Opioids for Chronic Pain: Deconstructing the Evidence

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Contextualizing the issues
Understanding the evidence
Implications

Opioids for Chronic Pain: Deconstructing the Evidence

Opioids and Pain: International Consensus

Opioid therapy is first-line for moderate to severe acute pain in some settings, e.g.,
- Postoperative pain
- Post-traumatic pain in monitored environments
- Breakthrough pain in opioid-treated patients with serious illness

Opioid therapy is not first-line in some settings, e.g., recurrent headache
Opioids and Pain: International Consensus

- Opioid therapy is a first-line approach for moderate to severe chronic pain due to active cancer or other serious or life-threatening illness
  - Considered to be a best practice in specialist palliative care

- Opioid therapy is not the first-line therapy for so-called “chronic non-cancer pain” and chronic headache

- Around the world, there is both
  - Concern about access and undertreatment
  - Concern about medical diversion and the potential for overtreatment

- Best practices are predicated on an understanding of this complexity

Documents calling for more access to opioids
- IASP Montreal Declaration on pain relief as a fundamental human right
- World Medical Association Declaration on access to pain relief
- Human Rights Watch reports on access to pain relief and palliative care in selected developing countries
- Union for International Cancer Control (UICC) Global Access to Pain Relief Initiative (GAPRI)
Opioids and Pain: What Are Best Practices?

- Issues in defining best practices
  - Clarifying definitions
  - A complicated history
  - An evolving evidence base

Opioids and Pain: Definitional Issue

- What is “chronic non-cancer pain”?
  - *Does it include*…any and all chronic pains?
    - Ex: Disabling low back pain due to degenerative spine disease in the 70 yo with advanced Parkinson’s disease
    - Ex: Severe lower body burning after spinal cord injury
    - Ex: PHN in a 90 yo with mild dementia
  - *Does it exclude*…any and all chronic pains in patients with cancer?
    - Ex: Low back pain in a patient in remission from cancer
    - Ex: Migraine in a patient with an indolent form of cancer

Opioids and Pain: Definitional Issue

- The term “chronic non-cancer pain” has no agreed-upon clinical meaning
- Without clarification, use of this term may:
  - Complicate the understanding of guidelines, policies, regulations and laws
  - Lead to categorical thinking and unreasonable conclusions
  - Discourage a balanced perspective in patient care
Opioids and Pain: A Complicated History

- Identifying best practices also may be complicated by the history of opioid therapy in the US
- History may be influenced by whom is recounting it

Stakeholders
- Those who have pain
- Those who treat pain
- Those who have addiction
- Those who treat addiction
- Those who enforce the law
- Those in the media
- Those who legislate opioid drug policy or professional practice
- Those who regulate opioid drugs or professional practice
- Those who adjudicate regulation and law enforcement
- Those in the public concerned about various parts of health policy

Opioids and Pain: A Complicated History

- Medical use of opioid drugs has fluctuated for centuries
- During most of the 20th century in the US, long-term opioid use was considered generally inappropriate, ineffective and risky

Opioids and Pain: A Complicated History

- Beginning in the mid-1980’s, increasing interest in opioid therapy for all types of pain
- Many possible drivers
  - Emerging medical literature and professional advocacy for opioid use in cancer pain
  - Evolution of pain as a medical subspecialty, with increasing outreach to the professions and the public
  - Media attention on pain as an unmet need
  - Early publications of positive case series and observational studies
  - Outreach to government to add “balance” to laws and regulation
  - Promotion by the pharmaceutical industry
Opioids and Pain: A Complicated History

Late 1980’s and 1990’s
- Accelerating educational efforts on the part of professional societies to inform clinicians about opioids and their potential use in chronic pain
  - Messages emphasized potential benefit and minimized risk, and highlighted bias inherent in “opiophobia”
- Accelerating activity in the policy arena
  - Survey data published showing lack of knowledge on the part of the Medical Boards
  - Survey data published showing that most states had laws or regulations with outdated or inaccurate definitions and overly restrictive requirements

Opioids and Pain: A Complicated History

1990’s-2000’s
- Many states passed “Intractable Pain Treatment Acts” or amended laws with outdated definitions or overly restrictive regulations
  - Texas was the first Intractable Pain Treatment Act, followed by California, Colorado, Florida, Washington, and others
- October 23, 2001: Unprecedented Joint statement from the Drug Enforcement Administration and 21 organizations, including AMA, ACS, and American Pharmaceutical Association, calling for a balanced approach to regulation
  - Emphasized the importance of crafting drug abuse prevention programs in a way that does not hinder legitimate use of opioids
Opioids and Pain: A Complicated History

1990’s-2000’s
- Many Medical Boards revised regulations and required education of members
  - 1998: Federation of State Medical Boards issued first Model Guideline for the Use of Controlled Substances in the Management of Pain
  - 2004: Federation expanded Guideline to a Model Policy

Opioids and Pain: A Complicated History

Beginning in the early 1990’s
- Accelerating opioid prescribing by both pain specialists and primary care physicians
- Initial data about adverse outcomes associated with this increase was reassuring

Later in the 1990s and continuing to the 2010’s
- Evidence accumulates that opioid-related adverse outcomes have increased rapidly
  - Addiction, abuse, diversion, and unintentional overdose

Opioids and Pain: A Complicated History

![Graph showing total number of hydrocodone and oxycodone prescriptions dispensed by US retail pharmacies from 1993-2009]
Opioids and Pain: A Complicated History

- Study of a health care claims database 1997 to 2005
  - Incidence of long-term opioid use increased by 16% to 87% in different age and gender groups
  - Prevalence of long-term opioid use increased by 61% to 135% in different age and gender groups

Campbell CI et al. Am J Public Health 2010;100:2541-7

- Another study of a claims database 1997 to 2005
  - Prevalence of long-term opioid use
    - Increased from 7.6% to 18.6% in patients with SUD
    - Increased from 2.7% to 4.2% in those w/o SUD


Opioids and Pain: A Complicated History

Past Year Initiates of Specific Illicit Drugs among Persons Aged 12 or Older: 2007 vs. 2010
Primary non-heroin opiates/synthetics admission rates, by State (per 100,000 population aged 12 and over)

Opioids and Pain: A Complicated History

Opioid-Related Deaths 1999–2006

Opioids for Chronic Pain: Deconstructing the Evidence

- Recent history has underscored the risks associated with opioid therapy
  - Addiction, abuse, unintended overdose, and diversion
- This history complements emerging data about previously unappreciated side effects
  - Sleep disordered breathing, hypogonadism, opioid-induced hyperalgesia
Opioids for Chronic Pain: Deconstructing the Evidence

- Contextualizing the issues
- Understanding the evidence
- Implications

Opioids for Chronic Pain: Interpreting the Data

- Framework
  - Evidence-based medicine
    - Quality of the evidence
      - Strength of recommendation
  - Efficacy vs. effectiveness vs. comparative effectiveness
  - How do the data match up against opioids for cancer pain, or data on other drug classes?

Opioids and Pain: Evidence in Cancer Pain

Evidence report on the treatment of pain in cancer patients


- Systematic review of RCTs of all treatments for cancer pain
- 213 RCTs limited by few subjects, low methodological quality, little detail about pain characteristics and mechanisms, and heterogeneous interventions and outcomes
**Opioids and Pain: Evidence in Cancer Pain**

Evidence report on the treatment of pain in cancer patients


- **Conclusion:** RCTs confirm efficacy of opioids, but data are inadequate to determine optimal use or overall effectiveness; the quantity and quality of evidence compare unfavorably with evidence related to treatment of other high-impact conditions.

**Opioids and Pain: Evidence in Cancer Pain**

Systematic review of RCTs of opioids for cancer pain


- Systematic review of RCTs of systemic opioids for cancer pain through 2010
- 15 RCTs identified, only 6 with moderate-to-high quality methodology

**Opioids and Pain: Evidence in Cancer Pain**

Systematic review of RCTs of opioids for cancer pain


- **Conclusion:** Few RCTs, limited by lack of detail about pain characteristics and mechanisms, and follow-up periods <4 weeks. There is fair evidence for the efficacy of transdermal fentanyl and poor evidence for morphine, tramadol, oxycodone, methadone and codeine.
Opioids and Pain: Evidence in Cancer Pain

Systematic review of observational studies of opioids for cancer pain


- Systematic review of observational studies of opioids with or without other treatments from 1996 through June 2010
- 7 studies met criteria of >3 months and >50 patients; one used IT therapy
- 4 studies had high quality and 3 had moderate quality
- Results showed all studies with positive outcomes at 3 months; three longer studies had positive outcomes at 12 months

Conclusion: Observational studies provide a moderate level of evidence of effectiveness and support a strong recommendation to use this therapy

In EBM terms, opioids for cancer pain have a high 'strength of recommendation' due to observational studies providing moderate evidence, despite little to no high quality evidence

Opioids in Chronic Non-cancer Pain: Systematic Reviews

Opioids in chronic non-cancer pain

- Kalso E et al. Pain. 2004;113(3):372-80

- Systematic review of RCTs through September 2003
- 11 RCTs (N=1025) of oral opioid therapy for any type of pain, with study duration 4 days to 8 weeks
- Mean decrease in neuropathic and musculoskeletal pain was at least 30%
- 44% of 388 patients on open label treatments continued for 7-24 months
Opioids and Pain: Systematic Reviews

Opioids in chronic non-cancer pain
Kalso E et al. Pain. 2004;112(3):372-80

- Conclusion: Opioids have short-term efficacy but data are insufficient to judge long-term outcomes.

Opioids and Pain: Systematic Reviews

Opioids for chronic noncancer pain
Furlan AD et al., CMAJ. 2006 May 23;174(11):1589-94

- Meta-analysis of RCTs through May, 2005
- 41 RCTs (N=6019) of any oral opioid therapy for any type of pain, with study duration averaging 5 weeks (range 1-16 weeks)
- Opioids outperformed placebo for pain and functional outcomes in all types of pain
- “Strong” opioids were superior to naproxen and nortriptyline only for pain relief

Opioids and Pain: Systematic Reviews

Opioids for chronic noncancer pain
Furlan AD et al., CMAJ. 2006 May 23;174(11):1589-94

- Conclusions:
  1) Opioids have short-term efficacy for pain and function in all types of pain
  2) Opioids are better than other drugs for pain, but not functional outcomes
  3) There are insufficient data to judge long-term outcomes
Opioids and Pain: Systematic Reviews

Opioids for neuropathic pain

- Systematic review and meta-analysis through 2005
- 23 RCTs of systemic opioids in central or peripheral neuropathic pain with study duration either short-term (hours or days) or intermediate-term (median 28 days)
- Short-term trials had contradictory results and intermediate-term trials demonstrated opioid efficacy; meta-analysis of 7 studies showed efficacy

CONCLUSIONS:
1) Opioids have short-term efficacy for neuropathic pain
2) There are insufficient data to judge long-term outcomes

Treatments for neuropathic pain

Opioids and Pain: Systematic Reviews

Opioid treatment for chronic back pain

- Systematic review and meta-analysis through 2005
- Mixed types of studies of oral, topical, or transdermal opioids for chronic back pain, with study duration less than 16 weeks
- Meta-analysis of 4 studies of opioids vs. placebo or nonopioid did not show efficacy ($p=0.136$)
- Meta-analysis of 5 studies of different opioids did not show reduction in pain from baseline ($p=0.055$)
- Aberrant medication-taking behaviors ranged from 5% to 24%

CONCLUSIONS:
1) Opioids have limited, if any, short-term value in chronic low back pain
2) Evidence about substance abuse is too limited to draw any conclusions
3) There are insufficient data to judge long-term outcomes

Opioids and Pain: Systematic Reviews

Opioids for chronic back pain

- Systematic review through May, 2007
- RCTs of oral opioids for >4 weeks
- Only 4 trials, three assessing tramadol
- All trials criticized for methodological problems
- Conclusion: There are insufficient data to judge outcomes in chronic LBP
Opioids and Pain: Systematic Reviews

Review of long-acting opioids


- 34 RCTs of varied drugs, pain syndromes, and methodologies
- All but one study 5 weeks to 24 weeks in duration; one study of 13 months
- All trials criticized for methodological problems

**Conclusion:** There are insufficient data to judge effectiveness or comparative effectiveness

Opioids and Pain: Systematic Reviews

Opioids for chronic noncancer pain

Manchikanti et al. Pain Physician 2011; 14:91-121

- Systematic review through 2010
- RCTs of systemic opioids for >3 months
- 20 studies, of which 16 had significant methodological deficiencies
- Studies varied in drug, pain syndromes, and methodologies
Opioids and Pain: Systematic Reviews

Opioids for chronic noncancer pain

Manchikanti et al. Pain Physician 2011; 14:91-121

- **Conclusion**: With the exception of fair evidence for tramadol in osteoarthritis, evidence of long-term efficacy is poor based on either weak positive evidence or indeterminate or negative evidence.

Opioids for noncancer pain: surveys

Noble M et al., J Pain Symptom Manage. 2008;35:214-228

- Systematic review of open-label prospective studies through April, 2007
- 17 studies (N=3079) of any oral, transdermal or neuraxial opioid for any type of pain, with study duration at least 6 months

Opioids and Pain: Systematic Reviews

Opioids for noncancer pain: surveys

Noble M et al., J Pain Symptom Manage. 2008;35:214-228

- Many patients stopped opioid treatment over time due to side effects or poor response
  - oral 32.5%, transdermal 17.5%, neuraxial 6.3%
  - Signs of addiction in 0.05%; abuse in 0.43%
  - Small but significant pain reduction for oral therapy (mean 1.99 points) and neuraxial therapy (mean 1.33 points); too few data to judge transdermal

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**Conclusions:**
1) Many patients stop therapy but there is weak evidence that those who continue have pain relief over time
2) There are insufficient data to judge other long-term outcomes, including function and drug abuse

Opioids and Pain: Systematic Reviews
Comparative effects of oral opioids for chronic non-cancer pain:

- Systematic review of both RCTs and observational studies
- 16 RCTs (comparative efficacy and adverse events) with 1427 patients, and 8 observational studies (adverse events) with 1190 included
- No good quality studies

**Conclusion:** Data are inadequate to determine whether any long-acting drug is better than any other, or long-acting drugs are preferable to short-acting drugs.
Opioids and Pain: Systematic Reviews

Development of dependence following treatment with opioids for pain

- Systematic review of 17 studies (N=88,235) including 3 systematic reviews, 1 RCT, and 12 observational studies
- Results: Incidence = 0-24% (median 0.5%); prevalence = 0-31% (median 4.5%)
- Conclusion: Opioids for chronic pain are not associated with a major risk for developing dependence

Opioids and Pain: Evidence Assessment

ASIPP Evidence Assessment

- Convened a multidisciplinary panel of 56 experts
- Evidence review using previously published reviews, systematic reviews, literature search and guidelines
- Methodological quality review

Opioids and Pain: Evidence Assessment

ASIPP Evidence Assessment

- Selected conclusions
  - Fair evidence of short-term effectiveness for pain relief and for improvement in QOL parameters
  - Lack of long-term (>3 months) high quality studies provides no evidence to judge long-term effectiveness for pain or for QOL parameters
Selected conclusions

• Good evidence that approximately one-third of chronic pain patients may not use prescribed opioids as prescribed.

• Good evidence that illicit drug use in chronic pain patients is significantly higher than the general population.
  - Illicit use is high in patients receiving opioids and higher in those abusing opioids.

• Good evidence that the increased supply of opioids, use of high dose opioids, doctor shopping, and patients with multiple comorbid factors contribute to the majority of fatalities.

• Good evidence that approximately 60% of fatalities originate from opioids prescribed within the guidelines.

• Good evidence that approximately 40% of fatalities occur in 10% of drug abusers.

• Lack of evidence that screening for opioid abuse using an instrument reduces abuse.

• Fair evidence that Prescription Monitoring Programs reduce drug abuse of doctor shopping.

• Lack of evidence that Prescription Monitoring Programs reduce ED visits, overdoses, or deaths.
Opioids for Chronic Pain: Deconstructing the Evidence

- Contextualizing the issues
- What are the data?
- Implications

Opioids and Pain: Implications

- Although the data are mixed, the systematic reviews generally support the efficacy of opioid therapy for a period of months and suggest that a subpopulation can benefit long-term.
- But there is no high-quality evidence about long-term effectiveness.

In the absence of adequate evidence, it is wrong to conclude that:
- Opioid drugs lack long-term effectiveness
- Risks exceed benefits overall, or in subpopulations

Alternative conclusions are equally likely:
- Some patients benefit, and some are harmed
- Some subpopulations may be "overtreated", and some are "undertreated"
Opioids and Pain: Implications

- Given the evidence, the best approach is balance
  - Balance in opioid policy
  - Balance in opioid regulation
  - Balance at the bedside

Opioids and Pain: Implications

- New FDA labeling:
  "for the management of pain severe enough to require daily, around-the-clock opioid treatment and for which alternative treatments are inadequate"
- Careful patient selection, competent risk management, regular assessment and the use of therapeutic trials and exit strategies are needed