**Pharmacodynamics**

Ok. Now the drug has been re-absorbed, and now it is finally where we want it to go. It’s going to go to the heart, the eye, or whatever our target organ may be. Now, once we get there, it can interact with other drugs present at the same site – two drugs may act at the same receptor. The effects from the direct competition at that receptor may be opposing, or they may be synergistic – it really depends on the drugs involved. I’ll give you examples here momentarily. The two medications make it past the hepatic enzymes and reach the target organ, and now they can act in additive or synergistic interactions, or they can be antagonistic or opposing.

Alcohol is a drug that significantly depresses CNS activity. If you combine it with any drug that also works to depress the CNS, an additive CNS depression may occur – this reaction may be therapeutic or toxic. In an antagonistic interaction, for example, combining anticoagulants and vitamin K, or sedative/hypnotic drugs combined with caffeine. Again, you put the alcohol and the caffeine together, with the alcohol trying to depress the CNS and the caffeine trying to stimulate it, somewhere in the middle is the actions. Thus, they fight with each other.

**Other Drug Reactions**

There are several drug-disease reactions that I want you to think about. In liver disease, we know our process – if the patient has active liver disease, or they have reduced liver functionality, really it could change the metabolism of the drug. Typically, the liver window of how long it is effective is very large. This condition is really only clinically relevant usually at end-stage liver disease, where we have to worry about the drug clearance through the liver.

Renal disease is fairly well established. There are reference texts you can go through to look at dosing in a complicated renal patient. Most of the time if you have a patient who is in complicated renal failure, I would want to be in consultation with a nephrologist and whoever is managing their renal failure. I would not play with that, because it is fairly well established.

Cardiac disease, however, when you’re looking at your VA patients with CHF or who are having other blood flow component issues, remember that will change the hepatic blood flow. If the cardiac disease is slowing the hepatic blood flow, that will change how quickly the drug is metabolized through the liver. The worse the condition of the cardiac system, the serum clearance rate may go up.

Acute myocardial infarction (MI), acute viral infection, hypothyroidism or hyperthyroidism all can possibly make changes, as well. When you get a patient who has an extreme viral infection, or hypo- or hyper thyroid, cardiac disease, renal failure, etc. before you start piling on orals, make sure you consult with their provider and whoever is managing that component of their condition.

We also have food interactions. We already talked about tetracycline and the calcium in milk products – they chelate and it keeps the tetracycline from being absorbed. If you are going to be prescribing any of the oxycyclines, you want to think about that, and make sure your patients know to watch out for milk.

Vitamin K-containing foods is not good to combine with blood thinners like Warfarin. Vitamin K reduces absorption.
Grapefruit juice inhibits CYP3A – this is a big one, and it’s a fairly significant effect. They did a study (Fig 8) looking at grapefruit juice combined with felodipine (Plendil) compared to taking the medication with just water, and it was found that just one serving of the grapefruit juice blocks that metabolism, so the patient’s serum levels went up. That then translates to the blood pressure reduction. Grapefruit juice can have a huge impact, and nobody thinks about grapefruit juice. Is it the same with orange juice? No – there is a specific bioflavin within the grapefruit that tends to be the problem. The orange juice supposedly does not cause the same reaction because it does not have the same bioflavin as grapefruit juice. Grapefruit juice has a huge impact on a lot of the medications we use because of its impact on the CYP3A component.

We also have drug-herbal interactions to consider. We see St. John’s Wort out there a lot – there are a lot of people that use it, and it’s a very popular herb in the health scene. There are studies, one after another, with St. John’s Wort and cyclosporine where it reduces plasma concentrations of the drug. We also see it interacting with indinavir and digoxin.

![Figure 8: Serum concentrations and blood pressure in patients taking felodipine with water or grapefruit juice](image)

Figure 9 shows the mean plasma concentration time course of indinavir (Crixivan). If you look at the difference in the serum concentration before and after St. John’s Wort. You have to be very careful with St. John’s Wort relative to whatever medications your patient is taking, and relative to the metabolism of the system.

**Risk Assessment**

How do you make the assessment of risk?

Drug-to-drug adverse drug reactions are highly variable. Patients vary. Their individual response can vary from something that is not observable to life-threatening. What you have to think about is that when you’re trying to evaluate the drug interaction, what was the sequence of administration? When did each product go in? How long was each product available? How long were they treated? What was the duration? Remember – some drugs, like inducers, take a week or two to react. This may change the level at which we are seeing toxicity.

We need to look closely at these patients that are taking lots of medications. A good drug history is paramount. You need to know what they are taking – not just the prescription medications, but also
what supplements they are taking. Patients seem to think that all over-the-counters (OTCs) are safe. We need to look at all of the other pieces, and not forget to put those in when we are going through our checklist for drug interactions.

Assess the level of risk:

- Route of administration. How is the drug being administered?
- Pre-existing medical conditions
- Other drugs
- Age of the patient
- Drug characteristics

Take appropriate measures to assure the interaction will not result in adverse effects!! You need to try to act preventatively to not prescribe a problematic medication in the first place.

Drug-drug interactions: A stepwise approach:

1. Take a medication history – **A.V.O.I.D. Mistakes**!
2. Remember high risk patients: any patient taking 2 or more medications. The risk goes up exponentially with 4 or more drugs, especially if that patient is taking anticonvulsants, antibiotics, digoxin, warfarin, amiodarone, etc.
3. Check your pocket reference
4. Consult pharmacists/drug info specialist
5. Check up-to-date computer program such as [www.epocrates.com](http://www.epocrates.com) (I am not endorsing epocrates, nor do I get any feedback from them. However, they are widely used and appear to be updated regularly.)

Here is the **A.V.O.I.D. Mistakes** acronym I mentioned above for you to use during your case history:

- Allergies? Previous ADR?
- Vitamins and herbs?
- Old drugs and OTC?
- Interactions?
- Dependence? Do you need a contract?
- Mendel: family Hx or genetic Hx of benefits or problems with any drugs?

How do you avoid drug interactions? Systems interventions, such as electronic prescription entry, computerized medication records, and drug interaction software can all help. Remember the limitations of all of this – right now the healthcare electronic system is still very fragmented. The e-prescribing formulary uplink is still fragmented, and not uniformly used in practice.

Other websites that offer tools to help avoid drug interactions include:

- [www.fda.gov/cder](http://www.fda.gov/cder) (Center for Drug Evaluation and Research)
- [http://www.healthline.com/druginteractions](http://www.healthline.com/druginteractions) (builds a drug list and checks for interactions)
- [www.epocrates.com](http://www.epocrates.com) (Drug formularies, interaction checker, etc. on your PDA)
The message, or the bottom-line on this: do not rely or become completely dependent on the technology. You need a basic knowledge of clinical pharmacology of drug interactions. Remember – 50% of the ADRs were not predicted by the paper version. You need to understand what the medication does. As you continue through this class, we will go through the mechanisms and pathophysiology of each medication. You need to think about how the medication interacts, and looking at all the medications, do you have synergistic medications that can add their effects, or inhibitory ones that can block each other?

**Summary**

- ADRs are common in clinical practice.
- The represent a significant cost to the patient, the practitioner, and the health care delivery system.
- Consequences can vary from sub-clinical to life-threatening.
- Interactions can occur across a wide spectrum of drugs, food, and supplements.
- Many or most are preventable with careful consideration and understanding.
- Examining medications encourages careful review of medications.
- Basic understanding of principles of drug interactions is critical to reduce risk.
- Utilization of all tools at your disposal to confirm and check interactions is critical for each patient.
- You must always be on your guard to determine if and then why an ADR is occurring in your patient.
- Case history is your most powerful tool.
- Hearing a patient’s complaints can help alert you to identifying previously unreported reactions.

Thank you very much for your time and attention.

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Appendix A: Diagnostic Algorithm

Medical history: symptoms, detailed medication list, temporal sequence
Physical examination
Clinical laboratory data

→ Is a drug reaction likely?
   → Yes
   → Is there a suspicion of drug-induced hypersensitivity/immunologic reaction?
     → Yes
     → Immune mechanism
       • IgE-mediated
       • Cytotoxic
       • Immune complex
       • Delayed, cell-mediated
       • Other immune mechanism
     → Evaluate with appropriate confirmatory tests.
     → Are tests supportive of immune drug reaction?
       → Yes
       → Diagnosis of drug hypersensitivity/immunologic reaction confirmed
       • Consider desensitization (IgE) or graded challenge (non-IgE) before administration, as appropriate.*
       • Anaphylactic reactions require prompt emergency treatment.
       • Avoid drug if possible.
       • Consider prophylactic regimen before administration (if shown to be effective).
       • Prudent use of drugs in future
       • Patient education
     → No
     → Other etiology likely
     → Evaluate and treat other causes of symptoms.
   → No
   → Nonimmune mechanism
     • Pharmacologic side effect
     • Drug toxicity
     • Drug-drug interactions
     • Drug overdose
     • Pseudoallergic
     • Idiosyncratic
     • Intolerance
     → Management
     • Modify dose.
     • Try drug substitution.
     • Treat side effects.
     • Consider graded challenges.
     • Implement patient education.

→ Other etiology likely
→ Evaluate and treat other causes of symptoms.
## Appendix B: Drugs Metabolized by Known P450’s 2000

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<th>2C19</th>
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<tr>
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<tr>
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### Inhibitors

- Amiodarone
- Cimetidine
- Ciprofloxacin
- Esomeprazole
- Fluoxetine
- Fluvastatin
- Indinavir
- Ketoconazole
- Metformin
- Nefazodone
- Paroxetine
- Prazosin
- Saquinavir
- Zafirlukast

### Inducers

- Carbamazepine
- Rifampin
- St. John's Wort
- Phenobarbital
- Theophylline
- Absent in 15-30% of Asians

### 3A

- Alprazolam
- Astemizole
- Bupropion
- Calcium Channel Blockers
- Carbamazepine
- Cisapride
- Cyclosporine
- HIV Protease Inhibitors
- Ketoconazole
- Macrolide Antibiotics (NOT Azithromycin)
- Metronidazole
- Nicorandil
- Nitrazepam
- Tolbutamide
- Verapamil

### 2D6

- Acetaminophen
- Chloroxazone
- Dapoxetine
- Ethanol
- Halothane
- Isoflurane
- Metrazol
- Midazolam
- Propafenone
- Propofol
- Quinidine
- Rifamycin
- St. John’s Wort

### 2E1

- Amiodarone
- Cimetidine
- Grapefruit Juice
- HIV Protease Inhibitors
- Ketoconazole
- Macrolide Antibiotics (NOT Azithromycin)
- Nefazodone

### 1A2

- Carbamazepine
- Rifabutin
- Rifampin
- Tobacco

### 2A6

- Chronic Ethanol
- Isoniazid
- Absent in 7% of Caucasians

### 2C19

- Absent in 15-30% of Asians

### 2C9

- Absent in 1% of Caucasians