A Review of GLP-1 Receptor Agonists and SGLT2 inhibitors for Type 2 Diabetes

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Lecture Objectives

- GLP-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2) inhibitors
  - Describe the mechanism of action (MOA) and pharmacokinetic properties
  - Make appropriate recommendations for type 2 diabetes utilizing patient scenarios
  - Counsel a patient on proper use
  - Discuss advantages and disadvantages

FDA Approved GLP-1 RAs and SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>GLP-1 RAs</th>
<th>SGLT2 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generics</td>
<td>Brand Name</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Byetta (BID)</td>
</tr>
<tr>
<td></td>
<td>Bydureon (Once Weekly)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza (Type 2 DM indication)</td>
</tr>
<tr>
<td></td>
<td>Saxenda (Weight loss indication)</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Tanzeum</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity</td>
</tr>
</tbody>
</table>

Audience Poll Question

- Who has counseled or dispensed:
  - Byetta or Victoza?
  - Bydureon, Tanzeum, or Trulicity?
  - Invokana?
  - Farxiga or Jardiance?

Patient Vignette

Demographics: BB is a 48 year old obese female patient with type 2 diabetes and fantastic prescription insurance

Continues to work on food choices and increasing physical activity

Patient prefers a medication that will help her lose weight

PMH:
- Type 2 diabetes
- No macro- or microvascular complications

Current medications:
- Metformin 1000 mg po BID
- Atorvastatin 20 mg po daily

Medication Allergies: NKDA

Home BGS:
- Fasting BG average = 148 mg/dL
- Two hour postprandial BG average = 226 mg/dL

Labs:
- A1c = 8.3%
- SCr = 1.0 mg/dL

Audience poll: What medication should be added in combination with metformin to reduce A1c?
ADA 2015 Dual Therapy Options

- High A1c lowering
- Low hypoglycemia risk
- Weight gain
- Medium cost

- Moderate A1c lowering
- Low hypoglycemia risk
- Weight gain
- Low cost

- Low A1c lowering
- Moderate hypoglycemia risk
- Weight loss
- High cost

Sulfonylurea

- High A1c lowering
- Low hypoglycemia risk
- Weight gain
- Medium cost

Thiazolidinedione

- Intermediate A1c lowering
- Low hypoglycemia risk
- Weight neutral
- High cost

DPP-4 Inhibitor

- Intermediate A1c lowering
- Low hypoglycemia risk
- Weight loss
- High cost

SGLT2 inhibitor

GLP-1 Receptor Agonists

Comparison of 2015 ADA & AACE/ACE Medication Recommendations for Type 2 DM (GLP-1 RAs and SGLT2 Inhibitors Place in Therapy)

ADA

- Monotherapy
  - 1st preference: metformin
  - 2nd preference: GLP-1 RAs
  - 3rd preference: SGLT2 inhibitors

- Dual therapy
  - 1st preference: GLP-1 RAs
  - 2nd preference: SGLT2 inhibitors

- Triple therapy
  - Similar to dual recommendation

- Insulin
  - GLP-1 RAs in combo with basal insulin

AACE

- Monotherapy
  - 1st preference: metformin
  - 2nd preference: GLP-1 RAs
  - 3rd preference: SGLT2 inhibitors

- Dual therapy
  - 1st preference: GLP-1 RAs
  - 2nd preference: SGLT2 inhibitors

- Triple therapy
  - Similar to dual recommendation

- Insulin
  - GLP-1 RAs or SGLT2 inhibitors in combo with basal insulin

Cost Considerations

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Quantity (Days Supply)</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta 10 mcg</td>
<td>1 pen (30 days)</td>
<td>574.01</td>
</tr>
<tr>
<td>Bydureon pen</td>
<td>4 pens (4 weeks)</td>
<td>570.32</td>
</tr>
<tr>
<td>Victoz 1.2 mg</td>
<td>2 pens (30 days)</td>
<td>512.78</td>
</tr>
<tr>
<td>Tanzeum 50 mcg</td>
<td>4 pens (4 weeks)</td>
<td>426.36</td>
</tr>
<tr>
<td>Trulicity 1.5 mg</td>
<td>4 pens (4 weeks)</td>
<td>586.00</td>
</tr>
<tr>
<td>Invokana 300 mg</td>
<td>30 tabs (30 days)</td>
<td>411.41</td>
</tr>
<tr>
<td>Invokamet 150/1000 (combo with metformin)</td>
<td>60 tabs (30 days)</td>
<td>411.41</td>
</tr>
<tr>
<td>Farxiga 10 mg</td>
<td>30 tabs (30 days)</td>
<td>411.53</td>
</tr>
<tr>
<td>Xigduo XR 10/1000 (combo with metformin)</td>
<td>30 tabs (30 days)</td>
<td>411.53</td>
</tr>
<tr>
<td>Jardiance 25 mg</td>
<td>30 tabs (30 days)</td>
<td>411.38</td>
</tr>
<tr>
<td>Glyxambi 25/5</td>
<td>30 tabs (30 days)</td>
<td>576.00</td>
</tr>
</tbody>
</table>

GLP-1 Receptor Agonists

- Glucagon-Like Polypeptide-1 (GLP-1)
  - A peptide (37 amino acid sequence)
  - Secreted by intestinal L-cells
  - INCRETIN (INtestinal seCRETion of INsulin)
  - t1/2 of 2-3 min (low in vivo stability)
  - Hydrolyzed by dipetidyl peptidase IV (DPP-IV)
**GLP-1 Receptor Agonists: MOA**

- GLP-1
- APPETITE
- DELAYS Gastric Emptying
- INSULIN Secretion
- GLUCAGON Secretion
- BLOOD GLUCOSE

**Renal impairment:** No dose adjustment

**Once-weekly administration**

- **t½ elimination:** 5 days

**Metabolism:** Possible proteolytic degradation

**Absolute bioavailability:** 47% - 65%

**GLP-1 analog + Linker + Modified IgG4 Fc Domain**

**U.S. Approval:** 2014

**Protein Binding (PB):** > 98% is bound to plasma albumin

**Bioavailability (BA):** SubQ: ~55%

**Modification:** C16 fatty acid chain attached to Lys26; Arg34

**96% homology to human GLP-1**

**U.S. Approval:** 2010

**Delays gastric secretion**

**Glucagon secretion**

**Appetite**

**Insulin secretion**

**Blood glucose**

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**Exenatide (Byetta)**

- **U.S. Approval:** 2005
- **Synthetic version of Exendin-4**
- **53% homology to human GLP-1**
- **IR (twice daily) formulation** t½ elimination: ~3-4 hours
- **ER (weekly) formulation** Bydureon t½ elimination: ~2 weeks
- **Microspheres** prolong the release from the S.C. tissue
- **Metabolism:** Possible proteolytic degradation
- **Severe renal impairment:** should not be used

**Liraglutide (Victoza)**

- **U.S. Approval:** 2010
- **96% homology to human GLP-1**
- **Modification:** C6 fatty acid chain attached to Lys26; Arg34--Lys;
- **Bioavailability (BA):** SubQ: ~55%
- **Protein Binding (PB):** > 98% is bound to plasma albumin
- **Once-daily administration**
- **t½ elimination:** 13 h
- **Use with caution:** Renal Impairment. No dose adjustment

**Albiglutide (Tanzeum)**

- **U.S. Approval:** 2014
- **GLP-1 dimer fused to albumin (fusion protein)**
- **Amino acid substitution** Ala (GLP1) to Gly (Albiglutide)
- **Absolute bioavailability:** Not evaluated
- **Metabolism:** Possible proteolytic degradation
- **Larger size → decreased renal clearance**
- **Once-weekly administration**
- **t½ elimination:** 5 days
- **Renal impairment:** No dose adjustment

**Dulaglutide (Trulicity)**

- **U.S. Approval:** 2014
- **GLP-1 analog + Linker + Modified IgG4 Fc Domain**
- **Absolute bioavailability:** 47% - 65%
- **Metabolism:** Possible proteolytic degradation
- **t½ elimination:** 5 days
- **Once-weekly administration**
- **Renal impairment:** No dose adjustment

**GLP-1 RA Comparison**

<table>
<thead>
<tr>
<th></th>
<th>Exenatide</th>
<th>Exenatide</th>
<th>Liraglutide</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Dose</strong></td>
<td>5 mcg BID x 1 month</td>
<td>2 mg weekly</td>
<td>0.6 mg once daily x 1 week, 1.2 mg once daily</td>
<td>30 mg weekly x 6-8 weeks</td>
<td>0.75 mg weekly or 1.5 mg weekly</td>
</tr>
<tr>
<td><strong>Dose Titration &amp; Maximum Dose</strong></td>
<td>10 mcg BID</td>
<td>NA</td>
<td>1.8 mg daily after 1 week if needed</td>
<td>50 mg weekly if needed</td>
<td>1.5 mg weekly</td>
</tr>
<tr>
<td><strong>Dose timing</strong></td>
<td>30 minutes before 2 main meals (6 hours apart)</td>
<td>Any time of day with or without regard to meals</td>
<td>Anytime of day independent of meals</td>
<td>Anytime of day without regard to meals</td>
<td>Anytime of day</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>Within days</td>
<td>2 weeks</td>
<td>Within days</td>
<td>1 week</td>
<td>1 week</td>
</tr>
</tbody>
</table>
**GLP-1 RA Comparison**

<table>
<thead>
<tr>
<th></th>
<th>Exenatide BID</th>
<th>Exenatide Q weekly</th>
<th>Liraglutide</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c lowering (%)</td>
<td>0.8-1.5</td>
<td>1.3-1.9</td>
<td>1.1-1.5</td>
<td>0.9-1</td>
<td>1.3-1.5</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL) lowering</td>
<td>11-25</td>
<td>32-41</td>
<td>19-39</td>
<td>16-25</td>
<td>34-42</td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>1.2</td>
<td>1.4-2.9</td>
</tr>
</tbody>
</table>

**Summary of Significant Differences from Head-to-Head Comparisons of GLP-1 RA**

- Liraglutide and Dulaglutide most effective
- Exenatide q weekly more effective than exenatide BID

**Postprandial glucose lowering:**
- Exenatide BID most effective

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**Patient Vignette – GLP-1 RA New Rx**

**Name**: BB  
**Address**: 22 Texan Rd  
**Date**: 7/10/15

- Victoza pen  
- Sig: 1.2 mg subq once daily  
- Ds: Type 2 DM

**Refills**: 2  
**Dispense as written**: C. Cauldon, PharmD  
**Substitution permissible**: X

**Audience Poll Questions:**
- What is your assessment of the dose?  
- What else will the patient need to administer the Victoza?  
- What adverse effects do you counsel the patient on and how should the patient manage the adverse effects?

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**GLP-1 RA Nausea/Vomiting ADR**

- **Nausea management tips**
  - Stop eating at first signs of feeling full  
  - Eat smaller meals  
  - Avoid high-fat meals  
  - Take exenatide BID closer to mealtime  
  - Prolong dose escalation or reduce dose  
  - Lower dose of metformin  
  - Switch to another GLP-1 RA  
  - Pre-medicate with oral antiemetics for 1-2 weeks  
- **Avoid use in patient with gastroparesis**

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**GLP-1 RA Weight Loss and N/V ADRs**

- **Weight loss is experienced by 80% of patients**  
  - Most weight loss seen with exenatide BID and liraglutide  
  - Nausea resolves within 28 weeks in all but 10% of patients  
  - Most nausea with exenatide BID and liraglutide

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**GLP-1 RA ADRs**

- **Exenatide q weekly**
  - Small lump at injection site due to microsphere formulation  
  - Disappears within 3-4 weeks
- **Albiglutide**
  - Local skin reactions more common than liraglutide (13 vs 5%)  
  - Prunus, rash (10-18%)
GLP-1 RA Warnings and Precautions

- Pancreatitis
  - Recent meta-analysis found risk is low
  - Continue to monitor and not recommended for patients with a history of pancreatitis

- Thyroid cancer
  - Rodent studies showed increase risk
  - Not recommended for patients with a history or family history

GLP-1 RA Device Counseling

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dosing Device</th>
<th>Mixing required</th>
<th>Storage – all should be refrigerated before first use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>Multiple dose pre-filled pen</td>
<td>No</td>
<td>Refrigerate before use; room temp when using</td>
</tr>
<tr>
<td>Exenatide weekly</td>
<td>Single dose pre-filled pen or single dose tray</td>
<td>Yes</td>
<td>Refrigerate; can be kept at room for 4 weeks prior to use</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Multiple dose pre-filled pen</td>
<td>No</td>
<td>Refrigerate before use; refrigerate or room temp when using</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Single dose pre-filled pen</td>
<td>Yes - requires 15 or 30 minutes for reconstitution</td>
<td>Refrigerate before use; can be kept at room temp for 4 weeks prior to use</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Single dose pre-filled pen</td>
<td>No</td>
<td>Refrigerate before use; can be kept at room temp for 14 days prior to use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Priming required</th>
<th>Extra Supplies Needed</th>
<th>Needle size</th>
<th>Hold time after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>Prime pen before first use; not each time</td>
<td>Pen needles are ordered separately</td>
<td>Multiple options</td>
<td>6 seconds</td>
</tr>
<tr>
<td>Exenatide weekly</td>
<td>No</td>
<td>No</td>
<td>23 gauge syringe and pen needle</td>
<td>10 seconds for pen only</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Prime pen before first use; not each time</td>
<td>Pen needles are ordered separately</td>
<td>Novofine 32 gauge pen manufacturer</td>
<td>6 seconds</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>No</td>
<td>No</td>
<td>29 gauge, 5 mm</td>
<td>5 seconds</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>No</td>
<td>No</td>
<td>29 gauge, ½ inch</td>
<td>5-10 seconds</td>
</tr>
</tbody>
</table>

GLP-1 RAs Summary

**Advantages**
- More efficacious than second line oral agents
- Low risk of hypoglycemia
- Weight loss
- Low risk of CV events; may be beneficial
- Can be given to patients with CKD (excluding exenatide)

**Disadvantages**
- Less efficacious than insulin
- GI ADRs
- High cost
- Injectable and additional supplies sometimes needed
- No data on prevention of microvascular complications

Sodium-glucose Cotransporter 2 (SGLT2)

- Kidneys: Regulate glucose levels
  - Reabsorb glucose after filtration
  - SGLT2 (major), SGLT1

- SGLT2
  - High capacity transporter: 90% reabsorption
  - S1 segment of Proximal convoluted tubule (PCT)
SGLT2 Inhibitors

- **Mechanism of Action**
  - Reduces reabsorption of glucose from the tubular lumen

  Canagliflozin (Invokana)
  - U.S. Approval: 2013
  - Bioavailability: ~65%
  - Protein binding: 99%
  - Metabolism: O-glucuronidation
  - t1/2 elimination: ~10-13 hours
  - Excretion: Feces and urine (unchanged drug and O-glucuronide metabolites)
  - Adverse effects: UTI, Polyuria, genitourinary infection
  - Hypotension, hyperkalemia
  - Renal Impairment: Monitor renal function

  [Link to FDA Approval](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf) [Accessed May 28, 2015]

Dapagliflozin (Farxiga)
- U.S. Approval: 2014
- Bioavailability: ~78%
- Protein binding: 91%
- Metabolism: O-glucuronidation
- t1/2 elimination: ~12.9 hours
- Excretion: Feces and urine (unchanged drug and O-glucuronide)
- Adverse effects: UTI, Polyuria, genitourinary infection
- Hypotension
- Active bladder cancer and prior history of bladder cancer: Should not be used
- Renal Impairment: Monitor renal function

[Link to FDA Approval](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf) [Accessed May 28, 2015]

Empagliflozin (Jardiance)
- U.S. Approval: 2014
- Bioavailability: 86%
- Protein binding: 86%
- Metabolism: O-glucuronidation
- t1/2 elimination: ~12.4 hours
- Excretion: Feces and urine (unchanged drug and O-glucuronide metabolites)
- Adverse effects: UTI, Polyuria, genitourinary infection
- Hypotension
- Renal Impairment: Monitor renal function

[Link to FDA Approval](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204629s000lbl.pdf) [Accessed May 28, 2015]

SGLT2 Inhibitors Comparison

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>100 mg daily, then 300 mg daily before the first meal of the day</td>
<td>5 mg daily, then 10 mg daily in morning with or without food</td>
<td>10 mg daily, then 25 mg daily in morning with or without food</td>
</tr>
<tr>
<td>Monotherapy A1c lowering (%)</td>
<td>0.77-1.25</td>
<td>0.82-1.58</td>
<td>0.7-0.8</td>
</tr>
<tr>
<td>Comb therapy A1c lowering (%)</td>
<td>0.61-2</td>
<td>0.6-2</td>
<td>0.87-1.27</td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>2.4 – 3.3</td>
<td>2.8 – 3.6</td>
<td>1.4 – 2.3</td>
</tr>
<tr>
<td>Systolic BP lowering (mmHg)</td>
<td>3.5-6</td>
<td>3.1 – 4.5</td>
<td>3.2 – 5.2</td>
</tr>
</tbody>
</table>

Patient Vignette – SGLT2 Inhibitor New Rx

TPA Annual Meeting
Woodlawn, TX

<table>
<thead>
<tr>
<th>Name</th>
<th>BB</th>
<th>Address</th>
<th>22 Texan Rd</th>
<th>Date</th>
<th>7/10/15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invokana 100 mg</td>
<td>Sig: one tablet po qam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refills</td>
<td>K. Cauthon_____________</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense as written</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. Cauthon, PharmD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Audience poll questions
- How long will it take before the patient sees the effect on blood sugars?
- What adverse effects do you counsel the patient about?
- How should the patient try to prevent and manage the adverse effects?
SGLT2 Inhibitors Risk of Infection

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vs. placebo</td>
<td>vs. placebo</td>
<td>vs. placebo</td>
</tr>
<tr>
<td>Genital mycotic</td>
<td>Females: 10.4-11.4% vs 3.2%</td>
<td>Females: 6.9-8.4% vs 1.5%</td>
<td>Females: 5.4-6.4% vs 1.5%</td>
</tr>
<tr>
<td>infection</td>
<td>Males: 3.7-4.2% vs 0.6%</td>
<td>Males: 2.7-2.8% vs 0.3%</td>
<td>Males: 1.6 -3.1% vs 0.4%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>4.3-5.9% vs 4.0%</td>
<td>4.3-5.7% vs 3.7%</td>
<td>7.6-8.3% vs 7.6%</td>
</tr>
<tr>
<td>infections</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SGLT2 Inhibitors ADRs & Counseling

- Genital mycotic infections and UTIs generally present within first 24 weeks of therapy
  - Usually of mild to moderate intensity
  - Respond to standard treatments
  - Led to few cases of drug discontinuation in clinical trials
- More common in women and uncircumcised men with history of infection and higher BMI
  - Females at increased risk: Premenopausal
  - Males at increased risk: Longer duration of diabetes
  - No difference seen in baseline A1c

SGLT2 Inhibitors ADRs & Counseling

- Symptoms
  - Females: vaginal odor, cottage cheese discharge, vaginal itching
  - Males: redness, itching, rash, pain, swelling of penis, foul smell
- Prevention
  - Hygiene practices and clothing choices
- Treatment mycotic infections
  - OTC miconazole and clotrimazole have been effective

SGLT2 Inhibitors and Risk of DKA

- FDA warning on 5-15-2015
  - Euglycemic
  - Triggering factors included
    - acute illness (urinary tract infection, urosepsis, gastroenteritis, influenza, or trauma)
    - reduced caloric or fluid intake
    - reduced insulin dose
- Case summary identified DKA in patients with type 1 and 2 diabetes
- Evaluate patients with N/V and malaise for urine and/or serum ketones

SGLT2 Inhibitors Summary

- Modest efficacy
- Low risk of hypoglycemia
- Weight loss
- Oral medication
- Can be used at any stage of type 2 diabetes
- Lowers blood pressure
- Less efficacious than insulin and GLP-1 RAs
- UTI and genital fungal infection ADRs
- High cost
- Not effective in CKD stage 3b – stage 5
- No data on prevention of macro- or microvascular complications

Conclusion

GLP-1 RAs and SGLT2 inhibitors are effective at lowering blood glucose but

"Drugs don't work in patients who don't take them" -C. Everett Koop, MD
Conclusion

- Predictors of non-adherence to diabetes medications
  - Fear of treatment adverse effects
  - Weight gain and hypoglycemia
  - Increased risk of heart attack
  - Persistent versus short term adverse effects
  - Needle anxiety
  - Complexity of the medication regimen
  - Cost
  - Low levels of patient knowledge about diabetes
- Treatment plan decision includes discussion with patient on medication efficacy, adverse effects, dosing regimen, and costs

References:
- Diabetes Care 2009; 32(12):2243-2245
- Diabetes Care 2011; 34(1):193-203
- Diabetes Res Clin Pract 2010; 87(2):204-210
- Diabetes Obes Metab 2008; 10(1):25-32
- Am J Manag Care 2012; 18:S49-S54