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
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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 (LDS)
  - Methylenedioxymethamphetamine
    “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®)\(^1,2\)
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
Examples include:

- Combination products containing less than 15 mg of hydrocodone per dosage unit
  - Vicodin®, Lortab®
- Combination products containing less than 90 mg of codeine per dosage unit
  - Tylenol with codeine®
- oxandrolone (Oxandrin®)
Controlled Substances, Schedule IV

- Lower potential for abuse relative to substances in schedule III
Controlled Substances, Schedule IV, con’t.

- 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®
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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
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%)
  - CYP2C8/9 (approx. 15%)
  - CYP1A2
  - CYP2C19
  - CYP2A6
  - CYP2E1
Cytochrome P450 Enzyme Processes, con’t.

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<th>1A2</th>
<th>2A6</th>
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<th>2C8</th>
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Cytochrome P450 Enzyme Processes, con’t.

Practical application:

- Methadone is a moderate inhibitor of CYP2D6
- All of the following are metabolized, at least in part, by CYP2D6:
  - QuiNINE
  - SSRIs (FLUoxetine, PARoxetine, sertraline)
  - Thiazide Diuretics
  - Zidovudine
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Equi-analgesic Dose (mg)</th>
<th>Parenteral</th>
<th>Oral</th>
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<tr>
<td>Buprenorphine (C-III)</td>
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<td>Methadone (C-II)</td>
<td>See guidelines</td>
<td>Variable</td>
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<tr>
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<tr>
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Risk Evaluation and Mitigation Strategy (REMS)
Risk Evaluation and Mitigation Strategy (REMS), con’t.

“…. 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.”

\(^4\)
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

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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
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>
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<tr>
<th>TRADE NAME</th>
<th>GENERIC NAME</th>
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<tr>
<td>Avinza</td>
<td>morphine sulfate extended-release capsules</td>
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<td>buprenorphine transdermal system</td>
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References