Pharmacotherapy for Obesity – Important New Options

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Disclosures: Professor John B Dixon

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

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

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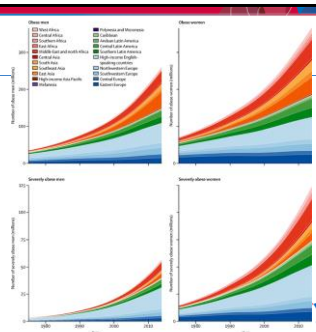
Global & Regional Obesity

High income English speaking countries

BLUE

Global & Regional Severe obesity



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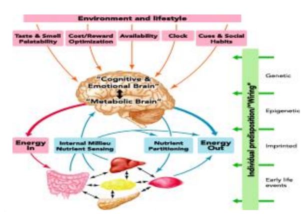
Schematic diagram showing the major factors determining neural control of appetite and regulation of energy balance



Huiyuan Zheng, and Hans-Rudi Berthoud Physiology 2008;23:75-83

The first 1000 days of life is critical for weight trajectory for life

Unfortunately a rise in weight (fat) is defended just as a rise in blood pressure is defended

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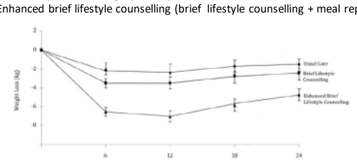
Weight Loss is Hard to Achieve[1]

Primary care setting, comparing usual care with:
Brief lifestyle counselling (quarterly GP visits with medical assistant counseling)
Enhanced brief lifestyle counselling (brief lifestyle counselling + meal replacements / medication)



1. Wadden, T.A et al 2011. N. Engl. J. Med. 365:1969-1979

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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	[illegible] >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	10	Improves steatosis, inflammation and mild fibrosis	Assy et al., 2007 (66) Dixon et al., 2004 (67) Patel et al., 2009 (68)
Sleep apnea	10	Little benefit at 5%	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.

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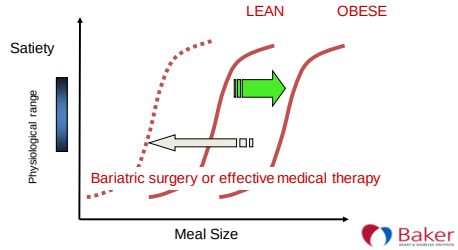
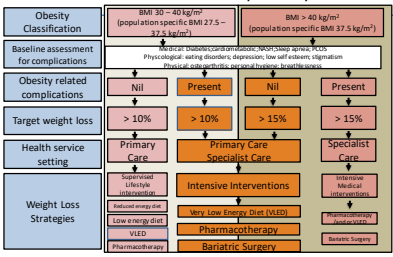
Dose response curve
"A change in regulation"



The Australian Diabetes Society Obesity Treatment Algorithm[1]



Developed in conjunction with ANZOS and representatives from RACGP

1. https://diabetessociety.com.au/documents/ObesityManagementAlgorithm18.10.2016FINAL.pdf

Indications for weight management pharmacotherapy[1,2]

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.

1. National Health and Medical Research Council (2013) *Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia.* Melbourne
2. https://diabetessociety.com.au/documents/ObesityManagementAlgorithm18.10.2016FINAL.pdf

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

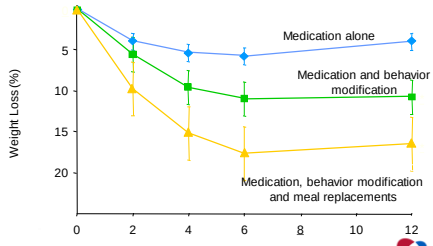
There is no point

- 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

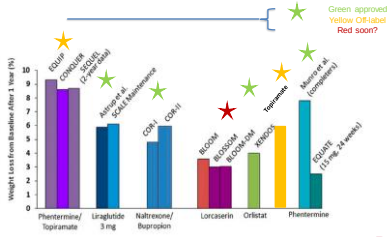
In chronic disease management we often combine therapy for greater efficacy so we need additional time if we increase therapy when synergy is expected

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)



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

Naltrexone-Bupropion (Contrave)

Orlistat (Xenical, Alli)
Phentermine (Duromine, Metermine)
Liraglutide (Saxenda)

How to use them?

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CONTRAVE®[1]

CONTRAVE is available in a formulation of extended-release tablets that contain 8 mg naltrexone HCl and 90 mg bupropion HCl[1]:

Naltrexone HCl[2]

- An opioid receptor antagonist
- Indications: treatment of **alcohol dependence** and prevention of relapse to **opioid dependence**
- TGA approved since **1998**

Bupropion HCl[3]

- A dopamine and norepinephrine reuptake inhibitor
- Indications: as an adjunct to **smoking cessation in Australia**
- TGA approved since **2000.**

CONTRAVE is not approved for either of the naltrexone or bupropion indications as monotherapies

1. Contrave Approved Product Information

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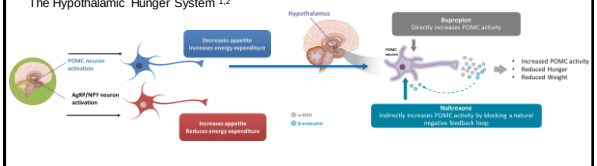
CONTRAVE Acts Synergistically in The Hunger System

The Hypothalamic Hunger System [1,2]



AgRP=agouti-related protein; NPY=neuropeptide Y; POMC=proopiomelanocortin.
1. Yu JH et al. *Diabetes Metab J.* 2012;36:391-398. 2. Dietrich MO et al. *Nat Rev Drug Discov.* 2012;11:676-691.

Figure adapted from Billes et al,[1] © 2014, with permission from Elsevier.
MSH=melanocyte-stimulating hormone; POMC=pro-opiomelanocortin.
1. Billes SK et al. *Pharmacol Res.* 2014;84:1-11.

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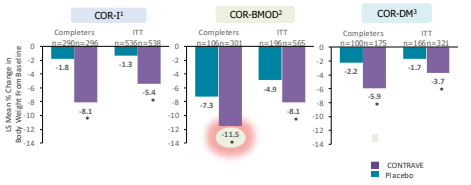
CONTRAVE Versus Placebo in Phase 3 Trials[1,2,3]



*P<0.001 vs. placebo. BMOD=behavior modification; DM=diabetes mellitus; ITT=intent-to-treat; LS=least squares; T2DM=type 2 diabetes mellitus. **1.** Greenway FL et al. *Lancet.* 2010;376:595-605. **2.** Wadden TA et al. *Obesity.* 2011;19:110-120. **3.** Hollander P et al. *Diabetes Care.* 2013;36:4022-4029.

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Indications and Usage of CONTRAVE®[1]

CONTRAVE ® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for the management of weight in adult patients (≥ 18 years) with an initial body mass index (BMI) of:

- ≥30 kg/m² (obese), or
- ≥27 kg/m² to <30 kg/m² (overweight) in the presence of one or more weight-related comorbidities (e.g., type 2 diabetes, dyslipidemia or controlled hypertension)

1. Contrave Approved Product Information

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Dosage and Administration of CONTRAVE®[1]

The maximum recommended daily dose of CONTRAVE is 2 tablets twice daily for a total dose of 32 mg naltrexone HCl and 360 mg bupropion HCl, which is reached at the start of week 4[1]

CONTRAVE® dosing should be escalated over a 4-week period		
	Morning	Evening
Week 1	●	
Week 2	●	●
Week 3	●●	●
Week 4 and onwards	●●	●●

The need for treatment should be evaluated after 16 weeks and reevaluated annually.

Administration

- **CONTRAVE** tablets should be swallowed whole with some water. The tablets should preferably be taken with food. The tablets should not be cut, chewed, or crushed.

1. Contrave Approved Product Information

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Dosage and Administration of CONTRAVE®[1]

The need for continued treatment should be evaluated after 16 weeks and re-evaluated annually

<5% weight loss — **Treatment with CONTRAVE should be discontinued if a patient has not lost at least 5% of baseline body weight at 16 weeks**

≥5% weight loss — **CONTINUE CONTRAVE if a patient has lost at least 5% of baseline body weight at 16 weeks**

Clinically meaningful weight loss was defined as having achieved ≥5% weight loss at week 56.

1. Contrave Approved Product Information

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Contraindications to Contrave[1]

- Uncontrolled hypertension
- Seizure disorder or a history of seizures
- Patients with known central nervous system tumour
- Patients undergoing acute alcohol or benzodiazepine withdrawal
- Patients with history of bipolar disorder
- Patients currently dependent on chronic opioids or opiate agonists (e.g., methadone), or patients with acute opiate withdrawal
- Pregnancy
- Patients with severe hepatic impairment
- Patients with end-stage renal failure

1. Contrave Approved Product Information

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Safety evaluated in 4754 Patients Up to 56 Weeks[1]

- 5 double-blinded placebo-controlled trials
- Discontinuation due to AE: 23.8% receiving CONTRAVE® vs.11.9% receiving placebo
- Most frequent AE leading to discontinuation: Nausea, headache, dizziness, vomiting

Most common gastrointestinal adverse events[1]		
	CONTRAVE®	Placebo
Nausea	31.8%	6.7%
Constipation	18.1%	7.2%
Vomiting	9.9%	2.9%

Most GI events reported during dose escalation and resolved within 4 weeks

Contrave Product Information

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CONTRAVE PHYSICIAN PRESCRIBING CHECKLIST

Treatment with Contrave should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.

PATIENT DETAILS

DOES THE PATIENT HAVE:	NO	YES

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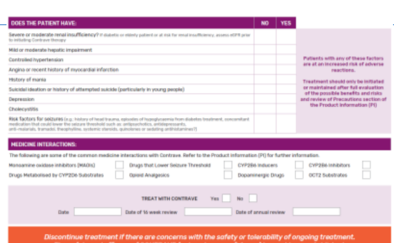
Contrave physician prescribing checklist cont...



DOES THE PATIENT HAVE:	NO	YES	
Severe or moderate renal insufficiency? If diabetic or elderly patient or at risk for renal insufficiency, assess eGFR prior to initiating Contrave therapy			Patients with any of these factors are at an increased risk of adverse reactions. Treatment should only be initiated or maintained after full evaluation of the possible benefits and risks and review of Precautions section of the Product Information (PI)
Mild or moderate hepatic impairment			
Controlled hypertension			
Angina or recent history of myocardial infarction			
History of mania			
Suicidal ideation or history of attempted suicide (particularly in young people)			
Depression			
Cholecystitis			
Risk factors for seizures (e.g.: history of head trauma, episodes of hypoglycaemia from diabetes treatment, concomitant medication that could lower the seizure threshold such as: antipsychotics, antidepressants, anti-malarials, tramadol, theophylline, systemic steroids, quinolones or sedating antihistamines?)			

MEDICINE INTERACTIONS:

The following are some of the common medicine interactions with Contrave. Refer to the Product Information (PI) for further information.

Monoamine oxidase inhibitors (MAOIs)	Drugs that Lower Seizure Threshold	CYP2B6 Inducers	CYP2B6 Inhibitors
Drugs Metabolised by CYP2D6 Substrates	Opioid Analgesics	Dopaminergic Drugs	OCT2 Substrates

TREAT WITH CONTRAVE Yes No

Date Date of 16 week review Date of annual review

Discontinue treatment if there are concerns with the safety or tolerability of ongoing treatment. The safety and efficacy of CONTRAVE for long term use (>1 year) has not been established.

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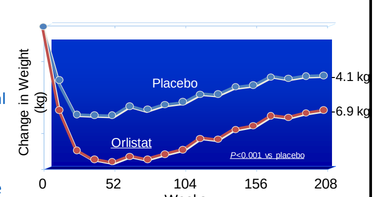
Orlistat prevention of diabetes study

XENDOS **n=3305 lifestyle plus orlistat 120x3/day or placebo x3/day**

4-year, double-blind, prospective study

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.

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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.

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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"

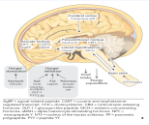
"I don't graze all day and night"

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

"I am not food focused"

"I feel in control"

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



3 - Factor eating questionnaire

Improved cognitive restraint

Lower levels disinhibition

Reduced hunger

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Phentermine – 15mg, 30mg, and 40 mg (Introduced 1960s)

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

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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

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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

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

I recommend taking the dose in the morning

Titrate dose to effectiveness

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

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Side Effects – Long term usage

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

Lewis KH, Fischer H, Ard J, et al. Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort. *Obesity (Silver Spring)* 2019;27(4):591-602.

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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

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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 ML et al. JAMA. 2015;314(7):687–699.

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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.

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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

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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

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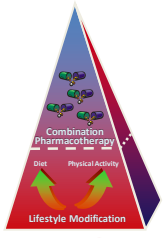
Obesity Treatment of the future

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

Effective therapy and a sense of control is a lifestyle enabler
Just this time it may work!



Adapted from source: www.obesityonline.org

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