Opioids for chronic non-cancer pain

Research evidence from systematic reviews and meta-analyses

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2017 Anesthesia Research Interest Group Meeting
Conflicts of Interest

• I have no conflicts of interest in relation to this presentation
Background

• Approximately 1 in 5 Canadians suffer from chronic non-cancer pain (CNCP)

• North America, which represents 5% of the world’s population, consumes 80% of all prescription opioids

• Benefits of opioids for CNCP are uncertain
Background

- Dependence will develop in all patients engaged in long-term opioid therapy
- Between 8% and 12% of patients prescribed opioids for CNCP will develop addiction
- Opioid patients have a 64% increased risk of death when compared with alternative medications for moderate-to-severe chronic pain (hazard ratio = 1.64; 95% CI = 1.26 to 2.12)
- Opioid poisonings result in 13 hospitalizations a day in Canada and 7 ED visits in Ontario every day in 2014-2015
Opioids guideline evidence

- Short-term efficacy & harms of RCTs
  - Addiction, fatal or non-fatal overdose, diversion

- Long-term harms of observational studies
  - Predictor of long-term harms

- Dose tapering, rotation

- Risk mitigation strategies
  - UDS, Tx agreement, naloxone

- Others, e.g. hypogonadism
Objectives

To assess the benefits and harms of opioids for chronic non-cancer pain (CNCP) using a systematic review & meta-analysis of RCTs.

Eligibility criteria

• P: Patients with CNCP
• I: Any oral/sublingual/patch of opioids (excluding epidural, IV opioids)
• C: Placebo, non-opioids (e.g. NSAIDs, anticonvulsants, antidepressants, etc)
• O: IMMPACT outcomes (e.g. pain, physical/emotional/role/social functioning, sleep, and AEs)
  • Time: >=4 weeks (or >=12 weeks if subgroup effect was found)
Searching strategies

- **Databases: From the inception to September 2016**
  - MEDLINE/PubMed
  - EMBASE
  - CINAHL
  - PsycInfo
  - AMED
  - HealthSTAR
  - CENTRAL

- No language limitation

Risk of bias assessment

- Adjusted criteria from Cochrane risk of bias assessment tool
  - Randomization
  - Concealment
  - Blinding of patients, healthcare providers, data collectors, outcome assessors, data analysts
  - Loss to follow-up
  - Stop early
Data selection, coding and extraction

• Literature selection, RoB assessment, and data extraction were performed independently and in duplicate

• Calibration exercises

• Code-books for all treatments, outcomes, and chronic pain conditions

• Data extraction: standardized forms and instruction
Data analysis

• Meta-analysis:
  • Random effects model to pool data for each outcome across studies
  • Relative risk (RR) & 95% confidence interval (CI) for binary outcome (e.g. AEs)
  • WMD & 95%CI for continuous outcome after converting all instruments to the most common scale, e.g.
    • 10cm pain VAS scale
    • SF-36 PCS for physical functioning
    • SF-36 MCS for emotional functioning
  • Converting WMD to RR/RD/NNT to help interpretation
  • Heterogeneity using both a chi-squared test and the I² statistic
  • Publication bias: funnel plots, Egger’s test
Subgroup and sensitivity analyses

**Subgroup analyses**

1) Functional symptoms vs objectively diagnosed conditions
2) RoB
3) Placebo vs active placebo
4) Disability benefits
5) Involved in litigation
6) Stronger vs weaker opioids

**Post-hoc:** cross-over vs parallel; enrichment trials vs not

**Meta-regression:**

- MED
- Duration of treatment

**Sensitivity analyses**

- SMD
- End score vs change score
- Missing data
  - Imputation for missing SD
  - Imputation for non-significant results
- Pooling from different doses in multi-arm trials
- Pooling from different type of opioids in multi-arm trials

- Duration of follow-up
- Proportion of loss to follow-up
Results

Study selection:

Flow diagram

Records after duplicates removed (n = 41,954)

Records screened (n = 41,954)

Records excluded (n = 40,893)

Full-text articles assessed for eligibility (n = 1,061)

Full-text articles excluded, with reasons (n = 961)

Studies included in qualitative synthesis (n = 100)
Opioids vs. Placebo

1) Opioids vs. Placebo for Pain relief

Pain reduction on a 10cm VAS

WMD & 95%CI

- >=12 weeks: \(-0.71\text{cm} (-0.84 \text{ to } -0.57)\)
- 4 to 12 weeks: \(-1.05\text{cm} (-1.25 \text{ to } -0.85)\)
- Interaction \(p=0.014\)

MID is 1cm

- RR of achieving the MID 1.29, 95% CI 1.24, 1.34
- RD for achieving the MID 12%, 95% CI 10%, 14% (baseline at 42%)
- NNT = 8
2) Opioids vs. Placebo for Physical Functioning

Physical functioning on the 100-point SF-36 PCS

- **WMD 2.16; 95% CI 1.56 to 2.76**

**MID is 5 points**

- **RR of achieving the MID 1.24, 95% CI 1.17, 1.30**

- **Risk Difference for achieving the MID 10%, 95% CI 7%, 13% (baseline risk at 42%)**

- **NNT = 10**
3) Opioids vs. Placebo for Emotional Functioning

Emotional functioning on the 100-point SF-36 MCS

- **WMD 0.45; 95%CI -0.37 to 1.28**
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<th>Year</th>
<th>Design</th>
<th>RR (95% CI)</th>
<th>Vomiting &amp;/or nausea</th>
<th>Control</th>
<th>Events, %</th>
<th>NNH</th>
<th>RD, %</th>
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**NOTE:** Weights for forest vector meta-analysis.
Publication bias

Funnel plots for pain, physical, emotional functioning and GI AEs
Opioids vs NSAIDs

Pain relief: NS

Physical functioning: NS
Opioids vs antidepressants

Pain relief: NS

Physical functioning: NS
Long-term harms

• Opioid addiction: 5.5% (95% CI 3.91-7.03%)

• Fatal overdose:
  • <20 mg/day: 0.10%
  • 20-49 mg/day: 0.14%
  • 50-99 mg/day: 0.18%
  • ≥100 mg/day: 0.23%

• Non-fatal overdose:
  • <20 mg/day: 0.2%
  • 20-49 mg/day: 0.7%
  • 50-99 mg/day: 1.8%

• Diversion (other people getting access to patients’ opioids):
  • nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%-5.22%) in US
Summary

• **Opioids vs. placebo:** high quality evidence
  • Small improvements in pain relief and physical function
  • No improvement in emotional function
  • Increase the risk of GI AEs

• **Opioids vs. NSAIDs or antidepressants:**
  • Moderate to low quality evidence: no improvement in pain relief or physical functioning
  • High quality evidence: increase the risk of GI AEs compared to NSAIDs

• **Long-term harms:** moderate to high quality evidence
  • Opioids increase risk of addiction, fatal & non-fatal overdose, and diversion
Practice: trade-offs between benefits and harms

1. Will you recommend a trial of opioids for patients with CNCP (vs continuing the current therapy without opioids)?

2. Will you recommend opioids as first-line therapy for CNCP (other than non-opioid therapies)?
1. Will you recommend a trial of opioids for patients with CNCP (vs continuing the current therapy without opioids)?

- **Benefits:** High quality
  - Reduced pain by **0.71cm** (95%CI 0.84 to 0.57) on 10 cm VAS (MID=1cm)
  - Increased physical function by **2.16** (1.56 to 2.76) on SF-36 PCS (MID=5)
  - Average effects are **below** what is considered a minimally important difference for patients
  - ~10% more patients achieving MID of pain reduction and physical improvement

- **Harms:** moderate to high quality
  - Gastrointestinal side effects: ↑63 more per 1000
  - Risk of addiction: 55/1000
  - Fatal overdose: 1-2/1000, depending on dose
  - Non-fatal overdose: 2-18/1000, depending on dose
  - Risk of diversion: 49/1000 nonmedical use of prescription opioids
2. Will you recommend opioids as first-line therapy for CNCP (other than non-opioids)?

**Benefits:** Low to moderate quality
- no significant difference in pain relief for opioids vs. NSAIDs/antidepressants
- no significant difference in physical functioning for opioids vs. NSAIDs/antidepressants

**Harms:** moderate to high quality
- Gastrointestinal side effects: ↑70 more per 1000 (opioids vs NSAIDs)
- Risk of addiction: 55/1000
- Fatal overdose: 1-2/1000, depending on dose
- Non-fatal overdose: 2-18/1000, depending on dose
- Risk of diversion (other people getting access to patients’ opioids): 49/1000 nonmedical use of prescription opioids
Recommendations

RC #2

Patients with persistent problematic pain despite optimized non-opioid therapy, without current or past substance use disorder or current serious psychiatric disorder

Weak Recommendation

We suggest a trial of opioids rather than continued non-opioid therapy

RC #1

When considering first-line therapy for patients with chronic non-cancer pain

Strong Recommendation AGAINST

We recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids
Acknowledgements

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