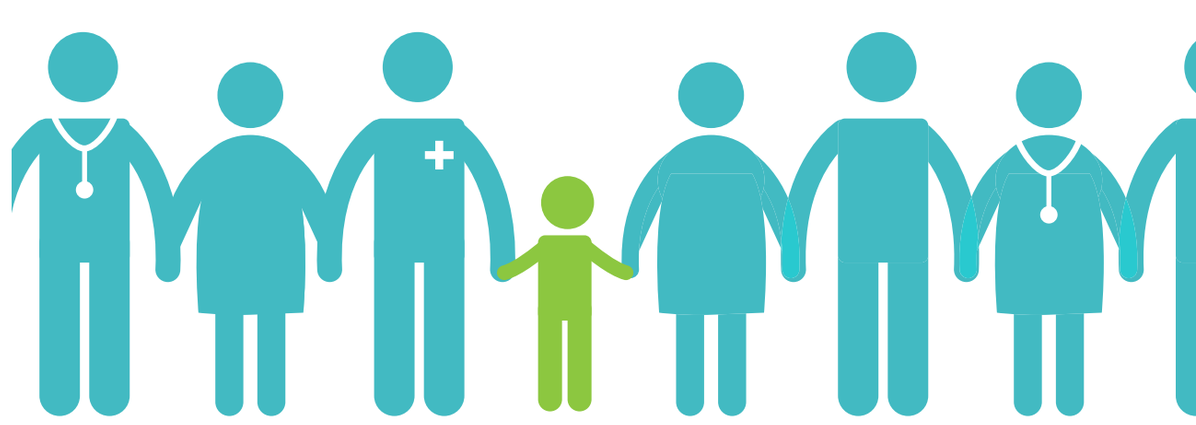

Clinical Practice Guideline for Pain Management in Children with Cancer

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Clinical Practice Guideline for Pain Management in Children with Cancer

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Foreword

Dear friends:
How much is the pain experienced by a child with cancer as direct result of the disease or a side effect of treatment? How do we alleviate it? Such questions continue to cause me considerable concern. Therefore, when I was invited to write the foreword for this guideline developed by the Nursing and Healthcare Research Unit of the Instituto de Salud Carlos III and funded by Cris Cancer Foundation, I asked the research group to explain the endpoint of their work. They did just that without euphemisms, detailed and to the point. Then I realised what an honour it would be to write a few words in recognition of the work and its protagonists and my thoughts were filled with hope.

In recent years, considerable progress has been made in the battle against cancer, however, nobody has focused so comprehensively on the pain of this disease in children. This Clinical Practice Guideline for Pain Management in Children with Cancer has been devised to fill that gap. Its aim is clear: that all those involved in the direct care of children with cancer (nurses, psychologists, carers, oncologists, paediatricians, etc.) have up to date information based on the outcome of scientific research, to alleviate pain in children with cancer. Therefore, improving the quality of life and reducing suffering, as well as lessening the anxiety of carers and families.

This guideline has been drafted with the collaboration of families of children with cancer through its Federation, the clinical practice nurses represented by professionals of the Hospital Universitario Infantil Niño Jesús and Hospital Universitario Vall d'Hebrón and revised by national and international experts. To all of who I give my heartfelt thanks. I would also like to thank the members of Cris Cancer Foundation and especially Eva Solache and Josep Santacana who have made this vital work possible.

I cannot sign off this humble note without congratulating the extensive team of researchers, nursing staff and clinicians who took on this study of pain in children with cancer and whose end goal is this guide. I hope that in spite of the hard times that we experience, its content must fill us with optimism as its ultimate aim is to relieve pain and reduce suffering in children with cancer.

Lola Manterola
Vice President of CRIS

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Conflict of Interest

All members of the work group, collaborators and external reviewers have issued a conflict of interest statement using a standard form and none of them consider that their personal and/or non-personal interests declared herein interfere in their participation in this guide. (Appendix 1).

How to cite this guideline

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Questions to answer

- What are the diagnostic tools for pain in children with cancer?
- What are the diagnostic tools for pain in children with cancer, according to age?
- What are the characteristics of pain to be assessed in children with cancer, according to their age and psycophysical development?
- What are the management strategies of diagnostic tools of pain in children with cancer?
- What is the role of carers of children with cancers in the diagnosis of pain?
- What is the role of the healthcare professionals in the diagnosis of pain in children with cancer?
- How to monitor pain control in children with cancer?
- How to monitor the effects of pharmacological and non-pharmacological treatment in children with cancer?
- What registries must be used to monitor pain in children with cancer?
- What is the role of carers of children with cancer in pain management?
- What are the non-pharmacological measures to prevent pain in children with cancer during painful procedures?
- What non-pharmacological measures exist to prevent and treat pain in children with cancer?
- What is the effectiveness of the non-pharmacological measures for preventing and treating pain in children with cancer?
- When can preventive non-pharmacological and pain relief measures be applied in children with cancer?
- What are the adverse effects of preventive non-pharmacological measures and treatment of pain in children with cancer?

- What pharmacological treatments exist to treat pain in children with cancer?
- What is the effectiveness of pharmacological treatment of pain in children with cancer?
- When can pharmacological treatments be applied to treat pain in children with cancer?
- What are the adverse effects of pharmacological treatment of pain in children with cancer?
- What routes of administration can be used in the pharmacological treatment of pain in children with cancer?
- What is the effectiveness of combining pharmacological and non-pharmacological treatment of pain in children with cancer?
- What are the barriers for pain management with pharmacological treatment in children with cancer?

Levels of Evidence and Grades of Recommendation

The following classification was used, adapted from the classifications of Joanna Briggs Institute (2013), and Centre for Evidence Based Medicine de Oxford (CEBM) (2009).

The levels of evidence (LE) and grades of recommendation (GR) of the documents reviewed in the CPG adapted to the following classification are included:

Levels of Evidence Diagnosis	Levels of Evidence Effectiveness
Level 1 Meta-analysis (with homogeneity) of diagnostic studies (validating studies)	**Level 1** Meta-analysis (with homogeneity) of experimental studies (eg RCT with concealed randomisation) OR One or more large experimental studies with narrow confidence intervals
Level 2 Validating diagnostic test studies with good reference standards, or clinical decision rules, or validating studies with good reference standards	**Level 2** One or more smaller RCTs with wider confidence intervals OR Quasi-experimental studies(without randomisation)
Level 3 Non-consecutive studies; or without consistently applied reference standards Case-control studies, poor or non-independent reference standard	**Level 3** Cohort studies (with control group) Case-control Observational studies (without control group)
Level 4 Expert opinion or consensus	**Level 4** Expert opinion, or physiology bench research, or consensus

Grades of Recommendation
A Strong evidence that support application
B Moderate quality of evidence that warrants consideration of application
C Lack of evidence, application not supported

Guideline Recommendations

(LE= Levels of Evidence; GR= Grades of Recommendation)

Recommendations for the diagnosis and monitoring of pain

1. The level of pain in a child is an essential vital sign and must be recorded regularly in clinical documentation. (LE: expert opinion; GR: C).
2. The intensity of pain and degree of relief must be considered as principle factors in the assessment of quality of life and the balance of additional benefits of curative or palliative treatments. (LE: expert opinion; GR: C).
3. Optimum control of pain starts with correct and detailed assessment. (LE: expert opinion; GR: C).
4. A comprehensive pain assessment in children with cancer must be carried out at each hospital admission or during each outpatient visit. (LE: 2,3. GR: B).
5. The detection and assessment of pain shall be carried out taking into account the different age brackets, given that the child manifests pain in different ways, accordingly. (LE: expert opinion; GR: C).
6. Detailed clinical history shall be included in the comprehensive pain assessment to determine the presence of pain and its effects. (LE: 3. GR: B).
7. The clinical history of pain shall include characteristics of pain, physical and psychological manifestations, associated symptoms, prescribed treatment, beliefs, knowledge and expectations on pain. (LE: expert opinion; GR: C).
8. The clinical history of pain shall be compiled by the nurse upon admission of the child, forwarding it to the psychologist, oncologist, paediatrician or another professional, if necessary. (LE: expert opinion; GR: C).
9. An initial assessment of the child with cancer must be carried out by a psychologist. (LE: expert opinion; GR: C).
10. Pain is a subjective perception and must be self-rated, wherever possible. (LE: 2,3. GR: B).
11. If the child does not have the capacity to self-reporting pain (due to age, cognitive or verbal capacity, pathology, sedation or other reasons), the assessment shall be carried out by the principle carer and secondly by healthcare professionals. (LE: expert opinion; GR: C).
12. The child must be observed closely, as on occasions, even though they are in pain they do not show visible signs, but rather discomfort or distress that only their carer can identify. (LE: expert opinion; GR: C).

13. Validated instruments must be used to assess pain at regular intervals, both to measure the intensity and the efficacy of the pain management plan and record each assessment in the clinical documentation. (LE: 3. GR: B).
14. The clinical documentation and pain records must be easily accessible to all professionals involved in the care of the child. (LE: expert opinion; GR: C).
15. The instruments for measuring pain intensity must be: self-administered, highly visual, simple, quick to complete, adapted to the characteristics of the child (cognitive, emotional and language development), used at regular intervals and systematically recorded. (LE: expert opinion; GR: C).
16. Pain must be assessed and recorded at regular intervals after starting the treatment plan, with each new episode of pain and at suitable intervals according to each pharmacological or non-pharmacological intervention. (LE: 3. GR: B).
17. The same assessment tool must be used in different measurements on the same child. (LE: expert opinion; GR: C).
18. If the child has no pain, assessment shall be carried out every time vital signs are measured (a minimum of twice a day) or when a procedure is carried out that may involve pain. (LE: expert opinion; GR: C).
19. If the child experiences pain, reassess at regular intervals after establishing a treatment plan or the appearance of a new pain. The assessment intervals shall depend on the analgesic regimen established. (LE: expert opinion; GR: C).
20. Carers must be trained on how to complete a pain diary in order to maintain continuity in the effective management of pain after hospital discharge. (LE: 3. GR: B).
21. Healthcare professionals be aware of regular syndromes that occur with pain, for their early detection and management. (LE: 3. GR: B).
22. Special attention must be paid to the preferences and needs of the children for whom education or cultural factors may affect communication of pain. (LE: 3. GR: B).

Recommendation for the management of pain related with invasive procedures

23. Pain related with painful procedures must be prophylactically treated with appropriate analgesics and/or sedation. The analgesia needs are reduced if the children have received preventive treatment before the painful procedures. (LE: 2,3. GR: B).
24. The children must be provided with information on the characteristics and anticipated duration of what they may experience during the painful procedure. (LE: 2,3. GR: B).
25. The sedation process must be supervised if administered to children who suffer from anxiety of painful procedures associated with the diagnosis and treatment of cancer. (LE: 3. GR: B).
26. Non-pharmacological alternatives must be offered to children who reject sedation to lessen the pain related with the painful procedure. (LE: 2,3. GR: B).
27. In the interventions to control pain and anxiety related with the procedure, the type of procedure, anticipated degree of pain and other individual factors must be taken into account, such as age and physical and emotional state. (LE: 3. GR: B).
28. Sedation must be considered for painful procedures that require patient cooperation to remain still especially in children aged under 6 years or disabled children. (LE: 2,3. GR: B).

Recommendations to prevent or treat pain with non-pharmacological interventions

29. The simplest techniques to alleviate pain can become more effective if the information, recording, assessment of the child and provision of guidelines and appropriate recommendations are taken into account. (LE: 3. GR: B).
30. Children and carers must be informed of non-pharmacological interventions available, anticipated effects, their effectiveness and possible adverse effects. (LE: expert opinion; GR: C).
31. Suitable comfort measures must be used in pharmacological and non-pharmacological interventions, as they can reduce the levels of anxiety, distress and pain. (LE: 3. GR: C).
32. Children must be encouraged to remain active and take part in their care whenever possible. (LE: 2,3. GR: B).
33. Carers must be with the child whenever possible, as their presence helps to minimise pain, by reducing anxiety and fear in children. (LE: 2. GR: B).

34. Non-pharmacological interventions must be considered, even if their effectiveness remains unproven, provided that they do not cause adverse effects, because they provide comfort and well-being to the child. (LE: expert opinion; GR: C).
35. The type of non-pharmacological intervention must be chosen by the child and their carer, based on the information received on the expected effects. (LE: 3. GR: C).
36. Use of psychological interventions adapted to child development can reduce the levels of anxiety, distress and pain. (LE: 2,3. GR: B).
37. Cognitive-behavioural interventions are more effective than the use of placebos or non-intervention. (LE: 2,3. GR: B).
38. Cognitive-behavioural interventions must be incorporated early in the treatment of the disease as part of a comprehensive approach to pain management, without this being a substitute for analgesics. (LE: 1,2. GR: B).
39. When offering cognitive-behavioural interventions, both active and passive, the intensity of pain and expected duration, the degree of psychophysical maturity of the child, previous experience of the child with these interventions and their desire to use them must be taken into account. (LE: 3. GR: B).
40. Distraction, hypnosis and cognitive-behavioural interventions reduce pain and distress associated with punctures in children and adolescents. (LE: 1,2. GR: B).
41. Cognitive-behavioural interventions combined can relieve pain, but no more effectively than other interventions. (LE: 2. GR: B).
42. Distraction used in isolation has little influence on reducing pain. (LE: 2. GR: B).
43. The use of virtual reality has little influence on the reduction of pain. (LE: 2. GR: B).
44. Listening to music can reduce pain. (LE: 2. GR: B).
45. The use of relaxation techniques has little influence on the reduction of pain. (LE: 2. GR: B).
46. Hypnosis is effective in pain relief, whether using direct or indirection suggestion. (LE: 2. GR: B).
47. Hypnosis is more effective than the placebo in pain relief and more effective than cognitive-behavioural interventions. (LE: 1. GR: A).
48. Evidence on the effectiveness of information on the reduction of pain is insufficient, however information helps reduce distress and fear in the children. (LE: expert opinion; GR: C).
49. The use of support measures and physical contact, such as caressing, has little influence on reducing pain, but it can provide comfort and reduce distress and anxiety. (LE: 3,4. GR: B).

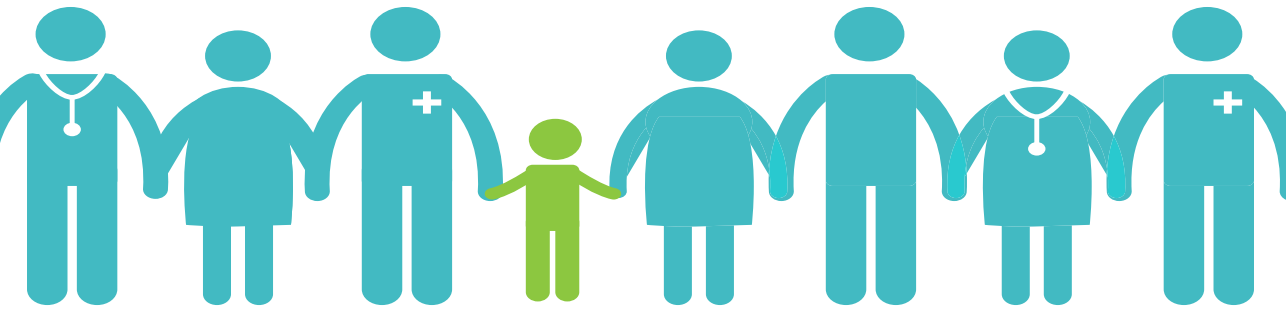
50. The use of massage has little effect on reducing pain but can provide comfort and reduce distress and anxiety. (LE: 2,3. GR: B).
51. Hot/cold application in children must be carried out with care due to risk of injury. (LE: 3,4. GR: C).
52. The use of topical anaesthetics is more effective than the placebo in pain relief. (LE: 1,2. GR: B).
53. The use of EMLA® is more effective than the placebo in pain relief, and more effective if applied 60 minutes before the procedure than if applied 40 minutes beforehand. (LE: 1,2. GR: B).

Recommendations for pharmacological treatment of pain

54. A systematic approach must be developed for pain management in cancer, to teach children and carers, within the treatment plan, how to use effective strategies to attain optimum control of pain and encourage active participation. (LE: 2, 3. GR: B).
55. Prescribe the treatment plan with the simplest type and regimen of administration and the least invasive method possible. (LE: 4. GR: C).
56. A comprehensive assessment of pain must be carried out and the treatment plan modified when a change or a new painful episode occurs, focusing on optimum relief throughout the disease. (LE: 3. GR: B).
57. The WHO principles on pharmacological treatment of pain must be followed:
    - 57.1. By the ladder, starting on the step adapted to the intensity of pain reported by the child. (LE: 2, 3. GR: B).
    - 57.2. By the clock, with additional rescue doses as required for breakthrough pain. (LE: 3, 4. GR: C).
    - 57.3. By the appropriate route. (LE: 3, 4. GR: C).
    - 57.4. By the child. An individual treatment regime must be following according to the characteristics of the child and their pain, until reaching maximum analgesia and minimum side effects. (LE: 3, 4. GR: C).
58. Management of pain on any step of the WHO's pain ladder includes acetaminophen and/or NSAIDs, except if contraindicated. (LE: 3, 4. GR: C).
59. An opioid must be used if pain persists or increases. (LE: 2, 3. GR: B).
60. The dose must be increased or stronger opioids used if pain persists or is moderate / intense. (LE: 1. GR: A).
61. Morphine is the treatment of choice in cases of intense pain. (LE: 3, 4. GR: C).
62. Placebos must not be used in the management of pain in cancer. (LE: 4. GR: C).

63. The use of tramadol, methadone, meperidine and acetylsalicylic acid is not recommended in cancer patients aged under 18 years. (LE: 3. GR: B).
64. The use of codeine in those aged under 12 years is not recommended due to the greater risk of serious adverse effects. (LE: 2, 3. GR: B)
65. Tricyclic antidepressants or anticonvulsants drugs are used for neuropathic pain as adjuvants to treatment. (LE: 3, 4. GR: C).
66. Corticosteroids are associated for pain caused by spinal cord compression or intracranial pressure, as adjuvant to treatment. (LE: 4. GR: C).
67. Opioids must be administered according to a regular schedule, with additional rescue doses as required for breakthrough pain. (LE: 3. GR: C).
68. The oral route must be used first, as it is the most widely accepted by children. Other routes must be used when it is not possible to administer oral treatment, according to the situation of the child and drugs, and must be the least invasive possible. (LE: 4. GR: C).
69. Rectal administration is contraindicated in children with cancer due to risk of lesion in the rectum or anus or risk of infection. (LE: 4. GR: C).
70. Intramuscular route is not recommended as it is less effective than intravenous administration and it can be painful and is poorly received in children. (LE: 3. GR: C).
71. The opioid doses must be adjusted to achieve pain relief with an acceptable level of adverse effects. (LE: 1, 2. GR: A).
72. The adverse effects of opioids must be monitored (LE: 2, 3. GR: B) and treated prophylactically. E: 2, 3. GR: C).
73. Prophylactic treatment for constipation must be started in conjunction with the start of opioid treatment. (LE: 2, 3. GR: B).
74. Naloxone is prescribed to reverse opioid-induced respiratory depression and its dose must be adjusted to improve respiratory function without reversing analgesia. (LE: 2, 3. GR: B).
75. Myths and incorrect beliefs on pain and its management with children must be dispelled, indicating to children and their carers that pain can be alleviated. (LE: 2, 3. GR: B).
76. The use of non-pharmacological treatment strategies must form part of a comprehensive approach in pain management without replacing analgesics. (LE: 2, 3. GR: B).
77. When the child is to be transferred, the corresponding information on pain management must be transferred. (LE: 2, 3. GR: B).
78. Children and their carers must be provided with accurate and comprehensive information on effective pain management in cancer, the use of analgesics, other methods to control pain and how to convey it to clinicians in the event of pain that is not alleviated. (LE: 1, 2. GR: A).

1. Introduction



According to the World Health Organisation (WHO), "Cancer" is a generic term that covers a wide range of diseases that can affect any part of the body; "malignant tumours" or "malignant neoplasms" are also mentioned. A characteristic of cancer is the rapid multiplication of abnormal cells that extend beyond their usual limits and can invade adjacent parts of the body or propagate to other organs; the cancerous cell can be disseminated to other parts of the body by the blood system and lymphatic systems, a process known as metastasis. Metastases are the main cause of death by cancer (PDQ, 2002).

Cancer is the main cause of death by disease in children in western countries (Kaatsch, 2010). The burden of disease is high and has a considerable impact on the healthcare systems (CDC, 2010). Cancer in children represents less than 1.5% of all cancers, approximately 1,000 children are diagnosed in Spain every year.

According to the National Registry of Infant Tumours of the Sociedad Española de Hematología y Oncología Pediátricas (RNTI-SEHOP Spanish Society of Paediatric Haematology and Oncology), the incidence rate of paediatric cancer in Spain is 14.6 cases for every 100,000 children. This incidence rate is very similar in Europe (13.85 per 100,000 children), a little lower than that of the United States (15.3 for every 100,000 children aged between 0 to 14 years and 16.9 for every 100,000 children aged from 0 to 19 years) (CDC, 2013).

The characteristics that have their own entity and differ from paediatric oncology include (Sánchez de Toledo et al., 2010):

a. A child is a being in constant development and evolution.
b. Age-related changes in physiological parameters and its influence on pathological manifestations.
c. Problems specific to new-born infants.
d. Congenital haematological diseases.
e. Epidemiology of infant cancer differs from that of adult cancer in frequency, histology, clinical presentation and response to treatment.
f. The repercussions and episodes of the disease and its treatment.

Pain can be described as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey & Bogduk, 1994). This appears in all evolutionary aspects of the disease, during its treatment and post-treatment due to occasional or permanent side effects, therefore pain is one of the consequences that children

fear most, affecting their physical, psychic and social development (Miaskowski et al., 2004; WHO, 1998).

There are several classifications of pain (Merskey & Bogduk, 1994; Miaskowski et al., 2004; WHO, 1998; RNAO, 2007):

1. **According to duration:**

   - **Acute:** recently pain and of probable limited duration. Normally, it has a temporal and causal relation that is identifiable with an injury or disease.
   - **Chronic:** pain that normally persists beyond the healing period of a lesion and often has no clearly identifiable cause.
   - **Breakthrough:** intermittent exacerbation of pain that can occur spontaneously or in relation with any type of specific activity.

2. **According to its physiopathology:**

   - **Nociceptive or somatic pain:** pain that involves a harmful stimulus that damages normal tissue and the transfer of this stimulus in a nervous system that functions normally.
   - **Visceral pain:** involves profound structures by infiltration, compression, stretching and extension of the viscera. It is poorly localised, deep and oppressive.
   - **Neuropathic pain:** pain initiated or caused by a primary lesion or dysfunction in the nervous system; it affects the peripheral and/or central nervous system

3. **According to its aetiology:**

   - **Pain related with a tumour.**
   - **Secondary pain** to treatment of surgery, chemotherapy, radiotherapy and diagnostic and therapeutic processes.

As regards the incidence of pain in children with cancer, there are few studies that provide sufficient data on this aspect (Miaskowski et al., 2004). These data indicate that pain is present at the time of diagnosis of cancer in 62% of children; during treatment, 25%-85% of children experience pain; and in advanced or terminal stages of the disease, 62% to 90% of children report pain, which is often intense and undertreated.

Many people who survive cancer continue to suffer from pain after treatment for the rest of their lives (Miaskowski et al., 2004).

The origin of pain is the cancer itself, the invasive procedures and /or the treatment. In children, pain is present during the oncological process in almost all cases, although there is considerable variation in its correct control and treatment, even being undertreated, which is well documented (Miaskowski et al., 2004).

All healthcare professionals should know how to assess and manage pain in any of the evolutionary stages of the disease (Miaskowski et al., 2004). It is necessary to establish good communication between the professionals and carers, as the child in pain often fails to show external signs, but rather discomfort or distress that only the carer is able to identify, as they know the child best: therefore it is necessary for them to spend as much time as possible with the child during hospitalisation (WHO, 1998).

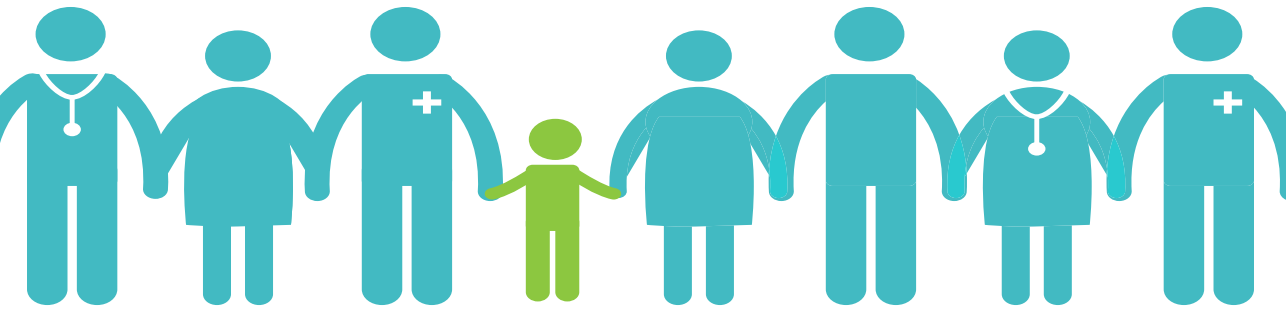
It has been demonstrated that effective care depends on a coordinated, interdisciplinary approach, which includes constant communication between healthcare professionals, the child and their carers, always taking into account the personal preferences and unique needs of each child and their carer (WHO, 1998).

The admission of a child or adolescent to Paediatric Oncology Unit is equally important, up to 18 years of age, so that minors may receive age-appropriate care to meet their needs (II PENIA, 2013; WHO, 1998).

Correct pain management is a challenge for healthcare systems. Studies are underway on the type of care required to better respond to the situation of these patients, as indicated in the Strategy of Cancer of the National Healthcare System of Spain (Sistema Nacional de Salud de España SNS, 2010).

This clinical practice guideline (CPG) endeavours to answer many of the questions faced by professionals responsible for the care of children with cancer and their families / carers. It has been conceived mainly as a support tool for pain management in children with cancer in our society; it offers updated recommendations, based on the evidence and contributions of clinical experts and relatives / carers.

2. Scope and Objectives



Focus / justification

The publication of this guideline is justified, first, due to the lack of clinical practice guidelines on the managent of pain specifically in paediatric oncology, both at national and international level, with publications and material of disparate quality, origin and updating. Second, because pain is deemed to be a common problem by children and healthcare professionals. Its drafting provides a framework to present a synthesis of the best evidence available and recommendations adapted to our environment.

This CPG is to be used by doctors, nurses, pharmacists, psychologists and other healthcare professionals who work with children who suffer from cancer pain; it will also help relatives / carers of these children. It endeavours to provide updated information based on the best evidence available, to alleviate pain in children, improve their quality of life and reduce distress in children and their carers. It proposes to answer many questions on the different aspects of pain management in children with cancer, which will aid decision-making in its approach, reduce variability in clinical practice and, consequently, improve health and quality of life of this population.

This CPG has been developed according to the following principles:

- To be useful for all professionals and carers.
- To take into account the perspectives of those who suffered from cancer during infancy and /or adolescence and that of their carers.
- To identify the areas that require further research.

Focus population
This guideline endeavours to answer questions related with the diagnosis process and the interventions carried out for prevention and treatment of pain in the infant population with an active oncological process.

Groups covered by the CPG are:
Children and adolescents, from birth to 18 years of age, diagnosed with cancer at any stage. In this guideline, the term “child” applies to all age groups up to 18 years.

Groups not covered by the CPG:
Adults (over 18 years), children with cancer in palliative care (as they must be treated in a specific way) and children with specific pain derived from side effects of treatment, such as mucositis.

Target users of the guideline
The recommendations contained in this guideline are directed at oncologists, psychologists, paediatricians, paediatric oncology nurses and all healthcare personnel who are in contact with the paediatric oncological patient, as well as the child and their carers. Likewise, it can be useful for educational groups, scientific societies and healthcare managers.

The experiences of children and their carers have been fundamental in defining the questions of this CPG and publishing the recommendations. The participation of children, their carers and healthcare professionals in drafting the CPG will encourage its acceptance and implementation.

CPGs must not be applied literally, but rather used as a tool in the decision-making of personalised care of the child. Healthcare staff shall make the decision by taking into account not only the evidence available but also the opinion of the child and carers, their clinical judgement through their own professional experience and the specific characteristics of its context or clinical practice environment.

As it concerns a CPG with national focus, it does not cover matters related with the particular organisation of healthcare services.

Levels of care covered by the CPG
This CPG centres its recommendations on the area of clinical practice in hospitals (Paediatric Haematology and Oncology Departments, Day Hospitals, etc.). Furthermore, it will be a great help for carers of children who are suffering from an oncological process, usually painful.

This CPG includes the following clinical areas:
- Diagnosis of pain: description of the criteria and diagnostic instruments (pain assessment scales).
- Prevention and management of pain.
- Interventions: assessment of their appropriate use, their indication and use. The following types of intervention are revised:
  - Non-pharmacological treatment.
  - Pharmacological treatment.

The CPG does not cover aspects related with communication, palliative care, specific healthcare problems such as mucositis, training of healthcare personnel, or the cost/effectiveness of interventions.

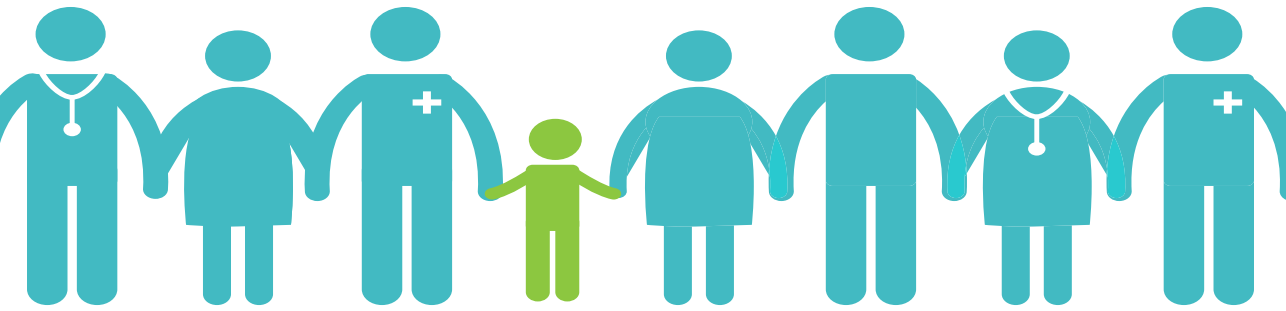
Objectives
The general aim of this CPG is to offer guidance on the various alternatives of care and treatment available to children who suffer from an oncological process, as well as to establish recommendations based on the most relevant and up-to-date evidence applicable in the health services, in order to improve the pain management in children with cancer.

Statement of intent
This CPG, under no circumstances, endeavours to replace the clinical judgement of healthcare professionals.

The specific objectives are presented in each of the main sections of this guide:

- Diagnosis and monitoring of pain in children with cancer.
- Non-pharmacological therapeutic interventions to prevent or treat pain.
- Pharmacological treatment of pain in children with cancer.

3. Methods for Guideline Development



A panel was formed with nurses, psychologists, adolescents and young adults who have had cancer (veterans), and representatives of parents' associations of children with cancer, to define the questions that this CPG must answer (Escandell-García et al., 2012). This panel has participated in the drafting of recommendations and in the review process. Equally, a review was carried out by external experts. Part of the panel members participated with the scientific team in the search and selection of evidence, by the critical appraisal of the documents found in the bibliographic search.

Two systematic reviews were carried out, one for the diagnostic and monitoring questions, and another for the questions on prevention and treatment of pain with non-pharmacological interventions, in children aged under 18 years with cancer. Systematic reviews and clinical practice guidelines were searched for the questions of pharmacological treatment of pain. A search was carried out in English, Spanish, French and Catalan in the databases: PubMed, CINAHL, Psychinfo, Cochrane, IME, Cuiden, CRD, Tripdatabase, Embase, NGH, Sumsearch, TESEO, Opengrey, from each database inception until December 2011. A search of grey literature was carried out, an inverse manual search since 2011 and secondary search.

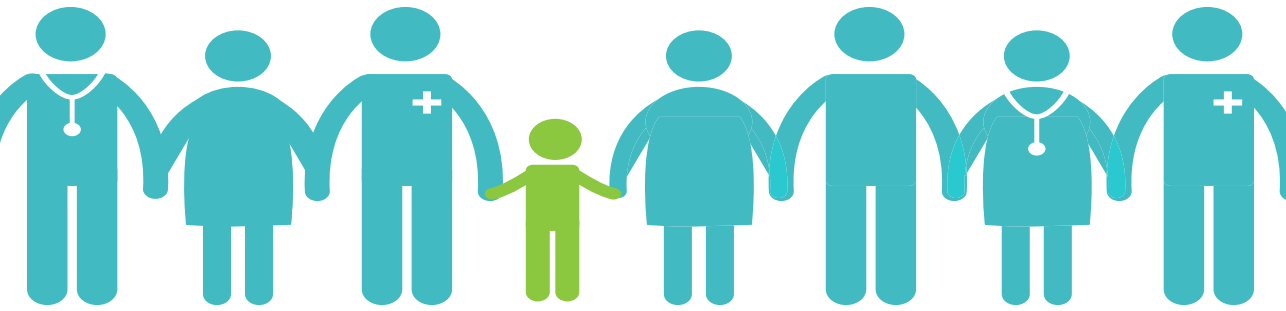
All the validation studies of diagnostic tools of pain in children with cancer; controlled randomised trials (CRT) and quasi-experimental studies of non-pharmacological interventions to prevent or treat pain, and the systematic reviews and clinical practice guidelines for the pharmacological treatment of pain have been included. The subjects of the studies had to be children aged 0 to 18 years diagnosed with cancer at any stage and pain had to be the main outcome. Non-pharmacological interventions excluded invasive interventions that aim to alleviate pain, such as radiotherapy, surgery or nerve block. Pharmacological treatment included evidence from patients with cancer of any age or children with other pathologies different from cancer, given insufficient research of the specific population.

The selection process of the studies was carried out by two blind and independent reviewers and in case of discrepancy it was revised by a third party, during the entire process, from the inclusion of the documents in the study to the critical appraisal of those selected.

Update /Revision of the guideline

The next update of this guideline shall be considered in 5 years (2018).

4. Diagnosis and monitoring of pain in children with cancer



4.1 Objectives

This section of the guideline shall help healthcare professionals and carers of children with cancer to:

- Identify the diagnostic tools validated for pain assessment in children with cancer.
- Assess the presence of pain, its characteristics, repercussions and associated factors.
- Know pain management and monitoring in children with cancer.

4.2 Target Population

Children from birth until 18 years, diagnosed for any type of cancer, still under follow-up for cancer, susceptible to experiencing pain.

4.3 Recommendations for the diagnosis and monitoring of pain

1. The level of pain in a child is an essential vital sign and must be recorded regularly in clinical documentation. (LE: expert opinion; GR: C).
2. The intensity of pain and degree of relief must be considered as principle factors in the assessment of quality of life and the balance of additional benefits of curative or palliative treatments. (LE: expert opinion; GR: C).
3. Optimum control of pain starts with correct and detailed assessment. (LE: expert opinion; GR: C).
4. A comprehensive pain assessment in children with cancer must be carried out at each hospital admission or during each outpatient visit. (LE: 2,3. GR: B).
5. The detection and assessment of pain shall be carried out taking into account the different age brackets, given that the child manifests pain in different ways, accordingly. (LE: expert opinion; GR: C).
6. Detailed clinical history shall be included in the comprehensive pain assessment to determine the presence of pain and its effects. (LE: 3. GR: B).
7. The clinical history of pain shall include characteristics of pain, physical and psychological manifestations, associated symptoms, prescribed treatment, beliefs, knowledge and expectations on pain. (LE: expert opinion; GR: C).

8. The clinical history of pain shall be compiled by the nurse upon admission of the child, forwarding it to the psychologist, oncologist, paediatrician or another professional, if necessary. (LE: expert opinion; GR: C).
9. An initial assessment of the child with cancer must be carried out by a psychologist. (LE: expert opinion; GR: C).
10. Pain is a subjective perception and must be self-rated, wherever possible. (LE: 2,3. GR: B).
11. If the child does not have the capacity to self-reporting pain (due to age, cognitive or verbal capacity, pathology, sedation or other reasons), the assessment shall be carried out by the principle carer and secondly by healthcare professionals. (LE: expert opinion; GR: C).
12. The child must be observed closely, as on occasions, even though they are in pain they do not show visible signs, but rather discomfort or distress that only their carer can identify. (LE: expert opinion; GR: C).
13. Validated instruments must be used to assess pain at regular intervals, both to measure the intensity and the efficacy of the pain management plan and record each assessment in the clinical documentation. (LE: 3. GR: B).
14. The clinical documentation and pain records must be easily accessible to all professionals involved in the care of the child. (LE: expert opinion; GR: C).
15. The instruments for measuring pain intensity must be: self-administered, highly visual, simple, quick to complete, adapted to the characteristics of the child (cognitive, emotional and language development), used at regular intervals and systematically recorded. (LE: expert opinion; GR: C).
16. Pain must be assessed and recorded at regular intervals after starting the treatment plan, with each new episode of pain and at suitable intervals according to each pharmacological or non-pharmacological intervention. (LE: 3. GR: B).
17. The same assessment tool must be used in different measurements on the same child. (LE: expert opinion; GR: C).
18. If the child has no pain, assessment shall be carried out every time vital signs are measured (a minimum of twice a day) or when a procedure is carried out that may involve pain. (LE: expert opinion; GR: C).
19. If the child experiences pain, reassess at regular intervals after establishing a treatment plan or the appearance of a new pain. The assessment intervals shall depend on the analgesic regimen established. (LE: expert opinion; GR: C).
20. Carers must be trained on how to complete a pain diary in order to maintain continuity in the effective management of pain after hospital discharge. (LE: 3. GR: B).
21. Healthcare professionals be aware of regular syndromes that occur with pain, for their early detection and management. (LE: 3. GR: B).

22. Special attention must be paid to the preferences and needs of the children for whom education or cultural factors may affect communication of pain. (LE: 3. GR: B).

4.4 Diagnosis and assessment of pain

Before starting any type of treatment for pain it must be identified and assessed, taking into account that indicated in the introduction, that pain is a subjective perception and that it must be, preferably, self-rated, as some studies indicate that the healthcare professionals and carers of children tend to rate pain lower when observed by them. Therefore, provided that the child is capable, the pain must be self-rated.

If the child does not have the capacity to self-rating pain (for reasons of age, cognitive or verbal capacity, pathology, sedation or other reasons), the closest assessment to that of the child would be that carried out by their main carer and secondly the healthcare professionals. Therefore, open communication between professionals and carers of children is vital.

When children are unable to describe their pain in words, as occurs with babies and small children, or in any situation that impedes them, they must be observed carefully to detect signs of behaviour that indicate pain. On occasions, these signs are very subtle, manifested as discomfort or distress, which are only detected by their carer (WHO, 1998). They must spend as much time as possible with the child in order to facilitate, among other aspects, the pain assessment if necessary (WHO, 1998).

According to their age, the child manifests pain in a different manner (Canbulat & Kurt, 2012; Hockenberry-Eaton et al., 1999).

Infants (up to 1 year of age) move less than usual, they cry more often and are restless, they can become pale and sweaty when they are in pain; they loose their usual appetite and cry if they are touched or moved.

Children aged between 1 and 3 years suffering pain, as infants, can cry more often, are restless and move less than normal. They can show signs that suggest localisation of pain, although they cannot state explicitly when they feel pain.

Children aged between 3 and 6 years (pre-school) do not always verbalise their pain. They can be asked to locate the pain and if necessary helped by using a picture of a body so that they can indicate the painful area. After determination of the presence and localisation, it is necessary to determine the level of pain with any of the scales available for this age group.

Children aged between 6 and 12 years (school-children) are capable of verbalising and measuring pain intensity. They can manifest physical signs and be influenced by cultural beliefs.

Adolescents present similar reactions to adults. They can have problems with sleeping, loss of appetite, avoid friends and family, feel nervous or angry and, however, outwardly appear calm. Sometimes they do not say when they feel pain for fear of addiction to narcotics (Miaskowski et al., 2004; MOH, 2003).

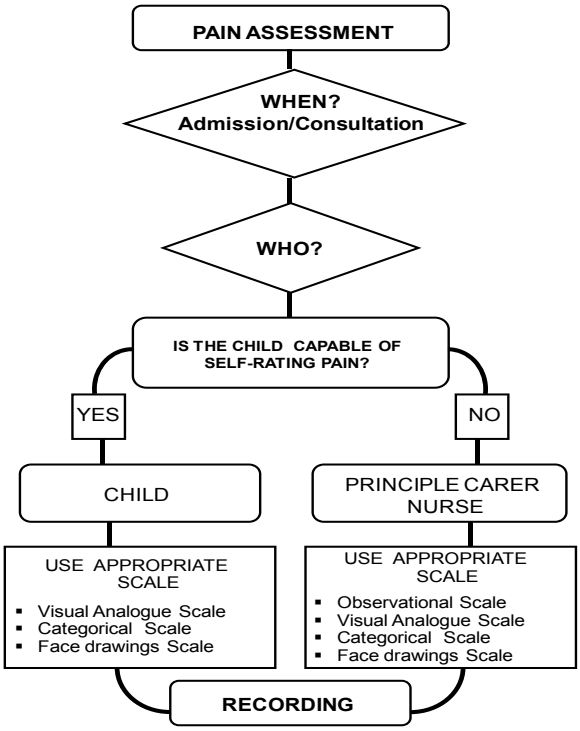
The expression of pain by age groups is indicated in Table 1 (based on Hockenberry-Eaton et al., 1999).

Table 1. Pain expression according to age of children

Age	Expressions of pain childs may exhibit
≤ 1 year	- Body rigidity or thrashing, may include arching - Facial expression of pain (brows lowered and drawn together, eyes tightly closed, mouth open and squarish) - Cry intensely and be inconsolable - Draw knees to chest - Hipersensitivity r irritability - Lose their usual appetite, be unable to sleep
> 1 - ≤ 3 years	- Be verbally agresive, cry intensely - Regressive behavior or withdraw - Physical resistance by pushing painful stimulus away after it is applied - Guard painful area of body - Be unable to sleep
> 3 - ≤ 6 years	- Verbalize intensity of pain - See pain as punishment or understand that there can be secondary gains associated with pain - Thrashing or arms and legs - Attempt to push stimulus away before it is applied - Need physical restraint - Cling to parent, nurse or significant other - Request emotional support (caresses, kisses, etc.) - Be unable to sleep
> 6 - ≤ 12 years	- Verbalize pain and use an objective measurement of pain - Be influenced by cultural beliefs - Stalling behaviors (eg, "Wait a minute", "I'm not ready") - Muscular rigidity, clenched fists and gritted teeth, white knuckles, contracted limbs, body stiffness, closed eyes, or wrinkled forehead - Include all behavios of preschoolers/young children - Experience nightmares related to pain and be unable to sleep
> 12 years	- Localize and verbalize pain - Deny pain in presence of peers - Have changes in sleep patterns or appetite - Be influenced by cultural beliefs - Muscle tension - Regressive behavior in presence of family

The orientation on who must assess pain in a child with cancer is indicated in the following algorithm (fig 1).

Figure 1. Flow chart on who must assess pain



Any measure related with pain must be carried out with correctly validated instruments and recorded in clinical documentation.

Although drafted some years ago, the WHO document on cancer pain management in children has and continues to serve as a base for the drafting of Clinical Practice Guidelines (WHO, 1998). Said document, already indicated that pain should be the fifth vital sign to measure systematically, which has been corroborated by other experts (Canbulat & Kurt, 2012; Joint Commission, 2001; Lanser & Gesell, 2001).

In 2001, the Joint Commission on Accreditation of Healthcare Organizations recommended several standards on correct pain management to healthcare organisations (hospitals, primary care centres, etc.).

- To acknowledge the patient's right to assess and suitably manage pain.
- To ask patients about pain in the initial assessment and when clinically necessary, carry out periodic assessments.
- To educate children who experience pain and their carers on pain management.

According to the WHO, the key points for pain assessment in children are:

- *"**Asses:** always evaluate a child with cancer for potential pain. Children may experience pain, even though they may be unable to express the fact in words. Infants and toddlers can show their pain only by how they look and act; older children may deny their pain for fear of more painful treatment.*
- ***Body:** be careful to consider pain as an integral part of the physical examination. Physical examination should include a comprehensive check of all body areas for potential pain sites. The child's reactions during the examination – grimacing, contracture, rigidity, etc. – may indicate pain.*
- ***Context:** consider the impact of family, health-care, and environmental factors on the child's pain.*
- ***Document:** record the severity of a child's pain on a regular basis. Use a pain scale that is simple and appropiate both for the developmental level of the child and for the cultural context in wich it is used.*
- ***Evaluate:** asses the effectiveness of pain interventions regularly and modify the treatment plan as necessary, until the child's pain is alleviated or minimized."*

The initial pain assessment must include (AHCPR, 1994; Miaskowski et al., 2004):

- Detailed history, including a pain intensity assessment and its characteristics.
- Physical examination, including the neurological examination.
- Psychosocial assessment.
- Appropriate diagnosis to detect signs and symptoms associated with pain.

The initial history of pain is important in understanding the state of pain of the child and the perspective of their carers. It is necessary for communication with the child to determine the words used to manifest their pain (for example "it hurts" or it is "sorely", etc.) and how and who conveys it. Other aspects to include

regarding pain are previous experiences, the child's response, expectations and preferences for assessment and treatment.

It is recommended to compile a specific history of pain that covers the following aspects (BPS, 2010; Macintyre et al., 2010; Miaskowski et al., 2004; SING, 2008):

1. Characteristics of pain:
   - Type of pain
   - Intensity and duration
   - Localisation (a doll can be used to help the youngest children)
   - Description
   - Etiology: by the cancer, the treatment or other circumstances

2. Physical and psychological manifestations:
   - Functional effects and interference with dayly-life activities
   - Psychosocial factors: anxiety, fear, effect on interpersonal relations and factors that affect tolerance of pain (anxiety, depression, etc.)
   - Associated circumstances (that influence the exacerbation or relief of pain)

3. Associated symptoms (nausea, insomnia, depression, anxiety, etc.)

4. Treatment regimen:
   - Type and dose
   - Effectiveness of treatment or other previous treatments, if applicable
   - Adverse effects

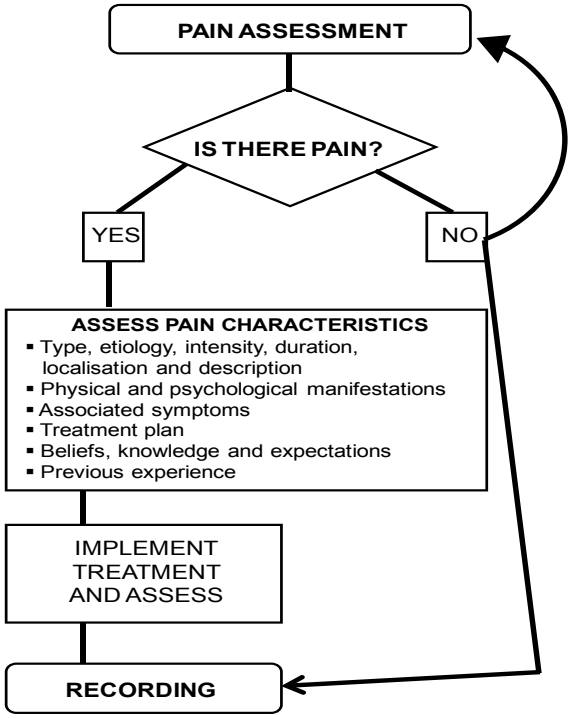
5. Beliefs, knowledge and expectations. They can be determined, among other aspects, by previous experiences of pain or through fear and uncertainty due to lack of information.

The history of pain shall be compiled by the nurse upon admission of the child, forwarded to the psychologist, oncologist, paediatrician, or other professionals if necessary. The child must be assessed by a psychologist. Validated instruments shall be used for all aspects contemplated in the history of pain, whenever possible.

Pain shall be assessed at established intervals.

After the pain assessment, the treatment plan for its management must be established and recorded, as indicated in the flow chart below (fig 2).

Figure 2. Flow chart on the assessment of pain



4.5 Pain intensity measurement instruments

Validated instruments shall be used to measure pain intensity. Correct validation shall involve assessment of all possible aspects on reliability and validity. Equally, its cultural and context adaptation and other aspects of the instrument. This process must be carried out in the population and the clinical situation in which they are used.

Pain intensity measurement instruments should be self-administered, highly visual, simple, quick to complete, suitable for the characteristics of the child (cognitive, emotional and language development), used at regular intervals and systematically recorded.

The capacity of minors to indicate and quantify their pain is limited by their cognitive development, their vocabulary and their experience of pain. Therefore, self-assessment scales must be used to assess the intensity of pain, although many of these scales have not been tested on children with cancer and their psychometric properties have been established for other types of pain (for example, post-operative, derived from invasive procedures and in pain from juvenile rheumatoid arthritis) (Miaskowski et al., 2004).

Another very important aspect is the use of the same assessment tool in different measurements on the same child.

In the systematic review carried out for this CPG, the scales were found that are indicated in table 2. Six of the nine articles found in the systematic review are of moderate methodological quality and 3 of poor quality; it is worth highlighting that no article of good quality was found.

Table 2. Characteristics of the studies included in the systematic review on pain measurement instruments

Study	Age	Scale	Scale parameters and compliance	Scale characteristics
Da Silva et al., 2011	7-17 years	Brazilian version of Faces Pain Scale Revised (FPS-R) and Face, Legs, Activity, Cry and Consolabilty (FLACC)	Intensity of pain by observation (FLACC) and by self-rating (FPS-R)	Both scales are easy to use to assess pain in children and adolescents with cancer in Brazil. Good reliability of FLACC and FPS-R and good convergent validity between both
Da Silva et al., 2008	7-17 years	Brazilian version of FPS-R and of FLACC	Intensity of pain by observation (FLACC) and by self-rating (FPS-R)	Both scales are easy to use to assess pain in children and adolescents with cancer in Brazil
Manworren et al., 2003*	< 3 years	FLACC (English)	Pain intensity by observation	Low interobserver reliability. Supplements the nurse's judgment
Van Cleve et al., 2001*	8-17 years	List of words in Spanish of pain: APPT (Adolescent Pediatric Pain Tool)	Qualities of pain by self-rating	Acceptable test-retest reliability. Small sample to measure correlations between dimensions of pain (intensity, localisation, quality)
Gauvain-Piquard et al., 1999	2-6 years	Douleur Enfant Gustave Roussy (DEGR) (French)	Pain intensity by observation	Good interobserver concordance and Cronbach coefficient of reliability. Good content validity. Satisfactory sensitivity and reproducibility of the scale
Gauvain-Piquard et al., 1987	2-6 years	DEGR (French)	Pain intensity by observation	Satisfactory sensitivity and reproducibility of the scale
Badr Zahr et al., 2006	4-10 years	DOLLS (Arabic)	Pain intensity by self-rating	Good correlation between DOLLS and FACES, in children and in parents and in nurses; between DOLLS and Observational scale of behavioural distress-revised (OSBD-R) in nurses and parents; between DOLLS and FLACC in nurses
Tseng et al., 2008	11-18 years	M.D. Anderson Symptom Inventory Taiwanese version (MDASI_T)	Intensity of symptoms (including pain) and interference of these symptoms with daily life, by self-rating	Good test-retest reliability and Cronbach coefficient of reliability. Moderate criterion and construct validity
McGrath et al., 2000*	5-16 years	Interview Experience of Pain: presence and type; Analogue Scale of color: intensity; Facial Affective Scale: affectation as a consequence of pain (English)	Presence, intensity and derived affectation; by observation	The instrument enables classification/prediction of the type of pain in children with cancer, that associated with invasive procedures, etc.

* Studies with considerable methodological limitations.

Therefore, taking into account the characteristics of the scales and the age of the children, it is recommended to use the following scales, due to their simplicity and ease of use, until instruments validated in Spanish and in children with cancer are available:

- Children who can self-rate pain: use the Visual Analogue Scale (VAS), Numeric Rating Scale (NRS) or Categorical Pain Scale (CPS). In smaller children the Wong-Baker FACES® Pain Rating Scale can be used (Wong & Baker, 1988; Wong et al., 2001).
- Children who cannot self-rate pain: carers of the children or professionals shall observe facial expression, the movement of legs, activity, cries and consolability. All these signs are reflected on the FLACC scale (Face, Legs, Activity, Cry and Consolabilty) (Merkel et al., 1997).

The Visual Analogue Scale (VAS) comprises a 10 cm horizontal line with extreme levels of pain at each end; the left side corresponds to the category "No Pain" and the right side corresponds to the category "Worst pain imaginable". Once verified that the child understands the scale, they are asked to indicate the point on the line that depicts the intensity of pain felt. It is measured with a ruler and the intensity of pain is expressed in centimetres or millimetres.

No pain_____Worst pain imaginable

The Numeric Rating Scale (NRS) comprises a numerical series from zero to ten, depicting the extreme levels of pain at each end; the left side corresponds to the value 0 and indicates the absence of pain and on the right side is the value 10, which corresponds to the worst possible pain. Once it has been verified that the child understands the scale, they are asked to select a number that best reflects the intensity of pain experienced.

0 1 2 3 4 5 6 7 8 9 10

No pain_____Worst possible pain

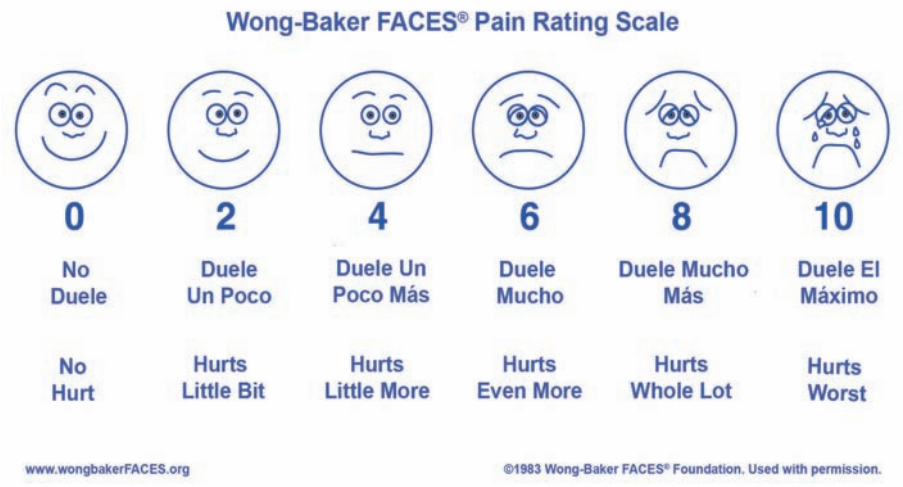
Although they have not been validated, the following cut-off points are recommended to assess the intensity of pain, according to the points on the Numeric Rating Scale (Miaskowski et al., 2004): no pain (points=0), mild pain (points=1–3), moderate pain (points=4–6), severe pain (points=7–10).

The Categorical Pain Scale (CPS) can be used when the child is incapable of quantifying numerically the intensity of pain. Once it is verified that the child understands the scale, they are asked to select the category that best corresponds to their level of pain.

0	4	6	10
None	Mild	Moderate	Severe

The Wong-Baker FACES® Pain Rating Scale is formed by drawings of a face, generally made by children, expressing different levels of pain so that the child selects the face that best represents the pain experienced. The happiest face corresponds to the absence of pain and the saddest face depicts the worst pain.

Each face corresponds with the numerical scoring to convert the face indicated by the child into a number; the scoring of six faces is 0, 2, 4, 6, 8, 10, where 0 is no pain, 2 is mild pain, 4-6 is moderate pain and 8-10 is severe pain.



There are numerous versions and adaptations of this scale, in which as well as the form of expression of drawings, the number of faces and their scoring often vary.

FLACC Behavioral Scale (Merkel et al., 1997).

Categories	Scoring		
	0	**1**	**2**
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractable	Difficult to console or comfort
Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.			

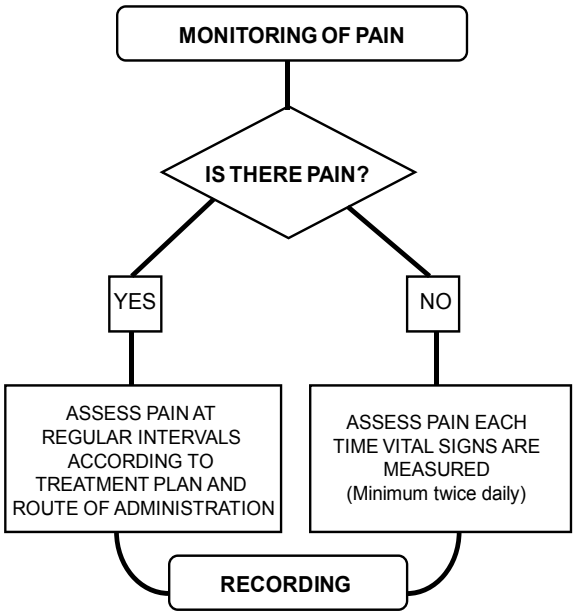
Cut-off points of FLACC Scale: relaxed and comfortable (points=0), mild discomfort (points=1–3), moderate pain (points=4–6), severe discomfort/pain (points=7-10).

4.6 Monitoring of pain

Pain shall be monitored according to the existence or not of previous pain and establishment of treatment and the realisation of painful invasive procedures. In the case of established treatment, the response to treatment must be assessed based on the degree of analgesia achieved, the time to achieve analgesia and the duration of its effect (Macintyre et al., 2010).

Pain must be assessed on each visit of the child to outpatient consultations or upon each admission to hospital (Macintyre et al., 2010; Miaskowski et al., 2004), following the model that are indicated in the flow chart (fig 3).

Figure 3. Flow chart on the monitoring of pain



If the child is pain-free and given that it is considered the fifth vital sign, the assessment must be carried out each time that the vital signs are measured (minimum twice daily) or when a procedure is planned that may involve pain.

If the child feels pain, reassess at regular intervals (always with the same scale) after the establishment of a treatment plan or the appearance of a new pain. The assessment intervals shall also depend on the analgesic regimen established and the level of pain (see section 7.4.1):

- Mild pain (first step of the WHO ladder): assessment at intervals between 1 and 4 hours.
- Moderate pain (second step of the WHO ladder): assessment every hour.
- Severe pain (third step of the WHO ladder): assessment every hour (or every 15 minutes if treatment is intravenous).

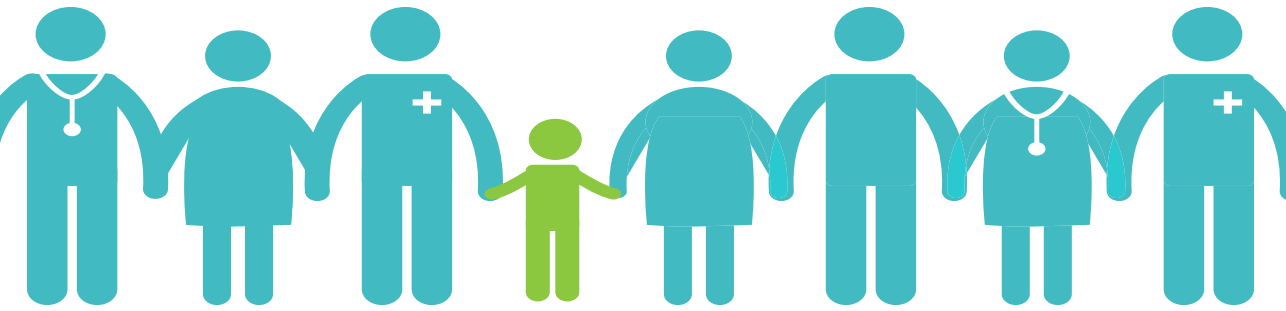
In order to assess the effectiveness of the established treatment, it is recommended to use the same scale used to assess pain intensity, as it can be otherwise difficult to relate results from scales with different categories. Notwithstanding, in certain cases the verbal rating scale is used, which contemplates four categories of pain relief: nothing, mild, moderate and complete (Macintyre et al., 2010).

The reduction in intensity of pain between 30 and 50% is deemed clinically relevant (Gordon et al., 2005; HUVH, 2009; Macintyre et al., 2010).

Follow-up after hospital discharge

It is useful to train carers and the child (whenever their age permits), when they are discharged from hospital, so that they may keep a pain diary. This should include the intensity of pain, relief, treatment carried out and the side effects to said treatment, the changes produced in pain, the appearance of new episodes of pain and the aspects that permit assessment of adherence to the management and treatment plan. Also, it would be relevant to include other aspects that help in the management of pain, such as the daily average of hours in pain, effect on daily life activities of the child, adherence to treatment and if additional treatment to that regulated was required.

5. Pain related with invasive procedures



Performing painful procedures is very usual in children with cancer, carried out repeatedly for diagnosis or treatment, a fact that must be taken into account when managing pain derived from them (Landier & Tse, 2010; Macintyre et al., 2010; Mercadante, 2004). These procedures include lumbar puncture, bone marrow aspiration or biopsy, placement of central lines and tissue biopsy. Various studies indicate that bone marrow punctures and aspirations are perceived by children with cancer, their carers and healthcare professionals as the two most painful and stressful procedures of all those associated with cancer treatment (Elliott et al., 1991; Ljungman et al., 1999; Ljungman et al., 1996; McGrath et al., 1990; Mercadante, 2004; Miser et al., 1987; Zernikow et al., 2005). Although venipunctures, insertion of intravenous catheters and intramuscular injections are less painful invasive procedures, their frequency and repetition are an important source of distress and fear.

Anxiety and previous painful experiences have a significant influence on distress before procedures when these are repeated (Mercadante, 2004; Weisman et al., 1998; Chen et al., 2000),

Therefore, the pain related with these procedures must be treated prophylactically with the suitable analgesia and/or sedation, offering children who reject sedation other non-pharmacological alternatives to reduce pain related with the procedure. In addition, information must be provided on the characteristics and duration of sensations expected to be experienced during the painful procedure, to achieve maximum collaboration of the child (Miaskowski et al., 2004).

Suitable monitoring must be carried out of pain and the sensations that may be caused by the invasive procedure.

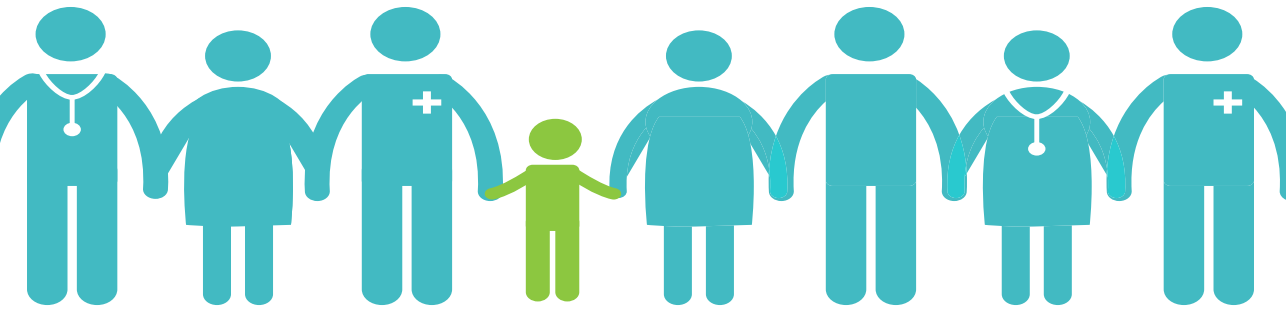
Pain management plans associated with painful procedures must address various questions (Miaskowski et al., 2004):

- What is the purpose of the procedure carried out?
- What is the expected pain intensity?
- How long is the pain expected to last?
- What is the expected anxiety intensity?
- How long is the anxiety expected to last?
- How often will the procedure be repeated?
- How do carers think that their child will react?
- What does the procedure mean for the child and carers?

5.1 Recommendation for the management of pain related with invasive procedures

1. Pain related with painful procedures must be prophylactically treated with appropriate analgesics and/or sedation. The analgesia needs are reduced if the children have received preventive treatment before the painful procedures. (LE: 2,3. GR: B).
2. The children must be provided with information on the characteristics and anticipated duration of what they may experience during the painful procedure. (LE: 2,3. GR: B).
3. The sedation process must be supervised if administered to children who suffer from anxiety of painful procedures associated with the diagnosis and treatment of cancer. (LE: 3. GR: B).
4. Non-pharmacological alternatives must be offered to children who reject sedation to lessen the pain related with the painful procedure. (LE: 2,3. GR: B).
5. In the interventions to control pain and anxiety related with the procedure, the type of procedure, anticipated degree of pain and other individual factors must be taken into account, such as age and physical and emotional state. (LE: 3. GR: B).
6. Sedation must be considered for painful procedures that require patient cooperation to remain still especially in children aged under 6 years or disabled children. (LE: 2,3. GR: B).

6. Non-pharmacological interventions to prevent or treat pain



6.1 Objectives

This section of the guideline will help healthcare professionals and carers of children with cancer to:

- Identify effective non-pharmacological therapeutic interventions to prevent pain.
- Identify effective non-pharmacological therapeutic interventions to treat pain.

6.2 Target population

Children from birth up to 18 years of age, diagnosed with any type of cancer, still under follow-up for cancer, susceptible to experiencing pain or who present pain.

6.3 Recommendations to prevent or treat pain with non-pharmacological interventions

1. The simplest techniques to alleviate pain can become more effective if the information, recording, assessment of the child and provision of guidelines and appropriate recommendations are taken into account. (LE: 3. GR: B).
2. Children and carers must be informed of non-pharmacological interventions available, anticipated effects, their effectiveness and possible adverse effects. (LE: expert opinion; GR: C).
3. Suitable comfort measures must be used in pharmacological and non-pharmacological interventions, as they can reduce the levels of anxiety, distress and pain. (LE: 3. GR: C).
4. Children must be encouraged to remain active and take part in their care whenever possible. (LE: 2,3. GR: B).
5. Carers must be with the child whenever possible, as their presence helps to minimise pain, by reducing anxiety and fear in children. (LE: 2. GR: B).
6. Non-pharmacological interventions must be considered, even if their effectiveness remains unproven, provided that they do not cause adverse effects, because they provide comfort and well-being to the child. (LE: expert opinion; GR: C).
7. The type of non-pharmacological intervention must be chosen by the child and their carer, based on the information received on the expected effects. (LE: 3. GR: C).

8. Use of psychological interventions adapted to child development can reduce the levels of anxiety, distress and pain. (LE: 2,3. GR: B).
9. Cognitive-behavioural interventions are more effective than the use of placebos or non-intervention. (LE: 2,3. GR: B).
10. Cognitive-behavioural interventions must be incorporated early in the treatment of the disease as part of a comprehensive approach to pain management, without this being a substitute for analgesics. (LE: 1,2. GR: B).
11. When offering cognitive-behavioural interventions, both active and passive, the intensity of pain and expected duration, the degree of psychophysical maturity of the child, previous experience of the child with these interventions and their desire to use them must be taken into account. (LE: 3. GR: B).
12. Distraction, hypnosis and cognitive-behavioural interventions reduce pain and distress associated with punctures in children and adolescents. (LE: 1,2. GR: B).
13. Cognitive-behavioural interventions combined can relieve pain, but no more effectively than other interventions. (LE: 2. GR: B).
14. Distraction used in isolation has little influence on reducing pain. (LE: 2. GR: B).
15. The use of virtual reality has little influence on the reduction of pain. (LE: 2. GR: B).
16. Listening to music can reduce pain. (LE: 2. GR: B).
17. The use of relaxation techniques has little influence on the reduction of pain. (LE: 2. GR: B).
18. Hypnosis is effective in pain relief, whether using direct or indirection suggestion. (LE: 2. GR: B).
19. Hypnosis is more effective than the placebo in pain relief and more effective than cognitive-behavioural interventions. (LE: 1. GR: A).
20. Evidence on the effectiveness of information on the reduction of pain is insufficient, however information helps reduce distress and fear in the children. (LE: expert opinion; GR: C).
21. The use of support measures and physical contact, such as caressing, has little influence on reducing pain, but it can provide comfort and reduce distress and anxiety. (LE: 3,4. GR: B).
22. The use of massage has little effect on reducing pain but can provide comfort and reduce distress and anxiety. (LE: 2,3. GR: B).
23. Hot/cold application in children must be carried out with care due to risk of injury. (LE: 3,4. GR: C).
24. The use of topical anaesthetics is more effective than the placebo in pain relief. (LE: 1,2. GR: B).

25. The use of EMLA® is more effective than the placebo in pain relief, and more effective if applied 60 minutes before the procedure than if applied 40 minutes beforehand. (LE: 1,2. GR: B).

6.4 Non-pharmacological therapeutic interventions

Some studies indicate that between 31-84% of children and adolescents with cancer use non-pharmacological complementary interventions during the course of the disease (Landier & Tse, 2010; Sencer & Kelly, 2007).

Non-pharmacological interventions can substantially modify some of the factors that influence increased pain, activating sensorial systems that block pain signals, triggering internal pain inhibitor systems (WHO, 1998). Factors such as fear, anxiety, distress, feeling of control, self-efficacy, etc. do not cause pain directly but influence the perception of pain and the response of each person to it (Kelsen et al., 1995; Main & Spanswick, 2000; Turk & Fernández, 1991; Zara & Baine, 2002), which has led to the development, fundamentally, of cognitive-behavioural interventions. These interventions vary from teaching the child how to confront pain, to those that modify the experience of pain and anxiety (Mercadante, 2004).

The effectiveness of non-pharmacological interventions, seen as a whole, in long-term pain relief in cancer sufferers is limited (Miaskowski et al., 2004), and varies between different modes of intervention; for some children and certain situations they have proven to be effective (Canbulat & Kurt, 2012). The most solid evidence is for their use in short-term pain relief and during diagnostic and clinical procedures (SIGN, 2008).

Non-pharmacological interventions are well accepted by children and their carers. Apart from their effectiveness, many children and carers find it a positive experience (SIGN, 2008), probably due to the feeling of comfort and wellbeing, increased feeling of control and active participation in the disease (Landier & Tse, 2010; Sencer & Kelly, 2007) and improved predisposition to treatment (Canbulat & Kurt, 2012). Children and carers are interested in using them again. Also, some of these interventions are easy to apply (Canbulat & Kurt, 2012; WHO, 1998).

Therefore, it is considered that the use of non-pharmacological interventions must be an integral part of pain management in children with cancer, used from

the time of diagnosis and during the entire treatment (AHCPR, 1994; BPS, 2010; Macintyre et al., 2010; Miaskowski et al., 2004; MOH, 2003; WHO, 1998).

Children and their carers must be the ones who decide to use non-pharmacological interventions and which they prefer, based on their age, degree of psychological maturity, physical state, attention span, level of anxiety or fear, capacity for active collaboration, previous experiences, type of procedures to undergo, expected duration of pain and availability of said interventions (Canbulat & Kurt, 2012; Macintyre et al., 2010; Miaskowski et al., 2004; Murat et al., 2003). This choice shall be based on the information provided by the professionals of their healthcare team.

This section of the guideline details jointly two aspects on pain management, prevention and non-pharmacological treatment.

Sources of direct evidence have been used to answer the questions in this section (studies directed specifically at pain management in children with cancer). The systematic review carried out included 28 articles, of which one reported the results of two studies (Kapelushnik et al., 1990).

It is important to consider that all the studies found refer to non-pharmacological interventions to prevent or treat pain in painful diagnostic or clinical procedures, without having found studies referring to non-pharmacological treatment for pain management due to the disease.

The use of topical analgesics has been considered as non-pharmacological intervention.

The aims of pain management in diagnostic or clinical procedures are (Schechter et al., 2003):

- **To minimise pain:** to coordinate planned painful procedures (venipuncture, lumbar puncture, etc.) so as to limit the number of attempts / occasions a procedure is carried out.
- **To maximise child cooperation:** to prepare the child and the carer with preventive action.
- **To minimise the risk of the child during any procedure:** to use suitable equipment / monitoring standards.

According to experts at the Agency for Healthcare Research and Quality (AHCPR, 1994) and the American Pain Society (Miaskowski et al., 2004), there are eight important aspects on structure and process for correct pain management:

1. A multi-disciplinary group that works constantly on improving pain management.
2. Define record systems and standards for pain assessment, guaranteeing that it is quickly diagnosed and treated.
3. Explain standardised practices to guarantee the safety and efficacy of administration of analgesics.
4. Clearly define the roles and responsibilities of each member of the healthcare team in relation with pain management.
5. Promote easy access of healthcare professionals to information on pharmacological and non-pharmacological treatment.
6. Inform the child and their carer of the importance of pain management.
7. Provide continuous training on pain and pain management to healthcare professionals.
8. Assess regularly the effectiveness of pain control to optimise its management.

Non-pharmacological interventions can be classified as shown in table 3 (adapted from Miaskowski et al., 2004 and WHO, 1998).

Table 3. Classification of non-pharmacological interventions

Method	Components	Description
Cognitive-behavioural	Distraction	Attract and hold their attention and distracting them from pain (music, images, games, etc.)
	Cognitive reformulation	Recognise thoughts that increase pain and replace then with positive thoughts
	Progressive muscular relaxation	Each muscular group contracts and relaxes, in order to interrupt the pain-tension cycle that can increase pain
	Autogenic relaxation	Centre the attention on noting a physical state and after relax the muscles
	Imagery/ visualisation	Once relaxed, centre on pleasant or neutral images. It has elements similar to the hypnosis but does not use the suggestion intentionally
	Deep breathing	Inspiration/expiration at a slower rate than usual and using the abdomen
Hypnosis	Induction	Capture and hold the attention of the child, intensifying the focus on mental activity
	Concentration	Includes images or physical sensations that modify the sensorial experience
	Suggestion	Suggestion to control an experience and reduce sensations
Support	Manifestation of concerns	To give an opportunity to express pain-related concerns
	Reaffirmation	Normalises the experience of pain when comparing it with other patients
	Support to communicate needs	Encourage children to communicate that the expected effect was not achieved with the treatment of pain
	Information	To explain the procedures to children and carers, expected pain and duration
Physical strategies	Cold and/or Heat	Surface application of heat and cold
	Physical contact	Massages with different techniques
	Transcutaneous electrical nerve stimulation (TENS)	Low voltage electrical stimulation on peripheral nerves
	Acupuncture	Insertion of needles in different areas of the body
	Others	Different techniques such as Reiki, reflexology, aromatherapy, etc.

The interventions identified that have been more widely studied for pain management due to procedures in children with cancer were distraction (alone or combined with other interventions), hypnosis and the use of local anaesthetics.

The pain measurement instruments used the most were the Visual Analogue Scale (VAS) and the FACES scale (five or six faces), both by the children and observers (parents, clinical professionals).

Overall, the studies carried out with non-pharmacological interventions in children with cancer vary considerably in type of intervention applied, its pattern, its form and its duration. Equally, the types of intervention carried out on the control groups also vary, from "usual care" to other non-pharmacological interventions or pharmacological interventions. Likewise, the samples studied are usually very small.

Considering the different types of intervention, the greatest effects are obtained with the use of hypnosis and local anaesthetics. The least effects are obtained with cognitive-behavioural interventions when used in isolation. Other authors reach similar conclusions (Miaskowski et al., 2004).

A systematic review was identified (Rheingans, 2007) on the efficacy of non-pharmacological therapies to treat symptoms associated with cancer treatment in children, such as pain, anxiety, stress and fear. Only 17 out of 41 studies included in the systematic review assessed pain reduction, in punctures or bone marrow aspirations, venipunctures or central venous access (Port-a-Cath®), both in experimental and qualitative designs.

The 17 studies included different types of interventions: cognitive-behavioural interventions, hypnosis, distraction, relaxation, physical contact, etc. The heterogeneity of interventions and measurements did not permit meta-analysis. The results of non-pharmacological interventions are inconsistent, without having demonstrated effectiveness of the non-pharmacological interventions if considered as a whole. It is necessary to analyse the type of intervention individually.

The majority of interventions reduce pain in the recipient group, but there is little information regarding the reduction of pain of some interventions compared with others. Of the interventions considered, hypnosis shows the most promising results. Five studies analysed the effectiveness of hypnosis, of which 3 found positive results in reducing pain derived from procedures (Hawkins et al., 1998; Hilgard & LeBaron, 1982; Liossi & Hatira 2003), 1 found results in favour of the

reduction of anxiety and discomfort (Kellerman et al., 1983) and another found no significant changes (Katz et al., 1987).

When comparing hypnosis with cognitive-behavioural interventions (CBI), pain reduced in all groups (Kuttner et al., 1988; Liossi & Hatira, 1999; Wall & Womack, 1989; Zeltzer & LeBaron, 1982). CBI show no consistent results, probably due to the great variability in the mode of the interventions used.

Evidence on the use of non-pharmacological interventions in cancer patients of any age and in children with other pathologies concludes equally the great variability and inconsistency of results (Canbulat & Kurt 2012; Landier & Tse, 2010; Miaskowski et al., 2004; SIGN, 2008), although between 75-90% of cancer patients of any age do find benefit (Miaskowski et al., 2004).

6.4.1 Cognitive-behavioural interventions (CBI)

Cognitive strategies aim at reducing cognitive and affective components of pain, helping patients to interpret feelings and events. Behavioural strategies aim at preparing patients so that they may change their actions in response to the perception of pain (Miaskowski et al., 2004). That is, the objectve of CBI is to influence thoughts and images of children.

They are used preferably as a support to other types of interventions, pharmacological or not; in many cases they are mainly used to manage distress, rather than pain. Their effects, in general, are mild and transitory, but they are more effective than the use of placebos or the absence of intervention (Miaskowski et al., 2004). It is advisable not to use these interventions in isolated form, but rather as part of a holistic approach.

Response to these interventions varies according to the characteristics of the children, their family and social background. Older children and adolescents must state their preferences for themselves and, in the case of the smallest, they can do so with help of their carers (WHO, 1998). The choice of the children and their carers is essential to decide on which intervention to apply (Gershon et al., 2004, Nilsson et al., 2009).

In the systematic review carried out for this CPG, different modes of CBI were used in 12 studies. Distraction was used in two (Hedén et al., 2009; Windich-Biermeier et al., 2007) with different modes (watching bubbles, reading stories, conversation, etc.), distraction with virtual reality in 3 studies (Gershon

et al., 2004; Nilsson et al., 2009; Sander Wint et al., 2002) and distraction with music was used in 2 studies (Nguyen et al., 2010; Pfaff et al., 1989). In five studies, different modes of CBI were applied simultaneously (Broome et al., 1998; Broome et al., 1992; Jay et al., 1991; Kuttner et al.,1988; Pederson, 1996).

Cognitive-behavioural interventions used during painful procedures in children with cancer provide pain relief, regardless of the type of intervention; however when compared with other interventions, with placebo or with "usual" treatment, in general, they show no greater effectiveness. Neither the active cognitive-behavioural interventions nor virtual reality interventions, compared with other interventions, showed effectiveness in the reduction of pain in children with cancer during painful procedures. However, the use of music, distraction and different interventions combined, reveal mixed results on the effectiveness, probably due to heterogeneity of interventions.

No adverse effects derived from the use of CBI were observed in any of the studies, although this result was not measured in the majority of them, but a subjective assessment was carried out by the children and/or parents on their intention to use these interventions again in future procedures. The degree of satisfaction with the use of these interventions was high and the majority of participants in the studies cited their intention to use them again.

Furthermore, it is necessary to take into account that they are easy to learn and use techniques (Hockenberry-Eaton et al., 1999).

Distraction

Distraction methods aim to attract and hold attention, averting them from the pain and the painful procedure (Hockenberry-Eaton et al., 1999). The more active the participation and the more involved the child is in an activity, the greater the distraction from the pain (WHO, 1998). Specific elements are necessary to hold their attention, which must be age appropriate and suitable for the degree of maturity of the child. It is an alternative to consider when there is little time for previous preparation (Doellman, 2003).

In two controlled, randomized clinical trials (RCT) distraction interventions were compared with the use of EMLA® in pain reduction during central venous access. In both studies, pain reduced in children who received the intervention, but the difference with the control groups was not significant.

Heden et al., (2009) compared distraction with bubbles versus the use of a warm pillow used as a distraction element (by having to concentrated on different points of this) in 28 children aged from 2 to 8 years. EMLA® was applied to the entire sample and the first venipuncture was carried out, measuring pain; then, the intervention with bubbles or with the pillow was assigned at random and a second venipuncture was carried out. Pain was assessed with VAS (0-100) by parents and nurses. Pain reduced between the two venipunctures both in the group that used bubbles (difference 15.6) and in the group that used the warm pillow (difference 3.8), although the differences were not significant.

No significant differences were found when comparing the two groups. According to the parents, both procedures helped to reduce distress and fear in children.

Windich-Biermeier et al., (2007) compared the effectiveness of distraction in 50 children aged from 5 to 18 years (the child chose between bubbles, books, music, virtual reality glasses or video games) after information of the procedure and application of EMLA®, versus the information and use of EMLA®. Sixteen children of the intervention group (72%) chose a videogame, 4 children (18%) virtual reality, 1 child bubbles and another child music. Children assessed the pain with a colorimetric visual analogue scale rated from 0 to 10. The pain score cited by the children was not significantly different between the two groups (p=0.68) although there was a tendency to favour the distraction group. Ninety one percent of the children stated that the distraction helped them avert their attention from the procedure and that they would use it again.

In other population groups in which distraction was studied to reduce pain derived from procedures, the effects are mild and the results inconsistent (Kleiber & Harper, 1999).

Virtual reality (VR)

In three experimental studies (two of them RCT) virtual reality was used to relieve pain during central venous accesses or lumbar puncture. Sedation and/or EMLA® were used in all groups for all three studies. Although use of virtual reality provided pain relief, the differences were not significant compared to the control groups for any of the studies.

Nilsson et al., (2009) carried out a controlled experimental study with 42 children aged between 5 and 18 years during central venous accesses, where non-immersive virtual reality was an interactive 3D game; both groups used a cold

spray or EMLA®. The children assessed pain using a colorimetric scale and an observer used the FLACC scale. The pain reduction was significant for each group, but comparison between groups showed no significant results. Fifteen out of 21 children of the intervention group would choose virtual reality again. It is necessary to take into account that it is not specified whether there was random assignment and the results come from statements from the authors, as numerical results were not provided.

Gershon et al., (2004) carried out a RCT with 3 groups of 59 children (total) aged between 7 to 19 years. The first group received interactive virtual reality, the second distraction without virtual reality (videogame) and the third the usual treatment with EMLA®, which was also used in all groups. Pain was assessed before and after central venous access with VAS (0-100) and CHEOPS (Children´s Hospital of Eastern Pain Scale), by children, parents and nurses. Pain reduced significantly in favour of VR and the distraction ($p<0.05$), only according to the nurses' assessment, probably due to improved physical patterns (reduced heart rate).

There was a greater tendency for reduced pain in the group of older children than the youngest children for both interventions. It is necessary to take into account the limitations of this study, the insufficient sample size for statistical power and that pain during the procedure was low, therefore there could have been a floor effect; also, the information provided by the authors was limited.

Sander Wint et al., (2002) carried out a RCT on 30 children aged between 10 and 19 years, to study the effectiveness of interactive virtual reality. Information was applied in the control group together with sedation (maintaining a conscious state) and/or EMLA®, as well as the presence of parents; the intervention group also received this regular intervention. Pain was assessed in lumbar puncture with the VAS (0-100). No significant differences were found between the groups although the VR group had a lower score on the VAS (pain median in the control group 19 and in VR group 5; $p>0.05$).

Out of 17 children of the VR group, 13 (77%) considered that the procedure distracted them and 15 (88%) cited that it had helped them during the lumbar puncture; 94% of the intervention group stated their desire to use the procedure in the next lumbar puncture. In the control group, 5 out of 13 children, deemed sedation helpful and 5 considered that it did not help them (3 did not respond).

Music

Music was also used as a distraction technique. It appears to influence pain by encouraging greater relaxation as shown by certain physical parameters (heart and respiratory rates, blood pressure), reducing tension (Burns et al., 2001; Canbulat & Kurt, 2012).

The effect of music was assessed in two experimental studies as an element of distraction to relieve pain during the puncture or bone marrow aspiration, with contradictory results; only one showed significant reduction of pain during the lumbar puncture and afterwards, although the study that did not find results in favour of the music had important limitations. It must be highlighted that there is no evidence that allows us to define the most appropriate type of music, or how prolonged the effect can be (Miaskowski et al., 2004), therefore an element to take into account can be the choice made by the child (Canbulat & Kurt, 2012).

Nguyen et al., (2010) used music with headphones in 40 children aged between 7 and 12 years who underwent a lumbar puncture in a double-blind RCT. The children chose their preferred music (either Vietnamese folk songs or children's songs). Pain was assessed during the lumbar puncture and after with a numerical scale (0-10). The mean pain score was less during the lumbar puncture with the use of headphones with music (standard deviation=SD) (2.35 SD:1.9 vs 5.65 SD:2.5) $p<0.001$, and post-puncture (1.2 SD:1.36 vs 3 SD:2), $p<0.003$. Equally, anxiety and physical symptoms (heart and respiratory rate) reduced significantly. All the children voiced their desire to use music and headphones in the next procedure.

Pfaff et al., (1989) carried out a quasi-experimental study on a single group of 9 children aged between 7 and 17 years. They used music during the bone marrow aspiration after having used distraction with reading or colouring and measured the level of pain in a previous bone marrow aspiration; the children chose their preferred music from five musical pieces offered. Self-rated pain was measured with the FACES scale (5 faces). The median of pain experienced by the children when listening to music did not fall significantly between the first and second bone marrow aspiration ($p=0.12$). As well as the lack of a control group, the sample size was small ($n=9$) and 3 children left the study.

Music was also used in patients of any age and in children with different pathologies other than cancer, to reduce pain in painful procedures, with inconsistent results (Landier & Tse, 2010; SIGN, 2008).

Hockenberry-Eaton et al., (1999) suggest the following distraction techniques according to age (table 4):

Table 4. Distraction techniques according to the age of the child

Age	Methods
0-2 years	Physical strategies, as touching, stroking, patting, rocking; playing music, using mobiles over the crib.
2-4 years	Puppet play, storytelling, reading books, breathing, blowing bubbles.
4-6 years	Breathing, storytelling, puppet play, talking about favorite places, TV shows, activities.
6-11 years	Music, breathing, counting, eye fixation, thumb squeezing, talking about favorite places, activities on TV shows, humor.

Combined cognitive-behavioural interventions

Five studies used combinations of different cognitive-behavioural interventions, both in punctures and in bone marrow aspirations. They all contributed to reducing pain. No significant differences were found when compared with that of non-intervention, except for the use of distraction and imagery compared with information/support in children aged between 7 and 10 years. The beneficial effects of combined interventions are attributed to the fact that they better hold the attention of the children and reduce distress during the intervention (Broome et al., 1992; HUVH, 2009).

Relaxation, distraction, imagery

In 1992, Broome et al. undertook a study of multiple cases in 14 children aged between 3 and 15 years, whereby visualisation/imagery, relaxation and breathing techniques were applied after a lumbar puncture, which parents and children practiced at home, during the following two lumbar punctures. The children measured pain on the FACES (6 faces) scale. Between the first and third lumbar puncture, the mean pain score reduced significantly (5.2; SD:1.5 vs 3.8; S.D:1.6 vs 2.7; SD:1.1), p=0.008. The best response was obtained by the children who are said to have played a more active role. However, the study had several limitations, such as design, sample size and lack of information on fulfilment of the intervention at home.

In 1998, Broome et al., carried out a RCT on 28 children aged between 4 to 18 years who underwent 3 lumbar punctures. After the first, the intervention was started in a group involving relaxation, distraction and visualisation techniques (it included explanatory material to practice at home between procedures and music to use during the relaxation and visualisation), which were applied throughout the entire study. In the second group, the same intervention was applied but after the second lumbar puncture.

Pain was measured by children and parents with the Oucher Scale (6 photograms and numerical scale of 0-100). During 5 months of study, the intensity of pain reduced significantly with the use of intervention in both groups ($F:1.27=13.05$, $p<0.01$), but they found no differences between them. The improvement correlated with the frequency with which the children practiced ($r=0.70$, $p<0.05$) and the parents ($r=0.57$, $p<0.05$), as well as with the comfort received by the children when using these techniques ($r=0.57$, $p<0.05$). It is necessary to take into account that there was 32% of withdrawals (9 children out of 28) and that it is not specified whether any measure is applied in those punctures in which it did not correspond to use the study intervention.

Distraction, imagery (pseudo hypnosis or variant of hypnosis), support/information

In a RCT of 3 groups, in 48 children stratified by age (group of small children of 3-6 years; group of older children aged from 7-10 years), Kuttner et al., (1988) studied the effectiveness of distraction (dolls, bubbles, games, etc. to choose, or breathing in the group of older children and questions to distract) versus imagery (suggestions on behaviour, experiences, etc.) and versus a control group (information and verbal or non-verbal support), during three bone marrow aspirations.

Pain was measured by observers using the Pain-Rating Scale, and by the children with a 5-drawings scale. Between the second aspiration and baseline, the distraction was effective compared to the control ($F=5.26$ $p<0.05$), as with the imagery ($F=4.76$ $p<0.05$), in the group of 7-10 years; in the group of 3-6 years, imagination achieved greater pain relief than distraction ($F=6.95$ $p<0.05$), but there were no significant differences with the control group. All the children referred to reduced pain in the third bone marrow aspiration compared to baseline aspiration ($F=8.32$; $p<0.01$); however, out of 56 children who started the study, almost 48% of children (26) failed to complete the study and there was contamination of the control group.

Together with the high number of withdrawals, it is important to consider that the scales used to self-rating pain were developed specifically for the study, without providing any details on their validity and no information was provided on the assignment or blinding.

Distraction, attention in breathing, attention in relaxation, imagination, change the perception of painful stimulus, support to parents

Pederson (1996) carried out a cross-over RCT, in 8 children aged between 6 and 14 years, applying the study intervention between three lumbar punctures. The habitual treatment (sedation) was applied in the three procedures and as intervention the children and parents were taught different techniques (attention in breathing, attention in relaxation and change in perception of painful stimulus), together with an element of distraction to be chosen by the child; the parents received support in the use of techniques throughout the process. The VAS (0-100) was used to measure the pain by children, parents and nurses, the latter also used an observational scale of behavioural distress (OSBD).

After the intervention, a lower level of subjective pain during the lumbar puncture was observed in all the children ($Z=1.69$ $p=0.1$), but significant differences were not found when comparing with the non-intervention. The children cited that these techniques helped them to feel more comfortable. It must be taken into account that the sample was approximately a quarter part of the sample calculated (8 out of 30) and that the pain assessment may have been influenced by the amnesic effect of medication provided.

Information, respiration, distraction/imagination, positive stimulation, behavioural assessment

Jay et al., (1991) carried out a RCT in 92 children aged between 3.5 to 12 years who underwent lumbar puncture or bone marrow aspiration indistinctly, in order to determine whether the addition of 0.15 mg/kg of oral Valium® to a combination of CBI improved effectiveness of the use of CBI. These interventions involved the use of an informative video on the procedure, breathing exercises, distraction / imagination, positive stimulation and role play (the child played at being the doctor who carried out the procedure on a doll).

The children assessed pain on a 5-faces scale. Pain reduced in both the group of CBI and that of Valium® plus CBI, but there were no significant differences

when comparing the two groups. This is one of the studies with the largest sample, in which 83 children completed the study; withdrawals were due to changes in protocol that meant a second lumbar puncture or aspiration was not necessary.

6.4.2 Hypnosis

It is a procedure in which the person is guided by therapists, starting with relaxation until achieving suggestion, which enables changes in a subjective experience (for example, alteration in the perceptions, emotions, thoughts, behaviour and feelings) (Landier & Tse, 2010).

The following 6 stages must be included when considering hypnosis: preparation, induction, deepening, therapeutic suggestions, posthypnotic suggestions and termination. When only a part of them are used it is deemed imagery (Wild & Espie, 2004), or when there is no intense imaginative immersion that places the child "outside".

Self-hypnosis can be taught, in order to achieve self-control over symptoms, including pain. The main difficulty in its application is that it requires specialist training (WHO, 1998).

Seven studies were included in the systematic review carried out for the drafting of this guide. Two modes of hypnosis were compared (direct versus indirect) in only one study (Hawkins et al., 1998); in the rest, hypnosis was compared with cognitive-behavioural interventions, without using topical anaesthetics (Wall & Womack, 1989; Zeltzer & LeBaron, 1982) or using them (Liossi et al., 2006; Liossi et al., 2009; Liossi & Hatira 1999), and in one study, different modes of hypnosis were compared with different non-hypnotic interventions (CBI, support interventions) (Liossi & Hatira, 2003).

Furthermore, a systematic review was included (Wild & Espie, 2004).

Overall, the effectiveness of hypnosis was not clearly demonstrated, probably due to the heterogeneity of the studies as regards the modes of intervention studied and the interventions with which it was compared, as regards application times of the intervention, the intervention itself and the measurement of pain. The results from high quality RCT have shown the effectiveness of hypnosis in reducing pain due to procedures (all from the same author). Notwithstanding,

studies must be carried out with control groups without hypnosis, to be able to establish the efficacy per se of hypnosis vis-à-vis pain.

Direct/ indirect hypnosis

Hawkins et al., (1998) carried out a RCT in 30 children aged between 6 to 16 years, which compared direct hypnosis (direct suggestion, which uses the procedure and anaesthesia as elements) with indirect hypnosis (indirect suggestion, which uses pleasant subjects such as holidays or food as elements) with 15 children in each group, applied between two lumbar punctures. None received anxiolytics or oral analgesia during the puncture (by medical decision). Pain was measured on the Whaley & Wong faces scale (6-point assessment).

No difference was observed in the reduction of pain between the types of suggestion (F=0.05; p=0.83), but the mean did reduced in the pain score in both groups, with direct suggestion (4.5; SD:0.74 vs 2.13; SD:1.3) and indirect suggestion (4.46; SD:0.74 vs 2; SD:1.25), (F=102.8; p <0.001).

Susceptibility to being hypnotised has a significant influence on the magnitude of the effect (p<0.01).

Direct hypnosis/ indirect hypnosis/ distraction/ information and support

In one RCT, of 4 groups, (Liossi & Hatira, 2003) two modes of hypnosis were studied (direct and indirect) compared with CBI (distraction) and with usual intervention (information and support), which was applied in the four groups. Eighty children aged between 6 and 16 years participated, who required at least 15 lumbar punctures. Usual treatment was applied during the first six punctures; pain was assessed in the following three with the FACES scale and then interventions were applied according to the assigned group. It began by establishing a therapeutic relationship and then each technique was shown.

Hypnosis was developed in the same way as in the study by Hawkins et al., (1998), starting with an induction adapted to each child and ending with post-hypnotic suggestion and the direct and indirect suggestion also followed the same elements (analgesic suggestion or suggestion with pleasant elements). The CBI group used distractions with games, television, conversations, etc.

Interventions were applied during two punctures; afterwards the interventions were reinforced to enable self-intervention of the child, teaching self-hypnosis to the child in the case of the two types of hypnosis, and a meeting with the therapist in the case of the CBI. Afterwards, pain was assessed again in three more punctures, alternately during which the child used self-intervention.

The level of pain was compared with the baseline measurement, the post-intervention measurements and the measurement after self-intervention. In all the groups, the baseline measurement of pain had an average score of 4.6 (SD:0.6). The two modes of hypnosis had similar results, with significant reduction of the mean pain score in the intervention phase and in that of self-intervention versus the baseline measurement (baseline 4.6; SD:0.7; intervention 2.0 SD:1.32; self-hypnosis 2.9; SD:1) ($p<0.001$), whilst the CBI and usual intervention showed no long-term difference from the different measurements. No differences were found between the two types of hypnosis, but between them and the control group ($p<0.001$). It is necessary to outline that the effect of hypnosis on pain reduced in the self-intervention phase, and in the last puncture differences were not maintained between hypnosis, CBI and control group.

Hypnosis/ CBI, without topical anaesthetics

Two RCT studied the effectiveness of hypnosis compared to cognitive interventions in pain relief in punctures or bone marrow aspirations. Pain was reduced significantly in both studies between the baseline procedure and the procedure after the intervention, both with hypnosis and with the cognitive interventions, but there were no differences in effectiveness between either method.

Wall & Womack (1989) studied the effectiveness of hypnosis versus CBI (the child chose between distraction, imagery or relaxation) between two lumbar punctures or bone marrow aspirations. A RCT was carried out on 42 children stratified by age (from 5-11 years and 12-18 years). Both interventions were explained in two sessions, and a recording and headsets were used during the procedure which recorded the instructions on how to follow the technique during the procedure and that enabled the observers to be blinded. Pain was assessed with the VAS (0-20) in the group of younger children and with the McGill Pain Questionnaire (MPQ) in the group of older children; external observers also used the VAS. Data are presented on the reduction of pain of both groups jointly versus the baseline measurement, assessed by children (reduction points: 11.80 vs 7.00; $p<0.03$) and by the observers (reduction points: 8.95 vs 5.70; $p<0.09$). The authors cite that

they found no differences in pain relief between the groups; 75% the children stated that they would like to use the same technique again. Out of 42 children who started the study, 20 completed it, due to changes in treatment protocol that reduced the need for procedures.

In the RCT of Zeltzer & LeBaron (1982) hypnosis was designed according to the individual characteristics of the child (age 6-17 years), the parents and the environment; cognitive-behavioral intervention involved a combination of deep breathing distraction and practical sessions to help control fear and prohibited the use of images or fantasy as distraction techniques. Pain was measured with a non standardised scale from 1 to 5 (1=no pain; 5=maximum pain), without contributing validation data. The comparison was made of each group compared with itself. Hypnosis significantly reduced the average pain score, both in bone marrow aspiration (4.42 vs 2.92; $p<0.001$) and in lumbar puncture (3.89 vs 2.18; $p <0.001$); the cognitive therapy significantly reduced the mean pain score in bone marrow aspiration (4.59 vs 3.93; $p<0.01$), but not in lumbar puncture (3.47 vs 3.18; $p>0.05$). A subsequent analysis found that hypnosis was more effective than non-hypnotic techniques ($p<0.001$). No differences were found in the reduction of pain by age group (6-11 years; >12 years). At the start of the study, the groups were equivalent; however, this study relied on a small sample (33 children) 9 of whom (26%) did not complete the three punctures or aspirations due to death or changes in protocol (without providing further information). The hypnosis used did not include the induction stage wherefore it could be deemed as imagery.

Hypnosis/ CBI/ topical anaesthetics

Three RCT were included with 3 groups, hypnosis versus CBI and versus topical anaesthetics. The painful procedure was different for each study. The three studies showed the effectiveness of hypnosis versus the use of topical anaesthetics; the effectiveness of the CBI versus the use of topical anaesthetics was inconsistent, probably related to the type and mode of administration of the CBI. Likewise, the superiority of hypnosis over CBI was inconsistent, probably related with the type of CBI and the time of application of hypnosis, as well as the type of painful procedure.

In 2009 Liossi et al. carried out a RCT with 45 children aged between 7 and 16 years, divided into three groups, who had to undergo at least 3 venipunctures over a 9-month period. The use of hypnosis was compared with distraction and usual treatment (EMLA® 60 minutes beforehand), the latter was applied in

all the groups. The hypnosis technique was taught individually so that it was self-applied; included induction adapted to the child, analgesic suggestion and post-hypnotic suggestion, a process that the child carried out during the procedure. The children were also taught the distraction technique, using the same time as in hypnosis and involved establishing a good relationship between the therapist and the child and discussing non-medical activities, mainly extracurricular. In the three groups, the parents were asked to take the hand of the children and encourage them. The pain was assessed with the VAS (0-10) during 3 venipunctures after learning each technique.

The lowest level of pain was observed in the three groups in the first venipuncture compared to the following two ($p<0.001$). Hypnosis proved to be effective versus the control group both in the first measurement (mean pain score: 2.74; SD:0.83 vs 4.79; SD:0.69) ($p<0.005$) and in the second (2.89; SD:0.79 vs 5.09; SD:0.84) ($p<0.001$) and in the third (2.89; SD:0.77 vs 5.09; SD:0.84) ($p<0.001$).

The mean pain score was less with distraction than with application of EMLA®, although this difference was only significant in the first measurement (4.17; SD:0.44 vs 4.79; SD:0.69) ($p<0.005$).

The same authors (Liossi et al., 2006) had carried out a similar RCT which studied children (45 children aged between 6 and 16 years) during 12 lumbar punctures. Usual treatment was applied only during the first six (EMLA® 60 minutes beforehand, together with information and support); then hypnosis was applied to a group together with the usual treatment, distraction was applied to another group (to establish a good relationship between the therapist and the child and talk about non-medical activities, mainly extracurricular) together with the usal treatment and the third group received only usual treatment. After another lumbar puncture in the hypnosis group, they were taught self-hypnosis and the same intervention continued in the CBI group. Pain was assessed with the FACES scale, at 4 times, in the lumbar puncture prior to the start of the study interventions, in the intermediate puncture and in another two subsequent punctures.

In the hypnosis group, the mean pain score reduced from 4.60 (SD:0.74) in the baseline measurement to 0.93 (SD:0.59) and 1.07 (SD:0.70) in the last two punctures. In the distraction group, the mean pain score reduced from 4.60 (SD:0.74) in the baseline measurement to 2.33 (SD:0.98) and 2.13 (SD:0.99) in the last two punctures. In the usual treatment group, the main pain score reduced from 4.40 (SD:0.74) in the baseline measurement to 2.27 (SD:0.59) and 2.20 (SD:0.56) in the last two punctures. Hypnosis reduced pain significantly

compared with distraction and the use of EMLA® and information and support ($p<0.001$) in the four measurements carried out; on the contrary, distraction was not effective versus habitual treatment in any of the measurements ($p=0.82$). Hypnosis was more effective in all the measurements when comparing hypnosis with distraction, ($p<0.001$).

In 1999, Liossi & Hatira carried out a RCT with 30 children aged between 5 and 15 years, using hypnosis or teaching coping skills; a third group received only an injection of lidocaine, which was also applied in the hypnosis group and in that of coping skills. The children underwent two bone marrow aspirations; the interventions were applied between the two aspirations, 5 days before the second. Hypnosis was induced by relaxation (progressive muscular relaxation and autogenic relaxation) and visual image (preferred place, favourite activity, television programme, etc.); later, an analgesic suggestion was offered; the session ended with a post-hypnotic suggestion that would be repeated in the treatment room in order to provide a feeling of comfort during the bone marrow aspiration. The cognitive-behavioural intervention involved relaxation, breathing exercises and cognitive restructuring. The children from the three groups were accompanied by their parents.

The children assessed their pain with the Whaley & Wong faces scale (6-point assessment). The median of pain in bone marrow aspiration prior to interventions was 4 in the three groups; the medians of pain after interventions were 2, 3 and 4 with hypnosis, CBI and lidocaine, respectively. The pain difference between the two aspirations was significant with hypnosis ($p=0.005$) and with the CBI ($p=0.008$). When comparing the interventions with the group that used only lidocaine, the differences in the reduction of pain were significant in favour of hypnosis ($p<0.001$) and also in favour of the CBI ($p<0.001$). The differences in the reduction of pain between hypnosis and CBI were not significant ($p=0.2$). The authors considered that hypnosis had a greater effect if induction was carried out during the procedures, but was not carried out to keep the observers blind. Although the study had good methodological development, it is necessary to take into account that its sample was small, although there were no withdrawals.

In 2004 Wild & Espie carried out a systematic review on the use of any mode of hypnosis compared with any intervention. In one of the studies, the procedure was venipuncture, the rest were lumbar punctures or bone marrow aspirations. It included 9 studies, all prior to 1999, carried out with children aged between 3-18 years. The studies were included when they were at low risk of bias, although some were quasi-experimental of a single group. These authors indicated that the

results are not conclusive and that the studies of higher quality show inconsistent results.

As in the systematic review carried out for this guide, Miaskowski et al., (2004), in their pain management guideline for patients with cancer of any age, concluded that hypnosis is the non-pharmacological intervention that has the greatest effect on reducing pain, although it does not eliminate pain completely and must be considered a procedure to be used together with pharmacological treatment. According to the cited authors, the effect of hypnosis does not depend on the subjective expectations of the patient, as occurs with placebos and is not related simply with diverting attention away from pain, but that physiological changes occur during hypnosis that modify the response to pain. Although there is controversy, numerous studies suggest that the effect of hypnosis is conditioned in part by the hypnotic susceptibility of each subject, wherefore it must be an aspect to consider in the studies carried out.

Different authors suggest that the interpretation of studies with hypnosis must be carried out taking into account that they mainly use very small samples, on many occasions the hypnotic susceptibility of the children is not considered and the pain measurement instruments used are not validated (Canbulat & Kurt, 2012; Miaskowski et al., 2004; SIGN, 2008).

6.4.3 Support strategies

Information

In 1993 Mansson et al., carried out a RCT with three groups in 30 children aged between 4 and 17 years who had to undergo a lumbar puncture. The intervention comprised information and preparation through the demonstration of the procedure using a doll and a book with photographs of the procedure. In the first group, it was applied once before the first lumbar puncture; in the second group it was applied 3 times, before each of the 3 lumbar punctures. The group with habitual treatment was given EMLA® and benzodiazepines, which were also given to the other two groups. The pain was measured using a VAS (0-10) by children and parents, comparing the values in the three punctures carried out. The intervention of information, applied both once and three times, reduced the pain, especially in the second puncture, but the differences were not significant. Neither were the differences in the reduction of pain between the control group and in the two groups who received the intervention. A secondary analysis was

carried out according to age and sex of the children and it was found that those aged over 8 years referred to slightly less pain than those under 8 years, and girls cited slightly more pain in the third puncture than boys. The parents rated the pain lower when it concerned children aged over 8 years than when they were aged under 8 years ($p<0.05$) and lower in all the assessments when compared with the self-rate of the children.

This study does not provide detailed information per group. It is necessary to take into account that the sample was small, randomisation was only carried out to receive one of the two modes of intervention, but the children included in the control group were not assigned at random, and neither the groups, nor their clinical status nor their previous experiences in lumbar punctures were equivalent.

Other authors inform of the mild effect of support therapies and informative strategies in pain relief (Miaskowski et al., 2004), as well as physical contact (taking the child's hand) (Weekes et al., 1993). However, they are well received by children and parents and can provide comfort, as the information for children on the disease and treatment of pain facilitates communication with the professionals.

6.4.4 Physical interventions

Massage

A single cross-over RCT was included in the review (Post-White et al., 2009), with 25 children aged between 1 and 18 years, in which the effectiveness of massage was studied to reduce pain, between 3 chemotherapy sessions. It was randomized who received a massage between the first two chemotherapy sessions and who received a massage between the last two.

The massage was given 4 times a week, firstly to the accompanying parent and then to the child, alternating gentle and energetic, using lotion and conversing during the massage. Whilst one group received a massage, the other remained in a hospital room with a "do not disturb" notice with videos, stories or chatting. The pain was assessed with the VAS (0-10) in children aged from 9 to 18 years and the Wong-Baker faces scale in children aged from 3-8 years. Parents assessed with the Pain Assessment Tool in children aged between 1 and 2 years. No significant differences were found in pain between the massage and those who remained quiet in a room ($Z= -16$; $p=0.11$), although the comparison of each subject with

themselves was only carried, without comparing between both interventions. It is necessary to take into account that 17 children completed the study (30% withdrawals) and that pain before each of the interventions with massage was less than 2. Pain data are not presented according to groups and comparisons.

Some authors cited the benefits of massage as a complement to relaxation, whereby it reduces pain, reduces tiredness (Soden et al., 2004) and favors sleep (Fellowes et al., 2004; Forchuk et al., 2004). The benefits of massage appear to be due fundamentally to a feeling of well-being (SIGN, 2008).

No studies were found that used other techniques (TENS, Reiki, etc.) carried out specifically in children with cancer to relieve pain from the procedures. As regards the use of cold / hot in children, it must be applied with care due to risk of causing injury (WHO, 1998).

6.4.5 Topical anaesthetics

Five articles were included that assessed the effectiveness of the use of local anaesthetics. One (Kapelushnik et al. 1990) included two studies. Of the 5 articles, in one the effectiveness of Amethocaine versus EMLA® was studied (Bishai et al., 1999), and the others (Calamandrei et al., 1996; Kapelushnik et al., 1990; Lüllmann et al., 2010; Miser et al., 1994) studied the effectiveness of EMLA® in different modes. They were applied during lumbar puncture in three studies and during venipunture in two studies.

Amethocaine did not prove to be effective versus EMLA®, with the latter being effective versus placebo, as well as application 60 minutes before the invasive procedure versus application 40 minutes beforehand. No differences were found as regards forms of administration, cream or patch. The appearance of adverse effects was observed (whitening of skin, erythema and toxicity), in spite of which the children would use EMLA® in the next procedure.

Amethocaine/EMLA®

Bishai et al., (1999) carried out a cross-over RCT with 39 children aged over 5 years who underwent central venous access (Port-a Cath®). In the first step, a placebo was applied to one group 60 minutes before the procedure and after 30 minutes Amethocaine gel, 1 g was applied. EMLA® cream 1 g was applied to the control group, 60 minutes before the procedure, lifting the occlusive patch

after 30 minutes and placing it again to match the procedure of the first group. After assessing the pain, the interventions were crossed over between the groups and assessed again in the following procedure. The children used a 6-face scale and the parents and nurses used the VAS. When comparing Amethocaine with EMLA®, the mean pain score was less with EMLA® but the differences were not significant according to the assessment of the children (2; SD:1.4 vs 1.5; SD:1.5) (p=0.09), or according to the parents (2.6; SD:2.4 vs 2.2; SD:2.0) (p=0.54), or according to nurses (2; SD:1.9 vs 1.9; SD:2.1) (p=0.78).

Adverse effects were found in 19 children who received Amethocaine versus 3 children with EMLA® (p<0.001), in transitory erythema form (clinically insignificant). Paleness of the skin was observed in the area with Amethocaine in 5 children versus 24 children with EMLA® (p<0.001).

EMLA® cream/ EMLA® patch

Calamandrei et al., (1996) carried out a cross-over RCT with 24 children aged between 3-16 years. After three lumbar punctures EMLA® cream 1 g was applied with Tegaderm® dressing, or EMLA® patch. The surface area of application was 10 cm^2 in both and was carried out between 60 and 120 minutes before the procedure. After assessing the pain, the intervention was crossed-over before the following lumbar puncture. The children assessed the pain with the VAS (0-100) or with the FACES scale if aged under 7 years. Comparing between interventions (cream versus patch) no differences were found; with the FACES scale the pain median was 1 (range 0-3) vs 0 (range 0-3); with the VAS the mean was 28 (SD:18) vs 29 (SD:17).

EMLA®/with or without placebo

Kapelushnik et al. (1990) reports two studies in the same article.

The first is a cross-over RCT with 18 children aged between 5-15 years. One group was applied with EMLA® cream, 2 ml at 5% covered with Tegaderm® dressing, between 45 minutes and 1 hour before a first lumbar puncture, nothing was applied to the other group. After assessing the pain, the intervention was crossed-over before the following lumbar puncture.

The pain was self-rated by the children and parents and nurses, using a VAS (0-5). Sixteen children indicated more pain relief with EMLA® (mean pain

score: 1.66; SD:0.83 vs 2.55; SD:0.6) (p<0.001); the same assessment was carried out by the parents (1.7; SD:0.9 vs 2.4; SD:0.7) (p<0.005) and the nurses (1.6; SD:0.8 vs 2.4; SD:0.5) (p<0.005). Although the pain relief with EMLA® was less than one point (over 5), the differences in the three assessments were significant.

The second study is a double-blind, placebo-controlled crossover RCT, with 10 children aged 4 and a half to 11 years. Equally, the procedure involved lumbar punctures. EMLA® cream (in the same way as the first study) or placebo were applied. The children measured the pain in the same way (VAS and FACES scale) and also the nurses (faces scale). According to both assessments, the use of EMLA® is effective in pain relief compared with placebo. According to the children, the mean pain score with the VAS was 3.1 (SD:1) vs 2 (SD:1.4) (p=0.05), and with the FACES scale 3.8 (SD:1.2) vs 2.9 (SD:1.7) (p=0.07). According to the nurses the level of pain was 3.7 (SD:1.8) vs 2.7 (SD:1.1) (p<0.05).

Miser et al., (1994) carried out a double-blind, crossover RCT with 52 children aged between 3-21 years. They compared the use of EMLA® cream (2.5 g. for children aged between 3-12 years and 5 g. for the older children) covered with Tegaderm®, 60 minutes before access to a central venous access (Port-a Cath®) versus the use of a placebo; after the first procedure, the intervention was crossed over. The children assessed the pain using a VAS and with the Cartoon Face Scale; the assessment was also carried out by an external observer using the same scales. The use of EMLA® was effective versus the placebo in all the comparisons made (p<0.002).

Adverse effects were reported by parents and professionals 24 hours after the procedure. Forty-five children suffered some type of toxicity, 5 of them on skin (4 with EMLA® cream and 1 with placebo). After 24 hours, 1 child showed mild irritation on the skin. In spite of this, 85% of children would choose EMLA® for the next procedure.

It is important to consider that 5 children failed to finish the study (9.5% withdrawals).

EMLA® 40 minutes/EMLA® 60 minutes

Lüllmann et al., (2010) carried out a crossover RCT with 87 children aged between 2-18 years. The application of EMLA® patch 5 g was compared 40 minutes before central venous access (Port-a-Cath®) versus the same application 60 minutes

before the procedure. After the assessment, the interventions were crossed over before the following procedure. The children assessed pain with the VAS (0-10) and the Bieri faces scale. During the procedure, the accompanying person or the nurse measured it with the VAS. The results were compared between the groups according to the application times.

With the VAS, the children found a difference of almost two points in favour of application 60 minutes beforehand (mean pain score in the group 40 minutes vs 60 minutes: 3.6 vs 1.8; group 60 minutes vs 40 minutes: 1.7 vs 3.4) ($p<0.001$); with the Bieri scale in both groups and at the different times, the pain median was 3 (range 1-6) ($p=0.06$). Both the accompanying persons and the nurses found more pain relief when using EMLA® 60 minutes before the procedure, although the differences were not significant.

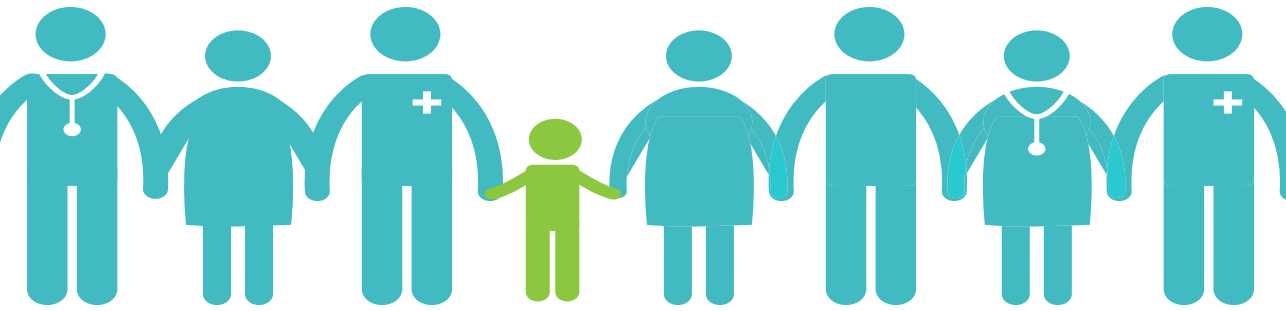
Adverse effects were observed in 9 children (mainly paleness of the skin), without reporting its relation with the application time of the topical anaesthetic. Seventy-seven out of 85 children stated that they preferred EMLA® for the following puncture; 2 did not prefer it.

Some studies on the effectiveness of Amethocaine versus EMLA® in venipunctures in children with any pathology find effectiveness in favour of Amethocaine (Macintyre et al., 2010).

Secondary results

Other results studied in the manuscripts included were anxiety, behavioural stress, fear and physiological variables. No study considered the health status, functional deterioration, quality of life or other aspects established in the research protocol established for drafting the guideline.

7. Pharmacological treatment of pain in children with cancer



7.1 Objective

This section of the guideline aims to help healthcare professionals and carers of children with cancer to:

- Know the most effective and safest pharmacological therapies for the treatment of pain in children with cancer.

7.2 Target population

Children from birth to 18 years, diagnosed with any type of cancer, still under follow-up for cancer, who have pain.

7.3 Recommendations for pharmacological treatment of pain

1. A systematic approach must be developed for pain management in cancer, to teach children and carers, within the treatment plan, how to use effective strategies to attain optimum control of pain and encourage active participation. (LE: 2, 3. GR: B).
2. Prescribe the treatment plan with the simplest type and regimen of administration and the least invasive method possible. (LE: 4. GR: C).
3. A comprehensive assessment of pain must be carried out and the treatment plan modified when a change or a new painful episode occurs, focusing on optimum relief throughout the disease. (LE: 3. GR: B).
4. The WHO principles on pharmacological treatment of pain must be followed:
   4.1. By the ladder, starting on the step adapted to the intensity of pain reported by the child. (LE: 2, 3. GR: B).
   4.2. By the clock, with additional rescue doses as required for breakthrough pain. (LE: 3, 4. GR: C).
   4.3. By the appropriate route. (LE: 3, 4. GR: C).
   4.4. By the child. An individual treatment regime must be following according to the characteristics of the child and their pain, until reaching maximum analgesia and minimum side effects. (LE: 3, 4. GR: C).
5. Management of pain on any step of the WHO's pain ladder includes acetaminophen and/or NSAIDs, except if contraindicated. (LE: 3, 4. GR: C).
6. An opioid must be used if pain persists or increases. (LE: 2, 3. GR: B).
7. The dose must be increased or stronger opioids used if pain persists or is moderate / intense. (LE: 1. GR: A).

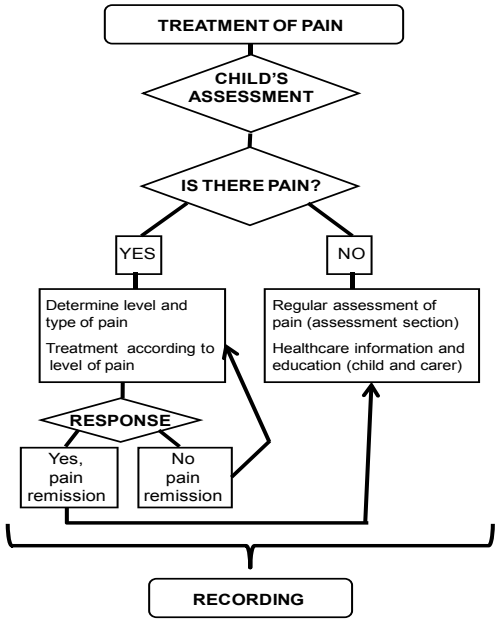
8. Morphine is the treatment of choice in cases of intense pain. (LE: 3, 4. GR: C).
9. Placebos must not be used in the management of pain in cancer. (LE: 4. GR: C).
10. The use of tramadol, methadone, meperidine and acetylsalicylic acid is not recommended in cancer patients aged under 18 years. (LE: 3. GR: B).
11. The use of codeine in those aged under 12 years is not recommended due to the greater risk of serious adverse effects. (LE: 2, 3. GR: B)
12. Tricyclic antidepressants or anticonvulsants drugs are used for neuropathic pain as adjuvants to treatment. (LE: 3, 4. GR: C).
13. Corticosteroids are associated for pain caused by spinal cord compression or intracranial pressure, as adjuvant to treatment. (LE: 4. GR: C).
14. Opioids must be administered according to a regular schedule, with additional rescue doses as required for breakthrough pain. (LE: 3. GR: C).
15. The oral route must be used first, as it is the most widely accepted by children. Other routes must be used when it is not possible to administer oral treatment, according to the situation of the child and drugs, and must be the least invasive possible. (LE: 4. GR: C).
16. Rectal administration is contraindicated in children with cancer due to risk of lesion in the rectum or anus or risk of infection. (LE: 4. GR: C).
17. Intramuscular route is not recommended as it is less effective than intravenous administration and it can be painful and is poorly received in children. (LE: 3. GR: C).
18. The opioid doses must be adjusted to achieve pain relief with an acceptable level of adverse effects. (LE: 1, 2. GR: A).
19. The adverse effects of opioids must be monitored (LE: 2, 3. GR: B) and treated prophylactically. (LE: 2, 3. GR: C).
20. Prophylactic treatment for constipation must be started in conjunction with the start of opioid treatment. (LE: 2, 3. GR: B).
21. Naloxone is prescribed to reverse opioid-induced respiratory depression and its dose must be adjusted to improve respiratory function without reversing analgesia. (LE: 2, 3. GR: B).
22. Myths and incorrect beliefs on pain and its management with children must be dispelled, indicating to children and their carers that pain can be alleviated. (LE: 2, 3. GR: B).
23. The use of non-pharmacological treatment strategies must form part of a comprehensive approach in pain management without replacing analgesics. (LE: 2, 3. GR: B).
24. When the child is to be transferred, the corresponding information on pain management must be transferred. (LE: 2, 3. GR: B).

25. Children and their carers must be provided with accurate and comprehensive information on effective pain management in cancer, the use of analgesics, other methods to control pain and how to convey it to clinicians in the event of pain that is not alleviated. (LE: 1, 2. GR: A).

7.4 Pharmacological treatment

To establish treatment for pain, firstly the presence or absence of pain must be assessed and its characteristics (see section 4), according to the following algorithm (fig 4).

Figure 4. Flow chart on the pharmacological treatment of pain



In preparation of this section and during the search for evidence 8 CPG of varying quality were selected (AHCPR, 1994; Hockenberry-Eaton et al., 1999; HUVH, 2009; Macintyre et al., 2010; Miaskowski et al., 2004; MOH, 2003; WHO, 1998; SIGN, 2008) and 1 systematic review (Zernikow et al., 2007) (Appendix 2). Other documents drafted by groups of experts were also consulted (AMA, 2013; BPS, 2010; Sickkids, 2010; AFSSAPS, 2009).

7.4.1 WHO Principles of pain management

By the 1980s, the WHO had already established a framework for the general pain management which has been used as a reference by numerous organisations (fig 5). In 1998, it confirmed the principles of pain management, specifically in children with cancer (WHO, 1998).

Following this framework, four general treatment guidelines of pain in children with cancer are defined:

- Pain must be managed "by the ladder", starting on the suitable step according to the intensity of pain (MOH, 2003; WHO, 1998).

  Various steps in the treatment of pain (fig 5) are considered; in each of them guidance is given on the type of drugs to use, according to the level of pain reported by the child (WHO, 1998).

- "By the clock", with additional rescue doses as required for breakthrough pain.

  The administration of analgesics on a regular schedule enables therapeutic levels of the drugs to be reached and maintained and provides continued pain relief; equally they facilitate the development of tolerance to side effects. On the contrary, the administration of analgesia on a as-required basis has not been proven to be effective; it provides periods of pain relief, generally brief, followed by potentially long periods of pain and increased side effects.

  To treat intermittent or breackthrough pain, analgesia on a as-required basis is used to provide additional doses to analgesic treatment established, (WHO, 1998). Any tratment regimen must consider the use of rescue treatment (Miaskowski et al., 2004; MOH, 2003).

- "By the appropriate route".

  The least invasive route of administration must be considered that enables reaching suitable levels of analgesia taking into account the limitations of each alternative (see section 7.4.2.4). It is necessary to consider age and degree of cooperation, as any traumatic procedures can influence the underreporting of pain by children and parents (WHO, 1998).

The oral route is the most widely-accepted by children (SIGN, 2008; Zernikow et al., 2009). Continuous infusion of opioids by intravenous or subcutaneous routes is equally effective (Nelson et al., 1997).

Intramuscular route (i.m.) is deemed unsuitable, as it is less effective than intravenous route (i.v.), given the variability in absorption (AHCPR, 1994; Miaskowski et al., 2004); it is also a poorly accepted route by children (Miaskowski et al., 2004; MOH, 2003).

The rectal route is contraindicated in children with cancer due to risk of lesion in the rectum or anus or risk of infection. Furthermore, it is not well accepted by children (Zernikow et al., 2009) and its absorption is highly variable (Miaskowski et al., 2004).

- "By the child", according to the characteristics of the child and pain, until reaching maximum analgesia and minimum adverse effects.

  The objective is effective management of medication (AMA, 2013) to keep the child pain-free and provide a level of analgesia that enables the absence of pain between doses (Bonica, 1990; WHO, 1988). The analgesic regime must be the simplest possible, starting from the type and level of pain, and assessing the previous responses to analgesia. The characteristics of each child must be taken into account (age, physical cognitive and psychological development) (BPS, 2010) and their family background, considering their needs, beliefs and those aspects that can pose an obstacle for treatment. In case of administration of opioids, it must be considered whether opioids have been supplied previously and the route of administration (HUVH, 2009; Miaskowski et al., 2004).

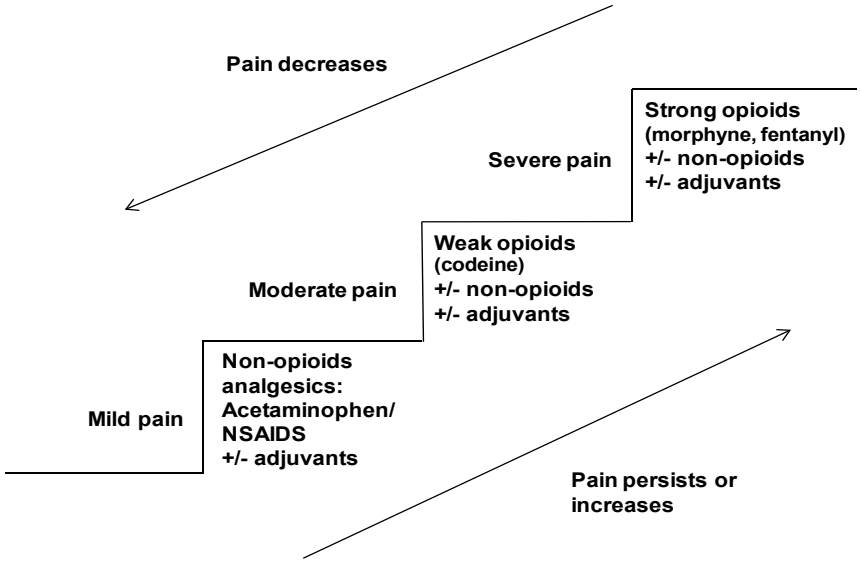
Pain management according to the WHO principles (appropriate analgesic, appropriate route, individualised, on a regular schedule) has shown effectiveness in pain relief. A retrospective study estimates a reduction in pain that reaches one third of initial pain in 71% of patients (Ventafridda et. al., 1987).

A 10-year longitudinal study on 2,118 patients found that 76% of the patients achieved "good" pain relief when treated according to the WHO principles (Zech et al., 1995). Overall, it is deemed to be effective in 45-100% of patients (Ferreira et al., 2006).

The use of placebos in pain management is not accepted (AHCPR, 1994; Miaskowski et al., 2004; McNicol et al., 2006).

Participation of the child and their carer in the care and shared decisions appear to improve the health results (Donovan et al., 1999; Gordon et al., 2005; de Wi et al., 1997).

Figure 5. General approach for treatment of pain in children with cancer (based on WHO ladder)



7.4.2 Administration of drugs

According to the WHO approah (1998), step 1 corresponds to mild pain, which can be treated with non-opioid analgesics; step 2 corresponds with moderate pain, which can be treated with minor opioids, combined with non-opioid analgesics if necessary; step 3 corresponds with intense pain, which must be treated with strong opioids, combined with non-opioid analgesics if necessary.

7.4.2.1 Non-opioid analgesics

There is not conclusive evidence on the effectiveness of non-opioid analgesics in children with cancer (Macintyre et al., 2010; McNicol, et al., 2006; Miaskowski et al., 2004). These analgesics have shown effectiveness for mild pain and a reduction in the need for opioids in children with other pathologies (SIGN, 2008).

The addition of non-opioid analgesics to an established regimen with opioids can reduce their requirement and therefore their adverse effects (Myers & Trotman, 1994; Sickkids, 2010).

Acetaminophen

It is a drug with a good safety profile and no relevant adverse effects (AMA, 2013). Useful in mild and moderate pain, it can be combined with opioids and has the ceiling effect (HUVH, 2009).

It does not cause erosive or ulcerous gastrointestinal lesions and has no platelet antiaggregant effect (HUVH, 2009). It can cause hepatotoxicity, when the maximum dose is surpassed or in prolonged treatments; therefore, the maximum daily dose must not be exceeded (<60 mg/kg/day) (AMA, 2013; HUVH, 2009), both if administered alone or combined with other drugs (Sickkids, 2010). In case of hepatotoxicity by overdose, N-acetylcysteine can be used as an antidote (oral or i.v.), in the 10 hours following overdose (HUVH, 2009).

The age and weight of the child must be taken into account together with the duration of treatment for calculation of the doses (Macintyre et al., 2010). Individual oral doses from 20 mg/kg/dose are less safe, therefore 10-15 mg/kg/dose are recommended.

If administered intravenously, it can be perfused for 15 minutes. (HUVH, 2009).

Before combining with opioids, it is worth ensuring that the correct dosage has been achieved (Sickkids, 2010).

Metamizole

Medication with good safety profile. It has no gastroduodenal toxicity. It has adverse effects such as hypersensitivity of skin, oliguria, anuria, proteinuria, interstitial nephritis and agranulocytosis; some adverse effects, such as hypotension or anaphylactic reaction, are more probable with i.v. administration. It is not recommended in new born or infants weighing under 5 kg. For its i.v. administration it is recommended to dilute in physiological saline solution and perfuse in 15-30 minutes (HUVH, 2009).

NSAIDs

Similar pharmacodynamics and pharmacokinetics to those of adults (Berde & Sethna, 2002). They have a ceiling effect (Sickkids, 2010). They have antiaggregant effect and can cause gastrointestinal lesions and renal toxicity (AMA, 2013). In children with cancer, they must be used with care because thrombocytopenia and renal failure, which increase the risk of digestive bleeding and intoxication, are frequent.

- *Ibuprofen*

For mild or moderate pain (AMA, 2013). It has reversible antiaggregant effect, wherefore it is not recommended in case of thrombocytopenia. It can cause acute renal failure, especially in cases of dehydration; also bronchospasm, urticaria, angioedema or hypotension (HUVH, 2009). Short-term oral use does not increase the gastrointestinal or renal side effects, compared with acetaminophen (Anderson, 2004; Lesko & Mitchell, 1999; Southey et al., 2009).

Use via i.v. there is insufficient evidence on its effects (HUVH, 2009).

- *Naproxen*

It is safety in children aged under 2 years has not been established. The evidence comes from studies in children with pathologies different than cancer (AMA, 2013).

According to the technical data sheet of the Spanish Agency of Medicines and Medical Products: "it must not be used in children, unless otherwise recommended by your doctor".

- *Ketorolac*

Administered intravenously, it is used alone or as coadjuvant of opioids (AMA, 2013; Sickkids, 2010) and its use is not recommended during more than 48 hours. Evidence on ketorolac comes from non-updated studies, on post-operative pain in children (Houck et. al., 1996; Vetter & Heiner, 1994). It has numerous adverse effects. Its use is not recommended.

7.4.2.2 Opioid analgesics

Opioids can be administered safely in children and provide excellent analgesia for nociceptive pain (AMA, 2013; Miaskowski et al., 2004, WHO, 1998; Sickkids, 2010; Ventafridda et. al., 1987; Zech et al., 1995). They can be administered both orally and intravenously (Macintyre et al., 2010) or by patient-controlled analgesia systems (PCA), that can be managed by children aged from 6-7 years if training is provided (Berde et al., 1991) or controlled by parents or nurses (Schechter et al., 2003; Shapiro et al., 1991).

The dose must be adjusted according to the child's age, weight, pain intensity, health status and interactions with the treatment established, so that analgesia is achieved with the lowest dose and with minimum adverse effects. It is necessary to take into account the drug to use (duration of action, peak effect and half-life) and the route of administration, as well as the individual response (Macintyre et al., 2010; Sickkids, 2010). Titration must be carried out with caution and on an individual basis, taking into account all these factors and under strict monitoring.

Potent μ-opioid receptor agonists (morphine, oxycodone, fentanyl) have no ceiling effect, however, the adverse effects are often the factor that limits the dose (Sickkids, 2010). When the opioid used fails to alleviate pain sufficiently or the adverse effects limit the increased dosage, the opioids are rotated, always within the framework of a multimodal therapy (HUVH, 2009).

When the need for analgesia is stable, sustained-release opioids are more suitable; in this case inmediate-release doses must be planned and available in case of exacerbation of pain (Sickkids, 2010).

When pain originates from bones or is neuropathic, weak opioids are usually of little use (BPS, 2010; Zernikow et al., 2009).

Hypersensitivity reactions to opioids are rare (Miaskowski et al., 2004). Use of opioids at high doses and for prolonged periods can cause cognitive alterations, tolerance and hyperalgesia (Ballantyne & LaForge, 2007).

Weak opioids

- *Codeine*

A weak μ-opioid receptor agonist with a ceiling effect (Chary et al., 1994; Quiding et al., 1982). It is widely used in children (AMA, 2013). Its efficacy and appearance of adverse effects vary considerably (Macintyre et al., 2010).

It is a relatively weak opioid and causes more adverse effects than other opioids, at equivalent doses. When the standard dosing fails to show an analgesic effect or adverse effects appear, it is necessary to consider its replacement for a stronger opioid (AMA, 2013; HUVH, 2009).

The benefit of using high doses of codeine versus low doses of morphine is not established, or of using codeine over other opioids (Grond et al., 1999; McNicol et al., 2006; Mercadante & Bruera, 2006; Mystakidou et al., 2004; Vielvoye-Kerkmeer et al., 2000; Zernikow et al., 2009).

The most common adverse effect is constipation and it can also cause sedation, nausea and vomiting. At high doses it is associated with the risk of respiratory depression.

Even though there are no conclusive results on the improvement of pain when adding non-opioid analgesics to a treatment already established with opioids (AMA, 2013; Zernikow et al., 2006), its use is very common in combination with acetaminophen (AMA, 2013).

Recently the Spanish Agency of Medicines and Medical Products (AEMPS) published a pharmacological warning regarding the restricted use of codeine as an analgesic in paediatrics (AEMPS, 2013). Said warning indicates the children aged under 12 years are at a greater risk of suffering serious adverse reactions after administration of codeine.

Strong Opioids

They are the treatment of choice for intense pain associated with cancer.

The pure μ-opioid receptor agonists (morphine, oxycodone, fentanyl) have no ceiling effect. Therefore, the dose must be adjusted to reach maximum pain relief (BPS, 2010; Miaskowski et al., 2004). There are no data that suggest that one is better than another, but morphine has been studied more in children (AMA, 2013; Siden & Nalewajek, 2003; Sirkiä et al., 1998; Zernikow et al., 2006). Given the individual variations in response to these drugs, if pain relief does not occur, substitution from one strong opioid to another must be considered, in order to provide more complete relief (AMA, 2013).

When there is oral intolerance, it must be administered intravenously (HUVH, 2009; Miaskowski et al., 2004). Intravenous administration peaks at 15 minutes, doses can be repeated more frequently and analgesia is reached more quickly (Miaskowski et al., 2004). There is insufficient evidence that supports the use in the first place of oral route (BPS, 2010).

Dose adjustment must take into account the general criteria indicated for the opioid analgesics. Furthermore, the level of pain must be considered together with the route of administration, whether the child has had opioid treatment previously or not and the effects of previous treatments and their side effects. When the dose is adjusted, sustained-release opioids can be used. Rescue doses must be planned in case of breackthrough pain (HUVH, 2009; Miaskowski et al., 2004; SIGN, 2008).

The pain must be reassessed periodically (see assessment).

They can cause constipation, nausea, sedation, pruritus, urinary retention and respiratory depression, which must be monitored.

It is important to assess whether pain intensity can lead to very aggressive treatments with opioids, which can result in respiratory depression (Gordon et al., 2005). It is necessary to carry out careful reassessment, not only on the type of pain, but its origin and take into account the possibility of using non-opioid analgesics and furthermore incorporating non-pharmacological interventions (SIGN, 2008).

- *Morphine*

It is a pure μ receptor agonist. It is the opioid of choice for moderate or intense pain, both orally and intravenously. (Hanks et al., 2001).

In moderate pain, the dose is usually adjusted with oral morphine (or another short half-life opioid) (HUVH, 2009; Miaskowski et al., 2004).

When oral administration is used in opioid-naive children, treatment is started with 0.15 mg/kg (<6 months of life), 0.3 mg/kg (≥6 months), and 5-10 mg (≥50 kg). In CPG consulted, there is a considerable divergence regarding the maximum amount per dose in children ≥50 kg, fluctuating between 10 and 30 mg.

If they have been treated previously with opioids, the daily dose can be increased. Response to treatment must be assessed and titration reached on an individual basis, either with monotherapy or with combined therapy, until the pain reduces more than 50% (or more than the threshold, which has been established as clinically relevant). The regimen with which said pain is reduced is that deemed effective and is that which shall be administered.

Rescue doses must be planned in case of brackthrough pain, 10-20% of the total of the morphine dose in 24 hours, every hour if necessary, based on the improved pain assessment (AHCPR, 1994; Hanks et al., 2001; HUVH, 2009; Macintyre et al., 2010; Miaskowski et al., 2004; Sickkids, 2010).

Constipation, nausea, confusion, sedation, pruritus, urinary retention and respiratory depression can occur, which must be strictly monitored, especially during titration.

In case of oral intolerance by the child, it must be administered intravenously and the i.v. dose must be 1/3 of the oral dose.

In cases of intense pain, it is used both orally and intravenously (HUVH, 2009; Miaskowski et al., 2004). The same regimen are followed orally as when the pain is moderate.

To adjust the dose intravenously, the treatment is started in opioid-naive children with a slow and diluted bolus of 0.05 mg/kg (<6 months of age), 0.1 mg/kg (≥6 months), 5-10 mg (≥50kg) (HUVH, 2009; Miaskowski et al., 2004). It is advised to dilute the dose in physiological saline solution and administer it slowly (5-15 minutes) (AMA, 2013; HUVH, 2009).

Pain is reassessed at 15 minutes and if necessary the bolus can be repeated. The doses for administration in infusion are 0.015-0.025 mg/kg (<6 months of age), 0.02-0.05 mg/kg (≥6 months), 0.03-0.05 mg/kg (≥50kg).

The response to treatment must be assessed and the dose adjusted individually, either with monotherapy or with combined therapy, until the pain reduces more than 50% (or more than the threshold that has been established as clinically relevant). The regimen with which said pain is reduced is that deemed effective and is that which shall be administered.

One quarter of this dose deemed effective can be administered every hour in continuous infusion, with rescue doses planned that can be administered every 15 minutes if necessary. Equally, the effective dose can be supplied every 4 hours, using rescue doses of 10-20% of the total dose of 24 hours every hour (Miaskowski et al., 2004).

Patient-controlled analgesia systems (PCA) or those controlled by the nurses or carers can be used, according to the child's age, which allows administration of small adjustment doses (Monitto et al., 2000). It is a system widely accepted by patients and can be used alone or combined with continuous infusion at low doses (AMA, 2013; Macintyre et al., 2010; Miaskowski et al., 2004).

Whether administered orally or intravenously, the aim is to reach at least a level of mild pain. When the child reaches this level of pain in a stable form, the inmediate-release opioid is replaced by one of sustained release, with the same total daily dose distributed every 8-10 hours, and always anticipating the rescue doses (HUVH, 2009; Miaskowski et al., 2004).

When the situation that causes pain changes or when pain is mild in maintained form, the need for maintaining the same doses must be assessed or a possible reduction considered (Sickkids, 2010). When in a 24-hour period, more than 3 rescue doses are required, it is necessary to assess the need to modify the treatment regimen (Sickkids, 2010).

- *Fentanyl*

It is a pure μ-opioid receptor agonist administered intravenously. It can be administered in slow bolus, 15 minutes, every 1-2 hours, or in continuous infusion (AMA, 2013).

Treatment can be started in slow bolus and diluted with 0.5-2 mcg/kg (<50 kg), 25-50 mcg (≥50 kg), which can be repeated every 1-2 hours. It can continue with continuous infusion with 0.5-2 mcg/kg (<50 kg), 25-100 mcg (≥50 kg), every hour (AMA, 2013, HUVH, 2009).

Transdermal route can be used from 50 kg, every 72 hours, provided that the needs for analgesia are stable (HUVH, 2009; Zernikow et al., 2009).

Table 5 shows the drugs used most often and the dosages according to the route of administration (table 5).

Table 5. Medications, dose and route of administration

Medication	Route	Dose <50kg	Dose ≥50kg	Frecuency (hours)	Maximum daily dose
Non-opioidS					
Acetaminophen	O	10-15 mg/kg	0.5-1 g	4-6	4-6 doses (or 60 mg/kg); 4 g (≥50kg)
	IV	7.5 mg/kg (<10 kg- ≤ 1 year)		4-6	30 mg/kg
		15 mg/kg (≥ 10 Kg < 50 kg)			60 mg/kg, or 2 g
			0.5 – 1 g		4 g
Metamizole	O	20-40 mg/kg	500-1,150 mg	6	
	IV	20-40 mg/kg	1-2 g	8	6 g
Ibuprofen	O	5-10 mg/kg	200-800 mg	6-8	30 mg/kg or 2.4g (<50kg); 3.2g (≥50kg) Newborns excluded
			200-600 mg/doses	4-6	2.4 g

Table 5. Medications, dose and route of administration (continuation)

Medication	Route	Dose <50kg	Dose ≥50kg	Frecuency (hours)	Maximum daily dose
Opioids					
Weak					
Codeine	O		30-60 mg Don't use for < 12 years	4-6	1.5 mg/kg every 4 hours (<50kg); 60 mg/4 h (≥50 kg)
Strong					
Morphine	O	(< 6 months): Starting (naive) 0.15 mg/kg		3-4	
		(≥6 months): Starting (naive) 0.3 mg/kg			
			Starting: 5-30 mg		
	IV	(<6 months): Bolus: 0.05 mg/kg		2-4	
		(<6 months): Infusion: 0.015-0.025 mg/kg		1	
		(≥6 months): Bolus: 0.1 mg/kg	Bolus: 0.05 - 0.1 mg/kg; or 5-10 mg	2-4	
		(≥6 months): Infusion: 0.02-0.05 mg/kg; ratio 10-40 µg/kg/	Infusion: 0.03-0.05 mg/kg; or 1.5 mg; / ratio 10-40 µg/kg/	1	
Fentanyl	IV	Starting, slow bolus 0.5-2 mcg/kg	Bolus: 25-50 mcg		
		Continuous infusion: 0.5-2 mcg/kg/ h	Infusion: 25-100 mcg	1	

O= oral; IV= intravenous; kg= kilograms; Max= Maximum

Boluses must be administered slowly (15 minutes) and diluted

Withdrawal or reduction in opioid doses

The reduction in doses of opioids, or their withdrawal, may be necessary in various situations, such as the reduction of pain, remaining stable at mild levels due to the influence of other treatments (co-adjuvant drugs or other therapies such as surgery, radiation, etc.), or due to acute kidney failure, serious adverse effects, etc. (Zernikow et al., 2009).

When withdrawal of opioids is necessary, it must be carried out progressively. If treatment with opioids was short-term (5 days or less) they can be withdrawn in 3-4 days (Zernikow et al., 2009). If treatment has been prolonged, 20-50% of the original dose is withdrawn per week. Some experts indicate that the longer opioids are administered, the slower the withdrawal (HUVH, 2009; WHO, 1998).

Twenty per cent of the dose of the previous day is required to avoid withdrawal symptoms. The need for adjuvants must be assessed if the withdrawal of opioids causes significant anxiety or other symptoms.

Drugs not recommended in those aged under 18 years

Certain drugs are not recommended for the treatment of pain in a child with cancer:

Tramadol. Oral administration is not recommended in children aged under 12 years. Due to its narrow therapeutic range, it must be prescribed under exceptional circumstances (HUVH, 2009).
Methadone. Not recommended in children aged under 18 years (AMA, 2013).
Meperidine. Not recommended due to the associated risks, fundamentally seizures (Sickkids, 2010).
Acetylsalicylic acid (ASA). Not recommended due to the risk of developing Reye's syndrome (AMA, 2013; Macintyre et al., 2010).

7.4.2.3 Adjuvant drugs

Adjuvant drugs are not classical analgesics but have analgesic properties or relieve symptoms when administered concomitantly with analgesic treatment under specific circumstances (Zernikow et al., 2009).

When pain is neuropathic or due to spinal cord / intracranial compression, opioids show no individual effectiveness, therefore other drugs must be added to the therapy used.

Neuropathic pain

Anticonvulsive drugs are used (carbamazepine, gabapentin, clonazepam) and tricyclic antidepressants (amitriptyline) (AFSSAPS, 2009; Ingelmo & Fumagalli, 2004; Miaskowski et al., 2004; MOH, 2003) or a combination of these when neuropathic pain is secondary to that of chemotherapy or from another origin (phantom limb, root compression, etc.) (Mishra et al., 2009).

No differences in effectiveness were observed between anticonvulsive drugs and tricyclic antidepressants (HUVH, 2009).

Regular doses are: carbamazepine oral 3-10 mg/ kg, every 8-12 h (<50 kg) and 200-400 mg every h (≥50 kg); gabapentin orally 3-10 mg/ kg, every 8-12 h (<50 kg) and 100-600 gr every 8 h (≥50 kg); clonazepam orally 0.01-0.03 mg/ kg, every 8-12 h (<50 kg) and 0.5-1 mg every 8 h (≥50 kg); amitriptyline orally 0.5-2 mg/ kg every 24 h (≥50 kg) and 30-100 mg every 24 h (≥50 kg).

There is no evidence to make recommendations on the use of benzodiazepines, local anaesthetics systemically and other antidepressants (AFSSAPS, 2009).

It is recommended to consult the hospital pain unit if possible (Sickkids, 2010).

Spinal cord or intracranial compression

Corticosteroids are used (Miaskowski et al., 2004; MOH, 2003; WHO, 1998; SIGN, 2008). The regular dose of dexamethasone is 0.1-0.5 mg/kg every 8-12 h (<50 kg) and 1-4 mg every 6-8 h (≥50 kg); oral and intravenous routes can be used.

It is important that as well as pain management, specific measures are applied directed at the cause of spinal cord compression (surgery, chemotherapy, radiotherapy, etc.) to avoid medium and long term episodes.

Bone pain

Bisphosphonates are used for this type of pain. The evidence is limited and contradictory and comes from patients of any age with cancer (SIGN, 2008).

7.4.2.4 Routes of administration of the drugs

The characteristics of the child, level of pain and the drugs properties must be taken into account to establish the route of administration of the drug (BPS, 2010; HUVH, 2009; Miaskowski et al., 2004; SIGN, 2008; Zernikow et al., 2009).

Oral

It is the route preferred by children. It is easy to administer, it permits dose adjustment effectively and pain control and the combination of fast-action and slow-release preparations is possible. There are different presentations that permit dose adjustment to body weight.

Limitations: its action is not fast enough in breakthrough pain, there is difficulty in using it in children aged under 2 years, there may not be slow-release tablets for all concentrations and inadequate adherence to treatment can be frequent in adolescents and in long-term use.

Intravenous

It is the preferred route to guarantee quick rescue, and that recommended in the presence of mucositis. If central venous access is established, this must be used. It allows the start of treatment and suitable dose adjustment for opioids; it is useful for administration of boluses or continuous infusion and suitable for PCA. This route is independent of the gastrointestinal function and allows the administration of more than one drug. It requires careful monitoring, especially whilst titration. When venous access is not well established, intermittent low-volume perfusions can also be used.

Limitations: the equipment can generate difficulties, it is expensive and invasive and the permanent central venous catheter poses a risk of infection.

Transdermal

It is a non-invasive route, independent of the gastrointestinal function; it is practical and can cause less constipation.

Limitations: it must only be used in situations of stable pain; it is contraindicated in opioid-naive patients, it is expensive and can cause skin problems.

Subcutaneous (s.c.)

It allows use of continuous infusion when intravenous access is not well established. It must be used with non-metallic needles and flow must be adjusted to the characteristics and situation of the child. It is useful for continuous infusion and suitable for PCA, which makes it a useful route for pain management at home.

Limitations: it can cause pain and is not well tolerated by children and can also cause local irritation and infection.

Patient controlled analgesia (PCA)

It is a route widely accepted by patients, but requires special infusion pumps and suitable training. It is not suitable for restless patients or those with altered mental state.

Intramuscular

Intramuscular injections must be avoided as they are painful and their absorption is inconsistent. They can cause bleeding in children with thrombocytopenia or coagulopathies.

Rectal

Rectal administration is contraindicated in children with cancer due to risk of lesion in the rectum or anus or risk of infection. Furthermore, it is not well accepted by children (Zernikow et al., 2009) and its absorption is highly variable (Miaskowski et al., 2004).

Other routes

Other routes of administration must be considered (sublingual, transmucosal, intranasal, spinal, etc.) which have advantages due to greater bioavailability and in some cases reduced side effects (Clark et al., 2004).

The sublingual route provides a fast iniciation of action, easy to adjust the dose and its use is independent of the state of consciousness. It can be useful for rescue doses. However, it is not well accepted in cases of dry mouths and it is often available only in special preparations.

Epidural and intrathecal routes can be useful for levels of intense pain and in short-term periods and they do not cause mouth dryness or constipation. They have a greater risk of delayed respiratory depression, wherefore careful monitoring must be carried out. Special formulations are necessary and can be expensive.

7.5 Care in children with cancer related with pharmacological treatment

7.5.1 Management of side effects of opioid analgesics

The most common side effects to opioid treatment are constipation and sedation. Other side effects are nausea, vomiting, drowsiness, dry mouth, urinary retention, pruritus, myoclonus, confusion, delirium, urinary retention and respiratory depression (HUVH, 2009; Miaskowski et al., 2004).

Their frequency varies. Constipation and sedation are common during therapy, as well as urinary retention. Nausea and vomiting, drowsiness and pruritus, however, are more usual at the start of treatment or when dosage is increased.

Dry mouth, sweating, hallucinations and myoclonus are effects that only occur occasionally. Respiratory depression, the most serious effect, is a rare event; also delirium, general oedema, bronchospasm and hypotension occur on rare occasions (Zernikow et al., 2009).

The presence of adverse effects may "indicate" the need to change opioid (AHCPR, 1994; HUVH, 2009; Miaskowski et al., 2004; WHO, 1998; Sickkids, 2010).

In the management of adverse effects, it is necessary to take into account that the children do not tend to report them voluntarily, therefore it is necessary to enquire and inform the children and their carers of the possibilities of controlling said effects (WHO, 1988; Sickkids, 2010; SIGN, 2008).

Possible adverse effects must be monitored and anticipated (Miaskowski et al., 2004; MOH, 2003). Some of them (nausea, vomiting, drowsiness) are resolved within a week of starting therapy (WHO, 1998; Zernikow et al., 2009) and most can be managed with simple interventions (Sickkids, 2010).

Rigorous monitoring is especially important during titration.

Constipation: it is a general adverse effect when using opioids, therefore all children must receive prophylactic laxative therapy (eg. lactulose or paraffin oil) unless contraindicated (eg: if the child has chronic diarrhoea) (Flogegard & Ljungman, 2003; Miaskowski et al., 2004; MOH, 2003).

Sedation, confusion, delirium: it is a common adverse effect when starting to use opioids (HUVH, 2009; Zernikow et al., 2009). It often develops from the first day of treatment or when increasing the dose, although most children develop tolerance, with reduced symptoms (HUVH, 2009; Miaskowski et al., 2004). Metabolic organic causes, intracranial tumour, etc. must be discounted. Non-essential central nervous system depressors must be avoided, such as benzodiazepines. If analgesia is insufficient and dose cannot be reduced, a psychostimulant can be added. If sedation persists, an adjuvant can be added, reducing the dose or changing the opioid (Miaskowski et al., 2004).

Nausea and vomiting: when they are associated to opioid treatment, they are often transitory. Normally such symptoms are resolved within 1 to 2 weeks from the start of treatment. The child may require administration of antiemetics.

Pruritus: morphine can cause pruritus; an alternative is fentanyl.

Respiratory depression: is the most serious adverse event although at therapeutic doses it is uncommon (Hertzka et al., 1989; HUVH, 2009; Kart et al., 1997; Miaskowski et al., 2004; Sabatino et al., 1997), except in children in immediate contact with opioids, in those with relevant pulmonary disease or in case of overdose. Pain acts as a natural antagonist to analgesics and the respiratory effects of opioids; children often develop tolerance to respiratory depression as well as tolerance to the analgesic effect of opioids. It must be monitored carefully, especially during titration and when opioids are administered by epidural or intrathecal route (through greater risk of delayed respiratory depression).

Other side effects: inadequate secretion of vasopressin, which is an effect that occurs rarely and is associated more to treatment with morphine. Other aetiologies must be discounted (paraneoplastic syndrome or chemotherapy) (HUVH, 2009; Zernikow et al., 2009).

Other effects of treatment with opioids

Hypersensitivity: it occurs on rare occasions. In such an event, it is possible to change opioid (Miaskowski et al., 2004).

Tolerance: it is an involuntary adaptation to the analgesic that is characterised by the reduction of the effect of medication with the previous dose or the need to increase the dose to maintain the effect. The first indication is a reduction in the duration of the effective analgesia. The needs to increase the doses correlate more with the advance of the disease. It is expected to occur in long-term treatment with opioids (Hockenberry-Eaton et al., 1999; HUVH, 2009; Miaskowski et al., 2004; Sickkids, 2010).

Physical dependence: it is an involuntary physiological effect characterised by physical symptoms that occur when suddenly stopping opioids or with the administration of an opioid antagonist. It is expected to occur in long-term treatment with opioids (Hockenberry-Eaton et al., 1999; HUVH, 2009; Miaskowski et al., 2004).

Addiction: it is a voluntary psychological behavioural pattern, characterised by an intense need for analgesics due to their properties in altering the state of mind, instead of its effects on pain. It is characterised by behaviour that include at least one of the following: poor control of use of medication, compulsive

use, continue use in spite of the adverse effects and abstinence (HUVH, 2009; Sickkids, 2010; Zernikow et al., 2009).

7.5.2 Monitoring of pharmacological treatment

For any treatment, especially with opioids, the suitability of the type of drug, route and dose to administer must be verified, based on the characteristics of the child, the duration of action of the drug, its peak effect and half life (Sickkids, 2010).

Due to their immaturity, children aged under 3 years must be monitored (AMA, 2013).

The effectiveness of the treatment over the level of pain must be monitored, according to the drug used and the route of administration. In general, it shall be carried out one hour after starting oral treatment, or after 15 minutes in intravenous treatment and at least every 4 hours when the pain is stable (HUVH, 2009; Miaskowski et al., 2004).

Sedation and respiratory depression are adverse effects that require special monitoring. The frequency, intensity and duration of the monitoring must be planned according to the characteristics of the child and the treatment administered.

Opioid-naive children must be monitored for the treatment with opioids and at times of greatest risk, dose adjustment (especially if administered in continuous perfusion), changes in the function of essential organs (liver, kidney and lung), change from one opioid to another or change in route of administration (Jarzyna et al., 2011; Miaskowski et al., 2004).

Regular assessments must be carried out on the level of sedation and respiratory response, especially during the hours of sleep, including respiratory rate per minute, rhythm, depth of respiratory movements (Jarzyna et al., 2011). Technology supported monitoring can be useful (e.g. continuous pulsioximetry) for children at high risk of unexpected severe sedation and respiratory depression, although there is little conclusive evidence regarding this (Jarzyna et al., 2011). In light of the reduced frequency and respiratory quality, the child can be stimulated, "reminding them that they have to breathe" (WHO, 1998). When the breaths are less than 10 per minute or there is a paroxysmal rhythm with poor respiratory work, treatment must be established with an opioid antagonist (Naloxone) and

precise and prolonged monitoring maintained until complete recovery (Jarzyna et al., 2011; Miaskowski et al., 2004). It must also be taken into account that analgesia will be reversed and can result in acute withdrawal symptoms, which can be complicated with intense pain and seizures. Therefore, opioid antagonists are not recommended to reverse non-life threatening effects, such as confusion or sedation. The dose must be adjusted carefully if they are used to reverse respiratory depression or life-threatening hypotension (Miaskowski et al., 2004).

7.5.3 Assessment of the suitability of pharmacological management of pain in children

Checklists can be used on the pharmacological management of pain (AHCPR, 1994). For example:

- Has the child or their carers been asked about their previous experience with pain and their preferences in the use of analgesics?
- Does the child or their carers have reservations about the use of opioids for treating pain?
- Has the child been suitably assessed at appropriate intervals?
- Has an analgesic regimen been established for prevention and pain relief?
- Is the analgesic sufficient for anticipated pain or pain currently experienced?
- Is the frequency of administration of the medication suitable for anticipated pain or pain experienced?
- Is the route of administration suitable for the child?
- Has the appearance of side effects been monitored suitably?
- Have the adverse effects been handled suitably?
- Does the analgesic regimen give a suitable level of comfort and satisfaction from the perspective of the child or the carers?

7.5.4 Barriers for the pharmacological management of pain

It is essential to take into account the beliefs and values of the children, their carers and professionals in the assessment of pain, its treatment and follow-up, as they can form barriers in the assessment and suitable management of pain and lead to its underreporting and undertreatment (SIGN, 2008).

Some possible beliefs are (Hockenberry-Eaton et al., 1999; MOH, 2003):

- Small children do not feel pain or tolerate it better than adults.
- Children rapidly develop addiction to narcotics.
- Children are incapable of explaining where and how must it hurts and are poor assessors of their own pain.
- Children become accustomed to pain or painful procedures.
- Children will inform that they are in pain when in fact they are.
- Children's behaviour reflects the intensity of their pain.
- Only terminal patients should receive opioids.

Some of the barriers that influence pharmacological management of pain are indicated below. It is necessary to assess which are present to try to minimise their effect.

Professional Barriers

- Inadequate knowledge in the assessment and treatment of pain, due to poor knowledge of the mechanisms that cause it, the tools for measuring it and the management of medication (strategies and dose).
- Underassessment of the pain intensity in the child.
- Concern for the side effects of analgesics, especially respiratory depression and excessive fear of toxicity induced by analgesics.
- Inadequate knowledge of the management of the adverse effects of analgesics.
- Difficulty in differentiating tolerance, physical dependence and addiction.
- Concern for the development of tolerance and iatrogenic addiction.
- Excessive precaution in the use of medication specially regulated by health authorities.
- Lack of time for assessment and effective management of pain or belief of the need for excessive additional time to carry them out.

(AHCPR,1994; AMA, 2013; Hockenberry-Eaton et al., 1999; Miaskowski et al., 2004; MOH, 2003).

Patients and relatives Barriers

- Reticence to manifest pain and take medication as prescribed.
- Religious and cultural influences that extoll the virtues of suffering.

- Fear that pain means the deterioration of the disease or that that they are nearing the end of their life.
- Fear to mask new symptoms.
- Concern about diverting the attention of the professionals from treatment of the disease.
- Lack of awareness of the pain as something treatable and the best way to access an effective therapy.
- Concern about developing a possible addiction or tolerance.
- Concern about not being able to manage the side effects or lack of knowledge on their effective management.
- Concern about not being a "good patient".
- Lack of complete healthcare cover for the treatment of pain and the cost of treatments (depending on the healthcare system).

(AHCPR, 1994; Hockenberry-Eaton et al., 1999; Miaskowski et al., 2004; MOH, 2003).

Healthcare system Barriers

- Failure to assign high priority to pain management.
- Lack of collaborative and systematic approach for assessment of pain and its treatment.
- Lack of equipment for suitable pain management.
- Lack of units or specific services of treatment of pain and difficulties in accessibility.
- Problems of availability or accessibility to treatment (depending on the healthcare system).
- Type of economic reimbursement (depending on the healthcare system).
- Regulation that restricts the prescription and dispensing of controlled substances.

(AHCPR, 1994; Hockenberry-Eaton et al., 1999; Miaskowski et al., 2004).

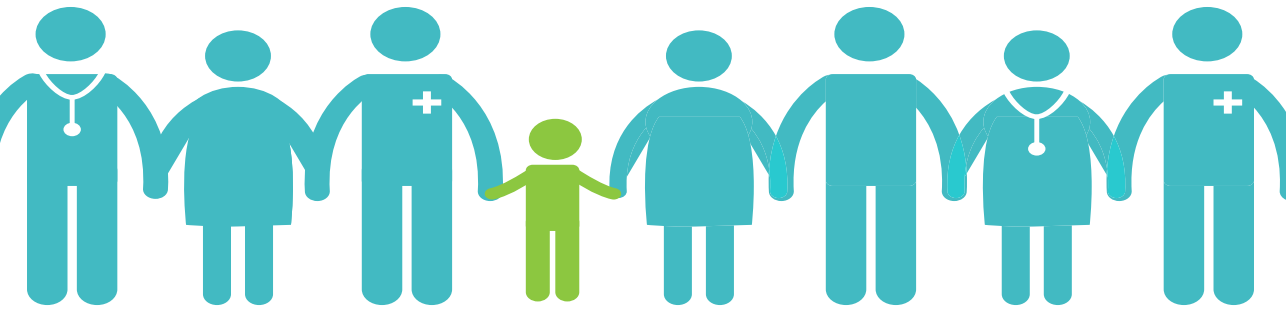
Information and education for children and carers on pain management

The AHCPR (1994) and APS (Miaskowski et al., 2004) suggest that the content of an educational programme must be considered based on the existing barriers and based on the following elements:

- General aspects:
  - Pain can be alleviated.
  - Explain the pain.
  - Understand the causes of pain.
  - Assessment of pain and use of pain scales to communicate it.
  - Communication between the healthcare team, children and their carer, regarding pain.
  - Use a preventive approach on pain control.

- The management of drugs must include:
  - General aspects of pain management with medication.
  - General aspects of management with non-pharmacological interventions.
  - How to overcome fear of addiction and tolerance to medication.
  - Control of the common adverse effects of the medication (eg. nausea and constipation).
  - Identify respiratory depression.

8. Dissemination and implementation



This CPG aims to guide professionals, children and their carers in their decision-making and help improve pain management in children with cancer.

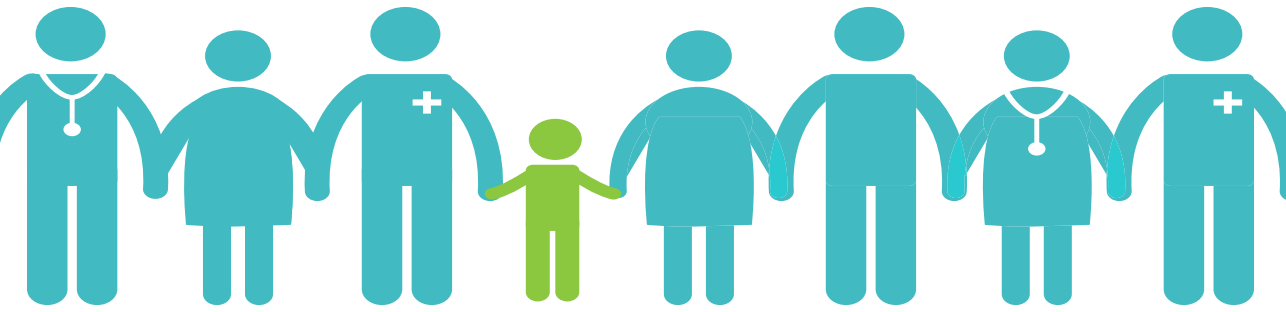
The following dissemination strategies are planned to provide access for all interested parties:

- Free access on the website of Cris Cancer Foundation (http://www.criscancer.org/en/index.php); also may be accessed from the websites of Nursing and Healthcare Research Unit (Investén-isciii) (http://www.isciii.es/investen), of the Patient Associations that participated in the project and others related with the issue dealt with in the Guideline, as well as from different healthcare 2.0 websites.
- Distribution of printed copies at Patient Associations related with the subject matter of the Guideline in hospitals and oncology centres, in professional bodys and healthcare administrations.
- Collaboration with associations and federations of patients and relatives with an interest in the CPG.
- Dissemination of the CPG and of the results of the systematic reviews carried out for its publication at scientific events (conferences, symposia, etc.) and in scientific journals.

The CPG includes a series of recommendations that respond to three areas related with pain management in children with cancer (diagnosis, non-pharmacological measures and pharmacological treatment).

For suitable pain management in children with cancer, each institution must prioritise the recommendations to implant and establish a planned process for their application, which requires the participation and collaboration of all the interested parties (professionals of different disciplines, children and carers).

9. Quality indicators



The implementation of recommendations requires the establishment of an evaluation plan that enables assessment of its application, suitability of the measures provided and their impact, both regarding pain management and pain reduction in children with cancer.

To assess the impact of the guideline, the following indicators are proposed (the numerator and denominator of each one are indicated to be able to be presented in percentage terms):

Numerator: Number of children with cancer with assessment and record of pain on admission
Denominator: Number of children with cancer and hospitalized

Numerator: Number of children with cancer who are hospitalized that have pain intensity assessed and recorded with appropriate scales
Denominator: Number of children with cancer who are hospitalized to whom pain intensity assessment was carried out

Numerator: Number of children with cancer who are hospitalized to whom pain intensity was regularly assessed
Denominator: Number of children with cancer who are hospitalized

Numerator: Number of children with cancer who are suitably prepared to prevent pain before undergoing painful procedures
Denominator: Number of children with cancer who underwent painful procedures

Numerator: Number of children with cancer and pain with analgesic treatment regimen according to the intensity and characteristics of pain
Denominator: Number of children with cancer and pain

Numerator: Number of children with cancer and suffering pain who were administered the established analgesic regimen
Denominator: Number of children with cancer and suffering pain with an analgesic regimen established

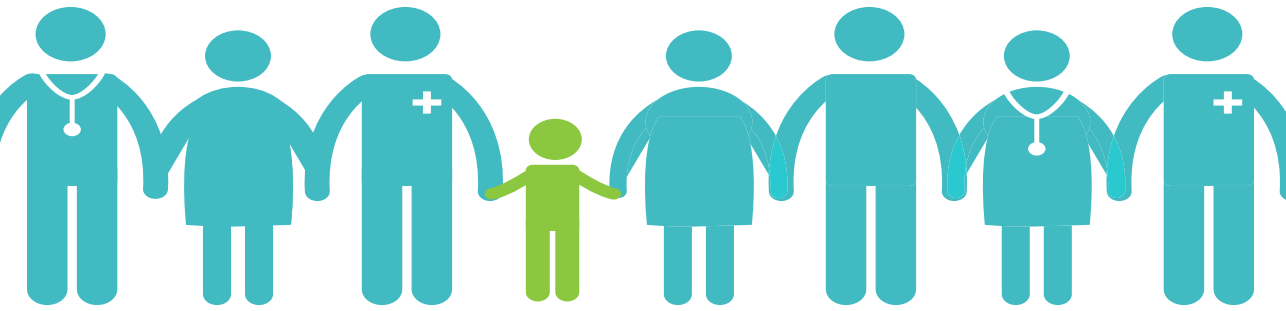
Numerator: Number of children with cancer who have moderate or intense pain (score according to scale used)
Denominator: Number of children with cancer to whom pain intensity was assessed

Numerator: Number of children with cancer treated with opioids who have prophylaxis established for constipation.
Denominator: Number of children with cancer treated with opioids

Numerator: Number of children with cancer treated with opioids who have prophylaxis established with antiemetics
Denominator: Number of children with cancer treated with opioids

Numerator: Number of children with cancer who receive non-pharmacological treatment
Denominator: Number of children with cancer with analgesic treatment regimen

10. Proposals for future research



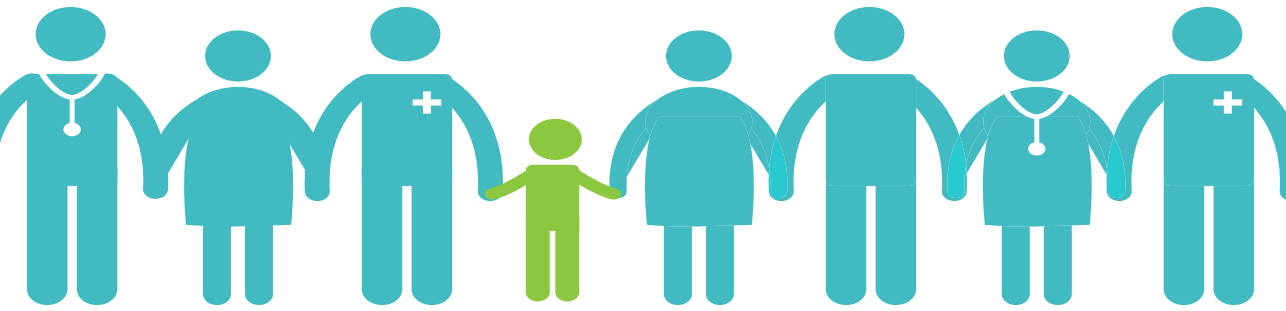
During the development of this CPG, sufficient evidence has not been identified to answer all the key questions raised. The research on pain management in children with cancer is generally poor or moderate/insufficient in quality. Part of the evidence managed internationally comes from adults with cancer or children with pathologies other than cancer.

Methodologically rigorous researches must be carried out, with children with cancer as study subjects and larger study samples.

The following areas have been identified for future research:

- Validation of pain detection diagnostic tools in children with cancer, by self-rate of children and adapted to their age and psychophysical situation.
- Validation of pain detection diagnostic tools in children with cancer, by declaration of an external observer (carers, healthcare professionals).
- Validation of comprehensive pain assessment tools in children with cancer, their characteristics and quality, as well as the consequences on their quality of life and well-being.
- Definition of the pain monitoring intervals, based on the type of treatment established.
- Determination of the individual effectiveness of the different non-pharmacological therapies and their adverse effects.
- Identification of the most effective strategies for the prevention and management of pain in painful procedures carried out on children with cancer, both for diagnosis and treatment.
- Determination of the effects of non-pharmacological therapies used simultaneously with the pharmacological treatment on pain, distress, comfort and quality of life.
- Determination of benefits and adverse effects of pain management by the ladder proposed by the WHO.
- Determination of the effectiveness, dose, adverse effects, etc. of the drugs, opioids and non opioids, which are used for management of cancer pain.

11. References



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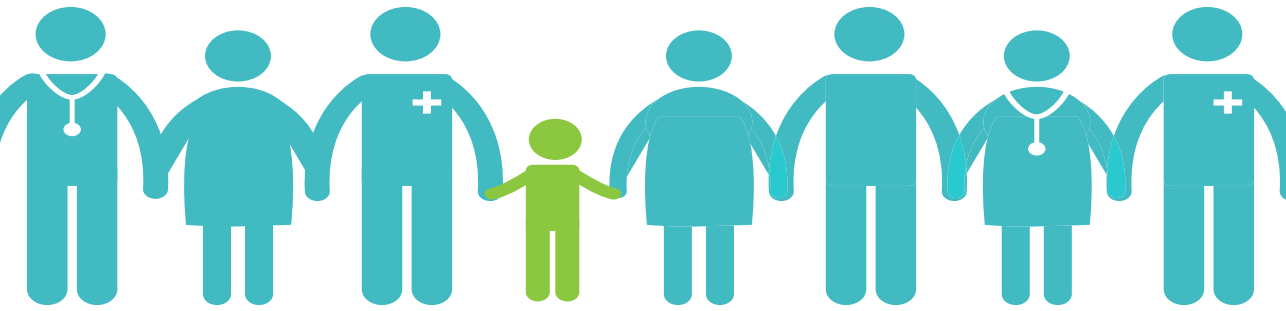
Appendices



Appendix 1. Conflict of Interest Disclosure Form

- Name and surnames:
- Institution where you work:
- Institution that links you to the CPG. Eg: scientific societies, foundations, etc. (answer only if different to the above):
- Contact telephone number:

Participation in the guideline as:

1. Author
2. Collaborator / expert
3. External reviewer

Having read and understood the information issued on the declaration of conflicts for this CPG project, I hereby give the following declaration:

A – Personal interests

- NO
- YES

If yes, please specify:

	Activity	Institution	Date
Funding for meetings and conferences, assistance to courses (inscriptions, travel grants, accommodation...)			
Fees as speaker (conferences, courses...)			
Financing of educational programmes or courses (contracting of personnel, hire of facilities			
Funding by participating in an investigation			
Consultancy for a pharmaceutical company / other technologies			
Shareholder or with commercial interests in a company (patents...)			
Economic interests in a health-related private company (as owners, employee, shareholder, private consultancy..) which can be significant in relation with the authorship of the guide.			
Non-economic conflicts of interest that may be significant in relation with the authorship of the guide			

B – Non personal interests

- NO
- YES

	Activity	Institution	Date
Funding or economic aid for creation of the unit or department			
Significant supply of material to the unit or department			
Contracting or financial aid for contracting personnel in the unit or department			
Financial aid for funding an investigation			
Financing of educational programmes or courses for the unit			

C – Other possible conflicts of interest not outlined in the previous sections (specify):

Signature

Date

Appendix 2. Clinical Practice Guidelines and systematic reviews selection for pharmacological treatment

Author/Institution, year	Country	Type of pain	Population
Clinical Practice Guidelines			
AHCPR (Agency for Health Care Policy and research), 1994	USA	Oncological	Childs and adults with cancer
Hockenberry-Eaton et al./Texas Cancer Council, 1999	USA	Oncological	Childs with cancer
HUVH/ Hospital Universitario Vall d'Hebron, 2009	Spain	Oncological	Childs with cancer
Macintyre et al./ ANZCA, Australian and New Zeland College of Anaesthetits and Faculty of Pain Medicine, 2010	Australia and New Zeland	Acute (any pathology; cancer included)	Childs and adults
Miaskowski et al./American Pain Society, 2004	USA	Oncological	Childs and adults with cancer
MOH/ Ministry of Health, Singapore, 2003	Singapore	Oncological	Childs and adults with cancer
WHO/World Health Organization, 1998		Oncological	Childs with cancer
SIGN/ Scotish Intercollegiate Guidelines Network, 2008	UK	Oncological	Childs older than 12 and adults with cancer
Systematic Reviews			
Zernikow et al., 2007		Oncological	Childs with cancer