The Toxicology of Substance Abuse: Opiates and Opioids

CAT Conference 2006

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Objectives

1. Characterize and contrast the toxicology for prototypical opiates and opioids.
2. Recognize risk factors for opiate and opioid poisoning deaths.
3. Describe the recent abuse trends for illicit and prescription agents.
Definitions

**Opiates:** “natural” – opium poppy, *Papaver somniferum* (morphine, codeine)

**Opioids:** “synthetic” – bind to receptors
(fentanyl, propoxyphene, dextromethorpan, meperidine)

**Semisynthetic:** “modified” opiates – heroin, oxycodone

**Narcotic:** Greek-stupor; imprecise term-legal
– any illicit psychoactive substance
History of Opiates

- 4000 BC – Sumerians
- 7th Century AD – China (opium – oral, smoking)
- 1803 – German pharmacist (F.W. Sertturner) isolated morphine (morpheus – Greek God of Dreams)
- 1830’s – Opium wars
- 1832 – Codeine
- 1860’s – Civil War – “army disease” or “soldiers disease”.

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“Vicious Cycle”

- 1800’s – injected morphine to treat “opium eating”
- 1870’s – physicians complained that morphine habit was harder to break
- 1900’s – used heroin to treat morphine addiction
# Medical Outcome by Opioid TESS(2004)

<table>
<thead>
<tr>
<th>Opioid</th>
<th># Exposures</th>
<th># Deaths</th>
<th>Case/Fatality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td>5,510</td>
<td>43</td>
<td>128 to 1</td>
</tr>
<tr>
<td>Methadone</td>
<td>3,965</td>
<td>96</td>
<td>41 to 1</td>
</tr>
<tr>
<td>Morphine</td>
<td>3,097</td>
<td>18</td>
<td>172 to 1</td>
</tr>
<tr>
<td>Heroin</td>
<td>1,730</td>
<td>34</td>
<td>50 to 1</td>
</tr>
</tbody>
</table>
## Comparison of Medical Outcomes TESS(2004)

<table>
<thead>
<tr>
<th></th>
<th># Exposures</th>
<th># Deaths</th>
<th>Case/Fatality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>7,430</td>
<td>51</td>
<td>145 to 1</td>
</tr>
<tr>
<td>Methadone</td>
<td>3,965</td>
<td>96</td>
<td>41 to 1</td>
</tr>
<tr>
<td>Calcium Antagonist</td>
<td>10,513</td>
<td>62</td>
<td>169 to 1</td>
</tr>
<tr>
<td>Benzos</td>
<td>65,998</td>
<td>202</td>
<td>326 to 1</td>
</tr>
</tbody>
</table>
Heroin

“Prevalent, Puffed, and Paralyzing”
Heroin – The Other Face

Tommie:
Dead
19 years old
Case Presentation: Breathless

A 31 year old male was brought into the ED by paramedics. Some “friends” became worried that he appeared to stop breathing and was turning blue. Paramedics noted the patient to be unresponsive with a RR of 4 and pinpoint pupils.
Case Presentation: Breathless

The patient was known to abuse heroin over the past 2 years. He was recently laid off from his internet start-up and would drink alcohol before he “shot-up”.

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Heroin

- Pro-drug (3,6-diacetylmorphine) – rapidly hydrolyzed to morphine
- 6-monoacetylmorphine + morphine (active)
- Absorbed by all routes
- More lipid soluble – crosses BBB (15-20 sec) 68% vs 5% (morphine)
Sources of Heroin

- **Southwest Asia (Afghanistan, Pakistan, Iran)**
- **Southeast Asia (Burma, Laos, Vietnam, Thailand) – “Golden Triangle”**
  - Cost: $40,000 - $190,000/kg
- **Mexico:** Cost - $13,000 - $175,000/kg
- **South America:**
  - Cost - $50,000 - $200,000/kg
Heroin Production

- Raw opium gum from pods (80mg per pod)
- Cooked opium (morphine alkaloid – 10%)
- Morphine extraction (add lime, precipitate, and press)
- Morphine base to HCl salt (bricks)
- Acetylation (acetic anhydride) to heroin
Types of Heroin

- Base (tan color)
- HCl salt – white crystals/powder with a bitter taste; water soluble and “cut” with fillers (mannitol) + flavorings (quinine, strychnine)
- Most illicit heroin varied in color (white – brown)
- “Black tar” – sticky and colored dark-brown to black
Street Use

- Street terms: Smack, thunder, big H, hell dust, skag, junk, Mexican black tar
- Routes of abuse: injection (IV, IM, Sq – “skin popping”), snorting, smoking
- “Chasing the Dragon”: thick white pyrolysate – heat heroin base on aluminum foil and inhale through a straw (may add crack cocaine)
- 20-50% purity: usually 150-400mg taken QID
## Heroin: Pharmacokinetics

<table>
<thead>
<tr>
<th>Route</th>
<th>F (%)</th>
<th>$T_{\text{peak}}$ (min)</th>
<th>Euphoria Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>100</td>
<td>&lt;1</td>
<td>7-8 sec</td>
</tr>
<tr>
<td>IM</td>
<td>no data</td>
<td>3-5</td>
<td>5-8 min</td>
</tr>
<tr>
<td>Smoke base</td>
<td>62</td>
<td>1-2</td>
<td>10-15 min</td>
</tr>
<tr>
<td>(76 with caffeine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoke HCl salt</td>
<td>17</td>
<td>no data</td>
<td></td>
</tr>
<tr>
<td>Intranasal</td>
<td>27-31</td>
<td>3-5</td>
<td>10-15 min</td>
</tr>
</tbody>
</table>

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# Opiate Receptors

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Subclasses</th>
<th>Anatomic Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>mu (μ)</td>
<td>1,2</td>
<td>Supraspinal, spinal</td>
</tr>
<tr>
<td>delta (δ)</td>
<td>1,2</td>
<td>Substata nigra, globus pallidus</td>
</tr>
<tr>
<td>kappa (κ)</td>
<td>1,2,3</td>
<td>Spinal cord</td>
</tr>
</tbody>
</table>
Receptor Binding and Activity

- Agonists:
- Partial agonists:
- Competitive antagonists:
- Dualism:
  - Pentazocine: weak mu; kappa agonist
  - Nalorphine: mu antagonist, kappa agonist
Intrinsic Receptor Activity

- Activity and receptor affinity are variable and may be opposed

- Agonist
- Partial Agonist
- Antagonist

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Receptor Binding and Activity

- Agonist
- Partial Agonist
- Agonist with Competitive Antagonist

Log [Dose]

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<table>
<thead>
<tr>
<th>Agent</th>
<th>mu</th>
<th>delta</th>
<th>kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>+++</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>+/-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Naloxone</td>
<td>---</td>
<td></td>
<td>--</td>
</tr>
</tbody>
</table>
### Pharmacologic Effects

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>mu</td>
<td>Analgesia, respiratory depression</td>
</tr>
<tr>
<td>delta</td>
<td>Analgesia, inhibits dopamine release</td>
</tr>
<tr>
<td>kappa</td>
<td>Supraspinal analgesia, sedation, psychotomimetic</td>
</tr>
</tbody>
</table>
Pharmacologic Effects

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Case: Breathless

The patient was administered naloxone 2 mg with an increase in respiratory rate to 14 and improvement in color. However, his lung sounds became course and a pink frothy liquid was coming from the mouth and nose.

ABG: 7.36/38/62; \(O_2\text{sat} = 81\%\)
Which patient will require and tolerate a higher dose of an opiate?

- Cachectic cancer patient on chronic pain management
- Morbidly obese patient in acute moderate-severe pain
Respiratory Failure with Opiates: Risk Factors

- Age (extremes)
- CNS depressants (alcohol)
- Tolerance (novice – detoxification)
- Opiate potency (high mu), purity + route (IV, IM)
- Obesity; co-morbidities (hypothyroid)
- External stimulus – dosing by weight
Opiate-Induced Non-Cardiogenic Pulmonary Edema

- **All opiates implicated**
- **Clinical course:** awaken; after minutes to hours develop hypoxia, rales, frothy pink sputum in airway
- **Mechanism**
  - Hypoxia
  - Histamine release
  - Antagonist use: withdrawal and "neurogenic"
  - Negative intrathoracic pressure
Case Presentation: Perplexing Paralysis

50 y/o woman with history of IVDA presented to ED with double vision, headache, nausea and dizziness. She was diagnosed and treated for a migraine headache. The following morning her symptoms persisted and now complained of difficulty swallowing and slurred speech.
Case Presentation: Perplexing Paralysis

She admitted to “skin popping” with “black tar” heroin. Over the next 4 days she became progressively weaker, and unable to get into a sitting position and keep head upright, until requiring intubation and respiratory support. An abscess was I&D’ed on her left arm.
Heroin and Wound Botulism

- Associated with “black tar” heroin.
- Organism: *Clostridium botulinum*; Spores use and abscessed wound allows germination of spores (tetanus, necrotizing fasciitis)
- Contamination in “cut” (dirt, boot polish) and spores activated with heating
Wound Botulism

- **Clinical presentation:**
  - Neurologic symptoms; “It’s in the eyes.”
  - Respiratory failure

- **Management**
  - Supportive and wound care
  - Anti-toxin: Type A
  - Antibiotics: Ampicillin
Heroin Cocktails and Substitutes

- Scopolamine
- “Speedball” – with cocaine
- “Loads”: 1 gram glutethimide (Doriden®) + 4 grains codeine (TC3)
- “T’s and B’s”: pentazocine and tripelennamine – 50mg each (2:1 ratio – dissolve and inject)
Oxycodone and Hydrocodone

“e-abuse”
Case: “Friends”

A 19 y/o female and her friend split 1.5 grams of cocaine, then drank 6-8 beers and split 3 OxyContin 80mg tablets. They were found together unresponsive and apneic. Paramedics resuscitated them with naloxone 2mg.
“Enjoying Opioids”

NeoHippy – Erowid Experience Vault

I have dosed oxycodone about 4 times in my life, hydrocodone about 10, OD’ing on it once. I almost always take my dope orally. I tried administering by snorting a few times, but concluded it wasn’t effective. This is a lot of material to snort – hard in your nose.  

Erowid.com
“Enjoying Opioids”

Approximately 20 minutes after ingestion the old familiar warmth, itchy, euphoric feeling set in. The euphoric feelings began to intensify until reaching a plateau about 3 hours, 50 minutes after ingestion…coordination was very impaired, the body is very relaxed and at peace, ……
OxyContin (Oxycodone)

- Street terms: hillbilly heroin, Oxy, OC, Killers, poor mans heroin
- Semisynthetic, from thebaine
- mu agonist
- Potency: IV oxy 1.5 – 3mg = MS 1mg
  PO oxy 1mg = MS 2mg
- Preparations (1996): 10-160mg/CR tablet; OxyFast 20mg/ml; combination with ASA and APAP (Tylox, Percocet, Percodan)
OxyContin Illicit Use

- Circumvent controlled-release (chew tablets, snort powder)
- Injection: remove coating, melt on spoon, add water and inject
- “Doctor shopping” – fabricated ailment and multiple physicians and pharmacies
- Pharmacy thefts: Virginia, Pennsylvania
- Gangs: South Maine, New Hampshire
OxyContin Illicit Use

- Illicit Internet distribution
- Foreign diversion: Mexico; stamped “EX” instead of “OC”.
- Price: $1 per mg
OxyContin Policy Actions

- FDA black box warning (2001)
  - Abuse liability similar to morphine
  - Not for prn use
  - 80 and 160mg only in opioid tolerant patients
  - Don’t break, chew or crush tablets
- Purdue – “Dear Health Care Professional” letter
- Law Suits: as of August 2003, 42 dismissals
OxyContin substitute

- Remoxy - IND filed
  - Abuse resistant form of OxyContin
  - Developed by Pain Therapeutics, Inc.
  - Sticky Gel cap
  - Resists extraction by alcohol & acids
Case: e-Shopper & Lost Liver

A 39 y/o woman presents to the ED unresponsive in respiratory distress. She is given naloxone with no effect. PMH: depression and migraine headaches. Her husband relays to medical staff that her medications include Effexor®, Paxil®, Soma®, Vicodin® and Lorcet®.
Case: e-Shopper & Lost Liver

Patient is transferred to the ICU. Labs are as follows:

- AST > 2600 U/I
- ALT > 2600 U/I
- Scr = 2.5mg%
- INR = 4.9
- pH = 7.15

Additional Medical History: Finished a bottle of Lorcet #120 tablets within the previous month and had been purchasing Vicodin® from internet pharmacies to treat migraine headaches.
Methadone

“Long-long acting & watch out – a sleeper!”
Case: Fatal Lesson

A 22 year old male took an overdose of 420 mg of methadone. In the ED, he was drowsy, refused care, left hospital and collapsed. Then admitted & treated for approx. 40 hours with naloxone. At 2 am he was walking & talking. At 3:30 am the naloxone and oximeter monitoring was stopped. At 4:00 he was sleeping and breathing, but at 6:55 am was found dead in his hospital bed.
Methadone: History

- Synthesized as a morphine substitute - Germany WWII
- Maintenance therapy for heroin addicts
- Analgesic (Dolophine)
Withdrawal: Symptoms and Signs

- Flu-like, sympathomimetic
- Lucid
- Craving, anxiety
- Cognitive deficits
- High risk: dehydrated, neonates, polypharmacy dependency
Heroin vs Methadone

Severity of Withdrawal vs Time

- Heroin
- Methadone
- Plus naloxone
Methadone: Pharmacology

- mu receptor agonist
- $t_{1/2} = 15-55$ hours, 3–4 days peak effect
- Duration of analgesia not equal to kinetics
- Risk of drug accumulation
- $V_d = 4-5$ L/kg – post-mortem redistribution
- $Q_t$ prolongation - risk of cardiac arrhythmias (LAAM)
**Methadone: Levels**

- **Death Case:** 0.822 mg/L femoral blood
- **Can be subject to 2X post-mortem redistribution**
- **CNS effects @ 0.03 mg/L**
- **Deaths range:** 0.05 – 7.4 mg/L
- **Maintenance:** 0.02 – 0.99 mg/L
- **Death levels overlap with therapeutic levels**
Fentanyl

“Potent progeny and patches”
As a long-term (yet moderated) heroin user, I’m always looking for ways to make my usage more cost effective and less harmful.

About a year ago I had the privilege of wearing a “Duragesic Transdermal System”.

What I really wish to know though is quite simple I suppose; can the Fentanyl within the patch be safely removed from the patch for IV usage?

Sincerely, A Conscientious User
Fentanyl: History

- 1950’s: synthetic (opioid) – phenylpiperidine family
- 1968 – analgesic + sedative
  - Rapid onset (1.5 minutes)
  - Short duration (30-40 minutes)
  - High potency
  - Reversed by naloxone
  - Minimal histamine release and hemodynamic effects
Fentanyl Designer Drugs

- Clandestine laboratories – 12 analogs
- Usually diluted to < 1% with “cuts” and “flavorings” to mimic heroin
- 1979-80: “china white” in CA – 3-methylfentanyl → 15 deaths
- 1988: Pittsburgh chemist
- Other street names: Apache, China girl, Chinatown, Dance fever, murder 8, TNT, He-man
Fentanyl Deaths
May, 2006

- Detroit - 100 deaths since Fall; 41 deaths in 8 days
- Philadelphia - 21 deaths since April - with heroin
- New Jersey - 10 deaths since April
- Chicago - 30 deaths Sept. thru March
Fentanyl Analog Poisonings

- Administered IV, smoked, or snorted
- Incidents started and ended abruptly
- Not picked-up on routine toxicology screen
- Victims found dead at scene with needles in arms
- Causes muscular (chest-wall) and glottic rigidity – contribute to respiratory failure
# Fentanyl Analogs: Comparative Potency

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50 – 100x</td>
</tr>
<tr>
<td>3-methyl-fentanyl</td>
<td>500 – 2000x</td>
</tr>
<tr>
<td>Carfentanly (animal immobilizer)</td>
<td>10,000x</td>
</tr>
</tbody>
</table>

May require larger doses of naloxone to reverse; prolonged with patch ingestion
Fentanyl Patches: Transdermal System

- **Duragesic®**: approved in 1990
- Drug delivery for 72hrs; 12-24 hr to plateau
- 4 layers
- Available in 2.5 – 10mg → delivers 25 – 100 mcg/hr
- Heat, cut or damage → impaired release characteristics
- Street value: $25 - $40/patch
Fentanyl Patches: Transdermal System Residues

- Fentanyl: 28 – 84% recovered from used patch after 3 days
- 10mg patch – retrieved 4.46 – 8.44 mg
- Lethal dose (70kg person) = 1mg

Fentanyl Patches: Poisonings

- Patients chewing patches and lodging into buccal cavity
- Placing multiple patches on skin (“Where it hurts”)
- Heating contents and inhaling fumes
- Aspirating contents and injecting
- Deceased patients (funeral home employee)
- Heating pad/warming blanket → enhanced absorption.
Oral Transmucosal Fentanyl Preparations

- **Actiq®**
  - 200 – 1600 mcg
  - Lozenge on a stick – lollipop
  - For breakthrough cancer pain

- **Fentanyl Oralet®**
  - 100 – 400 mcg
  - Lozenge
  - For hospital use – Anesthesia

- Black box warning: CI for children < 10kg

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Tramadol

“Multiple mechanisms and misunderstood?”
Tramadol Trials in Thailand
Erowid Experience Vaults

I was recently prescribed tramadol quite legitimately in Thailand, for severe headaches. Whereas one had no effect, upping the dose soon brought on very pronounced opiate effects. I began to feel extremely relaxed and pleasant with around 300mg. Although I was advised that it was not addictive, I found increasing intolerance and dependence did occur with time, and I ended up taking 700mg at a go.
Tramadol Trials in Thailand
Erowid Experience Vaults

After 2 months use at around 500 – 700mg a day, I moved on to Malaysia where tramadol was unavailable. I experienced a very unpleasant cold turkey experience after about 48 hours with muscle cramps, fever, shaking … and some horrific trainspotting type nightmares.
Tramadol: History

- Ultram®: prescription analgesic since 1995
- Synthetic opioid – weak mu agonist and inhibits re-uptake of norepinephrine and serotonin
- One of the top 50 most prescribed drugs
- Introduced as another “non-addictive” analgesic (like propoxyphene, pentazocine)
Tramadol: History

- Reports of abuse in Europe
- One of the top 10 diverted prescription drugs
- Controlled Substance Advising Committee: Postmarket surveillance program judged “abuse of tramadol found to be lower than hydrocodone but only marginally higher than NSAIDs.”
  

- Case report of Soma® plus tramadol abuse to mimic effects of controlled substance.

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Atypical Withdrawal

- Partial agonist
  - Pentazocine – chronic high doses > 500mg/d, mild symptoms
  - Buprenorphine – delayed onset, mild symptoms that persist 1-2 weeks

- Tramadol – classic + hallucinations, paranoid, panic, unusual sensory – norepinephrine and serotonin re-uptake inhibition
Tramadol: Acute Toxicity

- Miosis, coma, respiratory depression plus seizures, tachycardia, hypertension
- Additive with CNS depressants
- Metabolized by CyP2D6 – serotonin syndrome if co-administered with SSRI’s (fluoxetine, sertraline)
- Anaphylactic reaction in patient with codeine allergy (cross-sensitivity)
Tramadol: Toxicity Management

- Injected tablets – pulmonary edema and talc granuloma
- Naloxone – partially effective to reverse CNS and respiratory depression; NOT seizures
- Not detected in routine urine screening for opioids
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Tramadol generic

- Concern about confusion with trazodone (50mg strength)
- Request to FDA: urge manufacturer to use “tall man” lettering

traMADOL vs traZADONE
Propoxyphene

“Membrane-stabilizing metabolite”
Case: Darvon Dysrhythmia

A 43 year old male admitted propoxyphene addict is brought to the ED for altered MS. Claims he took 7–9 Darvon in an attempt to get some sleep after an argument with his wife; his wife believes he took more. Given 2mg of naloxone with improvement in MS and RR. In the ED, he was awake, oriented, and even smiling while sitting on the gurney. EKG showed wide-complex sinus rhythm with a left-axis deviation.
Propoxyphene: History & Abuse

- Darvon®: marketed in 1957
- Analgesic potency: 30-50% codeine
- Methadone analog and mu agonist
- In top 10 drugs reported by medical examiner in drug abuse deaths
- Chronic pain, abuse, sexual assault, and fatal poisoning in Nordic Countries (Sweden – 30% deaths)
Propoxyphene: Toxicity Management

- Toxic metabolite, norpropoxyphene
- Propoxyphene and metabolite produce myocardial sodium channel blockade – “membrane stabilizer” effects like TCAs.
- EKG: QRS widening; negative inotropy, seizures
- Sodium bicarbonate (1-2 mEq/kg bolus over 1-2 minutes)
- Lidocaine: displaces from Na channel
- Naloxone: not effective for seizure or dysrhythmias
- R/O APAP or ASA toxicity
Meperidine

“Seizures, stiff and so-long”
Cases: Parkinsonism from “Synthetic Heroin”

A group of heroin abusers, one female and three males (ages 26-42 years), obtained a “new heroin” sample in San Jose, CA. All became symptomatic within a week to include limb jerking and stiffness; generalized slowing and difficulty moving occurred within 2 weeks.

Meperidine Analogs

- MPPP → MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine); chemical intermediate and by-product; clandestine synthesis
- MPTP selectively destroys nigrostriatal dopamine neurons – irreversible
- Process inhibited by MAO-B inhibitors (selegeline)
- Lesions limited to basal ganglia
- Patients respond with levodopa therapy
Meperidine: History and Use

- **Demerol®, Mepergan®**: Analgesic since 1939
- Synthetic opioid with low potency
  - 75-100mg = morphine 10mg (IM/IV)
  - 300mg = morphine 60mg (PO)
- Short duration: 2-4 hours
- Often used for post-op pain in hospital
- No special benefit for biliary colic or pancreatitis
Meperidine: Neurotoxicity

- **Normeperidine**
  - Neurotoxic metabolite
  - $\frac{1}{2}$ analgesic potency and 2x neurotoxicity compared with meperidine
  - Renally excreted, $t_{\frac{1}{2}} = 15-40$ hrs (meperidine 3-6 hrs)

- **Sx:** tremors, myoclonus, seizures
Meperidine: Neurotoxicity

- Predisposing factors
  - Doses > 100mg q2h for > 24h
  - Renal failure
  - Oral dosing
  - Alkaline urine
  - CyP2D6 enzyme inducers
- Mu agonist effects (not miotic pupils)
- Naloxone ineffective for normeperidine-induced seizures
- Serotonin syndrome with MAOI and SSRI
Meperidine: Restrictions and Future Policy

- Shift in opinion and policy towards restricted use
- Not suitable for chronic pain
- Second-line agent for mod-severe pain
- Drug or blood product-induced rigors and post-anesthetic shivering
- Single injection for conscious sedation
- No oral dosing: duration < 48hrs; < 600mg/24 hrs
- CI: renal dysfunction
Summary

- **Heroin:**
  - Still common
  - Many routes of abuse
  - Pulmonary complications and wound infections

- **Methadone**
  - Long-acting & accumulates
  - Death levels overlap with therapeutic
Summary

- Internet
  - Source of information, sharing experiences and procurement

- Non-opioid effects
  - Propoxyphene and meperidine metabolites
Summary

- **Fentanyl Patches**
  - Proper disposal
- “Non-addicting”
  - Don’t always believe the marketing
- **Designer drugs**
  - Unpredictable and deadly