

PRC

THE EAPC OPIOID GUIDELINES: PROCESS, RESULTS AND FUTURE DEVELOPMENT

Jaegtvolden 4-5 June 2012



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European Palliative Care Research Centre (PRC)

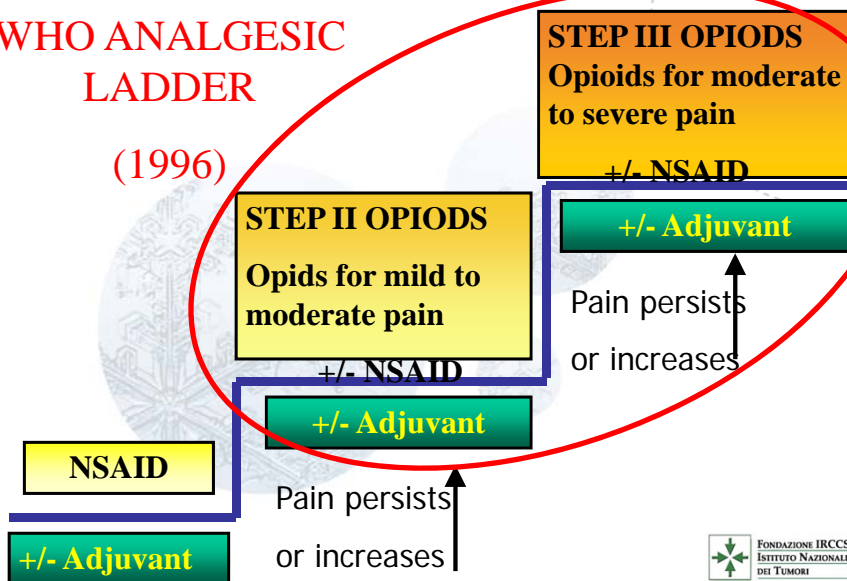


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WHO ANALGESIC LADDER

(1996)



THE EAPC RECOMMENDATIONS

Morphine in cancer pain: modes of administration

Expert Working Group of the European Association for Palliative Care

BMJ - 1996

Morphine and alternative opioids in cancer pain: the EAPC recommendations

Expert Working Group of the Research Network of the European Association for Palliative Care

BJC - 2001



European Palliative Care Research Collaborative

*A four-year EU 6th FM project with the EAPC Research Network
2006-2010*



2011 EAPC RECOMMENDATIONS distinctive features

- **Evidence based:** 18 systematic reviews (Palliative Medicine 2011)
- **GRADE** system
- Obtained through an **international consensus**
- **Independence** warranted by European funding and EAPC endorsement.
- To be **used and adapted to local needs all over the world**



I STEP: Content Development

REVIEW

Content development for
EUROPEAN GUIDELINES
 on the use of opioids for cancer pain:
 a systematic review and Expert Consensus Study

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 P. KLEPSTAD⁴, L. RADBRUCH⁵, A. CARACENI¹



II STEP: Systematic Reviews

- Bennett Michael
- Caraceni Augusto
- Cherny Nathan
- Dale Ola
- Fallon Marie
- Hanna Magdi
- Juhl Gitte
- King Samuel
- Klepstad Pål
- Laugsand Eivor
- Maltoni Marco
- Mercadante Sebastiano
- Nabal Maria
- Pigni Alessandra
- Radbruch Lukas
- Reid Colette
- Sjøgren Per
- Stone Patrick
- Tassinari Davide
- Zeppetella Giovambattista

Published in Palliative Medicine July 2011 special issue

III STEP: Public Discussion



- “USE OF OPIOID ANALGESICS IN THE TREATMENT OF CANCER PAIN: EVIDENCE-BASED RECOMMENDATIONS FROM THE EAPC”
- A. Caraceni, G. Hanks, S. Kaasa, M. Bennett, C. Brunelli, N. Cherny, O. Dale, F. De Conno, M. Fallon, M. Hanna, D. Haugen, G. Juhl, S. King, P. Klepstad, E. A. Laugsand, M. Maltoni, S. Mercadante, M. Nabal, A. Pigni, L. Radbruch, C. Reid, P. Sjogren, P.C. Stone, D. Tassinari, G. Zeppetella, for the *the European Palliative Care Collaborative (EPCRC) on behalf of the European Association for Palliative Care (EAPC)*

• *Lancet Oncology, February 2012*



The EAPC recommendations

- R 1: WHO Step II Opioids
- R 2: WHO Step III opioid of first choice
- R 3: Opioid titration
- R 4: The role of transdermal opioids
- R 5: The role of methadone
- R 6: Opioid switching
- R 7: Opioid relative analgesic potency
- R 8: Alternative systemic routes of opioid administration
- R 9: Opioids for breakthrough pain
- R10: Treatment of opioid-related emesis
- R11: Treatment of opioid-related constipation
- R12: Treatment of opioid related CNS symptoms
- R13: Use of opioids in renal failure
- R14: Role of paracetamol and NSAIDs in addition to Step III opioids
- R15: Role of adjuvant drugs for neuropathic pain (antidepressants and anticonvulsants)
- R16: The spinal route for opioid administration

WHO STEP II OPIOID

For patients with mild to moderate pain or whose pain is not adequately controlled by paracetamol or an NSAID given regularly by mouth, the addition of a Step II opioid (e.g. codeine or tramadol) (table 1) given orally might achieve good pain relief without troublesome adverse effects. Alternatively low doses of a Step III opioid (eg, morphine or oxycodone) may be used instead of codeine or tramadol. The data permit a weak recommendation to start a Step II opioid in these circumstances.

WHO STEP III OPIOID OF FIRST CHOICE

The data show no important differences between morphine, oxycodone and hydromorphone given by the oral route and permit a weak recommendation that any one of these three drugs can be used as the first choice Step III opioid for moderate to severe cancer pain.

OPIOID TITRATION

The data permit a weak recommendation that immediate-release and oral slow-release oral formulations of morphine, oxycodone and hydromorphone can be used for dose titration. The titration schedules for both types of formulation should be supplemented with oral immediate-release opioids given as needed.

THE USE OF TRANSDERMAL OPIOIDS

Transdermal fentanyl and buprenorphine are alternatives to oral opioids. The data permit a weak recommendation that either drug may be the preferred Step III opioid for some patients. For patients unable to swallow they are an effective, non-invasive means of opioid delivery.

USE OF METHADONE

Methadone has a complex pharmacokinetic profile with an unpredictably long half-life, but the data permit a weak recommendation that it can be used as a Step III opioid of first or later choice for moderate to severe cancer pain. It should be used only by experienced professionals.

OPIOID SWITCHING

The data permit a weak recommendation that patients receiving Step III opioids who do not achieve adequate analgesia and have side effects that are severe, unmanageable, or both, may benefit from switching to an alternative opioid.

RELATIVE OPIOID ANALGESIC POTENCIES

When switching from one opioid drug to another, dose conversion ratios can be recommended with different levels of confidence (Table 2). These conversion ratios are specific for patients in whom analgesia from the first opioid is satisfactory. Therefore, when the opioid is switched because of unsatisfactory analgesia, excessive side effects or both, clinical experience suggests that the starting dose should be lower than that calculated from published equianalgesic ratios. In all cases the dose needs to be titrated in accordance with clinical response.

ALTERNATIVE SYSTEMIC ROUTES OF OPIOID ADMINISTRATION

The data permit three strong recommendations:

- the subcutaneous route is simple and effective for the administration of morphine, diamorphine and hydromorphone and it should be the first choice alternative route for patients unable to receive opioids by oral or transdermal routes;
- intravenous infusion should be considered when subcutaneous administration is contraindicated (eg, because of peripheral oedema, coagulation disorders, poor peripheral circulation, requirement of high volumes and doses, etc);
- intravenous administration should be used for opioid titration when rapid pain control is needed.

ALTERNATIVE SYSTEMIC ROUTES OF OPIOID ADMINISTRATION

The data permit four weak recommendations:

- intravenous and subcutaneous infusions can be used to achieve optimum pain control in patients unable to achieve adequate analgesia with oral and transdermal administration;
- techniques for PCA can be adopted for subcutaneous and intravenous opioid infusions in patients who are able and willing to be in control of rescue doses;
- when switching from oral to subcutaneous and intravenous morphine administration the relative analgesic potency is the same for both routes and is between 3:1 and 2:1;
- although rectal opioids are effective, appropriate formulations are often not readily available and for many patients not acceptable and this route of administration should be used only as a second choice.

21

OPIOIDS FOR BREAKTHROUGH PAIN

The data permit a strong recommendation that pain exacerbations resulting from uncontrolled background pain should be treated with additional doses of immediate release oral opioids and that an appropriate titration of around-the-clock opioid therapy should always precede the recourse to potent rescue opioid analgesics. Breakthrough pain (eg, incident pain) can be effectively managed with oral, immediate release opioids or with buccal or intranasal fentanyl preparations. In some cases buccal or intranasal fentanyl preparations are preferable to the immediate-release oral opioids because of more rapid onset of action and shorter duration of effect.

Additionally, the data permit a weak recommendation that immediate - release formulations of opioids with short half-lives should be used to treat pre-emptively predictable episodes of breakthrough pain in the 20-30 min preceding the provoking manoeuvre .

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22

ROLE OF PARACETAMOL AND NSAIDs IN ADDITION TO STEP III OPIOIDS

The data permit a weak recommendation to add NSAIDs to Step III opioids to improve analgesia or reduce the opioid dose required to achieve analgesia. The use of NSAIDs, however, should be restricted because of risk of serious adverse effects, in particular in elderly patients and those with renal, hepatic or cardiac failure. The data also permit a weak recommendation that paracetamol should be preferred to NSAIDs in combination with opioids because of a more favourable side-effects profile, but its efficacy is not well documented.

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THE ROLE OF ADJUVANT DRUGS FOR NEUROPATHIC PAIN

The data permit a strong recommendation that amitriptyline or gabapentin should be considered for patients with neuropathic cancer pain that is only partially responsive to opioid analgesia. The combination of an opioid with these drugs is likely to cause more CNS adverse events unless careful titration of both drugs is undertaken.

SPINAL ROUTE OF OPIOID ADMINISTRATION

The data permit a weak recommendation that spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered for patients in whom analgesia is inadequate or who have intolerable adverse effects despite the optimal use of oral and parenteral opioids and non-opioids.

WEB VERSION

- Recommendations web version at
 - www.epcrc.org
 - www.eapcnet.org

NOT YET AVAILABLE

FUTURE DEVELOPMENT

- IMPLEMENTATION
- DISSEMINATION National language translations
 - heidi.blumhuber@istitutotumori.mi.it
- CLINICAL TRIAL - COMBAT

FUTURE DEVELOPMENT

- Crossing other Associations Guidelines
 - ECCO
 - ESMO
 - MASSC
 - ESTRO
 - Others
- National Guidelines Agencies ?
 - NICE ?
 - Others

FUTURE DEVELOPMENT

- SHOULD THE FOCUS BE CONVERTED FROM OPIOID USE TO CANCER PAIN MANAGEMENT?

FUTURE DEVELOPMENT

- MISSING SYSTEMATIC REVIEWS OF RELEVANT TOPICS ON ANALGESIA :
 1. STEP I
 2. KETAMINE
 3. CORTICOSTEROIDS
 4. INVASIVE PROCEDURE

FUTURE DEVELOPMENT

- MISSING OR INCOMPLETE EVIDENCE ON RELEVANT TOPICS:
 1. COMPARISON OF DIFFERENT TITRATION METHODS (TRANSMUCOSAL FENTANYL)
 2. NSAIDS AND PARACETAMOL IN COMBINATION WITH STEP III OPIOIDS
 3. ADJUVANTS FOR NEUROPATHIC PAIN (PREGABALIN, others?)
 4. NEW DRUGS (TAPENTADOL, OXYCODONE-NALOXONE COMBINATION)
 5. USE OF METHADONE AND DOSE CONVERSION RATIO
 6. LIVER FAILURE

Future development

- Assessment and classification
- Chemotherapy, hormone, biological therapies
medical
- Bisphosphonates
- Radiotherapy