OPIOIDS FOR CHRONIC PAIN: EVIDENCE ON EFFICACY, DURABILITY AND DOSE EFFECTS

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1. The efficacy issue
2. The dose issue

EFFECTIVENESS AND DURABILITY

15 RCTs (4 IV) strong opioids vs. placebo (1025 pts)
• duration of trials 4-8 wks
• pain intensity reduced by at least 30% in all trials
• neuropathic and musculoskeletal similar
• The small number of patients included and the short follow-ups do not allow conclusions concerning problems such as tolerance and addiction

Kalso E, Edwards J, Moore R, McQuay H
Opioids in chronic non-cancer pain: systematic review of efficacy and safety Pain 2004;112:327-80

Eisenberg E, McNicoll ED, Carr DB
Efficacy and safety of opioid agonists in the treatment of neuropathic pain of non-malignant origin: systematic review and meta-analysis of randomized controlled trials JAMA 2005;293:3043-52

• Significant analgesic benefit in 8 trials assessing non-parenteral therapy
• Used for up to 28 days
• Substantiates efficacy of opioids for neuropathic pain

RANDOMIZED CONTROLLED TRIALS

• Appeared in the 1980s-90s because of doubt about opioid efficacy for chronic (viz neuropathic) pain states
• They revealed:
  1) Opioids do work in chronic pain states, but higher doses may be needed
  2) At least 50% of patients abandon the treatment voluntarily
Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E

- 41 RCTs and 6019 patients
- Included weak opioids (eg tramadol)
- Treated for up to 16 weeks
- Pain relief overall improved by strong opioids but not by weak opioids or non-opioids

Martell BA, O'Connor PG, Kerns RD et al

- Included 6 RCTs comparing opioid to placebo or non-opioid control
- 4 used in a meta-analysis
- Found no reduction in pain with opioids
- No study conducted beyond 16 weeks

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Opioids in chronic non-cancer pain: systematic review of efficacy and safety Pain 2004;112:327-80

- 15 RCTs (4 IV) strong opioids vs. placebo (1025 pts)
- In open-label follow-up studies, only a minority (44%) of patients achieved significant long lasting analgesia with tolerable adverse events

Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E

- 41 RCTs and 6019 patients
- Included weak opioids (eg tramadol)
- Treated for up to 16 weeks
- Despite the relative shortness of the trials, more than 1/3 abandoned treatment because of lack of efficacy
Summary of RCTs

- Better analgesia with opioid treatment versus control in all studies (statistically significant overall)
- Addiction not assessed
- Reported length of treatment up to 8 months
- Doses moderate (up to 180 mg morphine equivalent per day)

Problems with RCTs

- Artificial treatment setting
- Enriched enrollment
- Problem patients selected out
- SHORT duration (longest 32 wks)
- Moderate doses (highest 180/day)

UNCONTROLLED STUDIES (Case series)

- Reports from single practice settings
- Portnoy and Foley landmark paper 1986, several since
- Used to provide support for chronic opioid therapy when it was first popularized in 1980s
- Satisfactory analgesia achieved using stable (non-escalating) doses of opioids
- Reported length of treatment up to 6 yrs
- Doses generally moderate (up to 195 mg morphine)

Limitations of case series

- BIAS
- Authors are strong advocates for the treatment
- Provide the treatment in a careful and structured manner, not necessarily reproduced in busy non-specialist practice setting

EPIDEMIOLOGICAL DATA
Eriksen et al
Critical issues on opioids in chronic non-cancer pain: An epidemiological study
Pain, 2006;125:172-9

Functional status, satisfaction with medical treatment and use of health care system: users v. non-users

OVERALL
This evidence supports short-term efficacy of moderate dose opioid therapy, but does not inform us about opioid efficacy over years rather weeks or months

DOSE, ANALGESIC EFFICACY AND TOXICITY
1. There is no scientific evidence that high doses either do, or do not, provide good analgesia, since they are not generally used or studied.

2. There is good evidence that high doses have adverse effects.

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**REASONABLE CONCERNS**

- High dose opioid therapy (>180 mg morphine/day) is unusual (“outside the box”)*
- Could indicate drug seeking, abuse or diversion
- Could indicate inadequate analgesia, or opioid non-responsiveness
- Could be a manifestation of tolerance/dependence which warrant reassessment

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**ADVERSE EFFECTS OF HIGH OPIOID DOSES**

- Myoclonus and asterixis (observed and reported in cancer population)
- Neuroendocrine suppression
- Immune suppression
- Neuroadaptations that reduce analgesic efficacy (including OIH)

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**Neuroendocrine and immune effects**

**Neuroendocrine effects**

- **Hypothalamic-pituitary-adrenal axis**
  - ↓plasma cortisol

- **Hypothalamic-pituitary-gonadal axis**
  - ↑prolactin
  - ↓LH, FSH, testosterone, estrogen

**Clinical consequences:**

- Male and female infertility
- Decreased libido, aggression & drive
- Amenorrhea or irregular menses
- Galactorrhea

**Those affected:**

- Heroin addicts
- Ex-addicts receiving methadone
- Majority of those receiving IT opioid
- Extent of problem in chronic pain pts unknown

Daniell 02a, Daniell 02b, Finch 06, Paice 96, Abs 00
**Immune effects**

- Clinical relevance is not clear
- Preclinical research convincingly demonstrates that opioids alter the development, differentiation and function of immune cells
- Cells affected are: macrophages, NK cells, immature thymocytes, T cells and B cells
- Preclinical evidence suggests that prolonged exposure and abrupt withdrawal are both implicated

Roy 96, Risdahl 98, Rahim 03

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**Tolerance/Dependence**

**Psychological**

- Associative (learned) tolerance
  - Environmental clues
  - Psychological factors

**Pharmacological**

- Nonassociative (adaptive) tolerance
  - Cellular process
  - Receptor down-regulation
    - turnover rate
    - number
  - Receptor desensitization
    - NMDA linked

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**The adaptations that render opioids less useful**

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**Negative reinforcing effects as important as positive reinforcing effects**

- withdrawal anhedonia (*mesocorticolimbic system*) during early withdrawal
- withdrawal hyperalgesia (*pain systems*)
- physical effects of withdrawal arising from physical dependence (upregulation of cAMP in *locus ceruleus* and other locations)

NOTE: These are significant driving forces in drug-seeking behavior but are reversible

Cellular adaptations affecting analgesia

- Interfere with efficacy, especially at high doses
- Pharmacological tolerance, opioid induced pain (hyperalgesia) and the hyperalgesia of neuropathic pain are closely linked
- It is not always clear which of the phenomena (or combination) produce the clinical syndrome of opioid tolerance

Tolerance and opioid-induced hyperalgesia may be indistinguishable clinically

- Long term use of opioids may be associated with the development of abnormal sensitivity to pain
- Preclinical and clinical studies suggest that opioid-induced abnormal pain sensitivity has much in common with the cellular mechanisms of neuropathic pain
- Opioid-induced abnormal pain sensitivity has been observed in patients treated for both pain and addiction

Hyperalgesia reported and demonstrated in opioid treated patients

- NMDA-receptor-mediated changes in dorsal horn neurons arise with prolonged opioid exposure resulting in abnormal pain sensitivity
- Animal models have shown that NMDA-receptor-mediated cellular mechanisms mediate irreversible neurotoxic changes, including apoptosis

Summary

Strong evidence that opioids provide good short-term pain relief in chronic pain states

- No firm evidence that high doses are, or are not, effective
- Common sense reasons to be cautious about using high doses
- Good evidence suggesting high doses have adverse effects, including neuroendocrine effects, and neuroadaptations compromising opioid efficacy
EVIDENCE SUPPORTING EFFICACY. EVIDENCE ON RELATIONSHIP BETWEEN DOSE, ANALGESIC EFFICACY AND TOXICITY

Jane C Ballantyne, prepared March 2008