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PRC

The European Association for Palliative Care (EAPC) Guidelines for Cancer Pain Update of pharmacological therapies

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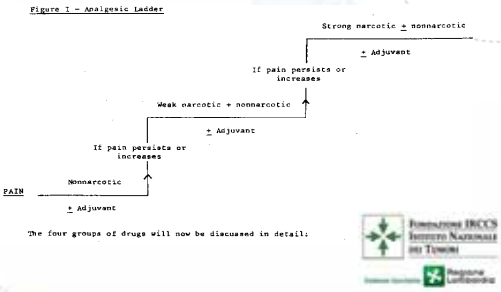
Original version of WHO analgesic ladder 1982



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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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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 every three years last release 2012 updated to 2009
- Present searches cover up to 2014

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CHALLENGES

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The EAPC recommendations : pharmacological pain therapy

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/incidente 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 adjuvants drugs for neuropathic pain (antidepressants and anticonvulsants)

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The EAPC recommendations : pharmacological pain therapy

R : -- WHO Step I
R : -- Role of steroids
R : -- Role of ketamine
R : -- Tapendadol
R : -- Oxycodone/naloxone
R : -- Role of bisphosphonates and Denosumab for bone pain

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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.

Updated by Marco Maltoni Davide Tassinari
Final formulation to be decided

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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 Step III 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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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.

Updated P. Klepstdad

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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.

Updated Marco Maltoni, Davide Tassinari

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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.

Updated O. Dale

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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 .

Updated G. Zeppetella

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Incident pain

	N° of papers assessed for eligibility	N° RCTs	N° of studies with a comparator (no placebo)
Zeppetella J Pall med 2011 and 2012 release Lancet oncology	125	8	2
UPDATE 2015	35	9	2

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Incident pain

AUTHOR (YEAR)	STUDY DESIGN	INTERVENTION	COMPARATOR	N of PTs ENROLLED (ANALYSED)	RISK OF BIAS	MAIN OUTCOME MEASURE DESCRIPTION
Coluzzi 2001	Multicentre, double-blind RCT	OTFC	NR-morphine	134 (89)	Allocation concealment not described	PI and PR
Mercadante 2007	Randomised, cross-over, controlled	OTFC	IV morphine	40 (25)	Not blinded	SPID at 30 min
Mercadante 2009	Open-label, randomised, cross-over comparison	INFS	OTFC	196 (139)	Not blinded	PID at 10 min
Fallon 2011	Multicentre double-blind RCT	FPNS	NR morphine	110 (79)	Randomisation method not described Allocation concealment not described	PID at 15 min

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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	Placebo Oral Morphine	496 (327)
Imanaka K 2014	RCT open label	Oral Morphine	100
Mercadante S 2012	Observational	-	Opioid naive 50
Mercadante S 2013	Observational	-	Opioid tolerant 37
Mercadante S 2014	Observational	-	Opioid tolerant 30
Mercadante S 2012	Case report	-	1 Methadone
Schikowski A 2015	Observational	-	123 43% on opioids

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- Kress HG et al 2014

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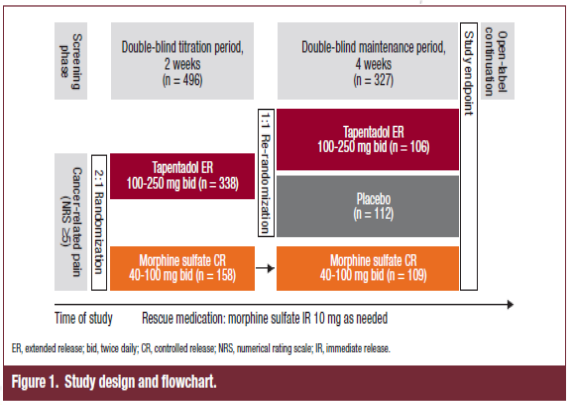

Figure 1. Study design and flowchart.

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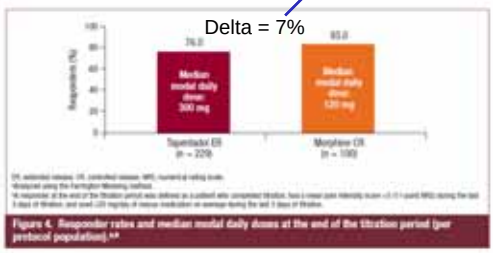
Results: Titration period, non inferiority vs oral morphine

BUT

Lower bound of 95% CI of the between group difference in the responding rates=-15.5 %

Delta = 7%



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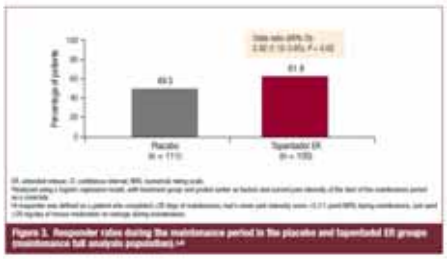
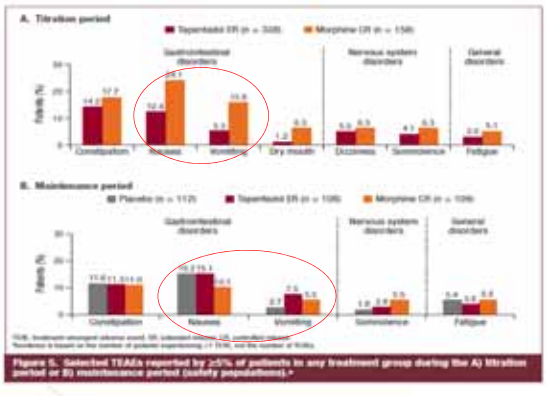
Results: Maintenance period



68.8

morphine (109)

24



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- Imanaka et al 2013

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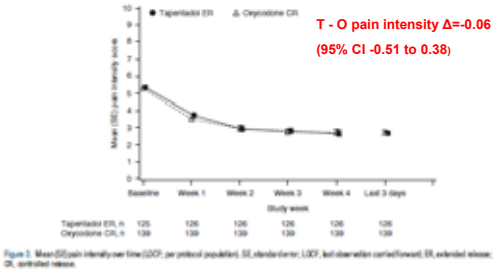
Non inferiority of tapentadol (64.5 mg) versus oxycodone SR (13.8 mg) within 1 point pain intensity difference



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

Imanaka et al 2013

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Tapendadol summary of available evidences

- 2 RCTs with double blind control
- Non inferiority with low dose Oxycodone
- Non inferiority with morphine not clearly demonstrated
- Data suggest that morphine can be more effective
- Clinical experience suggest that in some opiod tolerant patients it can be used with a ratio with oral morphine ofabout 3 : 1 with benefit up to about 500 mg per day
- It can induced less nausea/vomiting than morphine

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EAPC recommendation

- ?

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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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EAPC Recommendation

- ?

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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 since there is no clear evidence to support adding a potential burdersome, harmful and expensive treatment with no clear symptomatic benefit.

J. Porta and co. Conclusions from submitted review article

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Role of steroids for cancer pain

- New topic Ørnhulf Paulsen
  - SYSTEMATCI REVIEW 2013
  - CLINICAL TRIAL 2014
  - UPDATE OF LITERATURE REVIEW
  - COCHRANE REVIE 2015

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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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EAPC Recommendation

- ?

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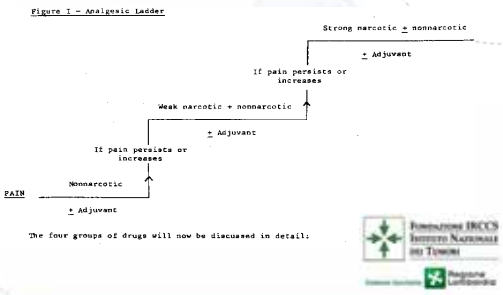
Original version of WHO analgesic ladder 1982



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EAPC Guidelines : the role drugs for cancer pain treatment

Parenteral morphine infusion IV SQ

Transdermal buprenorphine ?

Transdermal fentanyl

Morphine Oxycodone Hydromorphone (WHO III)

Tapentadol ?

Oxycodone/naloxone ?

WHO II Cod. Tram. ?

NSAID Paracetamol (WHO I)

NSAID Paracetamol as adjuvants to opioids

Adjuvants : Antidepressants, Anticonvulsants , Steroids ?

History of cancer pain from onset to death