Improving Outcomes in Patients with ASCVD: Dramatic Developments in Dyslipidemia Management

Learning Objectives

• Compare and contrast recommendations and guidelines on treatment of dyslipidemia
• Assess the ASCVD risk profile of patients with dyslipidemia
• Discuss newly approved agents for treatment of dyslipidemia
• Educate patients on strategies to overcome statin intolerance to reach LDL-C goals

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

85.6 Million Adults in the United States Aged ≥20 Years Have CVD: NHANES, 2009-2012

CVD = cardiovascular disease; NHANES = National Health and Nutrition Examination Survey.

Improving Outcomes in Patients with ASCVD: Dramatic Developments in Dyslipidemia Management

**Residual ASCVD Risk Despite LDL-C-Lowering Therapy**

ASCVD Event Reduction in Major Statin Trials

<table>
<thead>
<tr>
<th>Statin Type</th>
<th>N (Patients)</th>
<th>ASCVD Event Reduction (Relative Risk Reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>4444</td>
<td>~20%</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>6595</td>
<td>~25%</td>
</tr>
<tr>
<td>CARE</td>
<td>4159</td>
<td>~20%</td>
</tr>
<tr>
<td>LIPID</td>
<td>9014</td>
<td>~30%</td>
</tr>
<tr>
<td>MIRACL</td>
<td>3086</td>
<td>~31%</td>
</tr>
<tr>
<td>PROSPER</td>
<td>5804</td>
<td>~30%</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>10,305</td>
<td>~30%</td>
</tr>
<tr>
<td>CARDS</td>
<td>2838</td>
<td>~30%</td>
</tr>
<tr>
<td>SPARCL</td>
<td>4731</td>
<td>~30%</td>
</tr>
<tr>
<td>KLIS</td>
<td>3853</td>
<td>~30%</td>
</tr>
<tr>
<td>MEGA</td>
<td>7832</td>
<td>~30%</td>
</tr>
</tbody>
</table>

Atorva = atorvastatin; Prava = pravastatin; Simva = simvastatin.


**High Residual CVD Risk Remains, Even With High-Dose Rosuvastatin (JUPITER)**

- Primary trial end point: MI, stroke, unstable angina/myocardial infarction, CV death
- HR: 0.56 (95% CI: 0.46-0.69)
- P < 0.00001
- NNT5 = 25


**Definition of Non–HDL-C**

Non–HDL-C = TC – HDL-C

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; VLDL = very low-density lipoprotein.

Case Study: Meet Harry, 57

- Prior coronary artery bypass graft at age 55; taking aspirin
- Smoked 1 pack/d for 35 years; quit 5 years ago
- Body mass index: 32 kg/m²
- No regular exercise; sedentary job
- Blood pressure: 138/87 mm Hg (treated with losartan 50 mg/d, metoprolol 100 mg twice daily)
- Dyslipidemia (treated with simvastatin 40 mg/d)
- Type 2 diabetes mellitus (treated with metformin 2000 mg/d)

Laboratory Values

<table>
<thead>
<tr>
<th>Lipids (mg/dL)</th>
<th>TC</th>
<th>TG</th>
<th>HDL-C</th>
<th>LDL-C</th>
<th>Non–HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>187</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>285</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>160</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Fasting plasma glucose (mg/dL) 137
- A1C (%) 7.2

A1C = glycated hemoglobin; TG = triglycerides.

2013 ACC/AHA Cholesterol Guidelines

- Emphasis is on moderate- to high-intensity statin therapy
- Achieving specific LDL-C and non–HDL-C goals optional
- Clinicians are encouraged to:
  - Assess response and confirm adherence to prescribed therapy
  - Consider additional therapy in individuals with significant residual risk (however, no specific guidance given on therapy beyond high-intensity statin)

2013 ACC/AHA Statin Benefit Groups

- High-intensity statin therapy
  - Clinical ASCVD
  - Primary elevations of LDL-C ≥190 mg/dL (high intensity preferred)
  - Aged 40-75 years with diabetes, LDL-C 70-189 mg/dL, without clinical ASCVD but 10-year risk ≥7.5%°
- Moderate-intensity statin therapy
  - Aged 40-75 years with diabetes, LDL-C 70-189 mg/dL, without clinical ASCVD and 10-year risk <7.5%°

°http://www.cvriskcalculator.com/

Improving Outcomes in Patients with ASCVD: Dramatic Developments in Dyslipidemia Management

**ACC 2016 Update: Use of Nonstatin Therapies for LDL-C Lowering**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Role in Lipid Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary measures</td>
<td>Part of every LDL-C lowering regimen; consider before initiating nonstatin therapy</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Appropriate in all patients; first-line nonstatin therapy in patients with ASCVD and baseline LDL-C ≥190 mg/dL</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Second-line therapy after ezetimibe in patients with fasting TG &lt;300 mg/dL; colesevelam in patients with T2DM due to modest hypoglycemic effect</td>
</tr>
<tr>
<td>PCSK9 inhibitors</td>
<td>Patients with clinical ASCVD; patients without ASCVD but with LDL-C ≥190 mg/dL</td>
</tr>
<tr>
<td>Niacin</td>
<td>No longer recommended in combination with statins due to potential harms/lack of benefit</td>
</tr>
</tbody>
</table>

**Patients with FH should be treated by specialist**

FH = familial hypercholesterolemia


**ACC 2016 Update: Use of Nonstatin Therapies for Secondary Prevention**

- Clinical ASCVD with comorbidities
  - Has ≥50% LDL-C ↓ (may consider LDL-C <70 mg/dL in patients with diabetes, may consider non-HDL-C <100 mg/dL on maximum tolerated statin)
  - Clinician-patient factors to consider:
    1. Potential for additional ASCVD risk reduction with addition of nonstatin
    2. Potential for AEs or drug interactions from addition of nonstatin
    3. Patient preference
  - Optional nonstatin medications
  - Consider using ezetimibe first
  - Consider adding/replacing with PCSK9 inhibitor second

**Patient has ≥50% LDL-C ↓ (may consider LDL-C <70 mg/dL, or may consider non-HDL-C <100 mg/dL in patients with diabetes on maximum tolerated statin)**

AC = adjudication event


**ACC 2016 Update: Use of Nonstatin Therapies for Primary Prevention**

- No clinical ASCVD, baseline LDL-C ≥190 mg/dL, or consideration
  - ≥50% LDL-C ↓ (may consider LDL-C <100 mg/dL on maximum tolerated statin)
  - Clinician-patient factors to consider:
    1. Potential for additional ASCVD risk reduction with addition of nonstatin
    2. Potential for AEs or drug interactions from addition of nonstatin
    3. Patient preference
  - Optional nonstatin medications
  - Consider using ezetimibe first
  - Consider using PCSK9 inhibitor second
  - Patient has ≥50% LDL-C ↓ (may consider LDL-C <100 mg/dL on maximum tolerated statin)

- Repeat clinician-patient discussion, add other nonstatin med, consider specialist referral

## NLA ASCVD Risk Category Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Very high | - ASCVD  
- Diabetes mellitus (type 1 or 2)  
- ≥2 other major ASCVD risk factors, or  
- Evidence of end-organ damage |
| High | ≥3 major ASCVD risk factors  
- Diabetes mellitus (type 1 or 2)  
- ≥1 other major ASCVD risk factor, and  
- No evidence of end-organ damage  
- Chronic kidney disease stage 3B or 4  
- LDL-C ≥190 mg/dL |
| Moderate | ≥2 major ASCVD risk factors  
- Specific factors should be considered to reclassify risk, such as risk calculators, atherosclerosis imaging, and/or biomarkers |
| Low | ≥1 major ASCVD risk factor  
- Specific factors should be considered to reclassify risk, such as risk calculators, atherosclerosis imaging, and/or biomarkers |


## NLA 2014 Recommendations: Levels for Considering Drug Therapy, Treatment Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Consider Drug Therapy</th>
<th>Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-HDL-C and LDL-C (mg/dL)</td>
<td>Non-HDL-C and LDL-C (mg/dL)</td>
</tr>
<tr>
<td>Very high</td>
<td>≥100</td>
<td>&lt;70</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>≥70</td>
</tr>
<tr>
<td>High</td>
<td>≥130</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>≥100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥160</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>≥130</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Low</td>
<td>≥190</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>≥160</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

- Lifestyle therapy is always advocated as the basis for ASCVD prevention
- For patients with ASCVD or diabetes mellitus, consider use of moderate- or high-intensity statins, irrespective of baseline atherogenic cholesterol levels


## Dyslipidemia Management Strategies

- Encourage a healthy lifestyle (dietary measures, aerobic physical activity, healthy body weight, smoking avoidance, controlling hypertension and diabetes when present)
- Implement a patient-centered approach to decision making before utilizing statin therapy (especially for primary prevention in patients at lower ASCVD risk)
- Start statins per ACC/AHA guidelines and NLA recommendations
- Monitor response to therapy
  - If suboptimal, increase statin potency (not dose) add nonstatin in patients receiving maximally tolerated statin  
  - Monitor side effects

Improving Outcomes in Patients with ASCVD: Dramatic Developments in Dyslipidemia Management

Statin-Associated Muscle AEs and Risk Factors

- Statin-associated muscle AEs:
  - Myalgia
  - Myopathy
  - Myositis
  - Myonecrosis
  - Rhabdomyolysis

- Risk factors:
  - Female sex, older age, diabetes, renal/hepatic dysfunction
  - Concomitant agents that inhibit CYP3A4 or CYP2C9
  - History of myopathy on other LLT

CYP = cytochrome P; LLT = lipid-lowering therapy.


Management of Statin Myopathy

- Limit daily dosage, reduce dosing frequency, or institute drug "holidays"1,2
- ACC/AHA guidelines and NLA recommendations
  - Consider nonstatin with or without concomitant statin2,3
    - Ezetimibe, bile acid sequestrants often used3,2
    - Niacin (extended release) and fenofibrate (delayed release) no longer approved in combination with statins6

- Newer agents: PCSK9 inhibitors (alirocumab, evolocumab)
- Vitamin D deficiency may contribute to statin myalgia5; limited evidence that vitamin D repletion improves tolerability5

- Measure thyroid-stimulating hormone in patients with myalgias/myopathy6


Lack of Adherence and Persistence to Statin Therapy Is Common: USAGE Study

Population survey of statin use over 18 months (N = 10,138)

- One-fourth of patients discontinued statin after 1 month
- Half discontinued within 3 months
- As many as three-fourths discontinued use in first year
  - 57% stopped after an AE and had no further prescriptions filled
  - One-third stopped without asking or telling their clinician
- On average, 2 statins were tried before stopping altogether

Improving Outcomes in Patients with ASCVD: Dramatic Developments in Dyslipidemia Management

Adherence Obstacles and Barriers

Obstacles:
- Muscle-related AEs of statins are the primary reason for lack of adherence and treatment discontinuation
- More common than reported in clinical trials

Patient-Centered Barriers:
- Lack of knowledge about risks of dyslipidemia
- Lack of motivation
- Lack of confidence in adherence
- Concerns about cognitive impairment
- Concerns about diabetes
- Unclear expectations about treatment outcome
- Lack of conviction concerning consequences of poor adherence

Clinician-Centered Barriers:
- Inefficient knowledge and skills
- Inefficient confidence
- Inefficient education about patients to emphasize need for good adherence

Adherence Obstacles and Barriers

Obstacles:
- Muscle-related AEs of statins are the primary reason for lack of adherence and treatment discontinuation
- More common than reported in clinical trials


Case Conclusion: Harry’s Management

- You educate Harry on the risks of obesity, dyslipidemia, and CVD
- You refer him to a dietitian for counseling and urge him to engage in an exercise he enjoys, such as walking, for 45 minutes per day, 4-5 days per week
- Because Harry’s non–HDL-C and TG are elevated and his HDL-C is low, you add ezetimibe to his lower dose of statin therapy
- You educate him about his new regimen and advise him to notify you immediately if AEs develop
- Harry makes an appointment for follow-up in 3 months

Case Study: Meet Jason, 34

- Jason is a 34-year-old African American man presenting for follow-up
- No known ASCVD, non-smoker
- Despite high-intensity statin therapy with rosuvastatin (40 mg), his lipid levels are poorly controlled, even after ezetimibe (10 mg) and colesevelam (3750 mg/d) were added to his regimen

<table>
<thead>
<tr>
<th>Changes in Lipid Levels (mg/dL) Over Time</th>
<th>May 20, 2014</th>
<th>July 20, 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Parameter</td>
<td>No Lipid Medications</td>
<td>Taking Rosuvastatin/Ezetimibe/Colesevelam</td>
</tr>
<tr>
<td>TC</td>
<td>496</td>
<td>255</td>
</tr>
<tr>
<td>TG</td>
<td>100</td>
<td>110</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>LDL-C</td>
<td>430</td>
<td>173</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>447</td>
<td>195</td>
</tr>
</tbody>
</table>
### Familial Hypercholesterolemia

- Autosomal codominant disorder
- Very high levels of LDL-C, TC
- Early CVD
- HeFH – 1:200-1:300
- HoFH – 1:160,000-1:360,000
  - Extreme hypercholesterolemia with rapidly accelerated atherosclerosis
  - Very high mortality rate if left untreated
  - LDL apheresis is a treatment option

HeFH = heterozygous FH; HoFH = homozygous FH.


### Traditional Therapies for Elevated LDL-C

**Therapy** | **Mechanisms of Action**  
--- | ---  
Statins | Inhibit 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, the rate-limiting step in cholesterol synthesis; results in upregulation of LDL receptors and improved LDL clearance from circulation  
Cholesterol absorption inhibitor (ezetimibe) | Inhibits intestinal sterol absorption  
Bile acid sequestrants | Interfere with intestinal reabsorption of bile acid by binding these breakdown products of cholesterol in the gut and promoting excretion  
Niacin | Various mechanisms (eg, inhibition of peripheral mobilization of free fatty acids, reducing hepatic VLDL synthesis/hepatic secretion)


### Newer Therapies for Elevated LDL-C

**Therapy** | **Mechanisms of Action**  
--- | ---  
PCSK9 inhibitors (alirocumab, evolocumab) | Block binding of PCSK9 enzyme to LDL receptors on surface of hepatocytes  
- Reduce number of receptors on hepatocytes  
- Facilitate LDL-C clearance from blood  
Microsomal transfer protein inhibitor (lomitapide) | Inhibits lipoprotein synthesis (chylomicrons [intestinal] and VLDL [hepatic])  
Antisense oligonucleotide inhibitor of Apo B ( mipomersen) | Sequence-specific binding to messenger RNA encoding Apo B-100  
- Post-translational interruption of hepatic Apo B interference with VLDL synthesis/secretion


Newer therapies for HeFH or ASCVD when additional lowering of LDL-C is needed even with maximally tolerated statin therapy, medications also approved for HoFH. Rationales vary for HoFH.

Improving Outcomes in Patients with ASCVD: Dramatic Developments in Dyslipidemia Management

Blockade of PCSK9/LDL-R Interaction Lowers LDL-C Levels

OGSYSEY MONO: Alirocumab Versus Ezetimibe Monotherapy

MENDEL-2: Evolocumab Monotherapy Versus Ezetimibe or Placebo

LDL-R = LDL receptor; SREBP = sterol regulatory element-binding protein.
Adapted from LaGace TA. Curr Opin Lipidol. 2014;25:387-393.
Improving Outcomes in Patients with ASCVD: Dramatic Developments in Dyslipidemia Management

**ODYSSEY LONG TERM: Alirocumab Plus Statin in Patients at High Risk**

![Graph showing LDL-C levels over time with Alirocumab and Statin therapy](image1)

- Post hoc analysis: decrease in major CV events with alirocumab + statin (3.3% vs 1.7%; nominal $P = .02$)

**LAPLACE-2: Evolocumab + Statin**

![Graph showing LDL-C levels over time with Evolocumab and Statin therapy](image2)

- Placebo every 2 weeks
- Placebo every month
- Ezetimibe every day + placebo every 2 weeks
- Ezetimibe every day + placebo every month
- Evolocumab every 2 weeks
- Evolocumab every month

**GAUSS-2: Evolocumab in Patients With Statin Intolerance**

![Graph showing LDL-C levels over time with Evolocumab and Ezetimibe therapy](image3)

- Basal injection
- Monthly injection


LAPLACE-2: Evolocumab + Statin in Patients at High Risk

Candidates for PCSK9 Inhibitors: Indications

- Prescribed as an adjunct to diet and maximally tolerated statin therapy in adults with:
  - ASCVD (e.g., MI, stroke, peripheral artery disease) who require additional lowering of LDL-C
  - HeFH
  - HoFH (evolocumab only)

PCSK9 Inhibitors: Dosing and Administration

<table>
<thead>
<tr>
<th>Route</th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Prefilled, single-dose, 1-mL syringe or pen</td>
<td>Prefilled, single-dose, 1-mL syringe or pen</td>
<td></td>
</tr>
<tr>
<td>Recommended starting dose</td>
<td>75 mg every 2 weeks</td>
<td>140 mg every 2 weeks</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>150 mg every 2 weeks</td>
<td>420 mg monthly (recommended dose for HoFH)</td>
</tr>
</tbody>
</table>

*The US Food and Drug Administration has also approved a hands-free infusor that adheres to the body and provides 420 mg of evolocumab in a single dose (monthly).

PCSK9 Inhibitors: Follow-up After Initiating Treatment

- Measure LDL-C levels within 4-8 weeks of initiating or titrating to assess response and adjust the dose if needed
- If a dose is missed:
  - Instruct patient to administer injection within 7 days of the missed dose, then resume original schedule
  - If missed dose not administered within 7 days, instruct patient to wait until the next dose on the original schedule
- If allergic reactions appear, discontinue and treat patient according to standard of care
Improving Outcomes in Patients with ASCVD: Dramatic Developments in Dyslipidemia Management

**Common AEs Associated With PCSK9 Inhibitors (>5% of Patients)**

<table>
<thead>
<tr>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nasopharyngitis (11.3%)</td>
<td>• Nasopharyngitis (10.9%)</td>
</tr>
<tr>
<td>• Injection site reactions (7.2%)</td>
<td>• Upper respiratory tract infection (9.3%)</td>
</tr>
<tr>
<td>• Influenza (5.7%)</td>
<td>• Influenza (7.5%)</td>
</tr>
<tr>
<td>• AEs leading to discontinuation (5.3% [vs 5.1% with placebo])</td>
<td>• Back pain (6.2%)</td>
</tr>
<tr>
<td>• Serious hypersensitivity reactions requiring hospitalization have occurred with both agents</td>
<td>• Injection site reactions (5.7%)</td>
</tr>
<tr>
<td>• Potential for immunogenicity with all therapeutic proteins</td>
<td>• AEs leading to discontinuation (2.2% [vs 1% with placebo])</td>
</tr>
</tbody>
</table>

Serious hypersensitivity reactions requiring hospitalization have occurred with both agents. Potential for immunogenicity with all therapeutic proteins.

**Other Agents: Lomitapide and Mipomersen, Approved for HoFH Only**

- **Mechanism of Action**

  IDL = intermediate-density lipoprotein; MTP = microsomal triglyceride transfer protein.


- **Dosage forms:**
  - Lomitapide: daily oral capsule
  - Mipomersen: once-weekly subcutaneous injection

- **Pregnancy categories:**
  - Lomitapide: pregnancy category X
  - Mipomersen: pregnancy category B

- **Similar safety concerns:**
  - Boxed warnings citing risk of hepatotoxicity
  - Risk evaluation and mitigation strategy
    - Only certificated healthcare providers may prescribe the drug; only certified pharmacies may dispense it.

**Lomitapide and Mipomersen: Special Considerations**

- May be used in combination with other LLTs
- Dosage forms:
  - Lomitapide: daily oral capsule
  - Mipomersen: once-weekly subcutaneous injection
- Pregnancy categories:
  - Lomitapide: pregnancy category X
  - Mipomersen: pregnancy category B
- Similar safety concerns:
  - Boxed warnings citing risk of hepatotoxicity
  - Risk evaluation and mitigation strategy
  - Only certificated healthcare providers may prescribe the drug; only certificated pharmacies may dispense it.
Case Conclusion: Jason

- Jason has residual CVD risk that warrants additional therapy
- Genetic testing confirms a diagnosis of HeFH
- Diagnosis warrants referral to clinical lipidologist
- PCSK9 inhibitor is an option as add-on to current maximal statin therapy

Principles for Collaborating With Patients in Treatment Selection

- Ensure optimal pharmacotherapy through prudent use and monitoring of medications
- Educate patients about treatment options
- Encourage lifestyle changes that can reduce CVD risk

Future Directions: Sophisticated Assessment of ASCVD Risk and Treatment Response

- Genetic testing
  - Those with a genetic predisposition to CV disease may respond better to statins
  - Improved assessment of ASCVD risk
- Advanced lipid testing
  - Traditional lipid testing does not provide the best information to manage ASCVD risk
  - Determining lipid particle size, number, and subclasses is beneficial
Improving Outcomes in Patients with ASCVD: Dramatic Developments in Dyslipidemia Management

PCE Action Plan

☑ Encourage a healthy lifestyle to improve lipid lowering, involve patients in decision making regarding therapy
☑ Consider strategies to manage muscle symptoms in patients taking statins
☑ Address obstacles to medication adherence
☑ Collaborate with patients in selecting LLT to improve outcomes

PCE Promotes Practice Change
New Therapeutic Choices for Heart Failure: Keeping Up With the Latest Recommendations

Learning Objectives

• Recognize the clinical syndrome of HF and who is at risk
• Incorporate diagnostic testing essential for diagnosis and management of HF in patients at risk
• Describe appropriate pharmacologic and nonpharmacologic strategies for patients across the spectrum of HF, including new treatment strategies when conventional therapies have been exhausted

Definition of HF

• Complex syndrome in which the heart cannot pump blood at a rate commensurate with metabolic needs of the tissues, or can do so only with high pressures
• Results from structural or functional impairment of ventricular filling (diastolic HF, or HFpEF) or ejection (systolic HF, or HFrEF) of blood
• The term “heart failure” preferred over “congestive heart failure”; some patients present without signs or symptoms of volume overload

HF = heart failure
New Therapeutic Choices for Heart Failure: Keeping Up With the Latest Recommendations

Epidemiology of HF

- >5.7 million people affected in United States; >8 million by 2030
- >870,000 new cases/year; 1 in 9 deaths due to HF
- Before age 75, rates markedly higher in blacks than in whites
- Mortality ~50% within 5 years after diagnosis


Hospitalizations for HF

About 1 million hospitalizations per year, usually in patients previously hospitalized for HF


Pathophysiology of HF

Cardiac injury
- Increased load
- Activation of RAA system, SNS, and cytokines
- Reduced systemic perfusion
- Altered gene expression
- Growth and remodeling
- Ischemia and energy depletion
- Direct toxicity
- Apoptosis
- Necrosis
- Cell death

Pathway adapted from Eichhorn EJ, Bristow MR. Circulation. 1996;94:2285-2296.
New Therapeutic Choices for Heart Failure: Keeping Up With the Latest Recommendations

HFrEF and HFP EF

- HFrEF (systolic HF): EF ≤ 40%
  - Decreased pumping function of the heart
  - Result: fluid backup in the lungs and HF
- HFP EF (diastolic HF)
  - Thickened and stiff heart muscle
  - Result: heart does not fill with blood properly, causing fluid backup in the lungs and HF
- HFP EF more common, but medical therapies proven effective only for patients with HFrEF

Risk Factors and Comorbidities

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>CAD, hypertension, valvular heart disease, diabetes, cigarette smoking, highflow hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac comorbidities</td>
<td>ACS, tachy- or bradycardias, hypertension, myocarditis, cardiomyopathy, acute PE, acute valvular regurgitation, acute aortic dissection, cardiac tamponade</td>
</tr>
<tr>
<td>Noncardiac comorbidities</td>
<td>Renal dysfunction, respiratory diseases, anemia, arthritis, cognitive dysfunction, depression, COPD, thyroid disorder, polypharmacy, infection, inflammatory markers, sleep apnea</td>
</tr>
<tr>
<td>Patient-related factors</td>
<td>Aging, nonadherence, high salt or fluid intake, alcohol use</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; PE = pulmonary embolus.


The Continuum of HF

LVH = left ventricular hypertrophy; MI = myocardial infarction; QoL = quality of life.

Adapted from Dzau V, Braunwald E. Am Heart J. 1991;121:1244-1263.
New Therapeutic Choices for Heart Failure: Keeping Up With the Latest Recommendations

Powerful Role of Risk Factor Management

“Aggressive implementation of evidence-based management of risk factors for coronary heart disease should be at the core of HF prevention strategies.”

- Early diagnosis essential to address risk factors, prevent progression to structural, symptomatic HF
- Increased primary care focus on screening for risk factors in at-risk patients
  - Risk factor management: antihypertensive, antiplatelet, lipid-lowering proven to prevent HF
  - Even modest weight loss reduces hypertension, dyslipidemia, and glycemic control
  - Control of hypertension could significantly reduce incidence of HF
- Opportunity in primary care to dramatically reduce incidence of HF through guideline-based risk factor control


Case Study: Ginny

- Ginny, a 63-year-old musician, visits her primary care clinician with a 3-week history of fatigue, increasing shortness of breath
- Dyspnea worse with ordinary activity and lying flat; Ginny is comfortable sitting
- Her boots are “pinching” intermittently
- No chest pain
- Frequent abdominal discomfort
- History of hypertension, type 2 diabetes, dyslipidemia, MI (5 years ago; received stent)
- Nondrinker; quit smoking 7 months ago

Case Study: Ginny (cont’d)

- Physical examination
  - Height: 5 ft 6 in; weight: 175 lb (body mass index: 28.2 kg/m²)
  - BP (treated): 160/92 mm Hg
  - HR 116 beats/min; respiratory rate 22; temperature 98.4°F
  - 1+ pitting edema ankles; S3 heart sound; bilateral rales lung bases
- Laboratory findings
  - Random blood glucose: 139 mg/dL
  - Lipids (treated): total cholesterol 200 mg/dL, low-density lipoprotein cholesterol 135 mg/dL
- Medications
  - Furosemide 20 mg/d; metformin 500 mg/d; aspirin 81 mg/d; lisinopril 20 mg/d; atorvastatin 20 mg/d; carvedilol 6.25 mg twice daily
- No arrhythmias; mild cardiomegaly

BP = blood pressure; HR = heart rate.
Clinical Evaluation of HF: ACCF/AHA Guidelines

- Thorough history and physical examination essential to identify cardiac/noncardiac disorders or behaviors that may cause/accelerate development or progression
- In patients with idiopathic dilated cardiomyopathy, 3-generational family history needed to evaluate presence of familial dilated cardiomyopathy
- Assess volume status/vital signs at each visit
  - Serial assessment of weight, estimates of JVP and presence of peripheral edema/orthopnea

ACCF = American College of Cardiology Foundation; AHA = American Heart Association; JVP = jugular venous pressure.

Diagnostic Challenges in HF

- HF is a syndrome, not a disease; no single test is diagnostic
- Early detection hindered by nonspecific symptoms, presence of comorbidities
- Presentations may change from no symptoms to significant symptoms
- Rate of initial misdiagnosis up to 50% in primary care (clinical vs objective criteria)
- Misdiagnosis high for elderly patients with HFpEF (symptoms mild, absent, attributed to other causes)


History

- Dyspnea (focus of Boston criteria, other diagnostic models)
  - High sensitivity (>95%); if absent, HF unlikely
  - Progression: dyspnea on exertion → paroxysmal nocturnal dyspnea → orthopnea → dyspnea at rest
  - All symptoms except dyspnea have low sensitivity
- Common: fatigue, weakness, exercise intolerance, edema, nocturia, cough, weight gain
- Less common: cognitive impairment, delirium, nausea
- With progression: gastrointestinal symptoms, but can be misleading; better assessed through history than physical examination
- Evaluation of cardiac/noncardiac risk factors
  - CAD responsible for ≤50% of HF with ↓ LV function

LV = left ventricular.
New Therapeutic Choices for Heart Failure: Keeping Up With the Latest Recommendations

Physical Examination

- General appearance (resting dyspnea, cyanosis, cachexia)
- BP and HR (compensation, arrhythmia)
- JVP elevation (very high specificity for LV dysfunction)
- Point of maximal impact displacement (very high specificity)
- Heart sounds (S3 very high specificity)
- Pulmonary examination (wheezing, crackles)
- Lower extremity edema (limited diagnostic value)
- Hepatojugular reflux (high specificity)
- Patients with compensated HF often do not have congestion

Differential Diagnosis of HF: Signs and Symptoms

- Myocardial ischemia
- Pulmonary disease
- Sleep-disordered breathing
- Obesity
- Deconditioning
- Malnutrition
- Anemia
- Hepatic failure
- Chronic kidney disease
- Hypoalbuminuria
- Venous stasis
- Depression
- Anxiety, hyperventilation syndromes
- Hyper- or hypothyroidism

Noninvasive Imaging: ACCF/AHA Guidelines

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute, new-onset HF suspected: chest radiograph</td>
<td>C</td>
</tr>
<tr>
<td>2-D echo with Doppler for initial evaluation</td>
<td>C</td>
</tr>
<tr>
<td>Repeat EF measurement in patients with HF with significant change in clinical status or who have had treatment that might affect cardiac function or for consideration of device therapy (ICD or biventricular pacemaker)</td>
<td>C</td>
</tr>
<tr>
<td>Noninvasive imaging to detect myocardial ischemia and viability is reasonable in HF and CAD</td>
<td>C</td>
</tr>
<tr>
<td>Viability assessment is reasonable before revascularization in HF patients with CAD</td>
<td>B</td>
</tr>
<tr>
<td>Radionuclide ventriculography or MRI useful for assessing LVEF and volume</td>
<td>B</td>
</tr>
<tr>
<td>MRI reasonable when assessing myocardial infiltration or scar</td>
<td>B</td>
</tr>
<tr>
<td>Do not routinely reassess LV function</td>
<td>B</td>
</tr>
</tbody>
</table>

New Therapeutic Choices for Heart Failure: Keeping Up With the Latest Recommendations

**Chest Radiograph in HF**
- May show evidence of HF (eg, cardiomegaly) but not a good independent predictor
- Most useful for detecting alternatives for symptoms (eg, lung disease)
- During treatment, x-ray changes may lag behind clinical improvement

**Echocardiography**
- Essential screening tool if HF suspected
- 2-D echo with Doppler diagnostic standard for HF-EF and HFP EF
- Assesses EF, filling pressures, wall thickness and motion, valve function
- Low rates of false-positives and false-negatives

**Recommendations for Biomarkers**

<table>
<thead>
<tr>
<th>Biomarker, Application</th>
<th>Setting</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natriuretic peptides (BNP, NT-proBNP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis or exclusion of HF</td>
<td>Ambulatory, acute</td>
<td>A</td>
</tr>
<tr>
<td>Prognosis of HF</td>
<td>Ambulatory, acute</td>
<td>A</td>
</tr>
<tr>
<td>Achieve GDMT</td>
<td>Ambulatory</td>
<td>B</td>
</tr>
<tr>
<td>Guidance of acutely decompensated HF therapy</td>
<td>Acute</td>
<td>C</td>
</tr>
<tr>
<td>Biomarkers of myocardial injury (troponins, creatine phosphokinase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive risk stratification</td>
<td>Acute, ambulatory</td>
<td>A</td>
</tr>
<tr>
<td>Biomarkers of myocardial fibrosis (ST2, Galectin-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive risk stratification</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*BNP = brain natriuretic peptide; GDMT = guideline-directed medical therapy; NT-proBNP = N-terminal prohormone BNP.*


New Therapeutic Choices for Heart Failure:
Keeping Up With the Latest Recommendations

Laboratory Testing: BNP

- BNP and NT-proBNP increase when cardiac myocytes are under strain
- Normal BNP values rule out HF
- BNP important measure when cost/access limits use of echo
- May reveal HF with/without systolic dysfunction but does not distinguish HFrEF from HFpEF
- Increases with severity of HF
- Obesity, insulin resistance may lower BNP
- High values lack specificity; clinical correlates required
- Only ~40% of primary care practices use BNP for HF diagnosis


Causes of Elevated Natriuretic Peptide Levels

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Noncardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF, including RV syndromes</td>
<td>Advancing age</td>
</tr>
<tr>
<td>ACS</td>
<td>Anemia</td>
</tr>
<tr>
<td>Heart muscle disease, including LVH</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Pulmonary causes: obstructive sleep apnea, severe pneumonia, pulmonary hypertension</td>
</tr>
<tr>
<td>Pericardial disease</td>
<td>Critical illness</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Bacterial sepsis</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Severe burns</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>Toxic-metabolic insults, including cancer chemotherapy and envenomation</td>
</tr>
<tr>
<td>Cardioversion</td>
<td></td>
</tr>
</tbody>
</table>


Classification of HF

<table>
<thead>
<tr>
<th>ACC/AHA Stages</th>
<th>NYHA Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A High risk for HF but without structural heart disease or symptoms of HF</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause HF symptoms</td>
</tr>
<tr>
<td>B Structural heart disease but without signs or symptoms of HF</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause HF symptoms</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current symptoms of HF</td>
<td>II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in HF symptoms</td>
</tr>
<tr>
<td>D Refractory HF requiring specialized interventions</td>
<td>IV Unable to carry on any physical activity without HF symptoms, or symptoms at rest</td>
</tr>
</tbody>
</table>

New Therapeutic Choices for Heart Failure: Keeping Up With the Latest Recommendations

Goals of HF Management

- Improve symptoms and QoL
- Prolong life by slowing disease progression
- Relieve circulatory congestion
- Increase tissue perfusion
- Reduce vasoconstriction
- Inhibit activation of the RAA system and SNS
- Inhibit progressive ventricular enlargement or remodeling
- Optimize patient education, adherence, and referral
- Recognize and refer patients who will benefit from specialized care, including ventricular assist device and heart transplant

Barriers to Management Goals

- Gaps in outpatient and hospital care perpetuate cycle of HF exacerbations
- Patients at highest risk of death least likely to receive recommended therapies
- Treatment, patient education gaps evident even in cardiology practices

Clinical Course of HF With Type and Intensity of Management

- Transition to advanced HF
  - Oral therapies failing
  - A time for many major decisions
  - Consider MCS and/or transplantation, if eligible
  - Consider transition of care plan to one dominated by a palliative approach, which may involve formal hospice
**New Therapeutic Choices for Heart Failure: Keeping Up With the Latest Recommendations**

### Treatment of Stage A HF

- Treat hypertension and dyslipidemia using contemporary guidelines
- Other conditions/agents that may lead to or contribute to HF (eg, obesity, diabetes, tobacco use, and known cardiotoxic agents) should be controlled or avoided

---

### Therapies for HF: Stages B-D/NYHA Classes I-IV

#### Severity of HF vs. Treatment Options

<table>
<thead>
<tr>
<th>Stage B, Class I</th>
<th>ACE inhibitor or ARB β-blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage C, Class I-IV</td>
<td>ACE inhibitor and/or ARB (I-IV)</td>
</tr>
<tr>
<td>Stage D, Class IV</td>
<td>All Stage C treatments</td>
</tr>
</tbody>
</table>

ARNI = angiotensin receptor neprilysin inhibitor; CRT = cardiac resynchronization therapy

---

### Oral Drug Therapies for HF

- ACE inhibitors – captopril, lisinopril, ramipril, enalapril
- ARBs – losartan, valsartan, candesartan
- Aldosterone antagonists – spironolactone
- β-blockers – bisoprolol, carvedilol, metoprolol
- Digitalis – digoxin (HF/EF)
- Diuretics – furosemide, hydrochlorothiazide
- Vasodilators –isosorbide dinitrate/hydralazine
- Statins in patients with recent/remote history of CAD
- ARNI (sacubitril/valsartan) – in place of ACE or ARB
- Ivabradine – with maximally tolerated β-blocker

---

New Therapeutic Choices for Heart Failure: Keeping Up With the Latest Recommendations

Incremental Benefit of HF Therapies

<table>
<thead>
<tr>
<th>HF Therapies</th>
<th>Change in Odds of 24-Month Mortality (%)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blocker</td>
<td>-39% (–28% to –49%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>β-Blocker + ACEI/ARB</td>
<td>-63% (–54% to –71%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>β-Blocker + ACEI/ARB + ICD</td>
<td>-76% (–68% to –81%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>β-Blocker + ACEI/ARB + ICD + HF Education</td>
<td>-81% (–75% to –86%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>β-Blocker + ACEI/ARB + ICD + HF Education + Anticoagulation for AF</td>
<td>-81% (–72% to –87%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>β-Blocker + ACEI/ARB + ICD + HF Education + Anticoagulation for AF + CRT</td>
<td>-83% (–77% to –88%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

ACEI = ACE inhibitor; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.


Treatment of Stage B HF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of MI and ↓EF: ACE inhibitors or ARBs</td>
<td>A</td>
</tr>
<tr>
<td>History of MI and ↓EF: β-blockers</td>
<td>B</td>
</tr>
<tr>
<td>Post-MI: statins</td>
<td>A</td>
</tr>
<tr>
<td>Hypertension: GDMT to prevent symptomatic HF</td>
<td>A</td>
</tr>
<tr>
<td>All patients with ↓EF: ACE inhibitors</td>
<td>A</td>
</tr>
<tr>
<td>All patients with ↓EF: β-blockers</td>
<td>C</td>
</tr>
<tr>
<td>ICD reasonable with asymptomatic ischemic cardiomyopathy ≥40 days post-MI, LVEF ≤30%, with GDMT</td>
<td>B</td>
</tr>
<tr>
<td><strong>Caution:</strong> nondihydropyridine calcium blocker may be harmful in patients with low LVEF.</td>
<td>C</td>
</tr>
</tbody>
</table>


Treatment of Stage C HFpEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control hypertension according to published clinical practice guidelines</td>
<td>B</td>
</tr>
<tr>
<td>Diuretics to relieve symptoms of volume overload</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD and angina or myocardial ischemia despite GDMT</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to clinical practice guidelines to improve symptomatic HF</td>
<td>C</td>
</tr>
<tr>
<td>β-blockers, ACE inhibitors, and ARBs for hypertension</td>
<td>C</td>
</tr>
<tr>
<td>ARBs may be considered to decrease risk of hospitalization</td>
<td>B</td>
</tr>
<tr>
<td>Nutritional supplementation not recommended</td>
<td>C</td>
</tr>
</tbody>
</table>

Lacking direct clinical trial evidence to drive HFpEF management, guidelines are largely consensus-based.

Treatment of Stage C HFpEF

For all volume overload

- Add Loop diuretics
- Add Hydralazine-nitrates

For African Americans with NYHA class II-IV, consider additional strategies

- Add Aldosterone antagonist

*Data are limited for use of hydralazine-nitrates with ARNI. Careful monitoring of potassium advised in patients taking an ARNI with aldosterone antagonist.


Case Study Conclusion: Ginny's Uncertain Future

- Ginny was prescribed the following:
  - Increased furosemide dose (40 mg) for diuresis
  - Carvedilol, target dose 25 mg twice daily
  - Increased doses of metformin (1000 mg), atorvastatin (40 mg), lisinopril (40 mg/d)
- At 7 months, Ginny was hospitalized for HF symptoms after a 5-day lapse in adherence (did not refill medications)
- At 24 months, despite adherence, Ginny was hospitalized again for HF symptoms including dyspnea at rest (NYHA IV; Stage C; EF 34%)
  - Received intravenous therapy to counter bowel edema/malabsorption of medications
  - Referred to specialist for evaluation and treatment; lisinopril was held for 36 hours and ARNI therapy was initiated

New Medication Options in HF

Both ivabradine and sacubitril/valsartan (ARNI) evaluated in patients with NYHA class II-IV HF and ↓ EF

Ivabradine
  - Inhibits the I_f (“funny” (pacemaker) current in the sinoatrial node to decrease heart rate but does not impact contractility
  - Approval based on placebo-controlled SHIFT trial

Sacubitril/valsartan
  - Neprilysin (enzyme) inhibitor + ARB; increases peptides (eg, natriuretic peptide) usually degraded by neprilysin, to counter maladaptive mechanisms
  - Approval based on PARADIGM-HF trial vs enalapril

ARNI = angiotensin receptor-neprilysin inhibitor.

2016 ACC/AHA/HFSA Focused Update: Use of Newer Drugs for HF

<table>
<thead>
<tr>
<th>Sacubitril-Valsalan (ARNI)</th>
<th>Ivabradine</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with chronic symptomatic HFrEF NYHA class II-III who tolerate ACE inhibitor or ARB, replacement by ARNI is recommended to further reduce morbidity and mortality</td>
<td></td>
</tr>
<tr>
<td>Use with β-blocker</td>
<td></td>
</tr>
<tr>
<td>Can reduce HF hospitalization in patients with NYHA class II-III stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including maximally tolerated β-blocker, and who are in sinus rhythm with heart rate ≥70 bpm</td>
<td></td>
</tr>
</tbody>
</table>

ESC = European Society of Heart Failure; HFSA = Heart Failure Society of America.


SHIFT: Cardiovascular Death or HF Hospitalization With Ivabradine

Patients achieving HR <60 bpm or with >10 bpm reduction have best prognosis

<table>
<thead>
<tr>
<th>Placebo (n = 3290)</th>
<th>Ivabradine (n = 3268)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR = 0.82 (0.75-0.90)</td>
<td>P = .0001</td>
</tr>
</tbody>
</table>


SHIFT: Adverse Events

- Symptomatic/asymptomatic bradycardia more common in ivabradine group (11%) than in placebo group (2%) (both P < .0001); led to withdrawal from study in ≤1% in either group
- Visual symptoms (phosphenes) in 3% of patients taking ivabradine, 1% taking placebo (P < .0001); led to withdrawal in <1% in either group
- No relevant differences in laboratory values

Ivabradine: Precautions

- Fetal toxicity: women should use effective contraception
- Monitor patients for atrial fibrillation
- Monitor heart rate decreases and bradycardia symptoms during treatment
- Not recommended for patients with second-degree atrioventricular block


PARADIGM-HF: Cardiovascular Death or HF Hospitalization With Sacubitril/Valsartan

Kaplan-Meier Estimate of Cumulative Rates (%)

Sacubitril/valsartan (n = 4187)
Enalapril (n = 4212)

HR = 0.80 (0.73-0.87)
P = .0000002
Number needed to treat = 21

Trial stopped early due to overwhelming benefit of sacubitril/valsartan


PARADIGM-HF: Adverse Events

- Fewer patients in sacubitril/valsartan group than in enalapril group stopped study medication due to an adverse event (10.7% vs 12.3%; P = .03) or because of renal impairment (0.7% vs 1.4%; P = .002)
- Symptomatic hypotension more common with sacubitril/valsartan (14%) than with enalapril (9.2%) (P <.001)
- No significant difference in rate of angioedema

Sacubitril/Valsartan: Precautions

- Do not use in patients with angioedema
  - Patients with a history of angioedema and use of an ACE inhibitor should be treated with an ARB
- Discontinue ACE inhibitor for ≥36 hours before initiating therapy with sacubitril/valsartan


Strategies for Optimal Management of HF in Primary Care: Nonpharmacologic Interventions

- Patient and family education on self-care
- Regular, suitable physical activity
- Sodium restriction if congestive symptoms
- Cardiac rehabilitation for clinically stable patients
- Smoking cessation, weight loss
- Enhanced patient education—referral to HF management program (≥60 minutes, qualified educator or AHA interactive workbook)

Strategies for Optimal Management of HF in Primary Care

- Early re-evaluation crucial, especially for higher-risk patients; opportunity for:
  - Reassessment, including laboratory
  - Medication review, titration, assessment of adherence, absorption of drug
- Up-titrate drugs in small increments, with monitoring of vital signs before and after
  - Provide reassurance on transient symptoms
  - Discourage discontinuation without consult
- Carefully review doses of medications for risk factor control and need for dose increases
New Therapeutic Choices for Heart Failure: Keeping Up With the Latest Recommendations

PCE Action Plan

✓ Perform screening and guideline-based risk factor control to prevent progression to HF in at-risk patients
✓ Identify potential causes of progression in patients presenting with HF through thorough history, physical examination, and follow-up
✓ Use 2-D echo with Doppler to diagnose systolic and diastolic dysfunction
✓ Use guideline-based treatment for all patients with chronic heart failure
✓ Identify candidates who could benefit from therapy with sacubitril-valsartan or ivabradine
✓ Refer patients to a comprehensive HF management program to improve outcomes

PCE Promotes Practice Change
Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Learning Objectives

- Perform a thorough evaluation of a patient's risk for abusing ER/LA opioid analgesics
- Select the ER/LA opioid analgesic treatment regimen best suited for each chronic pain patient based on factors specific to that patient and the characteristics of the opioid prescribed
- Counsel patients and their caregivers on strategies to help them achieve the benefits of using ER/LA opioids in a safe, appropriate manner

ER/LA = extended-release/long-acting

Opioid Abuse: A Growing Epidemic

- Healthcare providers wrote 259 million prescriptions for opioid pain medications in 2012
- More Americans die every year from drug overdoses than from motor vehicle accidents
- 78 Americans die every day from an opioid overdose; since 1999, deaths have nearly quadrupled
- >6 of 10 of drug overdose deaths involve an opioid

Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Sources of Prescription Painkillers Among Past-Year Nonmedical Users

Controlled Substances Act

<table>
<thead>
<tr>
<th>Schedule Class</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No accepted medical use; high potential for abuse; potentially severe psychological and/or physical dependence</td>
<td>Heroin, marijuana, ecstasy, methaqualone, peyote, LSD</td>
</tr>
<tr>
<td>II</td>
<td>High potential for abuse (less than schedule I); potentially severe psychological or physical dependence</td>
<td>Opioids (including hydrocodone combination products), cocaine, methadone/pethidine, meperidine</td>
</tr>
<tr>
<td>III</td>
<td>Moderate to low risk of dependence; less abuse potential than schedule I or II</td>
<td>Ketamine, buprenorphine, anabolic steroids, &lt;90 mg of codeine/dose</td>
</tr>
<tr>
<td>IV</td>
<td>Lower potential for abuse than schedule III; limited quantities of certain narcotics</td>
<td>Acyclovir, carbamazepine, clonazepam, lorazepam, pentazocine, zolpidem</td>
</tr>
<tr>
<td>V</td>
<td>Low potential for dependence; low potential for abuse</td>
<td>Alprazolam, carisoprodol, diazepam, ketamine, pentazocine, zolpidem</td>
</tr>
</tbody>
</table>

LSD = lysergic acid diethylamide

Case Study: Karen, 56 Years Old

- Active and athletic; plays tennis regularly
- Taking ER opioid for knee osteoarthritis
  - “Nothing else gets rid of the pain”
- “Not ready” for surgery

<table>
<thead>
<tr>
<th>Physical Examination</th>
<th>Height</th>
<th>5’6”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight</td>
<td>165 lb</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>26.6 kg/m²</td>
</tr>
<tr>
<td></td>
<td>Blood pressure</td>
<td>125/72 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Pulse</td>
<td>76</td>
</tr>
<tr>
<td>Osteoarthritis history</td>
<td>5 years</td>
<td></td>
</tr>
<tr>
<td>Time on opioid therapy</td>
<td>3 years</td>
<td></td>
</tr>
</tbody>
</table>
Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Opioid Analgesics for CNCP: Current Guidelines

- CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016¹
  - For primary care providers who treat adult patients with chronic pain in outpatient settings²
- APS-AAPM Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain³

CNCP = chronic noncancer pain.


Before prescribing:
- Assess pain and function
- Consider if nonopioid therapies are appropriate
- Talk to patients about treatment plan
- Evaluate risk of harm or abuse

CDC Guideline for Prescribing Opioids for Chronic Pain


The Four A’s

Analgesia: does the patient have effective pain relief?
AEs: are they severe or limiting, or are they controlled?
Activity: evidence of increased function with opioids; meeting activity goals?
Aberrant behavior: screen/monitor

Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Tapering and Discontinuing ER/LA Opioid Analgesics

- Do not suddenly discontinue
  - May result in withdrawal
  - Look for physical signs and refer to patient history
- May use range of approaches
  - Slow 10% dose reduction per week
  - More rapid 25%-50% reduction every few days
  - Tailor to individual patient, opioid, treatment history


Karen’s Pain Management

You review nonopioid options with Karen for her knee pain:
- Nonpharmacologic
  - Exercise
  - Weight loss
  - Patient education
- Medications
  - First-line: acetaminophen, oral NSAIDs, topical NSAIDs
  - Second-line: intra-articular hyaluronic acid, capsaicin, limited number of intra-articular glucocorticoid injections

NSAID = nonsteroidal anti-inflammatory drug

Case Study: George, 47 Years Old

- George, a new patient, presents asking for medication for his chronic back pain
- History of degenerative disc disease and failed back surgery
- History of cocaine abuse but says that he is “not currently using”

Physical Examination

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>6'2&quot;</td>
</tr>
<tr>
<td>Weight</td>
<td>212 lb</td>
</tr>
<tr>
<td>BMI</td>
<td>27.2 kg/m²</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>130/80 mm Hg</td>
</tr>
<tr>
<td>Pulse</td>
<td>68 bpm</td>
</tr>
</tbody>
</table>
Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Assessing for Risk of Abuse

- Complete history of current and past substance use
  - Prescription drugs, illegal substances, alcohol, tobacco
- Substance abuse history does not prohibit treatment with ER/LA opioids, but may require additional monitoring and expert consultation/referral
- Family history of substance abuse or psychiatric disorders
- History of sexual abuse
- Social history
  - Employment, cultural background, marital history, legal history, behavioral patterns


Risk Factors for Opioid Abuse

- Current alcohol or substance abuse
- Personal or family history of substance abuse
- Legal, disability issues related to pain
- Young age
- Male sex
- Previous DUI
- Smoking
- Psychiatric or psychological disorders
- Poor social support
- Pre-adolescent sexual abuse
- Adverse childhood events


Opioid Risk Tool

- Predict and quantify potential for aberrant behavior during opioid therapy
- Self-administered
  - On initial visit
  - Prior to opioid therapy
- Scoring
  - 0-3: low risk (6%)
  - 4-7: moderate risk (28%)
  - ≥8: high risk (>90%)

Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Screener and Opioid Assessment for Patients With Pain – Revised (SOAPP-R)

- Self-administered
  - May be completed as part of interview with clinician
- 24 items
- <8 minutes to complete
- Cutoff score: ≥18 = positive; <18 = negative

Other Patient-Administered Risk Assessment and Screening Tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Items</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAST</td>
<td>28</td>
<td>Quantify extent of problems associated with drug abuse</td>
</tr>
<tr>
<td>CAGE-AID</td>
<td>4</td>
<td>Identify abuse/addiction</td>
</tr>
<tr>
<td>STAR</td>
<td>14</td>
<td>Predict, identify patients with addiction + pain</td>
</tr>
<tr>
<td>PMQ</td>
<td>26</td>
<td>Assess risk for opioid medication abuse</td>
</tr>
</tbody>
</table>

Clinician-Administered Tools for Risk Assessment and Screening

<table>
<thead>
<tr>
<th>Tool</th>
<th>Items</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIRE</td>
<td>7</td>
<td>Assess whether long-term opioid therapy is appropriate in patients with CNCP</td>
</tr>
<tr>
<td>SISAP</td>
<td>5</td>
<td>Predict probability of developing aberrant behavior during opioid therapy for CNCP by inquiring about alcohol, marijuana, cigarette use</td>
</tr>
<tr>
<td>POAC</td>
<td>5</td>
<td>Assess criteria that suggest prescription opioid abuse in patients with chronic pain</td>
</tr>
<tr>
<td>ABC</td>
<td>20</td>
<td>Track addiction behaviors related to prescription opioids</td>
</tr>
</tbody>
</table>

Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

**Initial Patient Counseling: Patient-Prescriber Agreement**

- Sets expectations of patient/clinician
  - Rationale for goals of opioid therapy
  - Responsibilities of clinician in prescribing opioids
  - Responsibilities of patient in using opioids
  - Potential AEs
- Should be signed after assessment, before starting opioid trial
- Should reflect patient literacy
  - In addition to standard version, low-literacy English-language version developed, validated


**Treatment Initiation**

- Consider initial treatment a therapeutic trial
  - Several weeks to several months
  - Conversion to long-term therapy based on careful consideration of trial outcome
- Considerations
  - Progress toward therapeutic goals
  - Changes in underlying pain condition
  - Opioid-related AEs
  - Changes in psychiatric or medical comorbidities
  - Aberrant drug-related behavior, addiction, or diversion
  - Dosing and other considerations


**Documentation and Other Key Practices to Protect the Patient—and the Prescriber**


Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics
Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Monitoring: Purposes and Techniques

<table>
<thead>
<tr>
<th>Purposes</th>
<th>Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify previous and current drug use</td>
<td>Screening tests</td>
</tr>
<tr>
<td>Determine basis of treatment</td>
<td>Patient-prescriber agreement</td>
</tr>
<tr>
<td>Decrease drug abuse and misuse</td>
<td>Patient education</td>
</tr>
<tr>
<td>Implement adequate pain management strategies</td>
<td>State PDMPs</td>
</tr>
</tbody>
</table>

George Is Using Other Opioids

- Urine testing reveals that George is getting additional opioid medications from another source
- As this is a violation of the patient-prescriber agreement he signed, you counsel him on tapering and discontinuing opioid therapy
- You inform him that symptoms of withdrawal may include drug craving, anxiety, insomnia, abdominal pain, vomiting, diarrhea, and tremors
- You advise him that psychosocial support is available and you refer him for treatment of opioid use disorder


Reasons for Discontinuing ER/LA Opioids

- No progress toward therapeutic goals
- Pain level decreases in stable patients
- 1-2 episodes of increasing dose without prescriber knowledge
- Sharing medications
- Unapproved opioid use to treat another symptom (such as insomnia)
- Intolerable/unmanageable AEs
- Nonadherence/unsafe behavior
- Aberrant behaviors suggesting addiction or diversion
- Use of illicit drugs or nonprescribed opioids from multiple outside services
- Prescription forgery
- Multiple episodes of prescription loss

Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Federation of State Medical Boards Model Policy: Opioid Analgesics in Pain Management

- Evaluation of patient
- Treatment plan
- Informed consent, agreement for treatment
- Periodic review
- Consultation
- Medical records
- Compliance with controlled substance laws and regulations

28 state medical boards have adopted the model policy; 10 others have adopted guidelines with similar language.

Opioid Analgesics for CNCP: General Principles

- Before starting and periodically during opioid therapy, discuss known risks and realistic benefits of opioids
- Discuss provider-patient responsibilities for managing therapy
- Within 1–4 weeks of starting opioid therapy, and at least every 3 months, evaluate benefits and harms with patient
- Assess patient’s pain and function regularly: a 30% improvement in pain and function is considered clinically meaningful
- Discuss patient-centered goals and improvements in function
- Assess pain using validated instruments

National Initiatives to Counter Opioid Abuse

- FDA: Risk Evaluation and Mitigation Strategy (REMS) established for all ER/LA opioid analgesics in 2012
- AAPA/AANP joined with 8 other organizations to launch Collaborative for REMS Education (CO*RE)
  - Emphasizes patient well-being without contributing to individual or public harm
- Pharmaceutical industry developing ER/LA opioids with abuse-deterrent characteristics

Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Why Opioid REMS?

- 35 million Americans have used opioid analgesics for nonmedical purposes
- 7 million Americans misuse or abuse prescription drugs each month
- Prescription drug abuse accounts for 25% to 30% of all drug abuse
- Pain and addiction are interrelated

American College of Preventive Medicine.

ER/LA Opioid Drug Information

Prescribers should understand the characteristics, toxicities, and drug interactions for ER/LA opioid products

Controlled Substances

- ER/LA opioid products are scheduled under the Controlled Substances Act
- Can be misused and abused

AEs

- Respiratory depression most serious AE
- Can be life threatening
- Constipation most common long-term AE
- Should be anticipated

Drug Interactions

- CNS depressants
- Alcohol
- MAOIs
- Diuretics
- QTc prolongation
- P450 interactions

MAOI = monoamine oxidase inhibitor.
US Food and Drug Administration.

ER/LA Opioid Analgesic Formulations: The Current Armamentarium

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine buccal film</td>
<td>Belbuca</td>
</tr>
<tr>
<td>Buprenorphine transdermal system</td>
<td>Butrans</td>
</tr>
<tr>
<td>Methadone hydrochloride tablets</td>
<td>Dolophine</td>
</tr>
<tr>
<td>Methadone hydrochloride tablets</td>
<td>Methadose</td>
</tr>
<tr>
<td>Fentanyl transdermal system</td>
<td>Duragesic</td>
</tr>
<tr>
<td>Hydromorphone hydrochloride ER tablets</td>
<td>Exalgo</td>
</tr>
<tr>
<td>Hydromorphone hydrochloride ER tablets</td>
<td>Insys ER</td>
</tr>
<tr>
<td>Hydromorphone hydrochloride ER tablets</td>
<td>Hydromorphone ER</td>
</tr>
<tr>
<td>Hydromorphone hydrochloride ER tablets</td>
<td>Kadian</td>
</tr>
<tr>
<td>Hydromorphone hydrochloride ER tablets</td>
<td>Zohydro ER</td>
</tr>
<tr>
<td>Hydrocodone and oxycodone ER products</td>
<td>Targiniq ER</td>
</tr>
<tr>
<td>Hydrocodone and oxycodone ER products</td>
<td>Troxyca ER</td>
</tr>
<tr>
<td>Hydrocodone and oxycodone ER products</td>
<td>Troxyca ER</td>
</tr>
<tr>
<td>Hydrocodone and oxycodone ER products</td>
<td>Troxyca ER</td>
</tr>
</tbody>
</table>

"…indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."
Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Case Study: Carol, 34 Years Old

- Carol is a recovering alcoholic; sober for 5 years
- Married; has a son, 3 years old
- Carol was in an automobile collision 2 years ago in which she had multiple broken bones and required surgery
- During recuperation, she took opioids for about 3 months
- She has not used opioids since then, but even after months of physical therapy, she continues to have severe chronic pain that is not relieved by nonopioid analgesics
- She asks if she might safely use opioids again, because the pain is interfering with her ability to care for her son
- Takes no other medications and considers herself otherwise healthy

Abuse-Deterrent Opioid Formulations

**Abuse-Deterrent Mechanism(s)**

- **Agonist/antagonist combinations**
  - Opioid antagonist added to interfere with, reduce, or defeat euphoria associated with abuse; can be sequestered and released only upon manipulation of the product
- **Aversion substances**
  - Combined to produce unpleasant effect if the dosage is manipulated before ingestion or if a higher dosage than directed is used
- **Drug-release design or method of drug delivery**
  - Drug-release design or method of drug delivery can offer resistance to abuse
- **Physical/chemical barriers**
  - Physical: prevent chewing, crushing, cutting, grinding
  - Chemical: resist extraction of opioid using common solvents
- **Prodrug**
  - Prodrug that lacks opioid activity until transformed in GI tract; unattractive for intravenous injection or intranasal consumption
- **Combination**
  - Combination of at least 2 of above methods combined

**Abuse-Deterrent Opioid Brand Name Mechanism(s)**

<table>
<thead>
<tr>
<th>Opioid Brand Name</th>
<th>Mechanism(s) of Deterrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine HCl + naloxone</td>
<td>Subcutaneous depot injection form</td>
</tr>
<tr>
<td>Hydrocodone HCl</td>
<td>Hydrocodone ER</td>
</tr>
<tr>
<td>Oxycodone HCl</td>
<td>Oxycodone ER</td>
</tr>
<tr>
<td>Oxycodone + naloxone</td>
<td>Oxycodone ER</td>
</tr>
<tr>
<td>Oxycodone + naltrexone</td>
<td>Oxycodone ER</td>
</tr>
<tr>
<td>Oxymorphone HCl</td>
<td>Oxymorphone ER</td>
</tr>
<tr>
<td>Hydromorphone HCl</td>
<td>Hydromorphone ER</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>Morphine sulfate ER</td>
</tr>
<tr>
<td>Morphine sulfate + naloxone</td>
<td>Morphine sulfate ER</td>
</tr>
<tr>
<td>Morphine sulfate + naltrexone</td>
<td>Morphine sulfate ER</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxycodone ER</td>
</tr>
<tr>
<td>Oxycodone + naloxone</td>
<td>Oxycodone ER</td>
</tr>
<tr>
<td>Oxycodone + naltrexone</td>
<td>Oxycodone ER</td>
</tr>
<tr>
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<td>Oxycodone ER</td>
</tr>
<tr>
<td>Oxycodone + naltrexone</td>
<td>Oxycodone ER</td>
</tr>
<tr>
<td>Oxycodone + naloxone</td>
<td>Oxycodone ER</td>
</tr>
<tr>
<td>Oxycodone + naltrexone</td>
<td>Oxycodone ER</td>
</tr>
</tbody>
</table>

**FDA-Approved ER Opioids With Labeling Describing Abuse-Deterrent Properties**

- Buprenorphine HCl + naloxone (Suboxone)
- Hydrocodone HCl (Hysingla ER)
- Oxycodone (Oxycodone ER)
- Oxycodone + naloxone (Oxycodone ER)
- Oxycodone + naltrexone (Oxycodone ER)
- Oxymorphone HCl (Oxymorphone ER)

**FDA** - US Food and Drug Administration.
Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

On the Horizon: Abuse-Deterrent Opioids in Development

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Brand Name</th>
<th>Mechanism(s) of Deterrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>Vantrela ER</td>
<td>Aversion; physical/chemical barriers; pharmacokinetics altered with manipulation</td>
</tr>
<tr>
<td>Hydrocodone + acetaminophen</td>
<td>Xartemis XR</td>
<td>Physical/chemical barriers. Currently not considered abuse-deterrent; ongoing studies</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>Arymo ER</td>
<td>Physical/chemical barriers</td>
</tr>
</tbody>
</table>

Carol Is Prescribed an Abuse-Deterrent Opioid Formulation

- In collaboration with a pain specialist, Carol is prescribed an ER abuse-deterrent opioid
- You educate her on the special risks and responsibilities she faces as a person with a history of substance abuse
- She is happy to sign a patient-prescriber agreement and agrees to monthly urine drug testing
- She is also attending a pain management meditation class
- When she returns 1 month later, she reports marked relief of her pain

Individualizing Treatment to Optimal Effect: Weighing Patient and Agent Factors

- Assess: Evaluate factors that could increase risk of harm from opioid therapy
  - Personal/family history of substance use
  - Anxiety/depression
  - Pregnancy
  - Age ≥65 years
  - COPD or other respiratory conditions
  - Renal or hepatic insufficiency

Individualizing Treatment to Optimal Effect: Weighing Patient and Agent Factors (cont’d)

• Check: Consider urine drug testing for other prescription or illicit drugs
• Verify state’s PDMP for:
  – Possible drug interactions
  – High opioid usage (≥50 MME/day)
  – Obtaining opioids from multiple providers

MME = morphine milligram equivalents.

Individualizing Treatment to Optimal Effect: Weighing Patient and Agent Factors (cont’d)

• Discuss: Individualize treatment to optimal effect by weighing patient and agent factors
• Ask your patient about concerns and determine any harms they may be experiencing, such as:
  – Nausea or constipation
  – Feeling sedated or confused
  – Breathing interruptions during sleep
  – Taking or craving more opioids than prescribed, or difficulty controlling use

Centers for Disease Control and Prevention.

Individualizing Treatment to Optimal Effect: Weighing Patient and Agent Factors (cont’d)

• Observe: Assess for signs of abuse and potential for overdose
• Look for early warning signs of overdose risk:
  – Confusion
  – Sedation
  – Slurred speech
  – Abnormal gait

Centers for Disease Control and Prevention.
Management of Chronic Pain: Optimizing Treatment and Reducing the Risk of Abuse

Carol's Pain Is Diminishing

- After 8 months, Carol reports that her pain seems to have stabilized.
- She would like to discontinue opioid therapy to see if she can now handle the pain.
- She is tapered off therapy over the course of 1 month.
- She is continuing her meditation and uses NSAIDs when needed.
- She is grateful for the support of her husband and is enjoying playing with her son.
- You tell her to report if her pain starts to worsen.

PCE Action Plan

- Discuss benefits, risks, and goals of opioid therapy and assess patient's pain and function regularly.
- Sign patient-prescriber agreements after assessment, before starting opioid trial.
- Examine all potential risk factors for opioid abuse in every patient.
- Use the four A's to determine whether to continue opioid treatment.
- Discuss with patients the benefits and risks of opioids and the availability of nonopioid therapies.

PCE Promotes Practice Change
Clinical Advances in Incretin Treatments for Type 2 Diabetes: Homing In on the Role of GLP-1 RAs

Learning Objectives

- Identify features that differentiate DPP-4 inhibitors from GLP-1 RAs
- Integrate GLP-1 RAs into the management of patients with T2DM based on current treatment guidelines and a personalized treatment approach
- Evaluate clinical trial data on current and emerging GLP-1 RAs in terms of their glycemic and nonglycemic features

DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus.

Current State of T2DM Management

- T2DM accounts 90%-95% of cases of diabetes; it is a progressive disease characterized by increasing insulin resistance and relative insulin deficiency and is associated with increased risk of CV complications
- Often undiagnosed for years (<30% in US not diagnosed)
- Progress in meeting cardiometabolic goals is mixed

BP = blood pressure; LDL = low-density lipoprotein cholesterol

Clinical Advances in Incretin Treatments for Type 2 Diabetes: Homing In on the Role of GLP-1 RAs

The "Ominous Octet": Multiple Defects in T2DM Present Multiple Targets for Intervention

- 5 major classes of oral agents
- 2 types of injected agents
- Multiple options within classes
- Multiple ways to combine classes

What Are Incretins? Why Are They Beneficial?

- Produced by GI tract in response to incoming nutrients: GLP-1, GIP
- Difference in insulin response between oral and intravenous glucose challenge = "incretin effect"
- ≤65% of postprandial insulin release is due to the incretin effect
- Incretins regulate glucose homeostasis in multiple ways:

<table>
<thead>
<tr>
<th>α cells</th>
<th>Liver</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ postprandial glucagon secretion</td>
<td>↓ glucagon, reduces hepatic glucose output</td>
<td>↓ insulin secretion, overcome insulin resistance</td>
</tr>
<tr>
<td>β cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 glucose-dependent insulin secretion</td>
<td>1 insulin secretion, overcome insulin resistance</td>
<td></td>
</tr>
<tr>
<td>1 β-cell growth, regeneration</td>
<td>1 peripheral glucose disposal</td>
<td></td>
</tr>
<tr>
<td>↓ β-cell apoptosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GI = gastrointestinal; GIP = gastric inhibitory polypeptide.

Patients With T2DM Have Reduced Incretin Effect

Clinical Advances in Incretin Treatments for Type 2 Diabetes: Homing In on the Role of GLP-1 RAs

Role of GLP-1

- Low plasma levels in fasting state increase rapidly in response to meals, which:
  - Enhances glucose-dependent insulin secretion
  - Inhibits gastric acid secretion and glucagon secretion
  - Slows gastric emptying and glucose absorption
  - Induces satiety (may induce weight loss)
  - Expands β-cell mass (inhibits apoptosis and stimulates new growth)
- However, endogenous GLP-1 is rapidly inactivated by the enzyme DPP-4, limiting its activity


Differing Mechanisms of Action to Enhance GLP-1 Action: DPP-4 Inhibitors

GLP-1 release after meal

- Pro tease inhibitors
  - Inhibit DPP-4 enzyme activity to prolong time that endogenous GLP-1 and GIP levels are elevated

- DPP-4 inhibitors
  - Alogliptin
  - Linagliptin
  - Saxagliptin
  - Sitagliptin

Physiologic effects

- Lower blood glucose


Incretin-Based Therapy to Enhance GLP-1 Action: GLP-1 RAs

GLP-1 release after meal

- Degradation-resistant GLP-1 RA
- Pharmacologic stimulation of GLP-1 receptor
- Enhances and prolongs actions of GLP-1

GLP-1 RAs with greater postprandial glucose control

- Exenatide twice daily
- Liraglutide once daily
- Dulaglutide once weekly
- Albiglutide once weekly
- Exenatide once weekly
- Liraglutide once daily

Physiologic effects

- Lower blood glucose

Clinical Advances in Incretin Treatments for Type 2 Diabetes: Homing In on the Role of GLP-1 RAs

Overview: GLP-1 RAs and DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GLP-1 RA</th>
<th>DPP-4 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Subcutaneous injection</td>
<td>Oral</td>
</tr>
<tr>
<td>Frequency</td>
<td>Twice daily, once daily, once weekly</td>
<td>Once daily</td>
</tr>
<tr>
<td>A1C absolute reduction</td>
<td>0.6% to 1.9%</td>
<td>0.5% to 0.8%</td>
</tr>
<tr>
<td>Body weight</td>
<td>Reduction</td>
<td>Neutral</td>
</tr>
<tr>
<td>Appetite</td>
<td>Suppressed</td>
<td>No effect</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>


CV Safety: Randomized Trials of DPP-4 Inhibitors With Primary CV End Point

<table>
<thead>
<tr>
<th>Study</th>
<th>DPP-4 Inhibitor</th>
<th>Population</th>
<th>Follow-up</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI (N = 16,492)</td>
<td>Saxagliptin</td>
<td>CV disease or CV risk factors</td>
<td>2.1 y</td>
<td>1.27 (1.01-1.51)</td>
</tr>
<tr>
<td>EXAMINE (N = 5389)</td>
<td>Alogliptin</td>
<td>Post-ACS: With HF</td>
<td>1.5 y</td>
<td>1.19 (0.90-1.58)</td>
</tr>
<tr>
<td>TECOS (N = 14,871)</td>
<td>Sitagliptin</td>
<td>CV disease</td>
<td>3.0 y</td>
<td>1.00 (0.83-1.20)</td>
</tr>
</tbody>
</table>

Risk of Hospitalization for HF

ACS = acute coronary syndrome; HF = heart failure.


CV Safety: Randomized Trials of GLP-1 RAs With Primary CV End Point

<table>
<thead>
<tr>
<th>Study</th>
<th>GLP-1 RA</th>
<th>Design</th>
<th>Population</th>
<th>Primary End Point</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA (N = 6,096)</td>
<td>Lixisenatide vs placebo</td>
<td>Non-inferiority</td>
<td>MI or unstable angina</td>
<td>Composite 1</td>
<td>1.02 (0.89-1.17)</td>
</tr>
<tr>
<td>LEADER (N = 9,340)</td>
<td>Liraglutide vs placebo</td>
<td>Non-inferiority</td>
<td>High CV risk</td>
<td>Composite 2</td>
<td>0.87 (0.78-0.97)</td>
</tr>
<tr>
<td>EXSCEL (N ~ 14,000)</td>
<td>Exenatide LAR vs usual care</td>
<td>Superiority</td>
<td>CV disease or CV risk factors</td>
<td>Composite 2</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

Composite 1 = CV death, MI, stroke, or hospitalization for unstable angina.
Composite 2 = CV death, cardiovascular death, or hospitalization for unstable angina.


Case Study: Meet Josef, 59

- Diagnosed with T2DM 4 years ago; works as UPS dispatcher
- Physical findings:
  - BP = 140/85 mm Hg on ACE inhibitor
  - 5 ft 10 in, 185 lb (BMI = 26.5 kg/m²)
- Taking venlafaxine 150 mg/d for depression
- Lab results:
  - A1C = 7.9%
  - LDL-C = 85 mg/dL 
  - Mild renal impairment (eGFR = 68 mL/min/1.73 m²)
- Current T2DM medications:
  - Metformin XR 1500 mg/d
  - Recently discontinued NPH insulin due to 2 episodes of symptomatic hypoglycemia

ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtration rate; XR = extended release.

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**Glycemic Targets in Context of Individual Patient Factors**

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Most Intensive: A1C ≤ 6.5%</th>
<th>For Many Patients: A1C ≤ 7.0%</th>
<th>Least Intensive: A1C &gt; 7.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Established</td>
<td>Long-standing disease</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Moderate</td>
<td>Short</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>None</td>
<td>Few/mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Vascular complications</td>
<td>None</td>
<td>Few/mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Hypoglycemia risk</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Attitude, resources,</td>
<td>Highly motivated; ready available</td>
<td>Motivated; some resources available</td>
<td>Less motivated; limited</td>
</tr>
<tr>
<td>support system</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**ADA and AACE: Individualized Goal-Setting and Treatment in Context of Team-Based Care**

- Set patient-specific glycemic goals:
  - Generally <6.5% to <7.5%
  - Implement lifestyle modifications, including weight-loss medication if necessary
- Address CV and other risk factors: hypertension, lipids, renal impairment, psychological well-being
- Manage patients across their life-span: T2DM diagnosed at younger ages and patients living to old age
- Use collaborative, multidisciplinary teams and a chronic care model to coordinate all aspects of care

AACE = American Association of Clinical Endocrinologists; ADA = American Diabetes Association.

Clinical Advances in Incretin Treatments for Type 2 Diabetes: Homing In on the Role of GLP-1 RAs

2016 ADA Standards: Rational Approach to T2DM Medication Choice

Choice based on:

- Efficacy (ΔA1C)
- Avoiding hypoglycemia and weight gain
- Side effects
- Costs

Consider initial dual therapy if A1C >9.0% at presentation
Proceed to dual therapy if A1C is not reached in ~3 months
Proceed to triple therapy if A1C is not reached in ~3 months

Metformin + DPP-4 inhibitor
Metformin + TZD
Metformin + SGLT2 inhibitor
Metformin + GLP-1 RA
Metformin + Insulin (basal)

Choosing initial therapy:

- Avoiding hypoglycemia
- Avoiding weight gain
- Minimizing cost

Metformin + DPP-4 inhibitor
Metformin + TZD
Metformin + SGLT2 inhibitor
Metformin + GLP-1 RA
Metformin + Insulin (basal)

AACE Algorithm for Glycemic Control, 2015

Entry A1C <7.5%
Entry A1C ≥ 7.5%
Entry A1C >9.0%

Monotherapy
- Metformin
- GLP-1 RA
- SGLT2 inhibitor
- DPP-4 inhibitor
- AG inhibitor
- TZD
- SU/Glinde

Dual therapy
- Oral: Metformin + GLP-1 RA
- Oral: Metformin + SGLT2 inhibitor
- Oral: Metformin + DPP-4 inhibitor
- Oral: Metformin + AG inhibitor
- Oral: Metformin + TZD
- Injection: Basal insulin

Triple therapy
- Oral: Metformin + GLP-1 RA + SGLT2 inhibitor
- Oral: Metformin + GLP-1 RA + DPP-4 inhibitor
- Oral: Metformin + GLP-1 RA + AG inhibitor
- Oral: Metformin + GLP-1 RA + TZD
- Injection: Basal insulin + GLP-1 RA + SGLT2 inhibitor
- Injection: Basal insulin + GLP-1 RA + DPP-4 inhibitor
- Injection: Basal insulin + GLP-1 RA + AG inhibitor
- Injection: Basal insulin + GLP-1 RA + TZD

Potential nonglycemic benefits or few AEs
- GLP-1 RA
- SGLT2 inhibitor
- DPP-4 inhibitor
- AG inhibitor
- TZD

Use with caution
- Basal insulin
- SU/Glinde

Further Recommendations for Common Anthyperglycemic Agents

**ADA recommended treatments by goals**
- Avoiding hypoglycemia: DPP-4 inhibitor, GLP-1 RA, metformin, TZD
- Avoiding weight gain: DPP-4 inhibitor, GLP-1 RA, metformin
- Minimizing cost: Metformin, sufonylurea, basal insulin

**AACE recommended treatments by properties**
- Potential nonglycemic benefits or few AEs: DPP-4 inhibitor, GLP-1 RA, metformin
- Use with caution: Basal insulin, sufonylurea, TZD

AE = adverse event.
Clinical Advances in Incretin Treatments for Type 2 Diabetes:
Homing In on the Role of GLP-1 RAs

Self-Monitoring of Blood Glucose (SMBG)

- An educational and motivational tool that should be used in conjunction with a diabetes management action plan, including:
  - Patient education in treatment and targets
  - Specific recommendations on treatment and timing
  - Identifying hypoglycemic and hyperglycemic patterns
  - Healthcare follow-up based on results, with additional education as appropriate

SMBG: General Principles

- SMBG is a valuable adjunct to the use of A1C targets in achieving glycemic control
  - Provides “real-time” feedback
  - Detects abnormal glycemic profiles
  - Facilitates appropriate medication management
  - Acts as both education and motivational tool
- SMBG should be performed at various times of day
- If FPG and preprandial blood glucose are controlled but A1C is above target, PPG should be emphasized

Cardiometabolic Factors: Goals for Patients With T2DM

<table>
<thead>
<tr>
<th>Blood Pressure Targets (mm Hg)</th>
<th>Lipid Goals (mm Hg)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;60 yrs: &lt;140/90</td>
<td>LDL-C: &lt;100</td>
<td>Normal BMI: (&lt;25 kg/m²)</td>
</tr>
<tr>
<td>Age 60+ yrs: &lt;150/90</td>
<td>HDL-C: ≥40 (men); ≥50 (women)</td>
<td>Weight loss education, nutrition counseling</td>
</tr>
<tr>
<td>Any age with T2DM or CKD: &lt;140/90</td>
<td>Triglycerides: &lt;150</td>
<td>Increase physical activity (if possible): 30 min 3X/week</td>
</tr>
<tr>
<td>&lt;130/80 appropriate for certain patients if achieved without excess treatment burden</td>
<td></td>
<td>Bariatric surgery if extreme weight loss required</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; HDL-C = high-density lipoprotein cholesterol.

Individualize Treatment in Patients With T2DM

- Consider individual patient factors when determining A1C target goals
- For patients with A1C <8.0%, obtain SMBG information to clarify which glycemic component predominates
- Manage all cardiometabolic factors and review at each visit

Fasting and Postprandial Glycemic Effects of GLP-1 RAs

- GLP-1 RAs with greater effect on FPG than on PPG:
  - Albiglutide once weekly
  - Dulaglutide once weekly
  - Exenatide LAR once weekly
  - Liraglutide once daily
- GLP-1 RAs with greater effect on PPG than on FPG:
  - Exenatide twice daily
  - Lixisenatide once daily

GLP-1 RAs With Greater Fasting Glucose Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Liraglutide</th>
<th>Exenatide LAR</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>11–15 h</td>
<td>2 weeks</td>
<td>6–7 d</td>
<td>&lt;4 d</td>
</tr>
<tr>
<td>Dosing</td>
<td>Once-daily</td>
<td>Once-weekly</td>
<td>Once-weekly</td>
<td>Once-weekly</td>
</tr>
<tr>
<td>Δ A1C, %</td>
<td>−0.64 to −1.50</td>
<td>−1.0 to −2.0</td>
<td>−0.24 to −0.83</td>
<td>−0.71 to −1.04</td>
</tr>
<tr>
<td>Δ FPG, mg/dL</td>
<td>−15.1 to −44.0</td>
<td>−31.1 to −47.0</td>
<td>−12.4 to −43</td>
<td>−26 to −43</td>
</tr>
<tr>
<td>Δ PPG, mg/dL</td>
<td>−29 to −49</td>
<td>ND</td>
<td>ND</td>
<td>−41.4 to −66.1</td>
</tr>
<tr>
<td>Safety</td>
<td>GI, H, HR</td>
<td>GI, gastrointestinal, H, SS, hypoglycemia</td>
<td>Headache, GI</td>
<td>GI, headache, anorexia, H, HR</td>
</tr>
</tbody>
</table>

HR = heart rate; SS = subcutaneous; ND = not determined.
Clinical Advances in Incretin Treatments for Type 2 Diabetes:
Homing In on the Role of GLP-1 RAs

GLP-1 RAs With Greater Postprandial Glucose Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exenatide</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>2.4 h</td>
<td>3-4 h</td>
</tr>
<tr>
<td>Dosing</td>
<td>Twice-daily</td>
<td>Once-daily</td>
</tr>
<tr>
<td>Δ A1C</td>
<td>–0.4% to –1.5%</td>
<td>–0.7% to –0.9%</td>
</tr>
<tr>
<td>Δ FPG, mg/dL</td>
<td>–5.4 to –28.8</td>
<td>–5.4 to –20.9</td>
</tr>
<tr>
<td>Δ PPG, mg/dL</td>
<td>–30 to –52.2</td>
<td>–55.8 to –143.3</td>
</tr>
<tr>
<td>Safety</td>
<td>Nausea, vomiting, diarrhea, URTI</td>
<td>GI, including nausea and vomiting</td>
</tr>
</tbody>
</table>

URTI = upper respiratory tract infection.

Characteristic Exenatide Lixisenatide
Half-life 2.4 h 3-4 h
Dosing Twice-daily Once-daily
Δ A1C –0.4% to –1.5% –0.7% to –0.9%
Δ FPG, mg/dL –5.4 to –28.8 –5.4 to –20.9
Δ PPG, mg/dL –30 to –52.2 –55.8 to –143.3
Safety Nausea, vomiting, diarrhea, URTI GI, including nausea and vomiting

Efficacy and Weight Change in Key Comparative Trials

<table>
<thead>
<tr>
<th>Comparators</th>
<th>∆ A1C, %</th>
<th>∆ FPG, mg/dL</th>
<th>∆ Weight, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lixisenatide vs exenatide BID&lt;sup&gt;1&lt;/sup&gt;</td>
<td>–0.79 vs –0.96</td>
<td>–22.0 vs –26.1</td>
<td>–2.8 vs –3.8</td>
</tr>
<tr>
<td>Liraglutide vs exenatide BID&lt;sup&gt;2&lt;/sup&gt;</td>
<td>–1.12 vs 0.79</td>
<td>–28.8 vs –10.8</td>
<td>–3.24 vs –2.87</td>
</tr>
<tr>
<td>Lixisenatide vs liraglutide&lt;sup&gt;3&lt;/sup&gt;</td>
<td>–0.06 vs –0.07</td>
<td>1.8 vs 1.6</td>
<td>–1.6 vs –2.4</td>
</tr>
<tr>
<td>Albiglutide vs liraglutide&lt;sup&gt;4&lt;/sup&gt;</td>
<td>–0.78 vs –0.99</td>
<td>–22 vs –30.2</td>
<td>–0.65 vs –2.19</td>
</tr>
<tr>
<td>Dulaglutide vs liraglutide&lt;sup&gt;5&lt;/sup&gt;</td>
<td>–1.42 vs –1.36</td>
<td>–34.7 vs –34.2</td>
<td>–2.9 vs –3.61</td>
</tr>
<tr>
<td>Exenatide LAR vs liraglutide&lt;sup&gt;6&lt;/sup&gt;, %</td>
<td>–1.28 vs –1.48</td>
<td>–31.7 vs –38.2</td>
<td>–2.68 vs –3.57</td>
</tr>
</tbody>
</table>

BID = twice daily.


Effects on PPG Versus FPG: Clear Differences Among GLP-1 RAs

Δ A1C: Lixisenatide –0.32% vs Liraglutide –0.51%

Added to background metformin in patients with inadequately controlled T2DM.
Clinical Advances in Incretin Treatments for Type 2 Diabetes: Homing In on the Role of GLP-1 RAs

Longer-acting Versus Twice-Daily GLP-1 RAs: Patients Achieving Glycemic Goals

- Exenatide LAR, baseline A1C: 8.5%
- Exenatide BID, baseline A1C: 8.4%

Patients achieving glycemic goals after 24 weeks of treatment:

Candidates for GLP-1 RAs

- Consider GLP-1 RAs for patients who require additional glycemic control:
  - Without hypoglycemia
  - With weight loss
- Determine whether patient requires additional PPG control or additional FPG control and choose GLP-1 RA accordingly

GLP-1 RAs: Safety

- Generally well tolerated; GI AEs most common, can be minimized with slow titration at initiation
- Beneficial effects on CV risk factors, including systolic blood pressure and LDL-C reductions
- May be used for patients with mild renal impairment; avoid exenatide twice daily for patients with ESRD
- Contraindicated in patients with personal or family history of medullary thyroid carcinoma or MEN2
  - Albiglutide, dulaglutide, exenatide LAR, liraglutide

MEN2 = multiple endocrine neoplasia syndrome type 2
Clinical Advances in Incretin Treatments for Type 2 Diabetes: Homing In on the Role of GLP-1 RAs

GI AEs in Comparative Clinical Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID vs lixisenatide</td>
<td>35.1 vs 24.5</td>
<td>13.3 vs 10.1</td>
<td>13.3 vs 10.4</td>
</tr>
<tr>
<td>Lixisenatide vs liraglutide</td>
<td>22.1 vs 22.5</td>
<td>10.4 vs 7.0</td>
<td>2.6 vs 15.5</td>
</tr>
<tr>
<td>Albiglutide vs liraglutide</td>
<td>9.9 vs 29.2</td>
<td>5.0 vs 9.3</td>
<td>14.9 vs 13.5</td>
</tr>
<tr>
<td>Dulaglutide vs liraglutide</td>
<td>20.0 vs 18.0</td>
<td>7.0 vs 8.0</td>
<td>12.0 vs 12.0</td>
</tr>
<tr>
<td>Exenatide LAR vs liraglutide</td>
<td>9.0 vs 21.0</td>
<td>4.0 vs 11.0</td>
<td>6.0 vs 13.0</td>
</tr>
</tbody>
</table>

All, added to metformin ± other oral antidiabetics.


FDA/EMA Statement Regarding Potential Pancreatitis Risk With GLP-1 RAs

- Comprehensive evaluation using multiple data sources, prompted by postmarketing safety signal
- Agencies agree that "...assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer...are inconsistent with the current data..."
- Conclusion: "...current knowledge is adequately reflected in the product information and labeling..."
- Investigation, including data from long-term safety trials, will continue

EMA = European Medicines Agency; FDA = US Food and Drug Administration.

Recommendations for GLP-1 RA Use: Potential Pancreatitis Risk

- Educate patients
  - Monitor for signs, symptoms
  - Ask about pancreatitis history and other risk factors (eg, gallstones, history of alcoholism, high blood triglycerides)
- Discontinue promptly if pancreatitis symptoms occur
- Consider other agents if patient has a history of pancreatitis
- If acute pancreatitis confirmed, do not restart GLP-1 RA
- Report cases of pancreatitis to www.fda.gov/medwatch

Minimizing GI Events With GLP-1 RAs

- Titrate GLP-1 RA dose slowly when starting treatment to reduce risk of nausea and other GI effects
- Explain to patients that GI effects are transient and usually diminish after a few weeks
- Reduce dose if nausea persists and retitrate slowly


Case Study: Conclusion

- Josef is doing well with a GLP-1 RA that addresses FPG
- Experienced some nausea, but it abated after 1 month; had only 1 episode of vomiting and rare diarrhea
- At his 3-month checkup:
  - A1C = 7.0%
  - BP = 135/85 mm Hg
  - Weight: 175 lbs (BMI = 25.1 kg/m²)

Emerging Options With GLP-1 RAs

- Fixed-ratio combinations of GLP-1 RA + basal insulin
  - Lixisenatide + insulin glargine
  - Liraglutide + insulin degludec
  - Associated with greater A1C reductions, less weight gain, fewer GI effects than individual components as monotherapy
  - In advanced development: semaglutide
    - Once-weekly administration
    - Greater reductions in A1C vs exenatide LAR (-1.5% vs –0.9%)³
    - SUSTAIN 6: semaglutide reduces CV risk by 26%³

Summary: Choosing GLP-1 RAs

- Associated with significant reductions in A1C and weight loss; low risk of hypoglycemia
- Improve cardiometabolic risk profile in patients with hypertension, dyslipidemia, obesity
  - Use individual agent profiles to choose appropriate GLP-1 RA
- If A1C ≥7.0% and FPG at target:
  - Consider exenatide twice daily, lixisenatide
  - Recommended as alternative to prandial insulin in patients inadequately controlled on basal1-3
- If A1C ≥7.0% and FPG uncontrolled:
  - Consider albiglutide, dulaglutide, exenatide LAR, tiraglutide
  - Recommended as a preferred add-on to metformin or an alternative to basal insulin1-3

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PCE Action Plan

- Use collaborative multidisciplinary care to coordinate all aspects of treatment
- Set goals and make treatment decisions based on individual patient factors and glycemic patterns
- Consider a GLP-1 RA for patients who require additional glycemic control without hypoglycemia or weight gain
- Titrate GLP-1 RAs slowly at initiation to reduce risk of nausea and GI AEs

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Keys to Achieving Optimal Glucose Control: Early Insulin Initiation and Control of Postprandial Glucose

Learning Objectives

- Explain the rationale for early, aggressive intervention in T2DM to preserve β-cell function
- Describe clinician and patient barriers to insulin use
- Incorporate new strategies that include complementary drug combinations with insulin that address postprandial glucose control

T2DM = type 2 diabetes mellitus.

T2DM Is a Progressive Disease

IFG = impaired fasting glucose; IGT = impaired glucose tolerance.
Keys to Achieving Optimal Glucose Control: Early Insulin Initiation and Control of Postprandial Glucose

Clinical Inertia Leaves Patients Unnecessarily Exposed to Hyperglycemia

Median time to addition of another OAD or insulin

![Graph showing median time to addition of another OAD or insulin]

OAD = oral antidiabetes agent.

*Indicates that <50% of subjects have intensified treatment.


Barriers to Taking Insulin

<table>
<thead>
<tr>
<th>Patient Barrier</th>
<th>Clinical Barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of hypoglycemia</td>
<td>Concern that patients would resist insulin therapy</td>
</tr>
<tr>
<td>Lifestyle interference</td>
<td>Lack of time:</td>
</tr>
<tr>
<td>Weight gain</td>
<td>• To educate patients and their families on the role of insulin replacement therapy</td>
</tr>
<tr>
<td>Pain associated with blood testing and injections</td>
<td>• For intensive monitoring needed during the initial phase of insulin initiation and titration</td>
</tr>
<tr>
<td>Patient perception that insulin therapy is complicated and time consuming</td>
<td>• For education required for the management of any crises/risk of hypoglycemia from insulin therapy</td>
</tr>
<tr>
<td>Social concerns</td>
<td></td>
</tr>
</tbody>
</table>


Insulin Therapy: Mechanism of Action, Physiologic Action, Pros and Cons

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Mechanism of Action (All)</th>
<th>Physiologic Action (All)</th>
<th>Pros (All)</th>
<th>Cons (All)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin analog</td>
<td>• Degludec</td>
<td>• Increases glucose disposal</td>
<td>• Nearly universal response</td>
<td>• Hypoglycemia risk</td>
</tr>
<tr>
<td></td>
<td>• Detemir</td>
<td>• Decreases hepatic glucose production</td>
<td>• Untreated efficacy (or therapy)</td>
<td>• Weight gain</td>
</tr>
<tr>
<td></td>
<td>• Glargine</td>
<td>• Suppresses hepatic glucose output</td>
<td>• Decreases microvascular risk</td>
<td>• Training requirements</td>
</tr>
<tr>
<td></td>
<td>• Glargine U-300</td>
<td>• Suppresses lipogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• U-500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Short-acting</td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>

*Degludec is considered an ultra-long-acting basal insulin.

What to Keep in Mind About Insulin Therapy

• Discuss insulin physiology to increase patients’ awareness of role insulin plays in T2DM
• Consider basal insulin for patients presenting with markedly elevated A1C or those inadequately controlled on existing treatment
• Avoid using insulin as a “threat” or “last resort”
• Prevent clinical inertia through timely intensification of therapy

Educating Patients About Their Medications May Improve Adherence and Reduce Patient Concerns That May Interfere With Adherence

<table>
<thead>
<tr>
<th>Adherence Category</th>
<th>Received Information From Primary Care Doctor</th>
<th>Received Information From Other Sources</th>
<th>Complains About Medication Interfering With Lifestyle</th>
<th>Worried About Side Effects Of Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly adherent: 0%-10% doses missed</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mostly adherent: 11%-26% doses missed</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somewhat nonadherent: 27%-47% doses missed</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonadherent: 47%-100% doses missed</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients who were referred to certified diabetes educators and community programs had the highest adherence.

Online survey of self-reported number of missed medication doses among 807 patients with diabetes (90% with T2DM).

Shared Treatment Decision Making: Mayo Clinic Online Decision Aid and Brochure

Keys to Achieving Optimal Glucose Control: Early Insulin Initiation and Control of Postprandial Glucose

Impact of Medication Adherence on T2DM Disease-Related Healthcare Costs and Hospitalization Risk

Estimated diabetes-related healthcare costs and hospitalization risk based on regression analyses. A plus sign (+) under a column denotes a value that is significantly higher than the outcome for the 80%-100% adherence group (P < .05).


Case Study: James, a 44-Year-Old Salesman With a 2-Year History of T2DM

- Obese (5 ft 9 in, 205 lb, BMI: 30.0 kg/m²)
  - BP: 130/85 mm Hg on ACE inhibitor
  - LDL-C: 98 mg/dL
- Current medications: MET 2000 mg/d and SGLT2-inhibitor
- A1C: 9.1%
- Symptoms of polyuria and polydipsia
- You discuss additional treatment options with James, including the possibility of adding basal insulin, but he is reluctant to initiate an injectable agent
- He promises to focus on lifestyle recommendations and lose weight

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; FPG = fasting plasma glucose; LDL-C = low-density lipoprotein cholesterol; MET = metformin; SGLT2 = sodium glucose cotransporter 2.

Patient Characteristics to Consider When Individualizing Glycemic Targets

3-Month Follow-up

- A1C: 9.0%
- Despite his efforts to lose weight, James has only lost 3 pounds and says he struggles to find the time to exercise
- You discuss insulin initiation again and James agrees to begin treatment with insulin detemir

Next 3-Month Follow-up

- A1C: 7.5%
- Reports no issues with injecting his insulin, which he does before bedtime
- Has experienced episodes of nocturnal hypoglycemia, which alarmed him and caused him to stop titrating his insulin at 32 units
- SMBG on several occasions showed hyperglycemia in the late afternoon
- Has gained 10 lb

Hypoglycemia: Definitions and Symptoms

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Counter-regulatory Symptoms</th>
<th>Neuroglycopenic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Blood glucose &lt;70 mg/dL is considered “alert” level for action to prevent further complications</td>
<td>- Tachycardia</td>
<td>- Difficulty concentrating</td>
</tr>
<tr>
<td>- Severe: patient requires assistance from another person to take corrective action (eg, carbohydrates or glucagon)</td>
<td>- Shakiness</td>
<td>- Weakness</td>
</tr>
<tr>
<td></td>
<td>- Sweating</td>
<td>- Tiredness</td>
</tr>
<tr>
<td></td>
<td>- Anxiety</td>
<td>- Irritability</td>
</tr>
<tr>
<td></td>
<td>- Dry mouth</td>
<td>- Headache</td>
</tr>
<tr>
<td></td>
<td>- Hunger</td>
<td>- Difficulty concentrating</td>
</tr>
<tr>
<td></td>
<td>- Pupil dilation</td>
<td>- Altered vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Slurred speech</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Severe: loss of consciousness, seizure, coma, death</td>
</tr>
</tbody>
</table>

Keys to Achieving Optimal Glucose Control: Early Insulin Initiation and Control of Postprandial Glucose

Importance of Minimizing Hypoglycemia

- Undermines adherence and achievement of glycemic goals
- Contributes to clinical inertia
- Incidence: 25% of insulin-treated patients have ≥1 episode/year
- Consequence: 18.5% of patients report reducing insulin dose after a single episode of nocturnal hypoglycemia

Risk Factors for Hypoglycemia

- Older age
- Longer disease duration
- Concomitant medications
- Renal dysfunction
- Hypoglycemia unawareness
- Cognitive dysfunction
- Peripheral neuropathy
- Intense glucose-lowering strategy

Basal Insulin Analogs Versus NPH

- Basal insulin analogs are recombinant insulins designed to slow insulin absorption and produce a minimally peaking ~24-hour profile
- Compared with NPH, insulin glargine and detemir lower A1C to a similar extent, but with:
  - Less hypoglycemia, especially nocturnal episodes, with glargine
  - Less within-patient glycemic variability and less weight gain with detemir

<table>
<thead>
<tr>
<th>Onset of Action</th>
<th>Peak Action</th>
<th>Effective Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>2-4 hours</td>
<td>4-10 hours</td>
</tr>
<tr>
<td>Glargine</td>
<td>2-4 hours</td>
<td>None</td>
</tr>
<tr>
<td>Detemir</td>
<td>2-4 hours</td>
<td>12-14 hours</td>
</tr>
</tbody>
</table>

Treat-to-Target Forced Titration Schedule

Start with 10 IU/day bedtime basal insulin dose and adjust weekly

<table>
<thead>
<tr>
<th>Mean of Self-Monitored Fasting Plasma Glucose (mg/dL) Values from Preceding 2 Days</th>
<th>Increase in Insulin Dose (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-120 mg/dL</td>
<td>2</td>
</tr>
<tr>
<td>120-140 mg/dL</td>
<td>4</td>
</tr>
<tr>
<td>140-180 mg/dL</td>
<td>6</td>
</tr>
<tr>
<td>≥180 mg/dL</td>
<td>8</td>
</tr>
</tbody>
</table>

Small decreases (2-4 IU/day per adjustment) in dose are allowed in instances of self-monitored plasma glucose ≥110 mg/dL, or the occurrence of a severe hypoglycemic episode.

Why Do We Need Improved Basal Insulins?

- Despite improvements over NPH, many patients on insulin detemir and Gla-100 have suboptimal glycemic control in clinical settings
  - Duration of action may be <24 hours
  - Some patients require twice-daily dosing
  - Associated with a degree of glycemic variability
  - Nocturnal hypoglycemia still occurs

Why Does Volume of Distribution Matter?

- When daily insulin requirements are >200 units/day, the volume of U-100 injected insulin is a challenge
  - Physically too large for a single subcutaneous administration
  - Multiple injections required to deliver single dose
  - Increased injections = adherence issues; poor glycemic control
  - Discomfort and unpredictable absorption
- Concentrated insulins help address this problem

Pharmacokinetic Profile of Insulins

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Onset of Action</th>
<th>Peak Effect</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro (U-100, U-200)</td>
<td>15-30 minutes</td>
<td>20-30 minutes in 1.5 hours</td>
<td>3-5 hours</td>
</tr>
<tr>
<td>Aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular insulin (U-100, U-500)</td>
<td>30 minutes to 1 hour</td>
<td>2-4 hours</td>
<td>4-8 hours</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH insulin</td>
<td>1-2 hours</td>
<td>4-10 hours</td>
<td>10-18 hours</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (U-100), glargine “follow-on biological” (U-100), glargine U-300</td>
<td>2-3 hours</td>
<td>None</td>
<td>≥24 hours</td>
</tr>
<tr>
<td>Detemir</td>
<td>1 hour</td>
<td>1 hour</td>
<td>≥24 hours</td>
</tr>
<tr>
<td>Degludec (U-100, U-200)</td>
<td>1 hour</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Insulin Degludec**

- Forms long, soluble hexamer chains that slowly break down to release insulin
- "Ultra-long" duration of action (≥42 hours) allows greater flexibility in dosing without compromising safety or glycemic control
- At steady state, exposure is evenly distributed over 24 hours (with glargine, exposure is higher during first 12 hours)
- Appropriate for any patient with T2DM requiring basal insulin
  - 200 U contains same amount of insulin in half the volume without affecting glycemic control or hypoglycemia risk
  - 100 U injection pen allows 1-U increments; 200 U injection pen offers only 2-U increments

---

**Once-Daily Insulin Degludec Versus Gla-100: 2-Year Results of BEGIN Once Long**

<table>
<thead>
<tr>
<th>Hypoglycemia Rate</th>
<th>Degludec</th>
<th>Gla-100</th>
<th>Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (Weeks 0-52)</td>
<td>1.52</td>
<td>1.85</td>
<td>0.82 (0.64-1.04)</td>
<td>.106</td>
</tr>
<tr>
<td>Nocturnal (Weeks 0-52)</td>
<td>.25</td>
<td>.39</td>
<td>0.64 (0.42-0.98)</td>
<td>.038</td>
</tr>
<tr>
<td>Overall (Weeks 0-104)</td>
<td>1.72</td>
<td>2.05</td>
<td>0.84 (0.68-1.04)</td>
<td>.115</td>
</tr>
<tr>
<td>Nocturnal (Weeks 0-104)</td>
<td>.27</td>
<td>.46</td>
<td>0.57 (0.40-0.81)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*Episodes per patient-year of exposure*

1-year, parallel-group, randomized noninferiority trial and 1-year extension; all patients also took MET ± DPP-4 inhibitor

DPP-4 = dipeptidyl peptidase-4

---

**BEGIN-FLEX: Flexible Insulin Degludec Dosing Compared With Fixed Dose Glargine**

- Primary outcome: non-inferiority of flexible insulin degludec dosing (8-40-hour intervals between doses) compared with glargine
- Flexible insulin degludec dosing was non-inferior to fixed-dose glargine after 26 weeks
- No statistically significant differences in rates of hypoglycemia
- Dosing intervals 8-40 hours did not compromise glycemic control or safety
Insulin Glargine 300 U/mL (Gla-300)

- Ultra–long-acting basal analog insulin delivers 300 U/mL glargine, with more constant and prolonged pharmacodynamic and pharmacokinetic profile than Gla-100
- Appropriate for any patient with T2DM using basal insulin
- Compared with Gla-100 in the EDITION trials (randomized, controlled, multicenter, 6-month studies)
  - EDITION 1: existing basal-bolus insulin therapy
  - EDITION 2: existing OADs + basal insulin
  - EDITION 3: insulin-naïve patients inadequately controlled on OADs


Gla-300 Versus Gla-100: Similar Glycemic Control With Less Nocturnal Hypoglycemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Baseline A1C, %</th>
<th>∆A1C at 6 Months, %</th>
<th>Nocturnal Hypoglycemiaa RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDITION 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gla-100</td>
<td>403</td>
<td>8.16</td>
<td>–0.83</td>
<td>0.79 (0.67-0.93)</td>
</tr>
<tr>
<td>Gla-300</td>
<td>404</td>
<td>8.15</td>
<td>–0.83</td>
<td>0.79 (0.67-0.93)</td>
</tr>
<tr>
<td>EDITION 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gla-100</td>
<td>406</td>
<td>8.24</td>
<td>–0.56</td>
<td>0.77 (0.61-0.99)</td>
</tr>
<tr>
<td>Gla-300</td>
<td>405</td>
<td>8.24</td>
<td>–0.57</td>
<td>0.77 (0.61-0.99)</td>
</tr>
<tr>
<td>EDITION 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gla-100</td>
<td>439</td>
<td>8.57</td>
<td>–1.46</td>
<td>0.76 (0.59-0.99)</td>
</tr>
<tr>
<td>Gla-300</td>
<td>439</td>
<td>8.51</td>
<td>–1.42</td>
<td>0.76 (0.59-0.99)</td>
</tr>
</tbody>
</table>

* confirmed or severe event.

Hpo ≥ hypoglycemia 100 + episode rap.

Reduced Hypoglycemia With Glargine U-300 Versus Glargine U-100

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Mean Age, yr</th>
<th>Male, %</th>
<th>A1C, %</th>
<th>FPG, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine U-300 (n = 400)</td>
<td>57</td>
<td>46</td>
<td>8.3</td>
<td>147</td>
</tr>
<tr>
<td>Glargine U-100 (n = 405)</td>
<td>58</td>
<td>45</td>
<td>8.3</td>
<td>141</td>
</tr>
</tbody>
</table>

**Results**

- Rates of hypoglycemia generally lower in patients treated with glargine U-300 reaching SMPG <130 mg/dL and patients not reaching SMPG <100 or <130 mg/dL.
- Rates for nocturnal hypoglycemia significantly lower in patients treated with glargine U-300 regardless of level of SMPG achievement.

Reid T, et al. ADA 2016. Abstract 96-LB.
Keys to Achieving Optimal Glucose Control: Early Insulin Initiation and Control of Postprandial Glucose

Basal Insulins: Dosing and Risk of Hypoglycemia

- Detemir and Gla-100 require standard dosing times to avoid hyperglycemia; bedtime dosing may lead to nocturnal hypoglycemia
- Insulin degludec and Gla-300 have duration of action >24 hours, allowing flexibility in dosing
- Insulin degludec and Gla-300 are associated with lower rates of hypoglycemia

Case Study (cont’d)

- You decide to switch James from insulin detemir to insulin glargine 300 U
- 3-month follow-up:
  - James returns and reports no issues with his new basal insulin and no hypoglycemia
  - He is still taking MET and an SGLT2 inhibitor
  - At this visit:
    - A1C: 7.2%
    - FPG: 119 mg/dL

PPG Undermines Glycemic Control When FPG Is Controlled but A1C Remains >7.0%

- PPG is increasingly important as A1C nears 7.5%; at A1C <7.3%, ~70% of hyperglycemia is PPG
- Elevated PPG reflects loss of insulin response and often is present years prior to elevated FPG
- Elevated PPG is present in most patients with T2DM and has been associated with increased CV risk independent of FPG levels
- Basal insulin and most oral agents have minimal effects on PPG; intensifying doses may lead to hypoglycemia

CV = cardiovascular; PPG = postprandial plasma glucose.
Keys to Achieving Optimal Glucose Control: Early Insulin Initiation and Control of Postprandial Glucose

PPG and Glycemic Control

- Elevated PPG is highly prevalent among patients with T2DM and has been associated with adverse CV outcomes.
- Elevated PPG is the predominant factor in residual hyperglycemia when FPG levels are controlled, especially as A1C drops below 8.0%.
- Diabetes medications have differential effects on PPG that should be considered when combining therapies to achieve glycemic goals.

Prandial Insulin Options

- Rapid-acting insulin analogs (insulin aspart, glulisine, lispro):
  - Mimic normal human postprandial insulin response
  - Minimize risk of hypoglycemia or weight gain
  - Have beneficial effects on PPG
  - Are as effective as regular human insulin with less hypoglycemia
  - Onset of action: ≤15 minutes

GLP-1 RAs With Postprandial Effects

- Short acting by delaying gastric emptying
  - Long-term or continuous stimulation reduces effect
  - GLP-1 RAs with postprandial effects therefore have greater control of PPG
  - Associated with substantial weight loss and A1C reductions similar to basal insulin analogs
  - Effectively reduce A1C in patients inadequately controlled on basal insulin
    - Can be added to existing basal insulin + OAD
    - Basal insulin can be added to existing OAD + GLP-1 RA

GLP-1 RA = glucagon-like peptide-1 receptor agonist.
GLP-1 RA Versus Prandial Insulin Analogs 
Added to Basal Insulin

- Exenatide twice daily versus insulin lispro 3 times a day
  - Similar A1C reductions (~1.13% vs ~1.10%)
  - Less nocturnal hypoglycemia
  - More nausea with exenatide
- Once-daily liraglutide versus once-daily insulin aspart
  - Greater A1C reduction (~0.74% vs ~0.39%; P = .0024)
  - Less confirmed and nocturnal hypoglycemia
  - More GI side effects with liraglutide


Combinations of Basal Insulin and GLP-1 RAs With Postprandial Effects Currently Under FDA Review

- Insulin degludec + liraglutide
- Insulin glargine + lixisenatide

Fixed Combination of Insulin Glargine + Lixisenatide in T2DM Inadequately Controlled With Oral Agents

- 4-week run-in to optimize MET and stop other OADs
- N = 1170
- Mean diabetes duration: 8.6 years
- BMI: ~31.7 kg/m²
- Primary outcome: A1C change at 30 weeks
- Results: Greater reductions in A1C from baseline were achieved with a fixed combination of insulin glargine + lixisenatide compared with either component alone

Keys to Achieving Optimal Glucose Control: Early Insulin Initiation and Control of Postprandial Glucose

Fixed Combination of Insulin Glargine + Lixisenatide in T2DM Inadequately Controlled on Basal Insulin and Metformin

- 4-week run-in: insulin glargine introduced and/or further titrated; OADs other than MET stopped
- Basal insulin–treated patients (N = 736)
- Mean diabetes duration: 12 years
- BMI: 31 kg/m²

Primary Outcome: Change in A1C levels at 30 weeks

Results: Greater reductions in A1C from baseline with fixed combination of insulin glargine + lixisenatide compared with insulin glargine alone; A1C goals reached by more patients with combination therapy


Fixed Combination Insulin Degludec + Liraglutide Compared With Individual Components

In the DUAL I trial (insulin-naïve patients) and DUAL II trial (patients previously treated with basal insulin), A1C was significantly lowered with the combination of insulin degludec + liraglutide


Improvement in A1C was accompanied by a mean body weight reduction of –0.5 kg with combination insulin degludec + liraglutide, compared with a weight increase of 1.6 kg with degludec and a weight loss of 3.0 kg with liraglutide

Combinations of Basal Insulin and GLP-1 RAs With Postprandial Effects: Safety

- Insulin degludec + liraglutide
  - Well tolerated
  - Mild to moderate GI symptoms: nausea, diarrhea, constipation, cramping
  - Hypoglycemia (1.8 events/patient-year in DUAL I trial; 1.5 in DUAL II trial)
  - Skin reactions at the injection site
- Insulin glargine + lixisenatide
  - Well tolerated
  - Mild to moderate nausea
  - Hypoglycemia (1.4 events/patient-year in LixiLan-0 trial; 3.03 in LixiLan-L trial)
  - Rare instances of severe allergic reactions
  - No increased CV risk in high-risk post-acute coronary syndrome ACS population

GLP-1 RAs With Postprandial Effects and Prandial Insulin to Control PPG

- Both prandial insulin and GLP-1 RAs with postprandial effects reduce A1C and strongly decrease PPG
- Compared with rapid-acting insulin analogs, addition of GLP-1 RAs leads to significant body weight reduction
- Fixed-dose combinations of basal insulin analogs and GLP-1 RAs are on the horizon

Case Study (cont’d)

- After adding a GLP-1 RA with postprandial effects to his existing insulin and oral therapies, James successfully avoids weight gain and does not have any issues with hypoglycemia
- At 3-month follow-up:
  - He has lost 4 lb
  - He has not had any nocturnal or other hypoglycemia
  - A1C: 6.6%
Intensifying Basal Insulin Therapy

- Start basal and titrate up 2-4 U once to twice weekly to reach FPG goal
- If FPG goal reached but A1C goal not reached:
  - Add GLP-1 RA
    - Once- or twice-daily GLP-1 RA with postprandial effects
    - Can consider SGLT2 inhibitor or DPP-4 inhibitor
  - Either less effective at reducing PPG than GLP-1 RA
  - Add prandial insulin
    - 1 rapid insulin injection before largest meal (4 U or 10% basal dose)
    - For A1C >5.0%, consider reducing basal dose
    - Titrate 1-2 U once to twice weekly until SMBG target reached

Glycemic control not achieved
- Consider basal bolus: ≥2 rapid insulin injections before meals (4 U or 10% basal dose)
- For A1C >5.0%, consider reducing basal dose
- Titrate 1-2 U once to twice weekly until SMBG target reached

PCE Action Plan

- Recommend insulin therapy at any stage of T2DM for patients requiring substantial A1C reductions
- Discuss hypoglycemia risk factors, symptoms, prevention, and treatment with patients using insulin
- Consider ultra–long-acting basal insulin for patients who require flexible dosing times, units of insulin >0.5 u/kg, and need to avoid hypoglycemia
- Assess PPG and address if elevated in patients whose A1C remains high despite adequate PPG control
- Consider a GLP-1 RA with postprandial effects or prandial insulin for patients who require additional A1C and PPG control on basal insulin

PCE Promotes Practice Change
Learning Objectives

- Initiate a discussion about bladder symptoms with patients, particularly those with associated comorbidities
- Individualize treatment plans for patients with OAB, including integrating lifestyle modification into a patient’s treatment strategy
- Select therapeutic agents based on an agent’s pharmacologic profile
- Provide effective counseling and follow-up

OAB = overactive bladder

Definitions of Incontinence From the International Continence Society

UI = complaints of involuntary leakage of urine
SUI = complaints of involuntary leakage upon exertion, effort, sneezing, or coughing
Mixed UI = complaints of involuntary leakage associated with urgency and upon exertion, effort, sneezing, or coughing
UUI = complaints of involuntary leakage associated with urgency

SUI = stress UI; UUI = urgency UI.
The ABCs of OAB: A Primary Care Guide to Optimal Management

Definitions of Incontinence From the International Continence Society (cont’d)

- **Nocturia**: Complaint that the individual has to wake at night 1 or more times to void.
- **Urgency**: Complaint of sudden, compelling urge to pass urine that is difficult to defer.
- **Increased daytime frequency**: Complaint that voiding occurs more frequently during waking hours than deemed normal by patient.
- **OAB**: Urinary urgency, usually accompanied by frequency and nocturia, with or without UUI.

Definitions of Incontinence From the International Continence Society (cont’d)

- **Incontinence**: In the absence of UTI or other obvious pathology.
- UTI = urinary tract infection.


Storage Problem: Incontinence

- **Normal (No incontinence)**
  - Large capacity, relaxed bladder
  - High-resistance urethra

- **SUI**
  - Low-resistance urethra
  - Urine loss resulting from sudden increase in intra-abdominal pressure (e.g., laugh, cough, sneeze)

- **Mixed**
  - Small capacity, hyperactive bladder
  - Low-resistance urethra
  - Combination of SUI and UUI


Estimated Cost of OAB in the United States

- **Total cost of OAB in 2000 was ~$12.6 billion**
  - Community-dwelling residents: $9.1 billion
    - Estimated $267/year per person
  - Institutional care: $3.5 billion
    - Roughly $15/day per person for laundry, pads, etc.

- Breakdown of costs among community residents
  - Lost productivity (5%)
  - Diagnosis (1%)
  - Treatment (31%)
  - Routine care (17%)
  - Health-related consequences (42%)


PCE 2016 Series 3
The ABCs of OAB:
A Primary Care Guide to Optimal Management

The Iceberg of Care for Women Aged ≥40 Years With UI: Underreported and Undertreated

- Women with UI who seek care tend to be older, have more severe symptoms of longer duration, and have bothersome symptoms that impact QoL.
- Primary care interventions are key to preventing worsening of UI, especially as so few patients ever see pelvic-floor specialists.

Proportion of women with UI receiving subspecialty care 12% (164/1366)
Proportion of women with UI receiving care 23% (313/1366)
Proportion of women with UI seeing care 25% (339/1366)
Prevalence of UI in women aged ≥40 years based on responses to a bladder health survey 41% (1366/3316)


Case Study: Janine, 58 Years Old

- Janine has T2DM and moderate osteoarthritis
- Presents with a sore throat
- Reduced length of daily walk because she is “nervous about being away from the bathroom too long”
- Mentions that she is tired; not getting restful sleep

T2DM = type 2 diabetes mellitus.

Janine’s Physical Examination and Laboratory Findings

- Current medications:
  - Metformin 500 mg twice daily
  - Atorvastatin
- Physical examination:
  - Height: 5 ft 2 in
  - Weight: 145 lb
  - BMI: 26.5 kg/m²
- Laboratory findings:
  - A1C: 8.1%
  - Fasting plasma glucose: 125 mg/dL
  - Lipids (mg/dL):
    - Total cholesterol, 216
    - Low-density lipoprotein cholesterol, 129
    - High-density lipoprotein cholesterol, 44
  - BP: 129/84 mm Hg

A1C = glycated hemoglobin; BMI = body mass index; BP = blood pressure.
Why Patients Do or Do Not Seek Help

- Survey: 56% of women with OAB wait longer than 1 year to seek treatment (mean = 3.1 years)
- Why not seek help?
  - Embarrassed
  - Not asked by clinician
  - Do not think it is serious
  - Cannot afford pads
  - Coping mechanisms
  - Misconception about disease/normal aging process
- Why seek help?
  - Getting worse
  - Fear of more serious condition
  - Concern of embarrassing accident

Survey: 56% of women with OAB wait longer than 1 year to seek treatment (mean = 3.1 years)


Useful Questions to Direct the Diagnosis of OAB

- Most patients indicate that they would prefer their clinician to initiate the conversation on OAB, yet only 14% of survey participants reported that their clinician asked them about urinary/bladder symptoms

Initiate discussion: “Are you bothered by lack of bladder control?”

Urinary: “Do you frequently have strong urges to urinate?” “Do you urinate more often than you think you should?” “Do you go to the bathroom so often that it interferes with your activities?”

Nocturia: “Are you bothered by waking up at night to go to the bathroom?”

UUI: “Do you have uncontrolable urgent to urinate that sometimes result in wetting accidents?” “Do you leak urine on the way to the bathroom?”


Janine’s Symptoms

- Upon further questioning, Janine tells you that she is experiencing frequency
- She is also going to the bathroom at least once per night, sometimes more than once
- Janine has been using incontinence pads for a few years, but she has had to increase her usage over the last few months
### Differential Diagnosis: OAB, SUI, and UTI

<table>
<thead>
<tr>
<th>Symptom</th>
<th>OAB</th>
<th>SUI</th>
<th>UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Daytime voiding frequency more than every 2 hours</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Leaking during physical activity</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Amount of urinary leakage</td>
<td>Variable</td>
<td>Small</td>
<td>Small</td>
</tr>
<tr>
<td>Ability to reach the toilet following an urge</td>
<td>Often no</td>
<td>—</td>
<td>Sometimes no</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Usually</td>
<td>Seldom</td>
<td>Rare</td>
</tr>
</tbody>
</table>


### Recognizing Comorbidities Associated With OAB

- UTI
- Chronic constipation and fecal incontinence
- Overweight (BMI 25-30 kg/m²) and obesity (BMI >30 kg/m²)
- Diabetes
- Depression
- QoL issues
  - Social activity
  - Work productivity
  - Sexual dysfunction
  - Sleep disturbances
  - Self-esteem
  - Anxiety
  - Self-esteem


### Key Populations: Patients With Diabetes and Obesity

- Survey of 1359 patients with T2DM: 22.5% had OAB, 48% of which had UI
- Higher A1C levels predict increased risk for OAB/urgency, UUI, and nocturia in patients with T2DM
- Women with overweight and obesity with T2DM: higher prevalence of UI than with other T2DM complications
- Women with obesity twice as likely to have OAB than women of normal weight

2014 AUA/SUFU Guidelines: OAB Diagnosis Algorithm

If no infection or other pathology, treat as OAB

- Abdominal examination
- Examination of external genitalia/pelvis/rectum
- Abbreviated neurologic examination
- Cognitive and motor functions assessment

Obtain patient history

Physical examination to exclude obvious pathologies

Obtain urinalysis to rule out UTI and hematuria

Consider other measures:
- Urine culture
- PVR, symptom questionnaires


Janine’s Bladder Diary

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Leakage</th>
<th>Urgency</th>
<th>Fluid Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:00</td>
<td>In bed/rushed to bathroom</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>6:30</td>
<td>Morning routine</td>
<td>Yes</td>
<td>Yes</td>
<td>20 oz coffee</td>
</tr>
<tr>
<td>8:40</td>
<td>Waited too long</td>
<td>Yes</td>
<td>Strong</td>
<td>8 oz water</td>
</tr>
<tr>
<td>10:00</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:15</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:30</td>
<td>Housework</td>
<td>Yes</td>
<td>Strong</td>
<td>12 oz cola</td>
</tr>
<tr>
<td>2:30</td>
<td>Yes</td>
<td></td>
<td></td>
<td>8 oz water</td>
</tr>
<tr>
<td>4:20</td>
<td>Strong</td>
<td></td>
<td></td>
<td>6 oz tea</td>
</tr>
<tr>
<td>6:20</td>
<td>Dinner</td>
<td>Yes</td>
<td>Strong</td>
<td>8 oz beer</td>
</tr>
<tr>
<td>7:35</td>
<td>No</td>
<td></td>
<td></td>
<td>8 oz water</td>
</tr>
<tr>
<td>10:10</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:20</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:00</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Frequency = 12; fluid intake = 80 oz.

Based on Evaluation, Janine Has OAB

- Responses to direct questions
- Negative history of medical conditions, current medication, past surgery
- Normal physical examination
- Negative urinalysis
- Bladder diary review

AUA = American Urological Association; SUFU = Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction.

Tailoring Treatment to Janine’s Needs and Preferences

- Janine is not interested in taking medicine but does want to get better sleep.
- Per AUA/SUFU guidelines, you provide education on:
  - OAB symptoms (normal and abnormal bladder function)
  - Behavioral modification strategies
  - Therapeutic options, expected outcomes, and potential side effects.

AUA Treatment Recommendations

<table>
<thead>
<tr>
<th>Line of Therapy</th>
<th>Treatment</th>
<th>Evidence</th>
<th>Strength</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Behavioral therapies [B]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Behavioral and pharmacologic therapies [C]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>Pharmacologic therapy* (antimuscarinics, β3-agonist) [B]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>OnabotulinumtoxinA [B]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral lateral nerve stimulation [C]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sacral neurostimulation [C]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fourth</td>
<td>Augmentation cystoplasty [Expert Opinion]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary diversion [Expert Opinion]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients who do not respond to or cannot tolerate first- or second-line therapies should be referred to a specialist for additional therapy.


Behavioral Therapy: Multiple Options

Less than one-third of patients with OAB and/or urinary symptoms are offered behavioral management options.

Lifestyle Changes

- Weight loss
- Smoking cessation
- Managing constipation
- Fluid intake (adequate)
- Caffeine consumption
- Physical exercise
- Awareness of toileting behaviors


Janine’s Initial First-Line Therapy: Behavioral Modification

- Limit evening fluid intake
- Pelvic floor exercises
- Urge-suppression techniques
- Scheduled voiding
- Weight loss

Pelvic Floor Rehabilitation: Pelvic Floor (Kegel) Muscle Exercises

- Exercises increase muscle tone/strength
- Help hold urine inside bladder, preventing leakage; decrease median number of voids per day
- Rapid, active pelvic muscle contractions ("quick flicks") inhibit unstable bladder contraction once it starts

Behavior Change: Reducing Fluid Intake

Reducing fluid intake by 25% significantly improves urgency, frequency, and nocturia

Water Intake Calculator

http://www.waterintakecalculator.com/Water%20Intake%20Calculator.htm

Janine’s 4-Week Follow-up Appointment

- Janine sees improvement in her symptoms
  - Leaks less
  - Still gets up at least once during the night to use the bathroom
  - Is interested in trying a medication

Enhanced Therapeutic Effects With Combined Pharmacologic and Behavioral Therapy

![Graph showing mean reduction in UUI, %]

- Behavioral Therapy: -57.5%
- Combined Therapy: -88.5%
- Pharmacologic Therapy: -72.7%
- Combined Therapy: -84.3%

N = 197
Behavioral therapy plus pharmacotherapy
Antimuscarinic Agents: Treatment of OAB

- **Mechanism of action**
  - Inhibit the action of acetylcholine by blocking M receptors
  - Prevent involuntary detrusor contractions (motor action)
  - Prevent urgency (sensory action)
- **Multiple formulations and delivery systems**
  - IR and ER
  - Transdermal, gel, oral osmotic

**Antimuscarinic Treatment Options**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Muscarinic Receptor Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin IR</td>
<td>5-20 mg</td>
<td>2 or 3 times daily</td>
<td>M3 selective</td>
<td>Linked to significant and unrecognized cognitive impairment in frail elderly</td>
</tr>
<tr>
<td>Oxybutynin ER</td>
<td>5-15 mg</td>
<td>Once daily</td>
<td>M3 selective</td>
<td>Linked to significant and unrecognized cognitive impairment in frail elderly</td>
</tr>
<tr>
<td>Oxybutynin transdermal patch*</td>
<td>3.9 mg/d</td>
<td>Twice weekly</td>
<td>M8 and M6 selective</td>
<td>Linked to significant and unrecognized cognitive impairment in frail elderly</td>
</tr>
<tr>
<td>Oxybutynin gel 10%</td>
<td>1 g</td>
<td>Once daily</td>
<td>M3 selective</td>
<td>Linked to significant and unrecognized cognitive impairment in frail elderly</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1-2 mg</td>
<td>Twice daily</td>
<td>M2 and M10</td>
<td>Linked to significant and unrecognized cognitive impairment in frail elderly</td>
</tr>
<tr>
<td>Tolterodine long acting</td>
<td>2-4 mg</td>
<td>Once daily</td>
<td>M2 and M3</td>
<td>Linked to significant and unrecognized cognitive impairment in frail elderly</td>
</tr>
</tbody>
</table>

*Approved for over-the-counter use in women.

**Antimuscarinic Treatment Options (cont’d)**

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<tr>
<td>Fesoterodine</td>
<td>4-8 mg</td>
<td>Once daily</td>
<td>M2 and M3</td>
<td>Linked to significant and unrecognized cognitive impairment in frail elderly</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>5-10 mg</td>
<td>Once daily</td>
<td>M3 selective</td>
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</tr>
<tr>
<td>T ropium</td>
<td>20 mg</td>
<td>Twice daily</td>
<td>M2 and M3</td>
<td>Linked to significant and unrecognized cognitive impairment in frail elderly</td>
</tr>
<tr>
<td>T ropium ER</td>
<td>60 mg</td>
<td>Once daily</td>
<td>M2 and M3</td>
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</tr>
</tbody>
</table>
The ABCs of OAB:
A Primary Care Guide to Optimal Management

Efficacy of Antimuscarinics on Incontinence Reduction


Efficacy of Antimuscarinics on Urgency Reduction


Potential AEs, Contraindications, and Possible Drug Interactions of Antimuscarinics

<table>
<thead>
<tr>
<th>Most Common Side Effects</th>
<th>Contraindications</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>Urinary or gastric retention</td>
<td>Medications with anticholinergic effects (ie, antidepressants, drugs to treat Parkinson’s disease and Alzheimer’s disease, antihistamines, etc)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Uncontrolled narrow-angle glaucoma</td>
<td>CYP450 3A4 inhibitors</td>
</tr>
<tr>
<td>Dry or itching eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired cognitive function</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Not All Antimuscarinics Are the Same

- All have comparable efficacy
- Adherence/persistence rates low
- ER medications preferred over IR formulations: lower rates of dry mouth
- Use caution in patients taking other medications with anticholinergic properties
  - Antidepressants, medications for Parkinson’s disease and Alzheimer’s disease, antinausea medications, etc.
- Use caution when prescribing to frail and elderly patients
  - Mobility deficits
  - Cognitive deficits


Case Conclusion: Janine’s Treatment Selection

- Janine is prescribed an ER antimuscarinic agent
- At 4-week follow-up, she reports she is adhering to the therapy plan (pharmacotherapy plus behavioral modifications)
- Her symptoms have improved, though they have not completely resolved
- She is satisfied with her progress

Case Study: Regina, 74 Years Old

- Regina has had OAB symptoms for many years
- She has been treated with an immediate- and extended-release antimuscarinic, but she is not satisfied with her current therapy
  - She complains about dry mouth and constipation
- Taking multiple medications due to T2DM, hypertension, and depression
- After reviewing behavioral interventions with Regina (eg, bladder training, prompted voiding, fluid management), you discuss switching her pharmacologic treatment
Factors to Consider for Elderly Patients With OAB

- OAB twice as prevalent in patients aged >65 years than ≤45 years
- Polypharmacy/multiple healthcare clinicians
  - Many medications can cause/aggravate urinary symptoms (e.g., diuretics, anticholinergics, narcotics, antidepressants, sedatives)
- Comorbid conditions and natural effects of aging
  - Impaired cognition, mobility
  - Incomplete bladder emptying (increased PVR)
  - Diminished ability to withstand invasive treatments/evaluation
- Increased risk of falls/fractures
- Dehydration (intentional reduced fluid intake)
- Impaired QoL
  - Rate of depression twice as high in elderly patients with UI


Treatment Selection in the Elderly: 2015 Beers Criteria

- Antimuscarinics/anticholinergics included in list of medications to avoid in older adults
  - Interactions between antimuscarinics and M1 receptors in CNS may cause cognitive impairment in the elderly—avoid use in older adults with history of delirium, dementia, or cognitive impairment
  - Avoid, if possible, in older patients with constipation


Mirabegron: A Different Mechanism of Action

- Activates β3-adrenergic receptors on the detrusor smooth muscle
  - Relaxes the muscle during the storage phase of the urinary bladder fill–void cycle and increases bladder capacity

Mirabegron: Incontinence Episodes Per 24 Hours

Co-primary end point: mean number of incontinence episodes/24-hours adjusted mean change from baseline to final visit (week 12)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.07</td>
<td>2.03</td>
<td>2.03</td>
<td>2.43</td>
</tr>
<tr>
<td></td>
<td>2.33</td>
<td>2.37</td>
<td>2.37</td>
<td>2.51</td>
</tr>
</tbody>
</table>

n = 291 n = 293 n = 325 n = 312 n = 262 n = 254

2.67 2.83 3.03 2.77 2.43 2.65 2.51

Study 1 Study 2 Study 3

–1.38b–1.36b–1.47b
–1.13
–1.57b–1.17
0
–0.5
–1
–1.5
–2

Baseline Placebo Mirabegron 25 mg Mirabegron 50 mg

Mean Number of Incontinence Episodes/24 Hours

*Adjusted mean is for baseline, sex, and geographical location; bStatistically significant improvement vs placebo at 0.05 level with multiplicity adjustments.


Subanalysis of Phase 3 Trials of Mirabegron in Patients Aged ≥65 and ≥75 Years

• No loss of efficacy in older patients
• Well tolerated

Incontinence Episodes/24 hours

<table>
<thead>
<tr>
<th>Incontinence Episodes/24 hours</th>
<th>Placebo</th>
<th>Mirabegron 25 mg</th>
<th>Mirabegron 50 mg</th>
<th>Tolterodine ER 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients: All ≥65 y</td>
<td>262</td>
<td>254</td>
<td>321</td>
<td>114</td>
</tr>
<tr>
<td>Adjusted Change (SE) From Baseline</td>
<td>–0.5</td>
<td>–1.0</td>
<td>–2.0</td>
<td>–1.75</td>
</tr>
</tbody>
</table>

<Statistically significant difference vs placebo.


Mirabegron: AEs and Precautions

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Mirabegron 25 mg (n = 432)</th>
<th>Mirabegron 50 mg (n = 1375)</th>
<th>Placebo (n = 1380)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensiona</td>
<td>11.3</td>
<td>7.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3.5</td>
<td>3.9</td>
<td>2.5</td>
</tr>
<tr>
<td>UTI</td>
<td>4.2</td>
<td>2.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Headache</td>
<td>2.1</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.6</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>URTI</td>
<td>2.1</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.6</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1.2</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.6</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.4</td>
<td>1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*aIncludes reports of BP above the normal range and BP increased from baseline occurring predominantly in participants with hypertension at baseline.

URO = upper respiratory tract infection.

The ABCs of OAB:
A Primary Care Guide to Optimal Management

Combination Therapy When Monotherapy Fails

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Solifenacin 5 mg (n = 728)</th>
<th>Solifenacin 10 mg (n = 719)</th>
<th>Combination (n = 725)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased BP*</td>
<td>6 (0.8)</td>
<td>15 (1.7)</td>
<td>12 (1.6)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Increased heart rate, palpitations, tachycardia, atrial fibrillation</td>
<td>5 (0.7)</td>
<td>7 (0.9)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3 (0.4)</td>
<td>2 (0.3)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>14 (2.2)</td>
<td>17 (2.3)</td>
<td>20 (2.6)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1 (0.1)</td>
<td>2 (0.3)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>6 (0.8)</td>
<td>7 (1.0)</td>
<td>6 (0.8)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>41 (5.6)</td>
<td>43 (5.9)</td>
<td>70 (9.7)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>10 (1.4)</td>
<td>10 (1.4)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>22 (3.0)</td>
<td>33 (4.6)</td>
<td>34 (4.7)</td>
</tr>
</tbody>
</table>

*P < 0.05 vs solifenacin 5 mg; †P < 0.05 vs solifenacin 10 mg.

Safety Results of Combination Therapy

Therapy for Refractory Cases

- Refer to specialist if refractory to behavioral and pharmacologic therapy
- OnabotulinumtoxinA: administered via injection no more frequently than every 12 weeks; 24 weeks is typical
  - Reduces number of incontinence episodes and urgency; improves QoL
  - AEs: UTI (34%-48%); urinary retention (6%)
- Peripheral tibial nerve stimulation: weekly 30-minute in-office sessions
  - Efficacy in refractory OAB
  - AEs: mild and uncommon
- Sacral neuromodulation: implanted device
  - Improves OAB symptoms and continence vs standard medical therapy
  - AEs: related to implanted device

Follow-up Evaluation

- Assess progress in meeting treatment, adherence, and AE goals
- If needed:
  - Consider formulation, dose, or medication change
  - Counsel patients on realistic expectations
  - Move to second-line therapeutic options when appropriate
- AUA/SUFU guidelines: assess response to treatment
  - Behavioral therapies: 8-12 weeks
  - Pharmacologic therapies: 4-8 weeks
- Combination therapy: establish partial success with 1 therapy before adding another

Patient Perceptions: Critical to Individual Treatment Success in OAB

- Objective outcomes do not always translate to improved QoL
- Successful treatment requires an informed and engaged patient
- Patient factors (subjective)
  - Most bothersome urinary symptoms
    - Frequency (27%), UUI (26%), urgency (23%), nocturia (15%)
  - Satisfaction: patient’s assessment of efficacy AND tolerability
  - Expectations: motivation for dose adjustment and influence of adherence
  - Among 1165 patients with OAB, use of multiple other drugs was significant predictor of perceived lack of efficacy of OAB treatment

PCE Action Plan

- Initiate discussion about bladder control with patients
- Use bladder diary to assist in diagnosis and monitoring of symptom improvement
- Consider AEs and patient factors when selecting a pharmacologic agent
- Counsel patients on expectations of therapy
Optimal Management of Patients With Major Depressive Disorder: Getting Ahead of a Complex Disease

Learning Objectives

• Evaluate first-line agents for major depressive disorder (MDD) and agents for treatment-resistant depression
• Review the impact of residual symptoms of MDD such as impaired cognition and the importance of treating to target
• Outline strategies to address side effects and improve adherence in patients with MDD

Depression in the Primary Care Setting

• Patients in primary care often have chronic depression (symptom duration ≥24 months at presentation) and multiple comorbidities
  – Clinical predictors of worse outcomes
• 12.5% of primary care patients have had MDD in the past year
• Primary care clinicians manage one-third to one-half of nonelderly adults and nearly two-thirds of older adults who are treated for MDD

Optimal Management of Patients With Major Depressive Disorder: Getting Ahead of a Complex Disease

**Undertreatment of Patients With MDD**

- Of those with MDD:
  - 47% are recognized clinically
  - 24% receive any treatment
  - 9% receive adequate treatment
  - 6% achieve remission of symptoms

**Treatment for MDD in Primary Care**

- Antidepressants prescribed by PCPs: 66%
- Antidepressants prescribed by psychiatrists or addiction specialists: 21%
- Other: 11%

**Treatment Goals for Depression: Remission and Full Recovery**

- Remission and recovery are viable and essential goals
- More than just symptom resolution
  - Normalization of functioning
  - Optimized quality of life (QoL)
  - Positive mental health (ie, optimism, self-confidence)
  - Return to premorbid psychosocial function
  - Subjective life satisfaction
  - Global sense of long-term well-being

References:

Optimal Management of Patients With Major Depressive Disorder: Getting Ahead of a Complex Disease

Primary Care Clinicians Can Get the Same Results As Psychiatrists With Measurement-Based Care in Patients With MDD

Case Study: Meet Joani, 29 Years Old

- Ultrasound technician
- Presents with complaints of fatigue and insomnia
- Diagnosed with depression 2 years ago
- Lives alone with 2 cats
- Family history of depression
- Has family nearby but “they don’t understand me”
- Broke up with boyfriend 2½ years ago
- Physical exam is normal and labs reveal normal thyroid
- Limits herself to a glass of white wine with dinner; denies illicit drug use
- Occasionally takes clonazepam to help her sleep

Screening and Evaluation Tools

<table>
<thead>
<tr>
<th>Scale</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>21 items • 2-10 minutes • Copyrighted, must be purchased</td>
</tr>
<tr>
<td>HAM-D-21</td>
<td>Administered by clinician • 21 items • 20-30 minutes</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>Public domain (downloadable from the Internet); Assesses DSM-5 criteria and psychosocial impairment • Available in many languages • Good test-retest reliability, internal consistency, sensitivity to change over time • Widely used in primary care settings</td>
</tr>
</tbody>
</table>

QIDS-SR(16) = Quick Inventory of Depressive Symptomatology (Self-Report); HAM-D-17 = 17-item Hamilton Depression Rating Scale.


Screening and Evaluation Tools

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Screening and Evaluation Tools (cont'd)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR-16)</td>
<td>- Public domain (downloadable from Internet) - Self-report - Assesses DSM-5 criteria for MDD - Good internal consistency, correlates with clinician ratings of depression severity, sensitive to change</td>
</tr>
<tr>
<td>Antidepressant Treatment Response Questionnaire (ATRQ)</td>
<td>- Self-report - Focuses on efficacy/functionality to determine treatment resistance for each antidepressant - 10 items</td>
</tr>
<tr>
<td>Montgomery-Asberg Depression Rating Scale – Self (MADRS-S)</td>
<td>- Self-report - 10 items - Brief</td>
</tr>
<tr>
<td>Brief Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER)</td>
<td>- Self-report—evaluates side effects of antidepressants - Measures 3 domains of impact (frequency, intensity, burden) - Brief</td>
</tr>
</tbody>
</table>


Case Study: Joani (cont’d)

- Joani’s score on the PHQ-9 is 18 (moderately severe MDD)
- She was prescribed escitalopram 10 mg for 7-10 days and then told to increase her dose to 20 mg
- You educate her on the importance of regular adherence but advise her to contact you if she has any concerns or intolerable side effects (though they are unusual with this agent)

Updated APA Guidelines for Treating Patients With MDD: Individualizing Treatment

- Tailor treatment based on:
  - Symptoms
  - Past/present therapeutic response
  - Medication side effects
  - Disease severity
  - Safety/tolerability
  - Pharmacologic properties
  - Cost of available agents
- During acute and continuation phases, evaluate/monitor:
  - Response to therapy
  - Side effects

Optimal Management of Patients With Major Depressive Disorder: Getting Ahead of a Complex Disease

First-Line Medications for MDD

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Medications (mg/day)</th>
<th>Common AEs of Medication Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>Citalopram 20-40*</td>
<td>Nausea/vomiting, Insomnia</td>
</tr>
<tr>
<td></td>
<td>Escitalopram 10-20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoxetine 20-60</td>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine 100-300</td>
<td>Agitation, Sedation</td>
</tr>
<tr>
<td></td>
<td>Paroxetine 20-50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sertraline 50-200</td>
<td></td>
</tr>
<tr>
<td>SNRI</td>
<td>Venlafaxine 75-757 (IR)</td>
<td>Nausea/vomiting, Insomnia</td>
</tr>
<tr>
<td></td>
<td>75-225 (SR)</td>
<td>Nervousness</td>
</tr>
<tr>
<td></td>
<td>Devenlafaxine 50-100</td>
<td>Sweating</td>
</tr>
<tr>
<td></td>
<td>Duloxetine 60-120</td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Milnortriline 100-200</td>
<td>Insomnia</td>
</tr>
</tbody>
</table>

AE = adverse event; IR = immediate release; SR = sustained release; SNRI = selective serotonin-norepinephrine reuptake inhibitor.

*Can cause dose-dependent QT interval prolongation. Maximum recommended dose in patients aged >60 years is 20 mg; Not approved for MDD.


First-Line Medications for MDD (cont’d)

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Medications (mg/day)</th>
<th>Common AEs of Medication Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine-</td>
<td>Bupropion 300-450</td>
<td>Nausea/vomiting, Insomnia</td>
</tr>
<tr>
<td>dopamine</td>
<td></td>
<td>Headaches</td>
</tr>
<tr>
<td>norepinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>modulator</td>
<td>Mirtazapine 15-45</td>
<td>Weight gain, Insomnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daytime drowsiness</td>
</tr>
</tbody>
</table>


Newer Antidepressants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Common AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vilazodone</td>
<td>SSRI, 5-HT1A partial agonist</td>
<td>Nausea/vomiting, Insomnia, Constipation, Headaches, Hypertension, Increased heart rate, Nausea, Vomiting, Paresthesias, Tachycardia</td>
</tr>
<tr>
<td>Levomilnacipran</td>
<td>SNRI</td>
<td>Constipation, Nausea, Vomiting</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>SSRI, 5-HT3 receptor antagonist, 5-HT1A antagonist</td>
<td>Constipation, Nausea, Vomiting</td>
</tr>
</tbody>
</table>

5-HT = 5-hydroxytryptamine

Optimal Management of Patients With Major Depressive Disorder: Getting Ahead of a Complex Disease

Considerations When Selecting an Antidepressant

- Patient comfort level with use of medication
- Efficacy of prior treatments/treatment of family members
- Insurance coverage, cost to patient
- Medical comorbidities
- Psychiatric comorbidities
- Drug interactions
- Side effects
- Tolerability (short- and long-term)
- Dosing and cost potential of using higher doses than approved by the US Food and Drug Administration (FDA)


Measurement-Based Care for MDD

- Systematically use measurement tools to guide treatment choices and monitor progress
  - Regularly scheduled visits
  - Time-efficient, validated tools
  - Regularly monitoring symptom improvement, side effects, medication adherence
  - Use a treatment algorithm with established critical decision points


Joani’s Follow-up Appointment

- Presents today for follow-up at 8 weeks
- Current PHQ-9 score is 15; reports adhering to medication
  - Some improvements
    - Has resumed flower arranging, a former hobby
    - Sees friends “from time to time”
  - Ongoing symptoms
    - Trouble sleeping
    - Impaired concentration, forgetfulness
    - No interest in dating
    - Feels “blah” and “down a lot of the time”
    - Hopeless about the future

The 6 R’s: Clarifying Confusing Terminology

<table>
<thead>
<tr>
<th>Commonly Used Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>• 50% reduction in depression score as a result of a treatment</td>
</tr>
<tr>
<td></td>
<td>• Partial response: 25%-50% reduction in depression score</td>
</tr>
<tr>
<td>Remission</td>
<td>• Minimal residual symptoms (≥60% reduction in symptoms using accepted rating scale)</td>
</tr>
<tr>
<td></td>
<td>• OR absolute cutoff score (eg, ≤7 on HAM-D-17 or ≤5 on PHQ-9)</td>
</tr>
<tr>
<td>Relapse</td>
<td>• Return of index major depressive episode after onset of remission but before fulfilling criteria for recovery</td>
</tr>
<tr>
<td>Recovery</td>
<td>• Remission sufficiently sustained, such that continued well-being may be expected</td>
</tr>
<tr>
<td></td>
<td>• Patient has rebuilt meaningful life, hope, optimism; decreasing dependence on mental health system</td>
</tr>
<tr>
<td>Residual symptoms</td>
<td>• Symptoms that remain despite adequate discontinuation of antidepressants</td>
</tr>
<tr>
<td></td>
<td>• Often occur during prodromal phase and may progress to relapse</td>
</tr>
<tr>
<td></td>
<td>• Often subthreshold</td>
</tr>
<tr>
<td></td>
<td>• Can be affective, attentional, anxiety, somatic, and/or pain</td>
</tr>
<tr>
<td>Recurrence</td>
<td>• Development of new episode after recovery</td>
</tr>
</tbody>
</table>


Residual Symptoms After Initial Antidepressant Treatment Is the Norm, Even in Responders

Frequency of Threshold and Subthreshold Residual MDD Symptoms in Responders (N = 108)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Threshold</th>
<th>Subthreshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>Interest</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Weight</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Sleep</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Guilt</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Concentration</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Somatic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


Phases of Treatment: APA Practice Guidelines

**Acute Phase**
- Goal: Eliminate symptoms to return to baseline functioning
- Duration: 4-12 weeks
- Pharmacotherapy:
  - SSRIs
  - SNRIs
  - Mirtazapine
  - Bupropion
- Nonpharmacologic interventions:
  - Psychotherapy
  - Somatic therapies for intractable symptoms
  - Acupuncture
  - ECT

**Continuation Phase**
- Goal: Prevent relapse
- Duration: 4-9 months
- Pharmacotherapy:
  - Continue antidepressant used during acute phase
  - Lithium + nortriptyline for ECT nonresponders
- Acrochemosocial interventions:
  - Depression-focused psychotherapy (CFT)
  - Continuing psychotherapy during acute phase and in evaluation or psychotherapy trials to maintain remission

**Maintenance Phase**
- Goal: Prevent recurrence
- Duration: As needed
- Consider for patients with:
  - 3 prior episodes
  - Chronic MDD
  - Additional risk factors for recurrence
- Pharmacotherapy:
  - Continue antidepressant
  - Acrochemosocial interventions
  - Continue psychotherapy (possibly reduced frequency)
  - Consider ECT continuation

ECT = electroconvulsive therapy
APA = American Psychiatric Association
Accessed September 16, 2016

PCE 2016 Series 3
Potential Reasons for Inadequate Treatment Response

<table>
<thead>
<tr>
<th>Reason</th>
<th>Possible Contributing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate treatment</td>
<td>• Misdiagnosis (eg, unipolar vs bipolar depression)</td>
</tr>
<tr>
<td></td>
<td>• Substance use disorders</td>
</tr>
<tr>
<td></td>
<td>• Undiagnosed medical disorder</td>
</tr>
<tr>
<td>Inadequate treatment</td>
<td>• Treatment duration</td>
</tr>
<tr>
<td></td>
<td>• Medication dose</td>
</tr>
<tr>
<td></td>
<td>• Poor adherence</td>
</tr>
<tr>
<td></td>
<td>• AEs</td>
</tr>
<tr>
<td></td>
<td>• Combination antidepressant use at subtherapeutic doses</td>
</tr>
<tr>
<td>Failure to address known concurrent</td>
<td>• Alcohol or substance use disorders</td>
</tr>
<tr>
<td>disorders</td>
<td>• General medical disorders</td>
</tr>
<tr>
<td></td>
<td>• Other psychiatric disorders</td>
</tr>
</tbody>
</table>


Improving Residual Symptoms After First Antidepressant Trial: Switch, Combine, or Augment (Pharmacologic Strategies)

Strategy | Agents
---|---
Switch antidepressants | Within class/across classes
Combination therapy (add-on antidepressants) | Bupropion, Tricyclic
Augmentation | Atypical antipsychotics, Mirtazapine, Omega-3 fatty acids, SAM-e, T3, L-methylfolate, Buspirone, Lithium, Propranolol, Methylphenidate

SAM-e = S-adenosylmethionine; T3 = triiodothyronine (thyroid hormone).


To Augment or to Switch?
STAR*D Sequence

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention</th>
<th>Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Citalopram</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Switch to:</td>
<td>Augment with:</td>
</tr>
<tr>
<td></td>
<td>• Bupropion (ER) or</td>
<td>• Bupropion (ER) or</td>
</tr>
<tr>
<td></td>
<td>• Venlafaxine (ER) or</td>
<td>• Buspirone or</td>
</tr>
<tr>
<td></td>
<td>• Sertraline or</td>
<td>• CBT</td>
</tr>
<tr>
<td></td>
<td>• CBT</td>
<td></td>
</tr>
<tr>
<td>2a (only for those receiving cognitive therapy in level 2)</td>
<td>Switch to:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bupropion (ER) or</td>
<td>Augment with:</td>
</tr>
<tr>
<td></td>
<td>• Venlafaxine (ER)</td>
<td>• Lithium or</td>
</tr>
<tr>
<td>3</td>
<td>Switch to:</td>
<td>• T3 thyroid hormone</td>
</tr>
<tr>
<td></td>
<td>• Mirtazapine or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nortriptyline</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Switch to:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tranylcypromine or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mirtazapine + venlafaxine (ER)</td>
<td></td>
</tr>
</tbody>
</table>

Joani Discusses a Change in Treatment

- You discuss potential treatment options with Joani
- Escitalopram is discontinued and treatment with duloxetine is initiated (titrated up to 60 mg/d)
- You again suggest CBT; Joani says she will “think about it” but first wants to see how the new medication works

Efficacy of Psychotherapy vs Pharmacotherapy

Efficacy of psychotherapy is measured across 12-16 weeks; efficacy of antidepressants is measured across 6-8 weeks


Joani Is Doing Better But Still Has Symptoms of Depression

- Joani returns after 8 weeks
- Her PHQ-9 score is 12 (moderate depression)
  - “I’m glad to be back doing flower arranging”
  - “Last Saturday, I got together with an old friend”
- But Joani is still symptomatic
  - “I’m so forgetful that it’s embarrassing. And simple chores that used to be so easy for me take forever to complete”
  - “I still can’t concentrate at work and I’m worried about my job”
Consistency of Cognitive Impairment in MDD: Meta-analysis

- Significant deficits in executive function, memory, and attention
  - 784 patients with MDD and 727 control subjects (24 studies)
- Significant deficits in executive function and attention
  - 271 patients with MDD not receiving medication and 267 control subjects (8 studies)

“Cognitive impairment represents a core feature of depression that cannot be considered an epiphenomenon that is secondary to mood symptoms…”


Cognitive Symptoms in MDD

- A core symptom domain in the diagnostic criteria for a major depressive episode¹
- >30% of patients who respond to antidepressant therapy report residual cognitive symptoms (forgetfulness, inattentiveness, mental slowing, apathy, word-finding difficulty)²
- Prevalence in patients with MDD:
  - Among all adults: 30% to 40%¹
  - Among patients aged >65 years: 50% to 60%²


Cognitive Impairment Often Not Assessed by Clinicians

- Clinicians infrequently or inadequately assess cognitive symptoms versus psychological and physical symptoms
- Existing tools and rating scales used almost exclusively in research; used rarely by clinicians because of:
  - Lack of familiarity with and training on use of scales
  - Intimidating length and complexity
  - Time limitations
- Cognitive symptoms can be reliably and systematically assessed via questions about work, home, and social function

Optimal Management of Patients With Major Depressive Disorder: Getting Ahead of a Complex Disease

Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH CPFQ)

- Cognitive self-rating scale
- Sensitive to treatment, easy to use clinically
- 7 items, 4 specifically address cognition:
  - Motivation/interest/enthusiasm
  - Wakefulness, alertness
  - Energy
  - Focus/sustain attention
  - Remember/recall information
  - Find words
  - Sharpness/mental acuity
- Each item rated 1 (greater than normal) to 6 (absent)
- Higher scores indicate greater impairment


Four Key Domains of Cognitive Dysfunction in MDD

<table>
<thead>
<tr>
<th>Domain</th>
<th>Definition</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Ability to focus on several objects or trains of thought</td>
<td>Difficulty with concentration, focus, or attention</td>
</tr>
<tr>
<td>Memory</td>
<td>Visual and verbal, episodic (time and places), semantic (meaning of things)</td>
<td>Word-finding difficulties, forgetfulness</td>
</tr>
<tr>
<td>Executive</td>
<td>Inhibition, working memory, mental flexibility, verbal fluency, planning, problem solving</td>
<td>Indecisiveness, inability to prioritize, multitask, make decisions, or plan</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>Time spent to perform motor actions that arise from mental activity (ie, reaction time, information-processing speed)</td>
<td>Slow speech, response, or processing</td>
</tr>
</tbody>
</table>


Association Between Cognitive Function, Disability, and QoL in Patients Treated for MDD

Cognitive dysfunction group had significantly greater impairments on the Zung Self-Rating Depression Scale

Raising the Bar: Evolving Treatment Goals for MDD

- Cognitive remission 2014
- Improved QoL
- Functional remission ~2010
- Improved function
- Remission ~2000
- Response
- Symptom reduction Before 1990


AEs: A Major Cause of Nonadherence

- 53% of patients in primary care discontinue antidepressant treatment, even after experiencing clinical improvement
- 24% do not inform their clinicians
- AEs are one of the most common reasons patients discontinue antidepressants
- The AEs most commonly associated with nonadherence are:
  - Weight gain
  - Sexual dysfunction
  - Being tired/low of energy

Encouraging Adherence to Treatment

- Depression outcomes are worse in patients who do not complete a full course of therapy and achieve remission
- Intolerance to medication can lead to nonadherence to therapy
- Rates of antidepressant discontinuation:
  - In first 3 months: >40%
  - In next 2 months: 50%
- Encourage patients to report AEs
- Urge patients not to stop medication by themselves
- Educate patients about MDD, importance of treatment, how medication can help

Addressing Potential Suicidality

- Suicide is the 10th leading cause of death in the United States
  - Depression is present in at least 50% of all suicides
  - 2% to 9% of people diagnosed with depression in their lifetime will go on to complete suicide
  - Suicide risk is 25 times greater in those with depression than in the general population
- The CDC recommends that primary care practitioners screen all patients for depression and suicide risk, especially:
  - Older patients
  - Patients with comorbid medical conditions

Joani’s Future Is Looking Brighter

- After 6 months of treatment with vortioxetine, Joani’s PHQ-9 score is 6 (mild depression)
- She is seeing a therapist for CBT
- She has re-initiated contact with her family
- Work is once again enjoyable, and she no longer fears losing her job
- Joani has completed her flower arranging course and is proud of her accomplishment
- While “not everything is perfect,” she is hopeful about the future
Optimal Management of Patients With Major Depressive Disorder: Getting Ahead of a Complex Disease

Summary

- The goal of MDD is remission of all symptoms, including cognition
- Alternative approaches—especially CBT—may be helpful
- Measurement-based care is critical to continuously monitor therapeutic response and adjust therapy accordingly
  - Validated instruments facilitate monitoring of response
- As with any chronic disease, the patient-provider relationship is critical for good outcomes

PCE Action Plan

- Use measurement-based care to guide treatment choices and monitor progress
- Individualize treatment according to patient history, MDD characteristics, drug characteristics, and preferences
- Document residual symptoms in patients who have partial response to therapy for MDD
- Evaluate strategies for improving residual symptoms in partial responders
- Evaluate remission of cognitive symptoms in patients with MDD

PCE Promotes Practice Change
Rheumatoid Arthritis: Treating to Target in Primary Care

Learning Objectives

• Describe current therapeutic management recommendations and emerging options for the treatment of patients with RA
• Implement strategies to increase treatment adherence for patients with RA who are nonadherent to their prescribed medical therapy
• Incorporate appropriate preventive care into long-term management plans for patients with RA to manage extra-articular manifestations and minimize drug-related exacerbations of common comorbidities

RA = rheumatoid arthritis.

Clinical Burden of RA

1.5 MILLION ADULTS in the US have RA

• High work disability rates: 37% of patients aged <65 years who were working at symptom onset (mean observation period, 9 years)
• Probability of continuing to work:
  – 80% at 2 years after onset
  – 68% at 5 years after onset

Clinical Burden of RA (cont'd)

- 47% increased risk of death compared with general population
- Mortality rates between 1965 and 2005:
  - Declined among general population
  - Constant among patients with RA (defined by 1987 ACR criteria)
    - Women: 2.4 per 100 person-years
    - Men: 2.5 per 100 person-years
- 2014 study found higher, but stable, all-cause mortality over 7 years among patients with RA (defined by the 2010 ACR/EULAR criteria) compared with general population: SMR 1.22

ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; SMR = standardized mortality ratio.


Environmental and Genetic Risk Factors for RA

RA thought to be associated with:
- Genetics
- Female sex
- Environmental factors (smoking, periodontitis, pollution, gut microbiota, others)

Gut dysbiosis in patients with RA may result from increased abundance of certain rare bacterial lineages. Managing RA by manipulating the gut microbiota is a new area of research.


The Link Between RA and Smoking

Environmental Trigger + Genetic Susceptibility = Risk of RA

Odds ratios for different amounts of smoking (in pack-years) with none, 1, or 2 copies of SE alleles

Heavier smoking and multiple genetic factors increase risk of RA

ACPA = anti-citrullinated protein/peptide antibody; py = pack years; SE = shared epitope.

Rheumatoid Arthritis: Treating to Target in Primary Care

The Link Between RA and Obesity
A Meta-analysis of Observational Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al., 2014, USA</td>
<td>0.57 (0.49-0.66)</td>
<td>6.0</td>
</tr>
<tr>
<td>Lafrenière, 2014, UK</td>
<td>1.00 (0.83-1.19)</td>
<td>10.0</td>
</tr>
<tr>
<td>Hedman et al., 2014, Denmark</td>
<td>1.20 (1.07-1.35)</td>
<td>18.0</td>
</tr>
<tr>
<td>Weisberg et al., 2013, Sweden</td>
<td>0.94 (0.81-1.11)</td>
<td>16.4</td>
</tr>
<tr>
<td>Czerwony et al., 2013, USA</td>
<td>1.31 (1.24-1.38)</td>
<td>12.3</td>
</tr>
<tr>
<td>Rovin et al., 2009, Sweden</td>
<td>1.98 (1.80-2.21)</td>
<td>14.3</td>
</tr>
<tr>
<td>Reddick et al., 2009, UK</td>
<td>0.90 (0.78-1.06)</td>
<td>10.4</td>
</tr>
<tr>
<td>Pedersen et al., 2006, Denmark</td>
<td>1.57 (1.25-2.24)</td>
<td>8.1</td>
</tr>
<tr>
<td>Uhlig et al., 1999, Norway</td>
<td>1.84 (1.28-2.62)</td>
<td>6.7</td>
</tr>
<tr>
<td>Synnema et al., 1997, UK</td>
<td>3.14 (1.14-9.27)</td>
<td>1.9</td>
</tr>
<tr>
<td>Overall (Heterogeneity F = 60.3%, P = .001)</td>
<td>1.21 (1.02-1.44)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

RR = risk ratio.

Articular Manifestations of RA

- Swelling, tenderness, warmth, and painful motion
- Morning stiffness
- May also manifest after brief periods of inactivity
- Inflammation of the synovial joints
- Joint and periarticular tissue destruction
- Joints most often involved:
  - Proximal interphalangeal (PIP)
  - Metacarpophalangeal (MCP)
  - Wrists, elbows, shoulders, knees, ankles, and subtalar and metatarsophalangeal joints


Extra-articular Manifestations of RA

- CVD
- Felty syndrome
- Glomerulonephritis
- Lymphadenopathy
- Myopathy, polymyositis
- Neuropathy (polyneuropathy, mononeuropathy, mononeuritis multiplex)
- Nodules
- Ocular inflammation (episcleritis, scleritis, keratoconjunctivitis perforans)
- Pericarditis
- Pleuritis
- Pulmonary fibrosis
- Raynaud phenomenon
- Secondary Sjögren syndrome
- Vasculitis (benign cutaneous and nail-fold, severe cutaneous, systemic)
- Other (weight loss, cachexia, malaise, fatigue, fever)

Case Study: Meredith

- 40-year-old woman with previously diagnosed RA seeks care at your practice
- New to the area; has had infrequent follow-up with her previous healthcare provider
- She has been taking MTX 15-25 mg orally for 14 months but says she is “not doing well”
  - Complains of flare-ups with swelling and joint pain in her hand
- Smoking status: 1/2 pack per day
- Height, 5 ft 5 in; weight, 185 lb; BMI, 30.8 kg/m²

MTX = methotrexate.

Smoking Dulls RA Treatment

Observations from the Epidemiological Investigation of RA and the Swedish Rheumatology Register Cohorts

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Overall Cohort</th>
<th>MTX</th>
<th>No DMARD</th>
<th>TNF Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>45%</td>
<td>40%</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>Past</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response in overall cohort and in subgroups receiving MTX or clinical care without a DMARD at baseline, as well as in those receiving subsequent TNF inhibitors.


Multidisciplinary Teams Improve Care for Patients With RA

- Demand for rheumatologists expected to exceed supply in 2016 by more than 1000 physicians (>2500 by 2025)
- NPs and PAs are in a unique position to partner with patients with RA, assess their individual needs, improve quality of care, promote better self-care, and provide ongoing support and education
- Patients who interact with NPs and PAs have increased levels of satisfaction and improved self-care versus those with no interaction with NPs and PAs

Meredith would benefit from the support of a multidisciplinary team to better manage lifestyle and medication strategies.

NP = nurse practitioner; PA = physician assistant.

Coordinating Multidisciplinary Treatment Teams

- Patient-centered care teams include referrals for extra-articular issues
- NPs and PAs should develop relationships with at least 1-2 rheumatologists to facilitate timely referrals when needed
- Multidisciplinary teams do not have to practice together in the same building or setting


Responsibilities of Primary Care Clinicians as Part of Multidisciplinary Team

- Smoking cessation
- Nutrition and weight management
- Symptom management
- Assessing need for changes in therapy
- Immunizations
  - Influenza, pneumococcal, hepatitis B
- Referrals for consultations
  - Rheumatology
  - Psychiatry
  - Cardiology
  - Pulmonary
  - Occupational therapy
- Pregnancy counseling
- Referrals for consultations
  - Rheumatology
  - Psychiatry
  - Cardiology
  - Pulmonary
  - Occupational therapy
- Pregnancy counseling


Establish a Multidisciplinary Team

- Multidisciplinary approach combines skills and knowledge of all team members, for both assessment and management of RA
- Primary care practices should have access to rheumatology specialists
- Requires a high level of communication and coordination
- NPs and PAs work more closely with patients and engage them as active members of the team
- Without sustained care and regular follow-up, patients can lose control of their disease, leading to erosion of bone and cartilage and functional disability

Measures of Disease Activity in RA

Continuous measures of disease activity
- Disease Activity Score (DAS)
- DAS28
- Simplified Disease Activity Index (SDAI)
- Clinical Disease Activity Index (CDAI)

Patient-reported outcome measures
- Routine Assessment of Patient Index Data (RAPID3)


Meredith’s Disease Activity Is Moderate

<table>
<thead>
<tr>
<th>SDAI Scoring</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s functional status</td>
<td>4.5</td>
</tr>
<tr>
<td>Patient assessment of pain</td>
<td>3.5</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>4.0</td>
</tr>
<tr>
<td>Provider global assessment</td>
<td>5.0</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Total: 25.58

<table>
<thead>
<tr>
<th>RAPID3 Scoring</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s functional status</td>
<td>4.3</td>
</tr>
<tr>
<td>Patient assessment of pain</td>
<td>3.5</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>4.0</td>
</tr>
<tr>
<td>Total</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Total: 11.8

Tool: High Moderate Low Remission
- RAPID3 >12.0
- SDAI >26.0

Importance of Early Diagnosis

- RA is progressive, not benign
- Structural damage and disability occur within first 2-3 years of disease
- Slower progression of disease is linked to early treatment with DMARDs
- Once bone and cartilage are damaged, they never return to normal

Rheumatoid Arthritis: Treating to Target in Primary Care

Principles of RA Management: Treat to Target

<table>
<thead>
<tr>
<th>Primary Therapeutic Goal</th>
<th>Achieved by Controlling Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximize health-related quality of life by:</td>
<td>Measure disease activity frequently using a validated clinical assessment tool</td>
</tr>
<tr>
<td>• Controlling symptoms</td>
<td>• Adjust treatment as needed to achieve and maintain therapeutic target</td>
</tr>
<tr>
<td>• Preventing structural damage</td>
<td></td>
</tr>
<tr>
<td>• Normalizing functional activity</td>
<td></td>
</tr>
</tbody>
</table>

Primary Therapeutic Goal

Achieved by Controlling Inflammation

With Targeted Treatment

Primary target: clinical remission (absence of signs & symptoms of significant inflammatory disease activity)

Alternative target: low disease activity if primary target not achievable (ie, because of established RA of long duration)

Clinical Remission Is the Goal

- Treatment of RA is a shared patient/clinician decision
- Primary goal of treatment is to maximize long-term health-related quality of life (control symptoms, prevent structural damage, normalize function and social participation)
- Reducing inflammation is the most important way to achieve these goals
- Treat to target with the goal of clinical remission

ACR-Recommended RA Treatment Options

<table>
<thead>
<tr>
<th>Conventional Synthetic DMARDs</th>
<th>Biologic (Anti-TNF) DMARDs</th>
<th>Biologic (Non-TNF) DMARDs</th>
<th>Targeted Synthetic DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>Adalimumab</td>
<td>Abatacept (T-cell costimulation antagonist)</td>
<td></td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Certolizumab pegate</td>
<td>Anakinra (IL-1 receptor blocker)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Etanercept</td>
<td>Rituximab (anti-B-cell agent)</td>
<td></td>
</tr>
<tr>
<td>Minocycline</td>
<td>Golimumab</td>
<td>Tocilizumab (IL-6 receptor blocker)</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Infliximab</td>
<td>Tofacitinib (Janus-associated kinase inhibitor)</td>
<td></td>
</tr>
</tbody>
</table>

Emerging Treatments - Phase 3

**Sarilumab**
- Fully human mAb inhibitor of IL-6 receptor
- SC injection every 2 weeks
- Patients treated with sarilumab showed significant improvements in symptomatic, functional, and radiographic outcomes
- Well tolerated

**TARGET Study**
- Anti-TNFα-IR Patients
  - N = 546

**MOBILITy Study**
- MTX-IR Patients
  - N = 1197

Emerging Treatments - Phase 3 (cont’d)

**Baricitinib**
- Targets JAK1 and JAK2
- Significant reduction of disease activity as early as 1 week after starting therapy, maintained through 52 weeks in phase 3 studies
- Demonstrated efficacy in patients unresponsive to csDMARDs and in patients with inadequate response to TNF inhibitors
- Studies have shown an acceptable safety profile in patients with moderate-to-severe active RA

**RA-BUILD Study: Baricitinib in csDMARD-IR Patients**
- More patients achieved ACR20 response at week 12 with baricitinib than with placebo (62% vs 39% P ≤ .001)

After 6 months, Meredith’s disease activity remains in the moderate category

- Meredith has successfully quit smoking
- She continues to work toward losing weight with diet and exercise, but often feels fatigued
- Tuberculosis test results are negative
- Despite these achievements, she has not responded adequately to the TNF inhibitor she has been taking for over 3 months
Adjust Treatment to Achieve the Therapeutic Target

- Current practice guidelines from ACR and EULAR emphasize treat-to-target as the overarching principle of disease management
- Frequent disease activity assessments (1-3 months for active disease) are recommended to assess treatment response
- If no improvement is seen at 3 months or the target has not been reached at 6 months, treatment adjustment is warranted


Reasons for Treatment Nonadherence

- Approximately one-third of patients with RA are treatment nonadherent
- Unintentional nonadherence results from:
  - Forgetfulness
  - Regimen complexity
  - Physical problems or practical barriers
- Intentional nonadherence is:
  - Driven by a conscious decision not to take the medication
  - Based on individual patient’s risk:benefit analysis
  - Influenced by patient’s beliefs about the medication, self-efficacy, and knowledge of the disease


Depression and RA

- Depression has been documented in several clinical populations of people with RA
  - Up to 50% of patients with RA have symptoms of depression
- Depression is associated with:
  - Increased disease activity and decreased physical function
  - Poor adherence to medical and nonmedical interventions
- Referral to a mental health provider is an option to treat depression and subsequently improve adherence to RA therapies

Strategies for Increasing Treatment Adherence

- Successful interventions to improve adherence include:
  - Comprehensive approach
  - Consideration of individual patient’s beliefs and concerns
  - Open communication
  - Shared decision making
- Discuss obstacles to treatment adherence with patients and provide solutions
- Simplify drug regimens and schedules
- Educate patients about the reasons for treatment
- Anticipate and address patients’ questions and concerns regarding treatment side effects


Meredith’s earlier problems with adherence were addressed with counseling and patient education

- She is also using a popular free mobile app to help track her progress and receive reminders for prescription refills
- There are many available tracking apps for patients for iPhone and Android devices


Do Not Overlook Nonadherence When Treatment Response Is Suboptimal

- DMARD therapy reduces disease activity and radiologic progression and improves long-term functional outcome in patients with RA
- Treatment nonadherence compromises efficacy and increases the risk of disease flares and functional disability
- Possible treatment nonadherence should be considered before treatment switching if therapeutic response is suboptimal

Extra-Articular Manifestations and Common Comorbidities in RA

- Present approach considers RA as a systemic disease, not just focused on prevention of joint damage
- Extra-articular manifestations: CVD, pulmonary disease, renal disease, ocular inflammation, nodules, neuropathies, and myopathies
  - Rates of MI and stroke are nearly double those in persons without RA
- Patients being treated for RA need to be monitored long term
  - To assess response to DMARD therapy
  - To identify and manage treatment-related side effects
- DMARDs affect disease course but also may contribute to or exacerbate comorbidities commonly encountered by patients with RA

MI = myocardial infarction.


High Prevalence of Preclinical Atherosclerosis in RA

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Controls</th>
<th>Patients With RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>40-49</td>
<td>12</td>
<td>52</td>
</tr>
<tr>
<td>50-59</td>
<td>21</td>
<td>52</td>
</tr>
<tr>
<td>60-79</td>
<td>44</td>
<td>80</td>
</tr>
</tbody>
</table>


EULAR Recommendations for CVD Risk Management in RA

- Regard RA as an independent risk factor for CVD due to:
  - Increased prevalence of traditional risk factors
  - Inflammatory burden
- Adapt CVD risk score models for patients with RA by introducing a 1.5 multiplication factor when 2 of the following criteria are met:
  - Disease duration >10 years
  - Rheumatoid factor or ACPA positivity
  - Presence of extra-articular manifestations

Rheumatoid Arthritis: Treating to Target in Primary Care

Do Not Neglect CVD Risk in Patients With RA

- RA: proatherogenic disease associated with increased CVD morbidity/mortality
- Absolute risk of CVD death highest in elderly male patients; RR highest in young female patients
- Inflammatory arthritis associated with unfavorable changes in the lipid profile that can be present 10 years before the onset of RA
- Retrospective study of 44,418 patients with RA found an association between:
  - Increased MI risk and higher CRP (>10 mg/L) and ESR levels (>42 mm/h)
  - Reduced MI risk and higher HDL-C levels (>60 mg/dL)
- Intensive statin therapy reduces CVD risk in patients with inflammatory arthritis
- DMARD therapy also shown to reduce CVD risk

HDL-C = high-density lipoprotein cholesterol.

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HZV = herpes zoster virus; TB = tuberculosis.

aContraindicated prior to pregnancy and during pregnancy and breastfeeding as well as in patients with active bacterial infection, active HZV infection, active or latent TB or acute or chronic hepatitis B or C.


Conventional Synthetic DMARDs: Risks and Side Effects

<table>
<thead>
<tr>
<th>Agent</th>
<th>Risks and Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>Retinopathy</td>
</tr>
<tr>
<td>Leflunomide*</td>
<td>Hyperleukocytosis, myelotoxicity</td>
</tr>
<tr>
<td>Methotrexate*</td>
<td>Hepatotoxicity, folic acid deficiency, myelotoxicity, opportunistic infection, leprosy, nausea, vomiting</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Nausea, vomiting, diarrhea, dyspepsia, dizziness, skin rash, leprosy</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Hepatotoxicity, hyperpigmentation reactions, myelotoxicity, reversible male infertility</td>
</tr>
</tbody>
</table>

HZV = herpes zoster virus; TB = tuberculosis.

*Contraindicated prior to pregnancy and during pregnancy and breastfeeding as well as in patients with active bacterial infection, active HZV infection, active or latent TB or acute or chronic hepatitis B or C.


Biologic and Targeted Synthetic DMARDs: Risks and Side Effects

<table>
<thead>
<tr>
<th>Class (Agent)*</th>
<th>Risks and Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell depletion (methotrexate)</td>
<td>Infusion reactions, infections</td>
</tr>
<tr>
<td>IL-1 receptor blockade (anakinra)</td>
<td>Injection site reactions, infections, neutropenia</td>
</tr>
<tr>
<td>IL-6 receptor blockade (tocilizumab)</td>
<td>Injection site reactions, infections, neutropenia, reduced platelet counts, elevated liver enzymes, elevated lipids, gastrointestinal tract perforation</td>
</tr>
<tr>
<td>TNF blockade (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)</td>
<td>Injection site reactions, infections, demyelinating disease exacerbation or new onset, heart failure worsening or new onset, lymphoma, melanoma</td>
</tr>
</tbody>
</table>

*Contraindicated in patients with active bacterial infection, active HZV infection, active or latent TB, or acute or chronic hepatitis B or C. Live vaccines should be avoided in patients currently taking immunosuppressive agents or likely to need immunosuppressive therapy within 6 to 12 weeks.

Case Resolution

• Meredith takes charge of her disease with the help of a committed multidisciplinary team
• She sustains her smoking cessation and loses 20 lb by exercising and following a Mediterranean diet with anti-inflammatory benefits
• She achieves remission

PCE Action Plan

✓ Identify members of your expanded care team, collect contact information, and plan collaborative care
✓ Inform every patient that your mutual goal is to achieve clinical remission
✓ Adjust treatment if the therapeutic target has not been achieved in 6 months
✓ Always consider treatment nonadherence when treatment failure is suspected
✓ Consider RA as an independent risk factor for CVD

PCE Promotes Practice Change