Breaking News: Practice Changes for Primary Care Providers

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Speaker has no relationship to disclose.

Objectives
• Describe changes in patient management related to use of new medications, dosage changes, or changes in medication use. (30 mins)
• Describe updated guidelines that are useful for treatment and prevention of common diseases seen in primary care. (20 mins)
• Describe changes in patient management related to use of new generic medications. (25 minutes)
True or False.
Quinolones should be considered first line to treat urinary tract infections.

Quinolones

- **2008**: FDA added a boxed warning for the increased risk for tendinitis and tendon rupture
- **2011**: FDA added to the boxed warning the risk for worsening symptoms in patients with myasthenia gravis
- **2013**: FDA required updated labels to reflect potential for irreversible peripheral neuropathy

Quinolones

- **2016**: FDA issued enhanced warnings about link between fluoroquinolones and disabling and potentially permanent side effects involving tendons, muscles, joints, nerves, and the central nervous system
- **July, 2018, BLACK BOX WARNING**: potential mental side effects, risk for coma with hypoglycemia
Quinolones: Feb, 2019

• Risk of aortic dissection, rupture, or aneurysm
• Includes oral and injectable quinolones

Why AAA?

• Quinolones may disrupt collagen in the aorta...possibly leading to vessel wall damage and aortic rupture

How common are AAA?

• Not very!
• 1 in 11,000 patients in general population annually
• 1 in 300 high-risk patients
• Quinolone use is linked to a doubling of these risks
WHO is at high risk?

• Older adults
• Patients with history of aneurysm,
• Patients with hypertension, vascular disease
• Smokers!!!!!

What do I do now?

• Assess patient’s risk of dissection, rupture, or aneurysm BEFORE prescribing a quinolone...
• Weigh risks and benefits....
• Use alternatives when possible

A New Antibiotic
A New Tetracycline
• Nuzyra (omadacycline)
• An aminomethylcycline
• Once-daily tetracycline
• Indications: community-acquired pneumonia or skin infections
• Usual tetracycline warnings: tooth discoloration, reversible inhibition of bone growth if used during the second or third trimesters of pregnancy

Why a New Tetracycline?
• Effective against some doxycycline resistant bacteria
• Can be given IV
• Transition to oral tabs ($400/oral dose)

For CAP
Preferred:
• High-dose amoxicillin PLUS azithromycin
• Respiratory fluoroquinolone in a patient at risk for resistance (age over 65, etc)
• Omadacycline
For Skin Infections

- FDA-approved for acute bacterial skin and soft tissue infections caused by *Staphylococcus aureus* (including MRSA), *Staphylococcus lugdunensis*, *Streptococcus pyogenes*, *Streptococcus anginosus* group, *Enterococcus faecalis*, *Enterobacter cloacae*, and *Klebsiella pneumoniae*

For Skin Infections

- For skin infections with an abscess or pus, cover MRSA with TMP/SMX (about $4/Rx) or doxycycline (about $6/day)

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A (Sort of) New Antibiotic
Delafloxacin (Baxdela) and MRSA

- November, 2017
- 4th generation Quinolone
- Indication: acute bacterial skin and skin structure infections
- Gram-positive bacteria, methicillin-resistant Staph aureus (MRSA)
- Not indicated for pneumonia, COPD exacerbations, or osteomyelitis

Non-purulent Skin Infections

- Use beta-lactams that cover Staphylococcus, Streptococcus...cephalexin, amoxicillin, first gen ceps
- For skin infections with an abscess or pus, provide MRSA coverage with TMP/SMX, doxycycline, or clindamycin
- Save twice-daily Baxdela as a last resort

Delafloxacin: 2 points

- Delafloxacin not included in IDSA guidelines for skin and soft tissue infections because it became available after guideline publication
- FDA-approved for skin and soft tissue infections with Staphylococcus aureus (including MRSA), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus group, certain other Strep species, Enterococcus faecalis, E.coli, Enterobacter cloacae, Klebsiella pneumoniae, and Pseudomonas aeruginosa
MRSA: Decolonization?

WHO?
• Select outpatients with two or more MRSA skin infections at different sites over a 6-month period despite proper hygiene and wound care
• Consider decolonizing close contacts (household members, athletes, etc) who may be passing MRSA back and forth

Prescriber’s Letter. Jan 2019, No. 350104

MRSA: Decolonization?

HOW?
• Intranasal mupirocin BID for 5 to 10 days.
• Prescribe generic topical mupirocin ointment ($15 per 15 g)
• Bactroban Nasal ointment is on long-term backorder
• Advise putting a blueberry-sized amount of mupirocin in each nostril using a cotton swab, then press nostrils and massage gently for a minute

Prescriber’s Letter. Jan 2019, No. 350104

MRSA: Decolonization?

HOW?
• Chlorhexidine (Hibiclens, etc) or dilute bleach baths
• No good evidence these prevent more skin infections in outpatients

Prescriber’s Letter. Jan 2019, No. 350104
True or False.
Probiotics prevent antibiotic associated diarrhea.

What are Probiotics?
• Live organisms
• Bifidobacteria and Lactobacilli are most common
• Saccharomyces boulardii (yeast)
• Used to repopulate the gut or vagina

Use of Probiotics
• Some guidelines recommend probiotics for acute infectious diarrhea and vomiting in adults and kids
• New data: treating infants/children with 5 days of Lactobacillus GG (Culturelle) does NOT reduce the duration or severity of symptoms
• Yogurt: no benefit; hydration and electrolytes-- best practice
Factoids: Probiotics

• Do not use in immunocompromised patients...they may be at higher risk of infection from probiotics
• What’s really in it? No USP Verified probiotic products (maybe mid 2019)
• Some probiotics (Culturelle, Florastor, etc) have evidence... for prevention of antibiotic-associated diarrhea

Mr. H

A 50 y/o Caucasian who had an MI 4 weeks ago. His HTN is controlled and he is on a high potency statin. He has smoked a pack a day for > 20 years. He has tried to quit since his MI but has not been successful at even decreasing his smoking. He asks whether e-cigs, vaping, ”the patch”, or something else could help him quit. How should you respond?

What’s safe in stable cardiac outpatients?

1. Nicotine replacement therapy (NRT)  
   PLUS a short-acting form (gum, lozenge, etc) for breakthrough cravings, or
2. Varenicline (Chantix), or
3. Bupropion SR (Zyban) (consider if also depressed)
***Counseling PLUS meds (work better than either one alone)
Varenicline
Bupropion

• Blocks alpha 4-beta-2 nicotinic acetylcholine receptors
• Bupropion: Inhibits uptake of NE and DA

What’s safe in cardiac inpatients?

• Nicotine patch
• Early use may enhance quit rates post-discharge

Smoking Cessation

• If unsuccessful with combo NRT or one oral med alone, consider...
  • NRT plus Chantix, OR
  • NRT plus bupropion, OR
  • Chantix plus bupropion?? Don’t know yet!
True or False.

E-cigs are as helpful as nicotine patches for smoking cessation.

What about e-cigs?

• Weak evidence that e-cigs help patients quit smoking...
• We don’t know about long-term cardiovascular effects
• Majority of e-cig users still smoke cigarettes


E-cigarettes

• FDA has described the use of e-cigarettes and vaping in youth as an epidemic
• E-cigarette products are attractive to youth: flavors, discreet, attractive on social media, online videos, etc.

E-cigarettes Facts

• 1 in 9 high schoolers use e-cigs
• 1 in 30 middle schoolers use e-cigs...more than any other tobacco product. And there's about a
• 4-fold increase in use of traditional cigarettes among teens who’ve used e-cigs


Do you ask adolescents if they smoke?

What to ask Adolescents

Don’t just ask if they smoke
• Ask if they use e-cigs
• Ask if they use pods
• Ask if they "vape"
Pods

- Pod e-cigarettes (e.g., Juul, Vuse, etc) account for more than half of e-cigarette sales


Educate Adolescents

- Adolescents become addicted more easily to nicotine if introduced as adolescents
- More likely to have attention and memory problems from nicotine
- Nicotine alters brain development (affect cognitive function, memory, and attention when used while the brain is still developing into the mid-20s)


To be fair.....

- Nicotine via e-cigarettes is less harmful than smoking tobacco cigarettes
- There are no long-term data on the risks of nicotine delivered via e-cigarettes
- Unknown effects from exposure to e-cigs contents: propylene glycol, glycerol, flavoring, diethylene glycol, ethylene glycol, ethanol

Nicotine Comparison

- E-cigarettes (average use 220 puffs/day; variable nicotine content): 353 ng/mL
- Tobacco cigarettes (26 per day): 340 ng/mL
- Nicotine patch 21 mg: 165 ng/mL
- Nicotine nasal spray, 24 doses per day: 150 ng/mL to 200 ng/mL

CBD, Cannabis

Cannabis

The cannabis family:
- Hemp
- Marijuana
- Synthetic cannabinoids

There are over 100 cannabinoids in cannabis.

Cannabinoids

2 active components of cannabis:
• Delta-9-tetraydrocannabinol (THC)
• Cannabidiol (CBD)


Cannabinoids

Two active components of cannabis:
• THC activates cannabinoid receptors in the brain (creates a “high”)
• CBD appears to work on other receptor sites (CBD does not produce a “high”)


Purified CBD

• Epidiolex oral solution is purified CBD
• Rx dronabinol (Marinol, Syndros, and nabilone (Cesamet) are synthetic THC
• Rx Epidiolex is about $32,500/year
• Rx Epidiolex is tested for safety, efficacy, or quality by FDA
Non-Purified CBD
Non-FDA-approved CBD: is
• Online
• Dispensaries
• Smoke shops (oral or topical oils, caps, tabs, SL sprays, edibles, inhalants, creams, etc.)
• May have inconsistent CBD amounts, THC or other contaminants

Is it Legal?
Cannabis Laws:
• https://medicalmarijuana.procon.org/view.resource.php?resourceID=006473

Uses: Synthetic THC
• Dronabinol (Syndros, Marinol) and nabilone (Cesamet) are both approved for nausea and vomiting due to chemo...dronabinol for AIDS anorexia
• Both also seem modestly effective for multiple sclerosis spasticity

CS II, III Synthetic THC
• Syndros and Cesamet are C-II
• Marinol is C-III

FYI Marinol’s oil formulation makes it hard to extract dronabinol for smoking or vaping


Metabolism
• THC and CBD are both primarily metabolized by CYP P450 enzymes 1A2, 2C9, 2D6, 2C19, and 3A4
• Medications that inhibit these enzymes could possibly increase CBD and THC levels
• Medications that induce these enzymes could possibly lower CBD and THC levels


Withdrawal Symptoms THC
• Physical and psychological dependence
• Withdrawal symptoms: anxiety, craving, irritability, dysphoria, insomnia, and nausea

**Deprescribing THC**

- **Tapering:** slowly reduce amount used or taken each day or each week
- **Non-Pharmacologic:** Decrease caffeine intake,
- **Relaxation techniques, meditation** for anxiety and insomnia


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**Cost of Synthetic THC**

- $18/dose for generic dronabinol caps
- $70/dose for Syndros
- $80/dose for Cesamet


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**Urine Drug Screens**

- **Most urine drug screens test for THC or its metabolites**
- **Tests can come back positive for about 7 to 10 days after use, or up to 6 weeks with heavy use**

2018 AHA/ACC Dyslipidemia Recommendations
- Updated 2013 guidelines
- Uses ASCVD risk calculator
- Left in place guidance on primary prevention


Abandonment of the LDL Targets
- Randomized, controlled clinical trials demonstrated benefit using specific statin doses---NOT achieving LDL targets
- Recommendation: Continue to measure LDL levels but don’t target specific numbers

2013 Guidelines

2018 AHA/ACC Dyslipidemia Guidelines

<table>
<thead>
<tr>
<th>Group</th>
<th>Characteristics</th>
<th>Recommended LDL Reduction with statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hx CHD or stroke</td>
<td>50% reduction “Best statin”</td>
</tr>
<tr>
<td>2</td>
<td>LDL &gt; 190 mg/dL (familial hyperlipidemia)</td>
<td>50% “Best statin”</td>
</tr>
<tr>
<td>3</td>
<td>DM, aged 40-75, LDL 70-189 mg/dL</td>
<td>30-49% “Good statin”</td>
</tr>
<tr>
<td>4</td>
<td>Global 10-year risk score ≥7.5% (primary prevention)</td>
<td>30-49% “Good statin”</td>
</tr>
</tbody>
</table>

> 50% = High potency; 30-49% = Moderate potency%
High Potency Statins

<table>
<thead>
<tr>
<th>Medication</th>
<th>LDL-Lowering Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin (Lipitor)</strong></td>
<td>10 mg: 35-39%</td>
</tr>
<tr>
<td></td>
<td>20 mg: 43%</td>
</tr>
<tr>
<td></td>
<td>40 mg: 50%</td>
</tr>
<tr>
<td></td>
<td>80 mg: 55-60%</td>
</tr>
<tr>
<td><strong>Rosuvastatin (Crestor)</strong></td>
<td>5 mg: 45%</td>
</tr>
<tr>
<td></td>
<td>10 mg: 46-49%</td>
</tr>
<tr>
<td></td>
<td>20 mg: 50-55%</td>
</tr>
<tr>
<td></td>
<td>40 mg: 55-63%</td>
</tr>
<tr>
<td><strong>“High Potency” Rosuvastatin, Atorvastatin</strong></td>
<td>Atorvastatin (40, 80 mg )</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin (20, 40 mg)</td>
</tr>
</tbody>
</table>

Moderate Potency Statins

<table>
<thead>
<tr>
<th>Medication</th>
<th>LDL-Lowering Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simvastatin (Zocor)</strong></td>
<td>5 mg: 26%</td>
</tr>
<tr>
<td></td>
<td>10 mg: 29%</td>
</tr>
<tr>
<td></td>
<td>20 mg: 38%</td>
</tr>
<tr>
<td></td>
<td>40 mg: 30-41%</td>
</tr>
<tr>
<td></td>
<td>80 mg: 36-47% (dose not recommended)</td>
</tr>
<tr>
<td><strong>Pitavastatin (Livalo)</strong></td>
<td>1 mg: 29%</td>
</tr>
<tr>
<td></td>
<td>2 mg: 36-39%</td>
</tr>
<tr>
<td></td>
<td>4 mg: 41-45%</td>
</tr>
<tr>
<td><strong>Pravastatin (Pravachol)</strong></td>
<td>10 mg: 22%</td>
</tr>
<tr>
<td></td>
<td>20 mg: 29%</td>
</tr>
<tr>
<td></td>
<td>40 mg: 34%</td>
</tr>
<tr>
<td></td>
<td>80 mg: 37%</td>
</tr>
</tbody>
</table>

2018 AHA/ACC Dyslipidemia Recommendations

- Updated guidance on secondary prevention (“Stable high risk” and “Very high risk”)
- Stable high risk: use the maximally tolerated statin therapy -unchanged from 2013
- Very High Risk: add on to statins to drive LDL down

“Very High Risk”

- Multiple CV events OR a single CV event plus additional CV risks (diabetes, smoking, etc)
- 70 mg/dL as the threshold to consider adding a non-statin
- Verifying adherence to statins and lifestyle changes before adding
- "lower is better" in “very high risk” patients

2018 Lipid Guidelines

- Use a high potency statin for very high-risk patients (Goal is <70 mg/dL)
- Consider ezetimibe first R/T cost and efficacy

Ezetimibe (Zetia)

*Cholesterol absorption inhibitors*

- Safe to combine with a statin
- Ezetimibe generic since 2016 ($360/yr for generic)
- Well tolerated
- Goal < 70 mg/dL
IF not at goal with statin plus ezetimibe:

- Consider adding a PCSK9 inhibitor plus statin

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The Newest Drug Class: PCSK9 Inhibitors

- Proprotein
- Convertase
- Subtilisin
- Kexin type 9
  - Monoclonal antibody

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PCSK9: Background

- PCSK9 is an enzyme in the liver, some people make A LOT!
- Causes degradation of LDL receptors
- Without LDL receptors, LDL “roams” the blood stream

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PCSK9 Inhibitors

• PCSK9 Inhibitors PREVENT the enzyme from binding to the LDL receptors
• And...they wreck your receptor sites!
• If the enzyme can’t bind, then there are lots of LDL receptors to bind LDL and keep it out of the blood stream!


PCSK9 Inhibitors

• Praluent (alirocumab)
• Repatha (evolocumab)
• $10,000-$14,000/year
• Subq injection every 2 weeks

PCSK9 Inhibitors: For Whom?

- Reduce LDL 60%
- Statins remain first line
- Myalgia rates: 3-5% (Statins: up to 30%)

What Drug Class Reduces CV Risks?

- **Statins are FIRST choice!**
- Statins are ONLY class to demonstrate reductions in mortality in primary and secondary prevention

Low Risk CV Patients

- Statin is first line
- No data shows improvement in CV outcomes if bile acid sequestrant, fibrate, or niacin is used **(AVOID in these patients!)**
Primary Prevention: CV Risk > 20%
• High-intensity statin if 10-year CV risk is 20% or higher
• Rosuvastatin, atorvastatin are the only 2 high intensity statins

Celecoxib back in the News!

**NSAIDs**
Cardiovascular Safety

True or False
Celecoxib is the safest NSAID for a patient with underlying cardiovascular risks.
COX-2 inh and CV risk
• Vioxx?
• Bextra?
• Celebrex?
• Remember these?
• Increased risk of MIs and strokes
• Now every NSAID contains a warning about CV risk

NSAIDs and CV risk
• PRECISION trial: similar rate of MI and stroke with celecoxib, naproxen, or ibuprofen in high-CV-risk patients
• 4 point elevation in SBP with ibuprofen compared to celecoxib, naproxen

Which NSAID for patients with cardiovascular risks?
**Risk Summary**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cox-2 Selectivity</th>
<th>GI Risk</th>
<th>CV Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>High</td>
<td>Low</td>
<td>Mod to High</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Mod to High</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Low</td>
<td>High</td>
<td>??</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Moderate</td>
<td>Low</td>
<td>Mod to High</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Low</td>
<td>Mod to High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Low</td>
<td>High</td>
<td>??</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Low</td>
<td>Mod to High</td>
<td>Mod to High</td>
</tr>
</tbody>
</table>

**NSAID Use after MI**

- Risk of reinfarction or death is increased if NSAID taken after recent MI
- Risk of reinfarction or death increased YEARS after MI
- CV risk after MI DOES NOT decline over time!
- Avoid NSAIDs indefinitely after an MI!


**Aspirin/NSAID Interaction**

**CV Risk: Increased risk of MI**
- Aspirin irreversibly inhibits platelets
- NSAIDs reversibly bind to platelets
- If NSAID and Aspirin are taken together, NSAID blocks aspirin’s ability to inhibit platelets
- Advice: Patient should take aspirin at least an hour prior to taking an NSAID!
Questions???

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