Update on New Treatment Options for Weight Management

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Disclosure

• Consultant: Amgen, Boehringer-Ingelheim, Gelesis, Janssen Global Services, KVK Tech, Novo Nordisk, Phenomix, Roivant, Sunovion Pharmaceuticals
• Advisory Board: Novo Nordisk
• Speakers Bureau/Honorarium: Novo Nordisk

How Safe is a Weight Loss Medication: CardioVascular Outcome Trials

• Enroll 10,000 or more patients with known cardiovascular disease or diabetes with multiple risk factors for impending cardiovascular disease
• Randomize to the study drug or placebo and follow for 3 to 5 years
• Primary outcome is number of cardiovascular events in the medications group vs the placebo group
• This has to be completed for most weight loss medications as well as diabetic medications
Kaplan–Meier Plots of the Incidence of a Primary Outcome Event and Death from Any Cause, According to the Time from Randomization

Status of CardioVascular Outcome (CVOT) trials

<table>
<thead>
<tr>
<th>Weight loss medication</th>
<th>Status of CVOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorcaserin</td>
<td>Completed (2018)</td>
</tr>
<tr>
<td>Phentermine/Topiramate</td>
<td>Not completed</td>
</tr>
<tr>
<td>Naltrexone/Bupropion</td>
<td>2015 CVOT trial stopped prematurely*</td>
</tr>
</tbody>
</table>
| Liraglutide 3.0 mgs    | FDA allowed use of Liraglutide 1.8 mg data  
So felt to be CVOT safe and not required |

*Orexigen shared the CVOT data with over 100 individuals both within and outside the company (data leaked). When the FDA found out the company was told to continue the trial but must do a second CVOT trial. The CVOT interim data was released by the company to the public in a patent application and the executive committee of the study felt the study was unblinded And it was completely terminated. Medpage Today in collaboration with AACE April 13,2016
Lorcaserin

**Mechanism of Action (MOA)**

- Selective 5-HT2C receptor agonist
- Stimulates α-MSH production from POMC neurons resulting in activation of MC4R
- Increases satiety
- Upside on MOA: Non Stimulating

**Indications and Dose**

- Approved by FDA June 2012
- Indication: Weight loss in patients with BMI ≥30 kg/m2 or BMI ≥27 kg/m2 with weight-related co-morbid condition(s)
- 10 mg po bid, no titration
- 20 mg extended release
- Schedule IV
- Discontinue if 5% weight loss is not achieved in 12 weeks


Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline
Caroline M. Apovian, Louis J. Aronne, Daniel H. Bessesen,
Cardiovascular Safety of Lorcaserin in Obesity

NEJM E.A. Bohula, S.D. Wiviott, D.K. McGuire et. Al. August 2018

- Randomize over 12,000 patients with Cardiovascular disease (75%) and or Diabetes (57%) with multiple cardiovascular risk factors
- Randomized Half the patients to Lorcaserin and half to placebo
- Primary outcome: cardiovascular event
  - (example stroke, myocardial infarction, heart failure, angina etc.)

- At the end of 36 months
  - 12.8% of patients in the Lorcaserin group had a Cardiovascular event
  - 13.3% of patients in the Placebo group had a Cardiovascular event

- Lorcaserin group lost more weight (4.2 kg vs 1.4 kg) at one year
  - This was a safety trial not a weight loss study

- Adverse events: 13 Lorcaserin patients vs 4 placebo patients had serious hypoglycemia
Effect of Lorcaserin on Prevention and Remission of Type 2 Diabetes

Erin A Bohula*, Benjamin M Scirica*, Silvio E Inzucchi, et.al. www.thelancet.com October 4, 2018

- Decreased incident of patients converting from pre diabetes to diabetes
- In the diabetics improved blood sugar control
- Reduced risk of microvascular complications
- Diabetic patients lost more weight as the trial progressed

February 13th 2020 Lorcaserin Withdrawn from the U.S. Market

- Secondary analysis of the Cardiovascular trial it was found:
- Found a higher rate of cancer in Patients taking lorcaserin 7.7%
  - Placebo rate in the study was 7.1%
  - Not statistically significant
  - But numerically higher
- A range of cancer types was reported, with several different types of cancers occurring more frequently in the lorcaserin group
  - Pancreatic
  - Colorectal
  - Lung
Non-systemic Superabsorbent Hydrogels: Technically a Device But in a Pill

Superabsorbent hydrogel made from naturally-derived building blocks

Building blocks are Generally Regarded As Safe (GRAS) by FDA

CMC is cellulose that has been oxidized

CMC is naturally found in citrus fruits

3D cross-linked matrix

Super Absorbent Hydrogel
Gelesis 100 Approved April 2019

- 3 Oral Capsule administered with 500 cc of water 30 minutes before Lunch and Dinner
- Particles released and expand in stomach by absorbing water
- Particles mix with the meal (lunch or dinner)
- Particles maintain their expanded 3D structure as they travel thru the small intestines
- Particles degrade in the large intestine, water is released and reabsorbed by the colon and remnants are eliminated
Primary Care Conference
Tuesday, July 7, 2020

GLOW pivotal study 2 co-primary endpoints:
A – Placebo adjusted weight loss, B - 5% Responders

(A) Percent change in body weight from baseline (day 0) to day 171 (after 2 days of washout) by treatment group. Error bars represent standard error of the mean (SEM).

(B) Percent responders with ≥ 5% (P = 0.0008), ≥ 7.5% (P = 0.0017), or ≥ 10% (P = 0.0107) weight loss in all patients.

(C) Percent change in excess body weight from baseline (day 0) to day 171 (after 2 days of washout) by treatment group. Error bars represent SEM.

(D) Adjusted odds ratio (95% confidence interval) for achieving ≥ 5% (2.0 [1.3-3.0]), ≥ 7.5% (2.1 [1.3-3.3]), and ≥ 10% (2.1 [1.2-3.8]) weight loss.

*P < 0.05; **P < 0.001. All P values are from logistic regression models adjusted for baseline weight and stratification factors. GLOW, Gelesis Loss Of Weight study; ITT, intention-to-treat.


Reaching 3% Weight Loss as Early as 8 Weeks Predicts Responders on Gelesis100 (sensitivity and specificity > 80%)

Ken Fujioka, MD
New Treatment Options for Weigh Management
### Adverse Events Coded as Possibly or Probably Related by Major Category – Most Common Category is GI

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients, n (%)</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AE probably or possibly related</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelesis100 (n = 223)</td>
<td>88 (39.5)</td>
<td>64 (30.3)</td>
<td>9.1 (–0.2, 18.2)</td>
</tr>
<tr>
<td>Placebo (n = 211)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>–0.5 (–3.0, 1.7)</td>
</tr>
<tr>
<td>GI Disorders</td>
<td>84 (37.7)</td>
<td>58 (27.5)</td>
<td>10.2 (1.0, 19.1)</td>
</tr>
<tr>
<td>General disorders</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
<td>–0.0 (–2.6, 2.4)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>2 (0.9)</td>
<td>1 (0.5)</td>
<td>0.4 (–2.2, 3.1)</td>
</tr>
<tr>
<td>Investigations</td>
<td>3 (1.3)</td>
<td>3 (1.4)</td>
<td>–0.1 (–3.3, 3.0)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0 (0)</td>
<td>4 (1.9)</td>
<td>–1.9 (–5.1, 0.6)</td>
</tr>
<tr>
<td>MSK and connective tissue disorders</td>
<td>2 (0.9)</td>
<td>0 (0)</td>
<td>0.9 (–1.5, 3.5)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>4 (1.8)</td>
<td>2 (0.9)</td>
<td>0.8 (–2.2, 4.0)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>0.4 (–1.8, 2.0)</td>
</tr>
<tr>
<td>Reproductive disorders</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>–0.5 (–3.0, 1.7)</td>
</tr>
<tr>
<td>Respiratory, thoracic disorders</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
<td>–0.0 (–2.6, 2.4)</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>1 (0.4)</td>
<td>3 (1.4)</td>
<td>–1.0 (–4.0, 1.7)</td>
</tr>
</tbody>
</table>

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**Diagram:**

- **Eat (Hunger) → Hypothalamus → NYP → Fat Cells → Leptin**
- **Stop Eating → Hypothalamus → POMC → Gastrointestinal Track → GLP-1, GLP-2, PYY, many more → Amylin, Insulin → Pancreas**
Dorsal Vagal Complex
Hind Brain
Stop Eating

Vagal Afferent fibers

Eat (Hunger)

Hypothalamus
NYP
Fat Cells
Gastrointestinal Track
Pancreas

Stop Eating

POMC

Lorcaserin

Dorsal Vagal Complex
Hind Brain
Stop Eating

Vagal Afferent fibers

Eat (Hunger)

Hypothalamus
NYP
Fat Cells
Gastrointestinal Track
Pancreas

Stop Eating

POMC

Lorcaserin

SHTa
Satiety

Fat Cells
Gastrointestinal Track
Pancreas

New Treatment Options for Weight Management
**New Treatment Options for Weight Management**

**Bupropion/Naltrexone**
- Phentermine/Topiramate

**Eat (Hunger)**
- Hypothalamus

**Stop Eating**
- NPY
- POMC

- Fat Cells
- Gastrointestinal Track
- Pancreas

**Dorsal Vagal Complex**
- Hind Brain
- Stop Eating

**Mesolimbic system**
- Reward centers
- Nucleus accumbens
- Prefrontal cortex

**Vagal Afferent fibers**

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**Liraglutide**

**Increase eating**
- Hypothalamus

**Stop Eating**
- NPY
- POMC

- GLP-1 Gastrointestinal Track

**Dorsal Vagal Complex**
- Hind Brain
- Stop Eating

**Mesolimbic system**

**Vagal Afferent fibers**
Putting Weight Loss into Perspective

• Diet and exercise: typical weight loss of 5% to 10%
• Current weightloss medications typical weight loss of 5% to 10%
• Bariatric surgery
  • Sleeve 20%
  • Gastric bypass 25%

GLP-1 (Glucagon Like Polypeptide -1) Basics

• GLP-1 secreted by the L-cells in the distal part of the small intestines in response to a meal
• GLP-1 receptors
  • Pancreatic beta cells
  • Gastrointestinal tract (small and large bowel)
  • Central (hypothalamus, hind brain, etc) and peripheral neurons (Vagas nerve)

• 1. GLP-1 signals the pancreas to increase Glucose mediated insulin release
• 2. Delays gastric emptying
• 3. Decreases plasma glucagon
• 4. Activates the brain to decrease food intake

GLP-1 agonist
Semaglutide 2.4 mgs Once Weekly

• Currently approved for diabetes at a dose of 1mg once weekly
• Typical weight loss in Diabetic trials looking at controlling A1c (and not weight loss trials) is between 3%-6.5%
• Compared to exenatide the weight loss was 5% vs 2%
  • 5% for semaglutide
  • 2.1% for Exenatide
• Now Studying for obesity treatment at a dose of 2.4 mgs per once weekly

1. Osmotic: Package insert

Weight Loss with GLP-1s in Diabetic Trials

Non-ideal Comparisons GLP-1 weight loss in Kgs in DM2

Obesity trials in non diabetics Liraglutide 1.8 mgs vs 3.0 mgs and Semaglutide


Sten Madsbad Review of head to head comparisons of glucagon-like peptide-1 receptor agonists Diabetes, Obesity and Metabolism 18: 317–332, 2016

Semaglutide 2.4 mgs Once Weekly

- 68 week trial Patients on Semaglutide 2.4 mgs once weekly
- 902 patients non-diabetic patients with overweight or obesity
- Weight management trial: patients received diet and exercise counseling
- Weightloss at the end of 68 weeks
  - 17.4% ITT
  - 18.2% completers
- Side effect profile the same as other GLP-1 agonist

  - Company announcement May 13, 2020 of Phase 3 data

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52 Year Old Engineer with a Recent Diagnosis of Type 2 Diabetes

- The patient is referred to you for recent diagnosis of Diabetes
- The patient has a BMI of 37
- He has never really cared about his weight before but when his HCP said that if he lost weight he might not need medications
- “I can do this myself I don’t need medications”
Treatment Options to Lose 7%-10%

- Diet, Exercise and Lifestyle modification
- Diet, exercise, Lifestyle modification and weight loss medications
- Bariatric surgery
  - Sleeve Gastrectomy
  - Gastric Bypass
- What are the odds that the above treatment options can accomplish 7%-10% weight loss?
  - Diet, Exercise and Lifestyle = 20%
  - Lifestyle with weight loss medications = 60%
  - Bariatric surgery = 85%

The 50 Year Old Engineer with New Onset DM2

- The patient has been consulting Dr. Google: he has looked at everything he can find on the internet
- He is aware that he is seriously overweight and understands that losing weight is a very good idea
- On his own he has sent off his saliva for genetic testing to find out what is the “perfect diet” for him
- He brings in his “genetic results” it says he should do a low fat diet, he is does not like this idea as his friends are doing a “keto diet”
- What do you tell him?
Effects of Low-fat vs Low Carb Diet on 12 Month Wt. Loss and the Association of Genotype Pattern and Insulin Secretion

- 609 overweight or obese non-diabetics patients
  - 12 month long study
- Randomized patients to a “healthy low fat” or ”healthy low carb”
- Patients also had their genetics looked at (genotype) and had insulin measured 30 mins after a glucose load
  - 40% of the patients had a low-fat genotype
  - 30% of the patients had a low-carb genotype


Insulin Study (insulin resistance)

- Patients did a 75 gram glucose challenge and the 30 minute insulin was used to separate high insulin producers from low insulin producers
  - Average BMI of 33
  - Average fasting blood sugar 98.5 mg/dl
  - About a third had metabolic syndrome
Diet: Low Fat vs Low Carb

<table>
<thead>
<tr>
<th></th>
<th>Carbs</th>
<th>Fat</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Fat</td>
<td>48%</td>
<td>29%</td>
<td>21%</td>
</tr>
<tr>
<td>Low Carb</td>
<td>30%</td>
<td>45%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Low fat diet: 205 to 212 grams of carbs
Low carb diet: 96 to 132 grams of carbs


Diet Based on Genotype and Insulin Secretion

- Healthy low fat diet patients lost 5.3 kilos
- Healthy low carb diet patients lost 6.0 kilos
- Based on Genotype
  - Genetics for low fat diet did not lose more weight on a low fat diet
  - Genetics for low carb diet did not lose more weight on a low carb diet
- Based on insulin response no increase is weight loss
  - High insulin secretors (insulin resistant patients) did not lose more weight on the low carb diet
  - Low insulin secretors (insulin sensitive patients) did not lose more weight on a low fat diet
- Conclusion: using genetics and measuring insulin may not be helpful in predicting the best diet
New Diets that have Some Interesting Scientific Data

- Intermittent or Alternate day fasting (ADF)
- Patients eat a relatively healthy diet but on alternate days or a few days a week they take in 25% of their caloric needs
  - Typical needs 2200 kcals per day
  - 25% would be 550 kcals per day

- Time restricted eating:
  - The patient eats between 12pm and 8pm (16 hours fasting) 16/8
  - The patient only eats between 4pm and 8pm (20 hours fasting) 20/4
  - The patient skips breakfast and possibly lunch

Does That Mean You Can Skip Breakfast?

- Randomized controlled studies actually do not say that we all need to eat breakfast
  - A lot of observational studies say “breakfast” is the most important meal of the day
- Randomized 24 overweight pts to having breakfast or not having breakfast
- Then measured their food intake after having breakfast or skipping breakfast
- In this study they served a typical carbohydrate rich breakfast
  - cereal with milk, toast and orange juice

Energy Intake 100kj=24kcals

Appetite Scores
Skipping Breakfast

- Skipping breakfast did not significantly affect the size of lunch or dinner later that day
- Subjects did not report increased hunger skipping breakfast later in the day
- The group that skipped breakfast ended up eating 400-450 kcal less that day

Skipping Breakfast Reduces Energy Intake and Physical Activity in Healthy Women Who are Habitual Breakfast Eaters: A Randomized Crossover Trial

- Randomized 20 healthy Japanese women to
  - Skipping Breakfast
  - Eating Breakfast
- Patients skipping breakfast
  - Ate 131 more calories at lunch
  - Total energy intake over the day (24 hours) was less then the breakfast eaters by 262 calories
  - Step count and physical activity were the same between the groups
  - In the morning mild decrease in activity of 41 kcal but over the course of the day no difference in physical activity between groups

Yoshimura E, Hatamoto Y, Yonokura S, Tanaka H. Physiol Behav. 2017 May 15;174:89-94
Back to Alternate Day Fasting (ADF)

- Randomized 26 patients to either fasting alternate days (Zero calories) or calorie deficit of 400 calories per day for 8 weeks
- Both groups lost 8 Kilos or about 2 pounds per week for 8 weeks
- The group that did ADF ended up cutting their daily caloric intake by 376 calories per day
- At the end 24 weeks no change in weight regain

Catenacci VA1,2, Pan Z3, Ostendorf D2, Obesity (Silver Spring). 2016 Sep;24(9):1874-83. doi: 10.1002/oby.21581

Does ADF Cause Compensatory Hunger or Change in Satiety Hormones

- 59 patients attempted Alternate day fasting for 8 weeks
  - 25% of caloric needs on fasting days
  - Patients lost about 4 kilos over 8 weeks
  - Patients decreased their RMR by 100 Kcal per day

Hoddy KK, Gibbons C, Kroeger CM Changes in hunger and fullness in relation to gut peptides before and after 8 weeks of alternate day fasting Clin Nutr. (16)00102-3 2016 Mar 30
Change in Satiety Hormones

- Ghrelin went up (increase hunger)
  - where does Ghrelin come from?
- Ghrelin comes from the stomach (Fundus) and increases hunger
- PYY went up (increased fullness when pts ate)
  - where does PYY come from?
- PYY comes from the small intestines (L-cells) and signals satiety or fullness after a meal
- Subjects overall did not feel more hungry at the end of the study
  - This shows a lack of compensatory hunger to weight loss?
  - Patient may also have had a bit more fullness after eating with ADF
    - (slightly higher levels of satiety hormones)

Intermittent Fasting (IF) Physiology
Time Restricted Eating

- IF is a variety of eating patterns in which no or few calories are consumed for time periods that can range from 12 hours to several days, on a recurring basis.
  - Example fast every other day (alternate day fasting)
  - Only eating daily between 4pm and 8 pm
- The goal is to switch from glucose metabolism to fatty acid-derived ketones metabolism
- This switch

Anton SD. Et al. Flipping the Metabolic Switch; Obesity (2018) 26, 254-268
utilization of glucose as our main energy source (glycogenolysis)
1. synthesizing lipids
2. Storing fat

Fast 12 to 36 hours
Goal: use up glycogen stores

mobilization of fat free fatty acids (FFAs)
fatty acid-derived ketones

Usual American diet
Yes exercise can push the patient into using up glycogen stores faster

Once in This State of Burning Fatty Acids and Ketones (what’s the big advantage)

- ketones serve as an energy source for muscle and brain cells during fasting and extended periods of physical exertion/exercise
- Thus, the primary energy source of energy shifts from glucose to FFA (from adipose tissue) resulting in:
  - lipolysis and ketones production
  - Helps preserve lean tissue (muscle)?

- Remember conventional dieting will have lean tissue lose:
  - for every 4 pounds a patient loses
    - Three pounds will be fat
    - One pound will be lean tissue
    - The older the patient the more lean tissue lost with weight loss
Hitting the “Switch” and Cell Signaling

- Change in glucose and lipid metabolism in the right direction
- Improved resistance
- Autophagia
- Improved cell survival

- End result: Health and Stress resistance
- Other potential benefits:
  - Cognitive function
  - Improved aging (less neurodegenerative disease)
  - Decreased cancer risk

50 Year Old Patient Referred for New Onset DM2

- 50 year old patient that you have seen before
- Work up is simple early DM2 with an A1c of 7.1
- His friends are doing the “Keto diet” they are losing a lots of weight
- He has gotten on the internet and Dr. Google claims:
  - It will get him to lose weight
  - Improve his memory
  - He can start going out again and order hamburgers “protein style”
  - Hell be in the “ZONE”

- What do you say? Is this a good idea or bad idea?
What is a "Keto Diet"

- Very low carb diet
- How many grams of carbs per day does one need to stay out of Ketosis
  - 50-55 grams per day
- The idea is to put a patient into Ketosis
- A diet high in protein and usually high in fat
- Example:
  - Breakfast is coffee with butter, eggs, and bacon
  - Lunch is a couple of burgers without the bun loaded with cheese
  - Dinner is crab stuffed mushroom with cream cheese and bacon blue cheese devil eggs
  - And some Keto drinks between meals

Clinical Pearl

- If you give a patient a diet prescription and have the patient track their food intake will they:
  - Underestimate their food intake
  - Overestimate their food intake
  - Or be pretty close

- If they underestimate: how much will they underestimate?
  - 37% *
  - This is why most diets tell pts to eat less than 20 grams of carbs to get into Ketosis

Back to our Patient that Wants to Do the Keto Diet: 
Diets that Promote Ketosis

❑ “Keto diet”, a diet high in Saturated fat, protein and very low in carbohydrates
❑ Any diet with fewer than 50 grams of carbohydrates a day will produce ketosis
❑ Intermittent fasting or time restricted eating
   • Between 12 hours and 36 hours of fasting, patients will go into ketosis
❑ “Keto drinks” drinks that have ketones in them to promote a decrease in hunger

Best Advice for This Patient

• If he wants to do a Keto diet he can
• But:
  • Don’t add saturated fat
  • Would not recommend Keto drinks
  • Lean protein
  • Keep up on fluids (ketones are diuretics)
  • Eat a lot of low carb, low calorie vegetables (constipation is a common problem)
• Consider getting help with a Dietitian when he is ready to stop doing a Keto diet or even help him with a keto diet (need an open minded RD)
• He should not get discouraged when he reintroduces carbohydrates as he will get some fluid regain