UPDATE ON OBESITY/DIABETES/LIPIDS

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CLINICAL CASE 1

- Jose 51 YO LA Male
- During physical Exam was told needed to loose weight
- BMI 36
- BP 150/95
- LDL 176
- TGS 350
- A1c 6.2
MEDICAL COMPLICATIONS OF OBESITY

Pulmonary disease
- abnormal function
- obstructive sleep apnea
- hypoventilation syndrome

Nonalcoholic fatty liver disease
- steatohepatitis
- cirrhosis

Gall bladder disease

Gynecologic abnormalities
- abnormal menses
- infertility
- polycystic ovarian syndrome

Osteoarthritis

Skin

Gout

Idiopathic intracranial hypertension

Stroke

Cataracts

Coronary heart disease

Diabetes

Dyslipidemia

Hypertension

Gastrointestinal disease
- breast, uterus, cervix
- colon, esophagus, pancreas
- kidney, prostate

Phlebitis
- venous stasis
**RELATIONSHIP BETWEEN BMI AND RISK OF T2DM**

BMI = body mass index.


**WEIGHT LOSS REDUCES CARDIOMETABOLIC RISK FACTORS IN PATIENTS WITH TYPE 2 DIABETES**

Randomized, controlled trial; n = 5145; Patients with type 2 diabetes, age >18 y; Mean ± SE.

Intensified lifestyle intervention (n = 2496) vs. diabetes support and education (n = 2463) therapy; *P<0.001 between groups.

REGULATION OF BODY WEIGHT

- **Genes** confer the potential for obesity

- **Environment** determines whether the potential is realized, and to what extent

OBESITY CONCEPTUAL FRAMEWORK

- Obesity directly and indirectly promotes, and/or causes, adverse health consequences.
- Current evidence indicates that obesity must be treated as a chronic, relapsing disease.


## PHENTYLAMINES

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>TRADE NAME</th>
<th>DOSE</th>
<th>DAILY DOSAGE</th>
<th>SERUM HALF LIFE</th>
<th>DEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHENTERMINE</td>
<td>ADIPEX FASTIN IONOMIN</td>
<td>15mg, 30mg, 37.5mg</td>
<td>15mg-37.5mg</td>
<td>19 – 24 hr</td>
<td>IV</td>
</tr>
<tr>
<td>DIETHYLPROPION</td>
<td>TENUATE TEPANIL</td>
<td>25MG 75MG</td>
<td>25MG TID 75MG TID</td>
<td>4 – 6 HR</td>
<td>IV</td>
</tr>
<tr>
<td>PHENDIMETRAZINE</td>
<td>BONTRIL</td>
<td>35MG</td>
<td>35MG TID</td>
<td>2-10HR</td>
<td>III</td>
</tr>
</tbody>
</table>

## ORLISTAT

- Approved for long term treatment
- Alters fat digestion by inhibiting pancreatic lipases
- Fecal fat is increased on a dose dependent fashion
- Available in 120mg capsules taken 3 times daily
Lorcaserin

- **Mechanism of Action**
  - Selective Serotonin Agonist
  - 5-HT$_{2c}$ Receptors in the central nervous system
  - Similar to the action of fenfluramine of Fen-Phen
    - Unlike fenfluramine, lorcaserin presumably does not stimulate the 5-HT$_{2B}$ receptor on heart valves.
    - Shown to reduce hunger and increase satiety.

![Graph showing weight loss at 1 year](image)

**A Weight Loss at 1 Yr**

- Lorcaserin (N=1538) vs Placebo (N=1499)

  - ≥5% Weight Loss: Lorcaserin vs Placebo: P<0.001
  - ≥10% Weight Loss: Lorcaserin vs Placebo: P<0.001

NEJM. 363; 3 July 15, 2010
Combination Therapy (phentermine/topiramate ER)

- PHEN/TPM ER Low (3.75/23) Starting dose
- PHEN/TPM ER Mid (7.5/46) Recommended dose
- PHEN/TPM ER Top (15/92) For patients not achieving weight-loss goal
**Phentermine/Topiramate**

- **Mechanism of Action**
  - Phentermine
    - Sympathomimetic
    - Anorectic effect likely mediated by catecholamine release in the hypothalamus.
  - Topiramate
    - Mechanism of Action for weight loss unknown
    - GABAergic and Carbonic Anhydrase Inhibitor

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**EQUIP: Weight Loss Over Time**

*Data from patients that completed 56 weeks on treatment.*

*Statistically greater number of patients completing study on PHEN/TPM ER vs placebo, P<0.0001.*
CONTRAVE MECHANISM OF ACTION

Nonclinical studies suggest naltrexone and bupropion have effects on two areas of the brain involved in regulation of food intake:

- Hypothalamus (appetite regulatory centers)
- Mesolimbic dopamine circuit (reward system)

CONTRAVE CORI

Greenway et al. Lancet 2010;376:595-605
CLINICAL CASE 1

- Jose 51 yo LA Male
- During physical Exam was told needed to loose weight
- BMI 36
- BP 150/95
- LDL 176
- A1c 6.2
**PREDIABETES TREATMENT ALGORITHM**

- Weight-loss agents orlistat, lorcaserin, and phentermine/topiramate can prevent progression to T2DM
  - Improve BP, triglycerides, and insulin sensitivity
- Metformin and acarbose can reduce progression to T2DM by 25% - 30%
  - Use for prediabetes is off-label
  - Both are safe, confer CVD risk benefit; metformin is well tolerated
- TZDs prevented progression to T2DM in 60% - 75% of patients in clinical trials
  - Associated with adverse outcomes
- GLP-1 receptor agonists may be as effective as TZDs
  - Promote weight loss, but inadequate safety data
- TZDs and GLP-1 RAs reserved for patients not responding to conventional therapies or at highest risk for T2DM

T2DM = type 2 diabetes mellitus
BP = blood pressure
CVD = cardiovascular disease
TZD = thiazolidinedione
GLP-1 RA = glucagon-like peptide-1 receptor agonist

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**THE TICKING CLOCK**

Increased risk for both microvascular and macrovascular disease begins early in the prediabetic state

- Insulin resistance is already present in patients with NGT who later develop T2DM
- Patients with prediabetes already have high insulin resistance and significantly decreased beta-cell function
- Both diabetic retinopathy, peripheral neuropathy, and nephropathy occur in patients with prediabetes
- Patients with prediabetes have a 2 to 3-fold increase in CHD risk, similar to patients with diabetes

CHD = coronary heart disease; NGT = normal glucose tolerance; T2DM = type 2 diabetes mellitus

MAIN PATHOPHYSIOLOGICAL DEFECTS IN T2DM
"THE OMINOUS OCTET"

- Islet β-cell
  - Impaired Insulin Secretion
- Islet α-cell
  - Increased Glucagon Secretion
  - Increased Glucagon Reabsorption
- Increased HGP
- Increased Lipolysis
- Increased Glucose Uptake
- Decreased Glucose Uptake
- Decreased Insulin Effect
- Decreased Incretin Effect


GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

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

MONOTHERAPY**
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGI
- SU/GLIN

DUAL THERAPY**
- MET or other 1st-line agent + other 1st-line agent
- MET or other 1st-line agent + TZD
- MET or other 1st-line agent + DPP-4i
- MET or other 1st-line agent + GLP-1 RA
- MET or other 1st-line agent + AGI
- MET or other 1st-line agent + SU/GLIN

TRIPLE THERAPY**
- MET or other 1st-line agent + other 1st-line agent + other 1st-line agent
- MET or other 1st-line agent + other 1st-line agent + TZD
- MET or other 1st-line agent + other 1st-line agent + DPP-4i
- MET or other 1st-line agent + other 1st-line agent + GLP-1 RA
- MET or other 1st-line agent + other 1st-line agent + AGI
- MET or other 1st-line agent + other 1st-line agent + SU/GLIN

* Order of medication represents a suggested hierarchy of usage: length of time effect, strength of recommendation

LEGEND
- Gray shade indicates insulin analogs that are more insulin-like
- Black line represents core oral agents
- Red line represents add-on or intensify insulin
- Yellow lines indicate potential options
- Blue line represents potential options

PROGRESSION OF DISEASE

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UKPDS: BENEFITS OF GLYCEMIC CONTROL

Every 1% decrease in A1C led to significant reductions in diabetes-related complications

Decrease was statistically significant for all comparisons shown

## EFFECT OF GLUCOSE-LOWERING DRUGS ON PATIENT WEIGHT

<table>
<thead>
<tr>
<th>Therapeutic Options</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea(^1,2)</td>
<td>↑</td>
</tr>
<tr>
<td>TZD(^3,4)</td>
<td>↑</td>
</tr>
<tr>
<td>Insulin(^5,6)</td>
<td>↑</td>
</tr>
<tr>
<td>Metformin(^7)</td>
<td>↔</td>
</tr>
<tr>
<td>DPP-4 inhibitor(^8)</td>
<td>↔</td>
</tr>
<tr>
<td>GLP-1 receptor agonist(^9)</td>
<td>↓</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors(^10)</td>
<td>↓</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium glucose co-transporter-2.

TZD = thiazolidinedione


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## Biguanides

**Metformin**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>↓ Insulin sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hepatic glucose production</td>
</tr>
<tr>
<td></td>
<td>FPG more than PPG</td>
</tr>
<tr>
<td>Efficacy</td>
<td>↓ A1C 1%-2%</td>
</tr>
<tr>
<td>Advantages</td>
<td>No weight gain or hypoglycemia, potential weight loss</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>GI side effects</td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis (rare)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Renal disease; CHF</td>
</tr>
</tbody>
</table>

Combinations available with SU, TZD, repaglinide, and DPP-4 inhibitors

A1C = glycated hemoglobin; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GI = gastrointestinal; PPG = post-prandial glucose; SU = sulfonylurea; TZD = thiazolidinedione

THE INCRETIN EFFECT

Control Subjects (n=8)

Incretin Effect

Type 2 Diabetes (n=14)

GLP-1 Modulates Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food

Brain promotes satiety and reduces appetite

Alpha cells: Glucose-dependent postprandial glucagon secretion

Beta cells: Enhances glucose-dependent insulin secretion

Liver: Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

Data from Nauck MA, et al. Diabetologia. 1996;39:1546-1553; Data from Drucker DJ. Diabetes. 1998;47:159-169

**STRATEGIES FOR ENHANCING GLP-1 ACTION**

- **GLP-1 receptor agonists** (injectable therapies)
  - Exenatide
  - Liraglutide
  - Albiglutide
  - Dulaglutide

- **DPP-4 inhibitors** (oral therapies)
  - Inhibit actions of DPP-4
  - Sitagliptin, Saxagliptin, Linagliptin, Alogliptin

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### Marketed GLP-1 RAs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Exenatide BID</th>
<th>Liraglutide</th>
<th>Exenatide ER</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Byetta</td>
<td>Victoza</td>
<td>Bydureon</td>
<td>Tanzeum (U.S.)</td>
<td>Eperzan (Europe)</td>
</tr>
<tr>
<td>Description</td>
<td>Synthetic exendin-4, a peptide identified in H. suspectum that activates the GLP-1 R and is resistant to DPP-4 degradation</td>
<td>GLP-1 modified* to be resistant to DPP-4 degradation</td>
<td>Exenatide contained in a hydrolyzable polymer microspheres for extended release</td>
<td>An albumin fusion protein made of 2 copies of modified human GLP-1</td>
<td>A fusion protein with 2 disulfide-linked human GLP-1 analog sequence chains, connected by a small peptide linker to human immunoglobulin G4 (IgG4)</td>
</tr>
<tr>
<td>Administration</td>
<td>Subcutaneous injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>2.4 hours</td>
<td>13 hours</td>
<td>&gt; 1 week</td>
<td>5 days</td>
<td>5 days</td>
</tr>
<tr>
<td>Dosing</td>
<td>2 × daily, before meals</td>
<td>1 × daily, any time</td>
<td>1 × weekly</td>
<td>1 × weekly</td>
<td>1 × weekly</td>
</tr>
</tbody>
</table>

* Amino acid substitution and addition of acyl chain.

## Sulfonylureas and Glinides

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Insulin secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Moderate</td>
</tr>
<tr>
<td>Advantages</td>
<td>Strong short term efficacy</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Weight gain, hypoglycemia, tend to lose efficacy after several years</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Avoid in severe hepatic and renal impairment</td>
</tr>
</tbody>
</table>

**Combinations available with metformin, TZD**

FPG = fasting plasma glucose; PPG = post-prandial glucose; TZD = thiazolidinedione

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- 
- 
- 

## Thiazolidinediones

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Insulin sensitivity, especially at muscle, lowers both FPG and PPG, but effect may be delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Moderate (↓ A1C 1.0%-1.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>No hypoglycemia, no reliance on renal excretion</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Fluid retention, edema, heart failure, weight gain, slow onset of action, bone fractures, macular edema, osteoporosis, anemia, and bladder cancer</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Class III or IV CHF or hepatic impairment w/ALT &gt;2.5 times upper normal limits</td>
</tr>
</tbody>
</table>

**Combinations available with metformin and sulfonylurea**

A1C = glycated hemoglobin; ALT = alanine aminotransferase; CHF = congestive heart failure; FPG = fasting plasma glucose; PPG = post-prandial glucose

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## Alpha-Glucosidase Inhibitors

**Acarbose, Miglitol**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>↓ Rate of gut polysaccharide breakdown, thereby slowing absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest (↓ A1C 0.5%-1.0%), PPG lowering</td>
</tr>
<tr>
<td>Advantages</td>
<td>Weight-neutral, non-systemic drug, targets post-prandial glucose</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Bloating, flatulence, diarrhea – ↓ w/slow titration, frequent dosing</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Severe renal impairment, diabetic ketoacidosis, malabsorption, obstruction, inflammatory bowel, or conditions aggravated by gas production</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; PPG = post-prandial glucose


## Dopamine Receptor Agonist

**Bromocriptine**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Exact mechanism of action unclear, believed to reduce sympathetic tone, inflammation, and insulin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest (↓ A1C 0.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>May decrease cardiovascular risk</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Hypotension, Syncope, Hypoglycemia, Nausea</td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of psychosis or during breastfeeding. Use caution with renal or hepatic impairment.</td>
</tr>
</tbody>
</table>

### Bile Acid Sequestrants

**Mechanism**

Raises cholecystokinin which slows gastric emptying and post prandial glucose.

**Efficacy**

Modest (↓ A1C 0.5%)

**Advantages**

 LDL-C, weight neutral, no hypoglycemia, can complement statin treatment in lowering LDL and cardiac event risk.

**Disadvantages**

Constipation, nausea, dyspepsia, myalgia, pharyngitis, ↑ triglycerides, drug interactions

**Contraindications**

History of bowel obstruction, TGs > 500 mg/dL; history of hypertriglyceridemia-induced pancreatitis

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### CHARACTERISTICS OF DPP-4 INHIBITORS

**Alogliptin, Linagliptin, Saxagliptin, Sitagliptin**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Inhibit enzymatic degradation of GLP-1 and GIP; glucose-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Decrease A1C levels 0.6%–0.9%</td>
</tr>
<tr>
<td>Dosing</td>
<td>Once daily</td>
</tr>
<tr>
<td>Side effects</td>
<td>Headaches, nasopharyngitis</td>
</tr>
<tr>
<td>Main risk</td>
<td>Viral infection; long-term safety unknown</td>
</tr>
</tbody>
</table>

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*A1C = glycated hemoglobin; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride*


Mechanism
Inhibits sodium-glucose transport protein subtype 2 (SGLT2) which is responsible for at least 90% of glucose reabsorption in the kidney causing blood glucose is eliminated in the urine

Efficacy
Modest (Δ A1C 0.8-1.2%)

Advantages
Insulin-independent glucose reduction, Low risk of hypoglycemia, Weight loss (to 4% BW), Blood pressure-lowering

Disadvantages
Osmotic diuresis causing Polyuria and lightheadedness, Bacterial urinary tract infections (≈5%), Fungal genital infections (≈10%), Increased LDL cholesterol, Hyperkalemia (canagliflozin), Bladder cancer concerns (dapagliflozin)

Contraindications
History of genital fungal infections, caution in chronic kidney disease

SGLT2 Inhibitors
Canagliflozin, Dapagliflozin, Empagliflozin

AACE 2013 Dyslipidemia Management Algorithm

When Atherogenic Markers not at goal:

To Lower LDL-C:
Intensify statin and/or, add ezetimibe and/or colesvelam and/or niacin

To Lower Non-HDL-C, TG:
Intensify statin and/or Rx-grade omega-3 ethyl esters and/or fibrates and/or niacin

To Lower Apo B, LDL-P:
Intensify statin and/or add ezetimibe and/or colesvelam

Apo B = apolipoprotein B; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglyceride

**PROPROTEIN CONVERTASE SUBTILISIN-KEXITIN 9**

- PCSK9 is widely distributed in Liver, Intestine, kidneys and CNS
- Regulates plasma LDL-C levels through increased degradation of LDL receptor proteins
- Overexpression of PCSK9 results in increased circulating levels of LDL-C
- Single point mutations associated with increased proprotein convertase function may result in familial autosomal dominant hyperlipidemia and increased risk of early MI and stroke

*New Eng J Med 2011;365:2507-2518*

**PCSK9 INHIBITORS**

- Reduce LDL-C levels
- Have been shown to reduce Cardiovascular endpoints

*New Eng J Med 2015;372:1489-1499*
*New Eng J Med 2015;372:1500-1509*
# PCSK9 INHIBITORS

## Indications
- Adjunct to diet and maximally tolerated statin therapy in adults
- Heterozygous familial hypercholesterolemia
- Clinical atherosclerotic CV disease who require additional lowering of LDL-C

## Side effects
- Injection site reactions
- Myalgias
- Neurocognitive (confusion, impaired memory)

## Dosage
- **Alirocumab** (Praluent)
  - 75 mg/2 weeks or 150 mg/2 weeks
- **Evolocumab** (Repatha)
  - 140 mg/2 weeks or 420 mg/month

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## ALGORITHM FOR MANAGING SEVERE HYPERTRIGLYCERIDEMIA (SH)

### Acute management SH +/- pancreatitis
- Dietary measures:
  - NPO; I.V. fluids; Insulin, if diabetes
- Add Rx-grade Omega-3 fatty acids
- Add fibrates to OM-3 fatty acids
- Add niacin to fibrates and OM-3 fatty acids
- Consider medium chain TG
- If poorly responsive, apheresis (plasmapheresis) until TG <1000 mg/dL

### Chronic management SH
- Dietary measures:
  - Low carbohydrate, low-fat <20 g LC-FA/day, MCT, abstinence from alcohol

1. THANK YOU