Review of Pain Management with Clinical and Regulatory Updates

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Disclosure

• Dr. Stellini has no financial or other conflicts of interest related to this presentation to report.
• Any mention of off-label use of drugs will be identified as such.
Objectives

• Attendees will know general techniques of pharmacological and non-pharmacological treatment of pain

• Attendees will be aware of recent changes in scheduling of opioids and their effect on access to medications for patients

• Attendees will know the rationale and impact of FDA initiatives to control diversion and harmful effects of opioids
PALLIATION

The physician’s duty is to cure when possible, relieve suffering often, comfort always.
• Pain is part of suffering

• Physical pain is part of total pain
How do we assess pain?

- Verbal report – 0-10 scale
  - Benefit – changes over time (with or w/o tx)
  - Limitations – person specific, cognitive impairment, “numbers challenged”

“How are we doing with your pain control?”
How do we assess pain?

• Observation

• e.g. Pain Assessment Behavior Scale
  Grimacing, Restlessness, Consolability, etc

• A lot of non-verbal patients are in pain
  Dementia, delirium, encephalopathy, intubated, children, etc.
What kind of pain is it?

- Acute pain – injury, post-op
- Chronic malignant pain
- Non-malignant chronic pain
What kind of pain is it?

- Somatic
- Visceral
- Neuropathic
- Combined
Components of Pain

• Physical

• Psychological

• Spiritual
INTERVENTIONS FOR PAIN CONTROL
Non-Pharmacological Treatment

- Physical Therapy
- Heat
- Acupuncture
- Relaxation, Biofeedback, Imagery
- Counseling, Psychotherapy
- TENS
- Chiropractic
- Aromatherapy
- “Healing Touch”
Pharmacologic Interventions
Before we try assisted suicide, Mrs. Rose, let’s give aspirin a chance.
Non-Opioid Analgesics

• Acetaminophen (analgesic, anti-pyretic, renal, liver toxicity)
• ASA (analgesic, anti-pyretic, anti-inflammatory, anti-platelet, Toxicities: GI, ulcer, bleeding, renal, Reyes)
• NSAIDS (see aspirin)
  17 compounds in clinical use in U.S.
  Ketorolac (Toradol)
• COX-2 inhibitors (1 currently on market) analgesic, anti-pyretic, anti-inflammatory, little anti-platelet activity)
• Tramadol (Ultram) (lowers seizure threshold, drug-drug interactions)
• Lidocaine Patch (Lidoderm)
• Capscacin
• Topical NSAIDS
• Cannabinoids? (Sativex)
Morphine

- Conjugated in liver.
- Morphine glucuronide is active.
- Excreted in urine.
- Decrease dose with renal impairment.
- *May* want to titrate dose down near end of life because of renal shut-down.
Hydromorphone

- More potent than morphine
- Oral or IV
- Safer in renal disease
- Mostly hepatic metabolism
Hydrocodone

- Only oral
- Always coupled with Acetaminophen or NSAID – until now.
- About equipotent with morphine
- The most commonly prescribed opioid
  *(Vicodin, Lortab, Norco, others)*
Adjuvant Analgesics

- Anti-depressants - neuropathic
- Anti-convulsants - neuropathic
- Corticosteroids – bone mets, large tumors, bowel obstruction
- Nerve blocks
  - anesthetic
  - lytic
- Epidural, intrathecal
  - opioids
  - local anesthetics
- Nerve stimulators
WHO Analgesic Ladder for Cancer Pain Management

• Pain - Non-opioid +/- adjuvant

• Pain persisting or increasing – low-dose opioid +/-non-opioid +/-adjuvant

• Pain persisting or increasing – increase dose of opioid  +/- non-opioid ........

• Freedom from pain
Rational Use of Opioids
“Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.”

*Thomas Sydenham*

(*17th century*)
“Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.”

Thomas Sydenham
(17th century)

“Amen”

Mike Stellini (2014)
Opioids

1. Analgesia
2. Sedation
3. Respiratory Depression (RARE)

(These effects occur in this order!)
Opioids

• Tolerance – need higher dose of drug to get same previous effect. (In cancer patients, increased need often due to increased disease)

A cancer patient on 300 mg/day morphine wide awake; me – not likely.

• Physical Dependence – defined by abstinence/withdrawal syndrome

• Psychological dependence = addiction
Opioids - Addiction

- Non-medicinal use
- Use despite negative physical, social, legal consequences
- Pre-occupation with obtaining the substance
- Not likely in cancer patients
“If it’s any consolation, toward the end he was high as a kite.”
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Codeine

- Oral
- Converts to morphine
- Effect ceiling (about 60 mg)
- Side effect ceiling higher than effect ceiling.
Fentanyl

- Much more potent than morphine/hydromorphone
- Oral (lollipop, orally dissolving tabs)
- IV - less hemodynamic effects than morphine
- Transdermal – generally change every 72 hours; 80% of original dose remains in the “used” patch. *Flush! (or sharps container)*
Meperidine

- Limited use – FORGET ABOUT IT!
- Toxic metabolite – normeperidine seizures, hallucinations, bronchospasm, Death.
- Some hospitals have eliminated from formulary
- APS Guidelines – procedure related pain; <48 hrs.; <600mg; not for chronic or prolonged post-op pain.
Methadone

• Unique opioid
• Intrinsically long half-life – can be problematic
• Multiple pain receptor activity (mu, delta, NMDA, serotonin and norepi reuptake)
• Inexpensive
• Probably best opioid for neuropathic pain
• Conversion ratio varies inversely with higher morphine doses
• Hepatic metabolism
## Conversion ratio of Morphine po to Methadone po

<table>
<thead>
<tr>
<th>Daily MS po dose (mg)</th>
<th>Conversion ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 mg</td>
<td>3:1</td>
</tr>
<tr>
<td>101 - 300 mg</td>
<td>5:1</td>
</tr>
<tr>
<td>301 - 600 mg</td>
<td>10:1</td>
</tr>
<tr>
<td>601 - 800 mg</td>
<td>12:1</td>
</tr>
<tr>
<td>801 - 1000 mg</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt; 1000 mg</td>
<td>20:1</td>
</tr>
</tbody>
</table>
Methadone

Cautions:

• Get supervised experience
• LONG half-life
• Only titrate every four days
• Very high doses – Qt prolongation/torsades de pointes (observed but rare)
We can give you enough medicine to alleviate the pain, but not enough to make it fun.
Opioids – Side Effects

• Constipation  **No tolerance**
  Prophylaxis - Laxative (senna) and softener (docusate).
  Treatment – Other stimulants (bicosadyl)
  Osmotics (lactulose, Miralax)
  Mg Citrate, Enemas
  MethylNaltrexone (new)
  sub-Q injection, non-centrally acting mu receptor antagonist
Opioids - Side Effects

• Pruritis – probably most common with morphine
  Not thought to be histamine mediated
  Treat with ondansetron or naltrexone or change drug.
Opioids - Side Effects

• Nausea
• Sedation (consider methylphenidate)
• Respiratory depression

TOLERANCE DEVELOPS TO ALL
Opioids - Side Effects

- Neuro/neuro-excitatory effects – sedation, confusion, delirium;
- High dose - myoclonus can develop and may be a dose limiting effect of morphine

  - May want to add benzodiazepine

  - Switch opioid. Methadone may be best alternative
Opioids - Side Effects

Hyperalgesia

• Allodynia – Painful sensation from normally non-painful stimulus

• Hyperesthesia – dramatically increased sensitivity to painful stimulus

• ?related to tolerance
Opioid Pharmacokinetics
Opioid Pharmacokinetics

Oral

- Short acting - almost all opioids
  oral dose - peak 90 minutes
  duration 2-4 hours
- Methadone - intrinsically long acting
  accumulates with repeat dosing
- Long acting preps - morphine, oxycodone
  fentanyl (patch)
Opioid Pharmacology
Oral

• Dose escalation - 1-2 hours
  mild/mod pain - 25% - 50%
  severe pain    50% - 100%

• Maximum dose -
  none except meperidine (avoid),
  propoxyphene (now off the market),
  combo with APAP, NSAID
Opioid Pharmacokinetics
Intravenous

• Push - Peaks in 6-10 min. IV; 30 min. subQ/IM
• Continuous - Give a loading bolus at the start and with each increase in basal rate
• Administer bolus slowly
Plasma Concentration

- IV
- SC/IM
- po/pr

Cmax

0

Half-life ($t_{1/2}$)

Time
Switching Opioids

• Use conversion table (see handout)
• Allow for incomplete cross-tolerance
  start with 50 - 75% of published dose ("safety factor")
• Transdermal Fentanyl -
  Approx 50 – 100 mg morphine/day ->
  25 mcg/hr patch
  (Difficult to calculate in reverse)
## Equi-analgesic Ratios

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral</th>
<th>Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30mg</td>
<td>10mg</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30mg</td>
<td>-</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20mg</td>
<td>-</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Opioids and Chronic Pain

Getting started

• Start with short acting to determine need and tolerance
• Don’t start an opioid naïve patient on long acting first! (How do you know where to start?)
• Mild/elderly w/moderate pain: 2-5 mg morphine every three hours PRN
• Moderate to severe pain: 5 -10 mg morphine
• If pt has known pre-existing tolerance start higher
Opioids and Chronic Pain

• Escalate dose at appropriate interval until pain relief achieved
• For oral – determine 24 hr need after 24-48 hours. This determines long acting daily dose.
• For IV – find effective bolus dose and start continuous at half of bolus.
• Monitor effect and side effects carefully
Opioids and Chronic Pain

• Long acting plus short acting for breakthrough q. 1-2 hrs. (10-20% of 24 hr. oral dose)
• Continuous IV – breakthrough dose is usually about 50% of hourly rate q 10 minutes.
• Observe closely and adjust dose and frequency based on effect and side effects
Opioids and Chronic Pain

• If frequent breakthrough dosing needed, adjust daily long acting/continuous dose.
• Monitor and control side effects:
  - constipation - treat proactively
  - nausea - short lived
  - pruritis - ondansetron
  - resp depression - RARE with proper titration
Opioids and Chronic Pain

- One long acting
- One short acting
- Opioid rotation may be needed if high doses are reached and pain not very well controlled

- NOTE: doses of morphine required for relief of dyspnea are usually smaller than those used for pain.
Opioids - Withdrawal

- *Cruel* to let patient withdrawal
- Dilated pupils, piloerection, nasal flaring

**ABDOMINAL PAIN**

- Avoid naloxone if at all possible.
- If used – dilute, administer slowly
- Naloxone has short half-life. If used for a patient overdosed on long acting opioid, overdose side-effects will recur when naloxone wears off.
Opioid rotation

• Improved pain control

• Incomplete cross tolerance

• Conversion charts

• Decrease dose
Bone Pain

- NSAIDS
- Corticosteroids
- Plus opioids
- Bisphosphonates
Recent Regulatory Activity

• Based on:
  Increasing deaths due to hydrocodone, methadone overdoses, common/inappropriate prescribing – primarily hydrocodone, misuse of sustained/extended release preparations
• Heroin overdoses also increased
Recent Regulatory Activity

- REMS
- Hydrocodone – re-scheduled to Schedule 2
  No refills, no phone-ins
- Acetaminophen content of hydrocodone/APAP limited to 325 mg per dose
- “Extra-strength Tylenol” – rec only 3 gm/day max.
- New drug – hydrocodone extended release “Zohydro”
- Tramadol rescheduled to Schedule 4
- Tamper-proof ER preparations – NOT Zohydro!
Multifactorial Nature of Pain

- Somatic or Visceral Nociception
- Psychosocial Influences
- Neuropathic Mechanisms
- Psychological State and Traits
- Loss of Work
- Physical Disability
- Fear of Death
- Social/Familial Functioning
- Financial Concerns

Pain

Total Pain

Suffering

(Adapted from Portenoy, 1988)
"His resistance to therapy could be due to death."