Work-package 3.1 Cancer Pain Guidelines

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New Guidelines for cancer pain relief

"EVIDENCE-BASED GUIDELINES FOR THE USE OF OPIOID ANALGESICS IN THE TREATMENT OF CANCER PAIN: THE EAPC* RECOMMENDATIONS"

A project of the European Palliative Care Collaborative (EPCRC) on behalf of the European Association for Palliative Care (EAPC)

Two decades of clinical practice guidelines for the management of cancer pain

- **1986**
  Cancer pain relief
  World Health Organization

- **1996 First edition - 2001 Second edition**
  Morphine and alternative opioids in cancer pain:
  EAPC recommendations

WHO analgesic ladder what are the evidences that it works ?

- Meta-analysis by Jadad e Browman (JAMA 1995):
  - No controlled clinical trial;
  - Validation on case series
  - Lack of homogeneous criteria to assess pain and outcomes;
  - Short Follow high number of missing data
  - 70%-100% pain control with medical treatment alone

WHO analgesic ladder what are the evidences that it works ?

The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it ? Ferreira K, Kimura M, Jacobsen Teixeira M *Support Care Cancer 2006, 14, 1086-1093*

- This article reviews studies concerning evaluation of patients with cancer pain treated according to WHO guidelines.
- Systematic search was performed and 17 studies were analyzed.
- According to the studies, 45 to 100% of patients achieved adequate analgesia **BUT** the evidence they provide is insufficient to grant the effectiveness of the WHO guidelines

Searching guidelines……

- MEDLINE
- Cinahl Information System
- Cochrane Database Syst Rev
- EMBASE
- Google

"Practice Guidelines"[Mesh]"Analgesics, Opioid"[Mesh] AND "Neoplasms"[Mesh] AND "Pain"[Mesh]

Guidelines on cancer pain published after EAPC recommendations (2001)

Scientific Societies or Associations

- American Pain Society. Principles of analgesic use in the treatment of acute and chronic cancer pain. 1988 (Update 2003)
- American Society of Anaesthesiology. Practice guidelines for cancer pain management: a report by the American Anaesthesiology task force on pain management, cancer pain section. 1996 (Update 2006)
- SIGN. Control of pain in patients with cancer. 2000 (under review, update in 2008)
- American Geriatrics Society. The management of persistent pain in older persons. 2002
- SIAARTI. Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva Recommendations on the assessment and treatment of chronic cancer pain. 2003
- Finnish Medical Society. Palliative treatment of cancer. 2003 (Update 2005)
- NHS Quality Improvement Scotland. The management of pain in patients with cancer. 2004
- ESMO European Society for Medical Oncology. Minimum clinical recommendations for the management of cancer pain. 2005 (Update 2007)
- National Guideline Clearinghouse. Guideline for the management of cancer pain in adults and children. 2005
- NCCN. Clinical Practice Guidelines in Oncology. Adult Cancer Pain. 2006 (Update 2008)

Guidelines on cancer pain published after EAPC recommendations (2001)

Istitution

- MD Anderson Cancer Center. Cancer pain. 2003
- University of Iowa. Persistent pain management. 2005
- Texas Cancer Council. Guidelines for treatment of cancer pain. 2005

Governative Institution

- National Institutes of Health. Symptom management in cancer: pain, depression and fatigue. 2002
- US Department of Health and Human Services AHCPR Clinical Practice Guideline 1994
- Singapore Ministry of Health. Cancer pain. 2003
- National Health and Medical Research Council-Australian Government. Guidelines for a Palliative Approach in Residental Aged Care. 2006

Non Governative Institution

- JCAHO Joint Commission on accreditation of Healthcare Organizations. Pain current understanding of assessment, management and treatments. 2001

….other guidelines

- Fèdèration Nationale des centres de lutte contre le cancer. Standards, options et recommandations pour les traitments antalgiques médicamenteux des douleurs canceréuses par excès de nociception chez l'adulte, mise à jour. France, 2002 (Update 2005)
- CeVEAS. Morfina orale e altri oppioidi nel dolore oncologico. Italy, 2006
- Interdisciplinary guidelines of the German Cancer Society. MedikamentöseSchmerztherapie. German, 2002
- Norwegian ...

Recommendations based on :

Evidence

-American Pain Society
-American Society of Anaesthesiology
-SIGN
-American Geriatrics Society
-SIAARTI. Società Italiana di Anestesia
-Finnish Medical Society
-NHS Quality Improvement Scotland
-National Guideline Clearinghouse
-NCCN
-Texas Cancer Council
-National Institutes of Health
-Singapore Ministry of Health
-National Health and Medical Research Council- Australian Government
-JCAHO Joint Commission on accreditation of Healthcare Organizations.

Experts opinion:

-MD Anderson Cancer Center
-University of Iowa
-ESMO European Society for Medical Oncology

1. The opioid of first choice for moderate to severe cancer pain is morphine. C

2. The optimal route of administration of morphine is by mouth. Ideally, two types of formulation are required: normal release (for dose titration) and modified release (for maintenance treatment). C

3. The simplest method of dose titration is with a dose of normal release morphine given every 4 hours and the same dose for breakthrough pain. This 'rescue' dose may be given as often as required (up to hourly) and the total daily dose of morphine should be reviewed daily. The regular dose can then be adjusted to take into account the total amount of rescue morphine. C

4. If pain returns consistently before the next regular dose is due the regular dose should be increased. In general, normal release morphine does not need to be given more often than every 4 hours and modified release morphine more often than 12 or 24 hours (according to the intended duration of the formulation). Patients stabilized on regular oral morphine require continued access to a rescue dose to treat 'breakthrough' pain. **A**

5. Several countries do not have a normal release formulation of morphine, though such a formulation is necessary for optimal pain management. A different strategy is needed if treatment is started with modified release morphine. Changes to the regular dose should not be made more frequently than every 48 hours, which means that the dose titration phase will be prolonged. C

6. For patients receiving normal release morphine every 4 hours, a double dose at bedtime is a simple and effective way of avoiding being woken by pain. C

7. Several modified release formulations are available. There is no evidence that the 12-hourly formulations (tablets, capsules or liquids) are substantially different in their duration of effect and relative analgesic potency. The same is true for the 24-hour formulations though there is less evidence to draw on. **A**

8. If patients are unable to take morphine orally the preferred alternative route is subcutaneous. There is generally no indication for giving morphine intramuscularly for chronic cancer pain because subcutaneous administration is simpler and less painful. C

9. The average relative potency ratio of oral morphine to subcutaneous morphine is between 1:2 and 1:3 (i.e. 20–30 mg of morphine by mouth is equianalgesic to 10 mg by s.c. injection). C

10. In patients requiring continuous parenteral morphine, the preferred method of administration is by subcutaneous infusion. C

11. Intravenous infusion of morphine may be preferred in patients:
    a. who already have an in-dwelling intravenous line;
    b. with generalized oedema;
    c. who develop erythema, soreness or sterile abscesses with subcutaneous administration;
    d. with coagulation disorders;
    e. with poor peripheral circulation. C

12. The average relative potency ratio of oral to intravenous morphine is between 1:2 and 1:3. **A**

13. The buccal, sublingual and nebulized routes of administration of morphine are not recommended because at the present time there is no evidence of clinical advantage over the conventional routes. B

14. Oral transmucosal fentanyl citrate (OTFC) is an effective treatment for 'breakthrough pain' in patients stabilized on regular oral morphine or an alternative step 3 opioid. **A**

15. Successful pain management with opioids requires that adequate analgesia be achieved without excessive adverse effects. By these criteria the application of the WHO and the EAPC guidelines (using morphine as the preferred step 3 opioid) permit effective control of chronic cancer pain in the majority of patients. In a small minority of patients adequate relief without excessive adverse effects may depend on the use of alternative opioids, spinal administration of analgesics or non-drug methods of pain control. B

16. A small proportion of patients develop intolerable adverse effects with oral morphine (in conjunction with a non-opioid and adjuvant analgesic as appropriate) before achieving adequate pain relief. In such patients a change to an alternative opioid or a change in the route of administration should be considered. B

17. Hydromorphone or oxycodone, if available in both normal release and modified release formulations for oral administration, are effective alternatives to oral morphine. **A**

18. Methadone is an effective alternative but may be more complicated to use compared with other opioids because of pronounced interindividual differences in its plasma half-life, relative analgesic potency and duration of action. Its use by non-specialist practitioners is not recommended. C

19. Transdermal fentanyl is an effective alternative to oral morphine but is best reserved for patients whose opioid requirements are stable. It may have particular advantages for such patients if they are unable to take oral morphine, as an alternative to subcutaneous infusion. B

20. Spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered in patients who derive inadequate analgesia or suffer intolerable adverse effects despite the optimal use of systemic opioids and non-opioids. B

Recommendation	EAPC	MdA	SIGN	NCCN	ESMO
1-The opioid of first choice for moderate to severe cancer pain is morphine	X		X	X	
2-The optimal route of administration is by mouth	X		X		X
3-The simplest method of dose titration is with NRM	X	X	X	X	
4-If pain returns the regular dose should be increased	X		X	X	X
5-Changes to the regular dose should not be made more than every 48 h	X				
6-A double dose at bedtime for avoiding being woken by pain	X				
7-Several modified release formulations are available	X				
8-The preferred alternative route is subcutaneous	X		X		
9- Ratio oral morphine – subcutaneous morphine1:2 1:3	X	X	X	X	
10-Subcutaneous infusion in patients requiring continuos parenteral morphine	X		X		

Recommendation	EAPC	MdA	SIGN	NCCN	ESMO
11- Indications for intravenious infusion	X				
12-Ratio oral to intravenous morphine 1:2, 1:3	X	X			X
13-Buccal, sublingual, nebulized route are not recommended	X				
14-OFTC is an effective treatment for BTP	X	X		X	
15-Oral morphine permits adequate analgesia in the majority of patients	X			X	
16-Side effects: change oppioids or route	X		X		X
17-Hydromorphone or oxycodone are alternative to morphine	X		X	X	X
18-Methadone used by specialists	X	X	X	X	X
19-Transdermal fentanyl if opioids requirements is stable	X		X	X	X
20-Spinal administration if inadequate analgesia	X			X	

Other recommendations from guidelines review

- 21. Adjuvants in 1,2,3 step (WHO, SIGN, National Institute of Health, NHS, NHMRC, TCC)
- 22. NSAIDs and acetaminophen for mild pain and in association with opioids for moderate to severe pain (MdAnderson, SIGN, National Institute of Health, French guideline, NHMRC)
- 23. Equivalent ratio of oral morphine to transdermal fentanyl is 100:1 (MdAnderson, CeVEAS)
- 24. Breakthrough analgesia should be one sixth of the total regular daily dose of oral morphine. (SIGN, NHS)
- 25. Transdermal fentanyl is an effective analgesic for severe pain and can be used in pts with stable pain states as an alternative to morphine. (SIGN)
- 26. Mixed agonist –antagonist and partial agonist opioids are not recommended. (NCCN, TCC)
- 27. Begin a bowel regimen to prevent constipation when patient is started on an opioid analgesic. (National Guideline Clearinghouse, French guideline, NHS, TCC)
- 28. Repetitive intramuscular and subcutaneous injections should be avoided because they are painful and absorption is inconsistent. (National Guideline Clearinghouse)
- 29. Paracetamol in first and second step. (SIAARTI, French guideline, NHMRC)
- 30. Do not use 2 opioids of the same pharmacologic class. (French guideline)
- 31. Buprenorphine can not be recommended as opioid of third step if there are other opioid. (French guideline)
- 32. Take into consideration the management of incident pain (NHS, NHMRC)
- 33. Tramadol as effective as morphine in treating mild to moderate pain (TCC)

- These recommendations were circulated among the steering group to collect suggestions about statements to include in the new guideline.

→ 17 new key-points were formulated

- **40** international experts on cancer pain were contacted by e-mail
- **30** of them answered:

  28 agreed to participate in revising opioid guidelines

  2 declined

Key points for: ***"Evidence-based guidelines for the use of opioid analgesics in the treatment of cancer pain: the EAPC recommendations"***

Delphi consensus method

Round 1

Please rate how relevant you feel the statements are to be included in the new guidelines, by using a 0 to 10 scale; 0 indicating no relevance and 10 indicating highly relevant.

Statement/ Key-points		**Relevance**: 0=no relevance ,10=highly relevance. Please, put a cross (x) under one option only										**Comments**
	0	1	2	3	4	5	6	7	8	9	10	
1. Identify the opioid of first choice for moderate to severe cancer pain (opioid of choice)												
2. Identify the optimal route of administration of opioid of choice												
3. Clarify the optimal method of opioid dose titration at the beginning of therapy												
4. Suggest when a regular dose of opioid should be increased												
5. Identify the roles of short acting and long-acting opioid of choice (while taking into account the availability of such formulation) to suggest different titration schedules												
6. Consider a specific dosing schedule at bedtime for patients receiving short acting opioid of choice												
7. Clarify that available formulations of long-acting first choice (and other) opioid do not differ in term of efficacy												

EPCRC Work Package 3.1 Example of 2 round delphi consensus collection and rating

Key points for: *"Evidence-based guidelines for the use of opioid analgesics in the treatment of cancer pain: the EAPC recommendations"*

Delphi consensus method

Round 2

Please rate how relevant you feel the statements are to be included in the new guidelines, by using a 0 to 10 scale; 0 indicating no relevance and 10 indicating high relevant.

Statement/ Key-points XY	Your prev. score	Ave rage	**Relevance**: 0=no relevance 10=high relevance Please, put a cross (x) under one option only											**Comments**
			0	1	2	3	4	5	6	7	8	9	10	
1. Identify the opioid of first choice for moderate to severe cancer pain (opioid of choice)	6	7.28												
			1	1	1	1	1	2	2	1	2	3	10	
7. Clarify that available formulations of long-acting first choice (and other) opioid do not differ in term of efficacy	7	7.83												
			0	0	0	0	2	1	2	7	1	2	8	

Status of guideline development on May 30 2008

Step	When	Who	How
Lofoten discussion session on 37 key points	Done	Expert group	Rapporteur
Final decision according to final round of Delphi consensus on key points formulation	June 08	Streering and Local group	Summarizing Delphi and expert meetings
Grading system for recommendation	Today	Guidelines WP leaders Steering committee	Consensus
Format of guideline visual impact	Today	Guidelines WP leaders Steering committee	Consensus
Systematic literature reviews on each subject	next	Local group	Database searching strategy
Draft of final guidelines proposal document	next	Local group Steering commitee	Summy document short version and long version

You can contribute

- go to EAPC Website and in the EPCRC window on guidelines click on

OPIODS

www.eapcnet.org