Psychotropic Drug Interactions

- Over the past 2 decades:
  - Treatment options: Several drug and non-drug therapies
  - Increasing number of psychotropic drugs
    - Increased risk of adverse outcomes
  - Overwhelming information on drug-drug interactions
  - Over 50% of ADRs among hospitalized patients - attributed to drug-drug interactions
- This workshop: A refresher on psychiatric drug interactions
- Aim: Optimize patient safety.

Downloaded from: http://www.medscape.com/viewarticle/775394 18.06.2015 - Adapted
Primary Worries in Primary Care: 1008 Patients

Cost of prescription once discharged
Suffering Pain
Receiving too many medications
Side effects of medicines
Getting Infection in the office / hospital
Not having enough information
Complications of treatment
Overall cost of treatment
Prescribing drugs that might interact
Being given a wrong drug

Psychotropic Drug Interactions

• Basics:
  o Prescriptions ought to reflect current state of ‘evidence’
  o Evidence based prescriptions are effective and safe
  o Each prescriber and user: Personal preference of drugs and drug combination
  o This workshop is to facilitate / revise prescribing practices

✓ All ingested drugs and substances (SUBSTRATE) are metabolized primarily by the liver, sometimes in the GI tract.

• Drug and substance metabolism is aimed at detoxifying and eliminate every exogenous and endogenous substrate.

• Applied inhaled or injected substances may or may not be metabolized by the liver (first pass metabolism)

• Prodrug: A precursor chemical compound of a drug administered to improve bioavailability:
  • Improve absorption from the gastrointestinal tract.
  • Improve how selective receptor action
  • Reduce adverse or unintended effects of a drug, - ADRs
Drug therapy

» Monotherapy or one-drug therapy

» Polypharmacy:

» Perspectives:
  • Synergistic actions,
  • Adjuvant actions,
  • Antagonist actions,
  • Cumulative effects,
  • Prophylaxis,
  • Idiosyncratic drug effects and interactions
  • ……
Drug interactions are enormously complicated.

Carlat report is an attempt to simplify *fundamentals* of psychotropic drug prescriptions.

Psychotropic drug-drug interactions: meet two criteria:

- Psychiatrists commonly encounter them;
- They are likely to cause clinically significant problems

A quick summary reference:

1. **Aim**: To avoid significant *increase* in the levels of another drug:
   - Avoid co-prescribing: Fluoxetine, Paroxetine, high dose Sertraline, Fluoxamine, Nefazodone, Valproate and ask your patient to stop drinking Grapefruit Juice.

2. **Aim**: To avoid significant *drop* in levels of another drug:
   - Avoid co-prescribing: Carbamazepine, St. John’s Wort and ask your patient to stop smoking.

Psychotropic Drugs: actions and interactions

✧ Dopaminergic drugs
✧ Serotonergic drugs
✧ Cholinergic drugs
✧ Glutamatergic drugs
✧ Gabaergic drugs
✧ Adrenergic drugs
✧ Second messenger system modifiers
✧ Psychotropic drugs + Drugs for systemic illness

✴ (DM, Cardiac, GI, Malignancy…)

Adapted: Nassir Ghaemi: Tufts medical center. available at: http://sites.google.com/site/tufutsmooddisorders/education/mood-stabilizers. 08.04.2015
Psychotropic Drugs: actions and interactions

» Clinical consideration while prescribing a drug:
  » Desired effects
  » Undesired effects
  » Side effects
  » Toxic effects

» Dose, frequency of administration, caution, precautions..

» Today’s deliberations: Focussed on Antidepressant Drugs
Psychotropic Drugs: actions and interactions

Anti Depressant Drugs:
» Options: TCAs / PCAs / SSRI / NSRIs / SRI / NRI / GABA / GM / MT…….

» Pharmacodynamics of drug interaction
  » Anticholinergic effects and intoxication
    » Trihexyphenidyl + AAPDs - ‘the pines’: dry mouth, blurred vision, delirium
    » TCAs + benztopine: constipation, heat stroke, urine retention,
  » Serotonin Syndrome: SSRIs, Opioids, Stimulants, Triptans, St. John’s wort…..
  » Sedation,
  » weight gain,
  » cardiac: Torsades de Pointes (TdP)
  » Blood dyscrasia
  » metabolic, reproductive and Androgenic actions,
  » ...............

» Pharmacokinetics
  » Absorptions
  » Metabolism
  » Distribution
  » Elimination
  » excretion
Metabolism - Pharmacokinetics of a drug:

1. Every ingested substance is absorbed from the intestines, metabolized by the liver enzyme.

2. With specific reference to drug metabolism:
   - Ingested drug is termed ‘Substrate’, metabolized drug: ‘Product’

3. Substrate:
   - a. A substance (drug, toxins..) that is metabolized into an end product
   - b. Eventually deactivated and eliminated
   - c. Rate of absorption & elimination: determines the $t_{\text{max}}$ & $c_{\text{max}}$ of the drug

4. Prodrug: Initially an inactive agent, metabolized to become an active drug

5. The first-pass effect / Metabolism:
   - 1. Loss in the quantity of the ingested drug during absorption
   - 2. Generally related to liver and gut wall enzymes
   - 3. Once swallowed, liver metabolizes to a significant extent
   - 4. Thus, bioavailability of the drug is greatly reduced

6. Determinants:
   - 1. Factors: enzymes, plasma protein and blood cell binding, and gastrointestinal motility.
   - 2. Enzymes: GI enzymes in the lumen & the gut wall, bacterial enzymes, & hepatic enzymes

Drug metabolism:

1. Cytochrome: CYP
   a. Major enzyme family, widely referenced in clinical pharmacology
   b. Cause oxidative biotransformation of most drugs
   c. Named as: Number - letter - number, equivalent of ‘family - genus - species’

2. Uridine 5’-diphosphate glucoronosyl transferases: Ugts:
   a. Activity: Phase II conjugative metabolism that follows phase I oxidative metabolism
   b. Function similar to CYP system also named as 1A4, 2B15...

3. OATP: Organic anion transporting polypeptides: A group of polypeptides that facilitate the absorption of drugs and other substrates.

4. P-glycoproteins: Pgp
   a. Line the gut and the blood brain barrier
   b. Control rate of absorption and excretion of the drug / substance: ‘FIRST PASS EFFECT’
   c. ‘extruding’ transporter: remove substances from the brain and cells back into the blood
   d. P-gp: substrates, inhibitors and inducers. In contrast with OATP, P-glycoprotein (Pgp), also know by several other names, is an efflux transporter: it pushes out drugs and other substances that were absorbed from the intestinal lumen.

SOURCES:
3 Andrade C. 2015. Personal Communication
Cytochrome Enzymes

- Cytochrome: A set of enzymes that metabolize several endogenous and exogenous substances, including drugs and toxins.
- Perform Phase I metabolism: oxidative metabolism.
- Substrate: The agent that is metabolized by the enzyme
- Product: Metabolic end product – eventual elimination
- Pro-drug: Initially inactive – activated after metabolism
Cytochrome Enzymes

Clinical Interventions

1. Inhibition of CYP enzyme actions
   - Competitive
   - Non-competitive / allosteric

2. Induction of CYP enzyme activity

Competitive Inhibition

CYP450

unchanged drug

bloodstream

biotransformed drug

drug

gut
Enzyme Inhibitors → Non-competitive Inhibition

CYP450

Enzyme Inhibitors → CYP450

Non-competitive Inhibition

Enzyme Inducers → CYP450

# Drug interactions - CYP

## Enzyme inducers
- Enhance drug metabolism
- Reduce active drug levels
- Do not affect / alter CYP enzyme activity
- Enhance production of the enzymes

## Enzyme inhibitors:
- Retard drug metabolism
- Elevate active drug levels
- Reduce / alter the CYP enzymes activity
- Irreversible inhibition of available enzyme
1A2

2D6

2C9

2C19

3A4

1 = family
A = subtype
1 = gene product

DEMETHYLATION

1A2 = fluvoxamine

= NO DEMETHYLATION

DEMETHYLATION

1A2


Gut

Bloodstream

= fluvoxamine

1A2

= theophyllin

clozapine

olanzapine

1A2

HYDROXYLATION

= TCA

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>TCAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>paroxetine, fluoxetine</td>
</tr>
<tr>
<td>Moderate to Low</td>
<td>secondary TCAs</td>
</tr>
<tr>
<td>Low to Minimal</td>
<td>venlafaxine, bupropion, citalopram, reboxetine, mirtazapine, sertraline, nefazodone, fluvoxamine</td>
</tr>
</tbody>
</table>

2D6 Inhibitors

NO HYDROXYLATION

paroxetine
fluoxetine
high dose sertraline

2D6

gut

bloodstream

clozapine
olanzapine
risperidone

2D6

NO HYDROXYLATION

Antihistamines
- clozapine
- quetiapine
- ziprasidone
- sertindole
- cisapride
- warfarin
- benzols....

INHIBITOR ➔

Reported cases of torsades de pointes with ketoconazole + terfenadine and astemizole

INHIBITOR ➔

3A4

ketoconazole
- erythromycin
- nefazodone
- fluvoxamine
- fluoxetine
- protease inhibitors

Six Possible Clinical Situations

- **Substrate** + **Inhibitor** = ↑ **Substrate Levels**
- **Inhibitor** + **Substrate** = ↑ **Substrate Levels**
- **Substrate** + **Inducer** = ↓ **Substrate Levels**
- **Inducer** + **Substrate** = ↓ **Substrate Levels**
- **Substrate** : **Inhibitor** = ↑ **Substrate Metabolism**
- **Substrate** - **Inducer** = ↓ **Substrate metabolism**

*Enhance the dose*  
*Taper the dose*

Stahl, SM. Essential Psychopharmacology. 2nd Edn. Cambridge, 2000

Sandson, 2003. Drug Interactions, Case Book
gut

bloodstream

= clozapine
quetiapine
ziprasidone
sertindole

3A/3,4

genetic polymorphism for cytochrome P450 2D6