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)**

Stevens DL, Bisno AL, Chambers HF, et al. Executive summary: practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2014;59:147-59. Errata: 2015;60:1448-9.

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 cephs
- 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 anginosis* 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

Hartmann-Boyce J, Begh R, Aveyard P. Electronic cigarettes for smoking cessation. *BMJ* 2018;360:j5543.

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.

FDA. Statement from FDA commissioner Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use. September 12, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620185.htm. (Accessed January 7, 2019).

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

FDA. Statement from FDA commissioner Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use. September 12, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620185.htm. (Accessed January 7, 2019).

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**

CDC. Sales of *JUUL* e-cigarettes skyrocket, posing danger to youth. October 2, 2018. https://www.cdc.gov/media/releases/2018/p1002-e-Cigarettes-sales-danger-youth.html. (Accessed January 19, 2019).

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)**

FDA. Statement from FDA commissioner Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use. September 12, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620185.htm. (Accessed January 7, 2019).

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**

Eaton an LY, Stratton K, Eds. The National Academies of Sciences, Engineering, and Medicine: public health consequences of e-cigarettes. Washington, D.C.: National Academies Press (US), 2018.

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.

The National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: current state of evidence and recommendations for research (2017). https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state. (Accessed January 8, 2019).

Cannabinoids

2 active components of cannabis:

- **Delta-9-tetraydrocannabinol (THC)**
- **Cannabidiol (CBD)**

The National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: current state of evidence and recommendations for research (2017). https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state. (Accessed January 8, 2019).

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")**

The National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: current state of evidence and recommendations for research (2017). https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state. (Accessed January 8, 2019).

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***

Continuing Education, *Medical Marijuana. Pharmacist's Letter/Prescriber's Letter.* Course no. 17-231. 2017.

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**

Continuing Education, *Medical Marijuana*. *Pharmacist's Letter/Prescriber's Letter*. Course no. 17-231. 2017.

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

Continuing Education, *Medical Marijuana*. *Pharmacist's Letter/Prescriber's Letter*. Course no. 17-231. 2017.

Withdrawal Symptoms THC

- Physical and psychological dependence
- Withdrawal symptoms: anxiety, craving, irritability, dysphoria, insomnia, and nausea

Addiction blog. How to withdraw from marijuana. November 2013. https://drug.addictionblog.org/how-to-withdraw-from-marijuana/. (Accessed January 10, 2019).

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

Continuing Education, *Medical Marijuana*. *Pharmacist's Letter/Prescriber's Letter*. Course no. 17-231. 2017.

Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *JAMA* 2015;313:2474-83.

Cost of Synthetic THC

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

Continuing Education, *Medical Marijuana*. *Pharmacist's Letter/Prescriber's Letter*. Course no. 17-231. 2017.

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

LabCorp. Cannabinoid (THC), screen and confirmation, urine. https://www.labcorp.com/test-menu/21831/cannabinoid-thc-screen-and-confirmation-urine#. (Accessed January 7, 2019).

2018 AHA/ACC Dyslipidemia Recommendations

- Updated 2013 guidelines
- Uses ASCVD risk calculator
- Left in place guidance on primary prevention

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018 Nov 8. [Epub ahead of print] Source Accessed November 14, 2018.

2013 Guidelines
Abandonment of the LDL Targets

(Goals: LDL < 100 mg/dL LDL < 70 mg/dL)

- 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

2018 AHA/ACC Dyslipidemia Guidelines

Group	Characteristics	Recommended LDL Reduction with statin
1	Hx CHD or stroke	50% reduction "Best statin"
2	LDL > 190 mg/dL (familial hyperlipidemia)	50% "Best statin"
3 ⇨	DM, aged 40-75, LDL 70-189 mg/dL	⇨ 30-49% "Good statin"
4	Global 10-year risk score ≥7.5% (primary prevention)	30-49% "Good statin"

≥ 50 % = High potency; 30-49 % = Moderate potency %

High Potency Statins

Medication	LDL-Lowering Capacity
Atorvastatin (Lipitor)	10 mg: 35-39% 20 mg: 43% 40 mg: 50% 80 mg: 55-60%
Rosuvastatin (Crestor)	5 mg: 45% 10 mg: 46-49% 20 mg: 50-55% 40 mg: 55-63%
"High Potency" Rosuvastatin, Atorvastatin	Atorvastatin (40, 80 mg) Rosuvastatin (20, 40 mg)

Moderate Potency Statins

Medication	LDL-Lowering Capacity
Simvastatin (Zocor)	5 mg: 26% 10 mg: 29% **Low potency** 20 mg: 38% 40 mg: 30-41% 80 mg: 36-47% (dose not recommended)
Pitavastatin (Livalo)	1 mg: 29% **Low potency** 2 mg: 36-39% 4 mg: 41-45%
Pravastatin (Pravachol)	10 mg: 22% 20 mg: 29% **Low potency** 40 mg: 34% 80 mg: 37%

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

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018 Nov 8. [Epub ahead of print] Source Accessed November 14, 2018.

"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

The Newest Drug Class: PCSK9 Inhibitors

- **P**roprotein
- **C**onvertase
- **S**ubtilisin
- **K**exin type 9
- Monoclonal antibody

Crossey, E. Amar, M.J, Sampson, M. Peabody, J. Schiller, JT, Chackerian, B. Remaley, A.T. (2015). Vaccine. A cholesterol lowering VLP vaccine that targets PCSK9. Oct 26;33(43):5747-55. doi: 10.1016/j.vaccine. Vaccine.2015.09.044. Epub 2015 Sep 26.

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

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!

Crossey, E. Amar, M.J, Sampson, M. Peabody, J. Schiller, JT, Chackerian, B. Remaley, A.T. (2015). Vaccine. A cholesterol lowering VLP vaccine that targets PCSK9. Oct 26;33(43):5747-55. doi: 10.1016/j.vaccine. Vaccine.2015.09.044. Epub 2015 Sep 26.

PCSK9 Inhibitors

PCSK9 Inhibitors

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

Crossey, E. Amar, M.J, Sampson, M. Peabody, J. Schiller, JT, Chackerian, B. Remaley, A.T. (2015). Vaccine. A cholesterol lowering VLP vaccine that targets PCSK9. Oct 26;33(43):5747-55. doi: 10.1016/j.vaccine. Vaccine.2015.09.044. Epub 2015 Sep 26.

PCSK9 Inhibitors: For Whom?

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

Crossey, E. Amar, M.J, Sampson, M. Peabody, J. Schiller, JT, Chackerian, B. Remaley, A.T. (2015). Vaccine. A cholesterol lowering VLP vaccine that targets PCSK9. Oct 26;33(43):5747-55. doi: 10.1016/j.vaccine. Vaccine.2015.09.044. Epub 2015 Sep 26.

What Drug Class Reduces CV Risks?

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

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013.

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

Drug	COX-2 Selectivity	GI Risk	CV Risk
Aspirin	Low	Moderate	Low
Celecoxib	High	Low	Mod to High
Diclofenac	Moderate	Moderate	Mod to High
Flurbiprofen	Low	High	???
Ibuprofen	Moderate	Low	Mod to High
Indomethacin	Low	Mod to High	Moderate
Ketorolac	Low	High	???
Meloxicam	High	Low	Moderate
Naproxen	Low	Mod to High	Mod to High

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!***

Schjerning Olsen AM, Fosbol EL, Lindhardsen J, et al. Long-term cardiovascular risk of NSAID use according to time passed after first-time myocardial infarction: a nationwide cohort study. Circulation 2012 Sep 10

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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