The Future of Pharmacotherapy for Obesity

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Disclosure

JP was Chair of the Medical Advisory Board for Liraglutide 3 mg (Saxenda) in Australia for Novo Nordisk. He has also given lectures on management of obesity for iNova marketers of phentermine (Duromine) and naltraxone plus bupropion (Contrave).
Why is pharmacotherapy necessary in the management of obesity?
Diet and behavioural intervention

Very-low-calorie diet
Modified diet plus behaviour therapy
Very-low-calorie diet plus behaviour therapy

Weight change (kg)

Years after intervention
Why do diets nearly always fail?
Why do diets nearly always fail? (and why have we failed to stem the obesity epidemic?)
Diagram of the central regulation of body weight (from Proietto J. MJA 195:144-146 2011)
Changes in leptin levels with dieting

Ghrelin levels after diet-induced weight loss

Body weight is defended

The New England Journal of Medicine

Long-Term Persistence of Hormonal Adaptations to Weight Loss

Priya Sumithran, M.B., B.S., Luke A. Prendergast, Ph.D.,
Elizabeth Delbridge, Ph.D., Katrina Purcell, B.Sc., Arthur Shulkes, Sc.D.,
Adamantia Kriketos, Ph.D., and Joseph Proietto, M.B., B.S., Ph.D.

Mean change in body weight and leptin levels from baseline to Week 62

**Weight**

*P*<0.001 vs baseline (Week 0). Data presented are mean ± standard error of the mean. VLCD = low energy dietary formulation (Optifast VLCD, Nestlé) and 2 cups of low-starch vegetables (500 to 550 kcal/day). ITT, intention-to-treat; VLCD, very low-calorie diet.

**Leptin**

*P*<0.001 vs baseline (Week 0). Data presented are mean ± standard error of the mean. VLCD = low energy dietary formulation (Optifast VLCD, Nestlé) and 2 cups of low-starch vegetables (500 to 550 kcal/day). ITT, intention-to-treat; VLCD, very low-calorie diet.

Mean fasting and postprandial levels of ghrelin, peptide YY, amylin, and cholecystokinin

Data presented are mean ± standard error of the mean.

PYY, peptide YY.

Fasting and postprandial ratings of hunger and desire to eat

Data presented are mean ± standard error of the mean.

The effect of rate of weight loss on long-term weight management: a randomised controlled trial

Katrina Purcell, Priya Sumithran, Luke A Prendergast, Celestine J Bouniu, Elizabeth Delbridge, Joseph Proietto

The Lancet Diabetes and Endocrinol 2: 954-62 2014
Results

• Mean weight change (% change, 95% CI) during phase 2 for study completers

Gradual WL group regained 71.2%
Rapid WL group regained 70.5%

*n=61 in rapid weight loss and n=43 in gradual weight loss group
Hormone changes at 3 year follow-up

- Despite the fact that most of the weight had been regained,
- Ghrelin was still 10% higher than at baseline 3 years after weight loss and
- Leptin was still lower in the 25% of individuals maintaining the most weight loss off.
The defence of body weight also involves changes in energy expenditure
Changes in energy expenditure associated with weight change

Mean (± standard deviation) observed-minus-predicted total energy expenditure based on the regression of total energy expenditure in a model with a variable combining fat-free mass and fat mass in the same subjects at their initial weight.

EE, energy expenditure.
Persistent Metabolic Adaptation 6 Years After “The Biggest Loser” Competition

Erin Fothergill¹, Juen Guo¹, Lilian Howard¹, Jennifer C. Kerns², Nicolas D. Knuth², Robert Brychta¹, Kong Y. Chen¹, Monica C. Skarulis¹, Mary Walter¹, Peter J. Walter¹, and Kevin D. Hall¹

Objective: To measure long-term changes in resting metabolic rate (RMR) and body composition in participants of “The Biggest Loser” competition.

Methods: Body composition was measured by dual energy X-ray absorptiometry, and RMR was determined by indirect calorimetry at baseline, at the end of the 30-week competition and 6 years later. Metabolic adaptation was defined as the residual RMR after adjusting for changes in body composition and age.

Results: Of the 16 “Biggest Loser” competitors originally investigated, 14 participated in this follow-up study. Weight loss at the end of the competition was (mean ± SD) 58.3 ± 24.9 kg (P < 0.0001), and RMR decreased by 610 ± 483 kcal/day (P = 0.0004). After 6 years, 41.0 ± 31.3 kg of the lost weight was regained (P = 0.0002), while RMR was 704 ± 427 kcal/day below baseline (P < 0.0001) and metabolic adaptation was −499 ± 207 kcal/day (P < 0.0001). Weight regain was not significantly correlated with metabolic adaptation at the competition’s end (r = −0.1, P = 0.75), but those subjects maintaining greater weight loss at 6 years also experienced greater concurrent metabolic slowing (r = 0.59, P = 0.025).

Conclusions: Metabolic adaptation persists over time and is likely a proportional, but incomplete, response to contemporaneous efforts to reduce body weight.
### Leptin Levels

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>End of weight loss 30 weeks</th>
<th>6 years after weight loss</th>
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<tbody>
<tr>
<td>Leptin (ng/ml)</td>
<td>41.1 ± 16.9</td>
<td>2.6 ± 2.2*</td>
<td>27.7 ± 17.5*#+</td>
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</tbody>
</table>

* P < 0.001 compared to baseline  
# p = 0.013 compared to baseline  
+ p < 0.001 compared to 30 weeks
What strategies should we adopt to help our patients to maintain weight loss long term?
Lifestyle advice

• Healthy eating
• Regular Exercise
• Measure weight once weekly in the morning with an empty bladder
• When there is 2 kg or weight regain, restart the intense diet and continue it until they have lost the 2 kg.
1. Phentermine
2. [Topiramate]
3. Phentermine 7.5 or 15mg/ topiramate 50 or 100 mg combination
4. Orlistat
5. Liraglutide 3.0 mg
6. Lorcaserin
7. Naltraxone plus bupropion

* Each of these drug or drug combinations have been approved for use in different parts of the World
Medications under investigation

The following medications are under investigation, none have so far been approved for weight management:

• Semaglutide
• Amylin (pramlintide)
• Leptin (Metreleptin)
• Amylin/Leptin combination
• Beloranib
• Combination of gut hormones
The aim of this study was to investigate the effect of a continuous infusion of GLP-1, OXM, and PYY (GOP) on energy intake and expenditure in obese volunteers.
Methods

Obese volunteers were randomized to receive an infusion of GOP or placebo in a single-blinded, randomized, placebo-controlled crossover study for 10.5 hours a day.

This was delivered subcutaneously using a pump device, allowing volunteers to remain ambulatory. Ad libitum food intake studies were performed during the infusion, and energy expenditure was measured using a ventilated hood calorimeter.
Results

Postprandial levels of GLP-1, OXM, and PYY seen post RYGB were successfully matched using 4 pmol/kg/min, 4 pmol/kg/min, and 0.4 pmol/kg/min, respectively.

This dose led to a mean reduction of 32% in food intake. No significant effects on resting energy expenditure were observed.
Major Points about Weight loss medications:

- Nature combines nine gut and pancreatic hormones and several nutrients to suppress hunger so, it is better to use multiple drugs at their lowest doses to control hunger rather than just one drug at a high dose.

- Because weight is predominantly genetic, the hormonal and energy expenditure changes that occur after weight loss, designed to return the weight to its set point, are long lasting. It follows that drug use has to be long term (life-long).