COPD Pharmacotherapy

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University of Washington
Division of Pulmonary & Critical Care
April 23, 2015

What is COPD?

Chronic Bronchitis
Emphysema
Post-BD
FEV1/FVC < 0.60
Permanent Airflow Limitation

Asthma
COPD

COPD Mortality Is Increasing

1963 1987 2007

% Change in Age-Adjusted Death Rates

Cardiovascular Disease -69 %
All Causes -44 %
COPD + 147 % 3rd leading cause of death

COPD uses resources and is costly

1.5 million emergency room visits/yr
725,000 hospital admissions/yr

Costs ($ billions)

Hospital 7.3
Mortality 7.3
Other 10.7
Morbidity 6.8

Outpatient Management: Stable COPD

Management of COPD

• Long-term oxygen therapy
  – Indications: RA sat \(\leq 88\%\); \(\text{paO2} \leq 55\)
  – Improves mortality

• Smoking Cessation
  – For all smokers
  – Only treatment to halt progression of AFO

Management of COPD

• Pulmonary Rehabilitation
  – For symptomatic patients
    • Strongest evidence for those with \(\text{FEV1} < 50\%\)
    – Improves: symptoms, HRQoL, exercise tolerance

• Surgical Therapies (for selected patients)
  – Lung volume reduction surgery
  – Lung transplantation

Goal of Pharmacologic Therapies

• Reduce symptoms
• Reduce frequency/severity of exacerbations
• Improve health status and exercise tolerance

• Do not modify decline in lung function
  – As primary or secondary outcome in trials
  – TORCH & UPLIFT: ? LABA and/or ICS

Lancet 2009;374:1171-8
AJRCCM 2008;178:322-8
Pharmacologic Therapies

<table>
<thead>
<tr>
<th>Pharmacologic Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta₂-agonists</td>
</tr>
<tr>
<td>Short-acting beta₂-agonists</td>
</tr>
<tr>
<td>Long-acting beta₂-agonists (LABA)</td>
</tr>
<tr>
<td>Anti-cholinergics</td>
</tr>
<tr>
<td>Short-acting anticholinergics</td>
</tr>
<tr>
<td>Long-acting anticholinergics (LAMA)</td>
</tr>
<tr>
<td>Combination short-acting beta₂-agonist + anticholinergic</td>
</tr>
<tr>
<td>Methylxanthines (Theophylline)</td>
</tr>
<tr>
<td>Inhaled corticosteroids (ICS)</td>
</tr>
<tr>
<td>Combination long-acting beta₂-agonist + inhaled corticosteroid</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
</tr>
<tr>
<td>Phosphodiesterase-4 inhibitors (Roflumilast)</td>
</tr>
</tbody>
</table>

Treat: Symptomatic Patients:

**Stable COPD**
- But with which inhaled medication?
  - Short-acting or long-acting?
  - LABA, ICS or LAMA?
  - Monotherapy or Combination therapy?
- What about side effects?
- What about oral medications?
  - Roflumilast?
  - Azithromycin?

**Case**: Mr. J is a 67 year old man with history of COPD, 75+ pack-year tobacco, presents to clinic with a complaint of slowly progressive SOB over the past 3-5 years.

- Quit smoking 2007 (when 1st noted SOB)
- 2 years ago- walk 1 mile before stopped now SOB after 1 ½ blocks
- Daily chronic cough- small, white sputum
- albuterol/ipratropium 4X day- "helps some"
- No hospitalizations or exacerbations in the past year

**Case (continued):**
**PMHx**
- COPD
  - FEV1/FVC 0.63; FEV1 2.06 L (55% pred)
- Coronary artery disease
- Diabetes mellitus
- Benign prostatic hypertrophy
  - history of previous episode of urinary retention – attributed to pain medications

**Physical Exam**: oxygen saturation 93% on room air
Gen: breathing comfortably, in no distress
Chest: Prolonged expiratory phase, o/w clear
Case (continued):

Which is (are) the best options for treatment?

A) Continue short-acting inhaler alone
B) Start long-acting beta agonist (LABA)
C) Start LAMA (Tiotropium)
D) Start an inhaled corticosteroid (ICS)
E) Start combination LABA/ICS

Old: Step-Wise Escalation by GOLD Stage

In patients with FEV1/FVC < 70
GOLD 1: Mild  FEV1 ≥ 80% predicted
- Add short-acting bronchodilator when needed
GOLD 2: Moderate  50% ≤ FEV1 < 80% predicted
- Add one or more long-acting bronchodilators
GOLD 3: Severe  30% ≤ FEV1 < 50% predicted
- Add inhaled glucocorticoids if repeated exacerbations
GOLD 4: Very Severe  FEV1 < 30% predicted

2011 Guidelines & Beyond: Focuses on Symptoms and Risk

- Treatment recommendations now based on:
  - Symptoms and Risk
  - High Risk:
    ≥ 2 outpatient exacerbations in past year
    OR
    ≥ 1 inpatient exacerbation in past year
    OR
    FEV1 <50% predicted

Combined Assessment

<table>
<thead>
<tr>
<th>Risk (GOLD Stage)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild</td>
<td>Moderate-Severe</td>
</tr>
<tr>
<td>“Less”</td>
<td>“More”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk (Exacerbations/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 admission</td>
</tr>
<tr>
<td>≥ 2 admission</td>
</tr>
</tbody>
</table>

Old: Step-Wise Escalation by GOLD Stage

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www.goldcopd.org
### GOLD: Recommended Initial Therapies

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>First Choice</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ipratropium</td>
<td>LAMA or LABA or SABA &amp; Ipratropium</td>
</tr>
<tr>
<td></td>
<td>or SABA pm</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA &amp; LABA</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA &amp; LAMA or Roflumilast or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LABA &amp; Roflumilast or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA and/or LAMA</td>
<td>ICS + LABA &amp; LAMA &amp;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Roflumilast or LABA &amp; Roflumilast</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**www.goldcopd.org**

### Beware: Overuse of ICS

- Long-term monotherapy with inhaled corticosteroids is not recommended—less effective than combination LABA+ICS (**Evidence A**)
- Long-term treatment containing ICS should not be prescribed outside indications due to increased risk of pneumonia and increased risk of fractures with long-term exposure (**Evidence A**)

### Increased Risk of Pneumonia

- Meta-analysis of 18 RCTs
- N=16,996 patients on any ICS vs. control
- RR any pneumonia:
  - 1.60 (95% CI 1.33-1.92) (p-value<0.001)
- RR serious pneumonia:
  - 1.71 (95% CI 1.46-1.99) (p-value<0.001)
- No difference in mortality

*Arch Int Med 2009; 169 (3):219-229*

### Increased Fracture Risk

- Meta-analysis of 16 RCTs + 7 obs studies
- N=17,513 + 69,000 participants
- Increased risk of fractures:
  - RCT: OR 1.27 (95% CI 1.1 to 1.6 (p=0.04))
  - Observational: OR 1.21 (95% CI 1.1 to 1.3 (p<0.001)

*Thorax 2011; 66 (8):699-708*
Comparison of LABA and LAMA

- Benefits of LABA
  - Exacerbations
  - Symptoms
  - Health-related QOL
  - Lung Function

- Benefits of LAMA
  - Exacerbations
  - Symptoms
  - Health-related QOL
  - Lung Function

www.goldcopd.org

Comparison of LAMA and LABA

- 1 yr: RCT, double-blind
- Tio vs. Salmeterol
- Exacerbation risk
- 7,376 patients:
  - Moderate-very severe COPD
  - Exacerbation Hx

HR 0.83 (95% CI 0.77-0.91)
P-value by log rank test= <0.001

NEJM 2011;364:1093-103

Comparison of LABA and LAMA

- Meta-analysis to evaluate differences in exacerbation risk with various treatments
- 26 RCTs; 36,312 patients

<table>
<thead>
<tr>
<th>Treatment vs. Comparator</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABA vs. placebo</td>
<td>0.84 (0.75, 0.93)</td>
</tr>
<tr>
<td>LAMA vs. placebo</td>
<td>0.74 (0.66, 0.81)</td>
</tr>
<tr>
<td>LAMA vs. LABA</td>
<td>0.88 (0.77, 1.00)</td>
</tr>
<tr>
<td>LABA + LAMA vs. LABA</td>
<td>0.96 (0.66, 1.35)</td>
</tr>
<tr>
<td>LABA + LAMA vs. LAMA</td>
<td>1.09 (0.77, 1.49)</td>
</tr>
</tbody>
</table>

Clinical Epidemiology 2011; 3: 107-129

Comparison of LABA and LAMA

- Long-Acting Bronchodilator
  - Associated Side Effects
    - B2-agonists
      - Dizziness and Headache; Tremor; Throat Irritation; Sinus tachycardia; Hypersensitivity Reaction
    - Tiotropium
      - Dry mouth; Urinary retention; Symptoms of narrow angle glaucoma; Hypersensitivity Reaction

? Concerns about cardiovascular safety:
- No increased events seen in two large trials
  - Salmeterol vs. placebo: 3045 pts; 3 yrs f-up
  - Tiotropium vs. placebo: 5993 pt; 4 yrs f-up

Risk of Acute Urinary Retention

- Nested case-control study 4/03-3/09
- Patients initiated on IACs
  - >565,000 patients aged 65 and older
  - 9,432 men AUR (ER, hospital, surgery)
  - AOR= 1.42 (1.20-1.68)
  - For those with BPH: AOR=1.81 (1.46-2.24)
  - Higher among those on both long- and short-acting anticholinergics

\[ \text{Arch Int Med 2011;171 (10):914-920} \]

ACP/ACCP/ATS/ERS Recommendation

- Prescribe monotherapy:
  - Either LAMA or LABA for symptomatic patients with FEV1<60% predicted
  - Strong recommendation
  - Moderate quality evidence
- Choice depends on:
  - Patient preference and cost
  - Side effect profile

\[ \text{Ann Intern Med 2011;155:179-91} \]

Ease of Dosing?

- LAMA: Tiotropium (Spiriva)
  - Once daily dosing

- LABA:
  - Twice daily dosing
    - Salmeterol, Formoterol
  - Once daily dosing
    - Indacaterol (Arcapta)

Case (continued): You start the patient on treatment with a LABA. Initially he reports improvement in his dyspnea, but over the next year is hospitalized 2 times for an acute exacerbation of COPD. Both exacerbations are characterized by severe increase in dyspnea as well as purulent sputum production.

You repeat his pulmonary function tests after he’s recovered and find his FEV1 has remained about the same. (2.0 L, 52% pred)
Combined Assessment

Risk (GOLD Stage) vs. Risk (Exacerbations/year)

- Mild: "Less" (0-
- Moderate-Severe: "More" (2+)

GOLD: Recommended Initial Therapies

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<td>LAMA &amp; LABA</td>
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<td>C</td>
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<td>LAMA &amp; LAMA or LAMA &amp; Roflumilast or LABA &amp; Roflumilast</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA and/or LAMA</td>
<td>ICS+LABA &amp; LAMA, ICS+LABA &amp; Roflumilast, LAMA + LABA, LAMA + Roflumilast</td>
</tr>
</tbody>
</table>

Combination LABA/ICS Therapy

- Meta-analysis: Combo LABA/ICS vs. placebo
- 19 studies; 10,400 patients
- RR Exacerbation: 0.73 (95% CI 0.69, 0.78)
- Clinical Impact: Exacerbation Frequency**
  - Patients had 1-2 exacerbations/year
  - LABA/ICS: 1 less exacerbation every 2-4 yrs
- Improved dyspnea and health status (small)
- Improvement in mortality (dominated by TORCH; not seen in previous large trial)

What about triple therapy?

- WISDOM trial
  - RCT, noninferiority trial
  - 2485 patients with FEV1<50% and at least one exacerbation in past year
  - 6 week run in: LABA/ICS + Tio
  - LABA+ICS+ Tio vs. LABA+placebo + Tio
    - Placebo: weaned ICS off over 12 weeks
    - No difference in moderate-severe exacerbations between groups (HR 1.06, 95% (0.94-1.19)

Cochrane Review 2013

**Case (continued):** Before he leaves the office, he says to you. “These inhalers are really a pain, I wish there was just a pill you could give me instead.”

Is there an oral medication that would help him?

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**Roflumilast**

- Once daily oral medication; PDE-4 Inhibitor
- Reduces inflammation: inhibits cAMP breakdown
- ↓ Moderate to severe exacerbations 15-20%
  - Patients with chronic bronchitis
  - Severe to very severe COPD
  - Chronic exacerbations
- ↑ Lung function with long-acting BD


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**Roflumilast**

- Use with caution:
  - Depression: Suicide related events (5 patients)
  - Inducers of cytochrome P450 enzyme
- Contraindicated in moderate-severe liver dz

* Clinical Therapeutics 2012;34:56-66

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**Roflumilast**

- Rec: chronic bronchitis, severe to very severe COPD, frequent exacerbations despite long-acting BD.” (Evidence B)
- ↑ Adverse effects than inhaled medications
  - Nausea and headache
  - Reduced appetite and weight loss*
    - Monitor weight and avoid in underweight
  - Abdominal pain and diarrhea
  - Sleep disturbances- Insomnia

* Clinical Therapeutics 2012;34:56-66
**Roflumilast and Combination Inhaler Therapy: REACT**
- Multi-site (N=203), blinded RCT
- 1945 pts: Severe COPD, chronic bronchitis & at least 2 exacerbations
- LABA/ICS+Roflumilast vs. LABA/ICS +placebo (Tio allowed)
  - 13% decrease in moderate to severe exacerbations
  - Higher adverse events (67% vs 59%); withdrawal 11% vs. 5%

*Lancet 2015;385:857-66*

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**Azithromycin**
- RCT of 1577 patients with COPD
  - ≥ 40 years old
  - Continuous O2 or steroids in previous year
  - ER or hospitalized for exacerbation and
  - No exacerbation for at least 4 weeks prior
  - Excluded: asthma, HR >100, prolonged QT and hearing impairment

- Azithromycin 250 mg daily vs placebo: 1 yr

*NEJM 2011;365:389-98*

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**Azithromycin**
- Primary outcome: Time to first exacerbation
  - 266 days (95% CI 227-313) vs. 174 days (95% CI 143-215)
  - 1.48 vs. 1.83 exacerbations/yr (p-value=0.01)
- Acute exacerbation/pt year
  - HR= 0.73 (95% CI 0.63-0.84)
- Improved HRQoL
- *Hearing decrements: 25% vs. 20%; p=0.04
- Not currently recommended by GOLD: due to risk/benefit profile

*NEJM 2011;365:389-98*
Case (cont): Mr. J returns to see you about 9 months later, this time complaining of a several day history of increased dyspnea. He now can walk only about 50 yards before short of breath. Additionally has complaints of dry cough. No change in sputum. On exam, oxygen saturation is 93% on room air, speaking in full sentences, with no use of accessory muscles. Chest x-ray with hyperexpansion, o/w normal.

You diagnose him as having a COPD exacerbation.

How will you treat?
- a) Prednisone 40 mg daily X 14 days
- b) Prednisone 40 mg daily X 5 days
- c) Prednisone 40 mg daily X 10 days with course of Azithromycin
- d) Prednisone 60 mg daily with taper over 3 weeks.

Duration of Prednisone: REDUCE
- RCT, noninferiority trial at 5 sites
  - Double blind, placebo controlled
- 314 patients with AECOPD
- Prednisone 40 mg X 5 days vs. 14 days
- Exacerbation within 180 days
  - 37% vs 38% - no difference
  - Significantly decreased steroid exposure

JAMA 2013;309:2223-2231

Exacerbation: Indications for Antibiotics
Cardinal symptoms:
- Increased dyspnea
- Increased sputum volume
- Increased sputum purulence
- Evidence B- all 3 present
- Evidence C- increase purulence + 1 other
- Evidence B- If require NIPPV or Invasive mechanical ventilation
Thanks…..Questions?

Muscarinic receptor subtypes in airways

Parasympathetic Nerves

M1 RECEPTORS
M2 RECEPTORS
M3 RECEPTORS

Tiotropium: high affinity all, rapid dissociation from M2, slow from M1 and M3

CNS Cranial Nerve X

Acetylcholine

AIRWAY SMOOTH MUSCLE CELLS
MUCUS GLANDS

Drawing by Dennis E. Doherty, MD, University of Kentucky Medical Center
Update in Direct Anticoagulants

Michael J Lenaeus, MD/PhD
April 23rd, 2015

Outline

1. Review of direct anticoagulants (indications)
   1. Updated information from 2014-2015
      - More numbers
      - Real world
      - Monitoring
      - “Patient-based” dosing
      - Reversal

Ol’ Reliable

Stroke reduction in AF

<table>
<thead>
<tr>
<th>Observed Events (%) (Stroke, emboli)</th>
<th>SPAC</th>
<th>AFASAK</th>
<th>BAATAF</th>
<th>CAFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>82</td>
<td>60</td>
<td>86</td>
<td>42</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from UpToDate
Recurrent VTE & fatal VTE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>3mo</th>
<th>6mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>19027</td>
<td>11032</td>
</tr>
<tr>
<td>Recurrent VTE %</td>
<td>3.4 (2.9-4.0)</td>
<td>3.3 (2.5-4.2)</td>
</tr>
<tr>
<td>Recurrent PE %</td>
<td>1.6 (1.3-2.0)</td>
<td>1.7 (1.1-2.5)</td>
</tr>
<tr>
<td>Recurrent fatal VTE %</td>
<td>0.4 (0.3-0.6)</td>
<td>0.5 (0.3-0.7)</td>
</tr>
</tbody>
</table>

Outcome 3mo 6mo

Patients, n 19027 11032
Recurrent VTE % 3.4 (2.9-4.0) 3.3 (2.5-4.2)
Recurrent PE % 1.6 (1.3-2.0) 1.7 (1.1-2.5)
Recurrent fatal VTE % 0.4 (0.3-0.6) 0.5 (0.3-0.7)

Bleeding

<table>
<thead>
<tr>
<th>Event</th>
<th>Current exposure</th>
<th>Recent exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bleeding</td>
<td>3.8 (3.4-4.2)</td>
<td>4.5 (3.7-5.5)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0.3 (0.2-0.4)</td>
<td>0.4 (0.2-0.8)</td>
</tr>
<tr>
<td>ICH</td>
<td>0.4 (0.3-0.5)</td>
<td>0.6 (0.4-1.1)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>0.9 (0.7-1.1)</td>
<td>1.5 (1.0-2.1)</td>
</tr>
</tbody>
</table>

Direct oral anticoagulants

Two major classes

Direct thrombin inhibitor → Dabigatran

Factor Xa inhibitors → Xa-bans

Rivaroxaban (2011)
Apixaban (2012)
Edoxaban (2015)

Dabigtran

Extrinsic pathway → Intrinsic pathway

Xa

Thrombin

Clot

Dabigatran
Dabigtran

- Twice daily dosing
- Activated by liver
- Renally cleared
- P-glycoprotein substrate

Approved for
1) Stroke prevention (AF)
2) VTE treatment
3) VTE prevention

Xa-bans

Extrinsic pathway
Intrinsic pathway

Xa
Thrombin
Clot

Variable | Apixaban | Edoxaban | Rivaroxaban
---------|----------|----------|----------
Dosing   | Twice daily | Once daily | Once daily |
Metabolism | Hepatic | Minimal | Hepatic |
Excretion | Renal | Renal | Renal |
Interactions? | Many | Some | Many |
AF? | Yes | Yes | Yes |
VTE? | Yes | Yes | Yes |

Updates from 2014-2015

1) Power in numbers (for AF, at least)
2) Real world data
3) Monitoring therapy
4) Individualized dosing
5) Reversal
## Pooled analyses (for AF)

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Relative risk (stroke)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Edoxaban</td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Adapted from Lancet. 2014 Mar 15;383(9921):955-62

## Pooled analyses (for AF)

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Relative risk</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>1389</td>
<td>0.1</td>
</tr>
<tr>
<td>Hem. stroke</td>
<td>393</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI</td>
<td>845</td>
<td>0.77</td>
</tr>
<tr>
<td>Mortality</td>
<td>4267</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Adapted from Lancet. 2014 Mar 15;383(9921):955-62

## Pooled safety analyses (for AF)

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Relative risk</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>3343</td>
<td>0.06</td>
</tr>
<tr>
<td>ICH</td>
<td>629</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>1342</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Adapted from Lancet. 2014 Mar 15;383(9921):955-62

## Pooled analyses (Cochrane, DTI)

<table>
<thead>
<tr>
<th>Outcome or subgroup</th>
<th>n</th>
<th>Method</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular death or stroke</td>
<td>12448</td>
<td>Odds Ratio</td>
<td>0.86 (0.75-0.99)</td>
</tr>
<tr>
<td>Fatal and non-fatal bleeding</td>
<td>12448</td>
<td>Odds Ratio</td>
<td>1.01 (0.89-1.16)</td>
</tr>
<tr>
<td>Adverse events (led to d/c)</td>
<td>18509</td>
<td>Odds Ratio</td>
<td>2.12 (1.77-2.56)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>18443</td>
<td>Odds Ratio</td>
<td>1.35 (1.12-1.63)</td>
</tr>
<tr>
<td>Mortality</td>
<td>18509</td>
<td>Odds Ratio</td>
<td>0.90 (0.80-1.01)</td>
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</tbody>
</table>

Cochrane Database Syst Rev. 2014 Mar 27;3:CD009893
Pooled analyses (Cochrane, Xa-bans)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients (n)</th>
<th>Illustrative risks (n/1000)</th>
<th>RR</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Warfarin</td>
<td>Xa-bans</td>
</tr>
<tr>
<td>Emboli</td>
<td>40777</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Strokes</td>
<td>40749</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>Bleeding</td>
<td>42078</td>
<td>46</td>
<td>39</td>
</tr>
<tr>
<td>ICH</td>
<td>39638</td>
<td>11</td>
<td>6</td>
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<tr>
<td>Deaths</td>
<td>38924</td>
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</table>

Cochrane Database Syst Rev. 2013 Aug 8;8:CD008980

Pooled analyses (VTE)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events, n</th>
<th>Relative risk</th>
<th>p</th>
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<tbody>
<tr>
<td>Recurrent VTE</td>
<td>559</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>277</td>
<td></td>
<td>0.95</td>
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<tr>
<td>Fatal PE</td>
<td>21</td>
<td></td>
<td>0.53</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Events</th>
<th>Favors NOAC</th>
<th>Favors warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Is there more bleeding in the real world?

FAERS (FDA Adverse Event Reporting System) from the first year of dabigatran usage suggested increased risk of fatal bleeding compared to trials.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial fatality rate</th>
<th>2010-2011 rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>9.1%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>13%</td>
<td>7.1%</td>
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</table>

Data plagued by unknown reporting rates

### Is there more bleeding in the real world?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate/1000py</th>
<th>Dabigatran</th>
<th>VKA</th>
<th>HR</th>
<th>p</th>
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<tbody>
<tr>
<td>Ischemic stroke</td>
<td>205</td>
<td>270</td>
<td>11.3</td>
<td>13.9</td>
<td>0.8 [0.7-1.0]</td>
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<tr>
<td>Hemorrhage</td>
<td>777</td>
<td>851</td>
<td>42.7</td>
<td>43.9</td>
<td>0.97 [0.9-1.1]</td>
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<tr>
<td>GI bleeding</td>
<td>623</td>
<td>513</td>
<td>34.2</td>
<td>26.5</td>
<td>1.28 [1.1-1.4]</td>
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<tr>
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<td>60</td>
<td>186</td>
<td>3.3</td>
<td>9.6</td>
<td>0.34 [0.3-0.5]</td>
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<tr>
<td>MI</td>
<td>285</td>
<td>327</td>
<td>15.7</td>
<td>16.9</td>
<td>0.92 [0.8-1.1]</td>
</tr>
<tr>
<td>Hospitalized bleeds</td>
<td>1079</td>
<td>1139</td>
<td>59.3</td>
<td>58.8</td>
<td>1.00 [0.9-1.1]</td>
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<tr>
<td>Mortality</td>
<td>603</td>
<td>744</td>
<td>32.6</td>
<td>37.8</td>
<td>0.86 [0.8-1.0]</td>
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</table>

### Is there more bleeding in the real world?

- **Age >75**
  - Dabigatran: 1.6 [1.4-1.9]
  - Warfarin: 2.1 [1.4-3.2]

- **Black race**
  - Dabigatran: 2.1 [1.7-2.6]
  - Warfarin: 1.9 [1.5-2.3]

### Monitoring therapy

**How do we know if a patient is anticoagulated with a DOAC?**

- **TT**
  - Low
  - On-target
  - High

- **APTT**
  - Low
  - On-target
  - High

- **PT**
  - Low
  - On-target
  - High

*Curr Med Res Opin. 2014 Jul;30(7):1317-25*

*Curr Med Res Opin. 2014 Jul;30(7):1317-25*
Monitoring therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>?Low</th>
<th>On-target</th>
<th>?High</th>
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<tr>
<td>Dabigatran</td>
<td>TT</td>
<td>Dilute TT</td>
<td>aPTT</td>
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<tr>
<td>Rivaroxaban</td>
<td>Anti-Xa activity</td>
<td>Anti-Xa activity</td>
<td>PT</td>
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<tr>
<td>Apixaban</td>
<td>Anti-Xa activity</td>
<td>Anti-Xa activity</td>
<td>Anti-Xa activity</td>
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Monitoring therapy (summary)

Do levels matter?

Do levels matter?


Dabigatran Trough Conc. Steady-State (ng/mL)

<table>
<thead>
<tr>
<th>Probability Stroke (%)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
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<td></td>
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<td></td>
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<td></td>
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<td>200</td>
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</tr>
</tbody>
</table>

Event Rate %

1) Xa-bans

2) Dabigatran
1) **Direct anti-coagulants** are 5 years old (!) and a substantial amount of data is now available regarding efficacy and safety.

2) Real world results have (so far) been similar to trial data.

3) Drug activity can be measured (imperfectly).

4) Safety can probably be improved.

5) Antidotes are in phase III trials, though not yet approved for use.
Anxiety, PTSD, and Adult ADD: Drug Therapy in the Primary Care Setting

Matt Schreiber
Staff Psychiatrist -- Seattle VA
Acting Assistant Professor
Department of Psychiatry and Behavioral Sciences
University of Washington

Objectives
- Review current drug therapy of anxiety and PTSD in the Primary Care setting
- Review current drug therapy of adult ADD in the Primary Care setting

Case Illustration 1: Anxiety

30 year old male pharmacist presents in Primary Care.
- "lifelong"history of worry.
- worse over the past year -- more responsibility at work and he and his wife have had their first child.
- constantly worried that something will go wrong at work, that he will be fired, or that something will happen to his baby, even though he realizes that he has "no reason to be worried."
- complains of muscle tension, feeling exhausted by worry, upset stomach, and irritability.

General considerations for anxiety
- very commonly seen in primary care
- often present with medical complaints
- similar to major depression and chronic diseases such as diabetes in functional impairment and decreased quality of life
Anxiety is a symptom...

In specific anxiety disorders:
- Social anxiety disorder (SAD)
- Panic disorder (PD)
- Generalized anxiety disorder (GAD)

Or other mental health conditions:
- Depression
- Adjustment Issues/Disorder

Anxiety is a symptom...

In many situations encountered in Primary Care:
- Medications
- Medical conditions
- Drugs

Case Illustration 2: Anxiety

A 56 year old architect presents to Primary Care:
- Feeling stressed, tense, preoccupied by worry about “everything.”
- She has a history of recent onset atrial fibrillation and complains of feeling “too hot all the time,” on edge, and “shaky.”
- Also admits to drinking 6 or 7 “energy drinks” a day, more when under a deadline.

Case Illustration: PTSD

25 year old cashier at a grocery store
- Involved in a robbery at the store 2 months ago; held at gunpoint with 5 co-workers for several hours; physically unharmed, but shaken and comes to see you in PC
- Nightmares every night about this event
- Thinks about it repeatedly during the day
- Startles and feels panicky whenever someone resembling the robber enters the store
- Feels on edge, very anxious, and depressed
- Has withdrawn from friends and family
Posttraumatic Stress Disorder

- Exposure to trauma (specifically defined)
- Symptoms in DSM-5 in four clusters:
  -- Re-experiencing (nightmares)
  -- Avoidance (anxiety)
  -- Negative cognitions/mood (depression)
  -- Altered arousal (irritability, hypervigilance)

Managing Anxiety and PTSD: Medication Choice

- SSRIs are still first-line treatment
- SSRIs with the least drug interactions are generally favored: escitalopram (Lexapro), start at 5 mg/day, can increase to 20 mg/day as QD dosing
- Consider other agents -- mirtazapine (Remeron), 15-45 mg QHS
- SNRIs such as venlafaxine (Effexor) or desvenlafaxine (Pristiq) are second line
- Avoid bupropion (Wellbutrin), it can increase anxiety

Managing Anxiety and PTSD: Prescribing Principles

- Start at low doses, and increase slowly
- Educate about common SEs and F/U 2-4 weeks
- Listen to SEs and take them seriously; empathic listening + shared decision-making often = success
- Consider a screener (GAD7) to track symptoms and treatment response

<table>
<thead>
<tr>
<th>Medication</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Anticholinergic</th>
<th>Sedation</th>
<th>Dry Mouth</th>
<th>Sexual</th>
<th>Weight Gain</th>
<th>Tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
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<td>0</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>3+</td>
<td>1+</td>
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<tr>
<td>Fluoxetine</td>
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<td>1+</td>
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<td>3+</td>
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<td>3+</td>
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<td>Venlafaxine</td>
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<td>2+</td>
<td>1+</td>
<td>2+</td>
<td>4+</td>
<td>1+</td>
<td>4+</td>
</tr>
</tbody>
</table>

Legend: (0 = none, 1+ = slight, 2+ = low, 3+ = moderate, 4+ = high)
Managing Anxiety and PTSD: Using a Benzodiazepine (BZD)

- If using a BZD, consider your approach, aim to limit to short-term use if possible
- Avoid rapid onset (diazepam) and short acting (alprazolam)
- If discontinuing long-term BZD, establish rapport 1st, set realistic expectations—tapering is often difficult, consider this whenever starting an agent

Anxiety: Managing Benzodiazepines

- Consider establishing clear limits before the first BZD prescription, for example:
  - Single provider and single pharmacy only
  - No early refills or refills from other providers
  - Intermittent UTx that must be provided same day
  - Let patient know that you will periodically review the state’s RX monitoring website to ensure compliance
- If use is intended to be brief, be specific when starting

Buspirone (BuSpar)

- 5HT-1A partial agonist
- May be more effective for cognitive anxiety symptoms (worry). **Non-sedating.**
- **Delayed onset of action** (2-4 weeks)
- **No evidence of tolerance/withdrawal**
- Side effects – nausea, dizziness, headaches
- *Does not treat benzodiazepine withdrawal*
- Wide dose range: start 5-7.5 mg BID up to 15-20 mg TID

Prazosin (Minipress)

- α1-adrenergic antagonist (anti-hypertensive)
- treatment for **PTSD-related nightmare**, efficacy based on clinical trials
- start at 1 mg, typically effective from 1-5 mg, taken QHS
- side effects: orthostasis/lightheadedness, improves with time; very cautious if combining with PDE-5 inhibitors (e.g. sildenafil)
Adult ADD in Primary Care: Case 1

32 year old woman presenting in Primary Care:
- BP 134/83, HR 91
- recently started college courses using her GI Bill
- “can’t focus” on schoolwork, worried about grades (B-, C)
- had difficulty all through school years, dropped out, got a GED
- “a lot of trouble” staying in relationships, and doesn’t really “understand what’s going wrong”

Adult ADD in Primary Care: Case 2

68 year old man presents to you in Primary Care with history of hypertension (lisinopril); hypercholesterolemia (simvastatin), reports “I can’t get anything done.”
- Retired electrical engineer, takes CC classes “to stay sharp”
- “always” found it hard to focus and concentrate, frequent minor disciplinary problems as a child (impulsive)
- married for the fourth time after three divorces
- borrowed ritalin at Senior Center – “It helped!”

Adult ADD: screening and diagnosis in Primary Care

1. There are no definitive tests to diagnose adult ADD
2. DSM-5 requires:
   - onset before age 12
   - inattention AND/OR hyperactivity/impulsivity
   - symptoms cause impairment in 2 or more settings
   - clear evidence the Sx interfere with/reduce quality of social, academic or occupational functioning

Adult ADD: screening and diagnosis in Primary Care

Comorbidity is important in ADD
- screen for and strongly consider treating depression or anxiety first, as primary disorders
- check for substance abuse in general, stimulants in particular
- what do you feel is manageable in your primary care setting versus specialty care?
Adult ADD: screening and diagnosis in Primary Care

Suggested approach:
- take a history that focuses on attention and impulsivity symptoms issues and their functional impact
- collateral informant if available and practicable is very helpful but not always available
- consider comorbidity and also risks of treatment

ADD: Treatment Considerations

Stimulants are the first-line treatment

Risks:
- misuse/diversion
- side effects in adults
- medical comorbidities and concerns

If prescribing stimulants, consider:
- setting behavioral expectations (UDAS, misuse)
- there is no strong medical concern about withdrawing

ADD: Treatment Considerations

Stimulants: methylphenidate family

- Stimulants: Two Main Families with Many Variants
- Short-acting vs. Longer-acting
- Risks, side effects associated with both are similar
- FDA black box warning for stimulants: abuse potential, use with caution in patients with substance use disorder history
- Clinical interactions with tics, psychosis, cardiac disease
- Side effects: anxiety, insomnia, appetite changes

- Short acting
  generic methylphenidate
  —dose range 40 – 80 mg/day divided BID
  —duration of action about 3-4 hours

- Long acting
  Concerta (proprietary extended release formulation)
  —duration 10-12 hours, dose range 18-72 mg QAM
  Focalin XR (dexamethasone enantiomer)
  —duration around 12 hours, 10-40 mg QAM
  Ritalin sustained action
  —duration 3-8 hours, typical dose range 20-60 mg QAM
Stimulants: **amphetamine family**

- **Adderall** (d- and l-amphetamine)
  - proprietary racemic mixture of d- and l-amphetamine
  - long acting, given QAM, around 12 hours duration of action
  - typical dose range 10-30 mg/day

- **Vyvanse** (lisdexamfetamine)
  - inactive pro-drug formulation metabolized to d-amphetamine
  - very long acting, given QAM, around 14 hours duration of action
  - typical dose range 30-60 mg/day

- **Generic dextroamphetamine** (dexedrine)
  - immediate release (4 hours duration of action), 10-40 mg/day, split BID, do not take late in the day
  - sustained action (6-8 hours), 10-40 mg/day, QAM

**Adult ADD: Non-stimulant treatment option**

- **Atomoxetine** (strattera)
  - **Not a controlled substance**; does not have abuse potential
  - NE reuptake inhibitor
  - Delayed onset of action
  - Also has cardiac concerns—recent MI, history of CAD
  - Typical dose range 40-80 mg/day, and available in many strengths
<table>
<thead>
<tr>
<th>Medication</th>
<th>Anti-cholinergic</th>
<th>Drowsiness</th>
<th>INSONMIA/AGITATION</th>
<th>Orthostatic Hypotension</th>
<th>QTc prolongation</th>
<th>GI toxicity</th>
<th>Weight gain</th>
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<td>0 – 1+</td>
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<td>3+</td>
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<tr>
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<td>2+ (IR)</td>
<td>1+ (SR)</td>
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<td>3+</td>
</tr>
</tbody>
</table>

**Legend:** (0 = none, 1+ = slight, 2+ = low, 3+ = moderate, 4+ = high)

Information adapted from UpToDate website article: “Unipolar major depression in adults: Choosing initial treatment” by Paul Ciechanowski; section editor, Peter Roy-Byrne. Adaptation courtesy of Dr. Beth Chmelik, UW/Seattle VA.
Objectives

- Review immunosuppressive medications used in solid organ transplant (SOT)
- Consider SOT medication side-effects, interactions and toxicity
- Use common primary care scenarios to illustrate important medication management considerations for SOT patients

Immunity 101

Figure 1: Schematic of mechanisms of action of immunosuppressive drugs
**SOT Meds - Triple Therapy**

- Calcineurin inhibitor – tacrolimus (FK506, Prograf), cyclosporine (Sandimmune, Neoral)
  - Acts by blocking calcineurin, blocks IL2 production
- Antiproliferative – mycophenolate (MMF, Cellcept), mycophenolic acid (Myfortic)
  - Acts by blocking the cell cycle in the nucleus
- Corticosteroid – (prednisone, prednisilone)
  - Acts on the APC complex, and blocks IL2

**Mechanism of Action – Calcineurin Inhibitors**

**SOT Meds - Other**

- Azathioprine (Imuran)
  - Used in patients intolerant to MMF
  - Acts on the cell cycle of the nucleus
- Sirolimus (Rapamune), everolimus (Afinitor, Zortress)
  - Used instead of/ or to lower dose of cyclosporine or tacrolimus
  - Acts by blocking TOR (target of rapamycin)
Mechanism of Action – Anti-TOR

Case

48 M s/p an orthotopic liver transplant 2007 for ETOH cirrhosis presents to clinic with a 1 day history of a hot red right 1st MTP joint. He tells you this is his 3rd bout of gout this year.

Meds: Cyclosporine, Azathioprine, Prednisone

You recommend...

A) ↑ PO prednisone acutely
B) Colchicine
C) Probenecid
D) Allopurinol + ↑ prednisone
E) Febuxostat (Uloric) + colchicine

Calcineurin Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
<th>Med Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>Nephrotoxicity</td>
<td>↑ levels</td>
</tr>
<tr>
<td></td>
<td>↑ Tk, ↓ Mg</td>
<td>Phenotoin</td>
</tr>
<tr>
<td></td>
<td>Drug induced DM</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>Phenoobarbital</td>
</tr>
<tr>
<td></td>
<td>Neurotoxicity</td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td>GI</td>
<td>↑ levels</td>
</tr>
<tr>
<td></td>
<td>HTN</td>
<td>Azoles</td>
</tr>
<tr>
<td></td>
<td>Mhtnulism</td>
<td>Fluorquinolones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Otilazem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sirolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grapefruit</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>HTN</td>
<td>Statins contraindicated</td>
</tr>
<tr>
<td></td>
<td>↓ Nephro and Neurotoxicity</td>
<td></td>
</tr>
</tbody>
</table>
Antiproliferatives

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side Effects</th>
<th>Med Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate (MMF, Cellcept)</td>
<td>GI ulceration (PPI)</td>
<td>+ Levels</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>Antacids</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Cholestyramine</td>
</tr>
<tr>
<td></td>
<td>GI</td>
<td>Neurotoxicity</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis (rare)</td>
<td></td>
</tr>
<tr>
<td>Mycophenolic Acid (Myfortic)</td>
<td>Same as above</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>GI</td>
<td></td>
</tr>
</tbody>
</table>

Other SOT Immunosuppressives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
<th>Med Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine (Imuran)</td>
<td>Leukopenia, Anemia,</td>
<td>Allopurinol</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia, GI</td>
<td>Febuxostat</td>
</tr>
<tr>
<td></td>
<td>Rare- hepatitis, pancreatitis</td>
<td>contrainicated- blocks metabolism, ↑ toxicity</td>
</tr>
<tr>
<td>Sirolimus (Rapamune)</td>
<td>Same home issues, HTN,</td>
<td>Same as calcineurin inhibitors</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Give sirolimus 4 h after cyclosporine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>contraindicated</td>
</tr>
</tbody>
</table>

Managing Gout in SOT

- ↑ risk for gout
  - ↓ excretion of uric acid via calcineurin inhibitors, ↑ serum uric acid
  - CKD ↑ uric acid excretion
- Medication considerations
  - NSAIDs contraindicated in general
  - Colchicine use may be limited by CKD/AKI
  - Probenecid is ineffective in CKD
  - Febuxostat (Uloric) + azathioprine contraindicated, ↑ azathioprine levels/toxicity
  - Allopurinol + azathioprine require monitoring and adjustment for ↑ toxicity

Case

33 M s/p pancreas-renal transplant 18 months prior for DM1 presents with 48 hours of rhinorrhea, cough productive of white sputum, and nasal congestion. VS are stable, PE is notable for nasal mucosa erythema, clear discharge, post nasal drip, and otherwise normal.

Which medication should be avoided in SOT patients?

- a) Diphenhydramine
- b) Guaifenesin
- c) Dextromethorphan
- d) Codeine
Case - Cough

• Acute cough should be assessed aggressively in SOT.
  – Immunosuppressants can dampen infectious responses like fever
  – More indolent course, have an atypical origin or have more severe manifestations
  – Low threshold for CXR, influenza assessment, or sinus evaluation

• ↓ immunosuppression >6 mo post transplant
  – Community acquired infections > opportunistic, reactivation, and nosocomial infections

Case – Cough Treatment

• Guaifenesin - ↑ ciliary motility, ↓ mucous thickness. Safe in SOT.
• Detromethorphan- centrally acting antitussive. Potential P450 2D6 competitive metabolism
• Diphenhydramine – non-selective antihistamine. Anti-cholinergic side-effects.

---

Case - Depression

57M 9 months post heart transplant presents with 1 month of anhedonia, low mood, sleep disruption, loss of hope and passive suicidality. Meds: Cyclosporine, prednisone, mycophenolate.

PHQ9 15
In addition to counseling your recommend:

a) Fluoxetine
b) Buproprion
c) Escitalopram
d) Paroxetine
e) Sertraline

---

Case- Cough Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Concerns</th>
<th>Safety in SOT</th>
</tr>
</thead>
</table>
| Guaifenesin  | ↑ ciliary motility, ↓ mucous thickness | Questionable efficacy for cough    | - First line  
|              |                                  |                                               | - May cause urinary tract stones  |
| Dextromethorphan | Centrally acting anti-tussive | Potential P450 2D6 competitive metabolism | - Beware in liver dysfunction  
|              |                                  |                                               | - Not helpful in lung tx        |
| Diphenhydramine | Locally acting anesthetic and centrally acting | Anti-cholinergic side-effects | - Caution with calcineurin inhibitors, check levels |
| Codeine      | Narcotic centrally acting antitussive | Drowsiness, decreased GI motility, orthostatic hypotension | - Beware in liver dysfunction  
|              |                                  |                                               | - Not helpful in lung tx        |

PMID: 21485938
SOT and Antidepressants

- ↑ rates of depression pre and post transplant
- ↑ morbidity related to depression
- Many antidepressants are P450 inhibitors
  - Fluoxetine, paroxetine, bupropion, sertraline*, nefazodone*
  - Citalopram, escitalopram and mirtazapine minimally inhibit P450
- St. Johns Wort is a potent P450 inducer
  - Beware in combination with tacrolimus and cyclosporine
- Citalopram and TCAs ↑ QT interval.
  - Beware in combination with tacrolimus and cyclosporine

**TAKE HOME:** Consider escitalopram or mirtazapine as first line antidepressant or anxiety prevention medications in SOT patients

Case- Hypertension

43F s/p cadaveric renal transplant 3 years ago presents for follow-up of elevated BP readings. Her 24 hour blood pressure monitor shows a lack of usual “circadian dipping” with an average SBP 153 and DBP 95. K 4.5, Cr. 1.5, U alb/Cr 20.

Besides diet and lifestyle modifications, what do you recommend?

a) HCTZ  
b) Furosemide  
c) Lisinopril  
d) Amlodipine  
e) Atenolol

Hypertension in SOT

- ↑ risk
  - 55-85% liver transplant, 70-90% renal transplant
  - Steroids, calcineurin inhibitors, renal impairment
  - Incremental ↑ graft failure with ↑ BP
  - Goal < 130/80 (NICE guidelines) JNC 8 <140/90
- ↑ complexity of medication selection
  - Coordinate care with transplant center
  - May require ↓ immunotherapy or surgery
  - Consider ambulatory BP monitoring (ABPM)
  - Circadian “nondipping” in renal transplant
# Hypertension Medications in SOT

<table>
<thead>
<tr>
<th>Antihypertensive</th>
<th>Considerations</th>
<th>Helpful for comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretic</td>
<td>↑ Serum uric acid levels, Mg, calcineurin inhibitor</td>
<td>CHF, volume overload</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>↑ Serum uric acid levels, ↑ CVD risk</td>
<td></td>
</tr>
<tr>
<td>CCB</td>
<td>Dose adjust cyclosporine and tacrolimus if using diltiazem and verapamil due to med interactions</td>
<td>↑ CVD risk, DM, Dihydropyridines preserve graft function in renal SOT</td>
</tr>
<tr>
<td>ACE-inhibitors and ARBs</td>
<td>Consider use once renal function is stable. If compelling indication Cr&lt;2.5, K&lt;5.5</td>
<td>Proteinuria, post-transplant ancyropoietinosis, DM, post MI/CVA, CKD</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>2nd line therapy</td>
<td>Stable CHF, post MI, ↑ CVD risk, arrhythmia</td>
</tr>
<tr>
<td>Potassium sparing diuretic</td>
<td>3rd line therapy, ↑K in CKD</td>
<td>CHF</td>
</tr>
<tr>
<td>Alpha blocker</td>
<td>3rd line add-on therapy</td>
<td>BPH</td>
</tr>
</tbody>
</table>
Antibiotic Update 2015

Shireesha Dhanireddy, MD
23 April 2015
Current Concepts in Drug Therapy

Antibiotic Update 2015: Disclosures
No Financial Conflicts of Interest

Antibiotic Update 2015: Outline
• Cystitis / UTI
• Rhinosinusitis
• Skin & Soft Tissue Infections

Case 1
“I think I have a UTI”
• A 21 year-old woman c/o increased urinary frequency & burning with voids. Recently became sexually active for the first time, uses diaphragm.
• No PMH, meds, or allergies.
• Afebrile. Modest suprapubic TTP.
• U/A: Many WBCs, moderate bacteria, few epis. SpGr 1.020 / pH 5 / +LE / +Nitrite

Working Diagnosis:
Acute uncomplicated bacterial cystitis
Fosfomycin

Table 8. Comparative studies of fosfomycin treatment for acute uncomplicated cystitis.

<table>
<thead>
<tr>
<th>Trial [reference], parameter</th>
<th>Fosfomycin SDT</th>
<th>Comparator</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosfomycin SDT vs. co-trimoxazole, ≥5 d [58, 59]*</td>
<td>91/94 (97)</td>
<td>74/90 (89)</td>
<td>NS</td>
</tr>
<tr>
<td>Endocidation</td>
<td>26/55 (32)</td>
<td>22/79 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>29/132 (26)</td>
<td>12/109 (11)</td>
<td>.004</td>
</tr>
<tr>
<td>Fosfomycin SDT vs. pipemidic acid, 3 d [57]</td>
<td>123/164 (74)</td>
<td>153/143 (98)</td>
<td>.018</td>
</tr>
<tr>
<td>Endocidation</td>
<td>9/132 (7)</td>
<td>8/132 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>22/164 (15)</td>
<td>21/143 (15)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE: Data are as: with parameter/total (%) NS = not significant, i.e., >.05; SDT = single-dose therapy.
* Meta-analysis.

- 3 gm sachet in 32 oz H2O x 1 dose
- Comparable efficacy to FQ... BUT bad choice for pyelo, and higher incidence of AE (headache, diarrhea)

Antibiotic Update 2015: UTI

Empiric Abx:
- Nitrofurantoin (Macrolid) 100mg PO BID x 5 days (avoid in pyelo!) OR
- TMP/SMX (Bactrim) ® <20%: 1 DS PO BID x 3 days OR
- Fosfomycin (Monoval) 3gm PO x 1 dose (avoid in pyelo)
- TMP/SMX ® >20%:
  - Cipro 500mg PO QD x 3 days OR
  - Cefpodoxime 100mg PO BID x 7 days

Cipro vs. Cefpodoxime:
- Women with acute cystitis randomized to 3 days of cipro vs cefpodoxime, f/u = 1 month.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cipro (n=150)</th>
<th>Cefpodoxime (n=150)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Cure</td>
<td>83%</td>
<td>71%</td>
<td>3%-21%</td>
</tr>
<tr>
<td>Micro Cure</td>
<td>96%</td>
<td>81%</td>
<td>8%-23%</td>
</tr>
<tr>
<td>Vaginal E.coli colonization</td>
<td>16%</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>
Antibiotics Update 2015: *UTI*

**Cipro vs. Cefpodoxime:**
- Women with acute cystitis randomized to 3 days of cipro vs cefpodoxime, f/u = 1 month.
- “Cefpodoxime not noninferior to cipro.”
- **Caveat:** Low dose & short course given!
- **Suggestion:** If cefpodox given, consider non-approved regimen: 200mg BID x 7 days.

---

**Antibiotic Update 2015: Pro-Biotics?**

- *Lactobacillus crispatus* is normal vaginal flora, drives down pH, keeps *E.coli* at bay.
- Phase 2 trial of Lactin-V (Ocel) Suppositories (daily x 5, then weekly x 10)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>L. crispatus (n=48)</th>
<th>Placebo (n=48)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI Recurrence</td>
<td>7/48 (15%)</td>
<td>13/48 (27%)</td>
<td>RR 0.5 CI 0.2-2.1</td>
</tr>
<tr>
<td>High Level Vaginal <em>E.coli</em> colonization</td>
<td>RR 0.07</td>
<td>RR 1.1</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

---

Antibiotic Update 2015: *UTI*

**The Future…**

- A 28 year-old woman c/o 2 days of subjective fever, rhinorrhea, nasal congestion, sore tx, HA. “I really want some antibiotics to get on top of this.”
- Meds: None.
- PMH: None.
- SH: Smoker, no drug abuse.
- AVSS, boggy turbinates, modest facial pain, neck supple, lungs clear.
- **PLAN:** Decongestants, analgesics, call in a week if not better.

---

Antibiotic Update 2015: *Rhinosinusitis*

- American adults have 2-3 / year
- ~98% viral (rhino, corona, paraflu, etc.)
- 2% bacterial (*S.pneumo, H.flu, M.cat*)
- Symptomatic relief indicated regardless of cause
- No ironclad symptoms or signs distinguish between viral & bacterial etiologies
- Single best predictor of bacterial involvement: **symptoms > 10 days**
Antibiotic Update 2015: *Rhinosinusitis*

Fundamentals…

- Reassurance: “Good news, no abx needed!”
- Scheduled anti-inflammatory / analgesics
- Judicious decongestants in *select* cases
- Consider topical steroids if h/o allergy
- Vitamin C: A fine way to acidify your urine
- Appropriate hygiene and infection control!

### ZINC

- Inhibits rhinovirus in vitro
- Oral zinc in Cochrane Meta-Analysis:
  - 15 placebo-controlled trials
  - 1,360 patients
  - Treatment started within 24 hours of sx

#### ZINC Summary

- May reduce symptoms by about a day
  - Duration of symptoms 0.97 days less
- May reduce antibiotic consumption
  - OR 0.27
- May lead to minor, temporary side effects
  - OR 1.59; leading side effects: bad taste, nausea, constipation

*Singh Cochrane Rev 2011*

### NETI POT

- Favorable Cochrane Meta Analysis
- Many patients adore it
- Advise filtered, boiled, distilled, or sterile water!
**Abx Update 2012: Rhinosinusitis**

**Warning Signs…**

- Persistent, high-grade fever (e.g. > 102°F)
- Altered Mental Status
- Dyspnea
- Ocular or orbital pain
- DKA
- Facial Erythema

Thorough, rapid evaluation required…

antibiotics may be appropriate!

**Case Continued…**

- She took your advice…
- No antibiotics were prescribed…
- Zinc made food taste funny…
- Ten days have elapsed…
- She is no better! Sinus pain is worse, headaches have increased! Chaotic fever persists!

---

**Which of the following will inform your choice of antibiotic?**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Cost?</td>
<td>G) Past microbiology?</td>
</tr>
<tr>
<td>B) Allergies?</td>
<td>H) Candida History?</td>
</tr>
<tr>
<td>C) Pregnancy?</td>
<td>I) Sun exposure?</td>
</tr>
<tr>
<td>D) Drug interactions?</td>
<td>J) Tendon rupture risk?</td>
</tr>
<tr>
<td>E) Past abx?</td>
<td>K) Diarrhea history?</td>
</tr>
</tbody>
</table>

---

**BACTERIAL PATHOGENS IN ADULT RHINOSINUSITIS**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.pneumoniae</td>
<td>41</td>
</tr>
<tr>
<td>H.influenzae</td>
<td>35</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>7</td>
</tr>
<tr>
<td>Streptococci</td>
<td>7</td>
</tr>
<tr>
<td>M.catharralis</td>
<td>4</td>
</tr>
<tr>
<td>S.aureus</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
</tbody>
</table>
Antibiotic Update 2015: Rhinosinusitis

None proven superior...

- Erythro base 500mg BID
- Amox/clav 875 BID
- Cefpodoxime 200 BID
- Cefdinir 600 QD
- Doxycycline 100 BID
- TMP/SMX 1 DS BID
- Levofoxacin 500 QD
- Moxifloxacin 400 QD

Concern: Pneumococcal Resistance

Antibiotic Update 2015: Rhinosinusitis

First-Line Empiric Abx

- Amox/clav 875-2,000 BID x 5-7 days

Second-Line Empiric Abx

- Doxycycline 100 BID or
- Levofoxacin 500 QD or
- Moxifloxacin 400 QD

5-7 days

No Longer Recommended

- Azithromycin or TMP/SMX

Antibiotic Update 2015: Case 3

“My leg is killing me!”

- 56 y/o diabetic man presents with red leg x 48 hours.
- No recalled trauma, no pus, no h/o MRSA, no household contacts with “staph.”
- Brawny erythema, macerated toe web spaces.

Skin & Soft Tissue Infections
SSTI New Guidelines 2014

• Management
  • Differs for purulent vs non-purulent infections
  • Stratified based on severity

Purulent
Furuncle/Carbuncle/Abscess

- Severe
  - I&D
  - C&S
  - Empiric Rx
  - Defined Rx

- Moderate
  - I&D
  - C&S
  - Empiric Rx
  - Defined Rx

- Mild
  - I&D

Purulent
Furuncle/Carbuncle/Abscess

- Severe
  - I&D
  - C&S
  - Empiric Rx
  - Defined Rx

- Moderate
  - I&D
  - C&S
  - Empiric Rx
  - Defined Rx

- Mild
  - I&D

Telavancin

- Bactericidal lipoglycopeptide antibiotic with activity against MRSA and other Gram + bacteria
- Mechanism of action – inhibits cell wall synthesis and disrupts bacterial membrane depolarization
- Approved for treatment of SSTI
- Also approved for treatment of HAP and VAP due to *S. aureus*
- Common/serious AE: Renal toxicity
Ceftaroline

- Anti-MRSA, 5th generation cephalosporin
- Available IV only
- Approved for treatment of SSTI and CAP
- Cost: $82/day (vs ~$12/day for vancomycin
- Reserve for patients with proven MRSA, consult ID

Tedizolid (Sivextro)

- FDA approved June 2014 for treatment of skin/soft tissue infections
- Dose: 200mg IV/PO daily x 6 days
- Mechanism of action: Same as linezolid (oxazolidinone)
- No dose adjustment for renal or hepatic impairment
- Precautions: Weak MAO inhibitory activity
- Cost: IV - $224 ; PO - $280
  - Linezolid IV - $90 ; PO - $237

Purulent Furuncle/Carbuncle/Abscess

**MRSA**
- TMP/SMX or doxycycline

**MSSA**
- Nafcillin or Cefazolin or Clindamycin

Purulent Furuncle/Carbuncle/Abscess

**Severe**
- I&D C&S
- Defined Rx

**Moderate**
- I&D C&S
- Defined Rx

**Mild**
- I&D C&S
- Defined Rx

**TMP/SMX or doxycycline**

**Empiric Rx**
- Defined Rx

**Empiric Rx**
- Defined Rx
Purulent Furuncle/Carbuncle/Abscess

- **Severe**
  - I&D
  - C&S
  - Empiric Rx
  - Defined Rx
  - MRSA
    - TMP/SMX
  - MSSA
    - Dicloxacillin or
      - Cephalexin

- **Moderate**
  - I&D
  - C&S
  - Empiric Rx
  - Defined Rx

- **Mild**
  - I&D
  - NO ANTIBIOTICS


Nonpurulent Necrotizing Infection/Cellulitis/Erysipelas

- **Severe**
  - Emergent Surgical Debridement
  - Empiric Vancomycin + Pip/Tazo
  - Defined Rx

- **Moderate**
  - IV Rx

- **Mild**
  - Oral Rx
Nonpurulent Necrotizing Infection/Cellulitis/Erysipelas

**Severe**
Emergent Surgical Debridement
Empiric Vancomycin + Pip/Tazo
Defined Rx

**Moderate**
IV Rx

**Mild**
Oral Rx

**Monomicrobial**
- *Strep pyogenes* → PCN + Clinda
- *Clostridium sp* → PCN + Clinda
- *Vibro vulnificus* → Doxycycline + Ceftazidime
- *Aeromonas hydrophila* → Doxycycline + Ciprofloxacin

**Polymicrobial**
Vancomycin + Pip/Tazo
Defined Rx

**PCN or Ceftriaxone or Cefazolin or Clindamycin**

**New Options for SSTIs in 2015**

The *New England Journal of Medicine*

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections
Dalbavancin

- Inhibits cell wall synthesis
- Active against Gram + bacteria (including MRSA)
- Long half life ~ 8.5 days, dosed once weekly
- Non-inferior to vancomycin
- Cost: $4500 / course

Oritavancin

- Semisynthetic derivative of vancomycin
- Broad Gram + coverage, including MRSA
- Long half-life, ~10 days
- Non-inferior to vancomycin
- Cost: $3000 single dose


Antibiotic Update 2015: Summary

- Cystitis / UTI
  - Consider local TMP/SMX resistance rate when determining empiric treatment
- Rhinosinusitis
  - Amox/clav first line treatment
- Skin & Soft Tissue Infections
  - New drugs available but their role unclear and cost may be prohibitive

Thanks!

Questions:
sdhanir@uw.edu
Dementia: Considering When to Start, Stop, and Continue Dementia Medications

Thursday, April 23 ~ 11:25 AM to 11:55 AM

Lianne Hirano, MD

Handout Not Available at this Time
CHRONIC PAIN

DAVID J. TAUBEN, MD, FACP
CHIEF, UW DIVISION OF PAIN MEDICINE
HUGHES M & KATHERINE G BLAKE ENDOWED PROFESSOR
CLINICAL ASSOCIATE PROFESSOR
DEPTS OF MEDICINE AND ANESTHESIA & PAIN MEDICINE
UNIVERSITY OF WASHINGTON, SEATTLE WA

OBJECTIVES

1. Evaluate the risks and benefits of drug and non-drug treatments used for pain.
2. Discuss new standards for use of opioids in chronic non-cancer pain.
3. Discuss the emerging models of drug and non-drug treatments of “central pain sensitization” syndromes
4. Make more informed pain drug treatment decisions in the outpatient setting

WHAT IS PAIN

Experience of the diminishment of one’s capacities

“Unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP 1979)

NOICEPTION

Nociceptors selectively respond to noxious stimulation

“THE LOESER ONION”

DISCLOSURES

No financial conflicts of interest.
- CME grant support from ER/LA Opioid Analgesics REMS Program Companies
- NIH Pain Consortium award: UW Center of Excellence in Pain Education

Off-label use of drugs will be mentioned
**PREDICTORS OF ABNORMAL PAIN RESPONSE**

- **History and examination:**
  - Demonstration of “non-anatomic” territory of pain
  - Depression or other preexisting mood disorder
  - Distressed socioeconomic status
  - Overall poor life coping status and satisfaction

- **Active emotional distress**
  - Particularly anxiety and fear (of the consequences or significance of an injury.)

- **Prior surgical complications or failure to resolve pain after previous surgery**

**Van Susante J, Acta Orthop Belg. 1998.**

**Von Korff M, Pain. 2005**

**Carroll LJ, Pain 2004**

**Carragee EJ, Spine J 2005**

---

**HOW PAIN SHOULD BE MEASURED**

1. **Pain intensity**
   - “How much does it hurt?”

2. **Pain interference with function**
   - “How much does pain interfere with your function”

3. **Mood (aka “distress”)**
   - Ask AND Measure

4. **Sleep**
   - Interference: Initiation and Maintenance

5. **Risks:**
   - Medical: ie. **Sleep Apnea**
   - Behavioral & Addictions

---

**IDENTIFYING CO-OCCURRING MOOD DIAGNOSES**

- Anxiety
  - GAD-7 (or PHQ-4)

- Depression
  - PHQ-9 (or PHQ-4)

- PTSD
  - PC-PTSD

---

In your life, have you ever had any experience that was so frightening, horrible, or upsetting that in the past month you:

1. Have had nightmares or thought about it when you did not want to?
2. Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?
3. Were constantly on guard, watchful, or easily startled?
4. Felt numb or detached from others, activities, or your surroundings?
"WHEN YOUR BRAIN IS ON FIRE
I CAN'T HELP YOUR PAIN..."

CHRONIC PAIN TREATMENT
“COMPARATIVE EFFECTIVENESS”
Extrapolated averages of reduction in Pain Intensity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>≤ 30%</td>
</tr>
<tr>
<td>Tricyclics/SNRIs</td>
<td>30%</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>30%</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>≥ 10*%</td>
</tr>
<tr>
<td>Cannabis</td>
<td>10-30%</td>
</tr>
<tr>
<td>CBT/Mindfulness</td>
<td>≥ 30-50%</td>
</tr>
<tr>
<td>Graded Exercise Therapy</td>
<td>variable</td>
</tr>
<tr>
<td>Sleep restoration</td>
<td>≥ 40%</td>
</tr>
<tr>
<td>Hypnosis, Manipulations, Yoga</td>
<td>+ effect</td>
</tr>
</tbody>
</table>


NON-DRUG MULTIMODAL ANALGESIA

- Cognitive:
  - Identify distressing negative cognitions and beliefs
- Behavioral approaches:
  - Mindfulness, relaxation, biofeedback
- Physical:
  - Activity coaching, graded exercise land & aquatic with PT, class, trainer, and/or solo
- Spiritual:
  - Identify and seek meaning and purpose of one’s life
- Education (patient and family):
  - Promote patient efforts aimed at increased functional capabilities


OPIOID SALES, ODs, AND ADDICTIONS

**OPIOID OVERDOSE RISK**

<table>
<thead>
<tr>
<th>Average Daily Dose of Prescribed Opioids (Morphine Equivalent Dose)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-user</td>
<td>0.04%</td>
</tr>
<tr>
<td>1-19 mg.</td>
<td>0.16%</td>
</tr>
<tr>
<td>20-49 mg.</td>
<td>0.26%</td>
</tr>
<tr>
<td>50-99 mg.</td>
<td>0.68% **</td>
</tr>
<tr>
<td>100+ mg.</td>
<td>0.79% **</td>
</tr>
</tbody>
</table>

9-fold increase in risk relative to low-dose patients

Significant increment in risk p<0.05

---

**BENZODIAZEPINES**

- Lack of evidence for sustained benefits
- Rebound insomnia
- Risk of over-sedation especially when combined with opioids
- Complicating development of tolerance, dependency, and addiction.

Use of benzodiazepines for sleep & anxiety are not recommended in chronic pain

---

**“BENDING THE CURVE”**

WA STATE FIRST IN NATION WITH DECLINE IN OPIOID RELATED ADVERSE EVENTS

Prescription Opioid Involved Overdoses Washington State

- Deaths
- Hospitalizations

Source: Jennifer Sabel PhD Epidemiologist, WA State Department of Health, April 18, 2014
METHADONE ODS >> OTHER OPIOIDS

For Pain Treatment
- Effective analgesic
- Chronic Opioid Therapy
- Long acting
- Inexpensive

For Addiction Treatment
- Requires special DEA licensing and treatment support
- Once daily liquid dosing eases administration
- Reduces mortality among heroin users

Significant accumulation with repeat dosing
- Initial T½ 13-47 hrs up to 48-72 hrs
- 100% hepatic cleared
- CYPs: 1A2, 2D6, 3A4

Inhibits its own CYP metabolism

DRUG OVERDOSES
WASHINGTON STATE 1999-2013

Source: C. Banta-Green WA State Department of Health

OPIOIDS
THE CLINICAL CONUNDRUM

Review
Annals of Internal Medicine

The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop

Roger Chen, MD; Joshua A. Tucker, PhD; Kelly A. Davino, PharmD; MD; MD; Bryan A. Hansen, PharmD; PhD; Sean D. Sullivan, PhD (in press); MPH; Tony Zee, MD; MS; Christine Buquere, MPH; and Richard A. Deyo, MD, MPH

Conclusion: Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms.

"Opioids are clearly the best treatment for some patients with chronic pain, but there are probably more effective approaches for many others."

Evidence is insufficient for every clinical decision that a provider needs to make about the use of opioids for chronic pain, leaving the provider to rely on his or her own clinical experience.

Ruben et al. 2015

OPIOIDS ARE PART OF PLAN, NOT THE PLAN

"Avoid primary reliance on opioid prescribing, which, when applied alone or in a non-coordinated fashion, may be inadequate to effectively address persistent pain as a disease process and, when employed as the "sole" treatment, is associated with significant societal expense and treatment failure."


ANTI-SPASM DRUGS

Antispasm drugs have limited evidence for effectiveness, are predominantly sedative, and add polypharmacy to chronic pain management with little benefit.

Carisoprodol should never be used because of no benefit and high risk.

When true spasticity is present, as in spinal cord injury and multiple sclerosis, baclofen and tizanidine may be useful.

Avoid abrupt withdrawal off baclofen because of the potential for severe rhabdomyolysis and fever.

van Tulder MW et al. Cochrane Library 2008
MONOAMINE ANALGESIA

DESCENDING INHIBITORY NOXIOUS CONTROL SYSTEMS
“Gate Theory”

Principal neurotransmitters in “descending inhibitory systems”

Multimodal benefits:
✓ PAIN, SLEEP, & MOOD

PROPOSED MECHANISMS OF ANTIDEPRESSANT ANALGESIC EFFECT

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Site of action</th>
<th>CTA</th>
<th>SNR</th>
<th>SNRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reuptake inhibition of norepinephrine</td>
<td>Neurontin</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Reuptake inhibition of serotonin</td>
<td>Serotonine</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>α-Adrenergic</td>
<td>α-Methylnorepinephrine</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>Gabapentin</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Potassium channel activator</td>
<td>Valproate</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>GABA receptor</td>
<td>Benzodiazepine</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Opioid receptor</td>
<td>(-)</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Opioid-mediated effect</td>
<td>(-)</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Decrease of PGE2 production</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Decrease of TNFα production</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

Verdu B. Drugs 2008

CLINICAL KEY POINTS
ANTIDEPRESSANT ANALGESIA

- Antidepressants that elevate synaptic norepinephrine (TCAs > SNRIs) are effective analgesics
- Sedating antidepressants are useful agents to improve both sleep initiation and maintenance
- Anticholinergic side-effects are most common with TCAs
- Nausea is common with SNRIs
- Dose related QTc prolongation occurs with TCAs >SNRIs
- Warn patient and family about risks of suicidality when any antidepressant is prescribed
- Mania may be precipitated by any category of antidepressant

fMRI IN FMS

Correlation map between subjective pain scores and brain activations in fibromyalgia

Pujol 2009
“CENTRAL SENSITIZATION SYNDROMES”

Yunus M. Semin Arth Rheum. 2007

TRICYCLIC ANTIDEPRESSANT EFFECTIVENESS:

Post Herpetic Neuralgia
NNT 2.1-2.7

Diabetic Peripheral Neuropathy
NNT 1.2-1.5

Atypical Facial Pain
NNT 2.8-3.4

Fibromyalgia/Central Pain
NNT 1.7

Saarto T, Wiffen PJ. Cochrane Database of Systematic Reviews 2007

NNT = Number needed to treat

“GABAPENTINOIDS” FOR PAIN

PROTOTYPIC CA** CURRENT INHIBITORS

<table>
<thead>
<tr>
<th>Gabapentin</th>
<th>Pregabalin</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Well studied</td>
<td></td>
</tr>
<tr>
<td>• Fewer side effects than other anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>• Limited drug-drug side effects</td>
<td></td>
</tr>
<tr>
<td>• 100% excreted in the urine</td>
<td></td>
</tr>
<tr>
<td>• Gabapentin absorption via active transport; not so pregabalin</td>
<td></td>
</tr>
</tbody>
</table>
| | Pharmacodynamics (“mechanism”):
| | Selective inhibitory effect on voltage-gated calcium channels containing the α2δ-1 subunit. |
| | Side-effects:
| | • Weight Gain
| | • Edema
| | • Cognitive slowing
| | • Dizziness/Ataxia
| | • Twitching
| | • Suicidality |


GABAPENTINOIDS EFFICACY: DIABETIC PN AND FIBROMYALGIA

- Diabetic Peripheral Neuropathy
  - Gabapentin
    - 1200-2400mg
  - Pregabalin
    - 600 mg: NNT 4
    - 300 mg: NNT 6
- Fibromyalgia
  - Gabapentin
    - 600-6000mg
  - Pregabalin
    - NNT
    - >30% improvement: 5-9
    - >50% improvement: 8-12
    - NNH: 6-14

Freeman R. et al Diabetics Care 2008
Hauser 2009
**BENEFIT/RISKS OF NA⁺ CHANNEL ANTICONVULSANTS**

Variable effectiveness in different disease states

- Carbamazepine: Trigeminal neuropathy (TN)
- Oxcarbazepine: TN, Multiple Sclerosis
- Lamotrigine: TN, HIV PN, ± Diabetic PN
- Topiramate: Migraine

**Risks of ACDs**

- SIADH
- Increased LFTs
- Sedation/Weight gain
- Suicidality
- Neutropenia¹
- Hyperammonemia²
- Rash/Stevens Johnson Syndrome³
- Metabolic acidosis⁴
- Glaucoma⁴
- Kidney stones⁴

¹ Carbamazepine & Oxcarbazepine
² Valproic Acid²
³ Lamotrigine³
⁴ Topiramate⁴
⁵ Lacosamide

**OTHER “OFF-LABEL” USE OF ANTIICONVULSANTS IN PAIN**

1. **Headache disorders:** Migraine, Chronic Daily Headaches, Tension-type
2. **Visceral “hyperalgesia” syndromes:** (gabapentinoids)
   - Chronic Pelvic Pain
   - Chronic Abdominal Pain
3. **Peri-operative hyperalgesia prevention:** (gabapentinoids)
   - Thoracotomy, abdominal and pelvic surgeries

*Variable levels of quality of evidence to support use

**KEY POINTS: CANNABIS USE FOR PAIN**

- Evidence supports use in neuropathic pain conditions
  - >30 published RCTs, positively supporting moderate efficacy. BUT most low quality
  - Most clinical trials use combinations of mixed varieties of cannabinoids
  - 50% pain reduction in multiple sclerosis patients in a good quality open label long-term one-year follow-up study
  - Demonstrated risks of reduced lifetime achievement, motor vehicle accidents and addiction
  - May reduce opioid requirements and lower accidental opioid overdose deaths
  - Complex regulatory and legal environment

Aggarwal SK, Clin J Pain 2013
### OTHER PAIN Rx

- **Capsaicin**
  - Transient receptor potential vanilloid (TRPV1) agonist
  - Transdermal analgesic and is available in several low-dose products (creams, gels, and lotions).

- **Menthol** (in combination with methyl salicylate)
  - Mechanism of effect is not fully established

- **Magnesium**
  - NMDA antagonist, calcium channel blocker, and inhibits catechol release from peripheral nerve endings.

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Primary Management of Irritable Bowel Syndrome

Jasmine Zia, MD
Acting Instructor, Division of Gastroenterology
Current Concepts in Drug Therapy CME Course
April 23, 2015

Irritable Bowel Syndrome (IBS)

ROME III Criteria:
Recurrent abdominal pain/discomfort at least 3 days/month in last 3 months associated with two or more of the following:
1. Improvement with defecation
2. Onset associated with change in stool frequency
3. Onset associated with a change in form (appearance of stool)
*In absence of selected alarm features

Epidemiology of IBS

Affects up to 20% of the US population
Top ten reasons why patients seek primary care
30 - 50% of gastroenterology consultations

Only 7-15% more effective than placebo.
You diagnose a previously healthy 26 year-old female with post-infectious irritable bowel syndrome, subtype diarrhea (IBS-D).

Which of the following pharmacological agent has NOT been shown to be effective at reducing IBS-D symptoms?

1. Antispasmodics (Dicyclomine, Hyoscyamine)
2. Loperamide
3. Ondansetron
4. Cromolyn sodium
5. Placebo

Antispasmodics

- Certain antispasmodics (hyoscine, cimetropium, pinaverium) may provide **short-term relief of abdominal pain/discomfort in IBS** (Grade 2C).
- Most effective in IBS patients with:
  - Crampy abdominal pain and diarrhea
  - Intermittent, meal-related symptoms.
- Evidence for long-term efficacy not available (Grade 2B)
- Evidence for safety and tolerability limited (Grade 2C)
  - Significant side effects: dry mouth, dizziness, blurry vision, confusion, urinary retention, constipation.
  - AVOID in elderly

Antidiarrheals: Loperamide

- Effective agent for the **treatment of diarrhea**, reducing stool frequency and improving stool consistency (Grade 2C).
- Not more effective than placebo at reducing pain, bloating or global symptoms.
- RCTs comparing loperamide with other anti-diarrheals have not been performed.
- Safety and tolerability data lacking.
**5HT₃-Antagonist: Ondasetron**
- Significantly improved stool consistency, urgency and frequency.
- Main benefit seen within 7 days.
- Median dose = 4 mg per day
- Slows down the accelerated colonic transit.
- Less bloating but no significant change in pain scores.
- Not associated with ischemic colitis.

**5HT₃-Antagonist: Alosetron**
- Most favorable in women with severe IBS and diarrhea who have not responded to conventional therapies (Grade 1B).
- Potentially serious side effects: (Grade 2A)
  - Constipation: 0.66 per 1,000 patients-years
  - Colon ischemia: 1.1 cases per 1,000 patient-years

**Cromolyn Sodium**
- No therapies proven to be effective specifically for the management of PI-IBS.

**Placebos without Deception**
Your patient comes to you during your next clinic visit requesting rifaximin for treatment of her IBS-D.

What would you advise her?

1. Prescribe her rifaximin as requested
2. Advise her to consider a trial of antispasmodics first for her symptoms
3. Send her for formal breath testing to evaluate for small intestinal bacterial overgrowth (SIBO) prior to initiating antibiotics
4. Refer her to GI

Rifaximin

- Two phase III trials in 1260 IBS patient
- Significant improvement in *global symptoms, bloating, abdominal pain and stool consistency* compared to placebo for up to 3 months.
- Safety profile during and after treatment comparable to placebo.

Antibiotics: Rifaximin

*The New England Journal of Medicine*

**Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation**

Mark Pimentel, M.D., Anthony Lembo, M.D., William D. Chey, M.D., Salam Zakko, M.D., Yehuda Ringel, M.D., Jing Yu, Ph.D., Shadreck M. Mareya, Ph.D., Audrey L. Shaw, Ph.D., Enoch Botway, Ph.D., and William P. Forbes, Pharm.D., for the TARGET Study Group*
Compare Rifaximin to Others

<table>
<thead>
<tr>
<th>IBS treatment</th>
<th>NNT vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alosetron</td>
<td>8</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>4</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>5</td>
</tr>
<tr>
<td>Fiber</td>
<td>11</td>
</tr>
<tr>
<td>Linacotideβ</td>
<td>8</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>12</td>
</tr>
<tr>
<td>“Placebo without deception” c</td>
<td>4</td>
</tr>
<tr>
<td>Peppermint oil</td>
<td>2.5</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>11</td>
</tr>
<tr>
<td>Tegaserod</td>
<td>10</td>
</tr>
</tbody>
</table>

Spiegel BMR. Clinical Gastro and Hep. 2011;9:461-469

Role of SIBO in IBS

Validity of Breath Testing for SIBO

Valid Intestinal Bacterial Overgrowth

Rapid Oro-Cecal Transit Time


A

B

Breath hydrogen (ppm)

Cecal radioactivity (hecto counts)
Let’s say you decided to prescribe your patient a course of rifaximin which completely alleviates her symptoms. Six months later, her symptoms return and she asks for another prescription for rifaximin.

What would your next best course of action be?

1. Prescribe her another course of rifaximin as requested
2. Tell her there is no benefit for another course of antibiotics
3. Send her for formal breath testing to evaluate for small intestinal bacterial overgrowth (SIBO)
4. Refer her to GI for jejunal aspirates to evaluate for SIBO

Your patient’s stool frequency and urgency has improved but she continues to feel pretty anxious which seems to exacerbate her abdominal pain. You plan on starting an antidepressant.

Which one would you start?

1. Lexapro
2. Mirtazapine
3. Amitriptyline
4. Desipramine
5. St. John’s Wort

Rifaximin Re-Treatment

- Can be safely and effectively used to re-treat patients who have relapsed after already being treated.
- Of the 42% of patients who responded initially to rifaximin, 36% did not experience symptom recurrence at 18 weeks post-treatment.
- Re-treatment response was better in patients treated with rifaximin than with placebo (33% vs 25%; p = 0.02)
- 2nd re-treatment: 37% vs 29%; p = 0.04
- Adverse events similar in two groups.

Antidepressants

- Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are more effective than placebo at relieving global IBS symptoms and appear to reduce abdominal pain (Grade 1B).
- Given their differential effects on intestinal transit time:
  - TCAs: IBS-D
  - SSRIs: IBS-C
- However, lack of available data from clinical trials to assess this clinical impression.


Brandt, LJ et al. AJG. 2009 January; 104(supp 1).
Mirtazapine?

- Antidepressant with noradrenergic and specific serotonergic activity
- Potent 5HT₃-receptor antagonist
- Evidence that this pathway modulates visceral perception at the CNS level.
- Pain relief from somatic symptoms well documented.
- May contribute to indirect involvement of the opioid system supraspinally

St. John’s Wort

- Greater improvement in placebo group

Herbal Medicines

- Meta-analysis in 2008 included 22 studies with 25 different herbal medicines.
- Only 4 considered good quality.
Let’s say this patient has IBS-constipation (IBS-C) instead. She is most bothered by her abdominal pain.

Which of the following options has **NOT** been shown to reduce abdominal pain/discomfort in IBS-C?

1. Fiber
2. Lubiprostone
3. Linaclotide
4. Miralax
5. Tegaserod

**Fiber**

- Non-digestible carbohydrates that increase stool bulk and water content resulting in decreased stool consistency and increased stool frequency.

**WARNING: Fiber Adverse Effects**

- Bloating, abdominal distention, flatulence
- Gradual titration advised, if used.

---

**Sources:**
Laxatives

- PEG laxative was superior to placebo for relief of constipation but no change in abdominal pain/discomfort (Grade 1B).
  - # of SBMs: Baseline -> Week 4
    - PEG arm: 1.28±0.91 -> 4.40±2.58
    - Placebo: 1.37±0.85 -> 3.11±1.94
- Other commonly used laxatives therapies (stimulants, stool softeners) have not been adequately studied as a treatment for IBS-C.

Prosecretory Agents

Prosecretory Agent: amitiza® lubiprostone

- More effective than placebo in relieving global IBS symptoms in women with IBS-C (Grade 1B).
  - Dosage: 8 to 24 μg BID
  - Most common side effects: nausea, diarrhea, HA

Brandt, LJ et al. AJG, 2009 January; 104(supp 1).

Chey et al. Gut Liver 2011;5:253-266.
Brandt, LJ et al. AJG, 2009 January; 104(supp 1).
Prosecretory Agent: \textit{Linzess} (linclotide) capsules

- In two phase III clinical trials on IBS-C patients, linaclotide treatment resulted in significantly greater percentages of patients who experienced improvements in abdominal and bowel symptoms compared to placebo.
  - 33.7\% linaclotide vs 13.9\% placebo response
  - Effects within 1\textsuperscript{st} week of treatment and sustained over entire 26-week treatment period.
  - Main side effect: diarrhea

![Graph showing pain and constipation](https://example.com/graph)

Prokinetics: Tegaserod (5-HT\textsubscript{4} agonist)

- More effective than placebo for global IBS symptoms as well as abdominal pain and constipation in IBS-C and IBS-M (Grade 1A/B).
- Adverse Events:
  - Increased incidence of cardiovascular and cerebrovascular events
    - 0.01\% versus 0.01\%
  - Colonic ischemia
  - Withdrawn from US and Canada in 2009

Questions?

- JZia@medicine.washington.edu

References:
- Brandt, L. et al. AJG 2009 January; 104(supp 1).
Complementary & Alternative Medications Commonly Encountered in Primary Care

Introduction:

<table>
<thead>
<tr>
<th>Rates of herbal medications</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES 2007</td>
<td>17.9% current users</td>
</tr>
<tr>
<td>Surgical population</td>
<td>57% of population were ever users, 16% current users</td>
</tr>
<tr>
<td>Non-pregnant rural female population</td>
<td>59% at least one agent, 14% &gt;/= 4 in the past year</td>
</tr>
<tr>
<td>Ophthalmologic population</td>
<td>8% current users</td>
</tr>
<tr>
<td>Patients with cancer</td>
<td>17% current users</td>
</tr>
</tbody>
</table>

Commonly used agents

<table>
<thead>
<tr>
<th>NHANES 2007</th>
<th>Current user of supplements, only allowed to report up to 2 agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinacea</td>
<td>17.3%</td>
</tr>
<tr>
<td>Ginseng</td>
<td>11.9%</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>10.6%</td>
</tr>
<tr>
<td>Flaxseed</td>
<td>15.7%</td>
</tr>
<tr>
<td>Garlic supplements</td>
<td>11.7%</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>21.9%</td>
</tr>
<tr>
<td>Chondroitin</td>
<td>12.1%</td>
</tr>
<tr>
<td>Fish oil/omega-3/DHA</td>
<td>38.9%</td>
</tr>
</tbody>
</table>

Case One

- 68 year old female with type 2 diabetes, osteoarthritis presents for follow-up after ED visit for uncontrollable epitaxis.
- Medication include: Metformin 1000 BID, Glipizide ER 5 daily, Simvastatin 20 q day, ASA 81. Non-prescription supplements include: flax supplement, Vitamin B complex, multivitamin, sesame, garlic, ginger, turmeric, gingko, cinnamon, ‘Joint Juice’, and Kangen water.
- Which agents may have contributed to her epitaxis?
Increase in bleeding risk

- Caution with the ‘G’ supplements!
- Use of ginkgo biloba, garlic, and likely to a lesser degree ginger, ginseng may increase risk of bleeding
- Risk likely increased if taken with anti-platelet or anti-coagulant medication
- Data regarding any one agent is weak

Ginkgo biloba

- Ginkgo biloba extract: used for dementia, less commonly PAD and tinnitus
- High quality RCT data does not support benefit in older adults with normal cognition or mild cognitive impairment (PMID: 20040554)
- Dose: 120-240 mg/day
- Common side-effects: None

PMID: 21649517, PMID: 17640426

Garlic

- Garlic: used for treatment and prevention of CVD and cancer
- High quality RCT data does not support benefit in lipid management (PMID: 1732298)
- Dose: garlic powder capsules 600-900 mg/d
- Common side-effects: halitosis

Why is everyone taking turmeric?

- A few of the many reported benefits online:
  - Treatment of Alzheimer’s disease
  - Prevention and treatment of cancer
  - Treatment of inflammatory arthritis
  - Delays ageing
Turmeric and its active compound, curcumin, are thought to potentially have antioxidants, anti-inflammatory and antitumor benefits. Some weak evidence of benefit in treatment of inflammatory conditions including RA, psoriasis (topical formulation), inflammatory eye disease (PMID: 21369559). RTC evidence supporting benefit in maintenance of remission in ulcerative colitis in combination with mesalamine or sulfasalazine (PMID: 23076948). Dose: curcumin 2g/d.

Your patient returns to clinic for follow-up. She has stopped her ‘G’ supplements and hasn’t had any additional nose bleeds. She continues her metformin, glipizide. Her diabetes control is poor. She is hesitant to add additional prescription medications. What herbal therapies may be of benefit?

Cinnamon and Chromium/brewer’s yeast.

Cinnamon: Meta-analysis of 5 RCT in patients with type 2 diabetes found very small but statistically significant improvement in A1c with cinnamon (-0.09% change in A1c) (PMID: 22579946). Doses of 1-3 g daily. Potential harms?

Chromium: Meta-analysis of 41 RTC, total of 1198 subjects prescribed chromium for diabetes or pre-diabetes (PMID: 17319436). Subgroup with DM (14 RTC) found A1c reduction of -0.6%. No benefit in patients with pre-diabetes. Dose: 200-1000 mcg chromium/d, possible that brewer’s yeast preparations had more glucose lowering than other chromium supplements. Side-effects: GI irritation/upset.
**Case Two**

A 72 yo male with h/o HLD and osteoarthritis presents to clinic for follow-up after a recent diagnosis of gout. His gout flare has now subsided. He has been reading on the internet about cherry extract for prevention of gout and would like your opinion on this.

**Cherries**

- Observational study, 2012: Consumption of cherries or cherry extract may reduce risk of gout flare – OR of 0.65 – regardless of risk factors (PMID: 23023818)
- Benefit when used in combination with allopurinol (great RR than that of either agent alone)
- Tart cherry juice may be more ‘anti-inflammatory’

**Case Three**

A 42 year old female with long history of migraines presents for follow-up. Over the years she’s been on several prophylactic medications, consistently unable to tolerate perceived side-effects. She would like to try a ‘natural’ therapy.

What herbal agents would you feel comfortable recommending to her?

**Herbal supplements for migraine prevention**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Evidence Level</th>
<th>Dose</th>
<th>Adverse Effects</th>
</tr>
</thead>
</table>
| Butterbur (Petasites) | Level A: Established efficacy | 50-75 mg BID | GI symptoms (burping)
|                   |                 |                     | There are multiple purified extracts on the market (natural form has toxic alkaloids) |
| Magnesium            | Level B: Probably effective | 300-600 mg daily | Diarrhea/GI symptoms |
| Feverfew (best evidence of MIG-99) | Level B: Probably effective | 100 mg daily or 6.25 mg tid (MIG-99) | Joint ache, GI symptoms, oral ulcers; Contraindicated in pregnancy; interactions with hepatic metabolized drugs and anticoagulants |
| Riboflavin (vitamin B2) | Level B: Probably effective | (25 mg?) 400 mg daily |                                                                                  |
| Co-Q10               | Level C: Possibly effective | 100 mg TID |                                                                                   |

American Academy of Neurology Guideline, 2012 (PMID: 22529203)
Case Four

- 67 yo female with diet controlled type 2 DM, HTN and depression presents to discuss lipid management. She has been tried on several statin medications, developed muscle pain on all of them.
- She inquires about potential natural therapies, specifically asking about red yeast rice, omega-3 fatty acids, flaxseed and co-enzyme Q10.
- Which would you recommend?

Red Yeast Rice

- Lipid lowering benefits: Meta-analysis of 13 RTC, 804 participants: Significant TC, TG and LDL lowering (13% reduction) (PMID: 24897342)
- Benefits in statin-intolerant patients: Small study from the U.S. showed LDL lowering (35 mg/dL at wk 24) without recurrence of myalgia; dose: 1800 mg BID (PMID: 19528462)
- But… where should your patient buy this?

Fatty Acid Supplementation

- Two recent large meta-analysis have failed to show cardiovascular benefit from fatty acid supplementation with omega-3 polyunsaturated fatty acids and/or alpha-linolenic acids (PMID: 22968891, PMID: 24723079)
- Harms? Minimal
Co-enzyme Q10

- **CV Benefits**: Cochrane Review in 2014 showed no evidence of benefit as a single agent for CVD primary prevention (PMID: 25474484)
- **Benefits in statin-intolerant patients**: Meta-analysis of RCT re: benefits of co-enzyme Q10 on statin-induced myopathy also showed no statistically significant benefit (PMID: 25440725)
- **Potential harms**: Minimal, may interact with warfarin
- **Dosing**: 50-300 mg/d

---

Case Five

- 74 year old female with longstanding poorly controlled type 2 diabetes reports bothersome pain attributed to peripheral neuropathy. She has been on gabapentin and tricyclic antidepressants previously, found both too sedating.
- **What supplement could you recommend?**

---

Alpha-lipoic Acid

- Several RTCs support benefit (iv > oral)
- Risk/benefit ratio best for dose of 600 mg daily (PMID: 17085849)
- Based on single study, NNT 2.7; compare to gabapentin NNT 3.7, venlafaxine 4.5 (PMID: 19738078)
- **SE**: muscle cramps, headache, at higher doses include nausea/vomiting, vertigo

---

Vitamin B12 deficiency & metformin

- Laboratory abnormalities are well established, clinical outcomes less clear.
- **Based on RTC** (PMID: 20489810)
- Absolute risk of vitamin B12 deficiency (<150 pmol/L):
  - 7.2% higher in metformin group
  - NNH 13.8 at 4 years
- Absolute risk of low vitamin B12 level (150-220 pmol/L):
  - 11.2% higher in metformin group
  - NNH 8.9 at 4 years
Summary

- Many of the G supplements are associated in increased risk of bleeding: Gingko, garlic, ginseng, ginger
- There may be small glucose lowering benefits of chromium supplementation and cinnamon in diabetes
- Don’t let gout be the pits – a gout free life may be a bowl of cherries away!
- Butterbur is an effective prophylactic medication for migraines, feverfew, magnesium and riboflavin may be as well
- Consider Red Yeast Rice in your statin intolerant patient
- Consider alpha-lipoic acid supplementation in patients with painful diabetic neuropathy
Using the New Lipid and Blood Pressure Guidelines in Your Clinical Practice

Michael Soung, MD, FACP
Section of General Internal Medicine
Core Clinical Faculty, Internal Medicine Residency
Virginia Mason Medical Center

New lipid guidelines

- 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
- Statins beneficial across broad range of LDLs and patient populations
  - Except CHF II-IV and hemodialysis?
- No RCTs titrated lipid therapy to goal
- Treat based on presence of certain high-risk features or calculation of overall risk

Question #1

- Which of the following groups does NOT have at least moderate or strong evidence supporting use of statin therapy?
  A) Age ≤ 75 with clinical atherosclerotic cardiovascular disease (ASCVD)
  B) Age ≥ 21 with LDL ≥ 190
  C) Age 40-75 with diabetes mellitus (DM)
  D) Age 40-75 (without ASCVD or DM) and estimated 10-year ASCVD risk ≥ 7.5%
  E) Age >75 with ASCVD and/or DM

4 “statin benefit” groups

1) Age ≤ 75 with clinical atherosclerotic cardiovascular disease (ASCVD)
   - High-intensity statin
   - Grade: A / I / A

2) Age ≥ 21 with LDL ≥ 190
   - High-intensity statin
   - B / I / B

4 “statin benefit” groups

3) Age 40-75 with diabetes mellitus
   • Moderate-intensity statin (A / I / A)
   • High-intensity if 10-year ASCVD risk ≥ 7.5%
     • E / IIa / B

4) Age 40-75 (without ASCVD or DM) and estimated 10-year ASCVD risk ≥ 7.5%
   • Moderate- to High-intensity statin
     • A / I / A


Statin intensity?

Roso\textsuperscript{u}va  Atorva  Simva  Lova/Prava  Fluva

(Roso\textsuperscript{u}va 5mg ≈ Atorva 10mg ≈ Simva 20mg ≈ Lova/Prava 40mg ≈ Fluva 80mg)

• High-intensity: atorva 40-80mg
• Medium-intensity: atorva 10-20mg

Answer: E


Question #2

➢ 56yo woman with total cholesterol of 302, HDL 68, TGs 71, and LDL 220. No history of hypertension, no family history of cardiovascular disease, no medications, BP 126/70.
➢ What is the most appropriate next step?

A) Recommend high-intensity statin / intensive lifestyle changes
B) Recommend intensive lifestyle changes alone
C) Estimate her 10-year ASCVD risk
D) Check a TSH, liver metabolic panel, urinalysis
E) Recheck a lipid panel in 1 year

Really high LDL (≥190)

ACC/AHA 2013 recommendations:
➢ High-intensity statin without estimation of 10-year risk (B / I / B)
   • Based on high lifetime risk of ASCVD
➢ Target ≥ 50% LDL reduction (E / IIa / B)

Lancet 2010;376:1670–81
Really high LDL (≥190)

- Eval for 2° cause if LDL ≥190 or TG ≥500

<table>
<thead>
<tr>
<th>Secondary Cause</th>
<th>Elevated LDL-C</th>
<th>Elevated Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Secondary or recurrent acne, weight gain, anemia</td>
<td>Weight gain, very low-fat diets, high intake of refined carbohydrates, excessive alcohol intake</td>
</tr>
<tr>
<td>Drugs</td>
<td>Diuretics, cyclosporine, thiazides</td>
<td>Oral anticoagulants, glucocorticoids, bile acid sequesterants, protease inhibitors, salicylic acid, anabolic steroids, sirolimus, interleukin, anti-hypertensives, metformin (met carbamazepine), thiazides</td>
</tr>
<tr>
<td>Diseases</td>
<td>Biliary obstruction, nephrotic syndrome</td>
<td>Nephrotic syndrome, chronic renal failure, hypothyroidism</td>
</tr>
<tr>
<td>Disorders and altered states of metabolism</td>
<td>Hyperthyroidism, obesity, pregnancy*</td>
<td>Diabetes (poorly controlled), hypothyroidism, obesity, pregnancy*</td>
</tr>
</tbody>
</table>

- Excess EtOH, uncontrolled DM, albuminuria, hypothyroidism, meds


Really high LDL (≥190)

- By the way, her 10-year ASCVD risk?
  → 2.7% (Lifetime risk: 39%)
- Would you recommend high-intensity statin?
  - Consider: family history, hs-CRP, coronary artery calcium score, ABIs. (E / IIb / B)
  - Don’t use CIMT
  - ?ApoB, CKD, Ualb, fitness level — no rec

Answer: D

Goff DC Jr, et al. 2013 ACC/AHA Cardiovascular Risk Guideline

Question #3

- 40 yo man with total cholesterol 170, HDL 50, LDL 90. African American, smokes 1/2 PPD, HTN on 2 meds but often forgets to take his pills. BP 160/90. 10-year ASCVD risk is 12.5%.
- Which of the following would NOT be an appropriate next step?
  A) Recommend a moderate-intensity statin
  B) Recommend diet / activity changes
  C) Explore barriers to medication adherence
  D) Assess motivation & confidence to quit smoking
  E) They are all appropriate

Low cholesterol, high CV risk

- Don’t forget about other modifiable risks
  - Smoking cessation
  - Blood pressure control
  - Aspirin
- Have some fun with the risk calculator…

Answer: E
Question #4

59 yo woman with total cholesterol 280, HDL 25, TGs 560 (fasting), LDL 85. HTN on lisinopril, no other meds, no smoking or alcohol. BP is 140/80. A1c is 5.9%, TSH, CMR, UA all normal. 10-year ASCVD risk is 11%.

In addition to intensive lifestyle counseling, what else would you recommend?

A) Statin
B) Fibrate
C) Niacin
D) Statin + fibrate
E) Statin + niacin

High TGs, Low LDL

- ATP III: fibrate or niacin (before statin) if TGs > 500 (to prevent pancreatitis)
- 2012 Endocrine Society guidelines and 2011 AHA scientific statement: Risk for pancreatitis is only if TGs >> 1000
  - Link between TGs and CVD also questionable

Fibrates and niacin

- No effect on all-cause or CV mortality
  - ↓ non-fatal MI in monotherapy only
- ACCORD Lipid -- Adding fibrate to statin
  - No CV benefit (except maybe if ↑TG + ↓HDL)
- AIM-HIGH, HPS2-THRIVE -- Adding niacin
  - No CV benefit (despite ↑HDL, ↓TG, ↓LDL)
Niacin concerns

➢ HPS2-THRIVE, AIM-HIGH (niacin)
  • ↑ flushing / GI side effects / glucose levels (no surprise)
  • Also ↑ infections (surprise)
➢ Also strong trend towards ↑mortality(!)
  • 0.5% ARI = NNH 200 (9% RRI)
  • p-value nearly significant (p=0.08)
→ AVOID Niacin due to harms (+no benefit)

Question #5

➢ 63yo man with total cholesterol of 170, HDL 50, LDL 95. BP 110/70, not on any medications. Caucasian, no history of diabetes, lifelong non-smoker.
➢ What is his 10-year ASCVD risk based on the ACC/AHA calculator?
  A) 1%
  B) 2.5%
  C) 5%
  D) 7.5%
  E) 10%

New ASCVD risk calculator

➢ Age at which 10-year ASCVD risk exceeds 7.5% despite “optimal” lipids, BP, etc?
  • Caucasian men: 63yo+
  • African American men: 66yo+
  • Women: 70-71yo+
➢ Uses cohort data from previous risk scores
  • e.g. Framingham, Reynolds, QRISK

Answer: A

Goff DC Jr, et al. 2013 ACC/AHA Cardiovascular Risk Guideline
Lancet 2013;382:1762-1765

Overestimates CV risk?

Lancet 2013;382:1762-1765
Outcome assessment issues?

- Women’s Health Initiative
  - WHI criteria: review of medical records
  - Medicare data: hospital discharge coding

- Outcome assessments
  - WHI criteria: 1345 MIs
  - Medicare criteria: 1501 MIs
  - WHI or Medicare: 1784 MIs

Recent validation studies

- REGARDS cohort
  - 18,498 adults, 45+ yo, 48 US states + D.C.
    - 42% Black, 58% Women
  - Outcome assessment:
    - q6mo telephone f/u
    - Also used Medicare claims data when possible

- Rotterdam Study
  - 4209 participants, 55+ yo, single Rotterdam suburb, not on statin
  - Outcomes via automated f/u system + manual review of pt records + hospital records + f/u interviews
Recent validation studies

- Women’s Health Study cohort
  - 27,542 women, 45-79yo, followed for 10y
  - Adjustments for statins, revascularizations
  - Analysis of under-ascertainment

- Multi-Ethnic Study of Atherosclerosis (MESA)
  - 4227 people, 50-74yo, no diabetes
  - 42% White, 26% African American, 20% Hispanic, 12% Chinese
  - 54% women
  - Evaluated new risk calculator along with 3 Framingham scores and Reynold Risk Score
  - Adjusted for ASA, lipid/BP meds, revascularizations
New ASCVD risk calculator

- The new risk calculator may overestimate risk – substantially in some cases
  - Consider calculating risk using multiple different calculators (e.g. Reynolds)
- Strict adherence to the 7.5% cutoff → statin therapy for 80% of 60+ yo adults
  → take calculated risk and 7.5% cutoff with a grain of salt

BMJ 2012;344:e3318 doi:10.1136/bmj.e3318
Goff DC Jr, et al. 2013 ACC/AHA Cardiovascular Risk Guideline

Age- and sex-specific thresholds?

- 7.5% threshold: may undertreat younger patients and overtreat older patients
- Studied sensitivities and specificities of varying treatment thresholds
- Consider (more study needed):
  - All 40-55yo and women 56-65yo: 5%
  - Men 56-65yo: 7.5%
  - Women 66-75yo: 10%
  - Men 66-75yo: 15-20%

Answer: D


Question #6

- 55 yo man with total cholesterol 220, HDL 40, TGs 150, LDL 150. Caucasian, no significant past medical history, no family history of vascular disease or smoking. His BP is 130/75. His 10-year ASCVD risk is 7.8%
- What is the most appropriate next step?
A) Recommend a statin
B) Recommend intensive lifestyle changes
C) A and B
D) Recheck lipids in 3 months
E) Engage in a shared decision making process
Putting it all together…

➢ Use of global CV risk information:
  • Improves accuracy of risk perception
  • Increases statin Rx’s in mod-high risk patients
  • May reduce predicted CV risk over time

➢ Use of decisions aids improves:
  • Knowledge of options, benefits, and harms
  • Informed values-based choices
  • Patient involvement in decision making
  • Patient-practitioner communication

Statin risks

➢ Liver failure: really rare -- 1 in 1,000,000 pt-years
  • Idiosyncratic; routine monitoring not helpful
  • Liver disease: not contraindication to statin use (except ALF or decompensated cirrhosis)

➢ Muscle: myalgias -- 5-10%, rhabdo – 1 in 10,000

➢ Diabetes: 1 extra case per 255 on statin for 4 years
  • 1 fewer CV event per 24 on statin for 5 years

Statin risks -- others(?)

➢ Statins and memory loss:
  • FDA 2012 label change – rare post-marketing reports of cognitive impairment
  • Onset 1 day to years, generally not serious
  • Reversible (median 3 weeks)

➢ 3 recent systematic reviews:
  • No adverse effect on cognition; possible reduction in Alzheimer’s

Statin risks -- others(?)

➢ Statins and Erectile Dysfunction?
  • 2002 review: possible link (case reports)
  • 2012 review: statins may improve erection quality (alone or w/ sildenafil)

► Probably a little of both

References:

BMC Health Services Research 2008;8:60-73
Arch Int Med 2010;170:230-9
Cochrane Database of Syst Rev 2011, Issue 11

Am J Cardiol 2006;97(suppl):77C–81C
Ann Intern Med 2009;150:858-868
Lancet 2010;376:1670–81
Lancet 2012; 380: 581–90

http://www.fda.gov/drugs/drugsafety/ucm293101.htm
Ann Intern Med 2013;159:688-697
J Gen Intern Med 2015;30:348-58

J Androl 2012;33:552–558
Family Practice 2002;19:95-98
Putting it all together…

- Mayo statin decision aid

67 yo woman w/ PMH of DM II, HTN, and hyperlipidemia, on metformin 1000mg BID, lisinopril 10mg daily, and atorvastatin 20mg daily. Average BP: 135/85. HbA1c 7.8%, Cr 0.9, Urine alb/cr ratio 16 mg/g.

Which of the following is the most appropriate next step in her blood pressure management?

A) Add diltiazem
B) Add amlodipine
C) Add hydrochlorothiazide
D) Increase the dose of lisinopril
E) No change in blood pressure meds

Blood pressure targets in diabetes

JNC 7:
- Goal blood pressure < 140/90
- Exceptions:
  - Diabetes Mellitus
  - Chronic Kidney Disease
  - goal blood pressure < 130/80

Blood pressure targets in diabetes

ACCORD BP:
- 4733 pts w/ high-risk DM, HbA1c ≥ 7.5%
- SBP goals of <120 vs <140 mmHg
- SBPs achieved: 119 vs 133.5 mmHg
- No change in primary CV outcome at 4.7y
  - reduction in CVA: 0.32% vs 0.53%
  - SBP <120: ↑ serious adverse events (ARI 2%)
- No difference for microvascular outcomes

JAMA 2003;289:2560-2572

NEJM 2010;362:1575-85

Kidney Int 2012;81:586-594
Blood pressure targets in diabetes

- 2011 meta-analysis (broad inclusion):
  - 13 RCTs, 37,736 pts, BP <135 vs <140
  - No difference in overall macro/microvascular outcomes
  - ↓ mortality by 10% (BP 130-135), ↓ CVA by 17%
  - ↑ serious adverse effects by 20%

- 2012 meta-analysis (strict inclusion):
  - 5 RCTs, 7312 pts, DBP <75-80 vs <90, + ACCORD
  - No difference in mortality or MI
  - ↓ CVA by 35% (1% ARI)

2011;123:2799-2810
Arch Intern Med 2012;172:1296-1303

Blood pressure targets in CKD?

- JNC 7 & NKF K/DOQI: < 130/80
- Extrapolated from recommendations for other high-risk groups (e.g. diabetes)
- Annals 2011 systematic review:
  - 3 RCTs, 2272 patients
  - No clear benefit from lower BP targets
  - Possible benefit in proteinuric patients

Am J Kidney Dis 2004;43:S1-S290
Ann Intern Med 2011;154:541-548

What’s new in JNC 8?

- Diabetes: BP goal < 140/90 (grade: E)
- CKD: BP goal < 140/90 (E)
  - Insufficient evidence for CKD + age >70

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC 8). JAMA 2013

Question #8

- 65 yo woman w/ PMH HTN and chronic stable angina on ASA, metoprolol, and lisinopril. No CP, SOB, edema, HAs, lightheadedness. Healthy diet, regular exercise. Average BP: 145/85. HR 60, nl CV exam, no edema. Cr 0.9, K 4.2, UA neg.
- Which of the following is the most appropriate next step in management?
  A) Add a thiazide
  B) Add losartan
  C) Add amlodipine
  D) Increase metoprolol dose
  E) No change in blood pressure meds

Answer: E
BP targets in older patients

- **SHEP** (chlorthalidone +/- atenolol) – age 60+
  - Target SBP: 20 pts lower (or <160)
  - Achieved SBPs of 143 vs 155
  - CVA: 3 fewer per 100 pts (also ↓ CV events)

- **HYVET** (Indapamide +/- perindopril) – age 80+
  - Target SBP: 150/80 (vs placebo)
  - Achieved SBPs of 144 vs 159
  - Death: 12.4 fewer per 1000 pt-yrs

Hypertens Res 2008;31:2115–2127
Hypertension 2010;56:196-202

What’s new in JNC 8?

- Age 60+: BP goal < 150/90 (A)
  - But okay if already <140/90 on meds (E)

- Minority dissent on this recommendation:
  - Citing SHEP / HYVET, and safety in JATOS/VALISH
  - JATOS/VALISH – short f/u, Japanese population
  - Many groups use 80+yo as cutoff for SBP < 150

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC 8). JAMA 2013
Ann Intern Med. Published online 14 January 2014 doi:10.7326/M13-2981

Other considerations

- SBP<130 + ≥2 BP meds in ≥80yo= bad
  - HR 1.78 for mortality (nursing home cohort)

- Caution w/ DBP <60 if ≥ 60yo or DM
  - 2015 AHA/ACC/ASH guideline (C level evidence)

- VA CKD cohort study: DBP < 70 associated w/ worse mortality than mod-high SBP (e.g. BP 155/75 better than 130/60)

JAMA Intern Med. doi:10.1001/jama.2014.8012
J Am Coll Cardiol. 2015. doi:10.1016/j.jacc.2015.02.038
Annals Intern Med 2013;159:233-242
Question #9

- 42 yo man w/ new diagnosis of HTN, average BP 145/90 after intensive lifestyle improvements. Normal serum electrolytes and creatinine, UA negative, EKG wnl. Otherwise healthy.

Which of the following is the most appropriate next step in management?

A) Lisinopril  
B) Chlorthalidone  
C) Amlodipine  
D) Atenolol  
E) No medication, continued monitoring

Initial Therapy in HTN

- BMJ 2009 meta-analysis:
  - All classes similar efficacy for reducing CHD events and CVA
  - Beta-blockers extra protection first few years post-MI
  - CCBs slight advantage for CVA prevention

- Cochrane 2009 meta-analysis:
  - Low-dose thiazides (HCTZ <50mg/day, chlorthalidone <50mg/day): strongest evidence
  - ACE-I: similar benefit, less evidence
  - CCBs: insufficient evidence
  - β-blockers (atenolol) and high-dose thiazides: inferior

Initial Therapy(?) in HTN

- Cochrane 2012: mild hypertension
  - BP 140-159 / 90-99, primary prevention
  - 4 RCTs, 8912 patients, 4-5y f/u
  - No change in mortality, CHD, CVA, CV events
  - 9% ARI of withdrawals due to adverse effects

- Caveats:
  - Low event rates, mostly driven by a single trial (MRC), half on propranolol-based Rx
  - Wide confidence intervals
  - Long enough follow-up?

Initial Therapy(!) in HTN

- 2015 update w/ individual patient-data from BPLTTC database
  - More power: 6391 additional pts (96% w/ DM, 61% w/ previous anti-HTsives)
  - 2x total # of pts, 4x # of CV events
  - Mostly ACE-I trials, a few CCB trials
  - Results: ↓CVA, ↓CV deaths, ↓mortality

  - Similar RRRs in BPLTTC and non-BPLTTC trials

Cochrane Database Syst Rev 2012;8:CD006742  
Anti-HTsives in normotension

- JAMA 2011 meta-analysis:
  - Anti-HTsives in normotensive patients w/ CVD
  - 25 RCTs, 64,000 patients
  - ↓ mortality, CVA, MI, CHF, total CVD events
- Eur Heart J 2012 meta-analysis:
  - ACE-I or ARB in normotensive patients w/ CVD or CVD risk factors
  - 13 RCTs, 80,000 patients
  - ↓ composite CV endpoint, CV mortality

Risk-based HTN treatment?

- Relative risk reductions (right):
  - Not affected by baseline risk (~15%)
- Absolute risk reductions (left):
  - ↑ baseline risk → ↑ absolute benefit
  - 5y NNT: 71 (if low risk) → 26 (if high risk)

Sound familiar?

CV events prevented: Lipid reduction w/ statin

CV events prevented: Blood pressure reduction

What’s new in JNC 8?

- Age < 60: DBP goal < 90 (A)
- Age < 60: SBP goal < 140 (E)
- First-line therapy: thiazide, CCB, ACE, or ARB (B)
  - African Americans: thiazide or CCB (B)

- Consider overall CV risk when managing HTN
- Really push lifestyle changes

Answer: A, B, C, E

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC 8). JAMA 2013
Take home points
- No more LDL “goals” – focus on CV risk
- Remember non-lipid risk factors
  - Consider statin if:
    - Age ≤ 75 with ASCVD
    - Age ≥ 21 with LDL ≥ 190
    - Age 40-75 with diabetes mellitus (DM)
    - Age 40-75 (without ASCVD or DM) and estimated 10-year ASCVD risk ≥ 7.5%

Take home points – lipids
- Minimize use of fibrates, avoid niacin
- New risk calculator may overestimate risk – substantially, in some cases
- Use the “guide”-lines as a guide for shared decision making

Take home points – BP
- Age 60+: goal BP < 150/90
  - Maybe age 80+?
- Age <60: goal BP < 140/90
  - 140 may be a soft goal if low-risk
- DM or CKD: goal BP < 140/90
  - Across ages (not sure for CKD and age 70+)
- 1st line: thiazide, CCB, ACE, ARB
  - Thiazide or CCB if African American
- Consider overall CV risk and med burden