Pharmacology A

New Drugs For The Primary Care Provider (Including Drugs For Obesity)

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University of Colorado
Anschutz Medical Campus
Sir William Osler

New Drugs:

“Use them while they are still safe”
Timing of Black Box Warnings and Withdrawals for Prescription Medications

• FDA approved drugs between 1975-1999

• 548 new chemical entities approved
  – 81 (14.8%) major changes to drug labeling
  – 45 (8.2%) acquired ≥1 black-box warning(s)
    – Half within the first 7 years
  – 16 (2.9%) were withdrawn from the market
    – Half within the first 2 years

• 20% probability of withdrawal or new black-box warning over 25 years

JAMA 2002;287(17):2215-2220.
<table>
<thead>
<tr>
<th>Drug: Brand (generic)</th>
<th>Approval</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trulicity (dulaglutide)</td>
<td>September</td>
<td>GLP-1 agonist for type 2 DM</td>
</tr>
<tr>
<td>Belsomra (suvorexant)</td>
<td>August</td>
<td>Orexin antagonist for insomnia (both falling a staying asleep)</td>
</tr>
<tr>
<td>Jardiance (empagliflozin)</td>
<td>August</td>
<td>SGLT-2 inhibitor for type 2 DM</td>
</tr>
<tr>
<td>Striverdi Respimat (olodaterol)</td>
<td>July</td>
<td>Once daily LABA for COPD</td>
</tr>
<tr>
<td>Kerydin (tavaborole)</td>
<td>July</td>
<td>Topical treatment of onychomycosis</td>
</tr>
<tr>
<td>Jublia (efinaconazole)</td>
<td>June</td>
<td>Topical treatment of onychomycosis</td>
</tr>
<tr>
<td>Zontivity (vorapaxar)</td>
<td>May</td>
<td>Reduce risk of heart attack, stroke in high-risk</td>
</tr>
<tr>
<td>Tanzeum (albiglutide)</td>
<td>April</td>
<td>GLP-1 agonist for type 2 DM</td>
</tr>
<tr>
<td>Farxiga (dapagliflozin)</td>
<td>January</td>
<td>SGLT-2 inhibitor for type 2 DM</td>
</tr>
</tbody>
</table>

Targets of Common DM Drugs

- **Glucose level decrease**
  - **Pancreas**
    - Beta-cell dysfunction
  - **Gut**
    - Alpha-glucosidase inhibitors
    - Reduced glucose absorption
    - DPP-4 inhibitors & Incretin mimetics
  - **Liver**
    - Hepatic glucose overproduction
  - **Muscle and fat**
    - Insulin resistance
  - **Biguanide**
  - **TZDs**
  - DPP-4 inhibitors & Incretin mimetics

References:
## Comparison of Diabetes Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>A1C Reduction</th>
<th>Severe Hypoglycemia</th>
<th>Weight Change</th>
<th>Daily Dosing Frequency</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5</td>
<td>No</td>
<td>Neutral</td>
<td>1-2</td>
<td>Oral</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5-1.4</td>
<td>No</td>
<td>Gain</td>
<td>1</td>
<td>Oral</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>1.5-2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1-2</td>
<td>SC</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1-2</td>
<td>Oral</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>0.5-1.5</td>
<td>Yes</td>
<td>Gain</td>
<td>3</td>
<td>Oral</td>
</tr>
<tr>
<td>Glucosidase Inhibitors</td>
<td>0.5-1.0</td>
<td>No</td>
<td>Neutral</td>
<td>3</td>
<td>Oral</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>0.6-0.8</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>Oral</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>0.5-1.5</td>
<td>No</td>
<td>Loss</td>
<td>1-2</td>
<td>SC</td>
</tr>
<tr>
<td>Prandial Insulin</td>
<td>1.5-2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>2-4</td>
<td>SC</td>
</tr>
</tbody>
</table>
Incretin Hormones

• GI hormones that cause and increase in the amount of insulin released from beta cells after eating
  – GLP-1 (glucagon-like peptide-1)
    – Increases insulin release
    – Suppresses glucagon
  – GIP (glucose-dependent insulinotropic polypeptide)
    – Increases insulin release

• Mechanism of action for GLP-1 agonists
  – Delayed gastric emptying and decreased glucagon secretion
  – Increased satiety and glucose-dependent insulin secretion
# GLP-1 agonists

<table>
<thead>
<tr>
<th>Dosing</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dulaglutide</strong> (Trulicity)</td>
<td>Single-use pens dosed as 0.75-1.5mg once <strong>weekly</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Liraglutide</strong> (Victoza)</td>
<td>One pen which expires after 30 days; Dosed at 0.6mg daily for 1 week, 1.2mg daily for 1 week, then 1.8mg daily</td>
<td></td>
</tr>
<tr>
<td><strong>Exenatide</strong> (Byetta or Bydureon)</td>
<td>Byetta: 5 or 10mcg (must titrate dose) Bydureon 2mg weekly</td>
<td></td>
</tr>
<tr>
<td><strong>Albiglutide</strong> (Tanzeum)</td>
<td>30mg weekly and titrated to 50mg <strong>weekly</strong></td>
<td></td>
</tr>
</tbody>
</table>

- All will lower A1c by 1-2%, have a low-risk of hypoglycemia, cause 3-5 kg of weight loss, and have a high cost
Dulaglutide (Trulicity)

• No pricing available

• Dulaglutide has been studied as monotherapy and in combination with metformin and pioglitazone:
  – The efficacy of dulaglutide has been studied against placebo, metformin and sitagliptin
  – In patients with type 2 diabetes mellitus, dulaglutide produced statistically relevant reductions in HbA1c
  – At 26 weeks, changes from baseline HbA1c were dulaglutide 1.5mg, -0.78±0.06%, dulaglutide 0.75mg, -0.71±0.06%
Albiglutide (Tanzeum™)

• 4 doses (1 month of therapy) = $325.96

• Albiglutide has been studied as monotherapy and in combination with metformin, metformin and a sulfonylurea, a thiazolidinedione and insulin glargine.
  – The efficacy of albiglutide was compared with placebo, glimepiride, pioglitazone, liraglutide, sitagliptin, insulin lispro, and insulin glargine
  – In patients with type 2 diabetes mellitus, albiglutide produced clinically relevant reduction from baseline in HbA1c compared with placebo
  – Albiglutide 30mg reduced HbA1c -0.7% from baseline and albiglutide 50mg reduced HbA1c -0.9% from baseline
  – No overall differences in glycemic effectiveness or body weight were observed across demographic subgroups.
SGLT-2 inhibitors

- Inhibit the sodium-glucose transporter 2 promotes the renal excretion of glucose resulting in osmotic diuresis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Renal adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>100mg, 300mg</td>
<td>GFR 45-60, max of 100mg daily GFR &lt; 45, do not use</td>
</tr>
<tr>
<td>(Invokana)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>5mg, 10mg</td>
<td>GFR &lt; 60, do not use</td>
</tr>
<tr>
<td>(Farxiga)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10mg, 25mg</td>
<td>GFR &lt; 45, do not use</td>
</tr>
<tr>
<td>(Jardiance)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- All will lower A1c by 0.8 to 1%, have a low-risk of hypoglycemia, cause 3-5 kg of weight loss, and high cost

- Side effects include UTI, genital mycotic infections and orthostatic hypotension
Canagliflozin (Invokana®)

• 30 tablets = $374.46

• Dapagliflozin has been studied as monotherapy and in combination with metformin, pioglitazone, glimepiride, sitagliptin and insulin
  – The efficacy of dapagliflozin was compared to glipizide added on to metformin and has also been studied in patients with type 2 diabetes and moderate renal impairment
  – Treatment with dapagliflozin as monotherapy and in combination produced statistically significant improvements in mean change from baseline at week 24 in HbA1c compared to control
  – Dapagliflozin 10mg reduced HbA1c -0.9% from baseline and dapagliflozin 5mg -0.8%. Reductions in HbA1c were seen across subgroups including gender, age, race, duration of disease, and baseline BMI
Empagliflozin (Jardiance®)

• 30 tablets = $361.06

• Empagliflozin has been studied as monotherapy and in combination with metformin, sulfonylurea, pioglitazone and insulin; It has also been studied in patients with type 2 diabetes with mild or moderate renal impairment
  – In patients with type 2 diabetes, treatment with empagliflozin reduced hemoglobin HbA1c, compared to placebo
  – Empagliflozin 10mg reduced HbA1c -0.7% from baseline and empagliflozin 25mg reduced HbA1c -0.8% from baseline
  – The reduction in HbA1c for empagliflozin compared with placebo was observed across subgroups including gender, race, geographic region, baseline BMI and duration of disease
Where do these drugs fit?

Monotherapy

**Metformin**

2- Drug Combo

- SU
- TZD
- DPP-4 Inhibitor
- GLP-1 Agonist
- Insulin
  (SGLT-2 Inhibitor?)

3-Drug Combo

- Any combo except:
  - DPP-4 + GLP-1
  - Insulin + SU
- OR: basal-bolus insulin
Zontivity (Vorapaxar™)

- FDA-approved (May 8, 2014) for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD).

- Manufacturer
  - Merck & Co., Inc.

- Mechanism of action
  - It is a reversible antagonist of the protease-activated receptor-1 (PAR-1) expressed on platelets, but its long half-life makes it effectively irreversible. It inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP) induced platelet aggregation.
Vorapaxar (Zontivity™)

- Approved dosing
  - 2.08 mg tablets
  - Starting dose: 2.08 mg orally once daily, with or without food
  - Used as an addition to aspirin and/or clopidogrel according to their indications or standard of care
  - Renal adjustment:
    - No dose adjustment is required
  - Hepatic impairment:
    - No dose adjustment in mild or moderate impairment
    - Not recommended in patients with severe impairment
Warnings and Precautions

• Black Box Warning
  – Antiplatelet agents, increase the risk of bleeding, including ICH and fatal bleeding. Do not use in patients with active pathological bleeding or a history of stroke, TIA or ICH

• Warnings
  – Vorapaxar increases the risk of bleeding in proportion to a patient’s underlying risk
  – Risk factors include: older age, low body weight, reduced renal or hepatic function, history of bleeding disorders and use of certain concomitant medications (anticoagulants, fibrinolytic therapy, chronic nonsteroidal anti-inflammatory drugs (NSAIDS), SSRIs, SNRIs)
  – Avoid the use with warfarin
Vorapaxar (Zontivity™)

- Side effects (> 2%)
  - Anemia, depression, rashes, eruptions and exanthemas
- Drug interactions
  - Strong CYP3A Inhibitors
  - Strong CYP3A Inducers
  - Warfarin
  - Prasugrel
  - Cost: AWP = $267/mo (RedBook Online®)

- Special populations
  - Geriatrics: relative risk of bleeding was similar across age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients
  - Hepatic impairment: based on the inherent risk of bleeding in patients with severe hepatic impairment, vorapaxar is not recommended in such patients
Vorapaxar (Zontivity™) median follow-up was 2.5 years (up to 4)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (n=13,224)</th>
<th>Zontivity (n=13,225)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with events (%)</td>
<td>K-M %</td>
<td>Patients with events (%)</td>
<td>K-M %</td>
</tr>
<tr>
<td>Primary Composite Efficacy Endpoint (CV death/MI/stroke/UCR)</td>
<td>1417</td>
<td>12.4%</td>
<td>1259</td>
<td>11.2%</td>
</tr>
<tr>
<td>Secondary Composite Efficacy Endpoint (CV death/MI/stroke)</td>
<td>1176</td>
<td>10.5%</td>
<td>1028</td>
<td>9.3%</td>
</tr>
</tbody>
</table>
## Vorapaxar (Zontivity™)
Post-MI or PAD patients without prior stroke or TIA

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<th>Placebo (n=13,224)</th>
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<td></td>
<td>Patients with events (%)</td>
<td>K-M %</td>
<td>Patients with events (%)</td>
<td>K-M %</td>
</tr>
<tr>
<td>Primary Composite Efficacy Endpoint (CV death/MI/stroke/UCR)</td>
<td>1073 (10.6%)</td>
<td>11.8%</td>
<td>896 (8.9%)</td>
<td>10.1%</td>
</tr>
<tr>
<td>Secondary Composite Efficacy Endpoint (CV death/MI/stroke)</td>
<td>851 (8.4%)</td>
<td>9.5%</td>
<td>688 (6.8%)</td>
<td>7.9%</td>
</tr>
</tbody>
</table>
Vorapaxar (Zontivity™)

- Conclusions
  - The addition of vorapaxar to standard therapy reduced the risk of cardiovascular death, myocardial infarction, or stroke among patients with stable atherosclerosis.
  - The benefit of this therapy was most apparent in patients with a history of myocardial infarction.
  - Vorapaxar also increased the risk of moderate or severe bleeding, including intracranial hemorrhage.
    - Intracranial hemorrhage occurring most frequently in patients with a history of stroke.
Belsomra (Suvorexant™)

• FDA-approved (August 13, 2014) to treat difficulty in falling and staying asleep (insomnia).

• Manufacturer
  – Merck & Co., Inc.

• Mechanism of action
  – The mechanism by which suvorexant exerts its therapeutic effect in insomnia is presumed to be through antagonism of orexin receptors. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1r and OX2R is thought to suppress wake drive
Belsomra (Suvorexant™)

• Schedule IV drug
  – Due to the ability of suvorexant to be abused or lead to dependence, the DEA placed the new drug on the controlled substance list

• Cost
  – AWP = Unknown
    – (RedBook Online®)
Belsomra (Suvorexant™)

• Approved dosing
  – Use the lowest dose effective for patient
  – Recommended dose is 10 mg, no more than once per night taken within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening
  – If 10 mg dose is well-tolerated but not effective, the does can be increased, not to exceed 20 mg once daily
  – Time to effect may be delayed if taken with or soon after a meal
  – Renal adjustment:
    – No dose adjustment is required
  – Hepatic impairment:
    – No dose adjustment in mild or moderate impairment
    – Not recommended in patients with severe impairment
Belsomra (Suvorexant™)

• Contraindications: patient with narcolepsy

• Warnings and Precautions
  – CNS depressant effects and daytime impairment
  – Need to evaluate for co-morbid diagnoses
  – Abnormal thinking and behavioral changes
  – Worsening of depression/suicidal ideation
  – Patients with compromised respiratory function
  – Sleep paralysis, hypnagogic/hypnopompic hallucinations, cataplexy-like symptoms
Belsomra (Suvorexant™)

• Drug interactions
  – Inhibitors of CYP3A
    – Recommended dose is 5 mg when used with moderate CYP3A inhibitors. Can be increased to 10 mg once daily if the 5 mg dose is not effective.
  – Strong CYP3A inhibitors
    – Not recommended for use in patients taking strong CYP3A inhibitors, efficacy may be reduced
  – Digoxin
    – Monitor digoxin concentrations

• Adverse effects
  – CNS depressant effects and daytime impairment, abnormal thinking and behavioral changes, worsening of depression/suicidal ideation and sleep paralysis
Efficacy of Belsomra™

• In two studies, the efficacy was determined to be superior to placebo for sleep latency and sleep maintenance as assessed both objectively by polysomnography and subjectively by patient-estimated sleep latency and total sleep time

• In both studies, non-elderly (age 18-64) and elderly (age > 65) were randomized separately. The non-elderly were treated with 20 mg or placebo and the elderly patients were treated with 15 mg or placebo
Where does Belsomra™ fit?

• By exploiting the mechanism of antagonizing orexin receptors will allow some patients that had poor efficacy or adverse effects an alternative, instead of another version of a benzodiazepine.
Other New “Me-too” Medications

- **Tasimelton (Hetlioz®) for insomnia**
  - Similar to ramelteon and they both exert their actions as agonists for melatonin MT1 and MT2 receptors.
  - 30 doses = $8,423.10 !

- **Olodaterol (Striverdi RESPIMAT®) for COPD**
  - Similar to Combivent Respimat but only once daily.
  - 4 gm = $184.84

- **Naloxegol (Movantik™) for opioid-induced constipation**
  - PEGylated derivative of naloxone with local intestinal effects

- **Diclofenac (Dyloject™) Injection for pain**
  - Similar to ketorolac
Novel Oral Anticoagulants (NOACs)

- XIIa
- Xla
- IXa
- Vlla
- Tissue factor

**Pathway:**
- Xla → IXa → Xa → II → IIa (thrombin)

**Drugs:**
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

**Reactions:**
- Fibrinogen → Fibrin
New Indications for NOACs

• Apixaban (Eliquis®)
  – Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)
  – Reduce the risk of blood clots following hip or knee replacement surgery

• Dabigatran etexilate (Pradaxa®)
  – Deep vein thrombosis (DVT) and pulmonary embolism (PE)

Comparison of NOACs: Indications, renal adjustment and use, warfarin switching protocols (see table)
New Indications

• Esomeprazole (Nexium®)
  – Available over-the-counter

• Tiotropium bromide (Spiriva Respimat®) inhalation spray
  – Handheld device delivering a slow-moving, soft mist that allows gentle and pleasant inhalation

• Liraglutide (Saxenda®)
  – New approval for chronic weight management at higher dose of 3mg daily, compared to type 2 DM indication
## Medications for Obesity

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Lorcaserin</th>
<th>Phentermine and topiramate</th>
<th>Naltrexone and bupropion</th>
</tr>
</thead>
<tbody>
<tr>
<td>US brand name</td>
<td>Belviq</td>
<td>Qsymia</td>
<td>Contrave</td>
</tr>
<tr>
<td>Initial US approval</td>
<td>2012</td>
<td>2012</td>
<td>2014</td>
</tr>
<tr>
<td>DEA schedule*</td>
<td>IV</td>
<td>IV</td>
<td>NA</td>
</tr>
</tbody>
</table>

# Medications for Obesity

<table>
<thead>
<tr>
<th></th>
<th>Lorcaserin (Belviq®)</th>
<th>Phentermine and topiramate (Qsymia®)</th>
<th>Naltrexone and bupropion (Contrave®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial approval</td>
<td>2012</td>
<td>2012</td>
<td>2014</td>
</tr>
<tr>
<td>DEA schedule</td>
<td>IV</td>
<td>IV</td>
<td>NA</td>
</tr>
<tr>
<td>Classification</td>
<td>Serotonin 2C receptor agonist</td>
<td>Sympathomimetic amine anorectic, with extended-release antiepileptic</td>
<td>Opioid antagonist with an aminoketone antidepressant</td>
</tr>
<tr>
<td>Indications</td>
<td>• Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index of ≥ 30 kg/m² (obese), or ≥ 27 kg/m² (overweight) in the presence of ≥ 1 weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Medications for Obesity

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Lorcaserin (Belviq®)</th>
<th>Phentermine and topiramate (Qsymia®)</th>
<th>Naltrexone and bupropion (Contrave®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Pregnancy; glaucoma; hyperthyroidism; during or within 14 days of taking MAOIs; idiosyncrasy to sympathomimetic amines</td>
<td>Pregnancy; uncontrolled hypertension; seizure disorders, anorexia nervosa or bulimia, or abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs; chronic opioid use; during or within 14 days of taking MAOIs</td>
<td></td>
</tr>
<tr>
<td>Boxed Warning</td>
<td>none</td>
<td>none</td>
<td>Suicidal thoughts and behaviors; neuropsychiatric reactions</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Several with all</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Medications for Obesity

<table>
<thead>
<tr>
<th></th>
<th>Lorcaserin (Belviq®)</th>
<th>Phentermine and topiramate (Qsymia®)</th>
<th>Naltrexone and bupropion (Contrave®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>10 mg twice daily; discontinue if 5% weight loss is not achieved by week 12</td>
<td>3.75 mg/23 mg daily in AM for 14 days, 7.5 mg/46 mg daily in AM; stop or increase if 3% weight loss not achieved after 12 weeks. Stop if 5% weight loss not achieved after 12 weeks on 15 mg/92 mg extended-release tablets of 8 mg/90 mg, titration schedule: week 1 – one in AM, none in PM; week 2 – one in AM and 1 in PM; week 3 – two in AM 1 in PM; week 4 – 2 in AM and 2 in PM.</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse effects (≥ 5%)</strong></td>
<td>Headache, dizziness, nausea, dry mouth, fatigue, constipation, hypoglycemia (in diabetes)</td>
<td>Paraesthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth</td>
<td>Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea</td>
</tr>
</tbody>
</table>

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Cleveland Clinic

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DOS Course 2015
## Medications for Obesity – Overall Efficacy

<table>
<thead>
<tr>
<th></th>
<th>% of patients losing ( \geq 5% ) body weight</th>
<th>% of patients losing ( \geq 10% ) body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lorcaserin</strong> 10 mg twice daily</td>
<td>Active: 46.4</td>
<td>Placebo: 22.1</td>
</tr>
<tr>
<td></td>
<td>Phentermine and topiramate 15 mg/92 mg</td>
<td>69.0</td>
</tr>
<tr>
<td></td>
<td>Naltrexone and bupropion 16 mg/180 mg twice daily</td>
<td>46.6</td>
</tr>
</tbody>
</table>

Medications for Obesity

Bottom line

• Efficacy is better than placebo, but…

• Several cautions and risks with all medications

• Incidence of adverse effects limits treatment for many patients

• Lifestyle modifications is still the cornerstone of therapy and is included in all clinical trials demonstrating efficacy

• Data evaluating long-term benefits, risks and adherence are still evolving
Every life deserves world class care.
Pharmacology B

Critical Caveats For Common Medications
(Pharmacology Potpourri)

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Department of Clinical Pharmacy and Department of Family Medicine
University of Colorado
Anschutz Medical Campus

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Cardiovascular
Updated Hypertension Guidelines

Tuesday December 17, 2013

Clinical Practice Guidelines for the Management of Hypertension in the Community

A Statement by the American Society of Hypertension (ASH) and the International Society of Hypertension (ISH)

Wednesday December 18, 2013

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

J Hypertens 2014 Jan;32(1):3-15
Hypertension/Blood Pressure

• Goals
  – <140/90 mmHg (A)
  – Systolic BP <130 mm Hg (C) or diastolic BP < 80 mm Hg (B), may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden

• Treatment
  – ACE inhibitor or an ARB (B)
  – Multiple-drug therapy (including a thiazide diuretic and ACE inhibitor/ARB, at maximal doses) is generally required to achieve BP targets (B)
Ongoing Telmisartan Alone and in Combination With Ramipril (ONTARGET)

- 25,620 patients
- Randomized, double-blind trial
- Combination vs. ramipril:
  - Hypotension: 4.8 vs. 1.7% (p<0.001)
  - Renal dysfunction: 13.5 vs. 10.2% (p<0.001)

Antihypertensive Use in Patients with Resistant Hypertension Prescribed 4 or More Agents

- 140,126 patients hypertension on ≥4 antihypertensive agents between May 1, 2008 and June 30, 2009

Hypertension. 2011;58:1008-1013
Combined Angiotensin Inhibition for Diabetic Nephropathy (NEPHRON-D)

- Double blind, controlled trial in 1448 patients with type 2 diabetes, a urinary albumin-to-creatinine ratio of ≥ 300 mg:g, and an eGFR of 30.0 to 89.9 mL/min/1.73m²
- All patients were treated with losartan 100 mg daily, then randomized to:
  - Placebo, or
  - Lisinopril Losartan 10-40 mg daily
- Primary Endpoint: change in eGFR, end-stage renal disease or death
- Stopped early at 2.2 median years due to safety:
  - Significantly increased risk of hyperkalemia and acute kidney injury with combination losartan + lisinopril
  - No difference in the primary or secondary efficacy endpoints

Co-trimoxazole and Sudden Death in Patients Receiving Inhibitors of Renin-Angiotensin System: Population Based Study

- Population based nested case-control study of patients age > 66 years treated with an ACE inhibitor or ARB

- Cases died (n=39,879) suddenly shortly after receiving an outpatient prescription for one of co-trimoxazole, amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin

- Relative to amoxicillin, co-trimoxazole was associated with an increased risk of sudden death:
  - Adjusted OR = 1.38 (1.09 to 1.76)
  - Unrecognized severe hyperkalemia suspected as the underlying cause

BMJ 2014;349: doi 10.1136/bmj.g6196
ACC/AHA Four ASCVD Statin Benefit Groups

Clinical ASCVD
- High-intensity statin if age ≤75 y
- Moderate-intensity statin if age > 75 y or not candidate for high-intensity

LDL-C ≥190 mg/dL
- High-intensity statin

Diabetes
- Type 1 or 2
- Age 40-75 y
- Moderate-intensity statin
- High-intensity statin if 10-y ASCVD risk ≥7.5%

≥7.5% estimated 10-y ASCVD risk and age 40-75 y
- Moderate-to-High Intensity Statin

Circulation. 2014;129[suppl 2]:S1-S45
### Secondary Prevention - High-intensity statin, all ages (A)

### Primary Prevention

#### CVD risk factors:
- LDL-C ≥100 mg/dL
- Hypertension
- Smoking
- Overweight/obesity

<table>
<thead>
<tr>
<th>Ages (yrs)</th>
<th>No CVD risk factors</th>
<th>With CVD risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>No statin</td>
<td>Moderate to high-intensity statin (C)</td>
</tr>
<tr>
<td>40-75</td>
<td>Moderate-intensity statin (A)</td>
<td>High-intensity statin (B)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>Moderate-intensity statin (B)</td>
<td>Moderate to high-intensity statin (B)</td>
</tr>
</tbody>
</table>

All in addition to lifestyle therapy

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American Diabetes Association, Diabetes Care 2015;38 (suppl 1):s49-s57.
Nonstatin Drug Recommendations

ACC/AHA

• No data supporting routine use of nonstatin drugs combined with a statin to further reduce ASCVD events

• If completely statin intolerant, reasonable to use nonstatin drugs shown to reduce ASCVD events in RCTs

ADA

• Statin/fibrate and statin/niacin not shown to provide benefit above statin alone and is generally not recommended

NLA

• In addition to statins to achieve targets or in place of a statin if contraindications or statin intolerance

Circulation. 2014;129[suppl 2]:S1-S45
Journal of Clinical Lipidology 2014;8;473-488.
IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)

- Double-blind trial in 18,144 patients with an acute coronary syndrome, age ≥50 years with a high CV risk feature, and LDL-C 50-125 mg/dL (50-100 if on lipid-lowering therapy)

- Randomized to simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg for 4.9 years

- Primary endpoint: CV death, MI, hospital admission for unstable angina, coronary revascularization, or stroke

- Mean LDL-C values
  - Simvastatin alone 69.9 mg/dL
  - Ezetimibe /simvastatin 53.2 mg/dL

Presented at the American Heart Association Meeting, November 17, 2014
IMPROVE-IT: Results

Simvastatin — 34.7%
2742 events

Ezetimibe/Simvastatin — 32.7%
2572 events

p=0.016

- Several questions remain
- Not yet published

7-year event rates

Presented at the American Heart Association Meeting, November 17, 2014
Increased Adverse-Event Risk With Clarithromycin Plus Some Statins

- Population-based cohort of older adults taking rosuvastatin, pravastatin, fluvastatin; newly prescribed clarithromycin (n = 51,523) or azithromycin (n = 52,518)

<table>
<thead>
<tr>
<th>30-day Adverse Event</th>
<th>Clarithromycin (# Events)</th>
<th>Azithromycin (# Events)</th>
<th>Absolute Risk Difference (%)</th>
<th>Adj RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for rhabdomyolysis</td>
<td>13</td>
<td>6</td>
<td>0.02</td>
<td>2.27 (0.86–5.96)</td>
</tr>
<tr>
<td>Hospitalization for acute kidney injury</td>
<td>175</td>
<td>122</td>
<td>0.11</td>
<td>1.65 (1.31–2.09)</td>
</tr>
<tr>
<td>Hospitalization for hyperkalemia</td>
<td>33</td>
<td>18</td>
<td>0.03</td>
<td>2.17 (1.22–3.86)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>200</td>
<td>155</td>
<td>0.09</td>
<td>1.43 (1.15–1.76)</td>
</tr>
</tbody>
</table>

- Interaction is not inhibition of CYP3A4; rather; inhibition of OATP1B1 and OATP1B3)
FDA Ruling on Aspirin

2003

• Petition sought by Bayer Corp. for reduction in risk of first MI in moderate risk patients (10-year CHD risk ≥10%)
  – 11 votes against, 3 for approval
  – Data from 5 major clinical trials was considered
  – Despite other organizations advocating benefits outweighing risks, the FDA was skeptical
# Summary of Primary Prevention Trials

<table>
<thead>
<tr>
<th></th>
<th>BMD</th>
<th>PHS</th>
<th>TPT</th>
<th>HOT</th>
<th>PPP</th>
<th>WHS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Men (Physicians)</td>
<td>Men (Physicians)</td>
<td>Men with high CV risk</td>
<td>Men &amp; Women with hypertension</td>
<td>Men &amp; Women with &gt;1 CV risk factor</td>
<td>Women (Health Professionals)</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>5,139</td>
<td>22,071</td>
<td>5,085</td>
<td>18,790</td>
<td>4,495</td>
<td>39,876</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>&lt;60 (47%) 60-69 (39%) 70-79 (14%)</td>
<td>Mean 53 (range 40-84)</td>
<td>Mean 57.5 (range 45-69)</td>
<td>Mean 61.5 (range 50-80)</td>
<td>&lt;60 (29%) 60-69 (45%) 70-79 (24%)</td>
<td>Mean 54.6 45-54 (60%) 55-64 (30%) ≥ 65 (10%)</td>
</tr>
<tr>
<td><strong>Duration (yrs)</strong></td>
<td>5.8</td>
<td>5</td>
<td>6.8</td>
<td>3.8</td>
<td>3.6</td>
<td>10.1</td>
</tr>
<tr>
<td><strong>Aspirin dose</strong></td>
<td>500 mg/day</td>
<td>325 mg every other day</td>
<td>75 mg/day</td>
<td>75 mg/day</td>
<td>100 mg/day</td>
<td>100 mg every other day</td>
</tr>
<tr>
<td><strong>Placebo Control</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>Open-label</td>
<td>Double-blind</td>
<td>Double-blind</td>
<td>Double-blind</td>
<td>Open-label</td>
<td>Double-blind</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Fair</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Fair</td>
<td>Good</td>
</tr>
</tbody>
</table>

BMD, British Male Doctors’ trial; HOT, Hypertension Optimal Treatment trial; PHS, Physicians’ Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial; WHS, Women’s Health Study.
Aspirin in Primary Prevention
Antithrombotic Trialists’ (ATT) Collaboration Meta-Analysis


RR: 0.82
(0.75-0.90)

RR: 0.86
(0.74-1.00)

RR: 0.97
(0.87-1.09)

RR: 1.32
(1.00-1.75)
Aspirin in Primary Prevention
Antithrombotic Trialists’ (ATT) Collaboration
Meta-Analysis

Major Coronary Event

<table>
<thead>
<tr>
<th>Gender</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.57</td>
<td>0.72</td>
</tr>
<tr>
<td>Women</td>
<td>0.14</td>
<td>0.14</td>
</tr>
</tbody>
</table>

P < 0.05

Ischemic Stroke

<table>
<thead>
<tr>
<th>Gender</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>Women</td>
<td>0.09</td>
<td>0.11</td>
</tr>
</tbody>
</table>

P < 0.05

# Aspirin for the Prevention of Cardiovascular Disease

## Clinical Summary of U.S. Preventive Services Task Force Recommendation

<table>
<thead>
<tr>
<th>Population</th>
<th>Men Age 45-79 Years</th>
<th>Women Age 55-79 Years</th>
<th>Men Age &lt; 45 Years</th>
<th>Women Age &lt; 55 Years</th>
<th>Men &amp; Women Age ≥ 80 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td>Encourage aspirin use when potential CVD benefit (MI prevented) outweighs potential harm of GI hemorrhage</td>
<td>Encourage aspirin use when potential CVD benefit (strokes prevented) outweighs potential harm of GI hemorrhage</td>
<td>Do not encourage aspirin use for MI prevention</td>
<td>Do not encourage aspirin use for stroke prevention</td>
<td>No Recommendation</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td><strong>A</strong></td>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### How to Use This Recommendation

Shared decision making is strongly encouraged with individuals whose risk is close to (either above or below) the estimates of 10-year risk levels indicated below. As the potential CVD benefit increases above harms, the recommendation to take aspirin should become stronger.

To determine whether the potential benefit of MIs prevented (men) and strokes prevented (women) outweighs the potential harm of increased GI hemorrhage, both 10-year CVD risk and age must be considered.

<table>
<thead>
<tr>
<th>Risk level at which CVD events prevented (benefit) exceeds GI harms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
</tr>
<tr>
<td>Age 45 – 59 years</td>
</tr>
<tr>
<td>&lt; 4%</td>
</tr>
<tr>
<td>Age 60 – 69 years</td>
</tr>
<tr>
<td>&lt; 6%</td>
</tr>
<tr>
<td>Age 70 – 79 years</td>
</tr>
<tr>
<td>&lt; 12%</td>
</tr>
<tr>
<td><strong>Women</strong></td>
</tr>
<tr>
<td>Age 55 – 59 years</td>
</tr>
<tr>
<td>&gt; 3%</td>
</tr>
<tr>
<td>Age 60 – 69 years</td>
</tr>
<tr>
<td>&gt; 8%</td>
</tr>
<tr>
<td>Age 70 – 79 years</td>
</tr>
<tr>
<td>&gt; 11%</td>
</tr>
</tbody>
</table>

The table above applies to adults who are not taking NSAIDs and who do not have upper GI pain or a history of GI ulcers. NSAID use and history of GI ulcers raise the risk of serious GI bleeding considerably and should be considered in determining the balance of benefits and harms. NSAID use combined with aspirin use approximately quadruples the risk of serious GI bleeding compared to the risk with aspirin use alone. The rate of serious bleeding in aspirin users is approximately 2 – 3 times higher in patients with a history of GI ulcers.

### Risk Assessment

For **MEN**: Risk factors for CHD include age, diabetes, total cholesterol level, HDL level, blood pressure, and smoking.

CHD risk estimation tool: [http://healthlink.mcw.edu/article/923521437.html](http://healthlink.mcw.edu/article/923521437.html)

For **WOMEN**: Risk factors for ischemic stroke include age, high blood pressure, diabetes, smoking, history of CVD, atrial fibrillation, and left ventricular hypertrophy.

Stroke risk estimation tool: [http://www.westenstroke/PersonalStrokeRisk1.xls](http://www.westenstroke/PersonalStrokeRisk1.xls)

### Relevant Recommendations from the USPSTF

The USPSTF has made recommendations on screening for abdominal aortic aneurysm, carotid artery stenosis, coronary heart disease, high blood pressure, lipid disorders, and peripheral arterial disease. These recommendations are available at [www.preventiveservices.ahrq.gov](http://www.preventiveservices.ahrq.gov).

For the full recommendation statement and supporting documents, please go to: [www.preventiveservices.ahrq.gov](http://www.preventiveservices.ahrq.gov). **Abbreviations**: CHD = coronary heart disease, CVD = cardiovascular disease, GI = gastrointestinal, HDL = high-density lipoprotein, MI = myocardial infarction, NSAIDs = nonsteroidal anti-inflammatory drugs.
FDA Ruling on Aspirin

2003

- Petition sought by Bayer Corp. for reduction in risk of first MI in moderate risk patients (10-year CHD risk ≥10%)
  - 11 votes against, 3 for approval
  - Data from 5 major clinical trials was considered
  - Despite other organizations advocating benefits outweighing risks, the FDA was skeptical

May 2, 2014

- “The FDA has reviewed the available data and does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke”

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm390574.htm
Gout
American College of Rheumatology Guidelines: Management of an Acute Gout Attack

**Assess Severity**

- **Mild-Moderate pain**, particularly for an attack affecting 1 or a few small joints, or 1-2 large joints
  - **Monotherapy A**

- **Severe-pain**, particularly for a polyarticular attack or an attack affecting multiple large joints
  - **Initial Combination Therapy: C**
    - Colchicine + NSAID
    - Colchicine + oral corticosteroid
    - I.A. steroid + oral agent (colchicine, NSAID, corticosteroid)

**Supplement with topical ice as needed B**

- **Use an NSAID or COX-2 inhibitor A**
- **Systemic Corticosteroids A**
- **Colchicine A**

American College of Rheumatology Guidelines: Management of an Acute Gout Attack

**Treatment Outcome**

- **Use an NSAID or COX-2 inhibitor**
- **Systemic Corticosteroids**
- **Colchicine**

Supplement with topical ice as needed

**Successful Outcome**

- Patient Education
- Consider ULT or adjusting ULT

**Inadequate Response**

- Alternate **C** Monotherapy
- Add-on **C** Combination Therapy

**Inadequate response is defined as:**
- <20% improvement in pain score within 24 hr, or
- <50% improvement at 24 hr or longer

**Off-Label Therapies in Development**

Arthritis Care & Research 2012;64(10):1447–1461.
Acute Gout Flare Receiving Colchicine Evaluation (AGREE)

**Primary Endpoint:**
≥50% Pain Reduction at 24 hr without rescue medication

- **P=0.005** and **P=0.034**, colchicine vs. placebo

**Diarrhea**

- **P=ns and P<0.05**, colchicine vs. placebo

Frequency of Recurrent Gout Flares

• 23,857 primary-care patients with new gout over 3.8 years; mean age 61.9 years

Predictors of Recurrent Gout:
• Men
• Age
• BMI
• Smoking
• CV disease
• Lack of allopurinol

![Bar chart showing flare frequency and predictors of recurrent gout](image)
Urate-Lowering Therapy (ULT)

• Titrate every 2-5 weeks to serum urate of <6 mg/dL (<5 mg/dL for some)

• Once at target, can re-evaluate every 6 months

• Xantine oxidase inhibitors (allopurinol or febuxostat) first-line with a uricosuric agent (probenecid) as an alternate first-line agent, or in combination

• As of the ACR 2012 guidelines:
  – Now recommended to start “Acute Gout Prophylaxis” by initiating concomitant pharmacologic anti-inflammatory gout attack prophylaxis whenever starting ULT
  – ULT can be started during an acute attack if “Acute Gout Prophylaxis” with concomitant pharmacologic anti-inflammatory is provided

INITIATE PROPHYLAXIS:
• With or just prior to starting ULT

First-Line
Low-Dose Colchicine: 0.6 mg once or twice daily
or
Low-Dose NSAIDs with a PPI if needed: e.g., naproxen 250 mg twice daily

Second-Line
Low-Dose Prednisone or Prednisolone: ≤ 10 mg daily
if colchicine and NSAIDs both not tolerated, contraindicated or ineffective

DURATION: Treat for the greater of the following
• At least 6 months
or
• 3 months after achieving serum urate target in patients without tophi
• 6 months after achieving serum urate target in patients with ≥1 tophi on physical exam

Evaluate Gout Symptoms while on ULT

No signs/symptoms
Continue Prophylaxis
Colchicine for Prophylaxis of Acute Flares When Initiating Allopurinol for Chronic Gouty Arthritis

- Randomized trial in 43 patients with gout who were starting allopurinol therapy

![Bar chart showing mean number of acute gout flares over different time periods with p-values]

- 0-3 months: Colchicine vs. Placebo, P=0.022
- 3-6 months: Colchicine vs. Placebo, P=0.033
- Overall: Colchicine vs. Placebo, P=0.008

J Rheumatol 2004;31:2429–32.
Marijuana Regulation

1937
- Federal Prohibition
- Prohibited by federal law (Controlled Substances Act 1970)

1996
- Medical Marijuana (23 states and Washington DC)
- Legal access under a physician’s supervision
- Marijuana may be possessed or grown for personal use

2012
- Legalization (CO, WA, OR, AK, Washington DC)
- Eliminates prohibition for possessing small amounts
- Requires legislatures to regulate recreational use
Potential Physiologic Responses to Cannabis

- Improves sleep
- Anti-seizure effects and neuroprotection
- Reduces anxiety and psychotic symptoms/PTSD
- Prevents nausea and stimulates appetite
- Reduces intraocular pressure
- Bronchodilator
- Relaxes muscles and reduces muscle spasms
- Relieves pain (especially neuropathic)
- Anti-inflammatory
- Anti-proliferative
- Anti-viral
3 Routes of Administration

**LUNGS**
Vaporized or Smoked
Organic material, hash, hash oil

**GUT**
Oral Ingestion
Lipophilic, alcoholic, supercritical fluidic extracts of plant material

**SKIN**
Topical Application
Creams, buccal tinctures, and patches made from plant extracts

## Treatment of Chronic Non-Cancer Pain: Systematic Review of Randomized Trials

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Overall result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoked cannabis (n=4)</td>
<td><strong>All trials found positive effect</strong> by improving neuropathic pain vs placebo with no serious adverse effects.</td>
</tr>
<tr>
<td>Oromucosal extracts (n=7)</td>
<td><strong>6/7 trials demonstrated positive analgesic effects</strong> for neuropathic pain, RA, mixed chronic pain. In one trial evaluating RA, <strong>significant decrease in disease activity</strong> (28 joint disease activity score).</td>
</tr>
<tr>
<td>Nabilone (n=4)</td>
<td><strong>Three showed significant analgesic effect</strong> in spinal pain, fibromyalgia, and spasticity related pain vs placebo. One showed <strong>similar effect in neuropathic pain vs dihydrocodeine</strong>.</td>
</tr>
<tr>
<td>Dronabinol (n=2)</td>
<td><strong>Significant reduction in central pain</strong> (MS) vs placebo. <strong>Significantly greater analgesia</strong> vs placebo for mixed chronic pain on opioids.</td>
</tr>
<tr>
<td>THC-11-oic acid analogue - CT-3 or ajulemic acid (n=1)</td>
<td><strong>Ajulemic acid led to significant improvement</strong> in neuropathic pain intensity <strong>at 3 hours, but no difference at 8 hours</strong> compared with placebo.</td>
</tr>
</tbody>
</table>

*Br J Clin Pharmacol 2011;72(5):735-44*
Cannabis Treatment for Chronic Pain
Systematic Review and Meta-Analysis

- 18 double-blind RCTs
- Synthetic derivatives included
- Efficacy outcome: “intensity of pain”
- Harms: number of adverse events
- Concluded moderate efficacy, but risks may be greater than benefit

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of pain</td>
<td>-0.61 (-0.84, -0.37)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>4.11 (1.33, 12.72)</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>2.56 (0.66, 9.92)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>8.34 (4.63, 15.03)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>2.18 (0.93, 5.11)</td>
</tr>
<tr>
<td>Disorientation/Confusion</td>
<td>3.24 (1.51, 6.97)</td>
</tr>
<tr>
<td>Dissociation/Acute psychosis</td>
<td>3.18 (0.89, 11.33)</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>4.13 (2.08, 8.20)</td>
</tr>
<tr>
<td>Ataxia, muscle twitching</td>
<td>3.84 (2.49, 5.92)</td>
</tr>
<tr>
<td>Numbness</td>
<td>3.98 (1.87, 8.49)</td>
</tr>
<tr>
<td>Impaired memory</td>
<td>3.45 (1.19, 9.98)</td>
</tr>
<tr>
<td>Attention disturbances</td>
<td>5.12 (2.34, 11.21)</td>
</tr>
</tbody>
</table>
Miscellaneous Updates
Generic Drug Prices Rising Rapidly
(Jarrett Murphy, CBS News December 27, 2014)

Generic drugs — which some hoped would cure the rising cost of health care — are leaping in price much faster than name-brand medications, a newspaper reports.

Some generic versions of popular medications have climbed more than 1000 percent in the past year, and at least one generic alternative is so expensive that a major insurer is not asking patients to switch from the name-brand version, reports the New York Times.

“The Promise Of Specialty Pharmaceuticals”
by Alan R. Weil

• Now in the era of specialty pharmacy drugs:
  – **Promise**  treat serious medical conditions
  – **Peril**  handled and administered with care to avoid serious adverse effects
  – **Price**  average month cost of $3000

• Projected to account for half of all drug spending before the end of this decade

• Biosimilar:
  – a biological product that is highly similar to an already approved biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar and the approved biological product in terms of the safety, purity, and potency

• New approval pathway: biological products are approved based on demonstrating they are biosimilar to, or interchangeable with, an FDA approved biological product (reference product)

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm291232.htm
Clinical Pharmacotherapy Caveats

• Dual Antiplatelet Therapy (DAPT) study:
  – Dual antiplatelet therapy beyond 1 year after placement of a drug-
    eluting stent, as compared with aspirin therapy alone, significantly
    reduced the risks of stent thrombosis and major adverse
    cardiovascular and cerebrovascular events but was associated
    with an increased risk of bleeding

• Large meta-analysis in patients with diabetes:
  – ACEi inhibitors reduced all-cause mortality, CV mortality, and
    major CV events in patients with DM, whereas ARBs had no
    benefits on these outcomes

• Endocrine Society Vitamin D recommendations:
  – Insufficient evidence to screening individuals who are not at risk
    for Vitamin D deficiency or to prescribe vitamin D to attain the
    noncalcemic benefit for cardiovascular protection
  – Treat vitamin D deficiency with vitamin D2 or D3

J Clin Endocrinol Metab 96: 1911–1930, 2011)
Cleveland Clinic
Every life deserves world class care.
Pharmacology C

Critical Caveats: Pregnancy and Lactation, Pain Management and Antibiotic Resistance Trends (Special Requests)

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Pregnancy and Lactation
Statistics

• Medication exposure accounts for <1% of all birth defects

• Factors which contribute to medication induced birth defects
  – Route of administration
  – Dose of the medication
  – Stage of pregnancy
## Traditional Pregnancy Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adequate, well-controlled studies in pregnant women have not shown that the drug increases the risk of fetal abnormalities</td>
<td><strong>Controlled studies show no human risk</strong></td>
</tr>
<tr>
<td>B</td>
<td>Animal studies show no evidence of harm to the fetus; however, no well-controlled studies have been conducted in pregnant women. <strong>OR</strong> Animal studies have shown adverse events; however, studies in pregnant women have not shown increased risk of abnormalities.</td>
<td><strong>No evidence of risk in humans</strong></td>
</tr>
<tr>
<td>C</td>
<td>Animal studies have shown an adverse effect on the fetus. There are no adequate studies in humans and the benefits from the drug in pregnancy may be acceptable despite its potential risks. <strong>OR</strong> Animal studies have not been conducted.</td>
<td><strong>Risk cannot be ruled out, no adequate studies</strong></td>
</tr>
<tr>
<td>D</td>
<td>Based on human data, the drug can cause fetal harm, but the potential benefits from the use of the drug may be acceptable, despite its potential risks.</td>
<td><strong>Positive evidence of risk</strong></td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities (or positive evidence of fetal risk based on reports and/or marketing experience) and the risk of using the drug in pregnant women clearly outweighs any possible benefit.</td>
<td><strong>Contraindicated in pregnancy</strong></td>
</tr>
<tr>
<td>Lactation Categories</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>L₁</td>
<td>safest to use, controlled studies fail to show risk or harm to infant or drug is not absorbed orally</td>
<td></td>
</tr>
<tr>
<td>L₂</td>
<td>safe to use, drug has been taken by limited # of women, remote possibility of risk</td>
<td></td>
</tr>
<tr>
<td>L₃</td>
<td>moderately safe, no controlled studies, risks may exist but are usually minimal, give if benefit outweighs risk.</td>
<td></td>
</tr>
<tr>
<td>L₄</td>
<td>possibly hazardous, positive evidence of risk to infant or to milk production, use only if absolutely needed</td>
<td></td>
</tr>
<tr>
<td>L₅</td>
<td>contraindicated</td>
<td></td>
</tr>
</tbody>
</table>
Limitations of Current System

Public hearings to evaluate the labeling regulations:

• Purpose was only to present adequate information to assist when prescribing for patients already pregnant, not following drug exposure during an unplanned pregnancy

• The meaning of these categories is commonly misunderstood and inappropriately applied in practice

• Oversimplification leads to a misinterpretation

• 65% to 70% of all prescription drugs are assigned to Pregnancy Category C yet have drastically different sets of supporting evidence and risks

• Lack of differentiation between data from animal and human studies
New Pregnancy Categorization

- Rule by the FDA on 12/04/2014
- Initiation prompted by the FDA’s goal to provide women and their healthcare providers with sufficient information when deciding which medications to prescribe in pregnant and breastfeeding patients
- Implementation
  - New labeling will be mandatory for any drug approved after June 30, 2015
  - For drugs that are approved before this, the deadline to implement the new labeling information ranges from 3-5 years depending on the original application date

New Pregnancy Subsection

- Elimination of the pregnancy letter categories

<table>
<thead>
<tr>
<th>General Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact information if pregnancy registry available</td>
</tr>
<tr>
<td>General statement about background risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fetal Risk Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on all available data, this section characterizes the likelihood that the drug increases the risk of developmental abnormalities in humans and other relevant risks. More than one risk conclusion may be needed</td>
</tr>
<tr>
<td>For drugs that are not systemically absorbed, there is a standard statement indicating that maternal use is not expected to result in fetal exposure</td>
</tr>
<tr>
<td>For drugs that are systemically absorbed, it will include:</td>
</tr>
<tr>
<td>- Where there are human data, a statement about the likelihood of increased risk based on these data. This statement is followed by a description of findings</td>
</tr>
<tr>
<td>- A standard statement about likelihood of increased risk based on animal data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>This section provides information on the following topics:</td>
</tr>
<tr>
<td>- Inadvertent exposure</td>
</tr>
<tr>
<td>- Known or predicted risk to the fetus from inadvertent exposure to drug early in pregnancy</td>
</tr>
<tr>
<td>- Prescribing decisions for pregnant women</td>
</tr>
<tr>
<td>- Description of any known risk to the pregnant woman and fetus from the disease or condition the drug is intended to treat</td>
</tr>
<tr>
<td>- Information about dosing adjustments during pregnancy</td>
</tr>
<tr>
<td>- Maternal adverse reactions unique to pregnancy or increased in pregnancy</td>
</tr>
<tr>
<td>- Effects of dosage, timing, and duration of exposure to drug during pregnancy</td>
</tr>
<tr>
<td>- Potential neonatal complications and needed interventions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human and animal data are presented separately with human data presented first:</td>
</tr>
<tr>
<td>- Description of study type, exposure information (dosage, duration, timing), and any identified fetal developmental abnormality or other adverse effects</td>
</tr>
<tr>
<td>- For human data, it will include positive and negative experiences, number of subjects, and duration of study</td>
</tr>
<tr>
<td>- For animal data, it will include species studied and description of dosages in terms of human dosage equivalents</td>
</tr>
</tbody>
</table>

http://www.hughesmedicine.com/2014/12/changes-to-fda-pregnancy-and-lactation.html#%2EVKdCO1VII%2Elinkedin
New lactation subsection

• When applicable, a sentence stating that the drug can be taken while breastfeeding will appear in “Risk Summary”

http://www.hughesmedicine.com/2014/12/changes-to-fda-pregnancy-and-lactation.html#%2EVKdCO1VII%2ELinkedin
Known Teratogens (Category X)

Pregnancy Related
• Anastrozole
• Misoprostol
• Clomiphene
• Combination contraceptives

Non-Pregnancy Related
• 5-α reductase inhibitors
• ASA (3rd trimester)
• Ergotamines
• Isotretinoin
• Itraconazole
• Live Vaccines
• Melatonin
• Methotrexate
• Raloxifene
• Ribaviron
• Statins
• Thalidomide
• Warfarin

This is not an all inclusive list. Always double check if uncertain.
Contraindicated Drugs During Lactation

• Dicyclomine
• Dronedarone
• Fenofibrate
• Ketorolac

• Methimazole
• Methotrexate
• Statins

This is not an all inclusive list. Always double check if uncertain.
Medication use in in Pregnancy

- Several physiologic alterations that can change drug pharmacokinetic (absorption, distribution, metabolism, excretion)

- Ideal Medication Characteristics

<table>
<thead>
<tr>
<th>PREGNANCY</th>
<th>LACTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>High molecular weight</td>
<td>Shorter half lives</td>
</tr>
<tr>
<td>Highly protein bound</td>
<td>Once daily dosing</td>
</tr>
<tr>
<td>Hydrophilic</td>
<td>Highly protein bound</td>
</tr>
<tr>
<td>Ionized drugs</td>
<td>Low oral bioavailability</td>
</tr>
<tr>
<td></td>
<td>Low lipid solubility</td>
</tr>
</tbody>
</table>
# Nausea and Vomiting in Pregnancy

<table>
<thead>
<tr>
<th>Place in Therapy</th>
<th>Drug Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line (Mild)</td>
<td>Nonpharmacologic options</td>
<td>Avoidance of triggers, dietary changes, acupressure-Sea Bands, and ginger</td>
</tr>
<tr>
<td>1st line (Moderate to Severe)</td>
<td>Vitamins</td>
<td>Vitamin B6 25mg q8˚, multivitamins</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
<td>Doxylamine, diphenhydramine, meclizine</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>Diclegis (pyridoxine/doxylamine)</td>
</tr>
<tr>
<td>2nd line</td>
<td>Dopamine Antagonist</td>
<td>Promethazine, prochlorperazine, metoclopramide</td>
</tr>
<tr>
<td>3rd line</td>
<td>Serotonin Antagonist</td>
<td>Ondansetron</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids (avoid 1st trimester)</td>
<td>Methylprednisolone, dexamethasone, prednisolone</td>
</tr>
</tbody>
</table>
Urinary Tract Infections in Pregnancy

Asymptomatic Bacteriuria and Acute Cystitis

• Oral antibiotics
  – Cephalosporins (cephelexin)
  – Nitrofurantoin (use contraindicated after week 37)
  – Beta-lactams (amoxicillin) are safe but E. coli resistance limits use

Pyelonephritis

• IV fluids and parenteral antibiotics
  – Cephalosporins (ceftriaxone, cefazolin)
  – Ampicillin + gentamicin
  – Ampicillin/sulbactam

• Oral antibiotics when afebrile x 48 hours
# Headaches in Pregnancy

<table>
<thead>
<tr>
<th>Place in Therapy</th>
<th>Drug Class</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>Nonpharmacologic options</td>
<td>Relaxation, stress management and biofeedback</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>Acetaminophen</td>
<td>Preferred agent in those that do not respond to non-pharm</td>
</tr>
<tr>
<td></td>
<td>Codeine</td>
<td>+/- acetaminophen</td>
</tr>
<tr>
<td></td>
<td>Other narcotic analgesics</td>
<td>Nausea, withdrawal SEs</td>
</tr>
<tr>
<td>Caution</td>
<td>Aspirin &amp; NSAIDs</td>
<td>Safe in the first two trimesters but contraindicated in the third trimester</td>
</tr>
<tr>
<td></td>
<td>Sumatriptan</td>
<td>Limited information in pregnancy</td>
</tr>
<tr>
<td>Contraindicated</td>
<td>Ergotamines</td>
<td>Sudden fetal death</td>
</tr>
<tr>
<td></td>
<td>Dihydroergotamines</td>
<td></td>
</tr>
</tbody>
</table>
Cough and Cold in Pregnancy

• Preferred therapies for symptomatic relief
  – Heated humidified air for congestion
  – APAP for sore throat/headache/fever

• Cough
  – All are Category C

• Sneezing/rhinorrhea
  – Ipratropium bromide nasal spray preferred
  – Chlorpheniramine or diphenhydramine are preferred/best studied

• Congestion
  – Intranasal – oxymetazoline (Afrin®) preferred
  – Oral – pseudoephedrine is preferred oral decongestant
    – Avoid in 1st trimester
# Constipation in Pregnancy

<table>
<thead>
<tr>
<th>Place in Therapy</th>
<th>Drug Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line/prevention</td>
<td>Non-pharmacologic options</td>
<td>Light physical exercise, dietary fiber 25-30 gm/d, and fluids &gt;8-8 oz servings/d</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>Fiber Supplements</td>
<td>Psyllium (Metamucil), polycarbophil (FiberCon), wheat dextran (Benefiber)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>Stool Softener</td>
<td>Docusate</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line</td>
<td>Osmotic laxatives</td>
<td>Polyethylene glycol, lactulose, magnesium sulfate</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line</td>
<td>Stimulants</td>
<td>Bisacodyl, senna</td>
</tr>
<tr>
<td>Not recommended</td>
<td>Emollient Stimulant</td>
<td>Mineral Oil, Castor Oil</td>
</tr>
</tbody>
</table>
## GERD in Pregnancy

<table>
<thead>
<tr>
<th>Place in Therapy</th>
<th>Drug Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line/prevention</td>
<td>Non-pharmacologic</td>
<td>Small meals, food modifications, elevate head of bed</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>Antacids</td>
<td>Tums, Mylanta, Maalox</td>
</tr>
<tr>
<td></td>
<td>Protectant</td>
<td>Sucralfate</td>
</tr>
<tr>
<td></td>
<td>Histamine 2 receptor blockers</td>
<td>• Ranitidine, cimetidine- evidence to support use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Famotidine, nizatidine- limited data but likely safe</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line/consult provider</td>
<td>Proton pump inhibitors</td>
<td>Omeprazole, lansoprazole</td>
</tr>
<tr>
<td></td>
<td>Dopamine antagonist</td>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Not recommended</td>
<td>Sodium bicarbonate, Bismuth products, magnesium trisilicate</td>
<td>Alka-Seltzer, Pepto-Bismol, Gaviscon</td>
</tr>
</tbody>
</table>
Depression in Pregnancy

• SSRIs are the preferred antidepressants
  – All pregnancy category C
  – Exception: paroxetine (category D)

• If not on therapy:
  – 1st line: behavioral therapy
  – Start an SSRI when benefit outweighs risk

• If stable on therapy:
  – Continue same antidepressant during pregnancy
  – If on paroxetine and not tried another SSRI, consider switching to a category C option prior to pregnancy

• Postpartum depression
  – Sertraline first-line; paroxetine and nortriptyline second-line
Epilepsy in Pregnancy

- All antiepileptic drugs are pregnancy category C/D

- Preconception planning
  - Folic acid (4-5 mg daily)
  - Use most appropriate drug for seizure type
    - Carbamazepine and lamotrigine likely safest
  - Use monotherapy if possible
  - Transition off valproic acid

- Anti-epileptic drug use during pregnancy
  - Folic acid (4-5 mg daily) at least through 1st trimester
  - Drug level monitoring if possible
Pain Management
## American College of Rheumatology (ACR) Osteoarthritis Guidelines

### Recommendations for Initial Management

<table>
<thead>
<tr>
<th>Knee OA*</th>
<th>Hip OA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditionally recommend that patients should use one of the following:</td>
<td>Conditionally recommend that patients should use one of the following:</td>
</tr>
<tr>
<td>- Acetaminophen</td>
<td>- Acetaminophen</td>
</tr>
<tr>
<td>- Oral NSAIDs</td>
<td>- Oral NSAIDs</td>
</tr>
<tr>
<td>- Topical NSAIDs</td>
<td>- Tramadol</td>
</tr>
<tr>
<td>- Tramadol</td>
<td>- Intraarticular corticosteroid injections</td>
</tr>
<tr>
<td>- Intraarticular corticosteroid injections</td>
<td></td>
</tr>
<tr>
<td>Conditionally recommend that patients should <strong>not</strong> use the following:</td>
<td>Conditionally recommend that patients should <strong>not</strong> use the following:</td>
</tr>
<tr>
<td>- Chondroitin sulfate</td>
<td>- Chondroitin sulfate</td>
</tr>
<tr>
<td>- Glucosamine</td>
<td>- Glucosamine</td>
</tr>
<tr>
<td>- Topical capsaicin</td>
<td></td>
</tr>
<tr>
<td>No recommendations regarding:</td>
<td>No recommendation regarding:</td>
</tr>
<tr>
<td>- Intraarticular hyaluronates</td>
<td>- Topical NSAIDs</td>
</tr>
<tr>
<td>- Duloxetine</td>
<td>- Intraarticular hyaluronates</td>
</tr>
<tr>
<td>- Opioid analgesics</td>
<td>- Duloxetine</td>
</tr>
<tr>
<td>- Opioid analgesics</td>
<td>- Opioid analgesics</td>
</tr>
</tbody>
</table>

*No strong recommendations were made*

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### Note: Other recommendations specifically for hand OA

ACR Recommendations for those at Risk for Gastric Bleeds

• History of symptomatic or complicated upper GI bleed but not within the past year, if an oral NSAID is prescribed they recommend using:
  – COX-2 selective, or
  – Non selective NSAID with a proton pump inhibitor

• History of symptomatic or complicated upper GI bleed within the past year, if an oral NSAID is prescribed they recommend using:
  – COX-2 selective with a proton pump inhibitor

NSAIDs

NSAIDs: ACR Recommendations

• Whenever an oral NSAID is prescribed chronically, they recommend clinician’s consider adding a proton pump inhibitor to reduce the risk of developing symptomatic or complicated upper GI events

• Avoid COX-2 selective NSAIDs in high CV risk
CV Toxicity with NSAIDs

• Increased BP; exacerbation of heart failure in patients with preexisting heart failure (related to kidney toxicity)

• Chronic NSAID therapy increases risk of CV events
  – Increased CV risk seen with all NSAIDs used chronically (except low-dose aspirin); naproxen may be least harmful
  – CV risk needs to be taken into account when prescribing any NSAID
  – Overall relative risk is small; however, risk/benefit considerations in patients with CV risk is very important and required medication guides address these risk
  – NSAID use is contraindicated immediately before or after coronary artery bypass graft (CABG) surgery
Topical NSAIDs

• ACR Strongly recommends topical rather than oral NSAIDs in elderly patients ≥ 75 years of age

• Minimal to no systemic absorption; ACR strongly recommends topical rather than oral NSAIDs in patients ≥ 75 years of age
  - Diclofenac Gel 1% (Voltaren Gel), others
  - Compounded NSAIDs (e.g., ketoprofen) as a cream or ointment
Opioid Crisis

MIAMI NEWS

June 11, 2013
Contact: Public Information Officer
Number: 954-660-4602

Walgreens Agrees to Pay a Record Settlement of $80 Million for Civil Penalties under the Controlled Substances Act

*Largest fine paid by a DEA registrant*

**JUNE 11 (MIAMI)** – Mark R. Trouville, Special Agent in Charge, Drug Enforcement Administration (DEA), Miami Field Division, and Wifredo A. Ferrer, United States Attorney for the Southern District of Florida, announced that Walgreens Corporation (Walgreens), the nation’s largest drug store chain, has agreed to pay $80 million in civil penalties, resolving the DEA’s administrative actions and the United States Attorney’s Office’s civil penalty investigation regarding the Walgreens Jupiter Distribution Center and six Walgreens retail pharmacies (collectively “Registrants”) in Florida. The settlement further resolves similar open civil investigations in the District of Colorado, Eastern District of Michigan, and Eastern District of New York, as well as civil investigations by DEA field offices nationwide, pursuant to the Controlled Substances Act (the Act).
DEA Example: Walgreens

• Six of Walgreens' Florida pharmacies ordered > 1,000,000 oxycodone tabs/yr
  – Average pharmacy in the US = 73,000 tabs/yr

• One pharmacy in Fort Myers increased from ordering 95,800 in 2009 to 2.2 million in 2011

• Another pharmacy in a town of 34,000 people purchased 2.2 million tabs in 2011
Opioid Crisis

• Outpatient pharmacy dispensing checklists prior to filling prescriptions for large quantities of opioids; opposed by the AMA through a 2013 resolution

• Routine checking of Prescription Drug Monitoring Programs (PDMP) in several states

• FDA Labeling Changes for ER/LA Opioids:

  BOXED WARNING
  
  WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL (last warning only for products that have an interaction with alcohol)

• ER/LA Opioid Analgesics REMS requires manufacturers to make available continuing education courses

FDA Post-Marketing Requirements for ER/LA Opioids

• Requirements for post-marketing studies
  – Evaluation of long-term use and known serious risks
    – Misuse, abuse, addiction, overdose, and death
    – Risks of developing hyperalgesia and tolerance
  – Validation of medical coding for opioid ADEs
  – Define and validate doctor/pharmacy shopping as outcomes of misuse/abuse
  – Study plans due 2014, with final results due 2015-2018

Opioid Overdose

• Higher opioid doses are associated with an increased risk of harm, specifically overdose and related mortality, bone fractures, and emergency department visits

• The increased risk of fatal overdose significantly increases in patients receiving opioid therapy consisting of 100-mg of morphine equivalents or higher
  — Intra-nasal nalaxone for overdose reversal

• Increased use of buprenorphine (Suboxone) to treat opioid addition

Antibiotic Resistance Trends
ANTIBIOTIC RESISTANCE THREATS in the United States, 2013

Antibiotic Resistance

• Estimated 2,049,442 illnesses & 23,000 deaths annually

• Running out of drugs to treat serious gram-negative infections

• Antibiotics are the most common cause of emergency department visits for adverse drug events in children

• Taking an antibiotic when it is not needed can lead to the development of antibiotic resistance

### People at Especially High Risk

<table>
<thead>
<tr>
<th>People at Especially High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cancer Chemotherapy</td>
</tr>
<tr>
<td>• Complex Surgery</td>
</tr>
<tr>
<td>• Rheumatoid Arthritis</td>
</tr>
<tr>
<td>• Dialysis for End-Stage Renal Disease</td>
</tr>
<tr>
<td>• Organ and Bone Marrow Transplants</td>
</tr>
</tbody>
</table>
Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*
Threat Report 2013 – Executive Summary

Urgent Threats

• *Clostridium difficile*

• Carbapenem-resistant Enterobacteriaceae (CRE)

• Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella Typhi*
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*
2010 CDC Guidelines: Gonorrhea Treatment
Uncomplicated Genital/Rectal, or Pharyngeal Infections

- IM preferred if possible
  - Can treat with Cefixime 400 mg + Azithromycin or doxycycline if ceftriaxone not available
  - Azithromycin 2 grams po once (if allergic to cephalosporin)
  - Need to do test of cure if alternative regimen used (preferably with culture)
  - Proposed: Move Doxycycline from recommended to alternative

Ceftriaxone 250 mg IM

Plus
(regardless of Chlamydia)

Azithromycin 1 gram po once

Or

Doxycycline 100 mg po twice daily for 7 days

http://www.cdc.gov/std/treatment
Common Resistance in Primary Care

• Methicillin-resistant Staphylococcus aureus (MRSA)
  – Community acquired MRSA more and more common
  – Growing resistance with clindamycin; trimethoprim/sulfamethoxazole and doxycycline still have adequate coverage in most institutions

• Streptococcus pneumoniae
  – Common consideration for commonly encountered upper respiratory infections in primary care
  – Developing resistance to amoxicillin and azithromycin

• Escherichia coli
  – Many institutions have >20% resistance to trimethoprim/sulfamethoxazole requiring empiric treatment with a beta-lactam or nitrofurantoin

Three Key Steps to Judicious Antibiotic Use

1. Ensure that an appropriate indication for antibiotic exits
2. When indicated, choose the antibiotic regimen with the narrowest spectrum of activity possible
3. Prescribe the shortest effective duration of therapy
Cleveland Clinic

Every life deserves world class care.