

Opioid Pharmacotherapy

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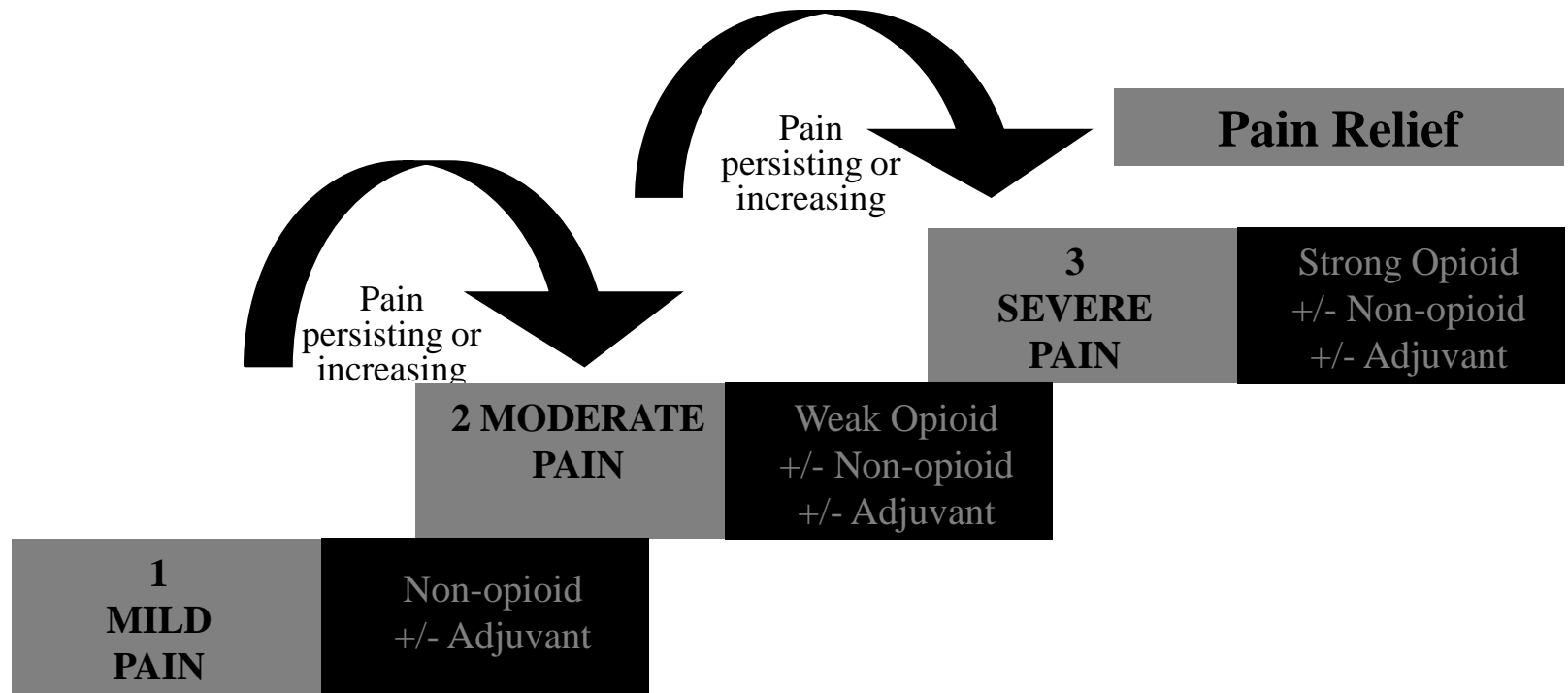


**COLUMBIA UNIVERSITY
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Outline

- Opioid pharmacology
- Opioid prescribing
- Management of opioid-related side effects

The WHO Three Step Analgesic Ladder



Adapted from World Health Organization. *Cancer Pain Relief*. Geneva: WHO, 1990.

Opioid Therapy

- Consider as first-line for patients with moderate-to-severe pain related to cancer, AIDS, or other life-threatening illness

Opioid Prescribing

Prescribing principles

- Drug selection
- Dosing to optimize effects
- Treating side effects
- Managing the poorly responsive patient

Drug Selection

- Patient preference and experience
- Availability of appropriate dosing forms and routes of administration
 - TD fentanyl not well absorbed in very thin patients
 - Dysphagia or poor GI absorption--use SL, parenteral or TD route
- Drug pharmacokinetics
 - Renal failure/dialysis
 - Cirrhosis
- Cost

Opioid Therapy: Drug Selection

Immediate-release preparations

- Used mainly
 - For acute pain
 - For determining optimum dose during initial treatment of chronic pain
 - For “rescue” dosing
- Can be used for long-term management in select patients

Opioid Therapy: Drug Selection

Immediate-release preparations

- Combination products
 - **Percocet, Endocet** (acetaminophen/oxycodone)
 - **Percodan** (aspirin/oxycodone)
 - **Vicodin, Zydone** (acetaminophen/hydrocodone)
 - **Vicoprofen** (ibuprofen/hydrocodone)
 - **Combunox** (ibuprofen/oxycodone)
 - **Tylenol #2, #3, #4** (acetaminophen/codeine)
 - **Darvocet** (acetaminophen/propoxyphene)
 - **Lortab, Norco** (acetaminophen/hydrocodone)
- Single-entity drugs,
 - morphine, oxycodone, oxymorphone, hydromorphone, fentanyl, codeine.
 - Tramadol

Opioid Therapy: Drug Selection

Extended-release preparations

- Preferred because of improved treatment adherence, maintenance of effective analgesic concentration, and the theoretically decreased risk in those with addictive disease
- Adjust dose q 2–3 d

Opioid Therapy: Drug Selection

Extended-release preparations

- **MSContin, Avinza, Kadian, Oramorph SR** (morphine)
- **Oxycontin** (oxycodone)
- **Levo-dromoran** (levorphanol)
- **Duragesic** (fentanyl TD)
- **Opana** (oxymorphone)
- **Buprenex** (buprenorphine)

Opioid Therapy: Drug Selection

Role of methadone

- Another useful long-acting drug
- Unique pharmacology when commercially available as the racemic (d- and l- isomer) mixture
- Potency greater than expected based on single-dose studies
- Variable and unpredictable half-life (12-150hrs)
- When used for pain: multiple daily doses, steady-state in 3-5 days to up to several weeks
- Close monitoring needed until steady-state approached to reduce risk of side effects

Not to be used for chronic pain

Meperidine

- Poor absorption and toxic metabolite

Propoxyphene

- Poor efficacy and toxic metabolite

Mixed agonist-antagonists (pentazocine, butorphanol, nalbuphine, dezocine)

- Compete with agonists → withdrawal
- Analgesic ceiling effect

Routes of Administration

- Oral and transdermal
 - preferred for most patients
- Oral transmucosal
 - available for fentanyl and used for breakthrough pain (Fentora, Actiq)
- Rectal route
 - limited use
- Parenteral
 - SQ and IV—for acute pain, feasible for long-term therapy
- Intraspinal
 - epidural and intrathecal. IT generally preferred for long-term use

Transdermal Fentanyl

- For stable, chronic pain
- 12-24 hours for onset and discontinuation of action
- Heat increases absorption
- Hydration and nutritional status may affect absorption

Transmucosal Fentanyl (Actiq and Fentora)

- For opioid tolerant cancer patients with incident pain (pain related to movement or other activity)
- Dosing individual
- Short onset and duration of action
- Apply to oral mucosa over 15 minutes (Actiq) or apply between cheek and jaw, let dissolve.

Opioid Therapy: Principles

- Consider use of a long-acting drug and a “rescue” drug—usually 5%–15% of the total daily dose
- Baseline dose increases: 25%–100% or equal to “rescue” dose use
- Increase “rescue” dose as baseline dose increases
- Treat side effects

Opioid-related Side Effects

Common

- Constipation
- Somnolence, mental clouding

Less common

- Nausea
- Myoclonus
- Pruritis
- Urinary retention
- Sweating
- Amenorrhea
- Sexual dysfunction
- Headache

Opioid Titration and Responsiveness

- Opioid dose titration over time is critical to successful therapy
- Increase dose until pain relief is adequate OR intolerable and unmanageable side effects occur
- No ceiling effect
- Responsiveness of an *individual* patient to a *specific* drug cannot be determined unless dose was increased to treatment-limiting toxicity

Dose Titration (PO)

- Start with PRN short acting opioid
- Add background opioid in dose equal to 75-100% of 24 hour dose of PRN opioid consumed
- Continue PRN opioid in dose equal to 10-15% of the 24 hour dose of background opioid

Dose Titration (parenteral)

- Start with PRN boluses of short acting opioid or PCA
- Add continuous infusion for background
 - Hourly rate based on amount used PRN over given time period
- Continue PRN bolus doses of 50-100% of hourly rate or PCA

Managing Poor Opioid Responsiveness

If dose escalation → adverse effects

- Better side-effect management
- Pharmacologic strategy to lower opioid requirement
 - Spinal route of administration
 - Add non-opioid or adjuvant analgesic
- “Opioid rotation”
- Non-pharmacologic strategy to lower opioid requirement

Opioid rotation

- Based on large intraindividual variation in response to different opioids
- Reduce equianalgesic dose by 25%–50% to account for incomplete cross-tolerance
 - Reduce less if pain severe
 - Reduce more if medically frail
 - Reduce less if same drug by different route
 - Reduce fentanyl less
 - Reduce methadone more: 75%–90%

Equianalgesic Conversions

| <u>Drug</u> | <u>Epidural</u> | <u>SC/IV(mg)</u> | <u>PO (mg)</u> |
|---------------|-----------------|------------------|----------------|
| Morphine | 1 | 10 | 30 |
| Codeine | | 130 | 200 |
| Oxycodone | | N/A | 20 |
| Hydromorphone | 0.15 | 1.5 | 7.5 |
| Oxymorphone | | 1 | 10 |
| Levorphanol | | 2 | 4 |
| Fentanyl | | 0.1 | N/A |
| Methadone* | | 10 | 20 |

*Dose ratios vary from 4:1 at morphine doses of <90 mg, to 8:1 at 90 to 300, and to 12:1 at doses of more than 300 mg of morphine. (Ripamonti, 1998)

Fixed ratio of 5:1 was safe and effective in cancer patients with poor morphine response. (Mercadante, 1999)

see other conversions for methadone: Ayonrinde, 2000; Lawlor, 1998; Morley, 1993.

Equianalgesic Conversions

Manufacturer's Suggested Starting Doses of Transdermal Fentanyl:

| PO MSO4 (mg/day) | Duragesic (mcg/hr patch) |
|------------------|--------------------------|
| 45-134 | 25 |
| 135-224 | 50 |
| 225-314 | 75 |
| 315-404 | 100 |
| 405-494 | 125 |
| 495-584 | 150 |
| 585-674 | 175 |
| 675-764 | 200 |

Equianalgesic Conversions

Recommended dose equivalents for Actiq and Fentora:

| Fentora | Actiq | Oxycodone | Morphine |
|----------------|--------------|------------------|-----------------|
| 100mcg | 200mcg | 5mg | 7.5mg |
| 100mcg | 400mcg | 10mg | 15mg |
| 200mcg | 600mcg | 15mg | 25mg |
| 200mcg | 800mcg | 20mg | 40mg |
| 400mcg | 1200mcg | 30mg | 50mg |
| 400mcg | 1600mcg | 40mg | 55mg |

**Both Actiq and Fentora should only be used in opioid tolerant patients. Recommended starting dose for Fentora is 100mcg.

Opioid Therapy and Chemical Dependency

Risk of addiction:

- Acute pain: Very unlikely
- Cancer pain: Very unlikely
- Chronic noncancer pain:
 - Surveys of patients without abuse or psychopathology show rare addiction
 - Surveys that include patients with abuse or psychopathology show mixed results

Continued Assessment--the 4 A's

- Analgesia--may use VAS or other measurement tool
- Activities of daily living (functioning)
- Adverse events
- Aberrant drug-taking behaviors
 - E.g. repeated dose escalation or non-compliance, hoarding drugs, acquiring drugs from other medical sources, etc.

Passik SD, Weinreb HJ. Managing chronic non-malignant pain: overcoming obstacles to the use of opioids. *Adv Ther* 17:70, 2000

Treating Opioid-related Side Effects

- Reduce the dose
- Change dosing intervals to achieve more consistent levels
- Try a different opioid (opioid rotation)
- Add another medication to manage the side effect
- Allow tolerance to the undesirable effect to develop

Opioid-induced Constipation

- Decreased peristalsis of intra-luminal contents
- Increased sphincter tone
- Tolerance does not develop
- May progress to ileus

Opioid-induced Constipation

- If appropriate, increase fluids, soluble fiber, exercise
- **Aggressive prophylaxis** with scheduled doses of
 - Stool softener- docusate (Colace)
 - Mild laxatives- senna, lactulose, Miralax
- Avoid bulk forming laxatives like Metamucil (psyllium), Citrucil (methylcellulose)

Opioid-induced Constipation

- Laxative Choices

- Saline – milk of magnesia, magnesium citrate
- Osmotics – lactulose, sorbitol, Miralax
- Stimulants – senna, bisacodyl, cascara
- Lubricants – mineral oil
- Enemas of saline, tap water, mineral oil, SSE
- Suppositories – glycerin, bisacodyl

Opioid-induced Constipation

- Oral opioid antagonists for intractable cases
 - Naloxone 1-6 mg BID-TID PO
 - Methylnaltrexone 0.8 mg/kg SQ QOD
 - Alvimopan (currently in clinical trials)

Neuropsychiatric side effects

Altered levels of:

- Consciousness
 - Cognition
 - Perception

- Mood

Varying intensities:

- Mild drowsiness → asleep
 - Inattention → disorientation
 - Vivid dreams → hallucinations
- Dysphoria → depression
- Euphoria → mania

Neuropsychiatric effect from opioids?

- Eliminate other etiologies
 - polypharmacy
 - CNS pathology
 - metabolic dysfunction
 - psychiatric distress

Managing neuropsychiatric effects

- Usual strategies
- If mild and at initiation of opioids, reassure and monitor
- Consider neuroleptics if delirium
- Consider psychostimulants if sedation or mild cognitive changes
 - Methylphenidate (Ritalin) 5-10 mg BID
 - Dextroamphetamine (Dexedrine) 5-10 mg BID
 - Modafanil (Provigil) 200 mg QD

Respiratory Depression

- Rare in opioid tolerant patients
- Preceded by sedation
- Polypharmacy may be a factor

- Management:
 - Decrease or hold the opioid
 - Provide stimulation
 - Oxygen therapy

Nausea

- Possible causes
 - Stimulation of CTZ
 - GI slowing
 - Sensitization of vestibular apparatus
- Most common with initial opioid doses
- Tolerance develops
 - Helped by slow steady titration
- May need anti-emetics initially
- If persistent, try opioid rotation

Antiemetics for opioid-induced nausea

- Stimulation of CTZ
 - Dopamine antagonists
 - Phenothiazines (Prochlorperazine)
 - Substituted benzamides (metoclopramide)
 - Neuroleptics (haloperidol)
- Vestibular activation
 - Anticholinergics
 - scopolamine
 - Antihistamines
 - meclizine

Itching

- Most common with intraspinal opioids
- Usually involves face, neck, upper thorax
- May be CNS mediated not histamine
- Management:
 - Stop the opioid
 - Administer antihistamine (diphenhydramine 25 mg IV), low dose naloxone or partial antagonist (nalbuphine 2.5-5 mg IV)

“The changing pattern in opioid use has resulted in the emergence of neurotoxicity as a major side effect of the treatment of cancer pain.”

Neurotoxicity

- Includes:
 - Delirium
 - Myoclonus
 - Hyperalgesia

- Risk Factors:
 - High opioid doses and/or rapid dose escalation for treatment of
 - Neuropathic pain
 - Incident pain
 - Psychological distress
 - Prolonged exposure to opioid
 - Dehydration
 - Renal Failure

Myoclonus

- Sudden brief shock like involuntary muscle movement
- If progressive, may lead to seizures
- Associated with morphine, hydromorphone, fentanyl, meperidine
- Cause:
 - Concentration of opioid and its metabolites in CSF?
 - Dehydration and/or renal impairment

Hyperalgesia & Allodynia & Paradoxical Pain

Hyperalgesia:

- Exaggerated response to noxious stimuli

Paradoxical Pain:

- Worsening pain despite ever increasing opioid dose

Allodynia:

- Nociceptive response to innocuous stimuli

Managing Neurotoxicity

- Opioid rotation
- Dose reduction
- Hydration
- Neuroleptics for delirium
- Sedatives to control myoclonus

Managing Opioid Side Effects

- **P** sychostimulants
 - **L** axatives
 - **A** ntiemetics
 - **T** olerance development
 - **O** piate Rotation
- persistent sedation
 - constipation
 - nausea with new drug or increased doses
 - Nausea, sedation, confusion with initial or increasing doses
 - pruritis, myoclonus, urinary retention, persistent nausea