Disclosures/Conflicts

• Dr. Stern has no direct conflicts of interests or disclosures to report related to the content of this presentation
Introduction

• General principles of psychopharmacology
• Antidotes
• Use of psychotropics
  • antidepressants
  • antipsychotics
  • anxiolytics
  • anticonvulsants/mood stabilizers
  • narcotics
  – side effects and drug-drug interactions
• Important drug-induced syndromes
Pre-Test: Question 1

Which of the following is not a characteristic feature of neuroleptic malignant syndrome?

- A. autonomic instability
- B. leukopenia
- C. hyperthermia
- D. increased creatine phosphokinase
- E. rigidity
Pre-Test: Question 2

Which of the following agents would not be expected to increase serum lithium levels?

- A. aminophylline
- B. NSAIDs
- C. tetracycline
- D. thiazide diuretics
- E. metronidazole
Pre-Test: Question 3

Which of the following agents would be most likely to contribute to a delirium with prominent myoclonus?

- A. digoxin
- B. phenobarbital
- C. atropine
- D. meperidine
- E. lorazepam
General Principles of Psychopharmacology
Types of Drug Interactions

• Pharmacokinetic
• Pharmacodynamic
• Idiosyncratic
Pharmacokinetic Drug Interactions

- Drug interactions that result in changes in plasma levels and/or tissue concentrations caused by the changes in:
  - absorption
  - distribution
  - metabolism
  - elimination
Pharmacokinetic Effects: Absorption

- Interactions that may alter the time to reach the maximum drug concentration
- Effects are usually less important than are the effects of metabolism and excretion
  - even in the elderly
Decreased Absorption

• Caused by drugs that bind to a drug and form unabsorbable complexes
  – antacids
  – charcoal
  – cholestyramine
  – kaolin-pectin
Increased Absorption

- Caused by drugs that speed gastric emptying
  - cisapride (Propulsid) & metoclopromide
- Caused by drugs that inhibit intestinal motility and promote greater contact with absorptive mucosal surfaces in the upper portion of the small intestine
  - e.g., TCAs & narcotics
- Caused by drugs that inhibit gut enzymes (e.g., MAO) that may increase amounts of substrates (e.g., tyramine) reaching the portal circulation
Pharmacokinetic Effects: Distribution

• Regional blood flow
• Lipophilicity
• Adiposity and lean body mass
• Protein binding
Protein Binding

- Interactions that involve competition for protein-binding sites by two or more drugs
- Results in displacement of previously bound (inactive drug) which in its unbound form is active
- Most psychotropics are highly bound
- Effects are usually inconsequential, except when:
  - drugs are highly bound and have a low therapeutic index and/or
  - low levels of serum proteins are present (e.g., liver failure or malnutrition)
Psychotropics with Low to Moderate Levels of Protein Binding

- Minimally Bound
  - lithium <3%
  - gabapentin <3%
  - topiramate <20%
  - venlafaxine <30%

- Moderately Bound
  - lamotrigene <60%
  - carbamazepine <80%
  - fluvoxamine <80%
  - citalopram <80%
  - bupropion <85%
Pharmacokinetic Effects: Distribution

- Decreases in lean body mass and total body water lead to increased plasma concentrations of water-soluble drugs.
- Increases in total body fat lead to decreased plasma concentrations and to slower elimination of fat-soluble drugs.
- Decreases in serum albumin lead to a higher % of unbound, metabolically-active drugs.
Pharmacokinetic Effects: Metabolism

• Phase I reactions
  – oxidation, reduction, and hydrolysis
  – often rate-limiting
  – often produces potentially active metabolites
    • e.g., diazepam to desmethyldiazepam to oxazepam

• Phase II reactions
  – conjugation and acetylation
  – typically produces inactive metabolites that are highly water-soluble and renally excreted
Metabolism: Induction and Inhibition

- **Induction**
  - Levels of substrate fall gradually
  - Mechanism involves enhanced synthesis of metabolic enzymes

- **Inhibition**
  - Levels of substrate rise rapidly
  - Mechanism:
    - competitive inhibition (with displacement of substrate)
    - covalent binding (with conformational change of enzyme)
Common Inducers of Metabolism

- Carbamazepine
- Charbroiled meats
- Cigarette smoking
- Cruciferous vegetables
- Chronic alcohol use
- Phenobarbital
- Phenytoin
- Primidone
- Rifampin
- Ritonavir
- St. John’s Wort
Common Inhibitors of Metabolism

- Amiodarone
- Antifungals
- Antiretrovirals
- Antimalarials
- Beta-blockers
- Calcium channel blockers
- Cimetidine

- Disulfiram
- Grapefruit juice
- Isoniazid
- Mexiletine
- Phenothiazines
- Psychostimulants
- Quinidine
- SSRIs
- Valproic acid
Cytochrome P450 Isoenzymes

- Largely located on microsomal membranes
- Responsible for phase I, oxidative metabolism of >80% of available drugs
  - they can be induced or inhibited
  - they commonly involve 1A2, 2C, 2D6, and 3A3/4
    - 5%-10% of Caucasians and 1%-3% of Asian Americans and African Americans are poor metabolizers of P450 2D6
    - 15%-20% of Asian Americans and African Americans and 1%-5% of Caucasians are poor metabolizers of P450 2C19
Cytochrome P450 Isoenzymes

- Some drugs are metabolized by more than one pathway
  - Tertiary amine TCAs (e.g., amitriptyline) are metabolized by P450 1A2, 2C, 2D6, and 3A
- Some drugs may inhibit one pathway yet induce another
  - Omeprazole (Prilosec) inhibits P450 2C19 and induces P450 1A2
Cytochrome P450 Nomenclature

• Example: 2D6
  – P450 pigment absorbing light at 450 nm
  – 2 family
  – D subfamily
  – 6 individual isoenzyme or gene product
P450 Isoenzymes: 1A2

- **Substrates**
  - acetaminophen, aminophylline, caffeine, clozapine, haloperidol, olanzapine, phenothiazines, TCAs (tertiary amines)

- **Inhibitors**
  - fluoroquinolones, fluoxetine, fluvoxamine, grapefruit, paroxetine, TCAs (tertiary amines)

- **Inducers**
  - omeprazole, tobacco
P450 Isoenzymes: 2C

• Substrates
  • barbiturates, diazepam, ibuprofen, omeprazole, phenytoin, propranolol, TCAs (tertiary amines)

• Inhibitors
  • fluoxetine, fluvoxamine, ketaconazole, omeprazole, sertraline

• Inducers
  • rifampin
P450 Isoenzymes: 2D6

• **Substrates**
  • codeine, dextromethorphan, ecanide, flecanide, haloperidol, maprotiline, paroxetine, propranolol, risperidone, TCAs, timolol, trazodone, venlafaxine

• **Inhibitors**
  • fluoxetine, haloperidol, paroxetine, perphenazine, quinidine, TCAs (secondary amine), sertraline, thioridazine

• **Inducers**
  • ---
P450 Isoenzymes: 3A3/4

- **Substrates**
  - alprazolam, amiodarone, calcium channel blockers, carbamazepine, cisapride, cyclosporine, diazepam, disopyramide, lidocaine, midazolam, nefazodone, omeprazole, quinidine, sertraline, steroids, tamoxifen, TCAs, vinblastin, zolpidem

- **Inhibitors**
  - dapsone, erythromycin, fluoxetine, fluvoxamine, ketoconazole, grapefruit, nefazodone, sertraline, TCAs

- **Inducers**
  - carbamazepine, phenobarbital, phenytoin, rifampin
Pharmacokinetic Effects: Elimination

• Elimination involves liver metabolism, renal excretion, and excretion into bile and sweat

• For example, in the elderly:
  – decreased hepatic enzyme activity
    • leads to decreased effectiveness of metabolism
  – decrease in renal function
    • leads to decrease in renal excretion and to a prolonged half-life of renally-excreted drugs
Pharmacodynamic Drug Interactions

- Pharmacological effects produced directly by interactions at a common biological site (receptor) or indirectly, at separate but interrelated biological sites
  - e.g., respiratory depression from combined use of alcohol, benzodiazepines, and barbiturates
  - e.g., anticholinergic toxicity from combined use of TCAs, low-potency antipsychotics, paroxetine, diphenhydramine, and benztropine
  - e.g., hypotension from combined use of TCAs, low-potency antipsychotics, trazodone, and atypical antipsychotics
Idiosyncratic Drug Interactions

• Episodic interactions that occur in a small number of individuals

• Not predicted by knowledge of pharmacokinetic or pharmacodynamic properties of drugs
  - e.g., agranulocytosis secondary to chlorpromazine
Antidotes
Beneficial Effects and Side Effects

– for benzodiazepine overdose
  • flumazenil (Mazicon)
– for narcotics overdose
  • naloxone (Narcan)
– for anticholinergic toxicity/delirium
  • physostigmine (Antilirium)
– for acute dystonic reactions
  • benztropine (Cogentin); lorazepam (Ativan)
– for nausea
  • compazine; omeprazole
Antidepressants
Somatic Therapies for Depression

- Polycyclic antidepressants
- SSRIs
- MAOIs
- Lithium
- Mood stabilizers/anticonvulsants
- Psychostimulants
- Electroconvulsive therapy (ECT)
Polycyclic Antidepressants: Side Effect Profile

- Orthostatic hypotension
- Anticholinergic effects
- Conduction system effects
- Drug-drug interactions
- Effects secondary to overdose
Orthostatic Hypotension (OH)

- Related to alpha blockade
- IMI/DMI/AMI > DOX > NT
  - 8%-20% stop tx b/c of OH
  - IMI causes OH in 7% of patients w/normal ECG, in 32% w/BBBs, and in 50% w/CHF
- OH is predicted by pre-drug orthostatic fall (>15 mm Hg) in BP
  - it predicts response to treatment
- OH occurs before therapeutic plasma levels achieved
Anticholinergic Side Effects

- Tertiary agents > secondary agents
- Tachycardia may persist > 1 year
  - typically trivial (7 beats/min) it may be clinically relevant
- Propranolol may decrease PCA-induced tachycardia
- Trazodone, fluoxetine, bupropion, and MAOIs have essentially no anticholinergic effects
Conduction System Effects

- All TCAs prolong atrial and ventricular depolarization
  - increases the PR, QRS, and QTc interval
- Conduction prolonged mainly in the H-V portion of the His bundle
- Significant clinical problems with conduction are uncommon with therapeutic levels
  - after TCA OD problems are evident in 6%-10%
Conduction System Effects

- Sudden death may occur with a QTc > 440 msec
- Since mortality is increased with class IA antiarrhythmics, TCAs (although they can decrease PVCs) should be used only after careful assessment of the risk:benefit ratio in patients with ventricular arrhythmias
Drug-Drug Interactions

- TCAs may block the effects of adrenergic-blocking antihypertensives
  - e.g., guanethidine, clonidine, reserpine
- TCAs are additive with antiarrhythmics and anticholinergics
- TCAs may potentiate the pressor effects of sympathomimetics (EPI, NE) by blocking reuptake of these pressors
SSRIs

- Less anticholinergic, antihistaminic, and alpha-adrenergic than TCAs
- Associated with fewer effects on cardiac activity than TCAs
  - OH uncommon
- Well-absorbed from the GI tract
- Extensively metabolized in the liver
- Half-life:
  - sertraline, paroxetine, citalopram: 1 day
  - fluoxetine: 2-3 days
Non-Cardiac Side Effects of SSRIs

- Agitation
- Anorgasmia
- Anorexia
- GI distress
- Insomnia
- Irritability

- SIADH
- Tremor
- A potentially fatal serotonin syndrome in combination with MAOIs
Cardiac Effects of SSRIs

• May:
  – raise TCA levels and increase conduction delays
  – cause bradycardia and syncope
  – cause AF, atrial flutter, and A-V block
  – increase intracoronary serotonin and cause vasospasm of diseased coronary arteries
  – slow metabolism and raise levels of ecanide, flecanide, and beta-blockers
Atypical Antidepressants

• Trazodone
  – causes significant OH
  – is associated with priapism (in 1: 6,000)
• Amoxapine
  – a dopamine blocker; it can lead to tardive dyskinesia
• Bupropion
  – carries low risk of cardiac toxicity
  – facilitates smoking cessation
Monoamine Oxidase Inhibitors (MAOIs)

- Cause OH: 47% mild; 5%-10% severe
  - maximum effect appears after 3rd or 4th week
  - not predicted by pre-drug orthostatic fall in BP
  - may be helped by addition of fludrocortisone or 1-inch cubes of cheddar cheese

- May cause profound hypertensive crises when taken with sympathomimetic medications or tyramine-containing foods
  - treated with IV phentolamine
Psychostimulants

- Used to treat medically-ill, apathetic, and anorexic, geriatric depressed patients
- Appears to work through release of dopamine and NE
- Primarily renally excreted
- Rarely causes tachycardia, HTN, or arrhythmia
- Relatively contraindicated with:
  - HTN, pregnancy, seizures, delirium, psychosis, angina, or with MAOIs
Lithium Carbonate

- Almost entirely renally excreted
- Causes flat or inverted T-waves and U-waves
- Can cause sinus node dysfunction and 1st degree A-V block
- Associated with sudden death in some patients with cardiac disease on brochodilators
- Hypothyroidism
- Problems with urinary concentration
Lithium: Factors that Increase or Decrease Serum Levels

- **Increase**
  - diuretics
    - thiazides, ethacrynic acid, spironolactone, triamterene
  - NSAIDs
    - indomethacin, ibuprofen, naproxin
  - antibiotics
    - metronidazole (Flagyl), tetracycline

- **Decrease**
  - aminophylline
  - theophylline
  - caffeine
  - osmotic diuretics
Lithium Toxicity

• Tremor
• GI distress & diarrhea
• Delirium
• Seizures
Electroconvulsive Therapy

• The most effective treatment for major depression
• No absolute contraindications
• Associated with exaggerated increases in BP, circulatory collapse, MI, arrhythmias, and ECG changes
  – ST depressions and repolarization abnormalities
• Can be used safely, even in the setting of cardiac disease
  – with beta-blockers and good anesthesia back-up
Antipsychotics
Typical Antipsychotics

<table>
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<tr>
<th>Drug</th>
<th>Mg equiv.</th>
<th>Sedation</th>
<th>OH</th>
<th>Ach</th>
<th>EPS</th>
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<tr>
<td>Thioridazine</td>
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<tr>
<td>Molindone</td>
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<td>++</td>
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<td>Perphenazine</td>
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# Typical Antipsychotics

<table>
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<th>Drug</th>
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<th>EPS</th>
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<td>+</td>
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<td>+++</td>
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<tr>
<td>Thiothixene</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Fluphenazine</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Haloperidol</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
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# Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
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<th>EPS</th>
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<td>Risperidone</td>
<td>Risperdal</td>
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<tr>
<td>Clozapine</td>
<td>Clozaril</td>
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<td>++++</td>
<td>++++</td>
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<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>++</td>
<td>++++</td>
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<td>Ziprasidone</td>
<td>Geodon</td>
<td>+</td>
<td>+++</td>
<td>+</td>
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</tbody>
</table>
Antipsychotics: Side Effects

• Sedation
• Hypotension
• Extrapyramidal effects
  – akathisia
  – dystonia
  – Parkinsonism
• Anticholinergic effects
  – dry mouth
  – urinary retention
  – blurred vision
• Weight gain
  – diabetes; DKA
• Hyperprolactinemia
  – amenorrhea
  – galactorrhea
  – sexual dysfunction
• Impaired heat regulation
• Conduction system effects
• Neuroleptic malignant syndrome
Antipsychotics: Drug Interactions

- Anticonvulsants (except valproate)
  - lower antipsychotic blood levels
- Tobacco
  - lowers antipsychotic blood levels
- Erythromycin
  - increases clozapine levels
- Fluvoxamine
  - increases levels of clozapine and thioridazine
- Fluoxetine
  - increases neuroleptic levels
- TCAs
  - levels are increased
Benzodiazepines
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mg equivalents</th>
<th>Onset of action</th>
<th>Half-life (hrs)</th>
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<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>0.5</td>
<td>intermediate to fast</td>
<td>12-15</td>
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<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>10.0</td>
<td>intermediate</td>
<td>5-30</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.25</td>
<td>intermediate</td>
<td>15-50</td>
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<tr>
<td>Clorazepate (Tranxene)</td>
<td>7.5</td>
<td>fast</td>
<td>30-200</td>
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# Benzodiazepines

<table>
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<th>Onset of action</th>
<th>Half-life (hrs)</th>
</tr>
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<tbody>
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<td>Diazepam (Valium)</td>
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<td>fast</td>
<td>20-100</td>
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<tr>
<td>Flurazepam (Dalmane)</td>
<td>5</td>
<td>Fast</td>
<td>40</td>
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<tr>
<td>Lorazepam (Ativan)</td>
<td>1</td>
<td>intermediate</td>
<td>10-20</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>15</td>
<td>slow</td>
<td>5-15</td>
</tr>
</tbody>
</table>
Anticonvulsants (Mood-Stabilizers)
Carbamazepine

- First-line for secondary generalized tonic-clonic seizures and partial seizures
- Usual dose: 400-1600 mg/d
- Therapeutic levels: 4-12 micro gm/ml
- Carbamazepine induces its own metabolism
  - therapeutic doses need to be adjusted
Valproic Acid

• First-line for primary generalized tonic-clonic seizures and absence seizures; second-line for secondarily generalized tonic-clonic seizures and partial seizures
• Usual dose: 750-3000 mg/d
• Therapeutic levels: 50-100 micro gm.ml
Ethosuximide

- First-line for absence seizures
- Usual dose: 75-1500 mg/d
- Therapeutic levels: 40-100 micro gm/ml
Lamotrigine

• Second-line for primary generalized tonic-clonic seizures, secondary generalized tonic-clonic seizures, and partial seizures
• Usual dose: 300-500 mg/d
• Therapeutic levels: ?
Gabapentin

• Second-line for secondary generalized tonic-clonic seizures and partial seizures
• Usual dose: 1200-3600 mg/d
• Therapeutic levels: ?
Phenobarbital

- Third-line for partial seizures
- Usual dose: 30-180 mg/d
- Therapeutic levels: 10-40 micro gm/ml
Narcotics
# Narcotics

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<th>Generic name</th>
<th>Brand name</th>
<th>Equiv. dose (mg) IM</th>
<th>Equiv. dose (mg) PO</th>
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<tr>
<td>Morphine</td>
<td>--</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Codeine</td>
<td>--</td>
<td>120</td>
<td>200</td>
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<tr>
<td>Hydromorphone</td>
<td>Dilaudid</td>
<td>1.5</td>
<td>7.5</td>
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<tr>
<td>Meperidine</td>
<td>Demerol</td>
<td>80-100</td>
<td>300</td>
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<tr>
<td>Methadone</td>
<td>Dolophine</td>
<td>8-10</td>
<td>20</td>
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<tr>
<td>Oxycodone</td>
<td>Percodan</td>
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<td>30</td>
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Drug-Induced Syndromes
Drug-Induced Syndromes

• Dystonic reactions
  – e.g., with high-potency neuroleptics

• Hypertensive crisis
  – e.g., with MAOIs and sympathomimetics

• Neuroleptic malignant syndrome (NMS)

• Serotonin syndrome
  – e.g., with MAOIs and meperidine, TCAs, mirtazapine, St. John’s Wort, sumatriptan, or lithium
Drug-Induced Syndromes

- Aplastic anemia
  - e.g., with neuroleptics
- Torsades de pointes
- Hepatitis
- Normeperidine toxicity
- SIADH
- Allergic reactions
Post-Test

• Which of the following is not a characteristic feature of neuroleptic malignant syndrome?
  – Autonomic instability; Leukopenia; Hyperthermia; Increased creatine phosphokinase; Rigidity

• Which of the following agents would not be expected to increase serum lithium levels?
  – Aminophylline; NSAIDs; Tetracycline; Thiazide diuretics; Metronidazole

• Which of the following agents would be most likely to contribute to a delirium with prominent myoclonus?
  – Digoxin; Phenobarbital; Atropine; Meperidine; Lorazepam

  – Answers: BAD
Selected References


Selected References


Selected References

