Obesity Treatment in 2018 and Beyond

Lee M. Kaplan, MD, PhD
Obesity, Metabolism & Nutrition Institute
Massachusetts General Hospital
Harvard Medical School

LMKaplan@mgh.harvard.edu

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Fernando Botero, 1932-
What is Obesity?

Excessive total body fat that presents a risk to health

- The presence and severity of obesity can be measured by body composition analysis.
- It can be estimated by a variety of biomarkers:
  - Body mass index (BMI)
  - Height-waist circumference ratio
  - Body fat distribution
  - Risk scores
  - Comorbidities

- But these markers should not define obesity.
Medical Complications of Obesity

- Metabolic
- Structural
- Inflammatory
- Degenerative
- Neoplastic
- Psychological

225+ comorbidities affecting EVERY organ system and medical specialty

Yuen M … Kaplan LM, Obesity Week 2016
Think About This …

- **Why** do people gain weight when started on selected medications? (hint: the medications don’t have many calories)?
  - Insulin
  - Sulfonylureas (all)
  - Corticosteroids (all)
  - Mood stabilizers (esp. clozapine, olanzapine, venlafaxine)
  - Anti-seizure medications (esp. valproate, oxcarbazepine)
  - β-blockers (all)

- Why do people gain weight when sleep deprived?

- Why do people gain weight when chronically stressed?
Competing Models of Energy Balance Regulation

Purposeful behavior *drives* the physiology of energy balance regulation

**Implications**
- Increased caloric intake drives weight gain
- All calories have similar effects
- Calories burned during physical activity drive weight loss

The physiological regulation of energy balance *drives* behavior

**Implications**
- Changes in the modern diet alter physiology
- The chemical nature of the calories is critical
- Re-regulation of abnormal physiology is essential for success
The Normal Physiology of Energy Balance

- Average adults require approximately 1300 kcal/day*
- Average adults consume 2000-2500 kcal/day
  - Average adults thus consume 1.5-2 times as much food as needed
  - Excess intake is available for physiological emergencies
- Maintenance of normal fat stores (and body weight) requires precise disposal of 40-50% of ingested calories daily
- Maintaining weight within 20 lbs. between ages 21 and 65 requires matching of intake and expenditure within 0.2%
  - Corresponds to accuracy of 4-5 kcal/day
  - Less than one-half potato chip

Thus, daily energy balance must be a tightly regulated physiological trait
The Body Seeks a Stable Adipose Tissue Mass

Similar to other regulated tissue mass

- Liver
- Red blood cells
Feedback Regulation of Energy Metabolism

This process is critical to life and involves nearly 20% of the human genome.
Why is Weight Regain So Prevalent?

Sumithran et al. NEJM 2011; 365:1597-1604.
Appetitive Drives Persistently Oppose Restriction Diet-induced Weight Loss

Sumithran et al. NEJM 2011; 365:1597-1604.
Gut Hormone Changes Persistently Oppose Restriction Diet-induced Weight Loss

Sumithran et al. NEJM 2011; 365:1597-1604.
Why Defend the Fat Mass?

• The body **needs** to defend a fat mass set point
  • To recover appropriately from acute illness or injury
  • To shed the excess calories consumed daily

• The body **defends** its fat mass set point
  • Even if it is abnormally high (i.e., obesity)

Sumithran et al. NEJM 2011; 365:1597-1604.
Obesity results from a failure of normal weight and energy regulatory mechanisms…

…leading to an abnormally high defended fat mass
Environmental Drivers to Obesity

- Labor-saving devices (decreased physical activity)
  (effects on muscle more than calories)

- Altered food supply
  (signaling more than calories)

- Chronic stress and distress (incl. sleep, circadian)
  (direct impact on relevant brain areas)

- Medications
  (up to 10% of obesity)

These influences act by raising the defended fat mass.
The Modern Environment Causes Obesity by Driving Up the Defended Fat Mass

Defended body fat mass

Abnormal dietary constituents

Unhealthy muscle

Sleep deprivation

Chronic stress

Disrupted circadian rhythms

Weight gain-inducing medications

Years of Exposure
Implications for Obesity Treatment
Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point

Defended body fat mass

Bariatric Surgery

- Abnormal diet
- Unhealthy muscle
- Sleep deprivation
- Chronic stress
- Disrupted circadian rhythms
- Weight gain inducing medications

Years of Exposure
Obesity Treatment Strategy

A Stepwise – and Additive – Approach
(progress through algorithm as clinically required)

- Post-surgical Combinations
- Weight Loss Surgery
- Pharmacotherapy
- Professionally-directed Lifestyle Change
- Self-directed Lifestyle Change = Patient Education
## Current Treatments of Obesity

### Lifestyle
- Low calorie diet
- Low-carbohydrate diet
- Low-fat diet
- Low glycemic index diet
- Paleo diet
- Mediterranean diet
- Very low calorie diet
- Aerobic exercise
- Resistance training
- Sleep enhancement
- Circadian enhancement
- Motivational interviewing
- Stress reduction
- Cognitive-behavioral therapy

### Pharmacological
- Remove weight-promoting
  - Phentermine
  - Topiramate
  - Zonisamide
  - Metformin
  - Lorcaserin
  - Bupropion
  - Naltrexone
  - Exenatide
  - Liraglutide
  - Dulaglutide
  - Pramlintide
  - Orlistat
  - Diethylpropion
  - Leptin
  - Canagliflozin
  - Empagliflozin

### Medical Devices
- Adjustable gastric band
- Vagal nerve block
- Gastric balloon
- Gastric aspiration
  - **Endoscopic**
    - Gastric plication
  - **Surgical**
    - Sleeve gastrectomy
    - Gastric bypass
    - Biliopancreatic diversion
    - Duodenojejunal bypass
Core Principles of Obesity Treatment

1. The goal of effective treatment is to reduce the elevated fat mass set point
2. There is wide heterogeneity in the causes and manifestations of obesity
3. This leads to wide patient-to-patient variability in the response to all anti-obesity therapies
Weight Loss Varies Widely Among Patients

**Diet** (Low-carbohydrate)

**Drug** (Liraglutide)

**Device** (Duodenal liner)

**Surgery** (Gastric Bypass)

Patients (%)
1. The goal of effective treatment is to reduce the elevated fat mass set point
2. There is wide heterogeneity in the causes and manifestations of obesity
3. This leads to wide patient-to-patient variability in the response to all anti-obesity therapies
4. People who respond to one therapy may not respond to another, and vice versa
5. The strategy is to match each patient with the treatment most effective and suited to them
Wide variability in therapeutic response is best explained by clinically relevant subtypes
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Classification</th>
</tr>
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<tbody>
<tr>
<td>Leptin deficiency</td>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>LepR deficiency</td>
<td>Bardet-Biedl syndrome</td>
</tr>
<tr>
<td>POMC deficiency</td>
<td>Alström syndrome</td>
</tr>
<tr>
<td>MC4R deficiency</td>
<td>BFL syndrome</td>
</tr>
<tr>
<td>αMSH deficiency</td>
<td>Hypothalamic</td>
</tr>
<tr>
<td>Sim-1 deficiency</td>
<td>Hyperphagic</td>
</tr>
<tr>
<td>PC-1 deficiency</td>
<td>Thermogenesis deficient</td>
</tr>
<tr>
<td>KSR2 deficiency</td>
<td>Circadian-disrupted</td>
</tr>
<tr>
<td>MRAP2 deficiency</td>
<td>Stress-induced</td>
</tr>
<tr>
<td>SH2B1 deficiency</td>
<td>Viral</td>
</tr>
<tr>
<td>BDNF deficiency</td>
<td>Central</td>
</tr>
<tr>
<td>trkB deficiency</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Carpenter syndrome</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Cohen syndrome</td>
<td>Neonatal</td>
</tr>
<tr>
<td>Ayazi syndrome</td>
<td>Early childhood</td>
</tr>
<tr>
<td>MOMO syndrome</td>
<td>Peripubertal</td>
</tr>
<tr>
<td>Rubenstein-Taybi syndrome</td>
<td>Gestational</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>Menopausal</td>
</tr>
<tr>
<td>Albright osteodystrophy</td>
<td>“Healthy”</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
</tr>
</tbody>
</table>

- **Multiple Subtypes = Variation in Treatment Response**

- **Inflammatory**
- **Diet-dependent**
- **Exercise-sensitive**
- **Sleep-sensitive**
- **Insulin-induced**
- **Steroid-induced**
- **Progesterone-induced**
- **Psychotropic-induced**
- **Antibiotic-induced**
- **Endocrine disruptor**
- **Phentermine-responsive**
- **Lorcaserin-responsive**
- **Topiramate-responsive**
- **Metformin-responsive**
- **Bupropion-responsive**
- **GLP-1 responsive**
- **Bypass-responsive**
- **Bypass-resistant**
- **Gastric band-responsive**

**The Obesities – A Plethora of Discrete Disorders**
What Differs Among Different Obesity Subtypes

- Timing of obesity onset
- Fat location and distribution
- Metabolic consequences
- Phenotypic differences
  - Hunger
  - Satiety
  - Reward-based eating (e.g., craving)
  - Energy expenditure (thermogenesis)
- Response to environmental causes
  - Dietary content
  - Lack of physical activity
  - Chronic stress
  - Sleep deprivation
  - Circadian rhythm disruption
- Response to therapies
Heterogeneity of Response

Number of Subjects vs. Weight Loss

Target Group
Obesity Treatment Strategy

A Stepwise, Additive Approach
(progress through algorithm as clinically required)

- Post-surgical Combinations
- Weight Loss Surgery
- Pharmacotherapy
- Professionally-directed Lifestyle Change
- Self-directed Lifestyle Change (Patient Education)
Obesity Treatment Strategy

A Stepwise, Additive Approach
(progress through algorithm as clinically required)

Professionally-directed Lifestyle Change

Self-directed Lifestyle Change (Patient Education)
Address Modifiable Environmental Factors

- Weight Gain Promoting Medication
- Diet
- Activity
- Sleep
- Circadian Rhythm
- Chronic Stress
Medication-induced Weight Gain

Medications account for 5-10% of obesity

In each relevant category, remove or substitute weight gain-promoting medications with weight neutral or weight loss-promoting alternatives
Use Checklists

Patient History and Self-assessment

- Weight-influencing medications
- Diet content
- Daily physical activity
- Sleep health
- Eating patterns
- Personal stressors
Readdress Modifiable Environmental Factors

Discontinue or substitute for weight gain-promoting medication

- CNS Agents
- Anti-diabetes
- Steroids
- Beta-blockers
- Anti-histamine
- Sleep Aids
Readdress Modifiable Lifestyle Factors

- Weight Gain Promoting Medication
- Diet
- Activity
- Sleep
- Circadian Rhythm
- Stress

OBESOGENIC DIET
INADEQUATE SLEEP
CIRCADIAN DYSRUPTION
PHYSICAL INACTIVITY

Stress
Lifestyle Strategy

• Keep the goal in mind: **durable** weight loss

• **Take a good history** – assess the patient’s current lifestyle and habits – and use it in formulating your treatment plan
  - **Identify greatest opportunities for lifestyle change**
  - Focus on changes that influence the obesity itself – **do not treat** only the complications or cardiovascular risk from the obesity

• Pursue sequential application of **limited** (doable) lifestyle changes
  - Determine effectiveness of each individual change
  - Include non-diet, non-exercise interventions (sleep, stress, circadian)
  - Use classic strategies of habit change (opportunity, cue, reinforcement)
  - Anticipate need for the additive effects of multiple lifestyle changes

• Aim for **clinically meaningful** weight loss
Obesity Treatment Strategy

A Stepwise, Additive Approach
(progress through algorithm as clinically required)

Pharmacotherapy

Professionally-directed Lifestyle Change

Self-directed Lifestyle Change (Patient Education)
# Medications Approved for Obesity – 2018

<table>
<thead>
<tr>
<th>Medication</th>
<th>Average Weight Loss*</th>
<th>Mechanism of Action</th>
<th>Potential Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine (Adipex™, Ionamin™)</td>
<td>~ 5%</td>
<td>Adrenergic</td>
<td>Tachycardia, hypertension</td>
</tr>
<tr>
<td>Phentermine / Topiramate (Qsymia™)</td>
<td>10%</td>
<td>Adrenergic, CNS</td>
<td>Tachycardia, hypertension, cognitive dysfunction, neuropathy, teratogenicity</td>
</tr>
<tr>
<td>Bupropion / Naltrexone (Contrave™)</td>
<td>4.5%</td>
<td>CNS; opioid antagonism</td>
<td>Seizures, confusion, anxiety, opiate withdrawal</td>
</tr>
<tr>
<td>Lorcaserin (Belviq™)</td>
<td>3.5%</td>
<td>Serotonergic (5HT₂C)</td>
<td>Headache</td>
</tr>
<tr>
<td>Liraglutide (Saxenda™)</td>
<td>7%</td>
<td>GLP-1 agonist</td>
<td>Nausea</td>
</tr>
<tr>
<td>Orlistat (Xenical™)</td>
<td>3%</td>
<td>Lipase inhibitor</td>
<td>Steatorrhea, incontinence</td>
</tr>
<tr>
<td>Medication</td>
<td>Other Uses</td>
<td>Mechanism</td>
<td>Potential Side Effects</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------</td>
<td>-------------------</td>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Seizures, Migraines</td>
<td>GABAergic</td>
<td>Cognitive impairment, paresthesias, kidney stones</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Depression</td>
<td>Dopaminergic</td>
<td>Seizures</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Opioid addiction</td>
<td>Opioid receptor antagonist</td>
<td>Acute opioid withdrawal</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Seizures</td>
<td>Unknown</td>
<td>Cognitive impairment, hypohidrosis, metabolic acidosis</td>
</tr>
<tr>
<td>Metformin</td>
<td>T2DM</td>
<td>AMPK activation</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>T2DM</td>
<td>GLP-1 receptor agonist</td>
<td>Nausea</td>
</tr>
<tr>
<td>Exenatide</td>
<td>T2DM</td>
<td>GLP-1 receptor agonist</td>
<td>Nausea</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>T2DM</td>
<td>GLP-1 receptor agonist</td>
<td>Nausea</td>
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<td>Pramlintide</td>
<td>T2DM</td>
<td>Amylin receptor agonist</td>
<td>Nausea</td>
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<tr>
<td>Canagliflozin</td>
<td>T2DM</td>
<td>SGLT-1 antagonist</td>
<td>Genital and urinary infections</td>
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<tr>
<td>Dapagliflozin</td>
<td>T2DM</td>
<td>SGLT-1 antagonist</td>
<td>Genital and urinary infections</td>
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<td>Empagliflozin</td>
<td>T2DM</td>
<td>SGLT-1 antagonist</td>
<td>Genital and urinary infections</td>
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</table>
Medications Establish a New Plateau (Set Point)

Topiramate ER + Phentermine Combination

Immediate Weight Regain after Treatment Cessation

Lorcaserin

Time (weeks)

Weight (kg)

Cessation vs. Continuation

Additive Benefits of Drug + Lifestyle Combination

Sibutramine + Lifestyle Therapy

- Sibutramine
- Structured lifestyle intervention
- Combined therapy (Sibutramine + structured lifestyle)

Combination Therapies Yield Improved Weight Loss

Phentermine + Topiramate

(28 Weeks)

Mean weight loss (%)

Placebo

Aronne LJ, et al., Obesity 2013
Combination Therapies Yields Improved Weight Loss

Lifestyle Therapy + Liraglutide

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Placebo</th>
<th>Liraglutide</th>
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<tr>
<td>-14</td>
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<td>-8</td>
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<tr>
<td>56</td>
<td></td>
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</tr>
</tbody>
</table>

Strategy for Using Anti-obesity Medications (AOMs)

1. Wait until the patient’s weight is stable for 2-3 months
   • Allows for best determination of whether the medication is effective
2. Choose a medication
   • Use Guidelines for Anti-Obesity Medications
3. Institute SafeUse™ protocol
   • Baseline evaluation (e.g., pulse, BP, review relevant history)
   • Educate patient on medication use and potential side effects (patient handout)
4. Start medication (use introductory dose and escalate as needed)
5. Evaluate for safety and effectiveness at 1 and 3 months
   • Escalate dose per medication protocol
6. Next steps based on patient response
Anti-obesity Medication Implementation Strategy

![Graph showing weight change over time after surgery with different medications (Rx 1, Rx 2, Rx 3).](image)

- **Rx 1** effect
- **Rx 2** effect
- **Rx 3** effect

**Weight (lbs.)**

**Time after Surgery (months)**

- 2-3 month pretreatment weight stability
- 2-3 month weight st failure
- 1-month treatment weight stability
- 2-3 month pretreatment weight stability
Variable Response to Anti-obesity Medications

- Inadequate response (replace)
- Partially effective (add new drug)
- Highly effective

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Weight Loss</th>
</tr>
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<tbody>
<tr>
<td>5% TBWL</td>
<td>10-20% TBWL</td>
</tr>
<tr>
<td>0</td>
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</tbody>
</table>

10-20% weight loss in a significant percentage of patients.
Anti-obesity Medication Algorithm

Start Drug Therapy
(e.g., Liraglutide, Lorcaserin, Qsymia, Belviq, Contrave)

Treat 1-3 months

< 5% Weight Loss
Stop Drug Therapy
Start New Drug
(from same list)

5-10% Weight Loss
Continue Therapy
Add New Drug
(from same list)

> 10% Weight Loss
Continue Therapy
(indefinitely)

Repeat Assessment for Each New Drug
Choosing an Anti-obesity Medicine

Contraindications and Side Effect Risk

- Additional Benefits (beyond weight loss)
- Patient Preference (e.g., dosing)
- Average Efficacy
- Cost to Patient

Drug

Average Efficacy

Cost to Patient

Patient Preference (e.g., dosing)

Additional Benefits (beyond weight loss)
Obesity Treatment Strategy

A Stepwise, Additive Approach

(progress through algorithm as clinically required)

- Weight Loss Surgery
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Bariatric and Metabolic Surgery

<table>
<thead>
<tr>
<th>Gastric</th>
<th>Weight-independent Metabolic Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjustable Gastric Banding</td>
<td></td>
</tr>
<tr>
<td>Vertical Sleeve Gastrectomy</td>
<td></td>
</tr>
<tr>
<td>Roux-en-Y Gastric Bypass</td>
<td></td>
</tr>
<tr>
<td>Biliopancreatic Diversion / Duodenal Switch</td>
<td></td>
</tr>
</tbody>
</table>
Average Effectiveness of Obesity Treatments

Swedish Obesity Subjects
Diabetes Prevention Program

- Lifestyle & Medications: 2%
- Gastric Banding: 13%
- Gastric Bypass: 27%

Percent Total Weight Loss vs. Time After Surgery (years)
Bariatric Surgery Reduces Mortality

US Veterans Administration Experience

Arterburn D, JAMA 2015; 313:62-70
Current Eligibility Criteria for Surgery

• BMI > 40 kg/m²

• BMI 35-40 kg/m² with a major comorbidity (e.g., T2DM)
  • Recent AACE/TOS/ASMBS guidelines have broadened these indications to include BMI 30-40 kg/m² with a major comorbidity
  • BMI criteria also lower for patients from South and East Asia

• Criteria similar for adults and adolescents
Addressing an Inadequate Response to Surgery

Similar to other anti-obesity therapies, outcomes of bariatric surgery vary widely from patient to patient.

Obesity Treatment Strategy

A Stepwise, Additive Approach

(progress through algorithm as clinically required)

Post-surgical Combinations

Weight Loss Surgery

Pharmacotherapy

Professionally-directed Lifestyle Change

Self-directed Lifestyle Change (Patient Education)
Obesity Management Summary

• Approach patient in confident, supportive and non-judgmental way

• Counsel patients with obesity on the risks of excess weight and the benefits of weight loss

• Identify the medical comorbidities of obesity in each patient

• Pursue a step-wise strategy for weight loss – lifestyle, medications, and surgery as needed – and explore combinations as needed, including combinations across categories

• Determine BMI at each patient visit to assess progress

• Help patients maintain weight loss by optimizing the patients lifestyle – healthy diet, regular exercise, adequate sleep, stress reduction
Go Slow and Try Different Approaches

- Test therapies sequentially
- Pursue combination therapies – including combinations of specific lifestyle changes with more classical medical approaches
- Be supportive
  - Be persistent
  - Be optimistic – you can be!
  - Be there for the patient

**Aim for the “cure,” but always provide the care.**
Primary Care Internal Medicine

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Lee M. Kaplan, MD, PhD
Obesity, Metabolism & Nutrition Institute
Massachusetts General Hospital
Harvard Medical School

LMKaplan@mgh.harvard.edu

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