Safe Prescribing and Drug-Drug Interactions for the Nurse Practitioner

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Disclosures

- Speaker Bureau: Novartis, GSK, Sanofi-Pasteur, Merck, Takeda, Vivus
- Consultant: Vivus, Sanofi-Pasteur, Takeda

Objectives

- Upon completion of this lecture, the participant will be able to:
  - Discuss the most common mechanisms for drug-drug interactions
  - Discuss techniques to ensure safe prescribing
  - Review cases involving prescribing errors and medical malpractice cases
Numbers of Nurse Practitioners
• 2013: 167,000 NP’s
• 2009: 147,295 nurse practitioners in the United States
• Numbers have increased by 100% in 10 years

Prescriptive Authority
• All states allow nurse practitioners to prescribe medications
  – 18 states: allow autonomous prescriptive authority
  – Remainder of states: NP’s can prescribe but requires MD involvement or delegation

Estimated Number of Prescriptions
• According to the results of a 2004 American Academy of Nurse Practitioners member survey:
  – Almost 97% of NPs prescribe pharmacotherapy
  – Almost 65% are authorized to prescribe at least some controlled substances
• In 2007, NP’s wrote > 500 million prescriptions
• Mean number of 19 prescriptions per day
  – 1.4 million prescriptions written by NPs per day
  – 10 million prescriptions per week by NPs
  – 500 million prescriptions per year by NP’s

The Journal for Nurse Practitioners; Volume 3, Number 1. January 2007
Average Number of Prescriptions in a Typical Day

- None: 3.5%
- 1 – 5: 15.7%
- 6 – 15: 35.4%
- 16 – 25: 27.6%
- More than 25: 17.8%

Longitudinal NP Prescribing Data – 2004 Cohort; www.npedu.com accessed 12/16/07

Common Prescribing Errors

Drug-Drug Interactions

- Drug interactions:
  - Are becoming increasingly more common
  - Individuals are taking more and more medications
  - For instance, the average patient with hypertension is on 3.2 agents to control blood pressure
  - The average patient with diabetes is on 5 different medications

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Malpractice Suits

• Drug interactions
  – Drug interactions: Now the 4th leading cause of death in the United States
  – Now: 6th leading cause of malpractice suits against nurse practitioners, physician assistants, and physicians

Many Common Complaints Can Occur From a Drug/Drug Interaction

• Fatigue
• Constipation or diarrhea
• Confusion
• Incontinence
• Falls
• Depression
• Weakness or tremors
• Excess drowsiness or dizziness
• Agitation or anxiety
• Decreased sexual behavior

3 Mechanisms For Drug Interactions

• Drug Interactions
  – 1. Drug interactions occur when medications utilize the same enzyme in the liver for metabolism
  – 2. Can also occur if one medication interferes with another medication’s excretion through the kidneys
  – 3. Can occur if multiple “highly protein bound drugs” are given to a patient
Let’s Start With Drug Interactions Which Occur Through CYP 450

Cytochrome P450

• History of CYP450
  – Not much was known about this drug metabolism system until Seldane and erythromycin began to producing Torsade de Pointe
• CYP450: Enzymes, found within the liver, which metabolize various medications
• Many medications utilize these pathways for metabolism

CYP450

• Purpose of this enzyme system is to metabolize a substance so that it may be broken down and excreted or so that it may be delivered to the tissues on which it will act
Pathways

• There are a number of enzymes or pathways
  – 1A2
  – 2C9
  – 2C19
  – 3A4
  – 2D6

Terminology

• Substrates
  – Metabolized by the isoenzyme
• Inhibitors
  – Block the activity of the isoenzyme
• Inducers
  – Accelerate the activity of the isoenzyme
Examples of Common Drug Interactions

<table>
<thead>
<tr>
<th>CY P450 Isoenzyme</th>
<th>Drug Substrate</th>
<th>Drug Inhibitor</th>
<th>Drug Inducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Caffeine</td>
<td>Cimetidine</td>
<td>Tobacco</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td>Fluvoxamine (Luvox)</td>
<td>Nicotine</td>
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<tr>
<td></td>
<td></td>
<td>Ticlopidine (Ticlid) Fluoroquinolones</td>
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Let Us Look At An Example!

- Patient drinks 4 cups of coffee per day
  - Caffeine is a substrate
- You prescribe ciprofloxacin
  - Ciprofloxacin is an inhibitor
- What happens to the caffeine levels?
- About what will the patient complain?

Another Example

- Patient is on theophylline for COPD
  - Substrate
- Smoking (Nicotine)
  - Nicotine is an inducer
- What have you had to do with the theophylline to get this patient to a therapeutic goal?
- Patient develops AECB and quits smoking
- What happens to theophylline levels?
CY P450 3A4

- This is the location of most drug-drug interactions
- 50% of medications are metabolized through this pathway

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<tr>
<td>3A4</td>
<td>Amiodarone</td>
<td>Aminophylline</td>
<td>Barbiturates</td>
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<tr>
<td></td>
<td>Diltiazem</td>
<td>Clonidine</td>
<td>Carbamazepine</td>
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<td></td>
<td>Felodipine</td>
<td>Phenytoin</td>
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<tr>
<td></td>
<td>Nifedipine</td>
<td>Rifampin</td>
<td>St. John’s</td>
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<td></td>
<td>Verapamil</td>
<td>Phenobarbital</td>
<td>Wort</td>
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<tr>
<td></td>
<td>Lovastatin</td>
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<td></td>
<td>Simvastatin</td>
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<td>Atorvastatin</td>
<td>Grapefruit</td>
<td>Barbiturates</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>juice</td>
<td>Carbamazepine</td>
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<tr>
<td></td>
<td>Alprazolam</td>
<td>Ritonavir</td>
<td>Phenytoin</td>
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<td></td>
<td>Diazepam</td>
<td>Fluoxetine</td>
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<td></td>
<td>Methadone</td>
<td>Nefazodone</td>
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Also Important

- Drugs that are substrates of the same CYP 450 substrate can inhibit each other’s metabolism, possibly resulting in drug toxicity

Let Us Look At Another Patient

- 78 year-old woman with asthma, hypertension, hyperlipidemia, obesity, osteoarthritis
  - Currently on numerous medications including Zocor (simvastatin) 80 mg qhs
- Develops chest pain, rules-in for an MI and undergoes a 6-vessel CABG
  - Started on Amiodarone
- 4 weeks later: Creatinine 3.0; LFTs-2x upper limits of normal (had all been normal in patient and before surgery)
  - Cardiology consulted – recommend gastroenterology evaluation; Gastro said it was a reaction to the Zocor
- 1 week later – Creatinine 3.2
- What really is going on?

Drugs Frequently Involved in Interactions

- Statins
  - Lova, simva, atorva
- Amiodarone
- Telithromycin, erythromycin, clarithromycin
- -Azoles
- -Antivirals
Ideally, a Medication Would Use Multiple Pathways for Metabolism

- Some medications use multiple pathways
- This is ideal
  - If one pathway is being utilized by multiple medications, the medication can be metabolized by the other pathway

Another Example

CW
- CW is a 52-year-old woman who presents to discuss her recent cholesterol profile
  - Lab results are as follows:
    - Total cholesterol: 286
    - HDL: 46
    - LDL: 199
    - Triglycerides: 154
    - Risk ratio: 6.22
    - LFT’s: normal
Treatment

- CW has been on a diet and exercise plan for the last 3 months attempting to lower her cholesterol without pharmacotherapy
- At today’s visit, atorvastatin therapy initiated
- Dosage: 20 mg qhs

HMG Co-A Reductase Inhibitors

- Metabolized through the liver
  - Liver is the primary site of elimination for the majority of medications on the market
  - Statins are no exception
  - The liver contains numerous enzymes that oxidize or conjugate drugs
- CYP450 is involved in the metabolism of most statins
  - In fact, most statins use the 3A4 pathway
  - Pravastatin is one exception; it is not metabolized through the CY P450 system; Crestor (rosuvastatin – 2C9)

Caution: CY P450 3A4

- Caution: Medications using CY P450 3A4
  - Avoid azole medications (rhabdomyolysis)
  - Avoid concomitant gemfibrozil (rhabdomyolysis)
  - Avoid erythromycin and clarithromycin (increases statin AUC by 50%)
Laboratory Monitoring

- Laboratory Monitoring
  - Lipid profile, liver function testing and CK before beginning medication
  - Repeat liver enzymes as deemed appropriate by provider (periodically)
  - Only recheck CK as needed for symptoms

6 Months Later

- CW calls complaining of cramping in her feet only at night
- It is occurring every night
- This is new; she has never had anything like this before and because of our discussion regarding potential side effects of the statin class, she decided to call
- She was advised to stop atorvastatin and come into the office for an evaluation and a few additional laboratory tests

Rhabdomyolysis

- Concern regarding rhabdomyolysis
  - Fatigue
  - Myalgias
  - Cramping
  - If these occur:
    - Discontinue the drug
    - CK (Done to exclude muscle involvement)
    - LFTs (full liver panel is recommended because we are now potentially dealing with a significant problem)
CW’s Labs

• Physical examination: normal; no evidence of tender or edematous muscles
• CK: 3305 (normal level: 20-170)
• Chemistry panel: normal
• Urinalysis: normal
• CBC with differential: normal

Rhabdomyolysis

• Laboratory Features:
  – Elevated CK-MM** Most sensitive test
  • With rhabdo, range is often: 500 - >100,000 units/L
  • Degree of elevation roughly correlates with the risk of renal failure

What Changed?

• Why did this happen?
• CW went to a walk-in center
• Diagnosed with “walking pneumonia”
• Given a prescription for clarithromycin
Remember CY P450 3A4

- Atorvastatin is a substrate
- Clarithromycin is an inhibitor
- Blocks 3A4 enzyme causing atorvastatin levels to increase significantly (50%)

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CYP450 and Statins


What Psychiatric Medications Can Do The Same Thing?

- Nefazodone
- Alprazolam
Interactions Involving Renal System

CF
- CF is a 62-year-old female with bipolar disorder
- Currently maintained on Lithium 300 mg 2 tablets po bid
- Has been on this dosage x years and doing relatively well; moods are stabilized
- Employed in a steady job; marriage going well
- Presented to family physician for bilateral knee pain
- Diagnosed with osteoarthritis; started on naproxen

Lithium

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CF Presents 3 Weeks Later

• Husband is concerned
• Seems more confused
• Complaining of dizziness, nausea, and tremor
• Began approximately 1 week ago and seems to be worsening
• CBC with diff, CMP, UA, Lytes, Lithium level, TSH and CT scan obtained

Laboratory Values

• CBC with diff: normal
• CMP: normal
• Lytes: normal
• UA: normal
• Lithium level: 2.2 mEQ/L (normal: 0.8 mEq/L – 1.2 mEq/L)
• CT scan: normal

What Changed???

• What caused a sudden change in this woman?
  – Is this delirium?
  – Medication
  – TIA?
  – CVA?
Lithium

- Lithium is cleared completely through the renal system
- Drugs and conditions that influence renal excretion stand the potential for increasing serum lithium concentrations
- Such drugs include: thiazide diuretics, NSAIDs, ACE inhibitors, Calcium channel blockers (diltiazem and verapamil), Caffeine

Let’s Talk About NSAIDs and Lithium

- NSAIDs
  - Have been associated with increasing lithium plasma levels to toxic levels
  - OTC medications can produce the same effect yet it is not seen as much as anticipated when they went OTC
  - ? Lower dosage
  - If you need to use an NSAID in a patient with lithium: consider aspirin and sulindac
  - Less likely to cause toxicity

Thiazides and Lithium

- In fact, concomitant use of diuretics has long been associated with the development of lithium toxicity
  - Thiazide diuretics are thought to be the worst because they act distally on the renal tubule (same location as lithium is cleared) causing an increase in the re-absorption of lithium
Think of All the Antihypertensives

- Most antihypertensives now have HCTZ in them
- Easy for a drug interaction to occur

Other Drugs Can Lower Lithium Levels

- Osmotic diuretics enhance lithium excretion and are often used for lithium toxicity
- Caffeine and theophylline also decrease lithium levels and therefore need to be monitored if used concomitantly

Laboratory Monitoring in Individuals on Lithium

- Consider lithium level q 3-5 days when initiating any new therapy
- Drugs like lithium have a therapeutic level that is close to the toxic level
  - This is called a Narrow Therapeutic Index (NTI)
  - Elders generally need 50% less the dose of a younger adult/individual
- Therefore, you must closely monitor lithium levels when new drugs are added
Other Labs to Monitor in Patients Taking Lithium

- TSH (lithium decreases thyroxine production by interfering with iodine absorption)
- Calcium (increased levels)
- Glucose (increased levels)
- Potassium (increased levels)

- If patient is on a stable dosage, can monitor these every year

Other Medications Which Can Alter The TSH

- Amiodarone
- Lithium
- Interferon

- Why??

Anticoagulation Therapy
GP

• 76 year-old-female who presents complaining of increasing shortness of breath, weight gain, and progressively worsening ankle edema
  – Began approximately 1 week ago and is worsening
  – Feels like her heart is “skipping beats”
• PE: Weight 348 pounds (up 24 pounds in past month)
• Lungs: bibasilar crackles
• Heart: irregularly irregular
• PV: 3+ pitting edema to the mid-shins

GP

• Echo: dilated cardiomyopathy
  – LAE and RAE
  – EF-45%
• ECG: Atrial fibrillation; Ventricular response: 100 bpm
  – No Q waves; T wave inversion in II, III, and aVF

GP

• Admitted to CICU for further evaluation
• Diagnosis:
  – CHF
  – Atrial fibrillation
  – Negative cardiac enzymes
• Anticoagulation initiated
Warfarin (Coumadin)

- First identified in the 1940’s
- Became prominent in 1955 when Dwight D. Eisenhower was given warfarin after he suffered an MI
- At present, 2 million individuals are taking coumadin
- Yet...Only 1/3-1/2 of eligible patients are currently prescribed this drug

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Actions of Warfarin

- Inhibits the synthesis of vitamin K-dependent clotting factors which include: Factors II, VII, IX, and X; and the anticoagulant proteins C and S
- Completely absorbed after oral administration
  - Peak concentration is attained within the first 4 hours
  - 98% of warfarin is bound to plasma proteins
- Therefore, need to be aware that any highly protein bound drug added on to the individual taking warfarin may end up displacing warfarin (increasing warfarin levels and thus raising INR)

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GP

- GP failed to convert to NSR despite elective cardioversion
- Opted to maintain her on warfarin
- 6 months into therapy: INR which was previously controlled at 2.5-3.0; average: 2.8
- Now...INR 4.3
- What has changed?????
Review of Diet and Medications

- GP decided to start herself on garlic and ginkgo for cardiovascular disease prophylaxis
- Also wanted to improve her memory
- Numerous herbs can affect warfarin and the INR

Drug Interactions

- Drug interactions involving warfarin are characterized as either pharmacokinetic or pharmacodynamic in nature
  - Pharmacokinetic interactions cause changes in systemic concentrations of warfarin by interfering with 1 or more of the following: absorption, protein binding, metabolism

Herbs and their Anticoagulant Effects

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Herbs or Anticoagulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Garlic, Ginger, Ginseng</td>
</tr>
<tr>
<td>Acenocoumarol</td>
<td>Aloe Vera, Alfalfa, Pea</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>Black cohosh, Feverfew, Ginkgo, Garlic</td>
</tr>
</tbody>
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Various Medications Can Also Affect INR

- Increases anticoagulant effect
  - Acetaminophen
  - Beta-blockers
  - Ketoconazole
  - Thyroid hormones
  - Lovastatin
  - Metronidazole

- Decreases anticoagulant effect
  - Dicloxacillin
  - Trazodone
  - Estrogens
  - Thiazide diuretics

So...We Then

- Eliminated the garlic and ginkgo and held 1 dose of warfarin
- Rechecked INR in 48 hours
  - Within 48 hours, it had decreased to 3.7
  - Another dose of warfarin held and INR rechecked in 48 hours
    - INR now: 3.1

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<tr>
<th>CYP450 Isoenzyme Inhibition by the SSRIs (<em>in vitro</em>)</th>
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<tr>
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</tr>
<tr>
<td>1A2</td>
</tr>
<tr>
<td>Sertraline</td>
</tr>
<tr>
<td>Escitalopram</td>
</tr>
<tr>
<td>Citalopram</td>
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<tr>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Paroxetine</td>
</tr>
</tbody>
</table>

0 = minimal or weak inhibition; +, ++, +++ = mild, moderate, or strong inhibition
* Clinical significance of in vitro data is unknown
There are limited in vivo data suggesting a modest CYP 2D6 inhibitory effect for escitalopram 20 mg/day.

von Moltke et al, 2006; Greenblatt et al, 2002; Greenblatt et al, 1998
Additional Concerns

• Trimethoprim/sulfamethoxazole with glyburide
  — hypoglycemia
• Clarithromycin with digoxin
  — digoxin toxicity
• Potassium sparing diuretics with ACE inhibitors
  — hyperkalemia

Macrolides

• Known QT prolongation
• Caution with other drugs which have similar potential:
  — Tricyclic antidepressants
  — Fluoroquinolones
  — Antipsychotics
  — Antiarrhythmics

Other Areas of Risk

• Case in NH
• NP wrote RX for Elocon for eczema; large tube with 5 refills
• Refilled 6 months later
• Patient sued; had been using the steroid cream as a moisturizer
• Developed striae over lower extremities
• What could have been done differently?
Techniques to Avoid Errors

- Clear writing and documentation
- EHR, if available
- Double check dosages
- Avoid writing RX’s when patient is talking to you or sitting in front of you
- Have a list of high risk drugs; when you see this list – bells should go off in your head
- Double check interactions

Thank You

I Would Be Happy To Entertain Any Questions

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