**Concurrent Medications, Drug Interactions, Adverse Reactions** (AOT Lecture #2)

**Corresponding Author:** Kenneth Eakland, O.D.

*A public service message on the adverse reactions for the number one, most used, drug in America…*

Do you have feelings of inadequacy?

Do you suffer from shyness?

Do you sometimes wish you were more assertive?

If you answered yes to any of these questions, ask your doctor or pharmacist about Tequila. Tequila is the safe, natural way to feel better and more confident about yourself and your actions. Tequila can help ease you out of your shyness, and let you show the world that you’re ready and willing to do just about anything. You’ll notice the benefits of Tequila almost immediately, and with a regimen of regular doses, you can overcome any obstacles that prevent you from living the life you want to live. Shyness and awkwardness will be a thing of the past, and you’ll discover many talents you never knew you had. Stop hiding and start living, with Tequila.

Tequila may not be right for everyone... women who are pregnant or nursing should not use Tequila. However, women who wouldn’t mind nursing or becoming pregnant are encouraged to try it. Side effects may include: dizziness, nausea, vomiting, incarceration, erotic lustfulness, loss of motor control, loss of money, loss of virginity, delusions of grandeur, table dancing, headaches, dehydration, dry mouth, and a desire to sing karaoke or play all night rounds of strip poker, truth or dare, and naked twister.

Warning: excessive consumption of Tequila may make you think you are whispering when you are not, is a major factor in dancing like an idiot, may cause you to tell your friends over and over that you love them, and also may cause you to think you can sing. Alcohol may make you believe that ex-lovers are really dying for you to call them at 4:00 in the morning. Alcohol may make you think you can logically converse with members of the opposite sex without spitting. It may create the illusion that you are tougher, faster, smarter, and better looking than most people. It may also lead you to think that people are laughing with you. Tequila may cause pregnancy. It also may be a major factor in getting your ass kicked.

So what are you waiting for? Stop hiding and start living! With Tequila!

I apologize for anybody who took offense at the introduction to this course. The goal was to point out that when we watch TV, and there is an advertisement for a medication, and it has this list of side effects at the end that just goes on, and on, and you just wonder, “Is it really worth taking the medication in the first place, because I don’t want all these side effects?” This is funny, but again, what you’re doing now is embarking as a profession for optometry to practice at a much higher level, that also provides the responsibility of optometry to make sure that we are careful on these adverse drug reactions (ADRs) because they are serious and they are important.
Learning objectives for this lecture:

- Understand the underlying causes, risks, and recognition of clinical features of ADRs
- Recognize health care costs associated with ADRs
- Recognize the importance of reporting ADRs and medication errors
- Identify mechanisms for specific clinically relevant drug interactions
- Identify methods and systems approaches to predict and prevent drug interactions

There is a lot of new material that we are going to go over. Hopefully you will remember your biology and your biochemistry from 20 or 30 years ago. What we are going to try and do is make this relatively simple.

Definition of Adverse Drug Reaction: an ADR is “any drug-induced noxious change in a patient’s condition that occurs at a normal dosage range” and that:

- Requires treatment
- Indicates decreased or cessation of therapy with the drug
- Suggests that future therapy with the drug poses an unusual risk to the patient

This typically excludes reactions that result from an overdose or failure of the drug to produce the expected pharmacological response.

The key on ADRs is that they are an adverse effect, require treatment, and you have to stop or decrease the therapy, and it suggests that if in the future they use the same combination or same thing again, that the reaction will repeat. That is an ADR. It excludes those that we typically think about that involve failure to take the drug, overdosing, or a standard complication of the medication (a standard pharmaceutical response of the medication).

**Mechanisms**

Now, if you go back and think about it, system-wise we have both the immunological systems (Type 1, 2, 3 and 4). We remember these. Again, we also have the non-immunological, aka the pharmaceutical side effects, and we know this really isn’t adverse. For example, dry mouth from taking antihistamines, dry eyes, etc.

One of the things that we will really be looking for, and what we will address most of this talk on, is the drug-to-drug interactions. This is where you’ve combined the two different systemic medications, or maybe even topical medications, and you’ve provided an oral medication. Drug-to-drug interactions is really where I want to spend a lot of our time.
We have to remember that we do have the immunological ADRs – the Type 1 and Type 4 are the ones that we deal with all the time. Right now, with the IgE complex that is creating urticaria, the different hives, vomiting, diarrhea, etc. We know, again that the Type 1 modulation comes on really quick, but remember that again these can be delayed hours or even an extended period of time. The other one is Type 4 – these are the usual delayed responses, where the immune system has to gear up at a cellular level. Type 4 can kick in 2 to 7 days later. Those are the two big types of Drug Hypersensitivity Reactions that we think about. We can have the cytotoxic ones, the Type 3 or the IgM modulations, the complex ones with our systemic meds, but Type 1 and Type 4 are the ones that we will see most frequently.

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
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<tbody>
<tr>
<td>Immunologic</td>
<td></td>
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<tr>
<td>Type I reaction (IgE-mediated)</td>
<td>Anaphylaxis from b-lactam antibiotic</td>
</tr>
<tr>
<td>Type II reaction (cytotoxic)</td>
<td>Hemolytic anemia from penicillin</td>
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<tr>
<td>Type III reaction (immune complex)</td>
<td>Serum sickness from anti-thymocyte globulin</td>
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<tr>
<td>Type IV reaction (delayed, cell-mediated)</td>
<td>Contact dermatitis from topical antihistamine</td>
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<tr>
<td>Specific T-cell activation</td>
<td>Morbilliform rash from sulfonamides</td>
</tr>
<tr>
<td>Fas/Fas ligand induced apoptosis</td>
<td>Stevens-Johnson syndrome  Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Other</td>
<td>Drug-induced, lupus like syndrome</td>
</tr>
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| Nonimmunologic                |                                              |
| Predictable                   |                                              |
| Pharmacologic side effect     | Dry mouth from antihistamines               |
| Secondary pharmacologic side effect | Thrush while taking antibiotics             |
| Drug toxicity                 | Hepatotoxicity from methotrexate            |
| Drug-drug interactions        | Severe myopathy from lovastatin while taking erythromycin |
| Drug overdose                 | Seizure from excessive lidocaine (Xylocaine) |

| Unpredictable                 |                                              |
| Pseudoallergic                | Anaphylactoid reaction after radiocontrast media |
| Idiosyncratic                 | Hemolytic anemia in a patient with G6PD deficiency after primaquine therapy |
| Intolerance                   | Tinnitus after a single, small dose of aspirin |

We have to remember that we do have the immunological ADRs – the Type 1 and Type 4 are the ones that we deal with all the time. Right now, with the IgE complex that is creating urticaria, the different hives, vomiting, diarrhea, etc. We know, again that the Type 1 modulation comes on really quick, but remember that again these can be delayed hours or even an extended period of time. The other one is Type 4 – these are the usual delayed responses, where the immune system has to gear up at a cellular level. Type 4 can kick in 2 to 7 days later. Those are the two big types of Drug Hypersensitivity Reactions that we think about. We can have the cytotoxic ones, the Type 3 or the IgM modulations, the complex ones with our systemic meds, but Type 1 and Type 4 are the ones that we will see most frequently.
When we look at the other ones, the non-IgE immune responses (Table 3), we all remember putting on our sulfonamides, our oral sulfas, in, creating Stevens-Johnson Syndrome. That’s another one that we need to look at. When you prescribe these medications, and go into the patient’s Adverse Responses and the reference texts or other materials that you use, most of these are listed there. I’ve included Table 3 mostly as a refresher for you, so that you can remember.

What are our risk factors? (Table 4) For general, non-immune, women by far have more ADRs and intercompatibility medication problems than men. Serious illness – the sicker the patient is; this means they are already compromised, and they are going to have more risk. Renal insufficiencies, liver problems, those deal with getting the medication out of the system through excretion and metabolism. We’ll talk in just a moment about polypharmacy – the more medications they take, the greater the probability of ADL’s. HIV, Herpes, Alcoholism, Systemic Lupus Erythematosus (SLE), all of these are risk factors.

For the immune factors, women, again, by far have more ADRs than men. Patients who are adults, or who have HIV, viral infections, asthma, are taking beta blockers, etc. We will talk a little bit about specific genetic polymorphisms that are out there. And again, SLE is a factor.

When you have patients who fit these profiles, what you want to do, especially as you are adding more medications, just like you do right now before you provide them a topical beta blockers, we ask about other systemic conditions such as asthma. The same thing is going to occur – it is same process.

Adverse responses – the intrinsic type. These are the predictable responses, the ones intrinsic to the medication that you are providing. It’s an inherent property of the drug, typically dose-dependent – the more you take, the more you have problems with it. Probably the vast majority (70-80%) of ADRs are the consequences of taking the medication, itself. Again, with beta-blockers, we know they can cause respiratory distress, confusion, or irregular heartbeat. This is a function of the medication, an intrinsic reaction.

Now, the idiosyncratic ADRs, in contrast to the intrinsic ones, are hard to predict. We just don’t know. It could be due to the difference in a genetic profile of an individual, it could be something going on with the way they metabolize the drug, it could even be a difference in alcohol metabolism. Again, we know certain genetic profiles cannot metabolize alcohol, and certain ones metabolize it better than others. This is the idiosyncratic aspect – how the individual is going to react to that drug relative to the dose.

<table>
<thead>
<tr>
<th>Causative drug</th>
<th>Syndrome</th>
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<tbody>
<tr>
<td>Hydralazine (Apresoline)</td>
<td>Lupus-like syndrome</td>
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<tr>
<td>Procainamide (Pronestyl)</td>
<td></td>
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<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Anticonvulsant hypersensitivity syndrome</td>
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<td>Phenytoin (Dilantin)</td>
<td></td>
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<tr>
<td>Sulfonamides Anticonvulsants</td>
<td>Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
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Table 3: Specific Drug Hypersensitivity Syndromes Caused by Non-IgE Immune Mechanisms

<table>
<thead>
<tr>
<th>General drug reactions (nonimmune)</th>
<th>Hypersensitivity drug reactions (immune)</th>
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<tbody>
<tr>
<td>Female gender</td>
<td>Female gender</td>
</tr>
<tr>
<td>Serious illness</td>
<td>Adult</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>HIV infection</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Concomitant viral infection</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Previous hypersensitivity to chemically-related drug</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Asthma</td>
</tr>
<tr>
<td>Herpes infection</td>
<td>Use of beta blockers</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Specific genetic polymorphisms</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Systemic lupus erythematosus</td>
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</tbody>
</table>

Table 4: Patient Risk Factors for ADRs
level that they are taking, or how they react within that therapeutic window. It varies and is almost impossible to predict.

We also have the withdrawal symptoms, or withdrawal reactions. We know, for example, that if you put the patient on a glucocorticoid, a corticosteroid, and then just cut it off, there’s again the possibility that they are going to have changes relative to their blood sugar, and that they will have different complications. We see the same type of thing with alcohol dependencies, narcotic analgesics, and Clonidine (Catapres antihypertensive). There’s actually a physical withdrawal response that we have to monitor and watch out for. With the amount of narcotic possibilities and the durations that we are typically using as an optometrist, we are not going to see these types of withdrawals relative to the narcotics. But you have to be careful when you are dealing with your other patients.

Hypersensitivity reactions, again, drug allergies recur usually after a previous exposure (Type 1). The patient has been exposed, the immune system has developed over the course of usually 8-10 days. Now, when we re-stimulate the patient, the patient reacts with an anaphylactic type response. This response is independent of the dose. All it needs is a small amount to trigger the full-blown effect. The response depends on the individual, but the widespread involvement usually results in respiratory tissue, blood eosinophilia and fever, and the symptoms usually subside if you take the causative agent away. We also react and try to help with the anaphylactic response with epinephrine. But, if you re-challenge the patient with the same thing again, they should react the same way because it is an immunological response.

Clinical manifestations of hypersensitivity reactions include:

- Anaphylaxis (NOT Anaphylactoid)
- Asthma
- Dermatitis (drug eruptions)
- Fever
- Granulocytopenia
- Hemolytic anemia
- Hepatitis
- Nephritis

As optometrists, we typically don’t have the systemic reactions – the granulomas, the hepatitis or nephritis, but we need to be aware of them, and aware of the systemic medications that can cause them, with each patient.

Anaphylactoid response, versus anaphylaxis, is not an IgE-dependent response. Anaphylactoid is secondary to the mast cell release. It is a direct response triggered by the release. I mention this here because usually we see this in response to our contrast material, such as when we do a fluorescein angiography when we put the large molecules in the veins, those big molecules banging along the walls of the vascular complex can release mast cells, and can cause those mast cells to degranulate into histamines. One of the interesting things on this, and a couple of things to be thinking about if you are going to be doing injections, is that with patients on beta blockers, if those patients have a known sensitivity to crustaceans and mussels, there’s a much higher probability of reaction. So again, if you are going to be sending your patients out for fluoresceins, or if you are going to be doing them in your office, consider having your patient off of the beta blockers first if they have the crustacean sensitivity.
You may also want to prophylactically treat them prior to the procedure with antihistamines and steroids so that we don’t trigger the anaphylactoid response.

**Epidemiology of ADRs**

Why do we need to learn about epidemiology of ADRs? If you look at just the pure statistics of ADRs, 2 million serious ADRs occur yearly in the US, and 100,000 deaths occur. This data is gathered through hospitalization studies, so the data may actually be a little bit higher. Within our ambulatory patients, such as the patients we get coming into our office, the rate of ADRs is actually unknown. Nursing home patients are being quoted as up to 350,000 deaths each year secondary to mixing the medications and ADR response. It’s a huge number.

If you look at the cost, the US spends $136 Billion a year in managing ADRs. One in five injuries or deaths in the hospital can be attributed to ADRs. That’s a lot! The mean length of stay, cost and mortality for those patients who are in the hospital and experience an ADR are double that of control patients. The economics and loss of life due to ADRs is phenomenal.

Why are there so many ADRs? I started looking at this and was amazed.

- 45% of Americans have taken at least 1 prescription drug in the last month.
- 71% of patient office visits result in a prescription.
- The average number of drugs ordered or provided per visit was 2.1.
- From 1997 to 2007, the number of prescriptions purchased increased 72% (2.2 billion to 3.8 billion annually). Compared to US population growth of 11%.

The number of drugs we are selling is growing exponentially. We have nearly 13 prescriptions purchased for every person in the United States annually – that is an amazing number. Now, when you think about this, and if you work at the VA you know what I’m talking about, what is the laundry list of medications for the average older patient? I read once that the average VA patient is on 13 different medications. When you go beyond 4 medications, the risk for ADRs and the risk of reactions between medications goes up again, exponentially. With these patients, we have so many combinations and so many variabilities, that we need to be careful and that should trigger our brain to say, “Hey, I really need to look at this patient with 16 different meds and make sure I understand what is going on before I add some more.”

The FDA, whether you love or hate them, does a good job in most cases, to protect us from the drug complications. The problem is when you go through clinical trials, we think, “Oh, wow... they’ve tested everything. They’ve tested all of these possibilities and should have found all of the reactions and side effects.” But when you look at a drug, by the time the medication gets through the process, it’s only been tested on about 1500 patients. If a patient has a rare condition, such as something with a 1 in 20,000 presentation, the probability that that drug response is going to seen in a clinical trial, is very remote. Are all the ADRs in the book or prescribing manual going to be covered for a newer medication? The possibility that these ADRs could be there and we’re not going to see it is high. Most of the time, the ADRs that we see come to light after the drug has been released.
Part of the reporting matrix for ADRs is you! In 1993, the FDA initiated a reporting program that is called MedWatch (http://www.fda.gov/medwatch/index.html) and has four main goals:

- Increase awareness of medical product (drug) induced disease and the importance of reporting
- Clarify what should (and should not) be reported
- Facilitate the ease of reporting
- Provide feedback to health professionals about new safety issues

This is a great site for you to start playing with and look at. This is voluntary reporting for any adverse event – a problem with a serious adverse event, product problem, or medication error that you suspect is associated with the use of an FDA-regulated drug, biological device or dietary supplement. If you find something that you think is an ADR, you can go to the website and print out the Form 3500, fill it out, and submit it. That will add to their repertoire, and as these things grow, they will find more ADRs. You can print it online (https://www.accessdata.fda.gov/scripts/medwatch), you can call (1-800-FDA-1088), you can fax the form (1-800-FDA-0178), or you can mail it using a postage-paid addressed form (http://www.fda.gov/medwatch/getforms.htm).

As you are going through your day prescribing meds, using meds, or even contact lenses or other FDA-monitored products, if you have an ADR, you need to report it. At this point, reporting is purely voluntary, but it should be done.

Misconceptions on ADR reporting

One of the problems is that there is a common misconception that all serious ADRs are documented by the time a drug is marketed. As I already said above, that is not true, especially the rare ones. In fact, rare ADRs are usually not documented by the time the drug is brought to market. We need to understand that with a new drug, we could be the first person to see that ADR.

It is also often thought that it is difficult to determine if a drug is responsible for a certain ADR. Many people wonder, can you really say ‘this caused that’? It can, in fact, be difficult to be absolutely 100% sure due to all of the different possible reactions between multiple medications, but the temporal relationship of a reaction to a new medication can help. By looking at how the side effect occurred relative to the time that the patient started using the new drug, that will give us an indication of if the new drug is responsible. Understanding the biological mechanism of how a drug works, so we know ‘this drug does this, and this is what I saw,’ and that fits within the mechanism, then it makes sense. Even when in doubt, though, you should try to report it. If your patient developed an unexpected reaction, report it!

Another misconception is that ADRs should only be reported if you are absolutely certain. No! Even if you
suspect an ADR, you should report it. It will heighten the FDA’s awareness of that product, and if everyone else is starting to suspect an ADR, the FDA will then see a pattern and be able to do something about it.

Many practitioners believe that one reported case cannot make a difference. That’s not true, either. Like any journey, it needs to start with the first step. Somebody needs to be the first to report a problem. A single case needs to start the process. A single report resulted in the ultimate removal of Seldane from the market. Now, almost all drugs are evaluated for cardiac arrhythmias prior to release to the market as a result of this single report. Thus, your single report of the patient that you saw with the medication that you used can be useful.

Drugs removed from or restricted in the US market because of drug interactions:

- Terfenadine (Seldane ®) February 1998
- Mibefradil (Prosicor ®) June 1998
- Astemizole (Hismanal ®) July 1999
- Grepafloxacin (Raxar ®) October 1999
- Cisapride (Propulsid ®) January 2000

The removal of each of these five drugs came as a result of people reporting them.

Figure 1: Primary worries of patients in primary care

Do patients worry about this? Do patients really think about this, or is it an excuse in futility? They did a study, doing phone calls of over 1,000 patients and just asked them, “What do you think about?” (Fig 1) Over 60% of patients worry about being given the wrong drug. That is a significant concern. Being given drugs that interact was a close second. Patients are aware of this – they don’t understand how it works,
but they are definitely aware that mixing medications causes problems. They worry about these items even more than they worry about cost! Our patients are aware of this.

**Diagnostic algorithm** (See Appendix A at the end of this lecture for the chart)

Basically, do your histories, look at your symptoms and get a detailed medical list. Look at the time sequence of when the symptoms occurred, and where the drugs were. You’re going to do your physical exam, and you may order labs. Is a drug reaction likely? Yes or no. Is it possibly a hypersensitivity or an immune response? Maybe? Could it be immune cytotoxic? Which one – 1, 2, 3 or 4? Maybe we’re going to do some blood work to look for eosinophils. Maybe we’re going to look at IgE concentration. Are the tests supporting a hypersensitivity response? If yes, how are we going to manage it? If not, is the lab test really accurate? We can work through the logic flow laid out in Appendix A to determine if this is an immune response, a non-immune response, a cytotoxic response, drug-on-drug, etc.

Management involves either monitoring the patient, trying a substitute drug, considering a prophylactic regimen, etc.

**Drug Interactions**

Remember when optometry fought for diagnostics? I do. Do you remember when we fought for topical therapeutics, and how the world was going to come to an end if optometry did this? And we were going to cause these people to die. We were going to cause them to go blind. We were going to cause all of these terrible things to happen if we did. The thing is, with drug-on-drug interactions, they thought it was an insidious threat that was going to kill all these people. In clinical practice, however, the human system is a miraculous thing. In clinical practice, drug-on-drug interactions appear, but they are not as menacing as they once appeared.

About 3-5% of all ADRs are drug-on-drug. Thus, it’s not a huge percentage. Many of these can be life-threatening, so I’m not devaluing this. But, it’s not like legislatures got sold on – that allowing us to throw medications at patients without any training, we’re going to kill everybody. While it is there, it’s not that big.

What is the epidemiology of drug-on-drug interactions? They’ve gone through and done retrospective analysis on hospital admissions to determine the odds of elderly patients requiring hospital admission after experiencing known (thus, preventable) drug interactions. (JAMA 2003 Apr2;289(13):1652-8) Back in 2003 they did this, but remember that these patients are going to the hospital because they have a problem, so it’s going to artificially raise the numbers a little bit. These patients have problems and thus have drug interactions.

What they did is they looked at the case reports trying to predict the frequency of drug interactions, and it’s probably higher than what is actually occurring out in general clinic, but again they arrived at 3-5% in patients taking a few drugs. But remember what we said before – the more medications a patient is on, the higher the probability of an ADR. These patients like those at the VA who are taking 10-20 drugs, are probably going to have some drug-on-drug interaction issues. Some patients you see in your practice who bring in longer lists of drugs.

So here’s the deal. They went through the cases and looked at the life-threatening cases, cases where you could have potentially killed the patient, and they said about 74% of patients who had those ADRs were either definitely or probably due to the drug-on-drug interaction. Of those, 89% were receiving
the usual and customary, or even below the standard dose. So it wasn’t only those patients who had to 
be in the really high dose ranges. Most of these patients were also middle-aged and only moderately ill 
– they weren’t then end-stage patients or the super old. The drug categories that were being used most 
were the centrally-acting depressants or stimulants, as well as the antimicrobials, which is the majority 
of what we will be prescribing. So these made up the majority of the life-threatening ADRs.

The event types were distributed as:

- Adverse drug reactions (50%)
- Allergic reactions (35%)
- Drug interactions (11%)
- Medication errors (4%)

What was fun is that they actually went through, identified the four different types, then they went to a 
commercial reference source. Of that, almost half of the drug interactions relative to that reference 
source were not even predicted. Thus, the reference sources that you will use will be a tool, but they 
are not the end-stage of the tool, so don’t bet your practice on the book; you have to use your brain, 
and you have to use your knowledge of the mechanisms of action, which we will talk about.

50% of those life-threatening events were preventable. If the person, whoever is under the care, had 
taken the time to figure it out and look. 50%. Now, the litigation piece of it: only about 1% of those 
cases actually went into litigation. Of those that did, however, the average settlement was $1.2 Million 
dollars. Again, while they are not that common, most ADRs can be prevented by taking care, 
concentration, and thought. The consequences of missing an ADR can be relatively damaging not only 
for you financially, but also for your patient because ADRs can be life-threatening.

Drug interactions (DDI) are defined as an interaction that is typically thought to occur when the effects of one drug are altered by the addition of a second drug.

This does not necessarily imply an interaction with another drug, but may result from:

- Drug/Drug
- Food/Drug
- Drink/Drug
- Environmental chemicals/Drug

Remember that DDIs aren’t just necessarily just drug-on-drug. You need to take a more holistic view of 
the patient – what they are drinking, what they are eating, and what their environment is. Again, not all 
interactions are bad. Some of them, we want to use the synergistic effect because it gives us a bigger 
bang for the medication. Not all DDI’s or Drug-food interactions may be bad – some of them are 
beneficial, and help us, but we have to be very, very careful in looking at the mechanisms of how they 
work.

A single drug interaction usually involves more than one mechanism, although generally all mechanisms 
involved act in concert and provide an additive effect. The pharmacokinetics are very important: how 
it’s absorbed, distributed, metabolized, and excreted are all important pieces that play together to 
create the final outcome of what the interaction is.
Now, let’s talk a little bit about how this works. Let’s break down how the medication goes through the body. (Fig 2) We know that we’re going to take the medication in, it will be absorbed, metabolized, and end up at the target organ, and then it will be excreted from the system. We need to look at each stage in detail.

Absorption

So, we’ve taken the pill, or the medication. The interactions that occur within the GI tract can either increase or decrease the rate of absorption, or the extent to which the medication is absorbed. We can change the amount of medication that moves from the GI tract into the vascular system. We can do it by changing pH, but chelation, how it’s absorbed, or changes in motility – how fast the intestinal system moves the drugs through.

Most cases of changes in GI absorption result in only slight reductions in serum concentrations of the object drug. It will change it, but the change is usually not as clinically significant as most of the other effects. If you think about antacids, you take it and it reduces the stomach acid that is within the system, and that can change how that drug is absorbed. Calcium and magnesium in the Kaopectate that you drink to help coat the stomach can form an insoluble complex that will block the drug from being absorbed. With antibiotics, like tetracycline, which you will be prescribing, you may not want to prescribe it with a Kaopectate, or you’ll want to know if the patient is taking Kaopectate because it will complex-out, and what will happen is that the drug will not get absorbed into the vascular system, and it will not achieve our therapeutic dose load that we need, and therefore our treatment method has become ineffective. Again, the Kaopectate reduces the tetracycline, and may actually increase the absorption for opiates so use caution if you are using narcotics. If you slow the system down, it makes sense that more of the opiates get absorbed. If you look at the tetracycline, however, Kaopectate or other antacids blocks it, so it won’t be absorbed.

Chelation is another piece of absorption. If you have patients on an iron supplement especially, that supplementation will prevent the absorption of our tetracycline. If your patient is taking Tetracycline, make sure you know what their dietary supplements are – are they taking iron supplements? Another of the pieces of this puzzle is Tagamet (cimetidine). Since Tagamet has gone over the counter, again iron supplementation will block the medication, so that is an interaction piece that we have to deal with as physicians.

Absorption can change based on pH. For instance, weak acids such as aspirin, need to have a lower pH to absorb better. If you raise the pH with an antacid, such as Tagamet, it will greatly reduce the absorption of aspirin. (Table 5) With a normal stomach pH of 1, you will have an absorption of about 61%. However, if you put the patient on Tagamet and bring the pH up to 8, you will only get about 13% absorption into the system. Thus, you need to understand the medication and how it is going to work with any alterations in the patient’s system.
Products containing aluminum, milk products, antacids, and oral iron preparations can block absorption of quinolones, tetracycline, and azithromycin. These are the antibiotics that we will be prescribing orally, so you’ll want to know before you give an antibiotic to your patient, if they are taking supplements. You also need to make sure they know to avoid milk, avoid the antacids, the iron supplementation, and any aluminum-containing products that they may have.

Other products can also cause interactions that will either slow or change the interactions within the GI tract, as well. Omeprazole, lansoprazole, and H2-antagonists reduce the absorption of ketoconazole and delavirdine. Cholestyramine (Questran) binds raloxifene, thyroid hormone, and digoxin, slowing or preventing absorption.

**Distribution**

Now, we’ve gotten through the absorption. Our patient has taken the medication, it’s been absorbed, and now it is going to be distributed. Many drugs are high-protein-bonding drugs, and these drugs will bond to the proteins found within the blood. If you have a protein carrier for a drug that the patient is taking, some drugs will have a higher affinity for the same protein, and will bump off the previous drug, and you will have two drugs fighting for the same protein in the serum. The first drug is bound, but since the second has a higher affinity, it literally bumps the original drug off of that protein. What happens then, is that the higher-affinity drug can cause a bump in drug interactions; within just a few days of taking the new drug, it reduces the serum load of the original drug, and thus will affect the systemic distribution, and the speed of elimination. The first drug that got bumped, its serum load will go higher, so you need to be very careful in looking at your binding protein.

The key with this one, though, is that if we look at distributions, ‘serum bumping’ is really clinically insignificant. We will see very little change in the serum load because what you will see is we have a transient increase in free drug, then it is quickly picked up and eliminated through the kidneys and through the body. Thus, ‘bumping’ has very little clinical significance. Most of the problems that we see now have been shown to be due to inhibition of elimination, not protein plasma displacement. Examples are: kidney failure, liver failure, or something else within the system that causes the adverse reaction. But still, we have to be careful. As discussed in the 1st lecture, we need to look at the patient’s overall health – what is their liver function, what is their renal function? We look at these two key pieces because of their involvement in drug elimination.

**Metabolism**

The next piece is metabolism of the drug that is now circulating through our patient’s system. Now the drug will be filtered typically through the liver and/or the intestinal enzymes. Alterations in drug metabolism are responsible for more specific drug interaction than any other mechanisms. This step is where most of the complications occur – within the metabolism of drugs.

Changes in gut metabolism: some of the drugs that we use are partially metabolized by the normal bacteria in the gut. If you think about it, anything that could change that normal flora could, therefore, change the available concentrations of the drug. A lot of our antibiotics, for instance, are broad-spectrum, like tetracycline. In a patient taking digoxin, the problem is that tetracycline breaks down or destroys the normal flora, which is in part responsible for the breakdown and metabolism of digoxin.
you remove the normal flora, it can cause an increase in the bioavailability of the drug, and you will get toxicity because there is more available digoxin within the GI system to be absorbed.

The other thing that we have to think about is changes in enzymatic metabolism. Here is the Cytochrome P450 (CYP) enzymes. Cytochrome P450 enzymes, both within the intestinal system and predominantly in the liver, are a huge, superfamily of proteins that help break down the chemicals. There are hundreds of Cytochrome P450 enzymes out there, but for our drug interactions, only about 9 seem to be relevant. The five that are most responsible for drug metabolism are (Fig 3):

- CYP1A2
- CYP3A
- CYP2C9
- CYP2C19
- CYP2D6

Let’s decode these names. In CYP2D6, CYP just basically says the enzyme is a Cytochrome P450 enzyme. The 2 indicates the genetic family, the D indicates the genetic sub-type or sub-family, and the 6 gives us the specific gene. Note that the nomenclature is genetically based – it as no functional implication! Thus, it is not something we can relate to a drug – it’s related to the enzyme’s genetic profile.

Each one of the enzymes, if we look at how it metabolizes in the individual person, we have genetic differentials and we have different capabilities. (Fig 4)

We have these poor metabolizers, the extensive metabolizers, and then the ultra-rapid metabolizers. Each one of us will metabolize, based on our genetic profile of these Cytochrome P450’s, slightly differently. The vast majority of us are extensive metabolizers, but there are a few of us that are poor, and a few that are ultra-rapid.

When you think about this, going back to your basic pharmacology, we understood that when we provide a medication, we are going to bring our serum
concentration up, more and more. Eventually, we will find that the serum level flattens out, and the therapeutic treatment starts to flatten out. (Fig 5) In this range, somewhere, is our therapeutic window – where we are getting our therapeutic action, but our toxicity is low. This window is what we use to design medication dosages. Some of us, like the ultra-rapid metabolizers, will metabolize the drug super-quickly, and they will metabolize it so quickly that we can’t get them to the therapeutic window. In other cases, the patient may metabolize the drug so slowly, so the therapeutic response goes up immediately, but so does the toxicity. Thus, the response depends a little bit on our genetic profile.

What we are finding is that with genetic testing becoming so common, they are doing Cytochrome P450 tests on quite a few medications, including Prozac, Strattera, etc. (Table 6) They are actually looking at the processing so that the therapeutic dose can be adjusted individually to each patient, instead of going only off of a patient’s height and weight. They are specifically looking at the metabolism component.

What they are finding is that each genetic phenotype has different metabolism speeds. Also, each phenotype can have different receptor variations. (Fig 6) For instance, one individual with a standard dose may have high-affinity receptors, and they immediately respond. Whereas another patient’s receptors may be lower affinity, and thus respond poorly to the drug. If a patient was not getting the effect of the drug, what we would normally do is increase the dose, but that could drive a patient with poor receptor affinity into a toxic reaction.

Wouldn’t it be nice to know that if we have a specific genotype, that receptor type has a very low affinity? In Figure 7, for the top genotype, we need a therapeutic window at 65%, and we have a very low toxicity response. In contrast to the bottom genotype, where our therapeutic window is only 10% and we have a high risk of toxicity. This kind of
Cytochrome P450 testing is going to be coming to your office very, very soon. They are already out and commercially available.

There are three kinds of metabolic interactions that we need to think about: the substrate, inhibition and induction. The substrate means that the CYP is acting directly on a medication. The medication is the substrate. You can also have the medication as an inhibitor, meaning that the medication binds to the enzyme so strongly that when it comes in contact with something else that it’s supposed to metabolize, it cannot. If both drugs your patient is on happens to be metabolized by the same enzyme, if one binds harder, the other one cannot be metabolized at all, so you have to look at the metabolism of each drug. The third and final kind of metabolic interaction is induction. Basically here, the drug binds to the enzyme and triggers a biological response to produce more enzymes, which will take a little while. Let’s go through each one in detail.

Enzyme inhibition – some drugs will inhibit, or block, an enzyme. Thus, it is going to increase pharmaceutical response of the inhibiting drug because it’s blocked – it cannot be broken down, or metabolized, but it’s also going to block any other drug that is metabolized by that enzyme. The enzyme is blocked from doing its job on any substrate it is supposed to affect – not just the causative drug. The free drug that is still there after the enzyme has been bound will be increased. This onset is usually rapid – within one or two doses. You will see the adverse reaction in the serum of the blood dramatically. For instance, Tagamet (I like picking on it) inhibits CYP1A2. If the patient has to also be on Elavil (amitriptyline), that drug is metabolized by the same enzyme. Co-administration of these two drugs results in elevated levels of Elavil, because the Tagamet inhibited the breakdown.

Enzyme induction – again, this increases the metabolism of the inducing drug as well as all of the other drugs that happen to be metabolized by the same enzyme, due to the increase in enzyme concentration. In this case, you will have to compensate for decreased pharmaceutical response, and you will have to monitor the patient very closely, especially when the inducing drug is withdrawn. As I said above, this reaction is much slower in onset, usually happening over one to two weeks. You have all had patients who have had to go in for a certain type of medication and they have had to wait for a couple of weeks to see what their serum levels actually plateau at. Thus, this determines their long-term therapeutic dose. That is due to this reaction. Remember – unlike substrates and inhibitors, inducers are not directly affected by typical pharmacodynamics, but rather stimulates the translation of new proteins (enzymes), and this process takes more time.

Let’s take a look at a couple of examples of enzyme induction. Cytochrome P450 3A is responsible for the metabolism of:

- Most calcium channel blockers (Verapamil)
- Most benzodiazepines (Valium, Xanax)
- Most HIV protease inhibitors
- Most HMG-CoA-reductase inhibitors
- Cyclosporine
- Most non-sedating antihistamines
- Cisapride (Propulsid)
CYP450 3A is inhibited by a lot of the medications we are using:

- Ketoconazole
- Itraconazole
- Fluconazole
- Cimetidine
- Clarithromycin
- Erythromycin
- Troleandomycin
- Grapefruit juice

But CYP450 3A is induced by some other common medications that we will see in our patients:

- Carbamazepine (Carbatrol anti-seizure)
- Rifampin (Rifadin antibiotic TB)
- Rifabutin (Mycobutin antibiotic)
- Ritonavir (Ritonavir HIV protease inhibitor)
- St. John’s Wort

When we look at CYP 2D6, this is absent in 7% of Caucasians, and in 1-2% of non-Caucasians. Yet it is hyperactive in up to 30% of East Africans. This enzyme is responsible for catalyzing the primary metabolism of: codeine, many beta-blockers, and many tricyclic antidepressants such as Elavil. How many of you have known patients who take codeine and it doesn’t do squat? Or people who take it and they get a very strong effect? Much of that is due to this. Personally, I lack this particular enzyme – I take codeine, and it doesn’t do anything. There is no therapeutic value to codeine for me, at all. CYP 2D6 is inhibited by fluoxetine (Prozac – SSRI), haloperidol (Haldol – antipsychotic), and quinidine (Cardioquin – cardiac antiarrhythmic). If you put your patient on beta-blockers, they will be inhibited if the patient doesn’t have CYP 2D6. Or they could be more effective. You just have to watch.

CYP 2C9 is absent in 1% of Caucasians and African-Americans. It is responsible for the primary metabolism of most NASIDs (including COX-2), S-warfarin (the active form of warfarin), and phenytoin (Dilantin – seizure control). It is inhibited by fluconazole (Diflucan – anti-yeast/anti-fungal). Thus, you have to be careful.

CYP 2C19 is absent in 20-30% of Asians, and 3-5% of Caucasians. It carries out the primary metabolism of diazepam (Valium) and phenytoin (Dilantin). It is inhibited by omeprazole (Prilosec), isoniazid (Nydrazid), and ketoconazole.

On CYP 1A2, smoking will actually induce this. Therefore, a smoker’s enzyme concentration will be much higher than a non-smoker’s. Their effectiveness of the catalysis of

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<td><strong>Substrates</strong></td>
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Theophylline (Quibron-T – asthma), imipramine (Tofranil – antidepressant), propranolol (Inderal – anti-hypertensive), and clozapine (Clozaril – antipsychotic) will be much higher. However, they will be inhibited by many of the fluoroquinolone antibiotics, as well as fluvoxamine (an antidepressant) and cimetidine (Tagamet).

How do you remember all of this? We have substrates, inhibitors and inducers. Which one does what? How does it work? Well, there are charts and clinical references, like Tables 7 and 8, which can help you. (A printable version of Table 8 is available at the end of this document in Appendix B.) Table 8 can actually be printed out. As an example, we will take a statin drug – Simvastatin, with an inhibitor – a patient on grapefruit juice. Grapefruit juice is an inhibitor of CYP 3A – it inhibits it, and therefore the serum concentration of the statin is going to change. Then, if you take St. John’s Wort, which is an inducer, it is going to cause more of the enzyme to metabolize, and thus the simvastatin will be metabolized at a higher rate, and lower your serum concentration more. Again, you have to look at each piece.

### Excretion

At this point, now our medication has gone into the body, been absorbed in the GI tract, circulated through the plasma, gone through the liver to be metabolized, and now it needs to be excreted – most of this is done through the kidney. Some chemical compounds, both exogenous and endogenous can cause changes in renal blood flow. Think about this: the faster the blood goes through the kidneys, that will increase the rate of renal clearance. Anything that slows the vascular perfusion through the kidney will decrease the renal clearance. Prostaglandins and NSAIDs may alter renal blood flow, as well as disease states such as congestive heart failure (CHF).

One of the big pieces that we look at is if the drug is excreted through the bile or through the urine. In regards to the urine, changes in the pH can make differences. Passive reabsorption from the renal tubules depends on the drug and its ability to cross the semi-permeable membrane. The pH can determine whether the drug exists as an ion or a non-ion, and whether or not it will be excreted. Thus, changes in urinary pH can and should also affect our dose. Drugs that are highly lipid soluble will more easily pass through the tubules for re-absorption. Drugs that are low pH and are ionized will not easily pass through the membrane as the pH changes.