Psychotropic Drug–Drug Interactions: The Most Important You Should Know About

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Objectives

• Discuss drug–drug interactions and their predictability

• Discuss combinations of psychotropic medications that have the potential to adversely interact through mechanisms involving the CYP450 metabolism

• Describe combinations of psychotropic medications that have the potential to adversely interact through pharmacologic mechanisms
Basic Concept: Metabolism

Drug → CYP450* → Metabolite #1

Metabolite #1 → UDPG* → Metabolite #2

*Activity modifiable by other meds, and by genetics
<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytochrome P450</td>
<td>N–acetyltransferases</td>
</tr>
<tr>
<td>Alcohol dehydrogenase</td>
<td>Sulphotransferases</td>
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<tr>
<td>Aldehyde dehydrogenase</td>
<td>Uridine diphosphate-glucuronosyltransferases</td>
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<tr>
<td>Monoamine oxidase</td>
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<tr>
<td>Nitroreductases</td>
<td>(UDPG)</td>
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</table>
## Psychotropic CYP Substrate Summary

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>1A2</th>
<th>2B6</th>
<th>2C9/19</th>
<th>2D6</th>
<th>3A4</th>
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<tbody>
<tr>
<td>Antipsychotics</td>
<td>Clozapine</td>
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<td>Risperidone</td>
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<td>Fluvoxamine</td>
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<td>Sertraline (9)</td>
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<td>Mirtazapine</td>
<td>Venlafaxine</td>
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<td>Mood Stabilizers</td>
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<td>Stimulants</td>
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<td>Tiagabine</td>
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<td></td>
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<td>Modafanil</td>
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</table>
Non–CYP 450 Metabolism

• Methylphenidate (Ritalin®)
• Lamotrigine (Lamictal®)
• Oxcarbazepine (Trileptal®)
• Valproic acid (Depakene®, others)
• Zonisamide (Zonegran®)
Renal Elimination

• Lithium
• 9–OH Risperidone (Invega®)
• Amantadine
• Baclofen (Lioresal®)
• Several AEDs
  * Gabapentin (Neurontin®)
  * Levetiracetam (Keppra®)
  * Pregabalin (Lyrica®)
  * Topiramate (Topamax®)
In Perspective

• Within psychiatry, hundreds of pk drug interactions reported
• Most are only problematic under specific circumstances
• Most are minor and do not require changes in drug dose or regimen
• Known risk factors for pk drug–drug interactions are…
  ✴ Narrow therapeutic index
  ✴ Increasing number of concurrent medications
  ✴ Increasing age
Predicting Pk Interactions

CYP450 Drug Interactions

With regard to commonly used psychotropic medications, those that treat mood disorders are the medications principally involved in cytochrome mediated interactions.

* Antidepressants...generally inhibit
  ▸ Several antidepressants do not inhibit

* Mood stabilizers...generally induce
  ▸ Several mood stabilizers do not induce; valproic acid inhibits glucuronidation
Metabolic Inhibition

• Substrate’s blood concentration increases
• All CYP450 enzymes can be inhibited
• A single drug/metabolite can inhibit multiple enzymes
  * e.g., fluoxetine, fluvoxamine
• Concentration–dependent interactions
  * Inhibition can be observed following a single dose
  * Competitive binding to an enzyme site by both inhibitor and substrate
• Beware of the Psychiatry:Medicine interface!
  * Patients taking both psychiatric and medical pharmacotherapies
Inhibitor Added to Susceptible Substrate

- Subtherapeutic
- Toxic

Amount of Drug in Body

Inhibitor Added

Time

1 2 3 4 5 6
Clinical Implications

(General Principle)

Inhibitor Taken from Susceptible Substrate

<table>
<thead>
<tr>
<th>Time</th>
<th>Amount of Drug in Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>20</td>
<td>80</td>
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Inhibitor Taken

Toxic

Subtherapeutic

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### CYP Inhibitory Potential

<table>
<thead>
<tr>
<th>Drug</th>
<th>1A2</th>
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<th>2D6</th>
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<tbody>
<tr>
<td>Fluoxetine</td>
<td>—</td>
<td>++</td>
<td>+++(+++++)</td>
<td>++(++)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>—</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>—</td>
<td>—</td>
<td>++++</td>
<td>—</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>++++</td>
<td>++</td>
<td>—</td>
<td>+++</td>
</tr>
<tr>
<td>Citalopram</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+++</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>—</td>
<td>—</td>
<td>(+)</td>
<td>—</td>
</tr>
<tr>
<td>Bupropion</td>
<td>—</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
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<td>—</td>
<td>—</td>
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<td>—</td>
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<td>—</td>
<td>—</td>
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<td>—</td>
</tr>
</tbody>
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[^1]: [— = none; + = mild; ++ = moderate; +++ = mild to moderate; ++++ = potent]  

*DeVane CL & Nemeroff CB. Primary Psychiatry 2001.*
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[— = none; + = mild; ++ = moderate; +++ = mild to moderate; ++++ = potent]
Important CYP450 Inhibitors

- Fluvoxamine (Luvox®)
- Fluoxetine (Prozac®)
- Paroxetine (Paxil®)
- Bupropion (Wellbutrin®; Zyban®)
- Duloxetine (Cymbalta®)
Important CYP450 Inhibitors

- Fluvoxamine (Luvox®) – 1A2
- Fluoxetine (Prozac®) – 2D6
- Paroxetine (Paxil®) – 2D6
- Bupropion (Wellbutrin®; Zyban®) – 2D6
- Duloxetine (Cymbalta®) – 2D6
Fluvoxamine Inhibits 1A2

(Fluvoxamine and Clozapine)

Fluoxetine Inhibits 2D6

(Fluoxetine and Risperidone)

- n = 12 pts
- Risperidone 4–6 mg/day
- Fluoxetine 20 mg/day added
- Risperidone levels increased an average of 75%

Paroxetine Inhibits 2D6

(Paroxetine and Risperidone)

- n = 12 pts
- Risperidone 8 mg/day
- Paroxetine 10-40 mg/day added
- Risperidone levels increased significantly at each paroxetine dose

• 83 year old WF being treated with nortriptyline for refractory depression

(Bupropion and Nortriptyline)

Duloxetine Inhibits 2D6

(Duloxetine and Desipramine)

- Area under the curve

Desipramine    2–OH Desip

Clinical Implications

(General Principle)

Inhibitor Added to Susceptible Substrate

<table>
<thead>
<tr>
<th>Time</th>
<th>Amount of Drug in Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
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<tr>
<td>80</td>
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</tr>
<tr>
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</tr>
</tbody>
</table>

Inhibitor Added

Subtherapeutic

Toxic
Poor Metabolizer

High risk of achieving excessive concentrations of drug with conventional dosing…
high risk of poor tolerability d/t adverse effects

Drug Concentration Using Conventional Dosing

Adverse

Therapeutic

Ineffective

Time
Metabolic Induction

• Results in the decrease of a substrate’s plasma concentration
• All CYP 450 enzymes can be induced
• Onset and offset are gradual…
  ★ Onset depends on the accumulation of the inducing agent and the increased production of enzyme
  ★ Offset depends on the elimination of the inducing agent and decay of the induced enzyme
• Beware of the Psychiatry:Medicine interface!
Clinical Implications

(General Principle)

Inducer Added to Susceptible Substrate

<table>
<thead>
<tr>
<th>Time</th>
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</thead>
<tbody>
<tr>
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<td>80</td>
<td>20</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
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</tbody>
</table>

- Toxic
- Subtherapeutic

Inducer Added

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Clinical Implications

(General Principle)

Inducer Taken from Susceptible Substrate

Amount of Drug in Body

0 20 40 60 80 100

1 2 3 4 5 6

Time

Inducer Taken

Toxic

Subtherapeutic
CYP 450 Inducers

• Medical pharmacotherapy
  ✴ Dexamethasone…2D6, 3A4
  ✴ Griseofulvin…3A4
  ✴ Insulin…1A2
  ✴ Nafcillin…3A4
  ✴ Omeprazole…1A2
  ✴ Primidone…3A4
  ✴ Rifampin…2B6, 2C9/19, 2D6, 3A4
  ✴ Troglitazone…3A4
# CYP 450 Induction

<table>
<thead>
<tr>
<th></th>
<th>1A2</th>
<th>2B6</th>
<th>2C</th>
<th>2D6</th>
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<tr>
<td>Barbiturates (1A2,2C,3A4)</td>
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<td>Modafinil (1A2,3A4)</td>
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<td>Oxcbz (3A4,UDP)</td>
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<td>Smoking (1A2)</td>
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<td>Phenytoin (1A2)</td>
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<td>Rifampin (2B6,2C,2D6,3A4)</td>
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<th>1A2</th>
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<td>Modafinil (1A2,3A4)</td>
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<td>Smoking (1A2)</td>
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</tbody>
</table>
Important CYP450 Inducers

- Carbamazepine (Tegretol®, Equetro®)
- Oxcarbazepine (Trileptal®)
- Modfinil (Provigil®)
- St. John’s Wort
- Smoking
Important CYP450 Inducers

- Carbamazepine (Tegretol®, Equetro®) – 3A4
- Oxcarbazepine (Trileptal®) – 3A4
- Modafinil (Provigil®) – 3A4
- St. John’s Wort – 3A4
- Smoking – 1A2
Carbamazepine Induces 3A4

(Carbamazepine and Quetiapine)

- Quet. 300 mg bid x 28 days and Cbz 200 mg tid for final 20 days of quet. treatment

(n = 18)

Oxcarbazepine Induces 3A4

(Oxcarbazepine and Oral Contraceptive)

- n = 22 women; 50 mcg EE and 250 mcg LN concurrent w/placebo, then OXCB 1,200 mg/d (levels measured on days 21-3).

Modafinil

- Has been shown to cause:
  * Moderate 3A4 induction
  * Moderate 2C19 inhibition
- Higher doses can cause greater and greater effects
- Same for Armodafinil (Nuvigil®) available June 1st

SJW Induces 3A4
(SJW and Alprazolam)

- n=12
- Alprazolam disposition tested prior to and after SJW tx
- Elimination half-life decreased from 12 hrs to 6 hrs

Smoking Induces 1A2
(Smoking and Clozapine)

- Change in clozapine blood levels after smoking cessation

Smoking Induces 1A2
(Smoking and Clozapine)

Inducer Added to Susceptible Substrate
Ultra-Rapid Metabolizer

High risk of not achieving adequate concentrations of drug with conventional dosing…
high risk of poor therapeutic response

Drug Concentration Using Conventional Dosing

Adverse

Therapeutic

Ineffective

Time
Other Drug Interactions
<table>
<thead>
<tr>
<th>Interaction</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Vpa</td>
<td>Increases lamotrigine blood [ ]s</td>
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<tr>
<td>OCs</td>
<td>Decreases lamotrigine blood [ ]s</td>
</tr>
<tr>
<td>EIAEDs</td>
<td>Decreases lamotrigine blood [ ]s</td>
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</table>
Stevens-Johnson Syndrome

### Lamotrigine Dosing

**Table 11. Escalation Regimen for LAMICTAL in Patients Over 12 Years of Age With Epilepsy**

<table>
<thead>
<tr>
<th>Weeks 1 and 2</th>
<th>For Patients Taking Valproate</th>
<th>For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate*</th>
<th>For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 mg every other day</td>
<td>25 mg every day</td>
<td>50 mg/day</td>
</tr>
<tr>
<td>Weeks 3 and 4</td>
<td>25 mg every day</td>
<td>50 mg/day</td>
<td>100 mg/day (in 2 divided doses)</td>
</tr>
<tr>
<td>Weeks 5 onwards to maintenance</td>
<td>Increase by 25 to 50 mg/day every 1 to 2 weeks</td>
<td>Increase by 50 mg/day every 1 to 2 weeks</td>
<td>Increase by 100 mg/day every 1 to 2 weeks</td>
</tr>
<tr>
<td>Usual Maintenance Dose</td>
<td>100 to 400 mg/day (1 or 2 divided doses)</td>
<td>225 to 375 mg/day (in 2 divided doses)</td>
<td>300 to 500 mg/day (in 2 divided doses)</td>
</tr>
<tr>
<td></td>
<td>100 to 200 mg/day with valproate alone</td>
<td>225 to 375 mg/day (in 2 divided doses)</td>
<td>300 to 500 mg/day (in 2 divided doses)</td>
</tr>
</tbody>
</table>

* Rifampin and estrogen-containing oral contraceptives have also been shown to increase the apparent clearance of lamotrigine (see PRECAUTIONS: Drug Interactions).
## Lamotrigine Dosing

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<td>Weeks 5 onwards to maintenance</td>
<td>Increase by 25 mg/day every 1 to 2 weeks</td>
<td>Increase by 50 mg/day every 1 to 2 weeks</td>
<td>Increase by 100 mg/day every 1 to 2 weeks.</td>
</tr>
<tr>
<td>Usual Maintenance Dose</td>
<td>100 to 400 mg/day (1 or 2 divided doses)</td>
<td>225 to 375 mg/day (in 2 divided doses).</td>
<td>300 to 500 mg/day (in 2 divided doses).</td>
</tr>
<tr>
<td>100 to 200 mg/day with valproate alone</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Rifampin and estrogen-containing oral contraceptives have also been shown to increase the apparent clearance of lamotrigine (see PRECAUTIONS: Drug Interactions).
Lithium Toxicity

• Initial transient effects (<1.5 mEq/L)
  ✴ Fine hand tremor, GI upset, muscle weakness

• Moderate toxicity (1.5–2.5 mEq/L)
  ✴ Coarse tremor, slurred speech, confusion, sedation/lethargy, hyperreflexia

• Severe toxicity (> 2.5 mEq/L)
  ✴ Seizures, coma, cardiovascular collapse
<table>
<thead>
<tr>
<th>Lithium Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazides, ACEIs, NSAIDs, Topiramate</strong></td>
</tr>
<tr>
<td><strong>Theophylline, Caffeine</strong></td>
</tr>
</tbody>
</table>
TCAs

Amitriptyline (Elavil®)

Imipramine (Tofranil®)

Nortriptyline (Pamelor®)

Desipramine (Norpramin®)
TCA Overdose

- 31 year old female was found unresponsive in her bed and brought to the ER by basic life support ambulance with an altered mental status. On arrival, the pt was lethargic; 110/60 mmHg, 120 bpm, 24/minute. EKG - sinus tachycardia, wide QRS complex, prolonged QT interval.

- Intervention - Endotracheal intubation, gastric lavage, IV sodium bicarbonate, charcoal via tube, admitted to ICU; TCA (amitriptyline) overdose confirmed. Medical hx was remarkable for MDD with previous suicide attempts.

- Pt recovered while in the ICU, and was discharged to a psychiatric facility.

TCA Overdose

- 18 year old female was transported to the ER by advanced life support ambulance with depression, suicidal ideation and TCA ingestion. The patient had reportedly ingested doxepin 2 hours before. On arrival to the ER, the patient had periods of agitation and lethargy; 100/70; 140 bpm; 34/min. In addition to an altered mental status, the exam revealed dilated pupils and absent bowel sounds. EKG showed: wide QRS, tachycardia.

- Intervention: endotracheal intubation, IV sodium bicarbonate, lavage, charcoal, ICU admission

- In the ICU, pt experienced a generalized convulsion. She then had a worsening of her wide QRS tachycardia which then developed in to ventricular fibrillation—she died soon after.

Desipramine/TCAs


  ✴ An 8 year old boy collapsed at school and experienced cardiac arrest during transportation to the hospital. The child arrived in the emergency room with ventricular fibrillation. He was converted to NSR, but subsequently had cardiac arrest (again) and died.

  ✴ Pt had been receiving desipramine 50 mg/d for about 6 months for the treatment of ADHD. Desipramine level was 85 ng/mL
2D6 Inhibitors Can Incr TCA Levels

![Graph showing TCA levels with 2D6 inhibitors]

Hypertensive Crisis

- 27 year old male was being treated for an atypical major depression with phenelzine 60 mg/day for 5 weeks. No prior history of: HTN, HAs, other neurological sx. Pt was a “moderate social drinker”.

- Within 45 minutes of consuming 14 ounces of “Upper Canada Lager beer” on tap he suddenly developed: palpitations, diffuse chest pain, mild nausea, and severe occipital HA radiating to the back of his neck.

- Subsequently: lightheadedness, blurred vision, abdominal cramps, hyperventilating, HR = 50 bpm, BP = 190/110 mmHg

Serotonin Syndrome

- A clinical triad of symptoms
  - Mental status changes
  - Autonomic hyperactivity
  - Neuromuscular changes
- Anticipatable outcome of excessive serotonin activity
- Clinical presentation ranges from barely perceptible to lethal
- Dx is highly dependent on pts medication hx

## Differential Dx

<table>
<thead>
<tr>
<th>Condition</th>
<th>Med Hx</th>
<th>Time to Develop</th>
<th>Pupils</th>
<th>Mucosa</th>
<th>Skin</th>
<th>Bowel Sounds</th>
<th>NM Tone</th>
<th>Reflexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin Syndrome</td>
<td>Pro-5HT</td>
<td>&lt; 12 hrs</td>
<td>Mydriasis</td>
<td>Sialorrhea</td>
<td>Diaphoresis</td>
<td>Hyperactive</td>
<td>Increased, mainly in LE</td>
<td>Hyperrelexive</td>
</tr>
<tr>
<td>Antichol. Toxicity</td>
<td>Antichol.</td>
<td>&lt; 12 hrs</td>
<td>Mydriasis</td>
<td>Dry</td>
<td>Erythema, hot and dry</td>
<td>Decreased or absent</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>NMS</td>
<td>Dopamine antagonist</td>
<td>1–3 days</td>
<td>Normal</td>
<td>Sialorrhea</td>
<td>Pallor, diaphoresis</td>
<td>Normal or decreased</td>
<td>Lead-pipe rigidity</td>
<td>Bradyreflexive</td>
</tr>
<tr>
<td>Malignant Hyperthermia</td>
<td>Inhalation anesthesia</td>
<td>30 min to 24 hr after</td>
<td>Normal</td>
<td>Normal</td>
<td>Mottled, diaphoresis</td>
<td>Decreased</td>
<td>Rigor-mortis type rigidity</td>
<td>Hyporeflexive</td>
</tr>
</tbody>
</table>

Clinical Presentation

- Potential findings
  ✴ Nausea / diarrhea
  ✴ Hyperactive bowel sounds
  ✴ Elevated blood pressure
  ✴ Tachycardia
  ✴ Shivering / diaphoresis
  ✴ Mydriasis
  ✴ Hyperreflexia
  ✴ Agitation / hypervigilence
  ✴ Rhabdomyolysis
  ✴ Seizures
  ✴ Renal failure
  ✴ Dissem. intravasc. coag.

Mechanism

• 5HT enhancing pharmacology
  ✴ Reuptake blockade
  ✴ MAOI
  ✴ Direct post-synaptic receptor activation

• Clinical scenario
  ✴ Single med, high dose
  ✴ Multiple meds, multiple mechanisms
  ✴ CYP 450 Poor Metabolizer

Serotonergic Medications

- Selective serotonin reuptake inhibitors (SSRIs)
  - Fluoxetine (Prozac®)
  - Sertraline (Zoloft®)
  - Paroxetine (Paxil®; Paxil® CR)
  - Fluvoxamine (Luvox®)
  - Citalopram (Celexa®)
  - Escitalopram (Lexapro®)
Serotonergic Medications

• Serotonin norepinephrine reuptake inhibitors (SNRIs)
  ✴ Venlafaxine (Effexor®, Effexor® XR)
  ✴ Desvenlafaxine (Pristiq®)
  ✴ Duloxetine (Cymbalta®)

• Other serotonergic antidepressants
  ✴ Trazodone (Desyrel®)
  ✴ Mirtazapine (Remeron®)
  ✴ TCAs
  ✴ MAOIs
Serotonergic Medications

• Miscellaneous
  ✴ Meperidine (Demerol®)
  ✴ Tramadol (Ultram®)
  ✴ Dextromethorphan
  ✴ The “Triptans”
  ✴ MDMA (Ecstasy)
  ✴ Lithium
  ✴ Linezolid (Zyvox®)
  ✴ SJW
SSRIs / Triptans

- Combination commonly co-prescribed
  * e.g., 20% of 240,000 over 12 mos btwn 2000–01
  * CYP450 interactions: Fluvoxamine/Zolmitriptan
- SSRIs broadly enhance serotonin activity, triptans are agonists (stimulators) of specific serotonin receptors (5-HT 1B/1D)
- FDA warning in 2006 regarding serotonin syndrome (27 cases) w/ this drug combination
- Literature does not have any conclusive information
- Risk seems very small; but, be aware and monitor

SSRIs / Triptans

• 29 cases reported to the FDA
  ✓ 9/29 (31%) had good–v. good evidence
  ✓ Sumatriptan (Imitrex®) was reported most often
  ✓ Near equal distribution of sertraline (Zoloft®), fluoxetine (Prozac®), paroxetine (Paxil®), and venlafaxine (Effexor®)
  ✓ Some cases also involved a third medication: lithium, buspirone (BuSpar®), tramadol (Ultram®), meperidine (Demerol®)

SSRIs or SNRIs w/ NSAIDs

- SSRI/SNRI package insert warning
  * These antidepressants may increase the risk of “bleeding events”
  * Bleeding events associated with SSRIs and SNRIs have included: ecchymosis, hematoma, epistaxis, petichiae, and life threatening hemorrhages.
  * Concurrent use with aspirin, NSAIDs [e.g., ibuprofen, naproxen], warfarin, and other anticoagulants may add to this risk
SSRIs or SNRIs w/ NSAIDs

• This drug combination may result in impaired platelet function via two different mechanisms
  ✴ Serotonin effects on platelets from these antidepressants seem to cause impaired platelet aggregation
  ✴ NSAIDs that inhibit the enzyme cyclooxygenase–1 (COX–1) can impair platelet aggregation too

• Case reports and retrospective epidemiologic studies have demonstrated a risk of upper GI bleeding associated with SSRIs / SNRIs
Methylphenidate Drug Interactions

- TCAs
  - Mph may increase TCA levels
  - Mph + TCA may result in hypertension
- MAOI + mph can result in hypertensive crisis
- AEDs / Mood Stabilizers
  - Mph may increase phenytoin (Dilantin) levels
  - Carbamazepine (Tegretol; Equetro) may increase mph metabolism and decrease effect
- Antipsychotics may block mph effects
Amphetamine Drug Interactions

- TCAs + Amph may result in hypertension
- Urinary alkalization may incr. amphetamine levels
  * Acetazolamide (Diamox®), topiramate (Topamax®)
- MAOIs + Amph may result in hypertensive crisis
- 2D6 inhibitors + Amph may increase amph levels
  * Fluoxetine (Prozac®), paroxetine (Paxil®), bupropion (Wellbutrin®)
- Venlafaxine (Effexor®) + Amph has one case report of a 32 yr old developing agitation, tremor, sinus tach…
Atomoxetine Drug Interactions

- Atomoxetine does not affect the activity of CYP 450 enzymes
- Strong 2D6 inhibitors may increase atomoxetine levels (e.g., fluoxetine, paroxetine, bupropion, TCAs)
- Strong 2D6 inducers may decrease atomoxetine levels (i.e., rifampin, dexamethasone)
- MAOIs added to atomoxetine could cause a hypertensive crisis
- Albuterol with atomoxetine may result in an increased rate of tachycardia/heart palpitations
• 9 yr old male pt with ADHD, developmental delay, mild chronic hypertension presented with: insomnia and involuntary hand and mouth movements.

• Atomoxetine 25 mg qd had been added to MAS 60 mg qam and clonidine 0.3 mg bid two weeks prior to presentation.

• 3 days after starting atomoxetine, the pt developed disturbed sleep and compulsive lip licking—he also began having visual hallucinations (seeing bugs on the floor) which frightened him.

• All symptoms, but especially the mouth and hand movements increased in severity over the next 5 days.

Atomoxetine/MAS Interaxn

- In the ER the pts HR = 89 bpm and BP = 145/93. He had continuous, involuntary twitching movements peri-orally, and with his fingers. His legs were restless as he lay on the exam bed.

- That night, the patient was not sleepy at 10pm and he did not end up sleeping at all that night. By 8am the next morning, the abnormal movements had stopped completely.

- The pt was sent home, and while receiving the prior medication regimen, did not have any movement disorders 5 months later.

Modafinil Drug Interaxns

• Increased TCA levels via 2C9/19 inhibition
  ✴ Other 2C9/19 substrates:

• Decreased oral contraceptive levels via 3A4 induction
  ✴ Other 3A4 substrates: alprazolam, clonazepam, quetiapine

• Strong 3A4 inhibitors added to modafinil may increase its levels (e.g., clarithromycin, itra-/ketoconazole)

• Strong 3A4 inducers added to modafinil may decrease its levels (e.g., carbamazepine, oxcarbazepine, phenytoin, rifampin, St. John’s Wort)