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PRC

The European Association for Palliative Care (EAPC) Guidelines for Cancer Pain 2015 . What's new ?

Augusto Caraceni

Palliative Care, Pain Therapy and Rehabilitation National Cancer Institute of Milan Italy , Vice Chair EAPC Research Network, Professor of Palliative Medicine Norwegian University of Science and Technology NTNU, Trondheim Norway

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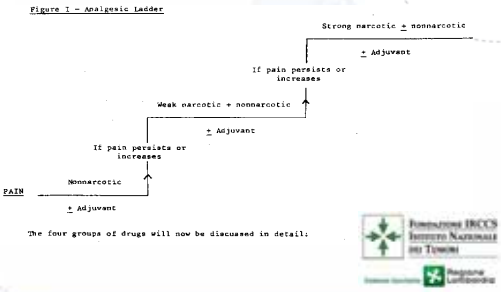
Original version of WHO analgesic ladder 1982



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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

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Review

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

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2012 EAPC RECOMMENDATIONS distinctive features

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

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GRADE principles

Study quality limitation RCTs

- Lack of allocation concealment
- Lack of blinding
- Incomplete accounting of outcomes
- Selective outcome reporting
- Other : early stopping for benefit

Quality of the evidence

- Limitations
- Imprecision
- Inconsistency
- Indirectness
- Publication bias

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Guidelines update process

- New topics will be added and appropriate PICOs will be defined.
- The GRADE method will be followed
- The AGREE criteria will be pursued in order to ensure quality; in particular a wider involvement of other stakeholders will be used to contribute in the GL development.
- The guidelines will be updated regularly every 3/5 years

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The EAPC pain guidelines 2015This set of recommendations focus on opiod drugs were included in 2012 version and have been updated

R 1: WHO Step II Opioids (M. Maltoni , D. Tassinari I)
R 2: WHO Step III opioid of first choice (A. Pigni, A. Caraceni I)
R 3: Opioid titration (P.Klepstad, N)
R 4: The role of transdermal opioids (Maltoni, Tassinari I)
R 5: The role of methadone (N.Cherny Is)
R 6: Opioid switching (O.Dale N)
R 7: Opioid relative analgesic potency (S. Mercadante I)
R 8: Alternative systemic routes of opioid administration (Radbruch, D)
R 9: Opioids for breakthrough/incident pain (J. Zeppetella UK)
R10: Treatment of opioid-related emesis (M. Fallon UK)
R11: Treatment of opioid-related constipation (P.Larkin IR, P.Stone UK)
R12: Treatment of opioid related CNS symptoms (P.Stone UK)
R13: Use of opioids in renal failure (M.Fallon UK)
R14: Role of paracetamol and NSAIDs in addition to Step III opioids (M.Nabal, E)
R15: Role of adjuvants drugs for neuropathic pain (M.Bennett UK)

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The EAPC pain guidelines 2015 These topics were added ,systematic reviews performed , recommendations will be developed if appropriate

- Pain assessment and classification (AK Knudsen, N) *
- Steroids (Ø. Paulsen, N) *
- NSAID and paracetamo as Step I (Radbruch L, D)
- Ketamine (M. Bennett , UK)
- Tapentadol (A.Pigni, I) *
- Oxycodone and naloxone combination (A. Pigni, I) *
- Opiods toxic interferences (D. Faksvåg Haugen) *
- Bisphosphonates and denosumab for bone pain (Porta J, E) *
- Radiotherapy and radionuclides (L.Lozza , I, R. Habermas N)
- Invasive procedures and spinal administrations (Sjogren P, Kurita G, D, S.Mercadante P Klepstad) *

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WHO STEP III OPIOID OF FIRST CHOICE (proposed new formulation)

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

Updated A. Pigni et al Milan

-Mercadante et al 2010
-Yu S et al 2014
-Riley J et al 2014
-Kamboj et al 2014

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- Pain assessment and classification

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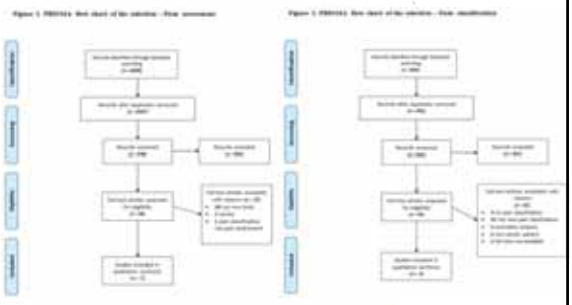
2015 Update Pain Assessment and Classification



Knudsen AK, Yulan Lin, Marianne Jensen Hjermstad, Barry Laird, Katrin Sigurdardottir

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New formulations/drugs

- In adult patients with moderate to severe pain directly due to cancer, which is the evidence that oral tapentadol is better than placebo, or other oral/transdermal opioids in the management of pain?
- In adult patients with moderate to severe pain directly due to cancer, which is the evidence that the combination of oxycodone with naloxone is better than placebo, or other oral/transdermal opioids in the management of pain and/or constipation?

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Tapentadol in cancer pain updated to february 2015

Author year	Study design	comparator	N patients enrolled analyzed
Imanaka K 2013	DB RCT	Oxycodone SR	343 (265)
Kress HG 2014	DB RCT enriched enrollment	Placebo (Oral Morphine)	218 (184) (100/93)
Imanaka K 2014	RCT open label	Oral Morphine	100
Wiffen et al 2015	Cochrane Review		

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Kress et al 2014

- Enriched enrollment design
  - 622 enrolled
  - 505 randomized titration to effect with either Tapentadol (338) or Morphine (158)
  - 219 rerandomized to Tapentadol (106) or placebo (112). 109 continued on morphine
  - 95 completed treatment (4 weeks) with placebo and 89 with tapentadol
  - Tapendadol superior to placebo

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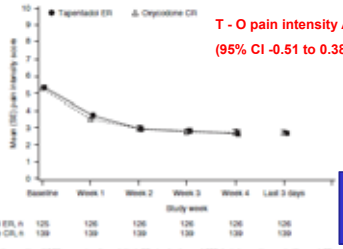
Non inferiority of tapentadol (64.5 mg) versus oxycodone SR (13.8 mg) within 1 point pain intensity difference



T - O pain intensity Δ=-0.06
(95% CI -0.51 to 0.38)

Randomized 168 Ta 172 Ox 65% and 70% completed

Imanaka et al 2013

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Tapendadol summary of available evidences

- 2 Double-blind controlled RCTs
- Superiority with placebo in one enriched –enrollment study of low quality
- Non inferiority with low dose Oxycodone in one study of moderate quality (significant attrition)
- No evidence from trials that it can cause less nausea/vomiting than morphine

Cochrane Implications for practice

- **For people with cancer**There is little in this review to suggest that tapentadol should be considered above other opioids for the treatment of cancer-relatedpain in terms of benefits or of harms.
- **For clinicians** Current policies on the use of opioids, particularly morphine, do not need to be amended.

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Oxycodone/naloxone combinations

Author	Study design	Comparator	N patints included /analysed
Meissner W 2009	RCT DB	CR Oxycodone	202 non cancer
Ahmedzai S 2012	RCT DB	CR Oxycodone	185 cancer (133)

Maximum approved dose 80/40 mg /day

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Oxy/naloxone summary of available evidences

- It reduces opiod induced costipation
- One RCT in cancer patients at mean doses of 46.6 (22.6 SD) mg of OXN and of 43.1 (19.1 SD) of CR Oxycodone it was non inferior to oxycodone with very narrow non inferiority bound (- 0.47)
- Its analgesic efficay in opiod tolerant patients using higher doses and for longer periods of time is unknown
- Case reports of antagonism of opiod analgesia have been reported

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Oxy/naloxone open questions

- Dose equivalent to about 60 mg of oral morphine (40 mg oxycodone) have been tested in one RCT in cancer pain and can be considered a 1st level of WHO Step III dose. What happens at higher doses up to 80 mg oxycodone ?
- In practice people combines oxycodone or other drugs with the highest doses of Oxy/Nal. What happens to overall opiod analgesia/tolerance ?
- What happens when switching from higher doses of Oxy/Nal to another opioid or parenteral morphine

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Bisphosphonates and denosumab

- Josep Porta and collaborators
  - 1585 retrieved papers were screened
  - 1471 were discarded based on abstract review as ineligible
  - 106 were examined in full
  - 35 eligible papers

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Role of Bisphosphonates and denosumab for bone cancer pain

Form the data available, we can conclude that the evidence of the analgesic role of BP and denosumab is weak, since more trials support the effect of BP and denosumab in preventing pain throught the delay of bone painful events than producing an analgesic effect per se.

In terms of clinical recommendations, cancer patients with a long life expectancy (months to years) could benefit for the administration of BP or denosumab in terms of sparing painful events, but for patients with a shorter prognosis time to live (weeks or few months) the prescription of BP or denosumab can be seen at least controversial.

J. Porta and co. Conclusions from submitted review article

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Role of steroids for cancer pain

- SYSTEMATIC REVIEW 2013
- CLINICAL TRIAL 2014
- UPDATE OF LITERATURE REVIEW
- COCHRANE REVIEW 2015

Ørnhulf Paulsen

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Steroids conclusions

- Weak evidence for analgesic effect in the 1st week of treatment in two adequately designed trials
- One negative trial

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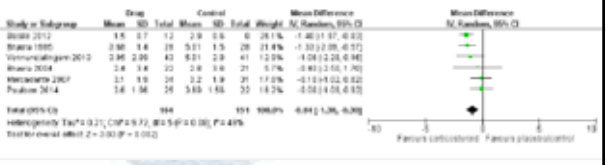
Corticosteroid and cancer pain metanalysis

(Haywood A et al 2015 Cochrane metanalysis)

Figure 4. Forest plot of pain at 1 week.



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Clinically significant drug–drug interactions involving opioid analgesics used for pain treatment in patients with cancer: a systematic review

- Cancer pain patients receiving opioids usually use multiple other drugs. A systematic review on drug-drug interactions (DDIs) involving opioids in cancer patients identified 32 published case reports and case series Opioid DDIs caused respiratory depression, CNS toxicity (sedation, delirium, serotonergic symptoms, myoclonus, and extrapyramidal symptoms), ventricular arrhythmia and impaired pain control. The most common mechanisms eliciting DDIs were changed opioid metabolism due to the effect on **CYP3A4** activity, a combination of several drugs with sedative and respiratory depressant properties, and DDIs due to an effect on opioid, dopamine, cholinergic, and serotonin activity in the CNS. It is recommended to recognize the risk associated with certain combinations of drugs (i.e. voriconazole or rifampicin plus oxycodone or fentanyl), and to as a general rule reduce polypharmacy as much as possible.

A. Kotlinska-Lemieszek, P. Klepstad, D. Faksvåg Haugen Drug Design Development Ther 2015

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The evidence of neuraxial administration of analgescic for cancer-related pain : a systematic review

- Is the spinal administration of opioids superior to systemic opioids ?
  - 1 RCT less side effects
- Is the coadministration of local anesthetics superior to only opioid administration ?
  - 2 RCTs No evidence
- Is the coadministration of clonidine superior to only opioid administration ?
  - 1 RCT better pain relief more hypotension with clonidine
- Is the administration of ziconotide superior to opioids ?
  - 1 RCT vs placebo , CNS side effects

Kurita GP, Benthien KS, Nordly M, Mercadante S, Klepstad P, Sjogren P Acta Anesthesiol Scand 2015

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Recommendations working formulation

- Intrathecal morphine administration alone
  - Indication for opiod responsive pain with excessive side effects from systemic analgesics
- Coadministration of intrathecal morphine and bupivacaine
  - Indication for pain which is poorly responsive to systemic analgesics
- Intrathecal clonidine or ziconotide in combination with morphine
  - No indication at the moment

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Sympathetic blocks for visceral cancer pain management: as systematic review and EAPC recommendations

- 3 Moderate quality RCTs on celiac plexus alcohol neurolysis for pancreatic cancer pain
- One Cochrane Review 2011 (57 and 54 pts)
  - Moderate level of evidence of reduction in pain and/or opioid consumption
  - Inconsistency across studies about pain relief duration and timing of block
  - Percutaneous, endoscopic and intraoperatory techniques

Mercadante S, Klepstad P, Kurita GP, Sjogren P Giarratano A Clinical reviews in Oncology/Hematology 2015

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The evidence of peripheral nerve blocks for cancer-related pain : a systematic review

- No randomized trials only anedcotal reports

Klepstad P, Kurita GP, Mercadante S, Sjogren P 2015

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Minimally invasive procedure for the management of vertebral bone pain due to cancer. The EAPC recommendations

- Radiofrequency -
- Kiphoplastly +
- Vertebroplasty -
- Cryoablation -

Mercadante S, Klepstad P, Kurita GP, Sjogren P, Pigni A, Caraceni A Acta Oncologica 2015

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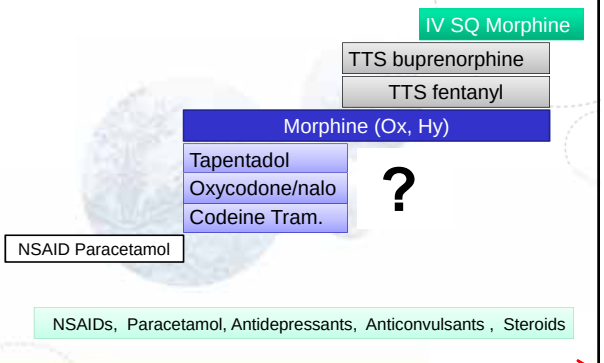
EAPC Guidelines : the role drugs for cancer pain treatment



NSAIDs, Paracetamol, Antidepressants, Anticonvulsants , Steroids

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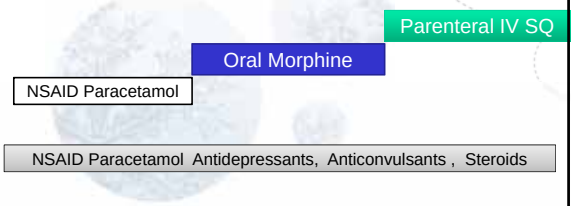
EAPC Guidelines for analgesic drugs only : a simplified vision



NSAID Paracetamol Antidepressants, Anticonvulsants , Steroids

History of cancer pain from onset to death