Objective

• To give you enough of a “tickler” that will make you want to “be an adult learner”

• Give you ideas about key things you need to evaluate prior to prescribing these medications
  – Clinical
  – Legal

• What to consider when the “drug rep” brings around the “lunch” with the nice glossy sales data

Controlled Dangerous Substances (CDS)

• How do you define controlled?
  – Are all prescription medications “controlled”?

• What makes something dangerous?
  – Abuse potential
  – Addictive qualities
  – Adverse effects during therapeutic use
  – Adverse effects during abuse
  – Adverse effects in an over dose
    • Acute OD
    • Chronic OD
Which is more dangerous?

- diazepam or digoxin
- lorazepam or atenolol
- oxycodone or morphine
- morphine or acetaminophen
- diazepam or acetaminophen

Sedative Hypnotics
Benzodiazepines

- Widely prescribed group of medications
  - Many indications
    - Anxiety
    - Insomnia
    - Phobias
    - Panic disorder
    - Mania
    - Adjunctive use in chronic pain
    - Muscle rigidity/spasm/cramps
    - Cocaine intoxication
    - Sympathomimetic intoxication
    - Sedative-hypnotic withdrawal
    - Ethanol withdrawal
    - Nerve agent poisoning
    - Seizures

Pharmacology

- GABA (γ-aminobutyric acid) is an inhibitory neurotransmitter
  - Involved in sleep induction, inhibition of neuroexcitation, modulation of anxiety

- Benzodiazepine receptor is near the GABA receptor
  - Stimulation enhances GABA binding to its receptor

- Benzodiazepines
  - Potentiats (GABA)

GABA/ benzodiazepine receptor

- Complex molecule
  - Contains binding sites for several drugs
  - Has a chloride channel

Current Medicine, Inc, online
GABA/benzodiazepine receptor

- discrete receptor sites for
  - benzodiazepines, GABA, barbiturates, alcohol

Pharmacology

- GABA receptors
  - CNS in the basal ganglia, hippocampus, cerebellum, hypothalamus, and spinal cord
- GABA
  - involved in sleep induction, inhibition of neuroexcitation, modulation of anxiety
- GABA binds to its receptor
  - chloride ion channels open
  - influx of chloride into the neuronal cell
  - hyperpolarization of membrane potential
  - prevention or limiting the cell's response to excitatory stimuli

Pharmacology

- Overall
- Depressant effects of benzodiazepines are due to their potentiation of GABA inhibitory activity

Clinically
- impaired psychomotor skills, cognitive dysfunction, short-term memory impairment, sedation, and low-grade coma.

Individual agents

- How do they differ from one another?
  - Potency
  - Onset of action
  - Duration of action
  - Metabolism
  - Drug interactions
  - Adverse effects
    - More similar than different
  - Indication
    - Approved
    - Non-approved
Specific use

Insomnia

- Difficulty with the initiation, maintenance, duration, or quality of sleep
  - “results in the impairment of daytime functioning, despite adequate opportunity and circumstances for sleep”
- “difficulty with sleep maintenance”
  - implies waking after sleep has been initiated but before a desired wake time
- Difficulty with sleep initiation
  - a delay of more than 30 minutes in sleep onset


Common Rx agents used to treat
- benzodiazepines, benzodiazepine-receptor agonists, and sedating antidepressants

Common OTC agents used to treat
- Sedating antihistamines

Insomnia

- Common Rx agents used to treat
  - benzodiazepines, benzodiazepine-receptor agonists, and sedating antidepressants

- Common OTC agents used to treat
  - Sedating antihistamines

- Benzodiazepines and benzodiazepine-receptor agonists
  - proven efficacious in many clinical trials

- Improved
  - sleep latency, total sleep time, number of awakenings, and sleep quality

- Primarily for short-term insomnia
  - no studies extend beyond six months of use
**Pharmacotherapy**

- Things to focus in on
  - Time to onset
  - Duration of action
  - Class related side effects
  - Agent specific side effects
  - Agent specific interactions
  - Duration of use in clinical trials

---

**Benzodiazepines**

<table>
<thead>
<tr>
<th>Rx</th>
<th>Onset</th>
<th>Duration</th>
<th>use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temazepam (Restoril)</td>
<td>30-60 min</td>
<td>T1/2 (8-15 hrs) Intermediate</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>Estazolam (ProSom)</td>
<td></td>
<td>(T1/2 10-24 hrs) Intermediate</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>~ 30 min</td>
<td>(T1/2 2-5 hrs) Short</td>
<td>Sleep onset</td>
</tr>
</tbody>
</table>

---

**Benzodiazepine Receptor agonists**

<table>
<thead>
<tr>
<th>Rx</th>
<th>Onset</th>
<th>Duration</th>
<th>use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>10 min</td>
<td>T1/2 (8-15 hrs) Intermediate</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>Zolpidem (Ambien) CR</td>
<td>7-27 min</td>
<td>Short</td>
<td>Sleep onset</td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>30 min</td>
<td>Ultra Short</td>
<td>sleep-onset or sleep maintenance</td>
</tr>
</tbody>
</table>

---

**Rebound insomnia**

- Rare after the discontinuation of long-duration benzodiazepines
- Mild after discontinuation of intermediate-acting benzodiazepines
- Marked rebound insomnia reported after the discontinuation of triazolam
  - usually lasting one to three nights
- zolpidem
  - little or no rebound insomnia
- zaleplon
  - None noted
## Tolerance

- Difficult to assess because most studies only last days to weeks

- Short-term tolerance
  - deterioration in sleep measures
    - has not been noted with 8 weeks of temazepam
    - Zolpidem continuously for 4 to 5 weeks or intermittently for 12 weeks
    - Zaleplon for 4 to 5 weeks.
    - 6 months of eszopiclone showed a sustained beneficial effect

## ADRs

- More frequent in the elderly
- More frequent with interacting medications

- Day time sedation, dizziness, in-coordination
  - Most common after of long-acting benzodiazepines
  - Less with intermediate-acting agents
  - Rare with short-acting agents

- Use of long-acting benzodiazepines
  - has been associated with an increased risk of falls and hip fractures in older patients

## ADRs

- drowsiness, fatigue
- confusion, weakness, and vertigo

## Considerations in elderly

- Increased risk of falls, possible slowed reaction time
  - increased risk of motor vehicle accidents
  - anterograde amnesia
**Choice of agent**

- Zaleplon and zolpidem
  - shorter-acting agents have less risk of daytime sedation than benzodiazepines
- Often used for treatment of sleep onset insomnia
- Temazepam slower time to onset
  - treatment of sleep maintenance difficulties

**Choice of agent**

- Difficulty staying asleep
  - a hypnotic with a slower rate of elimination may be more appropriate
  - temazepam, estazolam, flurazepam

---

**Metabolism**

- Why is it important to understand metabolism/clearance?
  - Drug-drug interactions
  - Drug-disease state interactions
  - Prolonged action despite “short” t1/2

**Pharmacokinetics**
### Why are they misused?
- To decrease unpleasant symptoms of stimulants or hallucinogens
- To self-treat withdrawal symptoms of other agents
- Often used to harm oneself/OD

### Important facts
- Hypnotics should not be used with alcohol
  - Why?
- In general, pregnancy is a contraindication
- Benzodiazepines should be avoided in patients with known or possible sleep apnea
- Smaller doses should be used in elderly patients

### Adverse effects
- Dose dependent
- Disease state dependent
- Co-medication/agent dependent

### Adverse effects
- Respiratory depression or cardiovascular instability
  - Less likely to occur compared to many sedative-hypnotics
  - Increased risk if used with other CNS depressants or in large doses
Anxiety

- Oxidized to active metabolites
  - Diazepam
  - Chlordiazepoxide
  - Clorazepate
  - Prazepam
  - Clonazepam
    - inactive metabolites but long t1/2 (>20 hours).

- Excreted in the urine
  - Oxazepam, lorazepam
  - t1/2 ~12 hours
    - May not be detected on UDS

- oxidized via the cytochrome P4503A4
  - alprazolam (t1/2 11-16 hrs)

Anxiety

- Agents with “longer” duration of action than sedatives
  - Diazepam (Valium)
  - Alprazolam (Xanax)
  - Lorazepam (Ativan)

Acute seizures & status epilepticus
### Acute seizures & status epilepticus

- Enhance inhibitory effect of GABA
  - binds to the benzodiazepine-GABA complex

  - Diazepam
  - Lorazepam
  - Midazolam

### Diazepam

- Highly lipohilic
  - Enters the brain rapidly
  - Re-distribution after 15 to 20 minutes
    - reduces its clinical effect
- T1/2~ 24 hours
  - Cumulative effects a potential with repeated administration
- IV 5 to 10 mg per min
- Avoid IM
- Available as a rectal product
  - Diastat

### Lorazepam

- Less lipophilic than diazepam
- Slower re-distribution half-life
  - 2-3 hrs vs 15 min. for diazepam
- binds with > affinity to the GABA receptor than diazepam
- longer duration of seizure control

### Ethanol withdrawal
**Ethanol withdrawal**

- Chemical balance is maintained in the CNS through inhibitory and excitatory neurotransmitters
  - GABA
    - Inhibitory neurotransmitter
  - glutamate
    - major excitatory neurotransmitters
    - Acts through the N-methyl-D-aspartate (NMDA) neuroreceptor

- Alcohol
  - enhances the effect of GABA
  - decreased brain excitability
  - chronic exposure causes a compensatory decrease of GABA receptor response to GABA
    - evidenced by increasing tolerance of the effects of alcohol
  - Alcohol inhibits NMDA receptors
    - chronic alcohol use results in up-regulation of NMDA receptors

- Abrupt ethanol cessation
  - results in CNS hyperexcitability
  - receptors previously inhibited by alcohol are no longer inhibited
    - anxiety, irritability, agitation, and tremors
    - severe manifestations include alcohol withdrawal seizures and delirium tremens
  - Benzodiazepines and GABAergic agents
    - effective because of cross-tolerance with ethanol at the GABA receptor

- Benzodiazepines
  - safe and effective
  - preventing or treating seizures and delirium

- How do you choose a specific agent?
  - Efficacy studies
  - ADRs
  - Interactions
GABA/benzodiazepine receptor

Ethanol withdrawal: Choice of agent

• Pharmacokinetics
  – Diazepam & Chlordiazepoxide
    – Long t1/2
  – Active metabolites
    • Good vs bad
    • Liver disease
  – Withdrawal is smoother?
  – Rebound withdrawal symptoms are less likely to occur?
  – > risk of drug accumulation

Ethanol withdrawal: Choice of agent

• Lorazepam & Oxazepam
  – intermediate-acting
  – may be preferable in those that have decreased metabolizing capabilities?
    • elderly
    • liver disease

Abuse

• Combination of benzodiazepines and ethanol
  • dangerous
  • "date rape" drug
  • markedly impair functions that normally allow a person to resist sexual aggression
**Typical ADRs**

- Dose related
  - \( \text{dose} \rightarrow \text{effect} \)
  - well tolerated
    - drowsy
    - dizzy
    - Confusion
    - Blurred vision
    - Weakness
    - Slurred speech
    - Lack of coordination
    - coma

- Hypotension

- respiratory depression
  - Risk increased by co-administration of other medications

**Physical and Psychological Dependence**

- Abuse results in Physical and psychological dependence
  - vs

- Physical and psychological dependence results in abuse (continued abuse)

**Physical and Psychological Dependence**

- Abrupt discontinuation
  - withdrawal symptoms
    - Anxiety
    - Insomnia
    - Anorexia
    - Headaches
    - Weakness
    - seizures

- Withdrawal
  - Can occur in those taking normal doses for short periods
  - More common after longer periods of time

- Symptoms
  - usually develop at 3-4 days from last use
  - can appear earlier with shorter-acting varieties
**Physical and Psychological Dependence**

- **Symptoms**
  - usually develop at 3-4 days from last use
    - can appear earlier with shorter-acting agents
    - greater intensity for a shorter period of time
  - long half-life drugs have a later onset
    - less intense
    - more prolonged course

**Signs of abuse**

- Abuse of benzodiazepines
  - often mimic the indications they are prescribed for
    - Anxiety
    - Insomnia
    - Anorexia
    - Headaches
    - Weakness

**Overdose**

- How should an acute OD be managed?
  - Symptomatic supportive care
  - Flumazenil

**Switch Gears**
Narcolepsy

- Narcolepsy
  - “combination of excessive daytime sleepiness and abnormal manifestations of REM phenomena including cataplexy, sleep paralysis, and hypnagogic hallucinations”
  - rare ~140,000 people in the United States

Cataplexy

- Cataplexy
  - “to strike down”
  - common symptom of narcolepsy
  - sudden bilateral skeletal muscle weakness triggered by intense emotions
    - Laughter, anger, surprise, fear, embarrassment, excitement, sexual arousal
  - extremely variable both in severity and frequency
    - occasionally to many times a day
    - Loss of muscle tone

Cataplexy

- Loss of muscle tone
  - from mild to severe
  - lasting from a few seconds to several minutes
    - arm weakness
    - drooping head
    - generalized weakness
    - knee buckling
    - sagging jaw
    - slumping of the shoulders
    - slurred speech
  - complete cataplexy
    - all postural skeletal muscles are affected
    - paralysis and collapse
  - affect most basic activities of daily living
    - talking, eating, standing, walking, or driving
    - it can prevent patients from holding a child, interviewing for a job, participating in a meeting, going to a movie, attending a party, or working out at the gym

Xyrem (sodium oxybate)

- GHB
  - naturally occurring inhibitory neurotransmitter
  - hypnotic-anesthetic properties
  - indicated for the treatment of cataplexy in patients with narcolepsy
Xyrem (sodium oxybate)

- Anti-cataplectic mechanism of action of it is not known
  - Patients have disrupted sleep
  - Hypothesis is that poor sleep might contribute to their daytime symptoms

Xyrem (sodium oxybate)

- Rapid absorption
  - Rapid onset of its CNS depressant effects
  - Given at bedtime only, while in bed
  - For at least 6 hours after ingestion
    - Patients must not engage in hazardous activities requiring complete mental alertness or motor coordination
      - Operating machinery, driving a motor, vehicle, or flying an airplane

Xyrem (sodium oxybate)

- ADRs
  - Respiratory depression
    - Excess doses
    - Drug interactions
  - Confusion
  - Depression
  - Nocturnal incontinence
  - Sleepwalking
    - Reported in 7% of 448 patients clinical trials

Xyrem (sodium oxybate)

- FDA in 2002 for treatment of cataplexy in narcolepsy
- Available through the Xyrem Success Program (1-866-997-3688)
- Schedule I status to prevent illicit GHB use instituted in 2000
## GHB abuse
- popularity starting in 1990s
  - nutritional supplement to enhance bodybuilding
  - recreationally at “rave” dance parties
  - date rape agent

## Stimulants
- Amphetamine related agents
  - Structurally similar agents
  - Pharmacologically similar agents
- Uses have included
  - weight loss/control
  - Narcolepsy
  - Attention deficit disorder
  - Depression
  - Enhance alertness

### What is the mechanism of action?
Amphetamine and related agents
Pharmacology

- Primary action
  - release of catecholamines from the presynaptic terminals
    - dopamine and norepinephrine

- Other mechanisms
  - Inhibit the reuptake of catecholamines
  - Increased release of serotonin (5-hydroxytryptamine, 5-HT)

Amphetamine and related agents
Pharmacology

- Slight alterations to chemical structure alters individual agents:
  - binding to receptor sites
  - location of action
  - pharmacokinetics
  - pharmacology

Amphetamines

- Slight alterations to chemical structure results in differences in clinical action
  - Appetite suppressant effects
  - Cardiovascular effects
  - Alertness
  - Hallucinogenic properties
<table>
<thead>
<tr>
<th>ADHD persistence into adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>• met with skepticism</td>
</tr>
<tr>
<td>• studies demonstrate persistence into adulthood</td>
</tr>
<tr>
<td>• age-dependent decline in symptoms</td>
</tr>
<tr>
<td>• symptoms may result in significant impairments</td>
</tr>
<tr>
<td>• by 30–40 yo many with a Hx in childhood no longer meet criteria for ADHD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• most prevalent childhood developmental disorder</td>
</tr>
<tr>
<td>• chronic condition</td>
</tr>
<tr>
<td>– impairs function both at home and in school</td>
</tr>
<tr>
<td>– frequently persists into adulthood</td>
</tr>
<tr>
<td>• sometimes not diagnosed until adulthood</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHD persistence into adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>• College students have unique challenges</td>
</tr>
<tr>
<td>• Structured days &amp; smaller classes are not routine in college:</td>
</tr>
<tr>
<td>• schedules differ from day to day and classes have many more students</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHD persistence into adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Many with ADHD who had good academic performance in elementary, middle, and high school often cannot cope in the college setting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHD persistence into adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>• “medications that are useful in the earlier years continue to be helpful in the adult years”</td>
</tr>
</tbody>
</table>
### ADHD

- At least 2 separate classification systems used internationally to diagnose ADHD

- Common classification
  - Persistent hyperactivity, impulsivity and inattention that are divided into three subtypes:
    - primarily inattentive
    - primarily hyperactive/impulsive
    - combined in

- Diagnosis is based upon
  - structured clinical interview
  - symptoms rated by parents and teachers in different settings
  - diagnostic scales

- Very important to “confirm diagnosis” prior to ordering medication

### Pharmacotherapy

- **Stimulants**
  - Methylphenidate

- **Tricyclic antidepressants**
  - Amitriptyline, Desipramine, Imipramine, Clomipramine, Nortriptyline

- **MAO inhibitors**
  - Phenelzine, Selegiline

- **Alpha 2 agonists**
  - Clonidine, Guanfacine

- **Others**
  - Atomoxetine, Modafinil, Bupropion
  - ?

### Psychostimulants

- Large evaluation of the literature
  - no difference
    - methylphenidate vs dextroamphetamine
  - clinical benefit in 70–80% of patients
  - no differences between forms

- improvement in core symptoms
- response may very from patient to another
Pharmacokinetics

- Majority of stimulants
  - Short t1/2
  - Effective time
    - 3-6 hrs
    - Multiple doses/day needed
      - embarrassment for children
        » take a dose at the nurse’s office during school
      - adults forget to take midday doses
- Newer dosage forms
  - Sustained release

Dosing suggestions

- Start with lowest dosing available
  - Titrate up to “best dose” for outcome
    - Reduce dose if ADRs occur
  - “school days only” vs 7 days a week?

Psychostimulants ADRS

- loss of appetite and weight
  - Beneficial?
- insomnia
- motor tics
- Rarely, with high doses
  - psychotic reactions, mood disturbances, hallucinations.

<table>
<thead>
<tr>
<th>Name</th>
<th>Duration</th>
<th>Dose schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritalin, Metadate, Methylin</td>
<td>5–20 mg BID to TID</td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Ritalin SR, Metadate ER, Methylin ER)</td>
<td>3-8 hr 20–40 mg QD or 40 mg in the AM and 20 mg in the afternoon</td>
<td></td>
</tr>
<tr>
<td>Extended Release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Concerta, Metadate CD, Ritalin LA)</td>
<td>8-12 hr 18–72 mg QD</td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Dexedrine, Dextrostat)</td>
<td>5–15 mg BID or 5–10 mg TID</td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Adderall, Dexedrine spansule)</td>
<td>6-8 5–30 mg QD or 5–15 mg BID</td>
<td></td>
</tr>
<tr>
<td>Extended Release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adderall-XR</td>
<td></td>
<td>10-30 mg QD</td>
</tr>
</tbody>
</table>
Psychostimulants-Concern

- Methylphenidate
  - Sudden Death
    - Association is possible
    - Several had underlying heart disease

- Psychostimulants-Concern
  - Is there an increase in the risk of substance abuse in later life?
    - Low levels of drug abuse reported in ADHD treated
    - Meta-analysis found that untreated ADHD adolescents were at a much higher risk of developing drug abuse

Psychostimulants-Height

- Growth continues
  - Transient delays associated with
    - ADHD vs pharmacotherapy
  - Overall height appears to be unaffected if treatment is discontinued in adolescence

- Monitor growth in children treated with stimulant drugs

Psychostimulants

- Other concerns
  - Tics
    - Early reports showed > risk in patients with tics or family history of tics
    - Recent data ? the previous data
    - New data does not demonstrate the > risk
**Psychostimulants**

- Methylphenidate
  - “contraindicated in those with seizure disorder”
  - ? Real risk vs lack of data

**Medication failure**

- Define ?
  - Almost all children will respond to at least one agent if “tried in a systematic way”

---

**CONTROLLED SUBSTANCES**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Insignia</th>
<th>Characteristics</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (C I)</td>
<td>![Controlled Substance Icon]</td>
<td>High abuse potential. May lead to severe dependence.</td>
<td>Heroin, Marijuana, Psycoke</td>
</tr>
<tr>
<td>II (C II)</td>
<td>![Controlled Substance Icon]</td>
<td>High abuse potential. May lead to severe dependence.</td>
<td>Morphine, Codeine, Methadone, Amphetamine</td>
</tr>
<tr>
<td>III (C III)</td>
<td>![Controlled Substance Icon]</td>
<td>Abuse potential less than Schedules I &amp; II. May lead to moderate dependence.</td>
<td>Drugs that are combinations of opiate and non-opiate drugs, i.e., Tylenol® with codeine (Tylenol® w/C)</td>
</tr>
<tr>
<td>IV (C IV)</td>
<td>![Controlled Substance Icon]</td>
<td>Moderate abuse potential. May lead to limited dependence.</td>
<td>Valium®, Mavnav®, Phenobarbital</td>
</tr>
<tr>
<td>V (C V)</td>
<td>![Controlled Substance Icon]</td>
<td>Small abuse potential. May lead to limited dependence.</td>
<td>Cough medications with codeine, certain antidiarrheals</td>
</tr>
</tbody>
</table>

---

**Update on the Pharmacotherapy of Pain**

Bruce Ruck, BS, Pharm.D.
Director of Drug Information & Professional Education
New Jersey Poison Information and Education System
How do you define pain?

**How DO you define pain?**

- Pain is what ever the patient says it is!

**Who Experiences Pain?**

- All ages
- Children
- Geriatrics
What are the common causes of analgesics failure?

Common causes of analgesic failure
- Improper conversion
  - between medications and routes of administration
- Prejudice
  - against a specific class of medication
  - against a specific medication

Barriers to Effective Pain Management
- Legal
  - Actual
  - Perceived
- Patient
- Health Care Professional
- Society
### Barriers to Effective Pain Management

- Perceived
- Someone will report me
  - So What!!!!!!!!

### Analgesic use

The right medication at the right dose at the right time can relieve almost all pain.

### Analgesic Classes

- Opioids
- Non-opioids
  - APAP, NSAIDs
- Analgesic adjuncts
  - TCA’s, carbamazepine, Gabapentum

### Opioids

Is one agent more efficacious than another?
### Opioids

- Equal efficacy when you account for:
  - Differences in bioavailability
  - Differences in potency

### Meperidine

**Avoid**

- Accumulation of metabolite in those with:
  - Renal insufficiency
  - Long term use
  - High doses
- Tremors
- Seizures
- Myoclonus

### Opioids

- Is one agent more toxic than another?

- Is one route superior to another?
Is one route superior to another?

- Not when you:
  - “manage” pain
  - Account for differences in bioavailability

Choosing a route of administration

- Ease of use
- Interference with lifestyle
- Nausea-vomiting
- NPO
- IV access

---

**Oral**

- Efficacious
- Convenient
- Relatively cheap

---

**Oral**

- Efficacious
- Convenient
- Relatively cheap
### IM
- Avoid
- Painful
- Sterile abscess
- No advantage compared to IV

### Topical
- Convenient
- Titration difficult
- Patient must be able to take oral prn meds
- Used once stabilized on a “oral/parental dose”

### Equal analgesic dosing (mg)

<table>
<thead>
<tr>
<th>Med</th>
<th>Oral</th>
<th>Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30-60</td>
<td>10</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>Methadone</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Codeine</td>
<td>200</td>
<td>NA</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>30</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Opioids
- Frequency of dosing
  - Around the clock vs prn
  - Short acting vs long acting
### Opioids

#### ADRs
- Constipation
- Sedation
- N/V
- Urinary retention
- Allergy

#### Opioids Interactions

- **Pharmacodynamic**
  - Medications that increase sedation or respiratory depression

- **Pharmacokinetic**
  - Avinza (morphine sulfate extended-release capsules)
    - Do not consume alcoholic beverages or medications containing alcohol while on AVINZA therapy
      - may result in the rapid release and absorption of a potentially fatal dose of morphine.

### Opioids

- Physical addiction
- Psychological addiction
- Pseudo-addiction

### Opioids

- “M” word
  - Vs
  - “O” word
Opioids

- Diseases progress
- Tolerance develops
- 1st time you see a patient is not the 1st time they are being seen

Barriers to Effective Pain Management

- Perceived
  - Someone will report me
    - So What!!!!!!!

Barriers to Effective Pain Management

- Actual
  - Maximum quantities ordered
  - Documentation of necessity
  - Does not differ from any other disease state

Barriers to Effective Pain Management

- Perceived
  - Legal
    - Cannot treat a patient for pain that has a non-terminal illness with a CDS:
      - For a long time/rest of life
      - For more than a few days-weeks
      - With a Hx of abuse

- NOT TRUE
<table>
<thead>
<tr>
<th>RX Changes For Chronic Pain</th>
<th>RX Changes For Chronic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Schedule II CDS</td>
<td>• Schedule II CDS</td>
</tr>
<tr>
<td>• Quantity not &gt; 120 dosage units or 30 day supply</td>
<td>• Quantity &gt; 120 dosage units</td>
</tr>
<tr>
<td>Unless</td>
<td>Not to exceed a 30 day supply</td>
</tr>
<tr>
<td>• Patient has pain from cancer</td>
<td>• Patient has pain from cancer</td>
</tr>
<tr>
<td>• Intractable pain</td>
<td>• Intractable pain</td>
</tr>
<tr>
<td>• Terminal Illness</td>
<td>• Terminal Illness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RX Changes For Chronic Pain</th>
<th>Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• When prescribed for &gt;/= 3 months</td>
<td>• Medical history</td>
</tr>
<tr>
<td>• Review of treatment course, progress, pain etiology</td>
<td>• Physical Exam</td>
</tr>
<tr>
<td>• Document problems associated with therapy</td>
<td>• Psychological function</td>
</tr>
<tr>
<td>• Periodically re-assess needs and try to D/C medications if clinically appropriate</td>
<td>• Underlying/coexisting disease</td>
</tr>
<tr>
<td></td>
<td>• Hx of substance abuse</td>
</tr>
</tbody>
</table>
## Documentation

<table>
<thead>
<tr>
<th>Frequency and Severity of Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain scale</td>
</tr>
<tr>
<td>– Visual analogue</td>
</tr>
<tr>
<td>– Faces</td>
</tr>
<tr>
<td>– Ruler</td>
</tr>
<tr>
<td>• 1-10</td>
</tr>
<tr>
<td>• 1-5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recognized medical indication for use of the medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete name of medication</td>
</tr>
<tr>
<td>Dose, strength, frequency</td>
</tr>
<tr>
<td>Instructions for use</td>
</tr>
</tbody>
</table>

### Amphetamines and Sympathomimetics

- Laws do not address the use as an adjunct to opiates
- Used to decrease the sedative effects of the opiates
  - High dose opiates in the terminal patient

### Bupinorphine

Bruce Ruck, Pharm.D.
Director Drug Information and Professional Education New Jersey Poison Information and Education System
buprenorphine

- Buprenorphine is an opioid agonist/antagonist (partial agonist)
  - agonist at the mu-opioid receptor
  - antagonist at the kappa-opioid receptor

- Can produce typical opioid agonist effects and side effects
  - Ceiling effect is present
    - Pain relief, euphoria and respiratory depression

buprenorphine

- Partial antagonists
  - Can precipitate the opioid withdrawal syndrome
  - Dysphoric mood
  - Nausea or vomiting
  - Muscle aches/cramp
  - Lacrimation
  - Rhinorrhea
  - Pupillary dilation
  - Sweating
  - Piloerection
  - Diarrhea
  - Yawning
  - Mild fever
  - Insomnia
  - Craving
  - Distress/irritability

buprenorphine

- Subutex (buprenorphine)
- Suboxone (buprenorphine/naloxone)

- Approved for the treatment of opiate dependence 10/02
  - treat opiate addiction by preventing symptoms of withdrawal from heroin and other opiates
    - reduces cravings

Subutex and Suboxone

- first opioid approved for office based treatment of opiate/opioid dependence
  - Used under the Drug Addiction Treatment Act (DATA) of 2000
  - Previously opiate dependence treatments could be dispensed in clinics that specialize in addiction treatment
Subutex and Suboxone

- Goal is to provide patients greater access to needed treatment
- Each physician is limited in the number of patients they are allowed to treat
- Special DEA registration for the use of this drug is needed

buprenorphine

- Subutex (buprenorphine) – for use at the beginning of treatment of opiate/opioid abuse
- Suboxone (buprenorphine/naloxone) – maintenance treatment of opiate addiction
  - Naloxone to decrease the risk of intravenous abuse of buprenorphine by individuals physically dependent on opiates

buprenorphine

- Suboxone (buprenorphine/naloxone)
  - 4:1 buprenorphine:naloxone
  - maintenance treatment of opiate addiction
  - Naloxone to decrease the risk of intravenous abuse of buprenorphine by individuals physically dependent on opiates
  - help discourage diversion and misuse

Buprenorphine/naloxone

- Why was naloxone added?
  - decrease the risk of IV abuse by those physically dependent on opiates
  - No significant effect when given sublingually
    - Poor bioavailability
  - Parenterally
    - opioid antagonist actions were similar to naloxone
**Subutex and Suboxone**

- **SUBOXONE**
  - uncoated tablet for sublingual administration
  - 2 mg buprenorphine with 0.5 mg naloxone
  - 8 mg buprenorphine with 2 mg naloxone

- **SUBUTEX**
  - uncoated tablet for sublingual administration
    - 2 mg buprenorphine
    - 8 mg buprenorphine

**Subutex and Suboxone**

- **Drug-drug interactions**
  - CYP 3A4 Inhibitors and Inducers may alter kinetics
    - CYP 3A4 inhibitors may increase buprenorphine levels
      -azole antifungal agents (e.g., ketoconazole)
      -macrolide antibiotics (e.g., erythromycin)
      -HIV protease inhibitors (e.g. ritonavir, indinavir and saquinavir)
    - CYP 3A4 inducers has not been investigated; closely monitor if inducers of CYP 3A4 are given
      - phenobarbital, carbamazepine, phenytoin, rifampicin

**Subutex and Suboxone**

- **DOSAGE**
  - 12-16 mg once a day sublingually
  - clinical effects between formulations are interchangeable
  - SUBUTEX
    - no naloxone
    - preferred during induction
  - SUBOXONE
    - for continued use

- **DOSAGE**
  - If using more than two tablets place all the tablets SL at once or place 2 at a time
  - swallowing tablets decrease bioavailability
**Induction:**
- Avoid precipitating withdrawal
  - Start when objective and clear signs of withdrawal are evident
  - Want patient in mild withdrawal
- One method
  - 8 mg of SUBUTEX on Day 1 and 16 mg SUBUTEX on Day 2
  - Day 3 onward patients received SUBOXONE tablets at the same buprenorphine dose as Day 2
  - Induction accomplished over 3-4 days depending on the target dose
  - To prevent patient from giving up titrate to clinical effects ASAP

**Induction**
- **Heroin or users of short-acting opioids**
  - SUBUTEX
  - Should be given at least 4 hours after the patients last used opioids
  - preferably when early signs of opioid withdrawal appear

**Induction**
- **long acting opioids**
  - withdrawal more likely during induction
  - > risk in patients maintained on higher doses of methadone (>30 mg)
  - when the first buprenorphine dose is administered shortly after the last methadone dose

**Maintenance**
- SUBOXONE is preferred
- naloxone is present

**Recommended target dose**
- 16 mg/day adjusted in increments / decrements of 2 mg or 4 mg to a dose that prevents opioid withdrawal effects
- range of 4 to 24 mg/day depending on the individual
Suboxone

- Reducing dosage and stopping treatment:
  - gradual and abrupt discontinuation have been used

- Which is best
  - ?

• Any?