Why is losing weight so difficult and maintaining weight loss even harder?

Presenters: Dr Priya Sumithran & Dr Marlene Tham

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Presenters

General Practitioner and Obesity Doctor.
Director of Melbourne Weight Loss;
Creator of Medical & Mind Weight Loss;
Honorary Research Fellow, Department of Psychiatry, University of Melbourne.

Endocrinologist at Austin Health,
Postdoctoral research fellow at the University of Melbourne, Department of Medicine (Austin)

Learning outcomes

- Explain to patients energy homeostasis and the body's defence against weight loss.
- Outline the stages of the Edmonton Obesity Staging System and summarise how to assign the EOSS score, to identify "at risk" patients.
- Describe pharmacotherapy: indications, contra indications, common side effects, interactions.
- Review the chronic disease model of care for patients with obesity including the setup of a recall system.

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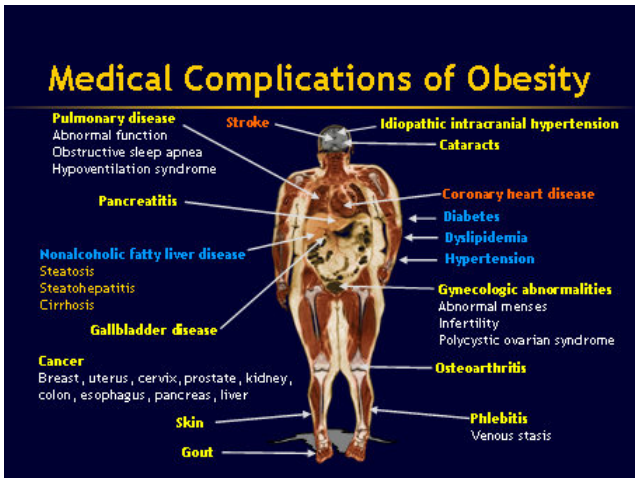
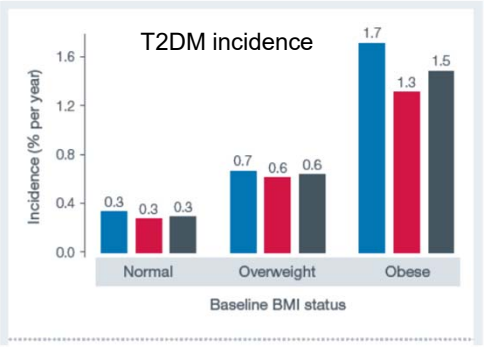
Complications of excess weight



medscape.com

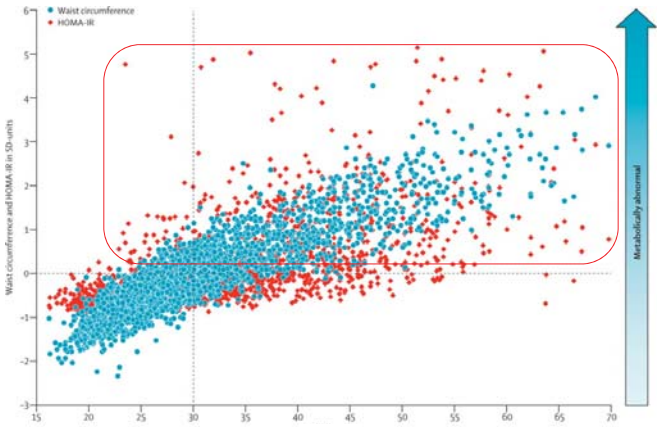
BMI can estimate risks associated with excess weight in populations

BODY MASS INDEX (KG/M²)	
Normal	<25.0
Overweight	25.0–29.9
Obese	≥30.0



AusDiab 2012

...but not in individuals



Stefan, Lancet 2013

Edmonton Obesity Staging System

International Journal of Obesity (2009) 33, 289–295

0307-0565/09 $32.00
www.nature.com/ijo

REVIEW

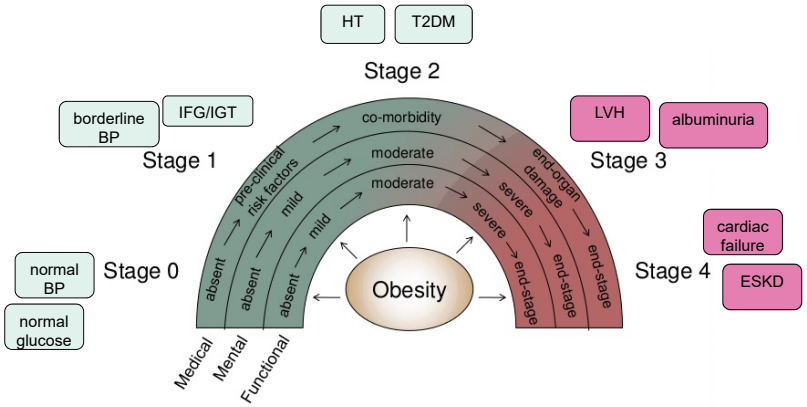
A proposed clinical staging system for obesity

AM Sharma[1] and RF Kushner[2]

[1]Division of Endocrinology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada and [2]Division of General Internal Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

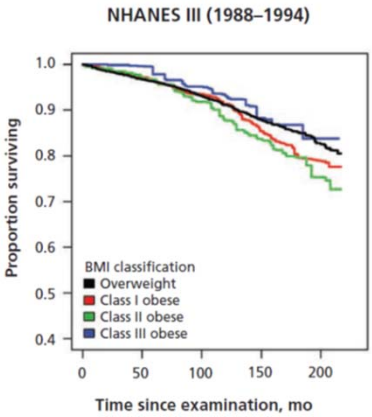
Current classifications of obesity based on body mass index, waist circumference and other anthropometric measures, although useful for population studies, have important limitations when applied to individuals in clinical practice. Thus, these measures do not provide information on presence or extent of comorbidities or functional limitations that would guide decision making in individuals. In this paper we review historical and current classification systems for obesity and propose a new simple clinical and functional staging system that allows clinicians to describe the morbidity and functional limitations associated with excess weight. It is anticipated that this system, when used together with the present anthropometric classification, will provide a simple framework to aid decision making in clinical practice.
International Journal of Obesity (2009) 33, 289–295; doi:10.1038/ijo.2009.2; published online 3 February 2009

EOSS

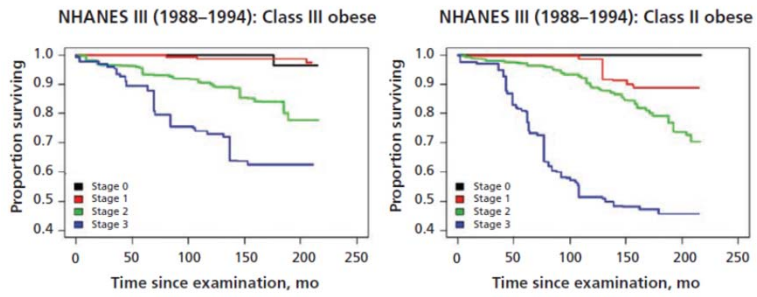


www.drsharma.ca Sharma AM & Kushner RF, *Int J Obes* 2009

Using the Edmonton obesity staging system to predict mortality in a population-representative cohort of people with overweight and obesity



Padwal, CMAJ 2011



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Padwal, CMAJ 2011

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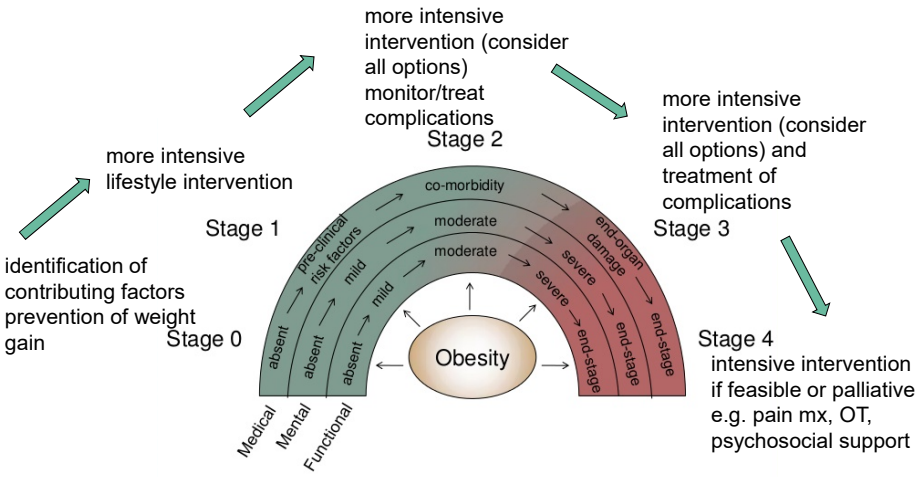
EOSS may be used to guide management



www.drsharma.ca Sharma AM & Kushner RF, *Int J Obes* 2009

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Case examples

Case 1

24 yo woman
BMI 32 kg/m^2

Physically active
No functional limitations
Normal BP and fasting glucose
No mental health issues

Class 1, Stage 0 Obesity

Sharma, Int J Obes 2009

Case 2

32 yo man
BMI 36 kg/m^2

Hypertension
Obstructive sleep apnoea
Depression

Class 2, Stage 2 Obesity

Sharma, Int J Obes 2009

Case 3

45 yo woman
BMI 54 kg/m^2

Arthritis – wheelchair

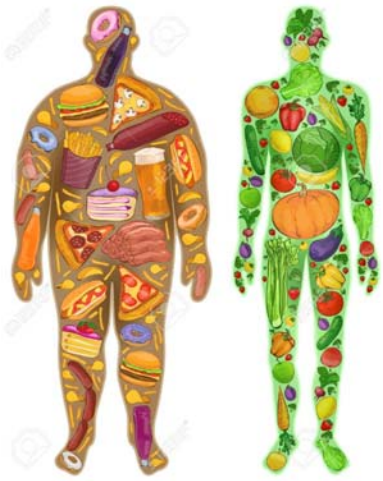
Class 3, Stage 4 Obesity

Sharma, Int J Obes 2009

Summary

- BMI is a useful measure of health risks in populations but not for individuals
- EOSS provides a framework for clinical staging of obesity according to severity of complications
- EOSS stage predicts mortality better than BMI
- EOSS can be used to guide management decisions

Regulation of body weight



Weight is genetically determined

There was a strong relation between the weight class of the adoptees and the body-mass index of their biologic parents — for the mothers, P<0.0001; for the fathers, P<0.02. There was no relation between the weight class of the adoptees and the body-mass index of their adoptive parents.

Volume 314 JANUARY 23, 1986 Number 4

AN ADOPTION STUDY OF HUMAN OBESITY

Furthermore, the relation between biologic parents and adoptees was not confined to the obesity weight class, but was present across the whole range of body fatness — from very thin to very fat. We conclude that genetic influences have an important role in determining human fatness in adults, whereas the family environment alone has no apparent effect.

Abstract ... parents. Cumulative distributions of the body-mass index ... effect. (N Engl J Med 1986; 314:193-8.)

BMI- Intrapair Correlations

Type	Correlation Men	Correlation Women
Monozygotic Reared together	0.74	0.66
Dizygotic Reared together	0.33	0.27

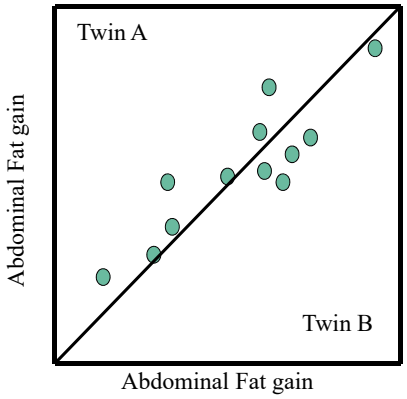
Stunkard AJ NEJM 1990

BMI- Intrapair Correlations

Type	Correlation Men	Correlation Women
Monozygotic		
Reared apart	0.70	0.66
Reared together	0.74	0.66
Dizygotic		
Reared apart	0.15	0.25
Reared together	0.33	0.27

Stunkard AJ NEJM 1990

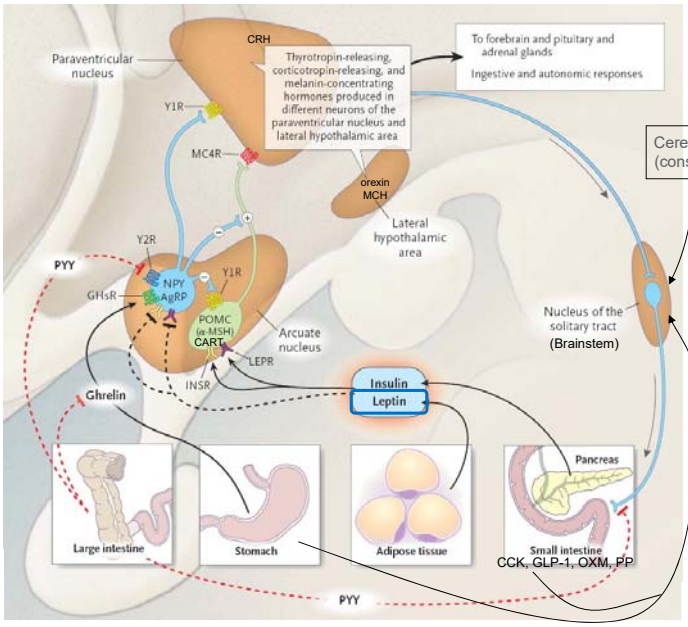
Genetic influence on effect of overfeeding



Bouchard C NEJM 1990

Weight is regulated by the brain

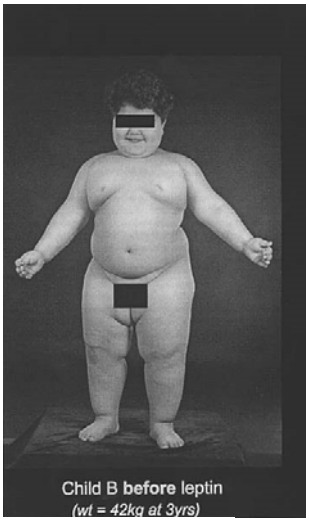
Central regulation of appetite



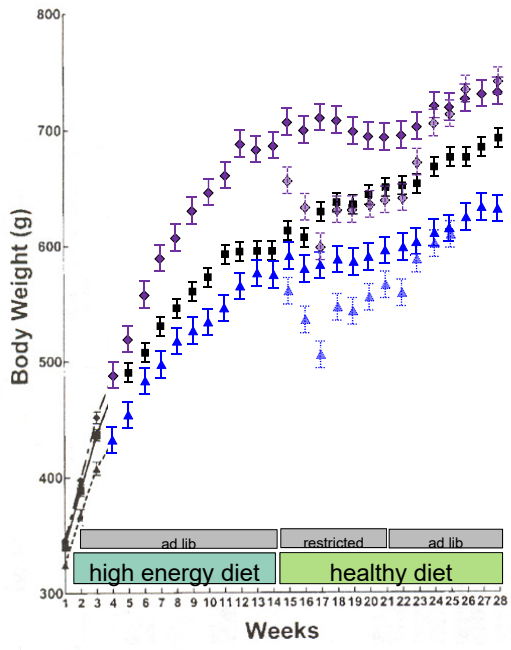
modified from Korner 2003

Leptin Deficiency

Leptin Deficiency



Weight is regulated homeostatically

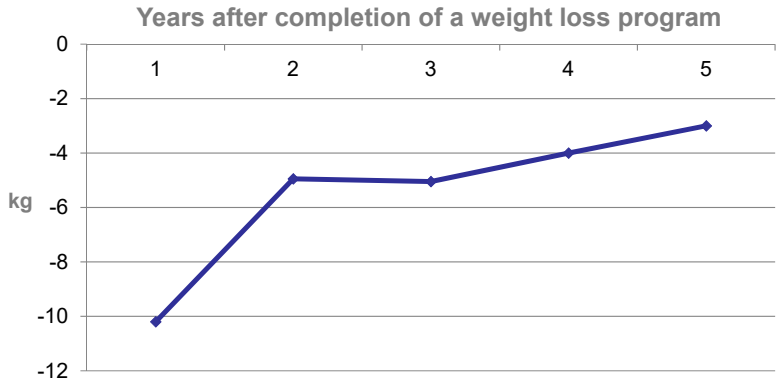


This suggests that in genetically susceptible rats, some component of a high fat diet triggers an obesity phenotype which is then defended – a true gene-environment interaction

Is there a human equivalent to this phenomenon?

Levin BE *Am J Physiol* 2000

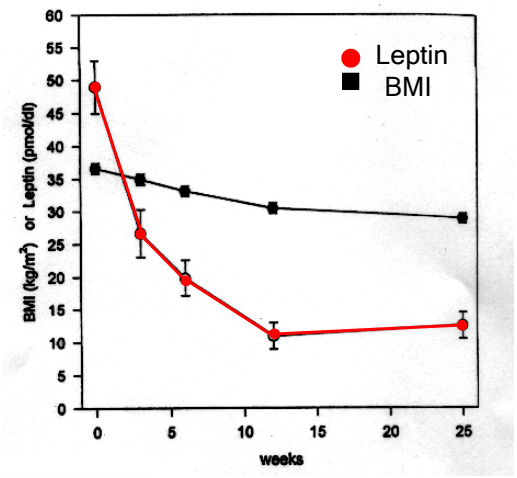
Weight loss maintenance



Anderson 2001

Physiological adaptations to weight loss

Change in leptin with dieting



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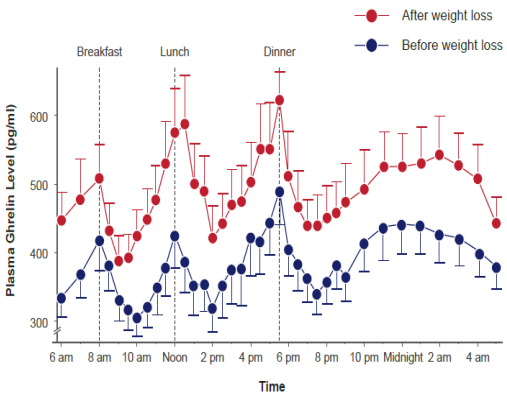
Geldszus *Eur J Endocrinol* 1996

Change in ghrelin with dieting



Cummings *NEJM* 2002

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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.

Change in body weight

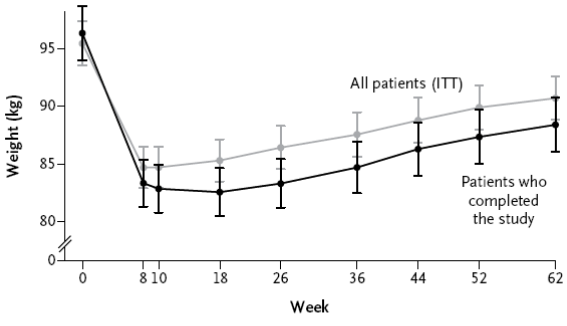

Figure 1. Mean (±SE) Changes in Weight from Baseline to Week 62.

The weight-loss program was started at week 0 and completed at week 10. ITT denotes intention to treat.

Sumithran *NEJM* 2011

Persistence of hormone changes

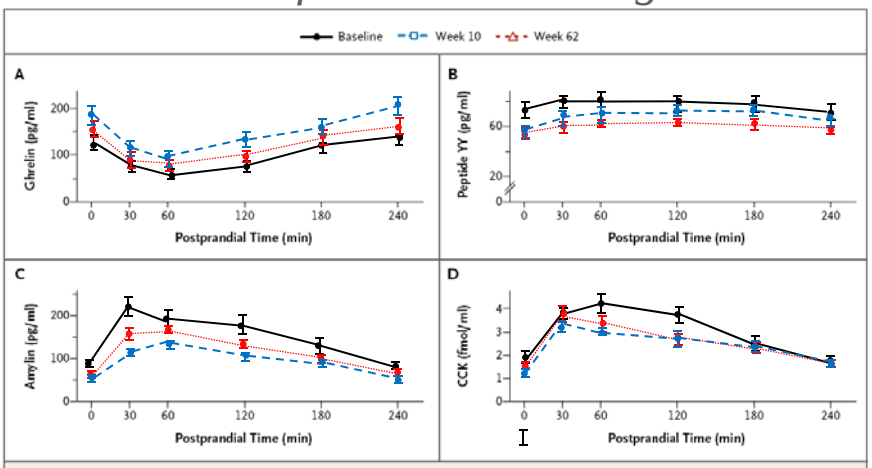

Figure 2. Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.

Sumithran *NEJM* 2011

Persistence of appetite changes

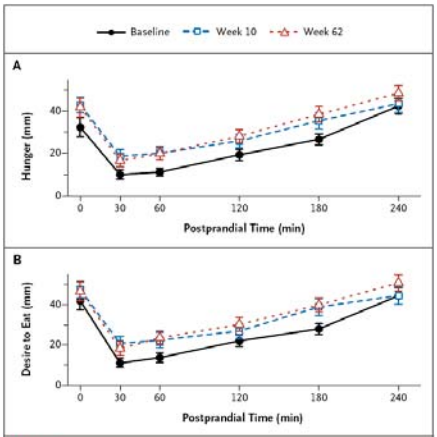

Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.
Ratings were based on a visual-analogue scale ranging from 0 to 100 mm. Higher numbers indicate greater hunger or desire.

Sumithran *NEJM* 2011

Summary of changes

Factor	Action	Change with weight loss
Leptin		↓
Insulin		↓
CCK		↓
Am		
PY		
GLP-1		↔
PP		↑
Ghrelin	↑ appetite	↑
GIP	↑ fat storage	↑
Appetite		↑

Changes are persistent

The defence of body weight also involves changes in energy expenditure

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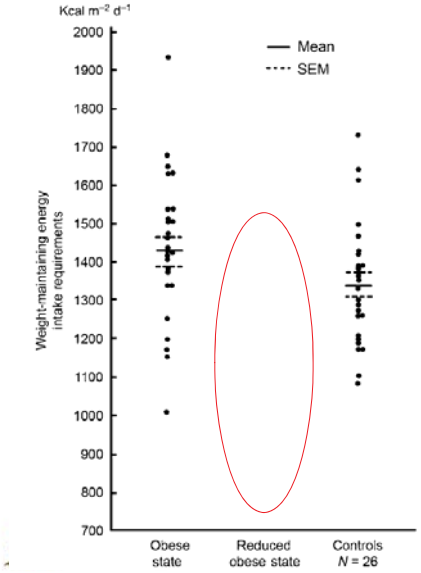
Reduced energy expenditure



- Reduced-obese showed 20% reductions in TEE beyond what could be accounted for by reduced body mass and composition (Leibel 1984)
- Not compensated for by proportional decrease in energy intake. In fact, hunger was increased (Leibel 2008)
- Largely due to increased muscle efficiency (Rosenbaum 2003, see also Goldsmith, Joanisse 2010)
- Equivalent reductions in obese and lean (Leibel 1995)

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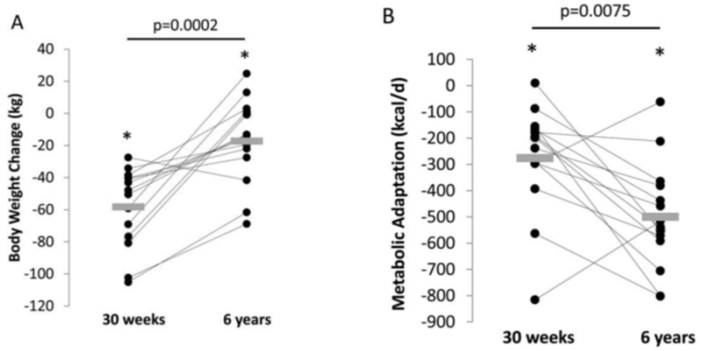
Persistent Metabolic Adaptation 6 Years After "The Biggest Loser" Competition

Erin Fothergill[1], Juen Guo[1], Lilian Howard[1], Jennifer C. Kerns[2], Nicolas D. Knuth[3], Robert Brychta[1], Kong Y. Chen[1], Monica C. Skarulis[1], Mary Walter[1], Peter J. Walter[1], and Kevin D. Hall[1]



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Fothergill *Obes* 2016

Summary

- Body weight is predominantly determined by genetic background
- Body weight is homeostatically regulated
- Multi-faceted long-lasting physiological adaptations occur in response to weight loss
  - this explains why weight regain is so common
  - this means that weight-reduced people must fight biology, indefinitely, in order to maintain weight loss
  - strategies to assist them, including control of appetite with pharmacotherapy and bariatric surgery, may be necessary

The role of pharmacotherapy in managing obesity:

How can we use these medications in General Practice

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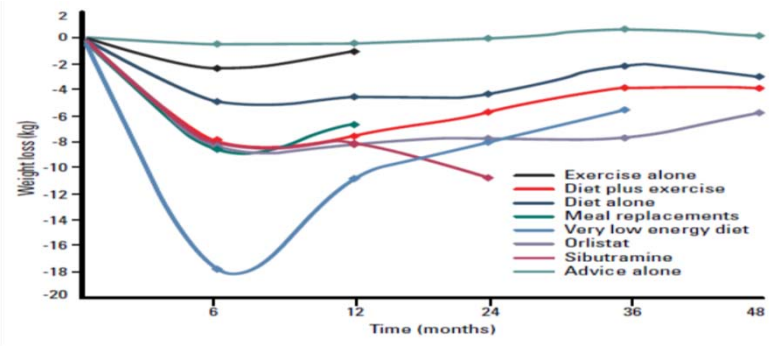
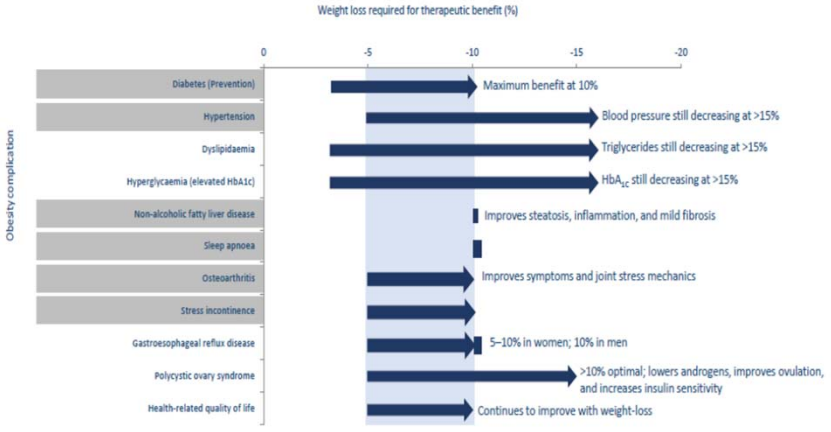
Non surgical weight loss therapy



Average weight loss of subjects completing a minimum 1 year weight management intervention; based on review of 80

5–10% weight loss is clinically meaningful



Cefalu WT et al. Diabetes care 2015;38(8):1567-82. Wright F et al. J Health Psychol. 2013;18:574-86.

Quick poll

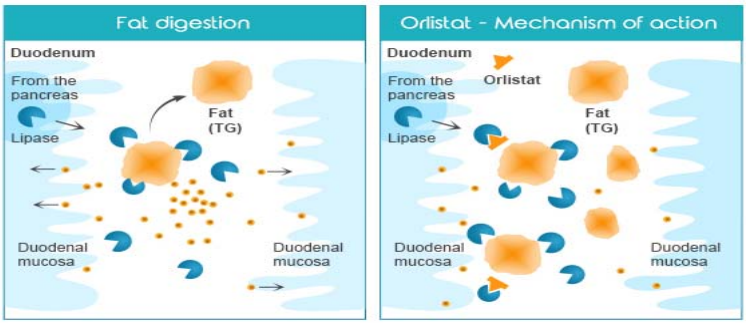
Which of these medications for have you used for managing patients with obesity?

Quick poll

Which of these medications are you comfortable and confident using on your patients?

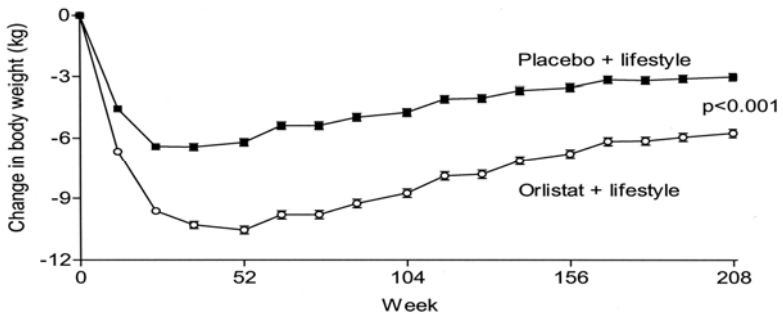
Orlistat

Lipase Inhibitor



Taken from Alfadoc *2017*

Effect of long term use of Orlistat on body weight



Weight loss during 4 years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients

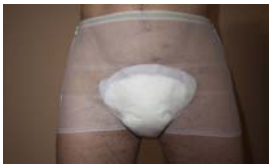
Torgenson et al. Diabetes Care 2004;27:155

Orlistat - Tolerability

- Dosing: Oral medication given three times a day
- Peripheral mechanism of action in intestinal lumen

- Side effects: faecal incontinence and fatty or oily stools, fat soluble vitamin malabsorption
- Rare effects: severe liver injury, potential risk of kidney injury, pancreatitis and kidney stones

- Contraindications: pregnancy

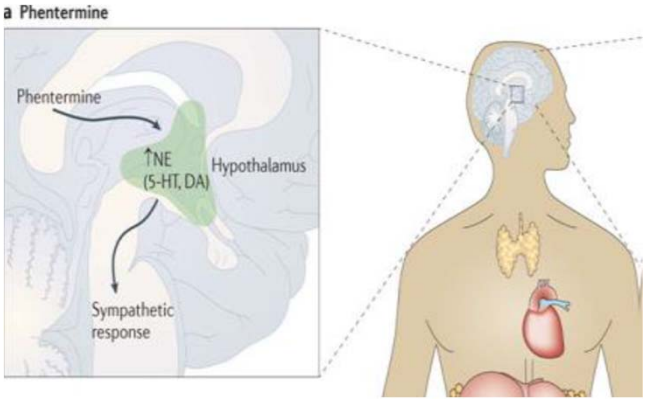


Impression:

- Accessible, over the counter
- Does not help with centrally meditated hunger such as those induced by medications
- Social implications

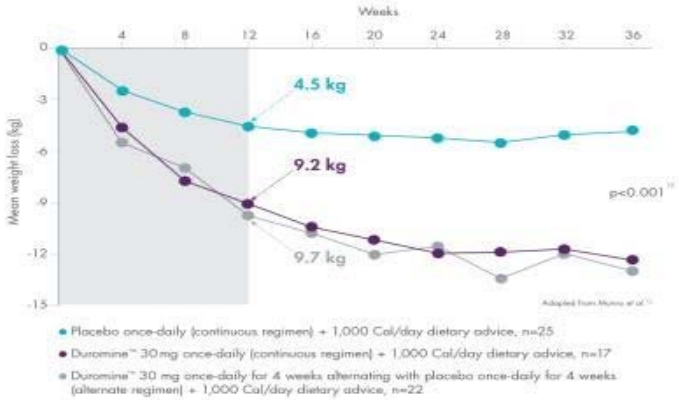
Phentermine

- Centrally acting sympathomimetic, anorectic agent



Dietrich & Horvath . Nature Reviews Drug Discovery11,675-691(September 2012)

Phentermine: weight loss over 36 weeks



Phentermine - Tolerability

Dosing: 15mg, 30mg or 40mg given once daily
Duration: recommended for 12 weeks with a review for further use

Side effects Cardiovascular: hypertension, tachycardia
CNS: insomnia, restlessness and mood changes, agitation
Others: dry mouth, reduced sex drive

Contraindications: Severe hypertension, cardiovascular disease, glaucoma, history of drug and alcohol abuse, psychiatric illness, pregnancy

Drug interactions: SSRIs (serotonergic effect) and MAO inhibitors

Phentermine: Impression

Impression

- Addictive potential: minimal effects on dopamine and serotonin
- Most adults can tolerate 30mg, but adjust for side effects and effectiveness
- Can be used longer term if no side effects: Consider "Pulse" therapy with several courses of medication if working.
  Concerns: Cardiovascular and mental health.
- Generally hypertension improves with weight loss

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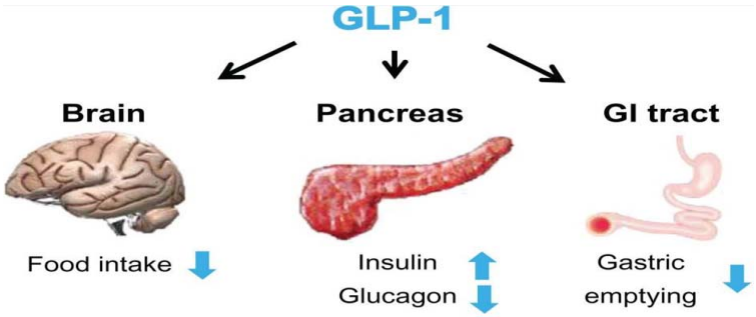
Liraglutide

glucagon-like peptide-1 (GLP-1) agonist



Yabe D, Seino Y. Liraglutide in Adults with Type 2 Diabetes: Global Perspective on Safety, Efficacy and Patient Preference. *Clinical Medicine Insights Endocrinology and Diabetes*. 2011;4:47-62. doi:10.4137/CMED.S5976.

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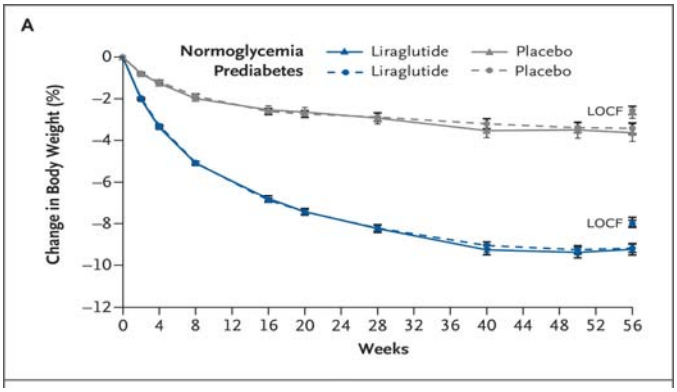
Liraglutide: Change in body weight after 56 weeks



3.2% (placebo) vs 9.2% (3.0mg Liraglutide) p< 000.1

Adapted from: Pi-SunyerX *et al. NEJM* 2015;373:11–22;

Liraglutide

- Self administered daily injection
- Consider using if poorly controlled diabetes, insulin resistance, pre-diabetes, PCOS, FHX Diabetes

- Main side effects: nausea, vomiting, diarrhoea, constipation, fatigue, rashes
- Less common, (but more serious): hypoglycaemia pancreatitis, gallbladder disease, renal impairment, mood changes, increased depressive behaviour suicidal thoughts.
- Drug Interactions: careful with insulin use
- Contraindications: Severe renal & hepatic insufficiency, pregnancy, PHX pancreatic Ca, Major depression & psychiatric illness

Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0mg of Liraglutide in Weight Management. N Engl J Med 2015; 373: 11

Liraglutide: Impression

Application to mental health population in General Practice

- Effective appetite suppressor, especially at "stopping" the hunger + improvement in insulin resistance

The evidence:

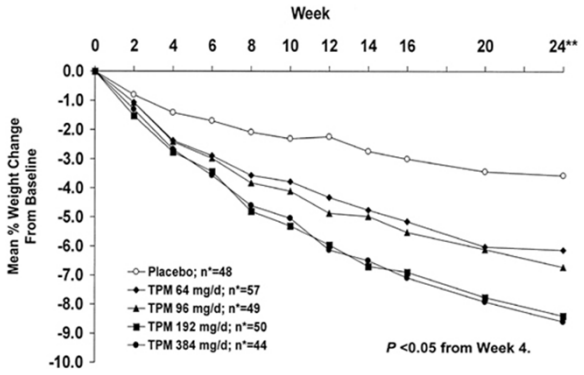
- Efficacy and safety in psychiatric patients yet to be demonstrated

  NEJM study (Pi-Sunyer, et al, 2015) , major depressive disorder or suicide attempt excluded. 6 out of 3384 (0.2%) reported suicidal ideation. (1 yr data)
- Low or negligible risk of "overdose", unless combined with insulin

Key points:

- Work with psychiatrist, and inform of commencement
- Monitor every week for the first month

Topiramate: weekly weight loss



A 6-Month Randomized, Placebo-Controlled, Dose-Ranging Trial of Topiramate for Weight Loss in Obesity

Bray, ObesRes. 2003;11(6):722-33

Topiramate

Cheap and accessible
"Off label" and "known by pharmacists as the "dirty drug"

Dosing: 12.5mg to 100mg. Start low, go slow
Start 12.5mg, then 25mg. Up by 25mg every 2 weeks.

Side effects:
Common: parathesia, "pins and needles"
Less common: brain "fog" or "cognitive dulling", drop in fatigue, "sleepiness" mood, suicidal ideation, lowered mood
Rarer: Increased myopia and angle closure glaucoma

Contraindications: glaucoma, renal stones, pregnancy

Drug Interactions: Other anti-convulsants, Sodium Valproate (Serotonin syndrome), Lithium Toxicity

Topiramate: Impression & Application

- Cheap: $13-$20/ month
- Tablet (for people with needle phobia)
- Dual benefits: migraines prevention & treatment
- Mental health: Drop in mood can happen quickly, and dramatically but uncommon. Need to watch closely initially.
  Also can used as a mood stabiliser
- Most common side effects: "pins and needles" & headaches

Medications that cause weight gain

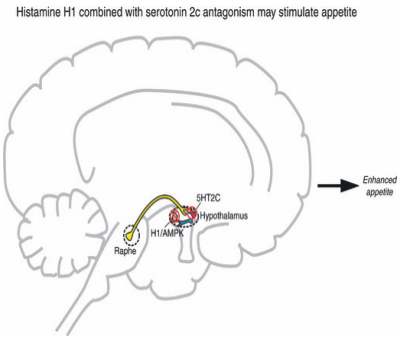
- Psychotropics: anti-depressants, anti-psychotics, mood stabilisers
- Antihistamines:
- Anti-convulsants
- Steroids (prednisolone)
- Antihypertensives - beta blockers (atenolol, metoprolol)
- OCP (Diane, Microgynon 50)

Psychotropic weight gain

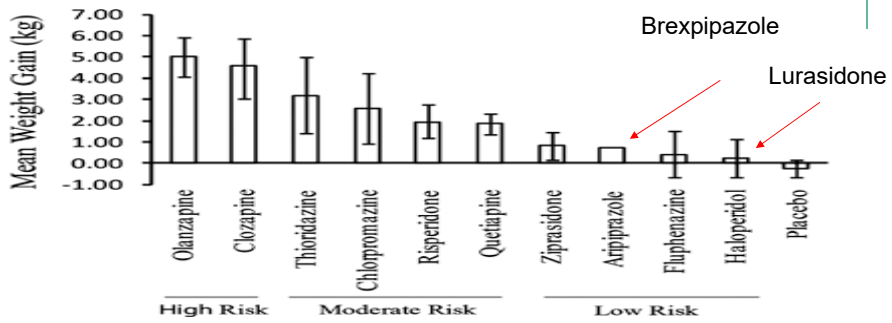
Mechanism of antipsychotics
•a central effect in the hypothalamic control of appetite regulation

•Blocking of 2 key receptors in the brain serotonin (5HT2c) and Histamine (H-1)

•40 -80% of patients taking an Antipsychotic drug experience weight gain



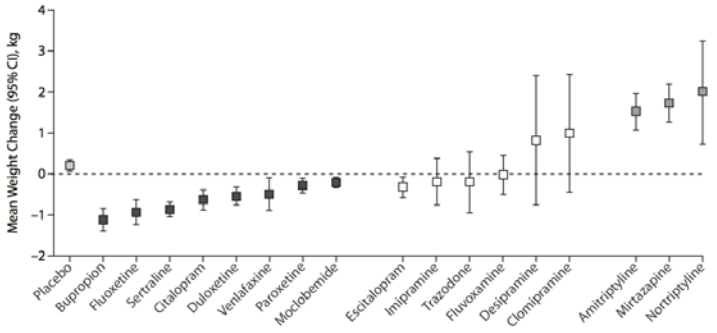
Antipsychotic associated weight gain risk



Lett et al, Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Molecular Psychiatry* (2012) **17,** 242–266; doi:10.1038/mp.2011.109; published online 6 September 2011

Anti-depressant weight gain on Commencement

Figure 2. Weight Change During Acute Treatment With Different Antidepressants[a]



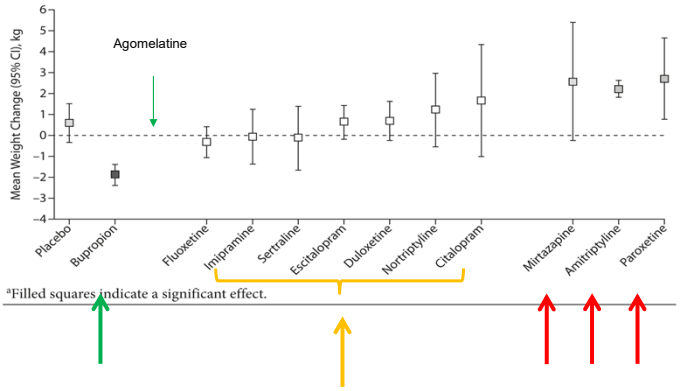
[a]Filled squares indicate a significant effect.

1-3kg average weight gain for 10-20% of population treated by them

Serretti & Mandelli, **Antidepressants and body weight: a comprehensive review and meta-analysis.** The Journal of Clinical Psychiatry [01 Oct 2010, 71(10):1259-1272]

Weight Gain Long Term

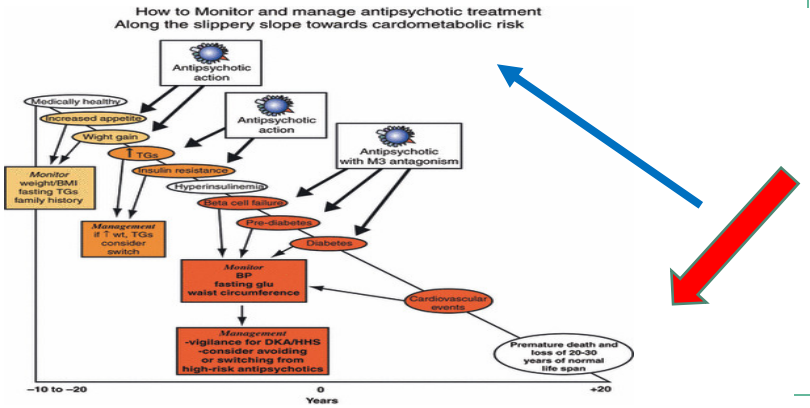
Figure 3. Weight Change During Maintenance Treatment With Different Antidepressants[a]



Green – Loss
Yellow – neutral
Red - Gain

Serretti & Mandelli, **Antidepressants and body weight: a comprehensive review and meta-analysis.** The Journal of Clinical Psychiatry [01 Oct 2010, 71(10):1259-1272]

The Metabolic Highway



Stahl's Essential Psychopharmacology, 3rd edition, 2008

Case 1: Gina

- 35 year old woman
- Single with no partner
- Works full-time as a PA
- Weight: 108 kg (BMI of 35)

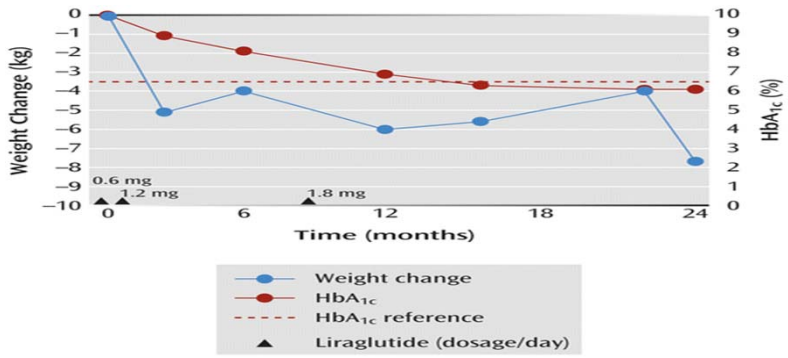
PMHx

- Bipolar Affective - Lithium 400mg BD, Quetiapine 100mg nocte, Desvenlafaxine
- Type 2 Diabetes -metformin 1000mg BD
  - Last HBA1c 10.1

Quick poll

Which anti-obesity medications would you consider for Gina?

Impact of Liraglutide on HBA1c and weight with psychotropic associated obesity



Ishøy PL, et al. Treatment of antipsychotic-associated obesity with a GLP-1 receptor BMJ Open 2014;4:e004158

Case 2: Russell

- 45 year old male
- Living with girlfriend
- Partner at law firm
- Weight: 115 kg (BMI of 34)

PMHx

- Fatty Liver – drinks 10 drinks a week
- Sleep Apnoea – on CPAP machine
- Hypercholesterolaemia – 40mg Atorvastatin
- OA of bilateral Knees R worse than L

Quick poll

Which anti-obesity medications would you consider for Russell ?

Case 3: Kim

- 26 year old woman
- married
- Stay-at-home mother of 2 children under 5
- Weight: 79 kg (BMI of 29)

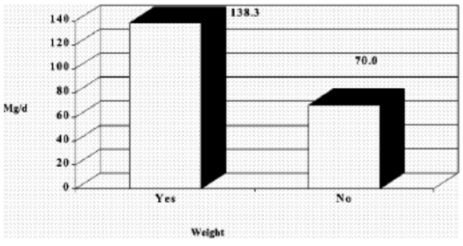
PMHx

- Insomnia – possible from having poor sleeping young children
- Migraines – once every month, lasting ½ day. Managed on aspirin and sleep. But increasing in frequency.
- Mother had thyroid cancer, surgical management

Quick poll

Which anti-obesity medications would you consider for Kim?

Topiramate dose for weight loss



- 50% reported weight loss (mean loss 6kg)
- No weight loss below 70mg, mean dose used 138.3 mg
- Mild improvements in mood
- Topiramate response and weight amount were both dose dependent

Ghaemi et al, Topirimate treatment of Psychiatric Disorders; Anals of Clinical Psychiatry, Vol 13, No. 4, December 2001

There is not a "one size fits all solution" for prescribing.

Things to consider

- Affordability
- Patient's goals
- Best predictor of long term weight loss is early weight loss
- More than 5% after 3 months – "Stoppi
- Phobias such as needles or tablets
- Side effects
- Other medications
- Relationship with specialists
- Ability to be reviewed
- Consider combination therapy

Role of pharmacotherapy in Weight loss Maintenance

- Patients often plateau at 6 months
- Try introducing a new agent or" pulse" therapy
- Beyond this pharmacotherapy appears to promote weight maintenance
- Combine for better outcomes with
  - VLCD
  - high protein diets
  - Lifestyle

Those who stay on anti-obesity medication have better long term outcomes
Liraglutide produced moderate but statistically significant improvements in several cardiometabolic risk factors compared with placebo when introduced after 1 year of weight loss (Wadden)

- 5% ceiling approach, for those who want to "attempt" coming off

Wadden, Int J Obes (Lond). 2013 Nov;37(11):1443-51. doi: 10.1038/ijo.2013.120. Epub 2013 Jul 1.

Obesity is a chronic disease

"Obesity is a complex, lifelong, progressive, costly, genetically related, multifactorial chronic disease which needs sustained long term management"

- It requires multi-modal management
- Pharmacotherapy plays a key role to long term management for both initial weight loss and weight loss maintenance
- In chronic disease we many have to combine medications and interventions

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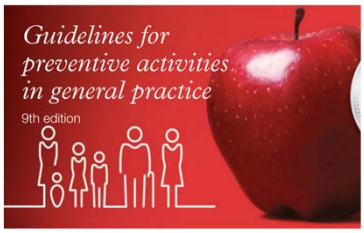
Recall Systems

2 yearly
Screening: Measure waist circumference and calculate BMI:
every 2 years in all patients

Yearly
for adults: with DM, CVD, stroke, gout, liver diagnosis
OR
from high risk groups (e.g. Aboriginal, Torres Strait, Pacific Islands)

every 6 months
for those already overweight



Drugs in the pipeline

- Phentermine and Topiramate (Sequel Study)
- selective 5-HT2C receptor agonist (Bloom)
- Naltrexone + bupropion (COR-1 STUDY)

Concluding points

- There is no one “best medication” for managing obesity
- Choose based on co-morbidities, costs, patient preference & goals
- If one doesn’t work, try another. There are “non responders, not failures”
- Like all chronic diseases, relapses occur
- Know and use the common anti-obesity medications first.
- Then look at combinations and/or future drugs
- Celebrate non-weight goals
- Be prepared to review patients regularly and communicate with specialists
- This is a chronic, relapsing, progressive condition which requires a muli-modal, multi-factorial approach

Questions?

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Thank you!

This is the end of the educational component.

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