Systemic Agents in the Treatment of Metabolic Disease: New Twists on an Old Problem

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Disclosures: Tracy Offerdahl

- Dr. Offerdahl has the following financial disclosure:
  - Boiron: honorarium, webinar/speaker

- Has not received any assistance from any commercial interest in the development of this course
Disclosures: Greg Caldwell

Dr. Caldwell has the following financial disclosures:

- Shire: Honorarium, Speaker; Allergan: Honorarium, Advisory Board, Speaker; Optovu: Honorarium, Speaker; BioTissue: Honorarium, Speaker, Booth Insertion; Envolve: Honorarium, Consultant, PA Medical Director; Alcon: Honorarium, Speaker; Aerie: Honorarium, Speaker

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Diabetes Mellitus

- **Type 1 DM**
  - pancreatic beta cells are destroyed = subsequent severe or absolute lack of insulin

- **Type 2 DM**
  - insulin resistance in tissue (circulating insulin concentrations increase as compensation, but is still not able to overcome the resistance, so blood glucose rises)
  - lean patients – primary defect occurs in the beta cells
  - overweight patients (majority of people) - primary defect is impairment of the target cells
Metabolic Syndrome (formerly Syndrome X) – quoted from the American Heart Association Website (http://www.americanheart.org/presenter)

“The metabolic syndrome is characterized by a group of metabolic risk factors in one person. They include:

* Abdominal obesity (excessive fat tissue in and around the abdomen)

* Atherogenic dyslipidemia (blood fat disorders — high triglycerides, low HDL cholesterol and high LDL cholesterol— that foster plaque buildups in artery walls)

* Elevated blood pressure

* Insulin resistance or glucose intolerance (the body can’t properly use insulin or blood sugar)
Interesting Perspective...

- Type 1.5 diabetes?
  - Has overlap of diagnostic markers with T1DM & T2DM

- Homeostasis: Medical versus “Self”
  - Medical perspective: we think about potential problems NOW, as well as what may occur in the future. We PLAN!
  - “Self” (ie. the human body): ONLY interested in NOW. The body wants to maintain homeostasis at all costs!

- Much of this is what happens with treatments associated with metabolic disease.
Hemoglobin A1C

- **A1C ≤ 6.5%**
  - More “stable” patients
  - For patients without comorbidities
  - Low hypoglycemia risk

- **A1C > 6.5%**
  - Less “stable” patients
  - For patients with comorbidities
  - High hypoglycemia risk
Biguanide

Metformin (Glucophage)
- Initial Drug of Choice / Cornerstone of Therapy

- Mechanism of Action (MOA)
  - Inhibits hepatic and renal gluconeogenesis
  - Stimulation of glucose uptake in peripheral tissues
  - Inhibits absorption of glucose from the GI tract
Metformin

Benefits:

- Does NOT cause weight gain; weight loss?
- Does NOT cause hypoglycemia
- Decreases TC, LDL, and TG; Increases HDL
- Decreases risk of macro-vascular complications
Metformin

- Effective in preventing new onset of T2DM

- Side Effects
  - GI disturbances
  - Lowers vitamin $B_{12}$ levels
  - Lactic acidosis
Sulfonylureas

Agents:

2nd generation agents (preferred)
glyburide (DiaBeta, Micronase)
glyburide, micronized (Glynase PresTab)
glipizide (Glucotrol, Glucotrol XL)
glimepiride (Amaryl)
Sulfonylureas

MOA: stimulate release of insulin from functioning pancreatic beta cells

Side effects:
- hypoglycemia - higher incidence with glyburide
  All can cause hypoglycemia
- Weight gain
## Insulin Preparations


<table>
<thead>
<tr>
<th>Action</th>
<th>Insulin Name</th>
<th>Onset</th>
<th>Peak</th>
<th>Effective Duration</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bolus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid Acting</td>
<td>Aspart (Novolog)</td>
<td>5 - 15 min</td>
<td>30 - 90 min</td>
<td>&lt; 5 hrs</td>
<td><strong>Bolus</strong> insulin lowers after-meal glucose. Post meal BG reflects efficacy.</td>
</tr>
<tr>
<td>Analogs</td>
<td>Lispro (Humalog)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Glulisine (Apidra)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Acting</td>
<td>Regular</td>
<td>30 - 60 min</td>
<td>2 - 3 hrs</td>
<td>5 - 8 hrs</td>
<td><strong>Basal</strong> insulin controls BG between meals and nighttime. Fasting BG reflects</td>
</tr>
<tr>
<td></td>
<td>Concentrated Regular Insulin 500 units/mL reg insulin “U-500”</td>
<td>30 - 60 min</td>
<td>2 - 3 hrs</td>
<td>Up to 24 hrs</td>
<td>efficacy.</td>
</tr>
<tr>
<td><strong>Basal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>NPH</td>
<td>2 - 4 hrs</td>
<td>4 - 10 hrs</td>
<td>10 - 16 hrs</td>
<td><strong>Side effects:</strong> hypoglycemia, weight gain.</td>
</tr>
<tr>
<td><strong>Long Acting</strong></td>
<td>Detemir (Levemir)</td>
<td>3 - 8 hrs</td>
<td>No peak</td>
<td>6 - 24 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glargine (Lantus)</td>
<td>2 - 4 hrs</td>
<td>No peak</td>
<td>20 - 24 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concentrated Glargine (Toujeo) 300 units/mL in 1.5 mL Pen</td>
<td>6 hrs</td>
<td>No Peak</td>
<td>24 hrs</td>
<td><strong>Typical dosing</strong> range: 0.5-1.0 units/kg body wt/day. Discard opened insulin</td>
</tr>
<tr>
<td><strong>Basal</strong> +</td>
<td>Combo of NPH + Reg 70/30 = 70% NPH + 30% Reg</td>
<td>30 - 60 min</td>
<td>Dual peaks</td>
<td>10 - 16 hrs</td>
<td>vials after 28 days.</td>
</tr>
<tr>
<td><strong>Bolus</strong></td>
<td>Intermediate + rapid</td>
<td>5 - 15 min</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Novolog® Mix - 70/30 Humalog® Mix - 75/25 or 50/50</td>
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</tr>
</tbody>
</table>

*Insulin action times can vary with each injection, time periods listed here are general guidelines only; please consult prescribing information for details.*

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Insulin Preparations

- Drug therapy of choice for all patients with type 1 DM and those with type 2 DM who cannot control their condition with diet, exercise, and OADs.

MOA: regulates glucose metabolism in the muscle and other tissues

Semisynthetic ("human") – identical amino acid composition to endogenous human insulin

SEs: weight gain and hypoglycemia
GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins

- GLP-1 secreted upon ingestion of food
- Pancreatic beta cells: Enhanced glucose dependent insulin secretion
- Pancreatic alpha cells: ↓ Postprandial glucagon secretion
- Liver: Reduced hepatic glucose output
- Stomach: Helps regulates gastric emptying
- PPG control
  - Promotes satiety and reduces appetite

(GLP-1) Agonists

Exenatide injection (Byetta) – SQ injection right before meal; Long-acting version (once/week) = Bydureon

Liraglutide injection (Victoza)
   Saxenda brand name = weight loss only

Abiglutide (Tanzeum)
Dulaglutide (Trulicity)
Semaglutide (Ozempic)
Lixisenatide (Adlyxin)
(GLP-1) Agonists

Mechanism of Action

- Stimulate the GLP-1 receptor – this receptor enhances glucose-dependent insulin secretion by the pancreatic beta-cell (in response to high blood glucose levels), suppresses secretion of glucagon after meals, and slows gastric emptying; some appetite suppression and weight loss.

Indications And Usage

- indicated as adjunctive therapy to improve glycemic control in adult patients with type 2 diabetes mellitus who are taking other oral antidiabetic agents.
(GLP-1) Agonists

**Side Effects:** In animal studies, liraglutide has been shown to cause dose-dependent and treatment duration dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures.

- Pancreatitis
DPP4 Inhibitors (dipeptidyl-peptidase-4)

Sitagliptin (Januvia) tablets
Saxagliptin (Onglyza) tablets
Linagliptin (Tradjenta) tablets

Mechanism of Action
• inhibits the breakdown of glucagon-like peptide-1 (incretin); incretin stimulates insulin release from the beta cells in the pancreas (in response to food) and inhibits the liver’s production of glucose = promotes insulin activity and inhibits gluconeogenesis by preventing incretin inactivation
DPP4- Inhibitors

Mechanism of Action of DPP-4 Inhibitors

- Ingestion of food
  - Release of active incretins: GLP-1 and GIP
  - Pancreas:
    - Glucose dependent
    - Insulin:
      - Glucose uptake by peripheral tissue
    - Hepatic glucose production
      - Fasting and Postprandial Glucose

- GLP-1 = glucagon-like peptide-1
- GIP = glucose-dependent insulino tropic polypeptide

Alogliptin, Linagliptin, Saxagliptin, Sitagliptin (DPP-4 inhibitors)
DPP4 Inhibitors (dipeptidyl-peptidase-4)

INDICATIONS AND USAGE

- indicated as adjunctive therapy to improve glycemic control in adult patients with type 2 diabetes mellitus who are taking other oral antidiabetic agents.

SEs:
- very low incidence of hypoglycemia
- Acute pancreatitis
- Hypersensitivity reactions
- Weight loss?
Sodium-Glucose Co-Transporter 2 (SGLT2 Inhibitor)

Canagliflozin (Invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)

• **MOA:** Inhibition of the SGLT2 = reduced absorption of filtered glucose, lowering of renal threshold for glucose, and increasing of urinary excretion of glucose
Sodium-Glucose Co-Transporter 2 (SGLT2 Inhibitor)

• Approved as an adjunctive to metformin, after trying typical 2\textsuperscript{nd}-line treatments

• **SEs:** genital fungal infections, UTIs, increased urination, thirst, diabetic ketoacidosis
SGLT2-I Advantages

- Low risk of hypoglycemia
- Weight loss
- Oral medication
- Lowers BP
- Able to use at any stage of T2DM
Basic treatment summary...

- Basic consensus on treatment:
  - T1DM – must start insulin within hours to days of diagnosis
  - T1.5DM – usually start insulin within months to years of diagnosis
  - T2DM – may not necessarily require insulin, although often used

- Gestational Diabetes – may use metformin and/or traditional standard of insulin
Hypertension

- Very common comorbid condition ("compelling indication")

  - "JNC 8"
    - 8th Joint National Committee – prevention and treatment of hypertension
    - 2014

- Pretty big changes
**Basic Principles of Treatment**: (from the JNC VIII)

* In persons > 60 years of age, systolic blood pressure (SBP) ≥150 mmHg or diastolic blood pressure (DBP) ≥90 mmHg should be treated with meds.
  
  - Goal should be SBP <150 mmHg and DBP <90 mmHg.

* In persons < 60 years of age, systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg should be treated with meds.
  
  - Goal should be SBP <140 mmHg and DBP <90 mmHg.
Hyperlipidemia

- Common comorbidity in patients with diabetes
  - The “American triumvirate”
    - DM/metabolic syndrome, hypertension, hypercholesterolemia

- Statins are the only group of drugs that consistently decrease mortality in patients with high cholesterol!
Proteinuria

- Protein in the urine is a harbinger of doom

- Chronic renal failure/hemodialysis
- Prevention is the key!
- Maintain normal blood pressure and blood glucose levels
Inflammation as a risk factor…

- CRP (C-reactive protein)
  - Marker for inflammation
  - Inflammation = increase in plaque formation
  - RA, celiac disease, DM, heart dz, food intolerances, etc.
Smoking cessation

Where do I start?
- There is NOTHING good about cigarette smoke
- Micro- and macro-vascular complications
- Increase in BP
- 2nd hand smoke is almost as bad
Vitamins...

- Vitamin D

- Sun may NOT be enough
- Two vitamins better absorbed through supplementation rather than from dietary sources: Vitamin D and folic acid!
- Get vitamin and vitamin B-12 levels checked!
  - Don’t forget that B-12 will likely be low in patients on metformin (and in those taking proton-pump inhibitors like Prilosec, Nexium, etc.)
Hyperhomocysteinemia

Patients with diabetes mellitus are prone to cardiovascular disease and risk factors presumably unrelated to diabetes, such as hyperhomocysteinemia, which may be involved in the atherothrombotic process in these subjects.

Hyperhomocysteinemia has been associated with microalbuminuria and retinopathy in type 1 and type 2 diabetes.

In patients with type 2 diabetes, plasma homocysteine concentration has also been shown to be related to macrovascular disease and death. This relation seems to be stronger in diabetics than in subjects without diabetes.
The underlying pathophysiological mechanism of this increased vascular risk remains unexplained but may relate to worsening of endothelial dysfunction or structural vessel properties.

Because homocysteine and diabetes have an apparent synergistic negative vascular effect, patients with diabetes are good candidates for screening and treatment with folic acid until the results of ongoing clinical trials are available.
Diabetic Neuropathy

- Peripheral vessels are largely affected
  - Decrease in pain sensitivity in feet and lower legs
  - Pain and amputation

- What about the gut??
  - Decrease in food and drug absorption
Aspirin Use in Diabetes

• Aspirin use in diabetic patients is not associated with an increased risk of hemorrhage or progression of retinopathy or macular edema !!!

• Aspirin use may actually slow the progression of diabetic retinopathy ???

• Aspirin Therapy (enteric coated 81-325 mg/day): ADA recommendations
  
  • Family History of coronary heart disease
  • Cigarette smoking
  • Hypertension
  • Obesity
  • Albuminuria
  • Elevated lipid levels
  • Age > 30 years

People with aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are not candidates for aspirin therapy.
Hyperlipidemia – Basic Treatment

- **LDL** – “bad cholesterol”
  - Drugs are usually the best choice
- **HDL** – “good cholesterol”
  - Protective
  - Exercise is the best treatment
- **Triglycerides**
  - Dietary changes and fish oil
The new guidelines recommend a statin for:

Anyone who has cardiovascular disease, including angina (chest pain with exercise or stress), a previous heart attack or stroke, or other related conditions; EVEN DM!

Anyone with a very high level of harmful LDL cholesterol (generally an LDL above greater than 190 milligrams per deciliter of blood [mg/dL])

Anyone with diabetes between the ages of 40 and 75 years

 Anyone with a greater than 7.5% chance of having a heart attack or stroke or developing other form of cardiovascular disease in the next 10 years (AKA “Framingham Index/Score”).
## Statin Treatment Table

<table>
<thead>
<tr>
<th>Age</th>
<th>No Risk Factors</th>
<th>ASCVD Risk Factors</th>
<th>ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 years old</td>
<td>No treatment</td>
<td>Mod/High Intensity dose</td>
<td>High Intensity dose</td>
</tr>
<tr>
<td>40-75 years old</td>
<td>Mod/High Intensity dose</td>
<td>High Intensity dose</td>
<td>High Intensity dose</td>
</tr>
<tr>
<td>&gt; 75 years old</td>
<td>Mod/High Intensity dose</td>
<td>Mod/High Intensity dose</td>
<td>High Intensity dose</td>
</tr>
</tbody>
</table>

**ASCVD** = Atherosclerotic CardioVascular Disease  
Risk Factors: LDL ≥100mg/dL, hypertension, smoking, obesity, family hx of premature ASCVD

**Moderate-Intensity Doses:**  
- Rosuvastatin (Crestor) 5-10 mg  
- Atorvastatin (Lipitor) 10-20 mg  
- Simvastatin (Zocor) 20-40 mg  
- Pravastatin (Pravachol) 40-80 mg  
- Lovastatin (Mevacor) 40 mg  
- Fluvastatin (Lescol) 80 mg  
- Pitavastatin (Livalo) 2-4 mg

**High-Intensity Doses:**  
- Rosuvastatin (Crestor) 20-40 mg  
- Atorvastatin (Lipitor) 40-80 mg
Statins

**MOA:** HMG-CoA reductase is the enzyme responsible for the conversion of HMG-CoA to mevalonate, the early rate-limiting step in cholesterol synthesis = decrease LDL, decrease TGs, increase HDL

***ONLY AGENTS PROVEN TO LOWER THE RISK OF CV EVENTS in patients with high cholesterol."
Statins

Side effects:

- < 0.1 % myopathy/myalgia/myositis/rhabdomyolysis
  - Including ocular muscles!!
- DM (FDA added warning of increased blood sugar and HgA1C to statin labeling)?
- Memory loss
Niacin

Niaspan

- Only other agent that decreases LDL, TG, and increases HDL
- Not proven to decrease death
- SEs:
  - Cutaneous flushing
  - GI problems (avoid in GERD or PUD)
  - Hyperuricemia
  - Loss of glycemic control in DM
Fibric Acid Derivatives

- Gemfibrozil (Lopid)
- Fenofibrate (Tricor)
- Fenofibric acid (Trilipix)

- Used for high triglycerides only
- No decrease in mortality
Fish Oil

- Lovaza (prescription product)
  - DHA and EPA
  - Used to treat high triglycerides only

- Many other benefits!
  - Inflammatory diseases

- SEs:
  - Fishy taste
  - Increased bleeding time
Types of fish oil...

- **Triglyceride form**
  - More “natural” and better tolerated
  - Less likely to cause fishy aftertaste

- **Ethyl ester form**
  - Cheaper to make
  - More likely to cause burps and fishy aftertaste
Interesting future for fish oil…

- Pro-resolving fish oil
  - SPM Active
  - A very pure formulation
  - Scavengers of inflammatory mediators in the blood stream
  - Good for any type of chronic, inflammatory conditions!

- Rheumatoid arthritis, Poly-myalgia rheumatica, macular inflammation?
Specialized Pro-Resolving Mediators (SPM)

α-linolenic acid

- Essential fatty acids
  - Must be acquired through diet

- Inefficient multi-step conversion

EPA

- Conditionally essential fatty acids support:
  - Cell membrane integrity
  - Brain and eye health
  - Healthy triglycerides levels
  - Heart health

DHA

- Inefficient Conversion to meet needs in the face of inflammation, particularly in an already compromised host

- Multi-step process, and production affected by certain health conditions*

- Unique role in supporting the resolution of the immune response and inflammation – necessary for healthy aging and active living
  - Neutrophil activity is curtailed
  - Macrophages remove dead neutrophils, bacteria and debris
  - Tissue is remodeled
  - Return to homeostasis (cells’ previous normal conditions)

SPMs

Cholesterol Absorption Inhibitor

- Ezetimibe (Zetia)
  - Lowers LDL only
  - No mortality data
  - Added to statins

- Ezetimibe + Simvastatin (Vytorin)
PCSK9 Inhibitors

**Agents:** Alirocumab (Praluent) & Evolocumab (Repatha)

**MOA:** PCSK9 (proprotein convertase subtilisin kexin type 9) is an enzyme – binds to LDL cholesterol receptors

- Basically, the PCSK9 receptor inhibitors increase the number of receptors that are available to bind to and clear LDL cholesterol = increased LDL cholesterol clearance and lower LDL plasma levels
  - = consistent decrease in LDL cholesterol by 60%
PCSK9 Inhibitors

**Dosing:**
- SC injection; once or twice per month
- $10,000 per year (average estimate)

**Who might benefit:** Certain types of familial hyperlipidemia; statin-intolerant patients; poor response to statins; contraindications to statins.
PCSK9 Inhibitors

SEs:
Arthralgias
Myalgia (with increase in CPK levels)

Neurocognitive impairment (amnesia, cognitive impairment, confusion)

Ophthalmologic events

Impairment of glucose homeostasis (b/c PCSK9 enzyme is also found on pancreatic islet cells) = increased risk of developing DM
Thank You!
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