Key Issues in Liver Transplantation for NASH

Role of Weight Reduction and Medical Treatment

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Obesity the Disease

- BMI > 30
- Type 2 Diabetes
- NAFLD
- NASH
- Cirrhosis
- HCC
- Parkinson’s Disease
- HIV / AIDS

Obesity
Medical Complications of Obesity

Enormous burden of associated disease, particularly in patients with metabolic complications such as NAFLD

Yuen M, Kaplan LM et al., Obesity Week 2016
Weight Loss in NASH Patients

- Goal: Improve current status and progression of disease
- Improve steatosis
  - Rapid
  - Can be profound with modest weight loss
  - No proven effect on prevention or delay of NASH
- Improve inflammation and fibrosis
  - Slow
  - Requires substantial and persistent weight loss
- Most reliable approach has been with bariatric surgery
  - May have weight loss-independent effects (as for diabetes)
- Anti-obesity medications – not well studied in NAFLD
Weight Loss in Pre-Transplant NASH Patients

• Most NAFLD patients with obesity, which is associated with adverse outcomes for all solid organ transplants
• Goal: Improve outcomes of liver transplantation
  • Preservation of donor liver
  • Improved management – altered pharmacokinetics and pharmacodynamics of immunosuppressants
  • Prevention of complications due to persistent or new obesity comorbidities
  • Prevention of NAFLD in transplanted liver
• Obesity treatment – stepwise escalation of therapy
  • Lifestyle → Medications → Bariatric surgery
  • No demonstrated difference among different approaches
• Transplant patients require accelerated escalation
  • Suggests greater value of anti-obesity medications
  • Bariatric surgery generally required earlier in progression, when cirrhosis evident but transplantation not yet indicated
The Body Seeks a Stable Adipose Tissue Mass

Similar to other regulated tissue mass

• Liver
• Red blood cells
Feedback Regulation of Energy Metabolism

Sensory Organs
GI Tract

Muscle
Liver
Bone

Environmental sensing

Irisin

Metabolic activity and needs

Leptin

Energy stores

Food intake
Nutrient handling
Energy expenditure

Adipose tissue
Why is Weight Regain So Prevalent?

![Graph showing weight changes over weeks with a note on very low calorie diet](image)

Sumithran et al. NEJM 2011; 365:1597-1604.
Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point

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

Body fat mass set point

Abnormal dietary constituents | Unhealthy muscle | Sleep deprivation | Stress | Disrupted circadian rhythms | Weight gain inducing medications

Years of Exposure

Bariatric Surgery
Obesity Treatment Strategy

Stepwise Approach
(progress through algorithm as clinically required)

Post-surgical Combinations

Weight Loss Surgery

Pharmacotherapy

Professionally-directed Lifestyle Change

Self-directed Lifestyle Change
### Current and Emerging 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
- Setmelanotide

#### Medical Devices
- Adjustable gastric band
- Vagal nerve block
- Gastric balloon
- Duodenal liner
- Gastric aspiration
- Expandable gel capsule

#### Endoscopic
- Gastric plication
- Intestinal bypass
- Mucosal resurfacing

#### Surgical
- Sleeve gastrectomy
- Gastric bypass
- Biliopancreatic diversion
- Duodenojejunal bypass
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)
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
Heterogeneity of Response

Number of Subjects

Weight Loss

Target Group
Obesity Treatment Strategy

Stepwise Approach

(progress through algorithm as clinically required)
Address Modifiable Environmental Factors

<table>
<thead>
<tr>
<th>Weight Gain Promoting Medication</th>
<th>Diet</th>
<th>Activity</th>
<th>Sleep</th>
<th>Circadian Rhythm</th>
<th>Stress</th>
</tr>
</thead>
</table>


Obesity Treatment Strategy

Stepwise Approach

(progress through algorithm as clinically required)

Pharmacotherapy

Professionally-directed Lifestyle Change

Self-directed Lifestyle Change
### Medications Approved for Obesity – 2016 (U.S.)

<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 (5HT&lt;sub&gt;2C&lt;/sub&gt;)</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>
</tbody>
</table>
## Other Medications that Promote Weight Loss

<table>
<thead>
<tr>
<th>Medication</th>
<th>Other Uses</th>
<th>Mechanism</th>
<th>Potential Side Effects</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>Pramlintide</td>
<td>T2DM</td>
<td>Amylin receptor agonist</td>
<td>Nausea</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>T2DM</td>
<td>SGLT-1 antagonist</td>
<td>Genital and urinary infections</td>
</tr>
<tr>
<td>Dapagliflozin</td>
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<td>Empagliflozin</td>
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<td>Genital and urinary infections</td>
</tr>
</tbody>
</table>
Strategy for Using Anti-Obesity Medications

1. Wait until the patient’s weight is stable for 1-2 months
   • Allows for best determination of whether the medication is effective
2. Choose a medication or combination of medications
   • Use Guidelines for Anti-Obesity Medications (AOM)
3. Institute SafeUse® AOM 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
6. Next steps based on patient response
Anti-obesity Medication Implementation Strategy

![Graph showing weight (lbs.) over time (months) with different medication stages: Rx 1, Rx 2, Rx 3.]

- **Rx 1**: 2-3 month pretreatment weight stability
- **Rx 2**: 2-3 month pretreatment weight stability, 1-month treatment failure
- **Rx 3**: 2-3 month pretreatment weight stability

**Time (months)**: 0, 4, 8, 12, 16

**Weight (lbs.)**

Rx 1 effect
Rx 3 effect
Conclusions

• Differentiate need for short- and long-term weight loss

• For short-term or urgent weight loss, calorie restriction generally most effective
  • But long-term weight loss extremely rare

• For long-term weight loss, change in physiology (fat mass set point) required

• For urgent need for long-term weight loss:
  • Optimize lifestyle and weight-influencing medications
  • Escalate rapidly to anti-obesity medications based on “safe-use” protocols
  • Reserve bariatric surgery for treatment of NAFLD, not as staged pre-transplant therapy
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