Overview of the Pharmacologic & Surgical Treatment for Obesity

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May 25, 2018

Components of an Effective Obesity Management Program

Currently Available Treatments: Risks and Efficacy

*Technic sleeve and vagal stimulator under phase 3 study
**SVLCD: very low calorie diet

Accessed May 12, 2014.
DIET

Which Diet is Best?

ETOH = ethyl alcohol; TEF = thermic effect of food.
What is the Relationship Between Macronutrient Proportion and Body Weight in Adults?

- There is strong and consistent evidence that when calorie intake is controlled, macronutrient proportion of the diet is NOT related to losing weight.
- No optimal macronutrient proportion was identified for enhancing weight loss or weight maintenance.

Weight and Metabolic Outcomes After 2 Years on a Low CHO vs Low-Fat Diet

A Randomized Trial

Predicted absolute mean change in body weight for participants in the low-fat and low-carbohydrate diet groups, based on a random-effects linear model. Error bars represent 95% CIs.

Meta Analysis: Comparison of Weight Loss Among Diet Programs in Overweight and Obese Adults

- 48 randomized trials; N=7,286 overweight or obese persons
- 25 of the studies examined weight loss at one year; n=5,000

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-fat diets</td>
<td>7.99 kg</td>
<td>7.27 kg</td>
</tr>
<tr>
<td>Low-carb diets</td>
<td>8.73 kg</td>
<td>7.25 kg</td>
</tr>
</tbody>
</table>

CONCLUSION

- Weight loss differences between individual diets were small.
- Any diet a patient will adhere to in order to lose weight is best.
Effects of Low-Carbohydrate and Low-Fat Diets
Randomized trial, 119 completers, 12 months

Conclusion: Low-carbohydrate diet was more effective for weight loss and cardiovascular risk factor reduction than the low-fat diet.

Rule of Thumb for Calculating Current Caloric Needs

- 8 calories per pound for women, no correction for exercise
  - 250 lb. women = ~2000 kcal/day upon presentation
  - Recommend 1500 kcal/day meal plan

- 10 calories per pound for men, no correction for exercise
  - 300 lb. man = ~3000 kcal/day upon presentation
  - Recommend 2500 kcal meal plan

Most Popular Commercial Programs With an Evidence Base to Evaluate

<table>
<thead>
<tr>
<th>Weight Watchers</th>
<th>Nutrisystem</th>
<th>Jenny Craig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two diet options, expanded from classic points program</td>
<td>Provides food and telephone counseling</td>
<td>Provides food and in-person or telephone counseling</td>
</tr>
<tr>
<td>Low cost (as little as $12 per week)</td>
<td>~$320-$370 per month</td>
<td>~$500-$650 per month</td>
</tr>
<tr>
<td>Choose between web-based and group setting</td>
<td>Shelf-stable dry or frozen foods with supplemental fruits and vegetables</td>
<td>Shelf-stable dry or frozen foods with supplemental fruits and vegetables</td>
</tr>
</tbody>
</table>
Online Programs

INTERNET-DELIVERED PROGRAMS

Most successful internet programs, that provide weekly email feedback to participants, will induce weight losses of ~ 2/3 the size of those achieved by traditional on-site behavioral programs.


Bottom-line on Diets

- Reduce Calories by ~ 500 kcal/day
- Stick with it!!
- Goal weight loss: 5-10% increments goals
Visceral Adipose Tissue: Associated with Cardiometabolic Risk


The Power of Monitoring and Accountability

Self-monitoring

Frequent Weigh-Ins

5/16/2018
Water Intake

AVOIDANCE OF

- Regular sodas
- Fruit juices
- Caloric beverages
The Lifestyle Approach

Tracking Physical Activity

Nike FUEL  JawBone  Accelerometer
Fitbug  BodyMedia  Fitbit

PHARMACOTHERAPY
### Criteria for Using FDA Approved Medications

<table>
<thead>
<tr>
<th>BMI</th>
<th>Weight Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>Normal</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>Obesity I</td>
</tr>
<tr>
<td>&gt;35</td>
<td>Obesity II</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Obesity III</td>
</tr>
</tbody>
</table>

BMI >27 kg/m² with ≥1 comorbidity

BMI >30 kg/m² with no comorbidities

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### FDA-Approved Pharmacotherapy Options for the Treatment of Obesity

- Phentermine (and other noradrenergic agents)
- Orlistat (Xenical/Alli)
- Phentermine/topiramate ER (Qsymia)
- Lorcaserin (Belviq)
- Bupropion SR/Naltrexone SR (Contrave)
- Liraglutide 3.0mg (Saxenda)

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### Phentermine

- Sympathomimetic amine, NE release
- Blunts appetite
- Approved in 1959 for short-term use, schedule IV
- Dosing: 8-37.5 mg qAM; use lowest effective dose
- Contraindications: pregnancy, nursing, MAOIs, glaucoma, drug abuse history, hyperthyroidism
- Relative contraindications: uncontrolled HTN, tachycardia, history of CAD, CHF, stroke, arrhythmia
Lorcaserin

- Selective 5HT-2c receptor agonist; stimulates α-MSH production from POMC neurons, activating MC4R
- Increases satiety
- Approved in 2012 for long-term use, schedule IV
- Single dose: 20 mg XR qday; discontinue if less than 5% weight loss after 12 weeks of use
- Contraindications: pregnancy
- Warnings: co-administration with serotonergic or antidopaminergic agents, valvular heart disease, psychiatric disorders (euphoria, suicidal thoughts, depression), priapism, risk of hypoglycemia with some diabetes medications

Phentermine/Topiramate ER

- Phentermine: sympathomimetic amine; blunts appetite
- Topiramate: increases GABA activity, carbonic anhydrase inhibitor, other actions; prolongs satiety
- Approved in 2012 for long-term use; schedule IV
- Treatment (“recommended” dose): 7.5/46 mg qAM; max dose: 15/92 mg
- Contraindications: pregnancy, glaucoma, MAOIs, hyperthyroidism
- Warnings: fetal toxicity, increased HR, suicidal thoughts, mood disorders, sleep disorders, cognitive impairment, metabolic acidosis, creatinine elevations, hypoglycemia with some diabetic medications

Bupropion SR/Naltrexone SR

- Approved by FDA September 10, 2014
- Bupropion: dopamine/noradrenaline reuptake inhibitor; activates POMC neurons in the hypothalamus, leading to decreased appetite
- Naltrexone: opioid receptor antagonist; blocks autoinhibition of POMC neurons and amplifies the effect of bupropion
- Dosing:
  - Week 1: 1 tab (8mg/90mg) in AM
  - Week 2: 1 tab BID
  - Week 3: 2 tabs in AM; 1 in PM
  - Week 4+: 2 tabs BID
- Consider discontinuation if <5% weight loss after 12 weeks
Liraglutide 3.0 mg

- Glucagon-like peptide 1 (GLP-1) receptor agonist
- Multiple actions; effect on weight is primarily via POMC neurons
- FDA-approved 3.0 mg/day for primary indication of obesity


Choosing Between Options

<table>
<thead>
<tr>
<th>Contraindications &amp; Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical scenario</td>
</tr>
<tr>
<td>Elevated seizure risk</td>
</tr>
<tr>
<td>I/o recurrent kidney stones</td>
</tr>
<tr>
<td>I/o glaucoma</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Moderate-severe renal impairment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Moderate-severe hepatic impairment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>SSRI use</td>
</tr>
</tbody>
</table>
Thoughts on Pharmacotherapy

- Treatment of obesity with pharmacotherapy as an adjunct to lifestyle modification is a valuable option for obesity treatment
- Several options are available and FDA approved
- Understand potential benefits and risks of agents when planning treatment
- Different patients respond to different medications
- If one option doesn’t work well, consider others
- REALISTIC EXPECTATIONS

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Bariatric Surgery Criteria

<table>
<thead>
<tr>
<th>BMI</th>
<th>&lt;18.5</th>
<th>18.5-24.9</th>
<th>25.0-29.9</th>
<th>30.0-34.9</th>
<th>&gt;35</th>
<th>&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>With ≥1 severe obesity-associated comorbidity (e.g., diabetes or OSA)</td>
<td>With no comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>
Most Common Bariatric Procedures

Sleeve Gastrectomy


260,000 procedures annually, 95% laparoscopic

Sleeve Gastrectomy
Bariatric procedure originally as part of BPDDS, now used as a first stage or stand alone if patient loses enough weight
Remove part of stomach, creating a sleeve from esophagus to antrum
A 36Fr bougie is used to size the sleeve
Now a covered benefit in US -- CMS

Roux-en-Y gastric bypass (RYGB)

Excess Weight Loss is ~65-70%*

Ghrelin
GLP-1
PYY
Insulin
Duodenal Switch

- Combination Operation
  - Sleeve
  - Biliopancreatic Diversion
  - Neurohormonal - decreased Ghrelin and increased GLP1
- Highest Remission rate for Type 2 Diabetes
- Excess Weight Loss is ~85%
- Significant risk of malabsorption of nutrients
- Usually performed on patients with a BMI>60kg/m2

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Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

Philip R. Schauer, M.D., Sangeta R. Kashyap, M.D., Kelly Wolski, M.P.H.,
Stacy A. Bremmer, M.D., John P. Hinman, Ph.D., Claire C. Petrie, M.P.H.,
Susan Thomas, R.N., Beth Aboud, R.N., Steven E. Nissen, M.D.,
and Deepak L. Bhatt, M.D., M.P.H.

ABSTRACT

BACKGROUND
Observational studies have shown improvement in patients with type 2 diabetes mel-
litus after bariatric surgery.

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STAMPEDE Trial
Surgical Therapy And Medications Potentially Eradicate Diabetes Efficiently

218 Patients Screened
150 Randomized

- A1c >7.0%
- BMI: 27-43 kg/m2
- Age: 20-60 years

50 Intensive Medical Therapy Alone
2 withdrew consent
2 lost to follow-up
40 Year 3 Population

50 Medical Therapy + Gastric Bypass
2 lost to follow-up
48

50 Medical Therapy + Sleeve Gastroectomy
49

91% Retention

STAMPEDE Trial: Change in A1c

Change in A1c (%)

0.0  -0.5  -1.0  -1.5  -2.0  -2.5  -3.0  -3.5

0 3  6  12  24  36

Medical

Gastric Bypass P <0.001

Sleeve P <0.001


STAMPEDE Trial: Change in BMI

Change in BMI (kg/m²)

0.0  -2.0  -4.0  -6.0  -8.0  -10.0  -12.0

0 3  6  12  24  36

Medical

Gastric Bypass P <0.001

Sleeve P <0.001


Weight Change After Bypass and Sleeve vs Medical Tx In Patients with Type 2 DM

Five-year data of patients with T2DM and BMI of 27 to 43

Mean BMI Value at Visit

Medical Therapy 34.4  34.1  35.0  34.8  35.1  34.0

Gastric bypass 31.9  28.9  27.4  28.2  28.6  28.9

Sleeve gastrectomy 31.6  26.9  27.7  28.1  28.2  29.3

Routine Vitamin and Mineral Supplementation for RYGB Patients

**Supplement**
- Multivitamin-mineral / Prenatal
- Calcium citrate w/ vitamin D
- Elemental iron
- Vitamin B12

**Dosage**
- 1 to 2 daily
- 1200 to 2000 mg/day + 3000 U/day Vitamin D
- 40 to 65 mg/day
- 5000 ug/day orally OR 1000 ug/mo IM OR 500 ug weekly intranasal

RYGB = Roux-en-Y gastric bypass.

Bariatric Surgery - Low Mortality

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bariatric Surgery</td>
<td>0.13%</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>0.52%</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>0.93%</td>
</tr>
<tr>
<td>Open</td>
<td>3.30%</td>
</tr>
<tr>
<td>CABG</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hip Replacement</td>
<td>1.0%</td>
</tr>
<tr>
<td>CPM</td>
<td>2.0%</td>
</tr>
<tr>
<td>When performed at a Bariatric Surgery Center of Excellence</td>
<td></td>
</tr>
</tbody>
</table>
Reduction of Premature Death

89% Reduction in Risk of Death Over 5 Years

Currently Available Treatments: Risks and Efficacy

*Includes perioperative (30-day) mortality of 0.4%

P = 0.001