The Opioid Spectrum: Promoting Health and Preventing Harm

Shawn Bugden B.Sc.(Pharm), MSc, PharmD
Associate Professor
May 8th, 2017
Disclosures

- The research elements of this presentation were funded from grants from the University of Manitoba, College of Pharmacists of Manitoba

- No other relevant relationships to disclose
Learning Objectives

- Consider and review the evolution of current guidelines on the use of opioids in management of chronic non-cancer pain
- Evaluate the current utilization of opioids in Manitoba against guideline recommendations
How to Avoid a Mess

How big is this box?  And this one?

Benefit

Harm

$$
Hierarchy of Evidence

- Meta-analysis of RCTs
- Individual RCT
- Observational Studies (Patient Important Outcomes)
- Basic Research (Test tube, animal/human physiology)
- Clinical Experience (Non-systematic clinical observation)
1979
Boston University
Boston Collaborative Drug Surveillance Program
How often do hospitalized patients given narcotic pain killers develop addiction
ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients\textsuperscript{1} who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,\textsuperscript{2} Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

Jane Porter
Hershel Jick, M.D.
Boston Collaborative Drug Surveillance Program

Waltham, MA 02154

BOSTON UNIVERSITY MEDICAL CENTER
Porter and Jick

- < 1% treated with opioids developed addition
- Educational seminars
- Only electronically archived in 2010
- Scientific American (1990) “an extensive study”
- Time (2001) “landmark study” “exaggerated fear that patients would become addicted” to opiates was “basically unwarranted.”

ADDITION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients1 who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,2 Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

Jane Porter
Hershel Jick, M.D.
Boston Collaborative Drug Surveillance Program
Waltham, MA 02154

Boston University Medical Center
WHO Ladder
Pain Treatment as a Right

- Jan Stjensword – WHO Geneva 1980
- Vittario Ventafridda
- Cancer pain
- Morphine as an essential drug
- Freedom from pain as universal human right
Response

- 1980 to 2011 30 fold increase in opioid use
- Not in developing world
- Fear and access issues opioids remain in developing world
- 20% of world consumes 90% of world’s morphine
Opioid Utilization in Manitoba
Opioid Utilization in Manitoba

Overall Opioid Utilization

- 14% increase in Users
- 233% increase in Morphine Equivalents
Chronic Use of Opioid Analgesics in Non-Malignant Pain: Report of 38 Cases

Russell K. Portenoy and Kathleen M. Foley

(Pain Service, Department of Neurology, Memorial Sloan-Kettering Cancer Center, and Department of Neurology, Cornell University Medical College, New York, NY 10021 (U.S.A.))

(Received 10 June 1985, accepted 28 October 1985)
Non-Cancer Pain

- Risk of addiction was low when opiates used to treat patients in pain
- Pain as the “fifth vital sign”
Non-Cancer Pain

- 1998 Veterans Health Administration makes pain “5th vital sign”
- The Joint Commission for Accreditation of Healthcare Organizations (JCAHO) – pain as 5th vital sign
Non-Cancer Pain

- Oxycodone 1916
- 30% adult population has acute or chronic pain
- OxyContin® 1996
- Chronic pain prevalence of 40% in older adults
Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain

Part A: Executive Summary and Background
Part B: Recommendations for Practice

PART B

— Recommendations for Practice —

Published by the National Opioid Use Guideline Group (NOUGG) a collaboration of:

Federation of Medical Regulatory Authorities of Canada
College of Physicians & Surgeons of British Columbia
College of Physicians & Surgeons of Alberta
College of Physicians and Surgeons of Saskatchewan

[Highlighted: College of Physicians & Surgeons of Manitoba]
College of Physicians and Surgeons of Ontario
Collège des médecins du Québec
College of Physicians and Surgeons of New Brunswick
College of Physicians and Surgeons of Nova Scotia
College of Physicians and Surgeons of Prince Edward Island
College of Physicians and Surgeons of Newfoundland and Labrador
Government of Nunavut
Yukon Medical Council

April 30 2010  Version 5.6
http://nationalpaincentre.mcmaster.ca/opioid/
R04  Before initiating opioid therapy, consider the evidence related to effectiveness in patients with chronic non-cancer pain. (Grade A).

R05  Before initiating opioid therapy, ensure informed consent by explaining potential benefits, adverse effects, complications and risks (Grade B). A treatment agreement may be helpful, particularly for patients not well known to the physician or at higher risk for opioid misuse. (Grade C).

R10  Chronic non-cancer pain can be managed effectively in most patients with dosages at or below 200 mg/day of morphine or equivalent (Grade A). Consideration of a higher dosage requires careful reassessment of the pain and of risk for misuse, and frequent monitoring with evidence of improved patient outcomes. (Grade C).
Table 2: Duration of opioid therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of studies</th>
<th>Duration of therapy (wk)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average</td>
<td>Minimum</td>
<td>Maximum</td>
<td></td>
</tr>
<tr>
<td>Nociceptive pain</td>
<td>25</td>
<td>4.8</td>
<td>1</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>12</td>
<td>4.4</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Mixed pain</td>
<td>2</td>
<td>8.5</td>
<td>1</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>2</td>
<td>8.8</td>
<td>6</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>5.0</td>
<td>1</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>
### Do they Work?

<table>
<thead>
<tr>
<th>Examples of CNCP conditions for which opioids were shown to be effective in placebo-controlled trials*</th>
<th>Examples of CNCP conditions that have NOT been studied in placebo-controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tramadol only</strong></td>
<td><strong>Weak or strong opioid</strong></td>
</tr>
</tbody>
</table>
| *Fibromyalgia* | • Diabetic neuropathy  
• Peripheral neuropathy  
• Postherpetic neuralgia  
• Phantom limb pain  
• Spinal cord injury with pain below the level of injury  
• Lumbar radiculopathy  
• Osteoarthritis  
• Rheumatoid arthritis  
• Low-back pain  
• Neck pain | • Headache  
• Irritable bowel syndrome  
• Pelvic pain  
• Temporomandibular joint dysfunction  
• Atypical facial pain  
• Non-cardiac chest pain  
• Lyme disease  
• Whiplash  
• Repetitive strain Injury |

*A limitation of these trials was that the duration of opioid therapy was a maximum of three months.*
Do They Work

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain, without current or past substance use disorder and without other current serious psychiatric disorders, whose therapy is optimized with non-opioids with persistent problematic pain

Intervention: Trial of opioids.

Comparator: Continue established therapy without opioids.

Busse JW et al. 2017 CMAJ 189:E569
Do They Work?

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (difference in patients who achieve the MID or greater) 3-6 months</td>
<td>Relative risk 1.25 (CI 95% 1.21 - 1.29) Based on data from 13,876 patients in 27 studies. (Randomized controlled) Follow up 3-6 months</td>
<td>Continue established therapy without opioids. Trial of opioids.</td>
</tr>
</tbody>
</table>

448 per 1000

560 per 1000

Difference: **112 more** per 1000 (CI 95% 94 more - 130 more)

Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.

Busse JW et al. 2017 CMAJ 189:E569
Do They Work?

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Measured by: 10 cm VAS</td>
<td>Continue established therapy without opioids.</td>
</tr>
<tr>
<td>3-6 months</td>
<td>Scale: 0-10 Lower better Based on data from: 13,876 patients in 27 studies. (Randomized controlled) Follow up 3-6 months</td>
<td>Difference: <strong>MD 0.64 fewer</strong> ( CI 95% 0.76 fewer - 0.53 fewer )</td>
</tr>
</tbody>
</table>

Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Recognition of Side Effects

- Other concerns with long-term use
  - Sexual dysfunction
  - Sleep apnea
  - Opioid-Induced Hyperalgesia

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Number of Studies</th>
<th>Incidence in Opioid Group</th>
<th>Incidence in Placebo Group</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>38</td>
<td>28%</td>
<td>9%</td>
<td>17% (13% to 21%) P&lt;0.00001</td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
<td>26%</td>
<td>7%</td>
<td>20% (15% to 25%) P&lt;0.00001</td>
</tr>
<tr>
<td>Somnolence/drowsiness</td>
<td>30</td>
<td>24%</td>
<td>7%</td>
<td>14% (10% to 18%) P&lt;0.00001</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>33</td>
<td>18%</td>
<td>5%</td>
<td>12% (9% to 16%) P&lt;0.00001</td>
</tr>
<tr>
<td>Dry-skin/ itching/pruritus</td>
<td>25</td>
<td>15%</td>
<td>2%</td>
<td>10% (5% to 15%) P&lt;0.0001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23</td>
<td>15%</td>
<td>3%</td>
<td>11% (7% to 16%) P&lt;0.00001</td>
</tr>
</tbody>
</table>
## Addiction

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction</td>
<td>Based on data from 22,278 patients in 9 studies</td>
<td>Continue established therapy without opioids.</td>
</tr>
<tr>
<td>FU not reported</td>
<td></td>
<td>Trial of opioids.</td>
</tr>
</tbody>
</table>

**Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%).**

Busse JW et al. 2017 CMAJ 189:E569
# Overdose

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal overdose median 2.6 years</td>
<td>Based on data from 285,520 patients in 1 studies</td>
<td>Continue established therapy without opioids.</td>
</tr>
</tbody>
</table>

Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18%, and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.

Busse JW et al. 2017 CMAJ 189:E569
## Diversion

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diversion</strong></td>
<td>Based on data from 472,200 patients in 1 studies</td>
<td>Continue established therapy without opioids.</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td>Trial of opioids.</td>
</tr>
</tbody>
</table>

Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%-5.22%) in 2013.

Busse JW et al. 2017 CMAJ 189:E569
Watchful Dose Analysis

Rates of Opioid Use by Dose Level - Non-Cancer Patients

- Dose Level: 200mg plus, 50-99mg, 100-199mg

Users per 10,000 persons

Watchful Dose Analysis

<table>
<thead>
<tr>
<th>Dosage Range</th>
<th>Cases, n/N</th>
<th>Controls, n/N</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥200 mg</td>
<td>116/498</td>
<td>223/1714</td>
<td>2.88 (1.79-4.63)</td>
</tr>
<tr>
<td>100-199 mg</td>
<td>82/498</td>
<td>181/1714</td>
<td>2.04 (1.28-3.24)</td>
</tr>
<tr>
<td>50-99 mg</td>
<td>97/498</td>
<td>273/1714</td>
<td>1.92 (1.30-2.85)</td>
</tr>
<tr>
<td>20-49 mg</td>
<td>118/498</td>
<td>514/1714</td>
<td>1.32 (0.94-1.84)</td>
</tr>
</tbody>
</table>

Primary analysis: overlapping opioid prescriptions
(Reference: 1-19 mg morphine equivalents)

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.

2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.
The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

Main editor
Jason Busse

Associate Professor, Department of Anesthesia
Associate Professor, Department of Health Research Methods, Evidence, and Impact
McMaster University, MDCL-2109
1280 Main St West, Hamilton, Ontario, Canada, L8S 4K1
bussejw@mcmaster.ca
Recommendation 1: When considering therapy for patients with chronic non-cancer pain

**Strong Recommendation**

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

Recommendation 2: For patients with chronic noncancer pain, without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized nonopioid therapy

**Weak Recommendation**

We suggest adding a trial of opioids rather than continued therapy without opioids.
Recommendations 6 and 7: For patients with chronic noncancer pain who are beginning long term opioid therapy

**Strong Recommendation**

Recommendation 6: We recommend restricting the prescribed dose to less 90mg morphine equivalents daily rather than no upper limit or a higher limit on dosing

Some patients may gain important benefit at a dose of more than 90mg morphine equivalents daily. Referral to a colleague for a second opinion regarding the possibility of increasing the dose to more than 90mg morphine equivalents daily may therefore be warranted in some individuals.

**Weak Recommendation**

Recommendation 7: For patients with chronic noncancer pain who are beginning opioid therapy, we suggest restricting the prescribed dose to less than 50mg morphine equivalents daily.

The weak recommendation to restrict the prescribed dose to less than 50mg morphine equivalents daily acknowledges that there are likely to be some patients who would be ready to accept the increased risks associated with a dose higher than 50mg in order to potentially achieve improved pain control.
Alberta

Figure 6a. Age and Sex Standardized, Patients Who Received Greater than 200 CME per Day per 1,000 Population by Subzone, 2014

Figure 6b. Age and Sex Standardized, Patients Who Received Greater than 200 CME per Day per 1,000 Population by Urban Subzone, 2014

Figure 6c. Age and Sex Standardized, Patients Who Received Greater than 200 CME per Day per 1,000 Population by Subzone, 2014

Note: Subzone 25.5 (North-RW) does not have any pharmacies and therefore no prescriptions are reported.
Manitoba Atlas of Opioid Utilization

Patterns of prescription opioid utilization in Manitoba from April 2001 to March 2014

K Friesen BSc (Pharm), S Bugden BSc (Pharm), MSc, PharmD
6/29/2013
Meperidine

**Figure 5: Trends Prescriber Patterns**

- **Low DDD Prescribers**
- **High DDD Prescribers**

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Number of Prescribers</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001/02</td>
<td></td>
</tr>
<tr>
<td>2002/03</td>
<td></td>
</tr>
<tr>
<td>2003/04</td>
<td></td>
</tr>
<tr>
<td>2004/05</td>
<td></td>
</tr>
<tr>
<td>2005/06</td>
<td></td>
</tr>
<tr>
<td>2006/07</td>
<td></td>
</tr>
<tr>
<td>2007/08</td>
<td></td>
</tr>
<tr>
<td>2008/09</td>
<td></td>
</tr>
<tr>
<td>2009/10</td>
<td></td>
</tr>
<tr>
<td>2010/11</td>
<td></td>
</tr>
<tr>
<td>2011/12</td>
<td></td>
</tr>
<tr>
<td>2012/13</td>
<td></td>
</tr>
<tr>
<td>2013/14</td>
<td></td>
</tr>
</tbody>
</table>
Oxycodone – Long Acting

1999 OxyContin® enters market

Pharmacare Change

OxyNeo® replaces OxyContin®
Oxycodone (Overall)
Opioid Utilization in Manitoba

Figure 1: Total Opioid Consumption

- Combined Total
- Immediate Release Opioids
- Controlled Release Opioids

Morphine Equivalents (kg)

Year

2001 2003 2005 2007 2009 2011 2013
Pregnancy

Falk et al. 2017 CMAJ Open in press
One Thing We Can Do?

McDonald EM et al. 2017 Pediatrics 139:e20162161
Balance

How big is this box? And this one?

Benefit

$$

Harm
Acknowledgements

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Population Health Research Data Repository under project #2012/2013-08 2013/2014-35. The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, Senior and Active Living, or other data providers is intended or should be inferred. Data used in this study are from the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health, Seniors and Active Living and the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba.