Opioid Therapy for Chronic Non-cancer Pain: Evidence from randomized trials

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Chronic Pain States

- Nociceptive/Inflammatory Pain
- Neuropathic Pain
- Dysfunctional Pain (central sensitization)
- Mixed Type (Cancer Pain)
## Opioids for Chronic Non-cancer Pain: The Evidence

### Will restrict discussion to:
- Evidence of **efficacy** from peer-reviewed publications of randomized controlled trials (RCTs) in nociceptive and neuropathic pains
- Meta-analysis and Critical reviews

### Not Included ...
- RCTs in Cancer and Dysfunctional pain
- Breakthrough pain
- Adverse effects
- Observational non-randomized studies (Ballantyne)
- Limitations of studies (Turk)
- Alternative therapies in light of limitations (Rowbotham)
## Opioids for Chronic Non-cancer pain: Clinical Models

<table>
<thead>
<tr>
<th>Chronic nociceptive pain</th>
<th>Chronic neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>Post-herpetic neuralgia</td>
</tr>
<tr>
<td>Low back pain</td>
<td>Diabetic neuropathy</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>Post-amputation pain</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Peripheral and central pain states</td>
</tr>
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## Randomized Controlled Trials (RCTs)

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
<th>STUDY DESIGNS</th>
</tr>
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<tbody>
<tr>
<td>Adults ≥ 18yr</td>
<td>Parallel double-blind</td>
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<tr>
<td>Pain ≥ 4 on a 0-10 scale</td>
<td>Cross-over</td>
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<tr>
<td>Moderate or severe pain</td>
<td>Enriched enrollment</td>
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<tr>
<td>Pain not adequately controlled by NSAIDs or COX-2 inhibitors</td>
<td></td>
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<tr>
<td></td>
<td>Placebo and/or active comparator</td>
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<tr>
<td></td>
<td>Usually 4-12 wk treatment periods</td>
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</tbody>
</table>
Enriched enrollment designs

- Screening
- Run-in period (open label)
- Double-blind Phase

Eligible patients
- Active drug
- Active Comparator
  - Assay sensitivity
  - Lack of inferiority
- Placebo

Treatment response
Tolerability
Opioids for Chronic Non-cancer pain: Drugs studied with RCTs

- Morphine
- Oxycodone
- Fentanyl
- Levorphanol
- Hydromorphone
- Oxymorphone

- Tramadol
- Tapentadol
- Buprenorphine

Mu-opioid receptor agonists
Mu-agonist + reuptake inhibition (NE/5-HT, NE)
Mu-agonist + κ and δ antagonist
Efficacy: Outcome measures

- Pain intensity
  - Responder rates
  - NNT_{30\%} and NNT_{50\%}
  - Pain relief
  - Patient Global Impression of Change (PGIC)
- Quality of sleep
- Physical function
- Quality of Life
Pain Assessment: Outcome measures

- **NRS-11**: pain intensity on a 0-10 scale (11 point, 0=no pain, 10= worst pain you can imagine)
- **5-point categorical scale**: 0= none to 4= excruciating
- **VAS 100**: 100 mm line from no pain to excruciating pain
- **WOMAC OA index**: pain subscale that includes 5 items each rated on a 0-4 range (during walking, using stairs, in bed, sitting/lying, standing)
Nociceptive Pain: Oral morphine for musculo-skeletal pain

- Double-blind, 2-period cross-over RCT (3+ 6 wk))
- Soft tissue, musculo-skeletal, rheumatic
- Pain >6 m, ≥ 5 on VAS
- Failure to respond to NSAID, TCA
- Pain, drug liking, psychological features, functional status, cognition

“In patients with treatment-resistant chronic regional pain of soft-tissue or musculoskeletal origin, 9 weeks of oral morphine in doses up to 120 mg daily may confer analgesic benefit with a low risk of addiction ....”

### Oxymorphone ER in Chronic Low Back Pain: Enriched enrollment withdrawal trial

#### 12 wk-double-blind Rx Period

<table>
<thead>
<tr>
<th>Day of clinic visit</th>
<th>Mean pain intensity (VAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>80</td>
</tr>
<tr>
<td>Baseline</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>14</td>
<td>40</td>
</tr>
<tr>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>Final</td>
<td>0</td>
</tr>
</tbody>
</table>

- **n=205**
- **n=100**
- **n=105**
- **n=325**

Well tolerated stable dose, 40 ± 25.8 mg

LOE = lack of efficacy

- **n=47 (47%)**, 35% due to LOE
- **n=71 (68%)**, 11.4% to LOE

**Transdermal Buprenorphine for Chronic Low Back Pain: Enriched enrollment comparator trial**

Mean difference (95% CI) from TD-Bup5 over 4, 8, 12 wk:
- TD-Bup20 mcg/hr = 0.67 (0.99, 0.35)
- Oxy-IR 40 mg/day = 0.75 (1.07, 0.44)

Tapentadol ER for Knee Osteoarthritis: Active and placebo-controlled parallel study

Baseline vs Ave. pain throughout maintenance period
Pain reduced with Tapentadol and Oxycodone CR vs placebo

Titration
12 wk-Maintenance
Cochrane review: Oral or Transdermal Opioids for OA Knee or Hip

- 10 controlled trials with 2268 subjects included
- Codeine, oral morphine, TD fentanyl, oxycodone, oxymorphone (51 mg MS equivalent)
- Pain: Placebo (29% decrease) vs Opioid (44% decrease, \( \Delta = 0.9, \text{ CI: -1.2 to -0.7} \))
- Function (WOMAC): Improvement larger in opioid vs placebo (\( \Delta = 0.7, 13\% \text{ difference in improvement} \))

Nuesch E et al. Cochrane Database Systematic Review 2009
Cochrane review: Oral or Transdermal Opioids for OA Knee or Hip

- “Overall opioids more effective than control interventions in terms of pain relief and improvement of function.”
- No substantial difference: type of opioid, analgesic potency (strong/weak), trial methodological quality, type of funding ..

Nuesch E et al. Cochrane Database Systematic Review 2009
Opioids for Neuropathic Pain: Efficacy of CR Oxycodone in Postherpetic Neuralgia

VAS Scores During Final, Fourth Week of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>CR Oxycodone (N=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady Pain</td>
<td>55</td>
<td>34</td>
</tr>
<tr>
<td>Brief Pain</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>Alloodynia</td>
<td>32</td>
<td>321</td>
</tr>
</tbody>
</table>

Moderate or greater pain relief
Oxycodone 58% vs placebo 18%

Weekly VAS Pain Score (0-100 mm)

Opioids for Neuropathic Pain: Opioid vs Tricyclic Antidepressant in Postherpetic Neuralgia

**VAS Pain Scores During Final Week of Treatment**

*P < .001 vs placebo.

**Patient Preference**
- Opioid Rx Period - 54%
- TCA Rx Period - 30%
- Placebo Rx Period - 16%

Randomized, double-blind, placebo-controlled, three-period crossover trial- antidepressant (TCA), opioid, placebo

Raja SN et al. *Neurology*. 2002
Levorphanol for chronic peripheral and central neuropathic pains


Parallel design
Both peripheral and central NP

Pain intensity

Capsule Intake

- Low-strength group
  - Ave. dose 2.7 mg/d
- High-strength group
  - Ave. dose 8.9 mg/d

No. of Capsules/Day vs. Week of Treatment

No. at Risk
81  80  77  70  67  60  60  59

P = 0.001
Efficacy of Opioids for neuropathic pain: Number needed to treat (NNT)

Finnerup NB et al
Pain 2010;150:573
Opioid vs Placebo or add-on Rx (Mean age ≥ 60yr)
- 18 RCTs, 78% excellent methodology score
- Significant reductions in pain intensity and physical disability, non-significant changes in sleep and QOL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Subjects Opioid / Placebo</th>
<th>Placebo mean change</th>
<th>Opioid Mean change</th>
<th>Mean ∆Effect (ES) (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAIN</td>
<td>18</td>
<td>3005 / 1865</td>
<td>-0.68</td>
<td>-1.25</td>
<td>-0.55 (&lt;0.001)</td>
</tr>
<tr>
<td>PHYSICAL FUNCTION</td>
<td>9</td>
<td>1822 / 935</td>
<td>-0.57</td>
<td>-1.0</td>
<td>-0.43 (0.001)</td>
</tr>
</tbody>
</table>

Papaleontiou M. J Am Geriatr Soc 58;1353:2010

ES= Active- Placebo
Opioids for Nociceptive versus Neuropathic Non-cancer Pains

- A review of 62 RCTs (enriched and non-enriched enrollment)
- Study design and pain etiology did not alter the efficacy and functional outcomes

Furlan et al.
Pain Res Manage
16;337:2011

Mean Difference and 95% CI

Δ Pain: 0.5 to <0.8
Medium effect
Long-term opioid for chronic non-cancer pain: a Cochrane review

- Open-label extension studies of RCTs-oral opioids
- Osteoarthritis, low back & diabetic neuropathic pain
- Follow-up 6 -18 m, pooled data from 4 studies (6-7.5 m)

..we conclude that pain relief that appears to be clinically important is achieved long-term for patients able to remain on oral opioids for six months.

Strength of evidence .. weak


Noble M et al. The Cochrane Library 2010:11
Opioids for chronic moderate to severe pain: Network Analysis

Riemsma R et al. Current Medical Research & Opinion 27,, 2011, 1907
Randomized short duration efficacy studies using various trial designs show that, compared to placebo, opioids significantly decrease nociceptive and neuropathic pains. The efficacy of opioids in nociceptive and neuropathic pain is similar. No clear difference in efficacy of the different opioids has been shown in comparative trials.

THANK YOU