Obesity: The Role of Pharmacotherapy

Professor John B Dixon, MBBS PhD

Professorial Research Fellow
Head, Clinical Obesity Research
Baker IDI Heart & Diabetes Institute
Melbourne, Australia

The Annual Women's & Children's Health Update
Saturday 16th June 2018

Baker

Disclosures: Professor John B Dixon

Apollo Endosurgery	Consultant
Bariatric Advantage	Consultant
BUPA	Research Support
I-Nova	Consultant
Medtronics	Consultant
Nestle Health Science	Consultant
NHMRC	Research Support
Nova Nordisk	Advisory board and speaker fees
Novartis	Advisory board and speaker fees

Pharmacotherapy for obesity
AFP July 2017

Phong Ching Lee, John Dixon

Lee, P. C. and J. Dixon (2017). "Pharmacotherapy for obesity." Aust Fam Physician **46**(7): 472-477.

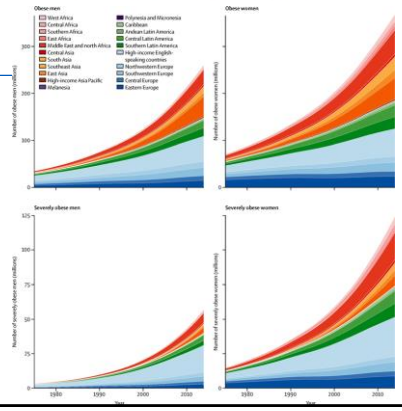
Baker

Global & Regional Obesity

High income English speaking counties

BLUE

Global & Regional Severe obesity



ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: The Year in Diabetes and Obesity

Managing obesity in primary care practice: a narrative review

Raymond Carvajal,[1] Thomas A. Wadden,[1] Adam G. Tsai,[2] Katherine Peck,[1] and Caroline H. Moran[1]

Clinically meaningful weight loss results are not achieved in the primary care setting– 1-3% at 6 months to 2 years

These quite intensive combination behavioural programs struggle to achieve 5% or 5kg weight loss

Achieving 5% is currently not achievable for the majority at 12 months and less likely at 2-years

Carvajal et al. Ann NY Acad Sci 2013;1281;191-206.

Baker

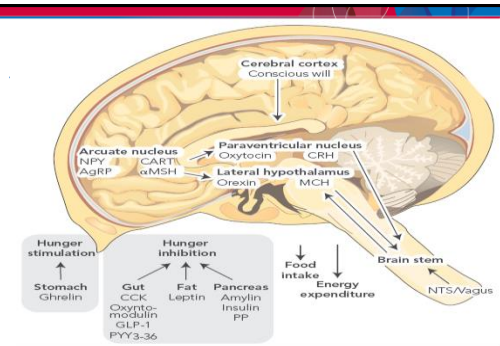
Benefits of modest weight loss 5-10%

Obesity complication	Weight loss required for therapeutic benefit (%)	Notes	References
Diabetes (prevention)	3–10	Maximum benefit at 10%	DPP Research Group, 2009 (63) Garvey et al., 2014 (64)
Hypertension	5 to >15	Blood pressure still decreasing at >15%	Wing et al., 2011 (65)
Dyslipidemia	5 to >15	Triglycerides still decreasing at >15%	Wing et al., 2011 (65)
Hyperglycemia (elevated A1C)	3 to >15	A1C still decreasing at >15%	Wing et al., 2011 (65)
NAFLD	5	Improves steatosis, inflammation, and mild fibrosis	Mohr et al., 2007 (66) Dixon et al., 2008 (67) Patel et al., 2009 (68)
Sleep apnea	10	Little apnea at 10%	Foster et al., 2009 (69) Winslow et al., 2012 (70)
Osteoarthritis	5–10	Improves symptoms and joint stress mechanics	Christensen et al., 2007 (71) Felson et al., 1992 (72) Aaboe et al., 2011 (73)
Stress incontinence	5–10		Burgio et al., 2007 (74) Subak et al., 2009 (75)
Gastroesophageal reflex disease	5–10 in women; 10 in men		Singh et al., 2013 (76) Tutuian, 2011 (77)
Polycystic ovary syndrome	5–15 (>10 optimal)	Lowers androgens, improves ovulation, and increases insulin sensitivity	Panidis et al., 2008 (78) Norman et al., 2002 (79) Moran et al., 2013 (80)

The US FDA, EMA and our TGA use these cutpoints in assessing drug efficacy

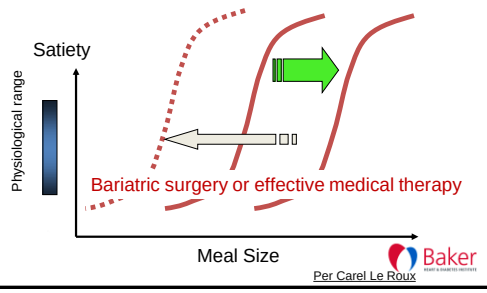
Cefalu WT, Bray GA, Home PD, et al. *Diabetes care.* Aug 2015;38(8):1567-1582.

Baker



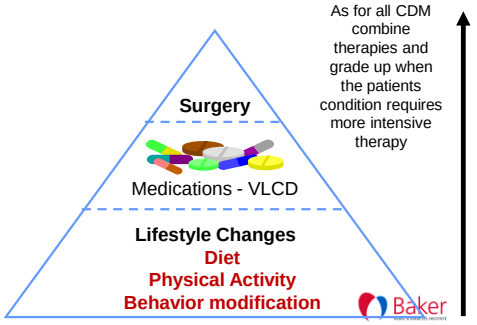
AgRP = agouti-related peptide. CART = cocaine and amphetamine-regulated transcript. CCK = cholecystokinin. CRH = corticotropin-releasing hormone. GLP-1 = glucagon-like peptide. MCH = melanin-concentrating hormone. αMSH = alpha melanocyte-stimulating hormone. NPY = neuropeptide Y. NTS = nucleus of the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

Dose response curve
"A change in regulation"



Per Carel Le Roux

Obesity Treatment Pyramid



Mechanisms

Reduce energy intake

Nutrient malabsorption

Supress appetite by effects on the central control of energy balance

Increase energy expenditure

- Stimulate brown fat
- Non-exercise activity thermogenesis (NEAT)
- Generate metabolic inefficiency

Aim: To reset energy balance

Indications for weight management pharmacotherapy

BMI >30 kg/m^2, or those with a

BMI of 27–30 kg/m^2 with obesity-related risks and complications.

Lower BMI thresholds (BMI >27 kg/m^2, or BMI >25 kg/m^2 with obesity-related complications) should be considered in Aboriginal and Torres Strait Islander and Asian populations.

The importance of a stopping rule

There is no point

- in taking a drug that is not effective
- in continuing a drug that produces unacceptable side-effects
- In taking drug if it increases net risk of future disease

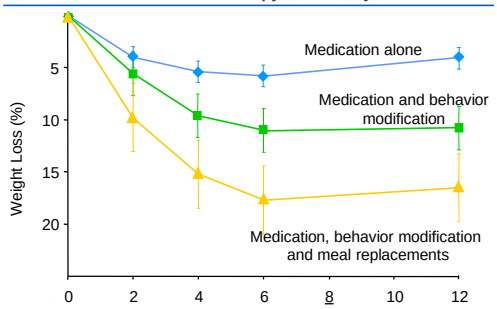
There is no point

- in stopping an effective drug if well tolerated and reduces risk

3-months on the full dose is usually a sufficient time to assess effectiveness

In chronic disease management we often combine therapy for greater efficacy so we need additional time if we increase therapy when synergy is expected

Additive Effects of Behavior and Meal Replacement Therapy With Pharmacotherapy for Obesity

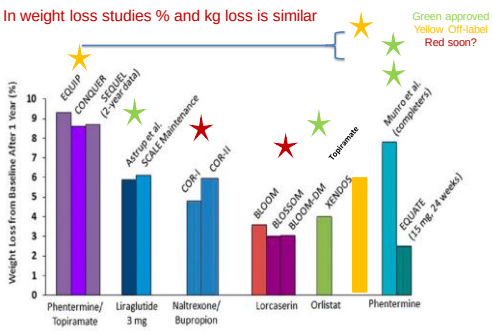


Wadden et al. *Arch Intern Med* 2001;161:218.

Comparison of weight loss medications at 1-year (placebo subtracted – ITT – LOCF)

In weight loss studies % and kg loss is similar

Green approved
Yellow Off-label
Red soon?



I am going to focus on the use of the 4 drugs we have available in Australia today

Orlistat (Xenical, Alli)

Phentermine (Duromine, Metermine)

Topiramate (Many) Off Label for weight loss

Liraglutide (Saxenda)

How to use them and combine them?

Orlistat prevention of diabetes study

XENDOS

4-year, double-blind, prospective study

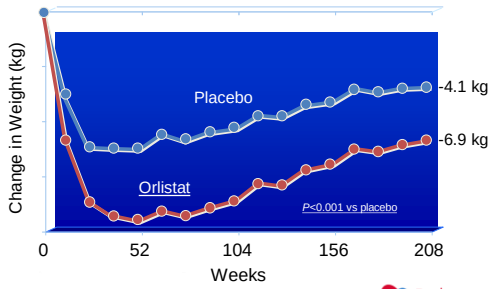
3,305 randomized to lifestyle changes plus either orlistat 120 mg or placebo, three times daily

BMI >/=30 kg/m2 and normal (79%) or impaired (21%) glucose tolerance (IGT)

Primary endpoints were time to onset of type 2 diabetes and change in body weight.

Torgerson JS. Et al. Diabetes Care 2004;27:155-61.

Effect of Long-term Orlistat Therapy on Body Weight



Torgenson et al. Diabetes Care 2004;27:155

Results at 4 years

52% completed in the treatment group compared with 34% of placebo recipients (P < 0.0001)

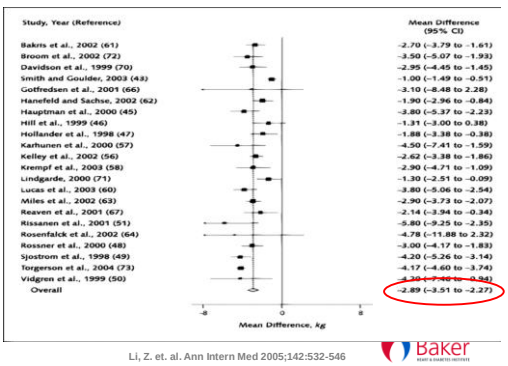
Diabetes incidence 9.0% with placebo and 6.2% with Orlistat a risk reduction of 37.3% (P = 0.0032)

Orlistat plus lifestyle changes resulted in a greater weight loss and reduction in the incidence of type 2 diabetes.

The latter restricted to the IGT group

Torgerson JS. Et al. Diabetes Care 2004;27:155-61.

Weight loss with orlistat versus placebo at 12 months



Li, Z. et. al. Ann Intern Med 2005;142:532-546

Side effects – related to fat malabsorption

- Steatorrhea, oily spotting, bloating and flatulence with discharge, faecal incontinence
  - Effects attenuated on a low fat diet
- Oxalate kidney stones – associated with fat malabsorption
- Fat-soluble vitamin deficiency – in the long term
  - Supplement and use caution with patients on warfarin

Drew, B. S., et al. (2007). "Obesity management: update on orlistat." Vasc Health Risk Manag **3**(6): 817-821.

- This drug is well tolerated in the long term and has beyond weight loss benefits in those with type-2 diabetes

Jacob S, Rabbia M, Meier MK, Hauptman J. Orlistat 120 mg improves glycaemic control in type 2 diabetic patients with or without concurrent weight loss. Diabetes Obes Metab 2009;11(4):361–71.

Baker

All other medications act centrally to reduce energy intake

When asked "What is the effect of the drug ?" obese patients treated with anti-obesity drugs offer a wide variety of answers such as:

"I don't eat as much."

"I can stop eating."

"I don't graze all day and night."

"I'm not hungry as soon as I stop eating."

"I'm normal" (in respect to eating).

3 - Factor eating questionnaire

Improved cognitive restraint

Lower levels disinhibition

Reduced hunger

Baker

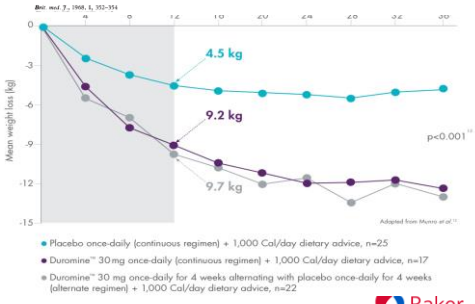
Phentermine
15mgs , 30mgs, 40mgs (oral)
Prepared with a slow release resin – single daily dosage

Approved in the 1960s this drug has been the most commonly used weight management drug in Australia and the United states for decades

Baker

Comparison of Continuous and Intermittent Anorectic Therapy in Obesity

J. F. MUNRO,* M.B., M.R.C.P.ED. ; A. C. MACCUISH,* M.B., CH.B.
ELIZABETH M. WILSON,* S.R.D. ; L. J. P. DUNCAN,* M.B., B.SC., F.R.C.P.ED.



Baker

Phentermine Contraindications and Precautions

Unstable hypertension, history of heart disease, hyperthyroidism, anxiety disorders, Hx of Drug & Alcohol abuse, Major psychiatric illness, pregnancy, breast feeding, MAOIs, and glaucoma

- Caution with combined use with SSRI's , ergot drugs, and clomipramine

Baker

Phentermine

It is primarily a sympathomimetic

It's effects on dopamine and serotonin are trivial

Therefore it has little or no addictive potential

While it may be expected in some to raise blood pressure there is no clear evidence that it does

No evidence of increased CV risk

There is generally the expected fall in BP associated with weight loss

Baker

Phentermine Treatment

Start with Duromine 15 mg/day.

Most adult patients tolerate 30 mg/day some may need 40mg

Evaluate for adverse effects.

Evaluate for effectiveness

I recommend taking the dose in the morning

- Weight loss
- Eating behavior – smaller meals – satiety – hunger - control

Titrate dose to effectiveness

- Tachyphylaxis with lower effect
- Higher doses can be used – up to 40 mg

Side Effects

Common

- Dry mouth - usually tolerable
- Insomnia – typically fades quickly
- Increased energy
- Feeling anxious / palpitations
- Other – e.g. constipation

Warn patients of these common early issues They usually resolve spontaneously

Less Common

- Impotence, decreased sex drive
- Irritability
- Mood elevation

If phentermine is effective and there are no adverse effects it can be continued

When may phentermine be continued on a long term basis?

- low-to-intermediate cardiovascular risk with no evidence of serious cardiovascular disease
- no serious psychiatric disease or history of substance abuse
- no clinically significant increase in pulse or blood pressure while taking phentermine
- close monitoring – monthly during dose escalation and at least every three months thereafter
- efficacy–safety stopping rule is followed

Phentermine is now US-FDA approved on a long term basis with topiramate.
Studies out to 2-years at this stage

Lee, P. C. and J. Dixon (2017). "Pharmacotherapy for obesity." Aust Fam Physician **46**(7): 472-477.

Topiramate

Approved for seizures in 1996

Approved for migraine prevention in 2004

Mono-therapy not approved for obesity

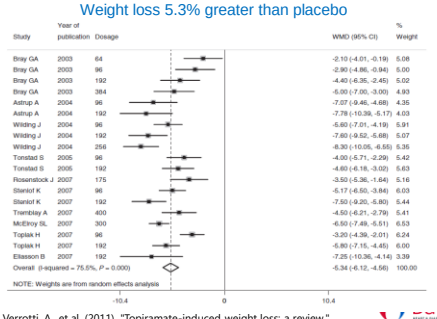
Doses

- Epilepsy: 400 mg/day
- Migraine prevention: 25 - 100 mg/day
- Obesity: 25 – 100 mg/day

Starting Rx 12.5 or 25 mg/day, titrate dose slowly

Meta-analysis of Topirimate RCTs

Weight loss 5.3% greater than placebo



Verrotti, A., et al. (2011). "Topiramate-induced weight loss: a review." Epilepsy Res **95**(3): 189-199.

Topiramate – Side effects

Paraesthesias, dry mouth, altered taste sensation, constipation, dizziness, insomnia, fatigue, somnolence

Cognitive effects may include psychomotor slowing, decreased concentration and attention, memory impairment, and language difficulties

Common mild dose related and usually resolve

Major mood change - suicidal thoughts or ideation

Acute Myopia & Angle Closure Glaucoma

Rare rapid onset serious and drug induced

Increased risk of oral clefts if taken during pregnancy in first trimester

Warn and manage risk

Contraindications: Pregnancy, Glaucoma, Kidney Stones

Using Topiramate Alone

Start with 25 mg/day; best given at night first

Stay at 25 mg/day at least 2 weeks

I recommend taking the dose at night

Evaluate for ASEs, cravings, binge eating

If marked improvement stay at 25 mg/day

If no ASEs consider increase to 50 mg/day

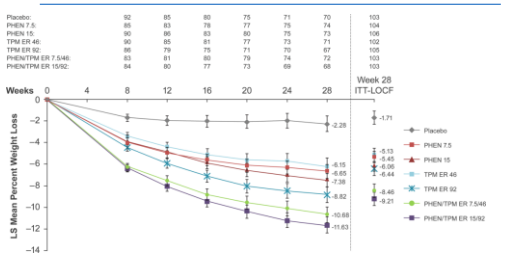
If appropriate increase to 75mg/day and 100mg/day (maximun)

If ASEs either reduce dose or stop depending on the nature of the ASE

If no cravings or binge eating look for weight loss +/or changes in eating behavior.

Baker

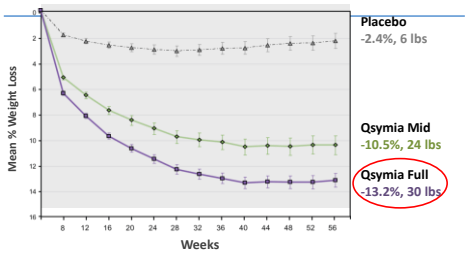
Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults



Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. Volume: 21, Issue: 11, Pages: 2163-2171, First published: 17 October 2013, DOI: (10.1002/oby.20584)

Baker

Qsymia : Weight Loss Over Time
(Completer Population)



Patients	Placebo	Mid	Full
Completers	564	344	634
(% of randomized)	57%	69%[1]	64%[1]

1. Statistically greater number of patients completing study on Qnexa vs. placebo, p<0.0001
* *Data from patients that completed 56 weeks on treatment*

Baker

Liraglutide 3mg for weight management
(TGA approved December 2015)

Liraglutide 3.0 mg	Liraglutide is a human glucagon-like peptide (GLP-1) analogue, with 97% amino acid sequence homology to endogenous human GLP-1 Like endogenous GLP-1, liraglutide binds to and activates the GLP-1 receptor (GLP-1R) GLP-1 is a physiological regulator of appetite and calorie intake

GLP-1 is hormone secreted from the distil gut in response to a meal
Slows gastric emptying = sense of fullness
Satiation
Central action to reduce hunger and provide prolonged satiety

Saxenda® Approved Product Information, December 2015

Baker

Weight loss with liraglutide 3.0 mg

Significantly greater and clinically meaningful weight loss in a wide range of patients

Obesity and prediabetes patient population1,2	**8.0%** at week 56 compared with 2.6% in the placebo group (p<0.0001)
Type 2 diabetes population1,3	**6.0%** at week 56 compared with 2.0% in the placebo group (p<0.0001)
Obstructive sleep apnoea population1	**5.7%** at week 32 compared with 1.6% in the placebo group (p<0.0001)

Treatment arm = Liraglutide 3.0 mg plus diet and exercise; Placebo = diet and exercise alone; Data are for patients in the full analysis set, with last observation carried forward; Changes from baseline are estimated mean weight loss

1. Saxenda® Approved Product Information, December 2015. 2. Pi-Sunyer X et al. N Engl J Med 2015;373:11–22. 3. Davies MJ, et al. JAMA. 2015;314(7):687–699.

Baker

Liraglutide weight-loss review

Patients who lost at least 5% of baseline weight after 16 weeks of treatment on average lost 11.2% of their baseline weight at week 56

Review progress at 16 weeks	Treatment with Saxenda® should be discontinued after 12 weeks (at week 16) on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight
Re-evaluate annually	The need for continuous use annually Long-term use should be informed by the limited long-term efficacy and safety data which are only documented for 1 year

Saxenda® Approved Product Information, December 2015. Pi-Sunyer X et al. N Engl J Med 2015;373:11–22.

Baker

Summary of liraglutide 3.0 mg safety profile

GI side effects are common	Most episodes of GI events were mild to moderate, transient and the majority did not lead to discontinuation of therapy	
Dehydration	Potential risk of dehydration in relation to GI side effects	
Gallbladder-related events	Associated with above average weight loss	
Low rates of pancreatitis	Mild grade and of short duration	Half the liraglutide-associated pancreatitis cases were associated with gallstones

Pi-Sunyer X et al. N Engl J Med 2015;373:11–22; Saxenda® Approved Product Information, December 2015

Baker

Drug	Starting dose	Available doses	Weight loss versus placebo (% or kg)	Side effects	Contraindications
Phentermine	15 mg	15, 30, 40 mg	3.6–4.5 kg at six months	Dry mouth, insomnia, agitation, constipation, and tachycardia	Severe hypertension, cardiovascular disease, glaucoma, history of drug or alcohol abuse, monoamine oxidase inhibitors, selective serotonin reuptake inhibitor use, pregnancy
Orlistat	120 mg TDS	120 mg	2.9–3.4% at one year	Steatorrhea, oily spotting, flatulence with discharge, faecal incontinence, fat-soluble vitamin malabsorption	Pregnancy
Liraglutide	0.6 mg	0.6–3.0 mg	5.4% at one year	Nausea, vomiting, diarrhoea, constipation Rare: Pancreatitis, cholecystitis	Severe renal or hepatic insufficiency, pregnancy, past history of pancreatitis and major depression or psychiatric disorder
Off-label pharmacotherapy (not approved by Therapeutic Goods Administration for weight loss)					
Topiramate	12.5 mg mane	25, 50, 100 mg	3.4–5.0 kg	Paraesthesia, dry mouth, constipation, altered taste sensation, insomnia, dizziness, cognitive effects Rare: Closed angle glaucoma, depression or suicidal ideation	Glaucoma, renal stones, pregnancy (if used for weight loss)
Phentermine (Phe)/ topiramate (Top)	Phe: 15 mg mane Top: 12.5 mg mane	Phe: 15 mg Top: 12.5, 25, 50, 100 mg	5.0–6.6% at one year	Side effects of phentermine and topiramate	Contraindications to phentermine or topiramate

Lee, P. C. and J. Dixon (2017). "Pharmacotherapy for obesity." Aust Fam Physician **46**(7): 472-477.

Baker

Where and how do we use medications?

If you cannot provide the behavioural program out source it

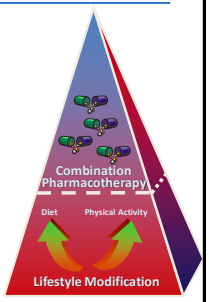
- To support weight loss and weight maintenance
- Reduce weight regain
  - Diets, VLCD, balloons, surgery, or any other ……
- The action plan always has short and long-term aims
- Combine medications to enhance effect and reduce individual doses
- Start low and go slow with the dosage
- Remember the stopping rule

Baker

Obesity Treatment of the future

As for dysregulation of blood pressure and blood glucose we will need combination drug therapy with lifestyle interventions to successfully manage clinically severe obesity

Please be realistic with your goals:
Achieving >5% or 10% sustained weight generates major health benefits wherever your patient starts



Baker

Adapted from source: www.obesityonline.org