

The Future of Pharmacotherapy for Obesity

Joe Proietto

Professor Emeritus University of Melbourne Head, Weight Control Clinic Austin Health Chair, Clinical Care Committee World Obesity j.proietto@unimelb.edu.au





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



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?)



Regulation of body weight



 $\begin{array}{l} AgRP = agouti-related peptide. CART = cocaine and amphetamine-regulated transcript. CCK = cholecystokinin. CRH = corticotropin-releasing hormone. GLP-1 = glucagon-like peptide. MCH = melanin-concentrating hormone. aMSH = alpha melanocyte-stimulating hormone. NPY = neuropeptide Y. NTS = nucleus of the tractus solitarius. PP = pancreatic polypeptide. PYY = peptide YY. \\ \end{array}$

Diagram of the central regulation of body weight (from Proietto J. MJA 195:144-146 2011)



Changes in leptin levels with dieting



Geldszus R et al. *Eur J Endocrinol* 1996;135:659–62.



Ghrelin levels after diet-induced weight loss



Cummings DE et al. N Engl J Med 2002; 346:1623–30.



Body weight is defended

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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., Adamandia Kriketos, Ph.D., and Joseph Proietto, M.B., B.S., Ph.D.

Sumithran P et al. *N. Engl J Med* 2011;365:1597–604.



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



*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.

Sumithran et al. N Engl J Med 2011;365:1597-604



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



Sumithran et al. N Engl J Med 2011;365:1597–604



Fasting and postprandial ratings of hunger and desire to eat

Week 0 Week 10 Week 62



Data presented are mean ± standard error of the mean.

Sumithran et al. N Engl J Med 2011;365:1597–604



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



*n=61 in rapid weight loss and n=43 in gradual weight loss group



- 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 maitaining 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.

Leibel et al. N Engl J Med 1995;332:621-8



Total (TEE), Resting (REE) and non-resting (NREE) Energy Expenditure



♦ Wt_{initia}

⊖ Wt_{loss-recent}

□ Wt_{loss-sustained}

Rosenbaum M. et al. Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. *Am J Clin Nutr* 2008 88:906-12



Original Article OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Persistent Metabolic Adaptation 6 Years After "The Biggest Loser" Competition

Obesity

Erin Fothergill¹, Juen Guo¹, Lilian Howard¹, Jennifer C. Kerns², Nicolas D. Knuth³, 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 \pm SD) 58.3 \pm 24.9 kg (P < 0.0001), and RMR decreased by 610 \pm 483 kcal/day (P = 0.0004). After 6 years, 41.0 \pm 31.3 kg of the lost weight was regained (P = 0.0002), while RMR was 704 \pm 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.

Obesity (2016) 00, 00-00. doi:10.1002/oby.21538

Obesity 24: 1612-1619 2016





	Baseline	End of weight loss 30 weeks	6 years after weight loss
Leptin (ng/ml)	41.1 ± 16.9	2.6 ± 2.2*	27 .7 ± 17.5*#+
* # +	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.



Pharmacotherapy for obesity*

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



Combination of hormones

Tan T et al. The effect of a subcutaneous infusion of GLP-1, OXM, and PYY on energy intake and expenditure in obese volunteers *J Clin Endocrinol and Metab* 102: 2364-2372 2017





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.





Obese volunteers were randomized to receive an infusion of GOP or placebo in a single-blinded, randomized, placebocontrolled 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.





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.



- 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).