Analgesic Use and Abuse

Analgesics
Top 200 Drugs 2012

• Opioid Agonists
  – Hydrocodone w/APAP (1,3,5,191)
  – Oxycodone w/APAP (35, 44)
  – Oxycontin (139) (continuous release oxycodone)
  – Oxycodone HCl (163)
  – Codeine w/APAP (150)

• Opioid Agonist/Antagonist
  – Suboxone (111) (Buprenorphine/Naloxone)

• NSAIDS
  – Celebrex (Celecoxib) (76)
  – Ibuprofen (14,66)
  – Meloxicam (49)
  – Naproxen (100, 193)

• Central Analgesics
  – Tramadol (52, 83,88)
Characteristics of Pain

- Acute Pain
  - Relief highly desirable
  - Dependence and tolerance unusual
  - Psychological component usually absent
  - Organic cause common
  - Environmental contributions and family involvement small
  - Insomnia unusual
  - Treatment goal: cure

- Chronic Pain
  - Relief highly desirable
  - Dependence and tolerance common
  - Psychological component often a major problem
  - Organic cause often absent
  - Environmental contributions and family involvement significant
  - Insomnia common
  - Treatment goal: rehabilitation
    - Improve quality of life while decreasing pain

Managing Pain

- Acute Pain
  - Managed with immediate release dosage forms (delivery systems)
  - Desire rapid onset, high peak concentration

- Chronic Pain
  - Often managed with controlled release dosage forms (delivery systems)
  - Desire constant effect
    - No fluctuations during dosing interval
Management of Acute Pain

• Eliminate the underlying cause
• Symptomatic relief
  – Therapeutic interventions
    • Psychological
      – introductory information about sensations to expect after a certain procedure
    • Pharmacologic

Pharmacologic Therapy

• Non-opioid
  – Acetaminophen
  – Acetylsalicylic acid (ASA, aspirin)
  – Nonsteroidal anti-inflammatory drugs (NSAIDs)
• Opioids
• Central
**Chronic Nonmalignant Pain**

- Pain unrelated to cancer that continues after the usual course of disease or injury
- > 50 million Americans
- $85-90 billion per year

**Nociceptive**
- Tissue injury resulting from muscular, inflammatory or mechanical compression disorders

**Neuropathic**
- Involves abnormal nerve conduction and neuropathies

**Combination**

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**Pharmacological Therapy**

- Non-opioid analgesics-first line
  - APAP
  - NSAIDs
  - ASA, salicylates
- Central and Opioid analgesics-moderate to severe
  - Combination with APAP, ASA or NSAIDs
  - Stronger opioids
  - Tramadol
- Adjunctive medications for neuropathic pain
  - Anticonvulsants
    - Carbamazepine, gabapentin, lamotrigine, phenytoin, pregabalin, valproic acid
  - Antidepressants
    - SSRIs, TCAs, SNRIs (duloxetine, venlafaxine)
  - Topical capsaicin or lidocaine (patches)
  - Cyclobenzaprine
NSAIDs:
Acute vs Chronic Pain or Inflammation

- Immediate release
- Analgesics vs anti-inflammatory agents
- Delayed release
  - DR, EC
- Controlled release
  - CR, SR, XR
  - Naprelan

Nonselective NSAIDs
Analgesic Doses

- Diclofenac
  - Voltaren
    - Delayed release
    - Extended release
    - Gel
  - Cambia packets
  - Cataflam tablets
  - Zipsor capsule
  - Flector (TD patch)
  - Pennsaid (TD sol)
  - Soloraze (TD gel)

- Etodolac
  - Tablet 400, 500 mg
  - Capsule 200, 300 mg
  - CR 400, 500, 600 mg
  - 200-400 mg q 6-8 h
  - do not exceed 1200 mg/day

- Fenoprofen (Nalfon)
  - 200, 400 mg capsules
  - 600 mg tablets
  - 200 mg q 4-6 h
Nonselective NSAIDs
Analgesic Doses

- Flurbiprofen
  - 50, 100 mg tablet

- Ibuprofen (Motrin, Advil)
  - 50, 100 mg chewable
  - 40/1, 50/1.25, 100/5 mg/cc susp
  - 200 mg tablets, capsules
  - 400, 500, 600 mg tablets (Rx)
  - 400/4, 800/8 IV solution (Rx)
  - Rx: 400 mg q 4-6 h , max 3200 mg/day
    - IV 400-800 qid (over 30 min)
  - OTC: 1200 mg/day

- Indomethacin
  - Indocin, SR, CR

- Ketoprofen
  - 50, 75 mg capsules
  - 200 mg extended release capsules
  - 25-50 q 6-8 h
Ketoralac

- Indicated for short-term (up to 5 day) management of moderately severe acute pain.
- Oral use only indicated as continuation therapy to IV/IM

Ketorolac oral

- 10 mg tablets

  - *Maximum dose*: 40 mg/day.

  - *Initial dosage*:
    - Patients weighing 50 kg or more: 20 mg orally as a first dose following IV or IM therapy.
    - Patients weighing less than 50 kg: 10 mg orally as a first dose following IV or IM therapy.

  - *Maintenance dosage*: 10 mg every 4 to 6 hours as needed.
Ketorolac IM/IV

- **IV/IM**
  - 15, 30 mg/ml (IM/IV)
  - 60 mg/2 ml
  - 300 mg/10 ml

- **Usual dosage:**
- **Single-dose treatment:** 60 mg IM or 30 mg IV.
- **Multiple-dose treatment:** 30 mg IV or IM every 6 hours.
  - **Maximum dose:** 120 mg/day.

- **Patients weighing less than 50 kg or elderly:**
- **Usual dosage:**
  - **Single-dose treatment:** 30 mg IM or 15 mg IV.
  - **Multiple-dose treatment:** 15 mg IV or IM every 6 hours.
  - **Maximum dose:** 60 mg/day.

Ketorolac IN

- **15.75 mg/spray Nasal Solution**
  - **Sprix**
  - Protect bottles from light and freezing. Store unopened bottles between 2° and 8°C (36° and 46°F). During use, keep between 15° and 30°C (59° and 86°F) and out of direct sunlight. Bottles should be discarded within 24 hours of priming.¹

- **Usual dosage:**
  - **Patients weighing 50 kg or more:** 1 spray (15.75 mg/spray) in each nostril (total dose of 31.5 mg) every 6 to 8 hours.¹
  - **Patients weighing less than 50 kg or elderly:** 1 spray (15.75 mg/spray) in only 1 nostril every 6 to 8 hours.¹
  - **Maximum dose:**
    - **Patients weighing 50 kg or more:** 126 mg/day (4 doses).¹
    - **Patients weighing less than 50 kg or elderly:** 63 mg/day (4 doses).¹
Nonselective NSAIDs
Analgesic Doses

- Meloxicam
  - Mobic 7.5, 15 mg tablets
  - Mobic 7.5 mg/5 ml susp

- Naproxen
  - Naprosyn 250, 375, 500 mg tablets
    - 500 mg stat, 250 mg q 6-8 h
  - Naproxen DR 375, 500 mg delayed release tablets
  - Naprosyn suspension 125 mg/5cc

- Naproxen sodium
  - Aleve 200 mg (220 mg naproxen Na)
  - Anaprox 250,500 (275, 550 mg naproxen sodium) tablets
    - 550 mg stat, 275 q 6-8 h
  - Naprelan 375, 500, 750 controlled release tablets

Naproxen

- **Management of pain:**
- **Usual dosage:** Naproxen sodium 550 mg every 12 hours or 275 mg every 6 to 8 hours as required.

- **Maximum dose:** The initial total daily dose should not exceed 1,375 mg of naproxen sodium. Thereafter, the total daily dose should not exceed 1,100 mg of naproxen sodium.

- **Initial dosage:** Naproxen sodium 550 mg as a starting dose.

Naproxen tablets may also be used but naproxen delayed-release tablets are not recommended for initial treatment of acute pain.
**NSAIDs**

**Dental Implications**

- Caution prescribing additional NSAIDs alone or in combination
- Non-selective
  - GI ADEs
  - Platelet inhibition
- Non-selective and Selective Cox-II Inhibitors
  - Decreased renal blood flow
  - Decreased efficacy (antihypertensive effect) of ACE inhibitors or Angiotensin Receptor Blockers

**Tramadol (Ultram)**

**Central Analgesic**

- Rybix ODT
- Ultram
- Ryzolt
  - 24 hr ER
- Ultram ER
  - 24 hr
- Ultracept
  - 37.5 mg tramadol
  - 325 mg acetaminophen
Tramadol (Ultram)

- Indicated for the management of moderate to moderately severe pain
- Binds to Mu opioid receptors
  - Addiction
  - Anaphylactoid cross hypersensitivity with Codeine allergy
- Inhibits reuptake of serotonin and norepinephrine
  - Increased risk with other antidepressants
  - Seizures
  - Serotonin Syndrome
- Naloxone will partially reverse

Tramadol (Ultram)

- Pregnancy Category C
- Not recommended in lactation or pediatrics
Tramadol

- May 2010, Labeling change to Warnings section
- Emphasizes the risk of suicide for patients who are addiction-prone, taking tranquilizers or antidepressant drugs and also warns of risk of overdosage.
- Tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs.
- Expected to have additive effects when used in conjunction with alcohol, other opioids or illicit drugs that cause CNS depression.
- Serious potential consequences of overdosage with tramadol are central nervous system depression, respiratory depression and death.
- Has mu-opioid agonist activity, can be abused and may be subject to criminal diversion.

Contraindication (?)

- Concomitant MAOI
- Selegiline Transdermal System
  - Emsam
    - Tramadol
    - Propoxyphene
Contraindications regarding MAOIs and most serotonin or norepinephrine affecting drugs

• Patients taking MAOIs within 2-3 weeks
  – Antidepressants
    • Isocarboxazid (Marplan)
    • Phenelzine (Nardil)
    • Tranylcypromine (Parnate)
    • Selegiline (Emsam)
      – Transdermal 6, 9, 12 mg/24h
  – Antiparkinson
    • Selegiline 5 mg tablet, capsule
      – Eldepryl 5 mg capsule
      – Zelapar 1.25 mg orally disintegrating tablet
  – Agitation, seizures, diaphoresis and fever; may progress to coma, apnea, and death.

Drug Interactions

Tramadol

• Increased serotonin
  – Seizure
  – Serotonin syndrome
• SSRIs
• SNRIs
• TCAs
• MAOIs
• Neuroleptics
Tramadol Drug Interactions
Serotonin Syndrome

• Serotonergic Drugs
  – Selective Serotonin Reuptake Inhibitors (SSRIs)
    • Fluvoxamine (Luvox)
    • Fluoxetine (Prozac)
    • Paroxetine (Paxil)
    • Sertraline (Zoloft)
    • Citalopram (Celexa)
    • Escitalopram (Lexipro)

• Cognitive-behavioral
  – Confusion/disorientation (51%)
  – Agitation/irritability (34%)

• Autonomic Nervous System
  – Hyperthermia (45%)
  – Diaphoresis (45%)
  – Sinus Tachycardia (36%)
  – Hypertension (35%)

• Neuromuscular
  – Dilated pupils (28%)
  – Tachypnea (26%)
  – Nausea (23%)

Serotonin/ Norepinephrine Reuptake Inhibitors (SNRIs)

• Amoxapine (Asendin)
• Maprotiline (Ludiomil)
• Duloxetine (Cymbalta)
• Venlafaxine (Effexor)
• Desvenlafaxine (Pristiq)
Inhibitors of CYP2D6 and CYP3A4 increase tramadol effects

- Antifungals
  - Fluconazole (Diflucan)
  - Ketoconazole (Nizoral)
  - Miconazole
- Metronidazole
- Macrolides
  - Erythromycin
  - Clarithromycin

Opioids
Dental Implications

- If rapid release, combination products—consider adverse effects of both ingredients
  - Acetaminophen (hepatic toxicity)
  - ASA, Ibuprofen (GI, platelet, renal)
- Tolerance of chronic users
- Prescribe for break through pain
- Addition of NSAIDs
Acetaminophen
Adverse effects

• Hepatotoxicity
  – overdose
    • >7 g for adults
    • children less susceptible
    • chronic alcoholics more susceptible
      – not a contraindication
  – Chronic toxicity
    • Adults 3-4 g per day
• Allergy
  – Swelling of face, mouth and throat, difficulty breathing, itching or rash
• FDA: 1/13/2011 Acetaminophen Prescription products limited to 325 mg per dosage unit
  • 3 year implementation to avoid drug shortage
  • Warning added to Rx drug products

Hydrocodone Combinations with Acetaminophen (CIII)

• 2.5/108 Solution
  – Hycet (7% alcohol)
    • 2.5/167 Elixir
      – Lortab
    • 2.5/500 tablets
      – Lortab 2.5/500
  • 3.3/100 Elixir
    – Lortab
  • 3.3/108.3
    – Zamicet Oral Solution (6.7% alcohol)
    • 3.3/167
      – Liquicit
• 5/300 tablets
  – Vicodin
  – Xodol
• 5/325 tablets
  – Norco *
  • 5/400 tablets
    – Zydone
  • 5/500 tablets
    – Co-Gesic, Lortab
  • 5/500 capsules
    – Hydrogesic
# Hydrocodone Combinations with Acetaminophen (CIII)

- **7.5/300 tablets**
  - Vicodin ES
  - Xodol
- **7.5/325 tablets**
  - Norco *
- **7.5/400 tablets**
  - Zydone
- **7.5/500 Tablets**
  - Lortab
- **7.5/650 Tablets**
  - Lorcet Plus
- **7.5/750 Tablets**
  - Vicodin ES

- **10/300 Tablets**
  - Vicodin HP
  - Xodol
- **10/325 Tablets**
  - Norco *
- **10/400 tablets**
  - Zydone
- **10/500**
  - Instah tablets
- **10/650 Tablets**
  - Lorcet 10/650
- **10/660 tablets**
  - Vicodin HP
- **10/750**
  - Maxidone

# Hydrocodone Combination with Ibuprofen (CIII)

- **2.5/200**
  - Repraxain
- **5/200**
  - Ibudone
  - Repraxain
- **7.5/200**
  - Vicoprofen
- **10/200**
  - Ibudone
  - Repraxain

- Additive Effect
- Anti-inflammatory effects
Oxycodone Combinations with Acetaminophen (CII)

- 2.5/325 Tablets
  - Percocet
- 5/300 Tablets
  - Primlev
- 5/325 Tablets
  - Endocet, Percocet, Roxicet
- 5/325 Oral Solution
  - Roxicet Oral Solution
- 5/400
  - Magnacet
- 5/500
  - Roxicet 5/500 Tablets
  - capsules
- 7.5/300
  - Primlev
- 7.5/325
  - Endocet, Percocet
- 7.5/400
  - Magnacet
- 7.5/500
  - Endocet, Percocet
- 10/300
  - Primlev
- 10/325
  - Endocet, Percocet
- 10/400
  - Magnacet
- 10/650
  - Endocet, Percocet

Dental Tx of Opioid Users

- High Risk for CNS and Respiratory Depression
  - Increased drowsiness
  - Decreased motor function
  - Increased risk of respiratory arrest
  - Increased risk with Nitrous and Rx of opioids, behavior modifying drugs, anti-emetics
- Tolerance to prescribed opioids
  - Require higher doses
  - Often identify drugs of choice
- Xerostomia
- Reduced salivary flow
- Orthostatic hypotension
  - Increased with anti-emetics
Opioid Pharmacologic Effects

- CNS Effects
  - Analgesia
  - Euphoria
  - Sedation
  - Respiratory Depression
  - Cough Suppression
  - Miosis
  - Truncal Rigidity
  - Nausea and Vomiting

- CV System
  - Hypotension

- GI Tract
  - Constipation

- Biliary Tract
  - Colic

- Genitourinary Tract
  - Urinary Retention
  - Decreased Renal Function

Opioid Misuse and Abuse

- Legal
  - Morphine
    - Duramorph, MS-Contin, Roxanol, Oramorph SR
  - Codeine
    - Tylenol w/, Empirin w/, Fiorinal w/, Robitussin AC
  - Hydrocodone
    - Tussionex, Vicodin, Hydromorphone, Lorcet
  - Hydromorphone
    - Dilaudid
  - Oxycodone
    - Percocet, Percodan
    - OxyContin

- Methadone
  - Dolophine, Methadose

- Fentanyl
  - Innovar, Sublimaze, Alfenta, Sufenta, Duragesic, Actiq
  - Meperidine
    - Demerol

- Illicit
  - Heroin
    - Horse, Smack
    - Injected, sniffed, smoked
Alabama Department of Public Health
Prescription Drug Monitoring Program
ADPH PDMP

- https://www.adph.org/PDMP/index.asp?id=4356

Practitioner is defined as “a medical, dental, podiatric, optometric, or veterinary medical practitioner licensed to practice in this state and authorized to prescribe, dispense, or furnish controlled substance under the Alabama Uniform Controlled Substances Act.”

Opioids

- Desired effects
  - Euphoria
- History of chronic pain
- History of opioid use
- Rx for methadone (Dolophine, Methadose) or Suboxone

- Signs and Symptoms of use
  - Drowsiness
  - Shallow and slow breathing
  - Constricted pupils
  - Nausea
  - Long sleeved clothing
Opioids

• Signs of withdrawal
  – Watery eyes
  – Runny nose
  – Yawning
  – Loss of appetite
  – Irritability
  – Tremors
  – Panic
  – Cramps
  – Nausea
  – Chills and Sweating

Opioids

• Phenanthrenes
  – Codeine
  – Hydrocodone
  – Oxycodone
  – Morphine
  – Hydromorphone
  – Levorphanol

• Phenylpiperidines
  – Meperidine
  – Fentanyl

• Diphenylheptanes
  – (Propoxyphene)
  – Methadone
Opioid Antitussives

- Hydrocodone
  - Tussionex, Tussi-caps
- Codeine

Fentanyl Transdermal Delivery Systems

- Not for acute pain management
- For chronic, severe pain management
- For opioid tolerant patients

- Illegal misuse, abuse and diversion
  - Cut or torn open, then applied or injected
  - Violating transdermal delivery system causes immediate availability of drug designed to be released over extended period of time
Other Fentanyl dosage forms

- SL tablet (Abstral)
- SL liquid (Subsys)
- Buccal lollipop (Actiq)
- Buccal tablets (Fentora)
- Buccal film (Onsolis)
- Nasal solution (Lazanda)
- The fentanyl lozenge, buccal and sublingual tablets, and buccal soluble film are indicated only for the management of breakthrough cancer pain in patients with cancer already receiving and tolerant to opioid therapy for their underlying persistent cancer pain.

Fentanyl Oral Transmucosal System (Lollipops)

- (Oralet)
  - pediatric
- Actiq
  - 200, 400, 600, 800, 1200, 1600 ug
  - Elderly
  - Fatal dose in children
- FDA required comprehensive risk management program
  - Accidental ingestion by children
  - Diversion and abuse
  - Inappropriate prescribing
- Patient Leaflet and Actiq Welcome Kit
TIRF REMS

- The FDA-approved transmucosal immediate-release fentanyl (TIRF) REMS program consists of a Medication Guide, and Element To Assure Safe Use that includes a restricted distribution system requiring prescriber certification, and enrollment of patients, pharmacies, and wholesalers/distributors. The program Web site is http://www.tirfremssaccess.com and the TIRF REMS Access program phone number is 1-866-822-1483.

- To mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by: ensuring that the drug is prescribed and dispensed only to appropriate patients, including only those who are opioid-tolerant; preventing inappropriate conversion between fentanyl products; preventing accidental drug exposure to children and others for whom the drug was not prescribed; and educating health care professionals and patients about potential misuse, abuse, addiction, and overdose.

OxyContin

- Sustained release oxycodone
  - Not for acute pain management
  - For chronic, severe pain management
  - Generally for opioid tolerant patients

- Illegal misuse, abuse and diversion
  - Crushed, then injected or snorted
  - Breaking, chewing or crushing causes immediate release of drug designed to be released over extended period of time
OxyContin
Misuse, abuse and diversion

• Problem
  – Excessive and aggressive marketing and promotion campaign
  – Public advertising
  – FDA gave indication for moderate to severe pain

• Solution
  – Boxed warning
  – No sampling
  – Educate prescribers on abuse and diversion
  – Develop abuse-resistant version before the end of 2002
  – Develop state prescription monitoring programs

OxyContin
New formulation Fall 2010

• Old formulation:
  • http://www.purduepharma.com/PI/Prescription/Oxycontin.pdf
  • (found on p. 2)
  • ammonio methacrylate copolymer
  • hypromellose
  • lactose
  • magnesium stearate
  • PEG 400
  • povidone
  • sodium hydroxide
  • sorbic acid
  • stearyl alcohol
  • talc
  • titanium dioxide
  • triacetin

• New formulation:
  • (found on p. 21)
  • butylated hydroxytoluene
  • hypromellose
  • PEG 400
  • polyethylene oxide
  • magnesium stearate
  • titanium dioxide
  • Theory: new formulation would create a sticky, resin-like substance resistant to dissolution for injection or crumbling for snorting
Dental Tx of Opioid Users

- High Risk for CNS and Respiratory Depression
  - Increased drowsiness
  - Decreased motor function
  - Increased risk of respiratory arrest
  - Increased risk with Nitrous and Rx of opioids, behavior modifying drugs, anti-emetics
- Tolerance to prescribed opioids
  - Require higher doses
  - Often identify drugs of choice
- Xerostomia
- Reduced salivary flow
- Orthostatic hypotension
  - Increased with anti-emetics

Dental Tx of Recovering Opioid Users

- Avoid prescribing any opioid or related drug
- Options
  - NSAIDs
    - Mild pain
      - Naproxen Na, Ibuprofen
    - Moderate to severe pain
      - Etodolac (Lodine), Ketoralac (Toradol)
  - [Tramadol (Ultram)]
    - Mu receptor agonist
Treatment of Opioid Dependence/Addiction

- Buprenorphine (Buprenex, Butrans, Subutex)
- Buprenorphine/Naloxone (Suboxone)
- Methadone
- Naltrexone (Revia®, Depade®, Vivitrol®)

Methadone

- Used to treat chronic pain
- Used to treat opioid withdrawal
  - Methadone maintenance programs
Opioid Agonist/Antagonist Combination

- Suboxone
  - Buprenorphine/
    Naloxone
  - SL
  - Used to treat opioid
    addiction

- Avoid use of opioid
  analgesics

Opioid Receptors

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<th>Mu (1 &amp; 2)</th>
<th>Delta</th>
<th>Kappa</th>
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<tr>
<td>Euphoria</td>
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<td>Dysphoria</td>
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<td>Abuse potential</td>
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<tr>
<td>Respiratory depression</td>
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<tr>
<td>Constipation</td>
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Mixed Agonists/Antagonists

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<tr>
<td>Buprenorphine</td>
<td>Partial agonist</td>
<td>Antagonist</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>Partial Agonist</td>
<td>None</td>
<td>Strong Agonist</td>
</tr>
</tbody>
</table>

- Nalbuphine (Nubain)
  - Ceiling effect on respiratory depression
  - Equal potency as morphine for analgesia
- Buprenorphine (Buprenex)
  - Limited respiratory depression
  - Resistant to naloxone
- Butorphanol (Stadol)
  - Good analgesic effect
  - May cause dysphoria
  - Significant sedation