Opioid resistant pain – Evidence-based Clinical Aspects

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Opioid Resistant Pain

“All pain is not equally responsive to opioid analgesics. It is useful to have a working classification of pain based on anticipated response to opioids” (Table 49.3)
## Table 49.3 Opioid Resistant Cancer pain Classification

<table>
<thead>
<tr>
<th>Pseudo-resistant</th>
<th>Semi-resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>underdosing</td>
<td>Bone metastases</td>
</tr>
<tr>
<td>poor absorption</td>
<td>Neuropathic (Some)</td>
</tr>
<tr>
<td>poor intake</td>
<td>RICP</td>
</tr>
<tr>
<td>ignoring</td>
<td>Activity related</td>
</tr>
<tr>
<td>psychological</td>
<td></td>
</tr>
<tr>
<td>aspects of care</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic (some)</td>
</tr>
<tr>
<td>Muscle spasm</td>
</tr>
</tbody>
</table>
Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain

S. Arnér and B.A. Meyerson

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(Received 9 November 1987, revision received 5 January 1988, accepted 7 January 1988)

**Main message:** nociceptive, idiopathic and neuropathic pains respond differently to opioids. Neuropathic pain is insensitive to opioids

“Some patients were …pleased to understand that lack of true analgesic effect [from the i.v. opioid test] indicated the futility of continuous use….”
"Opioid-responsive and opioid-non-responsive pain in cancer."

- “Cancer pain in general responds in a predictable way to analgesic drugs and drug therapy is the mainstay of treatment, successfully controlling pain in 70-90% of patients.”

- Non responsive
  - pain associated with nerve damage
  - 'incident' (movement-related) bone pain.
  - bladder and rectal tenesmus
  - pancreatic pain
  - pain associated with decubitus ulcers or other superficial ulcers

Unresponsiveness paradigm

• response of patients to opioid drugs may be influenced by properties inherent in the pain or pain syndrome (such as its pathophysiology)

• ➔ certain types of pain, e.g., neuropathic pains may be unresponsive to these drugs

• Implication
  – Use of opioids is futile and counterproductive
The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions

Portenoy RK, Foley KM, Inturrisi CE.

Portenoy Foley Inturissi Hypothesis

- Based on clinical experience and data derived from pharmacokinetic/pharmacodynamic opioid infusion studies in patients with neuropathic cancer pain
Portenoy Foley Inturissi Hypothesis

Definition of Opioid Responsiveness

• the degree of analgesia achieved during dose escalation to either intolerable side effects or the occurrence of 'complete' or 'adequate' analgesia
Portenoy Foley Inturissi Hypothesis

Characteristics of responsiveness

1. opioid responsiveness is a continuum, rather than a quantal phenomenon

2. opioid responsiveness is determined by a diverse group of patient characteristics and pain-related factors, as well as drug-selective effects
Portenoy Foley Inturissi Hypothesis

Regarding Neuropathic pain

• neuropathic mechanism may reduce opioid responsiveness, but does not result in an inherent resistance to these drugs.
Implications for practice

1. Given the complexity of factors contributing to opioid responsiveness and the observation that outcome cannot be reliably predicted, opioids should not be withheld on the assumption that pain mechanism, or any other factor, precludes a favorable response.

2. The clinical use of opioids should include dose escalation to maximally tolerated levels and repeated monitoring of analgesia and other effects.
Since 1990

- Subsequent research extensively validated the Potenoy/Foley/Inturissi hypothesis
Neuropathic pain
Opioids for Neuropathic Pain

2 meta-analyses

1. Tramadol in neuropathic pain
2. Opioids in Neuropathic pain
Tramadol for neuropathic pain

- 5 eligible trials
  - 3 vs placebo
  - 1 vs clomipramine
  - 1 vs morphine.
- 3 placebo trials
  - significant reduction in neuropathic pain
- NNT > 50% pain relief was 3.5 (95% CI 2.4 - 5.9).
- NNH 7.7 (95% CI 4.6 - 20).

Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials.

Intermediate-term Studies

- 8 trials provided data on 403 opioid-treated patients
- Number of patients per treatment group ranged from 12 to 82
- Duration of treatment varied from 8 days to 8 weeks (median, 28 days).
Intermediate duration study results

• All trials positive

• 6/8 studies provided data suitable for pooling

• The meta-analysis included 263 opioid- and 258 placebo-treated patients

• Mean pain intensity to be 14 points lower in opioid-treated patients than in those treated with placebo (95% CI, −18 to −10; P_ .001)
### Efficacy of Opioids in NPs

**Meta-analysis of Intermediate Term Studies**

*(Eisenberg et al, JAMA, 2005)*

<table>
<thead>
<tr>
<th>Author/ Year</th>
<th>Drug</th>
<th>Diagnosis</th>
<th>Opioid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gimbel 2003</td>
<td>OXY</td>
<td>DPN</td>
<td>82</td>
<td>77</td>
</tr>
<tr>
<td>Huse 2001</td>
<td>MO</td>
<td>PLP</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Morley 2003</td>
<td>Meth</td>
<td>Misc</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Raja 2002</td>
<td>MO</td>
<td>PHN</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Watson 1998</td>
<td>OXY</td>
<td>PHN</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>Watson 2003</td>
<td>OXY</td>
<td>DPN</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td>263</td>
<td>258</td>
</tr>
</tbody>
</table>

**Diagnosis**
- DPN, painful diabetic polyneuropathy
- PLP, phantom limb pain
- PHN, postherpetic neuralgia
- Misc, diverse aetiologies

**Weighted mean difference, 95%CI**
- **Favours opioid**
- **Favours plac**

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DPN, painful diabetic polyneuropathy
PLP, phantom limb pain
PHN, postherpetic neuralgia
Misc, diverse aetiologies
Dose-dependent analgesic

Demonstrated in 2 studies

1. Low and high doses of methadone were each compared separately with placebo, and the higher dose produced a larger effect than the lower dose.

2. In the other study, a direct comparison showed that a high dose of levorphanol produced a significantly larger analgesic effect than the lower dose.
Safety of Opioids in NPs
Meta-analysis of Intermediate Term Studies
(Eisenberg et al, JAMA, 2005)

### Numbers-Needed-To-Harm

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>NNH (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Nausea</td>
<td>3.6 (2.9-4.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4.6 (3.4-7.1)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>5.3 (3.7-8.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.2 (4.6-11.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.7 (4.8-10.0)</td>
</tr>
</tbody>
</table>
Dropouts

- 4 trials provided combinable information regarding the number of dropouts due to adverse events

<table>
<thead>
<tr>
<th></th>
<th>Opioid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.5%</td>
<td></td>
<td>7.6%</td>
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</table>
Opioids vs. TCA vs placebo in PHN
Multiple Cross-Over RCT

FLEXIBLE DOSING: TITRATED TO EFFECT

TCA, nortriptyline up to max. 160 mg/d or desipramine,
Opioid, morphine sulphate up to max 240mg/d or methadone

Raja et al 2002
Opioids vs. TCA vs placebo in PHN
Multiple Cross-Over RCT

76 patients recruited
44 completed all 3 arms

Pain relief: Opioid versus TCA equal

Patient preference for opioid (p 0.06)

Raja et al 2002
Morphine Vs Gabapentin vs Combination vs Placebo

- double-blind, active placebo-controlled, four-period crossover trial
- 5 week treatment periods
- 41/57 pts completed trial

NNT map of pharmacotherapy of NP

Tricyclics
Valproate
LTG/CBZ/PHT

Opioids
Tramadol
Gabapentin/Pregabalin
Mexiletine
SNRI antidepressants
NMDA antagonists
Capsaicin
SSRI antidepressants
Topiramate

Algorithm for neuropathic pain treatment: An evidence based proposal

Incident pain pain
Optimization of opioid therapy for preventing incident pain associated with bone metastases.

• Study to determine whether increasing the opioid doses above those sufficient to control pain at rest would reduce the occurrence of these pains.

• 25 consecutive patients with movement-related episodic pain associated with bone metastases, – no evident fractures

Optimization of opioid therapy for preventing incident pain associated with bone metastases.

3 phases

1. rapid intravenous titration of the opioid dose to obtain pain relief at rest.

2. opioid doses increased until dose limiting adverse effects

3. opioid dose increases were then stopped, or doses were even reduced, according to patients' satisfaction or development of adverse effects with moderate-severe intensity.

Optimization of opioid therapy for preventing incident pain associated with bone metastases.

**Measures**
- Basal pain intensity and pain induced by movement: NRS 0-10.
- Opioid-related symptoms
- Total daily doses of oral morphine and other symptomatic drugs were also recorded at daily intervals, and at time of discharge, when the best balance was presumed to be reached.

Optimization of opioid therapy for preventing incident pain associated with bone metastases.

Results

• Basal pain control was achieved after rapid intravenous titration.

• The day after, pain induced by movement significantly improved using mean doses of oral morphine equivalents of 102 mg.

• In the following days, the subsequent increase in opioid doses prescribed despite optimal basal pain control allowed an acceptable level of incident pain intensity until patients' discharge.

Optimization of opioid therapy for preventing incident pain associated with bone metastases.

Adverse effects

- A minority of patients developed adverse effects with an intensity of 2-3 on the scale, requiring symptomatic treatment or decreases in opioid doses.

Conclusions

• A priori determination of pain as opioid resistant is inappropriate

• Opioid responsiveness is a variable that is determined retrospectively after trials of opioid therapy

• It is determined by the degree of relief achieved after opioid titration to maximal effect or maximal tolerated dose

• Since there are intra-individual variability in response to different opioids, in the setting of dose limiting adverse effects, opioid rotation should be considered

• When opioid responsiveness is limited, other analgesic options need to be strongly considered.