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

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

Original version of WHO analgesic ladder 1982

2012 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

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
The EAPC recommendations: pharmacological pain therapy

1. WHO Step II Opioids
2. WHO Step III opioid of first choice
3. Opioid titration
4. The role of transdermal opioids
5. The role of nonsteroids
6. Opioid switching
7. Opioid relative analgesic potency
8. Alternative systemic routes of opioid administration
9. Opioids for breakthrough/incident pain
10. Treatment of opioid-related events
11. Treatment of opioid-related constipation
12. Treatment of opioid-related CNS symptoms
13. Use of opioids in renal failure
14. Role of paracetamol and NSAIDs in addition to Step III opioids
15. Role of adjuvant drugs for neuropathic pain (antidepressants and anticonvulsants)

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 (e.g., 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 (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.

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.

Updated Marco Malloni, Davide Tassinari

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

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

Incident pain

<table>
<thead>
<tr>
<th>INCIDENT</th>
<th>DESIGN</th>
<th>INTERVENTION</th>
<th>COMPARISON</th>
<th>N of PTs</th>
<th>RISK OF BIAS</th>
<th>MAIN OUTCOME MEASURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident</td>
<td>multicentre, double-blind RCT</td>
<td>OTFC NR</td>
<td>MR morphine</td>
<td>134 (89)</td>
<td>Allocation concealment not described</td>
<td>PI and PR</td>
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<tr>
<td>Multicenter 2007</td>
<td>randomised, cross-over, controlled</td>
<td>OTFC IV</td>
<td>MR morphine</td>
<td>40 (25)</td>
<td>Not blinded</td>
<td>SPID at 30 min</td>
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<tr>
<td>Multicenter 2009</td>
<td>open-label, randomised, cross-over, controlled</td>
<td>OTFC IV</td>
<td>MR morphine</td>
<td>196 (139)</td>
<td>Not blinded</td>
<td>PID at 10 min</td>
</tr>
<tr>
<td>Fallon 2011</td>
<td>multicentre double-blind RCT</td>
<td>ONF</td>
<td>MR morphine</td>
<td>110 (79)</td>
<td>Randomisation method not described</td>
<td>PID at 15 min</td>
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</tbody>
</table>

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?
### Tapentadol in cancer pain updated to February 2015

<table>
<thead>
<tr>
<th>Author year</th>
<th>Study design</th>
<th>Comparator</th>
<th>N patients enrolled analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imanaka K 2013</td>
<td>DB RCT</td>
<td>Oxycodone SR</td>
<td>343 (265)</td>
</tr>
<tr>
<td>Kress HG 2014</td>
<td>DB RCT</td>
<td>Placebo Oral Morphine</td>
<td>496 (327)</td>
</tr>
<tr>
<td>Imanaka K 2014</td>
<td>RCT open label</td>
<td>Oral Morphine</td>
<td>100</td>
</tr>
<tr>
<td>Mercadante S 2012</td>
<td>Observational</td>
<td>Placebo</td>
<td>496 (327)</td>
</tr>
<tr>
<td>Mercadante S 2013</td>
<td>Observational</td>
<td>Opioid naive</td>
<td>50</td>
</tr>
<tr>
<td>Mercadante S 2014</td>
<td>Observational</td>
<td>Opioid tolerant</td>
<td>37</td>
</tr>
<tr>
<td>Mercadante S 2012 Case report</td>
<td>-</td>
<td>Methadone</td>
<td>30</td>
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<tr>
<td>Schikowski A 2015</td>
<td>Observational</td>
<td>-</td>
<td>123</td>
</tr>
</tbody>
</table>

Results: Titration period, non-inferiority vs oral morphine

- Delta = 7%
- BUT

Results: Maintenance period

- 68.8% on morphine (109)
Non inferiority of tapentadol (64.5 mg) versus oxycodone SR (13.8 mg) within 1 point pain intensity difference

\[ T - O \text{ pain intensity} \Delta = -0.06 \]

(95% CI -0.51 to 0.30)

Tapentadol 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 opioid tolerant patients it can be used with a ratio with oral morphine of about 3:1 with benefit up to about 500 mg per day
- It can induce less nausea/vomiting than morphine

EAPC recommendation

-?

Oxycodone/naloxone combinations

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Comparator</th>
<th>N patients included/analysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meissner W 2009</td>
<td>RCT DB</td>
<td>CR Oxycodone</td>
<td>202 non cancer</td>
</tr>
<tr>
<td>Ahmedzai S 2012</td>
<td>RCT DB</td>
<td>CR Oxycodone</td>
<td>185 cancer (133)</td>
</tr>
</tbody>
</table>

Maximum approved dose 80/40 mg /day

Oxy/naloxone summary of available evidences

- It reduces opioid induced constipation
- 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 efficacy in opioid tolerant patients using higher doses and for longer periods of time is unknown
- Case reports of antagonism of opioid analgesia have been reported
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 opioid analgesia/tolerance?
- What happens when switching from higher doses of Oxy/Nal to another opioid or parenteral morphine?

EAPC Recommendation

Role of 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

Role of Bisphosphonates and denosumab for bone cancer pain

From 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 through 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 from 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 burdensome, harmful and expensive treatment with no clear symptomatic benefit.

Steroids conclusions

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

Original version of WHO analgesic ladder 1982

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. Tran.

NSAID Paracetamol (WHO I)

NSAID Paracetamol as adjuvants to opioids

Adjuvants: Antidepressants, Anticonvulsants, Steroids

History of cancer pain from onset to death