A Practical Approach To Prescribing Opioids for Chronic Pain

The Practical Aspects of Opioid Therapy for Chronic Non-Cancer Pain

Dr. Jeff Ennis

May 13, 2003
Personal Qualifications
Agenda

- History
- Structure and Function
- Addiction/Tolerance/ Pseudoaddiction/Abuse
- Practical Aspects of Prescribing Opioids
- Special issues
The History of Opioids I

The History of Opioids has been characterized by the ongoing struggle between medical use and recreational abuse.

Friedrich Sertuerner
A Brief History of Opium II

- **3400 BCE**: *Hul Gil* (joy plant) is cultivated in Mesopotamia.
- **460 BCE**: Hippocrates recognizes and records the analgesic effect of opium.
- **1527**: Paracelsus dissolves opium in alcohol creating Laudanum.
- **1606**: Elizabeth I charters ships to transport opium from India to England.
- **1803**: Friedrich Sertuerner of Paderborn, Germany isolates morphine—it is referred to as “God’s own medicine”.
- **1841**: China loses the first opium war and Britain gets Hong Kong as a spoil of war.
- **1843**: Dr. A. Wood of Edinburgh administers morphine, by injection.
A Brief History of Opium III

- **1853**: China loses the 2nd Opium War and opium is legalized in China.
- **1878**: Britain passes the Opium Act (only registered Chinese opium smokers and Burmese opium eaters can use opium)
- **1895**: Bayer produces ‘heroin’
- **1910**: Britain dismantles its opium trade
- **1914**: The Harrison Act (U.S) legalizes the use of opioids if prescribed by a physician only.
- **1978**: The U.S. and Mexican Gov’t spray poppy fields with Agent Orange. Opium importation shifts to Afghanistan. Iran & Pakistan
Structure and Function

Papaver somniferum
Opioid Receptors

- Forebrain/diencephalon
  - amygdala/nucleus accumbens
- Mesencephalon (midbrain)
- Periaqueductal grey
- reticular formation
- substantia nigra
- Lower Brainstem
- medial medulla
- Spinal Cord
- Primary Afferents
- C-fibres
Peripheral Opioid Receptors 2

- Gastrointestinal tract
- Cardiac Muscle
- Joints
- Skin
Mechanism of Action

- Hyperpolarization of nerves by opening potassium channels/Calcium Channels in 1st (receptor to medulla) and 2nd order neurons (medulla to thalmus)

- Inhibition of ascending pathways in the CNS

- Excitation of descending adrenergic and serotonergic pathways
μ Opioid Receptors

- **Analgesia**
- Euphoria
- Respiratory depression
- Cough Suppression
- Miosis
- Reduced GI motility
κ Opioid Receptors

- Analgesia
- Dysphoria
- Psychomimetic Effects
- Respiratory Depression (less than µ)
- Mioisis
- Reduced GI motility
δ Opioid Receptor

- Analgesia
- Some euphoria
- Decrease GI motility
- No effect on respiration
σ Opioid Receptor

- Hallucination
- Dysphoria
- Inhibits exogenous opioids
# Endogenous Opioid Peptides

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Endogenous peptide</th>
<th>Receptor Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-opiomelanocortin</td>
<td>β-Endorphin</td>
<td>μ and δ</td>
</tr>
<tr>
<td>Pro-enkephalin</td>
<td>[Met]enkephalin</td>
<td>δ</td>
</tr>
<tr>
<td></td>
<td>[Leu]enkephalin</td>
<td></td>
</tr>
<tr>
<td>Pro-dynorphin</td>
<td>Dynorphin A</td>
<td>κ</td>
</tr>
<tr>
<td></td>
<td>Dynorphin A(1-8)</td>
<td>μ and δ</td>
</tr>
<tr>
<td></td>
<td>Dynorphin B</td>
<td></td>
</tr>
<tr>
<td>Pro-nociceptin / OFQ</td>
<td>Nociceptin</td>
<td>ORL-1</td>
</tr>
<tr>
<td>Pro-endomorphin (?)</td>
<td>Endomorphin-1</td>
<td>μ</td>
</tr>
<tr>
<td></td>
<td>Endomorphin-2</td>
<td></td>
</tr>
</tbody>
</table>
Possible Roles/Effects of Endorphins

- Nociception
- Stress
- Physical exertion
- Sexual Activity
- Feeding and Drinking Behaviour
- Psychiatric Disorders
- Seizures
- Cardiovascular Regulation
- Respiration
- Thermoregulation
- Neuroendocrine Regulation
Synthetic Opioids
Synthetic Opioids 1

Phenanthrene Derivatives

prototype - morphine

Other related compounds
- codeine
- hydrocodone
- hydromorphone
- levorphanol
- oxycodone
- oxymorphone
- opium alkaloids (Pantopon®)
Synthetic Opioids II

Phenylpiperidine Derivatives

prototype - meperidine

Other related compounds
- anileridine
- fentanyl
- sufentanil
Synthetic Opioids III

Diphenylheptane Derivatives

Only available compound - methadone
Morphine as a model for synthetic opioids
Pharmacokinetics of Morphine

- Absorbed from GI tract, (30 % bioavailability)
- Opioids are more potent if given parenteral or transdermal by avoidance of first pass metabolism.
- Metabolized in liver by glucoronidation (water soluble), which is well preserved, even in hepatic failure (fentanyl goes thru oxidative metabolism)
- Excreted in the urine
Variable Brain Uptake
Metabolites of Morphine are Also Analgesic
CNS Actions of Morphine 1

- Analgesia
- Altered pain perception
- Euphoria
- Sedation
CNS Effects of Morphine 2

- Cognitive changes
- Nausea and vomiting
- Cough suppression
- Respiratory depression
- Dysphoria (common)
Peripheral Effects of Morphine 1

- Gastrointestinal: Constipation (decreased water and peristalsis)
- Cardiovascular: mild hypotension and peripheral vessel dilation (histamine release)
- Biliary tract: increased biliary tone (biliary colic)
Peripheral Effects of Morphine 2

- Genitourinary:
  - $\uparrow$ tone of bladder and ureter
  - $\downarrow$ uterine tone

- Other:
  - sweating and itching
  - flushing and warming of skin
  - sexual dysfunction
  - myoclonus
# Side Effects of Morphine 3

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>48%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30%</td>
</tr>
<tr>
<td>Pruritis</td>
<td>41%</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>34%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4%</td>
</tr>
<tr>
<td>Respiratory Depression</td>
<td>4%</td>
</tr>
</tbody>
</table>
Side Effects of Morphine 4

Drug Interactions:

- CNS depressants such as phenothiazines, TCA, and alcohol can potentiate depressant effects of morphine (sedation, respiration, and blood pressure).
- Do not mix meperidine and MAOIs. This is a deadly combination.
- Codeine/oxycodone have active metabolites which are metabolized by cytochromeP450-2D6 pathway. Paxil/Sertaline/Prozac, inhibit this metabolism.
- Clomipramine/Amitriptyline increase morphine bioavailability.
Tolerance/Dependence/Pseudoaddiction/Abuse
Tolerance to Morphine 1

A shift to the right of the dose response curve
# Tolerance to Morphine 2

<table>
<thead>
<tr>
<th>High Degree of Tolerance</th>
<th>Moderate Degree of Tolerance</th>
<th>Minimal or no Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>Cardiovascular Effects</td>
<td>Miosis</td>
</tr>
<tr>
<td>Euphoria, dysphoria</td>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidiuresis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough Suppression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Tolerance

The role of pain and the development of tolerance is just beginning to be appreciated. Case reports have shown that patients with significant pain disorders, will go into respiratory depression if pain is dramatically reduced. There is a change in tolerance.
Physical Dependence

- Physical dependence is common.
- Patients will have withdrawal when opioids are discontinued abruptly.
- Patients on short-acting opioids may show subtle evidence of withdrawal between doses.
Physical Dependence

- Occurs even with low doses of opioids
- Withdrawal Symptoms:
  - “flu-like disease”
  - vomiting
  - diarrhea
  - multiple aches and pains
  - gooseflesh
  - spasms
  - dilated pupils
Tolerance or Addiction

Addiction is a psychological/behavioural syndrome characterized by loss of control and the compulsive use of a substance despite harm.

This definition does not require evidence of tolerance or withdrawal.
Addiction

Behaviours more characteristic of abuse

☑ Selling prescription drugs/Prescription forgery/Obtaining prescription drugs from non-medical sources

☑ Stealing drugs from others

☑ Injecting oral formulations

☑ Concurrent use of alcohol or illicit drugs

☑ Repeated visits to other clinicians or ER w/out telling prescriber

☑ Drug-related deterioration: work, family, social

☑ Repeated resistance to change in therapy despite evidence of adverse drug effects.
Addiction or Pseudoaddiction

- Addiction is characterized by compulsive, aberrant behaviours, focused around the acquisition and taking of a substance in spite of harm and in the case of opioids, for its unintended effects.

- Pseudoaddiction is characterized by drug seeking behaviours, stimulated by poorly controlled pain. This constellation of behaviours is often mislabeled as addiction.
Behaviours Not as Suggestive of Abuse:

- Aggressive complaining about the need for more drugs
- Drug hoarding during periods of reduced symptoms
- Occasional unsanctioned dose escalation or other noncompliance
- Intense expressions of anxiety/dysphoria about recurrent symptoms
- Intense expression about pain
Risk of Addiction

- The Boston Collaborative Study:
  - Out of 11,882 patients there were 4 new cases of addiction, which is less than the general population.
  - Extrapolating from the cancer literature, the risk is low.
  - A recent review of surveys in multidisciplinary pain clinics found a range of 2-16%.
Reducing the Risk of Addiction

- Past history of addiction to any substance should alert the clinician to possible risk for future addiction. However, this is not an absolute contraindication.

- Past history of addiction to narcotics is a significant risk factor for future problems with addiction. However, patients with addiction can have chronic pain. In such cases the involvement of a multidisciplinary team, including specialists in addiction and pain management, may be required.

- Co-ordination of patient care amongst healthcare providers with only one prescriber of opioids.
Opioids are only one option for the treatment of chronic pain.

Opioids are prescribed within the context of a more extensive plan of treatment.
Prescribing Opioids

The primary outcome of opioid therapy for the treatment of pain of malignant origin is the reduction of pain.

The primary outcome in opioid therapy for the treatment of chronic pain of non-malignant origin in an increase in function.
Prescribing Opioids I

- Think about the issue of efficacy
  - Mechanism of pain
    - neuropathic/nociceptive/unknown (use cautiously)
- Think about the issue of tolerance/addiction/pseudoaddiction
- Think about side effects
- Think about increase in function
- Think about initiating therapy
1 Outline risks to the patient.
   - Side effects and their management
   - Tolerance and how it will be managed
   - Addiction and how it will be managed

2 Outline expected outcomes
   - Improved quality of life
     - Analgesia (full/partial)
     - Increase in level of function
The use of opioids should be associated with increased activity.

Consider a functional activation program

If there is no increase in a patient’s level of function associated with the use of opioids, either increase the dose of opioids or discontinue their use.
Initiating Treatment

- Initiate treatment with a low dose of a short acting opioid, (e.g. Morphine or Oxycodone)

- A typical starting dose of morphine sulphate is 5 mg. qid. up to 5 times per day. Round the clock dosing is important. The schedule for dosing is based on time, not pain.

- If necessary use morphotec liquid to build up tolerance to side effects. (e.g. nausea)

- Adjust the dose of morphine based on response, and side effects.
Prescribing Opioids IV

- Is there evidence of analgesia?
- Is there an increase in function?
- Is there a change in mood?
- Are there side effects and are they treatable or tolerable?
- Treat side-effects
- Is there evidence of any suspicious aberrant drug seeking behaviour? Is this evidence of addiction or pseudoaddiction?
Manage Side-Effects
Manage Side-Effects I

Constipation:

- Water
- Stool Softeners
- Lactulose (infrequent)
- Infrequent use of senacot/dulcolax
- Klean Prep 2 cups b.i.d. (don’t forget the Kool Aid)
Manage Side-Effects II

Nausea

- Is it reasonable to use anti-emetics?
  - Sedating
  - Risk of EPS/TD
  - Anticholinergic

- Lower the dose of opioid and build up tolerance
- Switch to a different opioid
Prescribing Opioids V

Titrate the dose of opioid based on response and side effects until maximum analgesia and function are attained with tolerable side-effects.

If possible, switch the short acting opioid to a long-acting opioid at equianalgesic doses. The dosing schedule is based on time, not pain. Long acting opioids reduce the likelihood that patient will ‘watch the clock’ and reduces peaks and valleys of pain control.

M-Eslon 10 mg  BID/MS Contin15 mg BID
Oxycontin 10 mg BID (approximately 2 x potent as morphine)
Duragesic 25 q3days = 45 mg –120 mg of morphine / day
Dealing with Tolerance

- Prevent Dose Escalation

- Use a medication ‘holiday’ following slow withdrawal

- Plan for this at the beginning of treatment.
There is no compelling evidence to date, to support the use of one opioid over another.

- There is evidence of patient preference for Duragesic over Morphine in regards to constipation.

- Opioid rotation has not been well studied in non-cancer pain. A recent retrospective study found improved analgesia with rotation from short-acting to long-acting opioids.

- Some clinicians will rotate opioids to improve analgesia. This is based on incomplete cross-tolerance. There is support for this maneuver in the cancer literature. Opioid rotation should be used with caution. (Is this just delaying having to deal with the problem of tolerance?)
The use of ‘breakthrough’ medications is controversial. Some clinicians will give regular daily breakthrough dosing.

Recommendations include an additional 4-6 doses per month. “A goal of optimal opioid titration for a stable chronic pain condition is to decrease the frequency of breakthrough doses to a minimum”

There are occasions where a short acting opioid is used along with a long-acting opioid. In these cases, the treatment dose of opioid is ‘in between’ doses of the long-acting opioid.
Discontinuation of Therapy

- Intolerable or unacceptable side-effects with little or no evidence of analgesia.

- High doses of opioids without analgesia.

- There is evidence of addiction.

- There is no evidence of any effort to increase function in the face of reasonable analgesia.

  ✓ A cognitive behavioural program may be necessary to help mobilize a patient.
When initiating therapy assess the patient at least once every 2 weeks until the trial is ended or an effective dose is found. If possible follow-up 1/month.

At each visit assess and document:

- Degree of analgesia
- Side effects
- Functional status (physical and psychosocial)
- Evidence of aberrant drug-related behaviours.
  - Differentiate addiction and pseudoaddiction.
Special Issues
Evidence of teratogenicity at toxic doses but not at clinical doses

Opioids cross the placenta. The newborn will go into withdrawal (Neonatal Withdrawal Syndrome)
Glucuronidation is the primary method of metabolizing most morphine analogues. This process continues with hepatic dysfunction, until hepatic dysfunction is extremely severe.

Opioids are eliminated through renal clearance. Compromised renal function will result in accumulation of metabolites.

- M6G, oxymorphone, normeperidine are active metabolites
- (norfentanyl/normethadol are not active metabolites
Special Issues: The young/elderly

The Young

- Pediatric pain is under-treated
- Think about the total context of treatment
- Dose range for morphine is 0.2-0.4 mg/kg. po, q4h

The Elderly

- Polypharmacy
- Cognitive problems
- Decreased Renal Function
Special Issues: Methadone

- Opioid agonist and NMDA receptor antagonist
- No active metabolites (normethadol)
- Reports that it is not associated with opioid induced hyperalgesia, unlike morphine/oxycodone.
- Long $\frac{1}{2}$ life of 190 hrs. that does not match analgesia which is variable at 6-24 hrs
- Reports of Torsade de Point
Conclusion

The Tarim Mummy
Thank-you