Weight Loss in NASH: Role of Weight Loss Medications and Surgery

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Effect of Calorie Restriction and Weight Loss on Body Composition

Weight Loss Induced Improvements in Liver Histology

## FDA-Approved Drugs for Weight Loss

<table>
<thead>
<tr>
<th>Year Approved</th>
<th>Generic Name</th>
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<tbody>
<tr>
<td>1947</td>
<td>Desoxyephedrine/methamphetamine</td>
</tr>
<tr>
<td>1956</td>
<td>Phenmetrazine</td>
</tr>
<tr>
<td>1959</td>
<td>Phentermine</td>
</tr>
<tr>
<td>1959</td>
<td>Diethylpropion</td>
</tr>
<tr>
<td>1959</td>
<td>Phendimetrazine</td>
</tr>
<tr>
<td>1960</td>
<td>Benzphetamine</td>
</tr>
<tr>
<td>1972</td>
<td>Fenfluramine <em>(Withdrawn 1997)</em></td>
</tr>
<tr>
<td>1973</td>
<td>Mazindol</td>
</tr>
<tr>
<td>1996</td>
<td>Dextrofenfluramine <em>(Withdrawn 1997)</em></td>
</tr>
<tr>
<td>1997</td>
<td>Sibutramine <em>(Withdrawn 2010)</em></td>
</tr>
<tr>
<td>1999</td>
<td>Orlistat</td>
</tr>
<tr>
<td>2012</td>
<td>Phentermine-Topiramate</td>
</tr>
<tr>
<td>2013</td>
<td>Lor-caserin</td>
</tr>
<tr>
<td>2014</td>
<td>Bupropion-Naltrexone</td>
</tr>
<tr>
<td>2015</td>
<td>Liraglutide</td>
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</tbody>
</table>
Placebo-subtracted Weight Loss of Obesity Medications (% Weight Loss at 1 Year, ITT-LOCF)
Obesity Pharmacotherapy
Side-effects and Contraindications

Phentermine: dry mouth, insomnia, nervousness, increased heart rate & blood pressure
Contraindications: unstable coronary artery disease, uncontrolled hypertension

Lorcaserin: dry mouth, headache, dizziness, nausea, fatigue, constipation
Contraindications: SSRIs, MAOIs (serotonin syndrome)

Phentermine/Topiramate: dry mouth, headache, dizziness, insomnia, constipation, dysgeusia, paresthesia (fingers, toes, perioral), cognitive impairment (attention/memory), acute glaucoma
Contraindications: pregnancy, hyperthyroidism, MAOIs

Naltrexone/bupropion: dry mouth, headache, dizziness, insomnia, nausea, constipation
Contraindications: MAOIs, opioids, uncontrolled hypertension, glaucoma, uncontrolled pain, Hx seizures or condition that predisposes to seizure (anorexia or bulimia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs)
Effect of Canaglifozin and Phentermine Coadministration on Body Weight in Obesity Without Diabetes

Effect of Canaglifozin (24 Weeks) on Intrahepatic Triglyceride Content in Type 2 Diabetes

# Effect of Liraglutide on Liver Histology and Body Weight

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Liraglutide</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH Resolution</td>
<td>9%</td>
<td>39%</td>
<td>0.02</td>
</tr>
<tr>
<td>Decreased ballooning</td>
<td>32%</td>
<td>61%</td>
<td>0.05</td>
</tr>
<tr>
<td>Decreased steatosis</td>
<td>45%</td>
<td>83%</td>
<td>0.01</td>
</tr>
<tr>
<td>Worse fibrosis</td>
<td>26%</td>
<td>14%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**LEAN:** 1.8 mg/d x 48 wks NAFLD; 1/3 T2D

**SCALE:** 3.0 mg/d x 3 yrs No T2D

Effect of 52 Weeks Semaglutide (SC) in Obesity w/o Diabetes

Weight loss (%)

0 4 8 12

Semaglutide (mg/d)

0.05 0.1 0.2 0.3 0.4 0.3 FE 0.4 FE

Liraglutide 3 mg  Placebo

P. O’Neil et al. Lancet. 2018;
Effect of Semaglutide on Plasma ALT Concentration

Unadjusted for change in body weight

Adjusted for change in body weight

Treatment ratio vs placebo (95% CI)

Criteria for Specific Obesity Drug Selection

Contraindications

Cost

Specific benefits related to mechanism of action:

Orlistat: constipation, high LDL-Cholesterol

Naltrexone/bupropion: food cravings, smokers, depression

GLP-1 agonist or SGLT2i: prediabetes, type 2 diabetes, CVD
Additive Effects of Behavioral Therapy with Pharmacotherapy for Obesity

*Sibutramine withdrawn from market.
Weight Loss Heterogeneity After RYGB Surgery

Effect of Bariatric Surgery on NASH

*RYGB, LAGB, SG, Biliointestinal bypass
Before and after (24% at 1 yr) weight loss

NAFLD Is the Hepatic Manifestation of a Systemic Disease That Benefits from Weight Loss