Drugs: Can’t Live with Them, Can’t Live Without Them.
A Focus on Adverse Drug Effects

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Disclosure

- I have the following financial relationship to disclose:
  - Speaker’s Bureau for Abbott Laboratories
- I will not discuss off-label use of medication.
- I will not discuss investigational drugs.
Educational Objectives

At the conclusion of this session, the participant should be able to:

- Define a “Black Box” warning and the concept of REMS, and list 10 current boxed warnings on medications.
- Evaluate adverse effects for clinical significance.
- List 10 recently reported adverse drug effects.

Drug Interactions, Adverse Drug Effects, Boxed Warnings

![Diagram](image)
Drug-Drug (DDI) Interactions in Tennessee

According to Tennessee CMS Medicare Part D data:
- Highest rate of drug-drug interactions (DDI) in the country
- 6th highest rate of potentially inappropriate medication (PIM) use

Source: Medicare Part D data July-December 2007
Drug Interactions Lead to Nursing Home Fines

- July 1, 2011, The Tennessee Department of Health suspended new admissions to a Maryville nursing home after a complaint investigation found violations that put residents in "immediate jeopardy."


Drug Interactions Lead to Nursing Home Fines

- The most serious violations stemmed from incidents when at least 4 patients taking Coumadin® (warfarin) were also given antibiotics that interact when given together.
  - One resident was hospitalized with a "massive gastrointestinal bleed" because nurses didn't know to watch for interactions.

New Interaction/Boxed Warning for Oxycodone

- There is a new black box warning for OxyContin® (oxycodone) about interactions with CYP3A4 drugs.
- CYP3A4 is a major pathway for metabolizing oxycodone, therefore 3A4 inhibitors or inducers can affect oxycodone levels.

Prescriber’s Letter, June 2010

Boxed Warning for Oxycodone with CYP3A4 Drugs

- INCREASED oxycodone levels can be seen when it's combined with 3A4 INHIBITORS such as macrolides (clarithromycin, etc),azole antifungals (ketoconazole, etc), or protease inhibitors (ritonavir, etc).
- For example, voriconazole (Vfend®) can almost double oxycodone peak levels and prolong its effects.

Prescriber’s Letter, June 2010
**Boxed Warning for Oxycodone with CYP3A4 Drugs**

- **DECREASED oxycodone levels** can be seen if it's combined with 3A4 INDUCERS such as carbamazepine, phenytoin, rifampin, St. John's wort, etc.
  - Rifampin decreases oxycodone peak levels by more than 50%.

*Prescriber’s Letter, June 2010*

**Avoid Linezolid (Zyvox®) with SSRIs**

- Linezolid (Zyvox®) has properties as a monoamine oxidase inhibitor (MAOI), so drug interactions with adrenergic and serotonergic agents are possible.
- In 2011, the FDA warned of use of linezolid in combination with serotonergic agents such as SSRIs to avoid a potential drug interaction causing serotonin syndrome.

*FDA.gov, July 26, 2011*
Side and Adverse Effects: Drugs Can Be Deadly

Lists of Prescription Meds' Side Effects Keep Growing

- Lists of the side effects for prescription medications on drug labels, packaging, and advertisements have mushroomed up to an average of 70 per medication.
- "Having a high number of side effects on a drug's label should not suggest that the drug is unsafe. In fact, much of this labeling has less to do with true toxicity than with protecting manufacturers from potential lawsuits," the study's lead author stated.

Archives of Internal Medicine, May 23, 2011
Lists of Prescription Meds' Side Effects Keep Growing

- An analysis of more than 5,600 drug labels and more than 500,000 side effects found that prescription drug labels include an average of 70 different potential adverse reactions—a number that jumps to 100 side effects for some commonly prescribed drugs.
  - Some drugs in the upper range even listed up to 525 reactions.

*Archives of Internal Medicine, May 23, 2011*

Adverse Drug Reaction Reports

- In the 2nd quarter of 2010, the FDA received 33,068 reports of serious injury, disability or death associated with drug therapy.
  - This was an increase of 12%.
- The 3 leading drugs were:
  - Chantix®—psychiatric effects (depression, hostility, psychosis)
  - Levaquin®—tendon rupture
  - Multaq®—heart rhythm disturbances
    - Note: July, 2011, FDA is “investigating” the safety of Multaq®.

*ISMP, January 27, 2011*
Boxed ("Black Box") Warnings and Other Adverse Effects

- Currently there are approximately 350 drug entities with a black box warning.
  - With this large number of medications, it is difficult for clinicians to stay knowledgeable regarding the recommendations given in warnings.
- The following web site lists all boxed warnings:
  - www.formularyproductions.com/blackbox


FDA Boxed Warnings: Common Drug Classes with Boxed Warnings

- Aminoglycosides
  - Ototoxicity & Nephrotoxicity
- ACE Inhibitors and ARBs
  - Injury or death to developing fetus
- Beta-blockers
  - Exacerbation of angina and risk of MI with abrupt discontinuation
- Loop diuretics
  - Volume and electrolyte depletion
- Estrogen
  - MI, stroke, DVT, PE and breast cancer in postmenopausal women

American Family Physician, February 1, 2010
FDA BoxedWarnings:
Common Drug Classes with Boxed Warnings

- Iron supplements, oral
  - Overdose may be fatal in children
- NSAIDs
  - Cardiovascular events, ulcer and GI bleed
- Oral contraceptives, combined
  - Increased cardiovascular risk in smokers, especially in those >35 years
- Salicylates
  - Reye syndrome in children; potential for serious allergic reaction
- SSRIs
  - Increased suicidality in children and adolescents

*American Family Physician, February 1, 2010*

FDA BoxedWarnings:
Select Drugs with Boxed Warnings

- Amiodarone (Cordarone®)
  - Pulmonary toxicity, hepatotoxicity
- Atomoxetine (Strattera®)
  - Increased suicidality in children and adolescents
- Fentanyl (Duragesic®)
  - Respiratory depression, especially with initiation or conversion from a different opioid; QT prolongation
- Medroxyprogesterone (Depo-Provera®)
  - Decreased bone mineral density
- Quinine (Qualaquin®)
  - Renal failure and TPP
- Ketoconazole
  - Hepatotoxicity

*American Family Physician, February 1, 2010*
FDA Boxed Warnings:
Select Drugs with Boxed Warnings

- Methadone
  - Respiratory depression
- Metronidazole (Flagyl®)
  - Carcinogenic in mice and rats
- Quinine for nocturnal leg cramps
  - Benefit does not outweigh risks
- Raloxifene (Evista®)
  - DVT and PE
- Rosiglitazone (Avandia®) and pioglitazone (Actos®)
  - May cause or exacerbate heart failure

*American Family Physician, February 1, 2010*

FDA Boxed Warnings:
Select Drugs with Boxed Warnings

- Fluoroquinolones
  - Tendinopathy and tendon rupture
  - Exacerbation of myasthenia gravis
- Oral sodium phosphate
  - Acute phosphate nephropathy
- Salmeterol (Serevent®)
  - Increased asthma-related mortality
- Metoclopramide (Reglan®)
  - Tardive dyskinesia
- Warfarin (Coumadin®)
  - Increased risk of bleeding

*American Family Physician, February 1, 2010*
Not Just Rx Drugs: Adverse Effects from Supplements

- It’s not just Rx drugs that cause adverse effects.

Calcium Supplements Raise Heart Attack Risk by 30%

- Patients who took calcium increased their risk of a heart attack by about 30%.
- In five studies with more than 8,000 patients, half of whom were on calcium, the supplement users had 143 heart attacks during the research compared with 111 for people on placebo.
- The risk was greatest when calcium intake from food was above average, regardless of patients’ age or sex, according to the analysis.

*British Medical Journal, July 29, 2010
BMJ 2010;341:c3691*
Calcium + Vitamin D Also Raise Heart Attack Risk

- A year after publishing a meta-analysis finding a link between calcium supplements and cardiac event risk, a New Zealand–based research team says calcium supplements containing vitamin D are also linked to elevated cardiac risk.
  - The pooled increased risk was 25%-30% for myocardial infarction and 15%-20% for stroke.

Too Much Calcium: Renal Impairment

- High doses can lead to nephrocalcinosis and renal insufficiency.
  - The milk-alkali syndrome arose in the early 1900s when patients ingested abundant amounts of milk and antacids to control their ulcers.
  - This practice increased individuals’ risk of developing dangerously high levels of calcium in the blood, which could cause high blood pressure and even kidney failure.

*British Medical Journal*, April 20, 2011
doi:10.1136/bmj.d2040

*Journal of the American Society Nephrology*, June 2010
Too Much Calcium: Renal Impairment

- The obvious preventive strategy against the calcium-alkali syndrome is to limit the intake of calcium to no more than 1200 to 1500 mg/day, except in pregnancy when you may need 2000 mg/day.

Journal of the American Society Nephrology, June 2010

What is the Upper Limit of Calcium that is Effective and Safe?

- Might increasing dietary intake of calcium better help to protect older bones against osteoporosis and fractures?
- Previous evidence has led to uncertain conclusions, as reflected by the wide variety of daily calcium recommendations for individuals older than 50:
  - 700 mg in the UK
  - 800 mg in Scandinavia
  - 1200 mg in the US
  - 1300 mg in Australia and New Zealand

BMJ. 2011;342:d1473
Is There An Upper Limit of Calcium that is Effective?

- "Dietary calcium intakes below approximately 700 mg per day in women were associated with an increased risk of hip fracture, any fracture, and of osteoporosis," the study authors conclude.
- "The highest reported calcium intake did not further reduce the risk of fractures of any type, or of osteoporosis, but was associated with a higher rate of hip fracture."

BMJ. 2011;342:d1473

Vitamin D: The “Hot” Vitamin: But Be Cautious!

- Over the last ten years, the public has heard conflicting messages about the benefits of calcium and vitamin D.
- In November 2010, the Institute of Medicine (IOM) reported on a review of the evidence and found that the evidence supported a role for these nutrients in bone health but not in other health conditions.

Drugs: Can’t Live With Them, Can’t Live Without Them. Focus on Adverse Drug Effects

Vitamin D: The “Hot” Vitamin: But Be Cautious!

- Overall, the committee concludes that most are receiving adequate amounts of both calcium and vitamin D.
- Further, there is emerging evidence that too much of these nutrients may be harmful.


Propoxyphene Withdrawn

- The FDA has asked that propoxyphene be removed from the US market.
- The drug puts patients at risk for potentially serious or even fatal heart rhythm abnormalities, including prolonged Q-T interval.
- An estimated 10 million patients have used these products.

FDA.gov, November 19, 2010
Sibutramine (Meridia®) Withdrawn from Market

- Facing increased FDA scrutiny regarding adverse cardiovascular effects, in October 2010 Abbott voluntarily withdrew sibutramine (Meridia®).
  - It was withdrawn from the U.S., Canadian and Australian markets.

Hypnotics and Anxiolytics May Increase Mortality Risk by 36%

- Respondents who reported having used medication to treat insomnia or anxiety at least once in the month preceding the survey had a mortality rate of 15.7%, compared to a rate of 10.5% in subjects not taking such drugs.
  - This is an increase of 36% relative risk.

Sleeping Pills Risky in Seniors

- A study in the January 13, 2011 *Journal of the American Geriatric Society* reports that zolpidem (Ambien®) is risky for seniors.
- 58% of volunteers over the age of 60 stumbled off a beam when awakened after taking zolpidem, as compared to no stumbles in the placebo group.

*Journal of the American Geriatric Society, January 13, 2011*

FDA Warns of Suicidality with all Antiepileptic Drugs

- A FDA meta-analysis of nearly 200 clinical studies involving 11 anti-seizure drugs found a doubling of the risk of suicidal thinking or behavior.
- Patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%).

[http://www.fda.gov](http://www.fda.gov), May 5, 2009
Not All Epilepsy Drugs Raise Suicide Risk

- The FDA requires that all epilepsy drugs bear a warning label about an increased risk of suicidal behaviors, but a German study reports that only certain medications may increase the risk of self-harm.

**Neurology, July 27, 2010**

These Are Likely

- The study of more than 44,000 epilepsy patients in the UK revealed that those who took relatively new antiepileptic drugs with a higher risk of causing depression were three times more likely to harm themselves or attempt suicide than those who weren't taking any epilepsy medications.
  - levetiracetam (Keppra®)
  - topiramate (Topamax®)
  - vigabatrin (Sabril®)

**Neurology, July 27, 2010**
These Are Not Likely

- The researchers found that patients who took conventional epilepsy medications or those with a low risk of depression faced no increased risk of self-harm or suicidal behavior:
  - divalproex (Depakote®, Depakote ER®, Depakene®)
  - phenytoin (Dilantin®)
  - gabapentin (Neurontin®)
  - lamotrigine (Lamictal®)

*Neurology, July 27, 2010*

Antiepileptic Drugs Do Not Increase Suicide

- The current use of antiepileptic drugs was not associated with an increased risk of suicide-related events among patients with epilepsy.
  - However, it was associated with an increased risk of such events among patients with depression.

Antiepileptic Drugs Do Not Increase Suicide

Commenting on the data, study author Alejandro Arana said "in our opinion, in the long term, it is not the drugs themselves that raise the risk of suicide, but the underlying disease for which these drugs are prescribed."

He added that "treatment with antiepileptic drugs helps to control the psychiatric syndromes that are at the root of suicidal behavior in these patients."


“Epidemic: Responding to America’s Prescription Drug Abuse Crisis”

*FDA.gov*, April 19, 2011
“Epidemic: Responding to America’s Prescription Drug Abuse Crisis”

- Key elements of the plan:
  - Expansion of state-based prescription drug monitoring programs
  - Recommending convenient and environmentally responsible ways to remove unused medications from homes
  - Supporting education for patients and health care providers
  - Reducing the number of “pill mills” and doctor-shopping through law enforcement

Risk Evaluation and Mitigation Strategy (REMS) for Opiates

- Elements of the new REMS due to be finalized in 2012:
  - Prescribers will be asked, but not required, to complete training on pain management and how to recognize misuse and abuse.
  - Patients will get new educational materials from prescribers about opioid risks and their proper use, storage, and disposal.
  - Pharmacies will NOT need to verify if prescribers have completed the training. Manufacturers will monitor this.

*Prescriber’s Letter, June 2011*
Prescription/Illlicit Drug Death Chart 2002-2005

PRESCRIPTION AND ILLICIT DRUG DEATHS STATEWIDE 2002-2005
Prescription-drug deaths, which are on the rise, outpace deaths from illicit drugs in Tennessee.

<table>
<thead>
<tr>
<th>Year</th>
<th>Prescription Drug</th>
<th>Combination</th>
<th>Illegal Narcotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>211</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>2003</td>
<td>232</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td>2004</td>
<td>266</td>
<td>45</td>
<td>54</td>
</tr>
<tr>
<td>2005</td>
<td>312</td>
<td>69</td>
<td>89</td>
</tr>
</tbody>
</table>

SOURCE: Tennessee analysis of state medical examiner’s records
THE TENNESSEAN

Total Number of Drug Related Deaths in Tennessee

Tennessee Medical Examiner’s Office, Compiled October 2010
Drugs: Can’t Live With Them, Can’t Live Without Them. Focus on Adverse Drug Effects

Tennessee Department of Public Health
September 16, 2011

Drug Related Deaths by Region
All Ages 2006-2008

<table>
<thead>
<tr>
<th>Year</th>
<th>East Tennessee</th>
<th>Middle Tennessee</th>
<th>West Tennessee</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>230</td>
<td>246</td>
<td>152</td>
</tr>
<tr>
<td>2007</td>
<td>260</td>
<td>245</td>
<td>209</td>
</tr>
<tr>
<td>2008</td>
<td>314</td>
<td>267</td>
<td>194</td>
</tr>
</tbody>
</table>

Tennessee Medical Examiner’s Office, Compiled October 2010

NSAIDs Increase Risk of Cardiovascular Events

- A meta-analysis published in the January 11, 2011 issue of BMJ suggested that the use of all NSAIDs can increase the risk of heart attack and stroke compared to placebo.
  - Ibuprofen was linked with a 3-fold increase in risk of stroke.
  - Naproxen "seemed least harmful" but still doubled the risk.

BMJ 2011; 342:c7086
NSAIDs Increase Risk of Cardiovascular Events

- Lead researcher Peter Juni stated:
  - "If you are taking the drugs for acute conditions…and you are under 65, don't have heart problems, have normal cholesterol and don't smoke, it is probably fine," but warned that NSAIDs will "double or treble" the cardiovascular risk in "elderly people who take the drugs regularly for chronic pain and have heart trouble."

  BMJ 2011; 342:c7086

Patients at Risk of Subsequent Heart Attack, Death Following Short-Term Use of NSAIDs

- Patients with a history of heart attack are at increased risk of suffering a subsequent attack or death following treatment with some NSAIDs, even when treatment lasts for as little as one week.

  Circulation on line, May 9, 2011
Opioid Intolerance ("Allergy") Decision Algorithm

- When patients say they're allergic to an opioid, are all opioid analgesics off limits?
- The key is getting a detailed description of the reaction.

Opioid Intolerance Decision Algorithm

- If the patients experienced a true allergy, options include:
  - A nonopioid analgesic (e.g., acetaminophen, an NSAID)
  - An opioid in a chemical class different from the one to which the patient reacted, with close monitoring.

*Pharmacist’s Letter, June 2010*
Opioid Intolerance Decision Algorithm

Phenylpiperidines:
- meperidine (Demerol®)
- fentanyl (Duragesic®, Actiq®, Onsolis®)
- sufentanil (Sufenta®)
- remifentanil (Ultiva®)

Diphenylheptanes:
- methadone (Dolophine®)
- propoxyphene (Darvon®)

Morphine group:
- morphine
- codeine
- hydrocodone (Vicodin®, Lorcet®)
- oxycodone (Percocet®, OxyContin®)
- oxymorphone (Opana®)
  - Previously (until 2006) known as Numorphan®
- hydromorphone (Dilaudid®)
- nalbuphine (Nubain®)
- butorphanol (Stadol®)
- pentazocine (Talwin®)
Opioid Intolerance Decision Algorithm

- Tramadol (Ultram®, Ultracet®, Ryzolt®) is contraindicated in patients with opioid allergy per U.S. product labeling.
- There is not good evidence for cross-sensitivity of tramadol with opioids.
- However, experts recommend using tramadol only for patients who have mild reactions to opioids.

Pharmacist’s Letter, June 2010

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Opioid Intolerance Decision Algorithm

- The product labeling for tapentadol (Nucynta®) does not contain this same contraindication, but the FDA considers tapentadol structurally related to tramadol.
  - Experts also suggest cautious use of tapentadol in patients with opioid allergy.
- Tapentadol is a Schedule II Controlled Substance.
  - 100 mg of tapentadol is said to be equal to 15 mg of oxycodone, with reported less constipation, nausea and vomiting.

Pharmacist’s Letter, June 2010
GI Bleeding From Aspirin:
Dose More Important than Duration of Action or Enteric Coating

- Doses above 81 mg/day significantly increase GI bleeding risk.
- Lowering the dose of aspirin appears to be more important than limiting the course of treatment in determining risk of GI bleeding.
- The study also found that the influence of enteric coating on bleeding risk is not significant.

*Am J Med. 2011;124:426-433*

Plavix® + Prilosec® Where Do We Stand?

- Several reports suggest that some PPIs might decrease the efficacy of Plavix® by inhibiting its conversion to the active drug.

*Circulation 2008;118:1894-909*
FDA: Boxed Warning: Clopidogrel (Plavix®) Lack of Effect in Poor Metabolizers

- In March 2010, the FDA announced a boxed warning for clopidogrel (Plavix®).
- The warning states that patients who carry a variant CYP2C19 gene affecting the enzyme that converts clopidogrel into its active form have a potentially significant lack of effect.
- About 2% to 14% of patients are classed as “poor metabolizers.”

FDA.gov, March 11, 2010

 FDA: Boxed Warning: Clopidogrel (Plavix®) Lack of Effect in Poor Metabolizers

- Options include using Effient®, which is not affected by the CYP2C19 gene, but causes more bleeding.
- Another option is to use a double dose of Plavix®.

FDA.gov, March 11, 2010
Medical Letter Conclusion: Clopidogrel and Omeprazole

- To some extent, all PPIs reduce the enzymatic activity of CYP2C19, which is thought to be mainly responsible for the bioactivation of clopidogrel.
- Omeprazole is a strong inhibitor of CYP2C19; pantoprazole (Protonix®) appears to have less effect on CYP2C19 and not to attenuate the antiplatelet effect of clopidogrel.

The Medical Letter, November 29, 2010

Medical Letter Conclusion: Clopidogrel and Omeprazole

- Medical Letter consultants believe that patients at risk for upper GI bleeding who take clopidogrel should also take a PPI, but not omeprazole.
- Until more data become available on other PPIs, pantoprazole (Protonix®) would be a reasonable choice.

The Medical Letter, November 29, 2010
FDA Warns of Statin Risk For Myopathy

- In March, 2010, the FDA warned that higher doses of statins, in this study 80 mg of simvastatin (Zocor®), carry an increased risk of muscle injury.
- The FDA also warns that mixing statins with certain other drugs also increases patients' risk of muscle injury, including the rare but serious complication rhabdomyolysis.

FDA.gov, March 19, 2010

FDA Warns of Statin Risk For Myopathy

- Muscle damage was seen in nearly 1% of patients taking the 80 mg dose of simvastatin but in only 0.02% of patients taking the 20 mg dose.
- Rhabdomyolysis occurred in only 11 of 6,031 patients (0.02%) in the 80 mg group, but was not seen in patients taking the 20 mg dose.

FDA.gov, March 19, 2010
Cardiovascular Events with Varenicline (Chantix®)

- June 2011, FDA announced that varenicline may be associated with a small increased risk of cardiovascular events in patients with cardiovascular disease.

- A meta-analysis of 14 clinical trials suggests that varenicline is associated with a 72% relative risk of cardiac events.
- The absolute risk was 0.24%.
  - 1.06% in the varenicline group versus 0.82% in the placebo group.

*Canadian Medical Association Journal, July 4, 2011*
Sanofi issues “Important Safety Update for Multaq® (dronedarone)”

- Multaq® should not be prescribed for patients with permanent AF (atrial fibrillation).
  - Healthcare professionals are advised to monitor patients regularly (at least every six months) in order to ensure that they remain within the approved indication and do not progress to permanent AF or new or worsening heart failure.

WebMD, August 16, 2011

Sanofi issues “Important Safety Update for Multaq® (dronedarone)”

- The REMS has been modified to reflect previously communicated information regarding the potential risk of liver injury, including life-threatening acute liver failure.
  - Sanofi-aventis issued a Dear Health Care Professional Letter in January 2011 to inform about the potential risk of liver injury.
  - Subsequently, the REMS was modified to reflect this risk, including an update to the Health Care Professional Information Sheet.
Guidelines for Postpartum Contraceptive Use: Wait 21 Days

- The CDC have updated their guidelines for postpartum contraceptive use to include advising postpartum women not to use combined hormonal contraceptives during the first 21 days after delivery because of a high risk for venous thromboembolism (VTE).

Morbidity and Mortality Weekly, July 8, 2011

FDA Reviewing Safety of Drospirenone-containing Oral Contraceptives Amid VTE Risks

- In June, 2011, the FDA began conducting a safety review of drospirenone-containing oral contraceptives looking at an increased risk of VTE.
- The FDA noted that this elevated risk has not been observed in other studies and that it is "currently evaluating the conflicting results from these studies and will look at all currently available information to fully assess the risks and benefits of drospirenone-containing birth-control pills."

FDA.gov, May 31, 2011
Low-dose HRT Patches Offer Lower Stroke Risk than Oral Drugs

- Study results published in the June 2010 British Medical Journal confirmed that women who use low-dose hormone replacement therapy transdermal patches are less likely to incur a stroke, compared to use of the oral versions of the therapy.

Boxed Warning on Bone Loss with DMPA (Depo-Provera®)

- In 2004, the FDA issued a "black box warning" to highlight the fact that prolonged use may result in significant loss of bone density, that the degree of loss is proportional to the amount of time on DMPA, and that the loss may not be completely reversible.
- The warning also indicates that a woman should use all dosages of Depo-Provera® for more than 2 years only if other contraceptive methods are inadequate for her.
What Do We Know About DMPA and Its Impact Upon BMD?

- Currently, the WHO recommends that women in the age range of 18 through 45 years can use DMPA without restriction (WHO category 1).
- For women who are less than 18 or more than 45, the benefits of using DMPA generally outweigh the known or theoretical risks (WHO category 2).

Association of Reproductive Health Professionals,
*Clinical Facts Sheets*, September 2008
Society for Adolescent Medicine Guidelines for Use of DMPA in Adolescent Girls

- Continue prescribing DMPA to adolescent girls who need contraception, giving an adequate explanation of the benefits and potential risks of its use
- Inform patients of the possible risk of bone loss
- Consider including bone density monitoring
- Duration of use need not be restricted to 2 years
- Recommend daily intake of 1300 mg of calcium carbonate plus 400 IU of vitamin D and daily exercise


DMPA and Its Impact Upon BMD: Conclusions

- The FDA’s black box label does not mandate serial BMD testing or the provision of “add-back” estrogen supplementation
- The current FDA guidance does not prohibit use of DMPA for more than two years
  - Existing data do not suggest the need to place any time limit on DMPA use for adolescents or women in general

Association of Reproductive Health Professionals, Clinical Facts Sheets, September 2008
FDA Warns of Atypical Femoral Fractures with Bisphosphonates

The FDA has issued a warning regarding an increased risk of atypical femoral fracture in patients treated with bisphosphonates used for osteoporosis.

- No warning was issued for bisphosphonates used for the treatment of Paget’s disease, cancer or hypocalcaemia.

FDA.gov, October 13, 2010

The agency noted that "while it is not clear whether bisphosphonates are the cause, atypical femur fractures…have been predominantly reported in patients taking bisphosphonates."

FDA.gov, October 13, 2010
FDA Warns of Atypical Femoral Fractures with Bisphosphonates

- Noting that the risk of these fractures may be related to use of the drugs for five years or more, FDA is evaluating the safety and effectiveness of bisphosphonates for long-term osteoporosis treatment.

FDA.gov, October 13, 2010

Is ONJ Seen Only With IV Bisphosphonates?

- Oral bisphosphonates do not increase the risk for osteonecrosis of the jaw, according to a study at the IADR meeting in 2011.
  - Reachers looked at millions of patients in databases and hundreds in controlled trials and did not find any increased risk.
  - The study did find a 6-fold increased risk for osteonecrosis of the jaw in patients taking intravenous (IV) bisphosphonates.

International Association of Dental Research (IADR) 89th General Session and Exhibition. Abstract 890. Presented March 17, 2011
Bisphosphonates and Esophageal Cancer: Conflicting Data

- In July 2011, the FDA announced that it is reviewing conflicting studies on whether oral bisphosphonates prescribed for osteoporosis are linked to an increased risk for esophageal cancer.

- The FDA stressed that it has not concluded that these increase the risk for esophageal cancer, and that it believes their ability to lower the risk for fractures in patients with osteoporosis outweighs their potential risks.

FDA.gov, July 21, 2011

TCADs Safer Than SSRIs in Older Patients?

- A population-based cohort study in the UK published online in the August 2, 2011 British Medical Journal showed significant associations between the use of antidepressants and adverse outcomes, including falls, stroke, seizures, and all-cause mortality in elderly people with depression.

- Patients prescribed SSRIs fared worse than those receiving the older tricyclic antidepressants.

BMJ. Published online August 2, 2011
Valproic acid (Depakene®, Stavzor®) and Divalproex (Depakote®); I.V. Depacon®: Lower IQ in Pregnancy

- June 2011, FDA issued a safety announcement to underline the increased risk for lower cognitive test scores among children born to mothers taking valproate sodium or the related products valproic acid and divalproex sodium during pregnancy, relative to other antiepileptic medications.

FDA.gov, June 30, 2011

High Dose Fluconazole (Diflucan®) and Birth Defects

- The FDA has warned that chronic use of fluconazole (Diflucan®) in high doses (400 - 800 mg/day) during the first trimester of pregnancy may be associated with certain birth defects in infants.
  - The risk does not appear to be associated with a single, low dose of fluconazole (150 mg) used to treat vaginal candidiasis.

FDA.gov, August 3, 2011
Cardiovascular Risk Associated with Inhaled Anticholinergic Agents?

In 2010, the FDA announced that it completed a safety review of Spiriva® (tiotropium), determining that "available data do not support an association" between the use of this drug and an increased risk of stroke, heart attack or death due to cardiovascular causes.

Cardiovascular Risk Associated with Inhaled Anticholinergic Agents?

However, in 2011, a meta-analysis the British Medical Journal concluded that tiotropium was associated with a 52% increase in the risk of mortality, compared with COPD patients given only a placebo.

Better Outcomes When Limiting OTC Cough Cold Medicines in Kids

- New evidence verifies the benefit of limiting OTC cough/cold medicines in children.
  - The infant versions are no longer marketed, and the remaining children's products are no longer labeled for children under age 4 or 6.
  - A new report suggests this is making a big difference.
  - ER visits related to cold medicines in children under age 2 are half what they were before the changes 3 years ago.

Pharmacist's Letter, January 2011

PPIs Linked to Fractures

- The FDA warned consumers and healthcare professionals that PPIs may be associated with an increased risk of fractures and updated the drugs labeling to reflect these risks.
- While the agency noted that this risk was observed "with the use of PPIs for one year or longer, or at high doses," it opted to add the warning to all PPIs.

FDA.gov, May 25, 2010
PPIs Decrease Magnesium Levels

- Long-term use of prescription PPIs can be associated with hypomagnesemia, which can in turn cause serious muscle spasms (tetany), arrhythmias, and seizures, but may instead be asymptomatic.
- A baseline magnesium level and periodic monitoring is recommended.

FDA.gov, March 2, 2011

Less Use of Drugs for Colds in Kids = Less Problems

- A study at the University of Maryland has revealed a 46% drop in reported “therapeutic errors” after drugmakers in October 2007 removed from the market a number of OTC cough and cold medications labeled for children under the age of 2.

Beta-Blocker Eye Drops and Systemic Effects

- Ophthalmic administration of beta-blocker eye drops can result in significant blood levels. One drop of timolol (Timoptic®, Betimol®, Istaol®) 0.5% in each eye equals about 10 mg orally.
- This can cause bronchoconstriction in some patients with asthma or COPD, and arrhythmias or heart failure in some cardiac patients.
- Betaxolol (Betoptic®) is less likely to cause problems in patients with stable COPD, but is still contraindicated.

Pharmacist’s Letter, March 2010

5-α-Reductase Inhibitors Finasteride (Proscar®), Dutasteride (Avodart®) and Prostate Cancer

- 5-ARIs are used off-label as a preventative for men who are at high risk of developing prostate cancer.
  - And they do show a reduction in all types of prostate cancers.
- But in 2011 the FDA warned of a link between the 5-ARIs and an 1.3% absolute risk of high-grade aggressive prostate cancer.

FDA.gov, June 9, 2011
FDA Adds Risk for Severe Liver Injury to Orlistat Label

- In May 2010, the FDA required a revised label for orlistat (Xenical®, Alli®) to include new safety information about rare cases of severe liver injury.
- Signals of significant liver damage did not emerge in preclinical or clinical trials.
  - However, the FDA identified 13 postmarketing cases of severe liver injury — 12 of them foreign cases involving Xenical® and the other a US case involving Alli®.
  - Some patients died or needed a liver transplant.

FDA.gov, May 26, 2010

Not Just Liver, Kidney Damage Reported with Orlistat

- A Canadian study showed a 2% increase in acute kidney injuries within one year of patients starting orlistat (Xenical®, Alli®).

Archives of Internal Medicine, April 12, 2011
Questions?