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

Wright, 2014
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

Wright, 2014
Prescriptive Authority

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

Wright, 2014
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
Wright, 2014
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

Wright, 2014
Common Prescribing Errors

Wright, 2014
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

Wright, 2014
Malpractice Suits

• **Drug interactions**
  - Drug interactions: Now the 4\textsuperscript{th} leading cause of death in the United States
  - Now: 6\textsuperscript{th} leading cause of malpractice suits against nurse practitioners, physician assistants, and physicians

Wright, 2014
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

Wright, 2014
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

Wright, 2014
Let’s Start With Drug Interactions Which Occur Through CYP 450

Wright, 2014
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**

Wright, 2014
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

Wright, 2014
Pathways

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

Wright, 2014
Weighted Importance of CYP450

Relative Importance of CYP450 in Drug Metabolism

- CYP3A
- CYP2D6
- CYP2C
- CYP2E1
- CYP1A2

Wright, 2014
Terminology

• **Substrates**
  – Metabolized by the isoenzyme

• **Inhibitors**
  – Block the activity of the isoenzyme

• **Inducers**
  – Accelerate the activity of the isoenzyme

Wright, 2014
Examples of Common Drug Interactions

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<td>1A2</td>
<td>Caffeine</td>
<td>Cimetidine</td>
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<td>Theophylline</td>
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<td>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?

Wright, 2014
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?

Wright, 2014
CY P450 3A4

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

Wright, 2014
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• Drugs that are substrates of the same CYP 450 substrate can inhibit each other’s metabolism, possibly resulting in drug toxicity

Wright, 2014
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Wright, 2014
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? Wright, 2014
Drugs Frequently Involved in Interactions

• Statins
  – Lova, simva, atorva
• Amiodarone
• Telithromycin, erythromycin, clarithromycin
• -Azoles
• -Antivirals

Wright, 2014
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

Wright, 2014
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

Wright, 2014
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)

Wright, 2014
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%)

Wright, 2014
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

Wright, 2014
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

Wright, 2014
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

Wright, 2014
What Changed?

- Why did this happen?
- CW went to a walk-in center
- Diagnosed with “walking pneumonia”
- Given a prescription for clarithromycin

Wright, 2014
Remember CY P450 3A4

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

Wright, 2014
# CYP450 and Statins

<table>
<thead>
<tr>
<th>CYP 1A2</th>
<th>CYP 2C9</th>
<th>CYP 2C19</th>
<th>CYP 2D6</th>
<th>CYP 2E1</th>
<th>CYP 3A4</th>
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Wright, 2014
What Psychiatric Medications Can Do The Same Thing?

- Nefazodone
- Alprazolam
Interactions Involving Renal System

Wright, 2014
Lithium

Wright, 2014
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

Wright, 2014
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

Wright, 2014
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
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

Wright, 2014
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

Wright, 2014
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

Wright, 2014
Think of All the Antihypertensives

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

Wright, 2014
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

Wright, 2014
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

Wright, 2014
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

Wright, 2014
Other Medications Which Can Alter The TSH

• Amiodarone
• Lithium
• Interferon

• Why??

Wright, 2014
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

Wright, 2014
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

Wright, 2014
• Admitted to CICU for further evaluation
• Diagnosis:
  - CHF
  - Atrial fibrillation
  - Negative cardiac enzymes
• Anticoagulation initiated
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

Wright, 2014
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)

Wright, 2014
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????

Wright, 2014
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

Wright, 2014
Herbs and their Anticoagulant Effects

<table>
<thead>
<tr>
<th>Anticoagulant components</th>
<th>Effects or constituents</th>
<th>Anticoagulant components</th>
<th>Effects or constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfalfa</td>
<td>Coumarin</td>
<td>Garlic</td>
<td>May prolong prothrombin time</td>
</tr>
<tr>
<td>Angelica</td>
<td>Coumarin</td>
<td>Ginger</td>
<td>Inhibition of platelet activity</td>
</tr>
<tr>
<td>Aniseed</td>
<td>Coumarin</td>
<td>Ginkgo</td>
<td>Inhibits platelet aggregation</td>
</tr>
<tr>
<td>Arnica</td>
<td>Coumarin, anticoagulant in vivo</td>
<td>Ginseng, Panax</td>
<td>Reduction of blood coagulation/decreases INR</td>
</tr>
<tr>
<td>Asafoetida</td>
<td>Coumarin, anticoagulant in vivo</td>
<td>Horse chestnut</td>
<td>Coumarin</td>
</tr>
<tr>
<td>Bogbean</td>
<td>Hemolytic activity</td>
<td>Horseradish</td>
<td>Peroxidase stimulates synthesis of arachidonic acid metabolites</td>
</tr>
<tr>
<td>Cassia</td>
<td>Inhibits platelet aggregation</td>
<td>Licorice</td>
<td>Inhibition of platelet activity</td>
</tr>
<tr>
<td>Celery, seed or extract</td>
<td>Coumarin</td>
<td>Meadowssweet</td>
<td>Salicylate</td>
</tr>
<tr>
<td>Chamomile, German or Roman</td>
<td>Coumarin</td>
<td>Melilot</td>
<td>Coumarin</td>
</tr>
<tr>
<td>Clove</td>
<td>Eugenol, a powerful inhibitor of platelet activity</td>
<td>Poplar</td>
<td>Salicylate</td>
</tr>
<tr>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>Fibrinolytic potential</td>
<td>Prickly ash, Northern and Southern</td>
<td>Coumarin</td>
</tr>
<tr>
<td>Evening primrose oil, Primula veris, Primula clatior</td>
<td>May decrease platelet aggregation and increase fibrinolytic activity</td>
<td>Quassia</td>
<td>Coumarin</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Inhibits platelet aggregation in vitro</td>
<td>Red clover</td>
<td>Coumarin</td>
</tr>
<tr>
<td>Fucus</td>
<td>Anticoagulant action</td>
<td>Sweet woodruff</td>
<td>Coumarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tonka beans</td>
<td>Coumarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Willow</td>
<td>Salicylate</td>
</tr>
</tbody>
</table>

Key: INR, international normalized ratio.
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

Wright, 2014
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

Wright, 2014
## CYP450 Isoenzyme Inhibition by the SSRIs (*in vitro*)

<table>
<thead>
<tr>
<th>CYP Isoenzymes</th>
<th>1A2</th>
<th>2C9</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>+</td>
<td>+</td>
<td>+ to ++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Citalopram</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>+</td>
<td>++</td>
<td>+ to ++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</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., 2001; 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

Wright, 2014
Macrolides

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

Wright, 2014
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?

Wright, 2014
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
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WendyARNP@aol.com
Thank You

I Would Be Happy To Entertain Any Questions