Schedule II
Controlled Substances: Basics and Beyond

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Objectives

• Definition(s)
• Cytochrome P450 processes/drug interactions
• Equi-analgesic dosing for pain management
Controlled Substances

- a drug or other substance listed in the Controlled Substance Act (CSA) of the Code of Federal Regulations (CFR)

Controlled Substances, con’t.

- divided into five schedules based on:
  - currently accepted medical use
  - relative abuse potential
  - likelihood of causing dependence

Controlled Substances, Schedule I

- No currently accepted medical use

- Examples:
  - Lysergic acid diethylamide (LSD)
  - Methyleneoxyamphetamine “Ecstasy”
Controlled Substances, Schedule II

- High potential for abuse which may lead to severe psychological or physical dependence
- Examples of narcotics:
  - morphine
  - hydromorphone (Dilaudid®)
  - meperidine (Demerol®)
- Examples of stimulants:
  - amphetamine (Dexedrine®)
  - methamphetamine (Desoxyn®)
  - methylphenidate (Ritalin®)

Controlled Substances, Schedule III

- Less potential for abuse than substances in schedules I or II and abuse may lead to low or moderate physical dependence or high psychological dependence

Controlled Substances, Schedule III, con’t.

- Examples include:
  - Combination products containing less than 15 mg of hydrocodone per dosage unit
    - Vicodin®, Lortab®
  - Combination products containing less than 30 mg of codeine per dosage unit
    - Tylenol with codeine®
  - oxandrolone (Anadrol®)
Controlled Substances, Schedule IV

- Lower potential for abuse relative to substances in schedule III

Controlled Substances, Schedule IV, cont.

- Example of schedule IV narcotic:
  - propoxyphene (Darvocet-N 100®)

- Other examples:
  - alprazolam (Xanax®)
  - diazepam (Valium®)
  - lorazepam (Ativan®)
  - midazolam (Versed®)
  - triazolam (Halcion®)

Controlled Substances, Schedule V

- Lower potential for abuse relative to substances listed in schedule IV
- Consist primarily of preparations containing limited quantities of certain narcotics
- Generally indicated for antitussive, antidiarrheal and analgesic purposes
- Examples include cough preparations containing not more than 200 mg of codeine per 100 ml
  - Robitussin AC®
  - Phenergan with Codeine®
Objectives

• Definition(s)

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Cytochrome P450 Enzyme Processes

- Many drugs eliminated from body by being chemically altered to LESS lipid-soluble products
  - Process of metabolism
    - Phase 1: drug hydrolysis, oxidation and reduction
    - Phase 2: glucuronidation, sulfation, glutathione conjugation, acetylation and methylation
  - Excreted by the kidneys or the bile

Cytochrome P450 Enzyme Processes, con’t.

- Phase I and Phase II enzyme activity can be either inhibited or induced
  - Inhibition will result in increased concentration of the drug
  - Induction will result in decreased concentration of the drug
Cytochrome P450 Enzyme Processes, con’t.

- Cytochrome P450 enzymes (CYP) may be responsible for at least partial metabolism of approximately 75% of all drugs
- Family designated by numbers (1, 2, 3, etc.)
- Subfamily designated by letters (A, B, C, etc.)
- Key human enzyme sub-families include: CYP1A, CYP2A, CYP2B, CYP2C, CYP2D, CYP2E, and CYP3A

Cytochrome P450 Enzyme Processes, con’t.

- CYP enzymes are found in the endoplasmic reticulum of human tissues
  - Liver*
  - Intestine*
  - Skin
  - Kidneys
  - Brain
  - Lungs
- *most predominant

Cytochrome P450 Enzyme Processes, con’t.

- Concentration of CYP enzymes is relatively equally distributed throughout the body, the relative contribution to metabolism is:
  - CYP3A4 (approx. 50%)
  - CYP2D6 (approx. 25%)
  - CYP2C9 (approx. 15%)
  - CYP1A2
  - CYP2C19
  - CYP2A6
  - CYP2E1
Cytochrome P450 Enzyme Processes, con’t.

<table>
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<tr>
<th>Drug</th>
<th>1A2</th>
<th>2A6</th>
<th>2B6</th>
<th>2C8</th>
<th>2C9</th>
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Practical application:
- Methadone is a moderate inhibitor of CYP2D6
- All of the following are metabolized, at least in part, by CYP2D6:
  - Quinidine
  - SSRIs (FLUoxetine, PARoxetine, sertraline)
  - Thiazide Diuretics
  - Zidovudine

Objectives
- Definition(s)
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- Equi-analgesic dosing for pain management
### Drug Equi-analgesic Dose (mg)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral</th>
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<tr>
<td>Buprenorphine (C-III)</td>
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<tr>
<td>Butorphanol (C-IV)</td>
<td>2</td>
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<tr>
<td>Fentanyl (C-II)</td>
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<tr>
<td>Hydromorphone (C-II)</td>
<td>1.5</td>
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<tr>
<td>Levorphanol (C-II)</td>
<td>Acute: 2</td>
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<tr>
<td></td>
<td>Chronic: 1</td>
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<td>Meperidine (C-II)</td>
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<tr>
<td>Methadone (C-II)</td>
<td>See guidelines</td>
<td>Variable</td>
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<tr>
<td>Morphine (C-II)</td>
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<tr>
<td>Nalbuphine (N/A)</td>
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<tr>
<td>Opioid Analgesics</td>
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<tr>
<td>Oxymorphone (C-II)</td>
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<td>[1]</td>
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<td>Paroxetine (C-IV)</td>
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<td>Tramadol (C-II)</td>
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### Risk Evaluation and Mitigation Strategy (REMS)

Risk Evaluation and Mitigation Strategy (REMS), cont.

“…. a strategy to manage a known or potential serious risk associated with a drug or biological product. A REMS will be required if the Food and Drug Administration (FDA) determines that a REMS is necessary to ensure the benefits of the drug or biological product outweigh its risks. A REMS can include a Medication Guide, Patient Package insert, a communication plan, elements to assure safe use and an implementation system.”

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1/29/2013
Risk Evaluation and Mitigation Strategy (REMS), con’t.

- Risk management plan
- Required of the pharmaceutical company
- Goes beyond a drug’s written prescribing information
- Developed to address the unique risk-benefit profile of a drug or drug class

Risk Evaluation and Mitigation Strategy (REMS), con’t.

- Required for long-acting and extended-release prescription opioids
- Amount of opioid can be much more than the amount of opioid contained in an immediate-release dosage form because extended-release dosage forms are designed to release the opioid over a longer period of time
- Long-acting opioids can take many hours to be cleared from the body
- Thus, risk is magnified

Opioid REMS

- Central component of an opioid REMS program is an education program for providers (physicians, nurse practitioners, physician assistants) and patients
Opioid REMS: Providers

Education will include:

- information on weighing risks/benefits of opioid therapy
- choosing patients appropriately
- managing and monitoring patients
- counseling patients on safe use of these products
- how to recognize evidence of and potential for opioid misuse, abuse and addiction

Opioid REMS: Patients

Education will include:

- Patient-friendly language on:
  - how to use and store medication
  - product risk

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>GENERIC NAME</th>
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<tbody>
<tr>
<td>Avinza</td>
<td>morphine sulfate extended-release capsules</td>
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<td>Butrans</td>
<td>buprenorphine transdermal system</td>
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<td>Dolophine</td>
<td>methadone hydrochloride tablets</td>
<td>Roxane</td>
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<td>Duragesic</td>
<td>fentanyl transdermal system</td>
<td>Janssen Pharmaceuticals</td>
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<td>Embeda</td>
<td>morphine sulfate/naltrexone extended-release capsules</td>
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References