Pharmacotherapy for Obesity – Important New Options

Are drugs of any use in obesity management?

Presented by
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Conflicts of Interest

- Obesity Advisory Board for Novo Nordisk and Inova
- Advisory Boards for Novo Nordisk, Lilly and Astra Zeneva
- Honoraria from Novo Nordisk, Astra Zeneva, Lilly, Boehringer Ingelheim, Sanofi, Inova and Merke Sharp and Dohme
- Research support from Novo Nordisk and GSK

Key Learning Objectives

- Greatest challenge in obesity management is maintaining weight loss
- Few individuals successfully maintain weight loss with lifestyle
- Modest weight loss has metabolic benefit
- Pharmacotherapies for obesity in Australia
  - Phentermine
  - Liraglutide
  - Orlistat
  - Bupropion / Naltrexone
- Prepare patients for side-effects & explain mechanism of action & expected weight loss

Maintaining weight loss is the greatest challenge in obesity management

Why do most people tend to regain weight after weight loss?

Original Article

Long-Term Persistence of Hormonal Adaptations to Weight Loss

Priya Sumithran, M.B., B.S., Luke A. Prendergast, Ph.D.,
Elizabeth Cederblad, Ph.D., Katrina Pucello, B.Sc., Arthur Shulkes, Sc.D.,
Adamantia Krikotos, Ph.D., and Joseph Proietto, M.B., B.S., Ph.D.
50 patients who were overweight or had obesity lost weight on a 10-week very-low-calorie diet.

References:

Long-term persistence of hormonal adaptations to weight loss: fasting hormonal changes

The result of hormonal adaptations to weight loss

- Increase in appetite
- Increase in preference for high-calorie food
- Reduction in energy expenditure
- Increased propensity to store fat
- Weight regain

Australian algorithm for the management of obesity


Goal of weight loss: BMI centric vs complications centric

Goal: Improve health
- Improve quality of life

' dose-response ' relationships between weight loss and obesity-related complications

Treatment options for Australians with obesity

1. Life-long lifestyle modification
   - Weight loss maintainers from the National Weight Control Registry (NWCR)
     - Moderate exercise for >60 min each day
     - Low energy diet (1400–1700 kcal/day)
     - Frequent self-monitoring of weight

2. Lifestyle modification plus pharmacotherapy
   - Orlistat
   - Phentermine
   - Liraglutide 3mg

3. Surgery (endoluminal therapies)
   - Not accessible for all
   - Not desirable for all

Catenacci VA et al. Obesity 2008;16:153
### Liraglutide 3.0 mg – mechanism of action

**Hypothalamus:**
- Appetite regulation
  - Satiety
  - Fullness
  - Hunger
  - Prospective food consumption
  - Energy intake

Liraglutide lowers body weight through decreased caloric intake and loss of predominantly fat mass.

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**Registered anti-obesity medications in Australia**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Approval Year</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>1996</td>
<td>Increases fat absorption</td>
</tr>
<tr>
<td>Phentermine</td>
<td>1937</td>
<td>Sympathomimetic amine</td>
</tr>
<tr>
<td>Liraglutide 3.0 mg</td>
<td>2010</td>
<td>GLP-1 analogue, central action to reduce hunger</td>
</tr>
<tr>
<td>Naltrexone/Bupropion</td>
<td>1991</td>
<td>Central action to reduce hunger &amp; cravings</td>
</tr>
</tbody>
</table>

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**Liraglutide 3.0mg as an adjunct to lifestyle modification over 52 weeks**

- **Mean baseline weight:** 106 kg
- **Mean baseline BMI:** 38.3
- **Mean baseline weight:** 106 kg

- **Change in weight from baseline (%):**
  - Placebo: 0%
  - Bupropion: 2.4%
  - Liraglutide 3.0 mg: 10.4%

- **64% completed 56 weeks of treatment
- 72% completed 56 weeks of treatment

- **Superscript:**
  - 1. Saxenda® Approved Product Information, December 2015
  - 2. Pi, 2015

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**Scale program – Liraglutide 3.0 mg**

<table>
<thead>
<tr>
<th>Population</th>
<th>Change in weight from baseline (%):</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5% weight loss</td>
<td>6.5% VS 26.8%</td>
</tr>
<tr>
<td>&gt;10% weight loss</td>
<td>3.3% VS 10.0%</td>
</tr>
<tr>
<td>&gt;15% weight loss</td>
<td>1.6% VS 3.1%</td>
</tr>
</tbody>
</table>

- **Placebo**: 0%
- **Bupropion**: 2.4%
- **Liraglutide 3.0 mg**: 10.4%

- **ETD at week 160 [4.9; 7.1]**
- **p < 0.0001**
**Liraglutide – safety and tolerability**

- Subcutaneous injection – 0.6 mg – 3.0 mg once daily
- Gastrointestinal side-effects
  - Nausea and vomiting
  - Gall bladder related events
  - Elevated amylase and lipase levels
  - Pancreatitis?
- Stopping rule if insufficient weight loss after 3 months on max. dose

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**Naltrexone + bupropion – mechanism of action**

- **Bupropion** directly increases POMC activity
- **Naltrexone** blocks negative feedback loop

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**Effect of naltrexone + bupropion** on weight loss in overweight and obese adults (COR-I)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>16 Weeks</th>
<th>20 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=511)</td>
<td>-1.8%</td>
<td>-2.1%</td>
</tr>
<tr>
<td>NB16 (n=471)</td>
<td>-6.7%</td>
<td>-8.1%</td>
</tr>
<tr>
<td>NB32 (n=471)</td>
<td>-6.7%</td>
<td>-8.1%</td>
</tr>
</tbody>
</table>

**Naltrexone / Bupropion Clinical Trial Program**

- **NB16** = naltrexone 16 mg plus placebo
- **NB32** = naltrexone 32 mg plus placebo
- **ITT** = intent-to-treat
- **LOCF** = last observation carried forward

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**Naltrexone + bupropion – safety and tolerability**

- Oral medication given twice a day
- Titrate from 1 to 4 tablets with weekly dose increases
- Contraindications: chronic opioid use, seizure disorder, HT, Bipolar disorder, severe haptic impairment, severe renal impairment
- Side-effects
  - Nausea, vomiting, constipation
  - Headache
  - Insomnia
  - Dry mouth
- Stopping rule if insufficient weight loss after 16 weeks
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Thanks for your attention