Professor John Dixon

Head of Clinical Obesity Research

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Head of Child & Adolescent Health

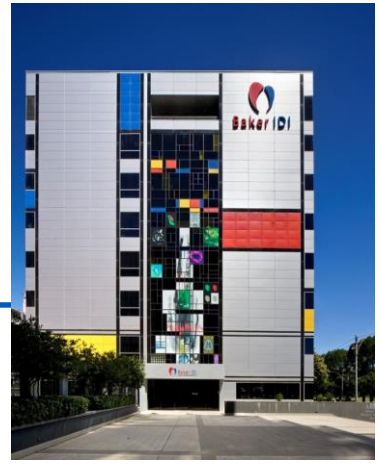
University of Sydney

Saturday, August 10, 2019 (Room 4)

8:30 - 9:25 WS #71: Managing Obesity with Very Low Calorie Diets, Meal Replacements and Drug Therapy

9:35 - 10:30 WS #81: Managing Obesity with Very Low Calorie Diets, Meal Replacements and Drug Therapy (Repeated)

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

Phong Ching Lee, John Dixon

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

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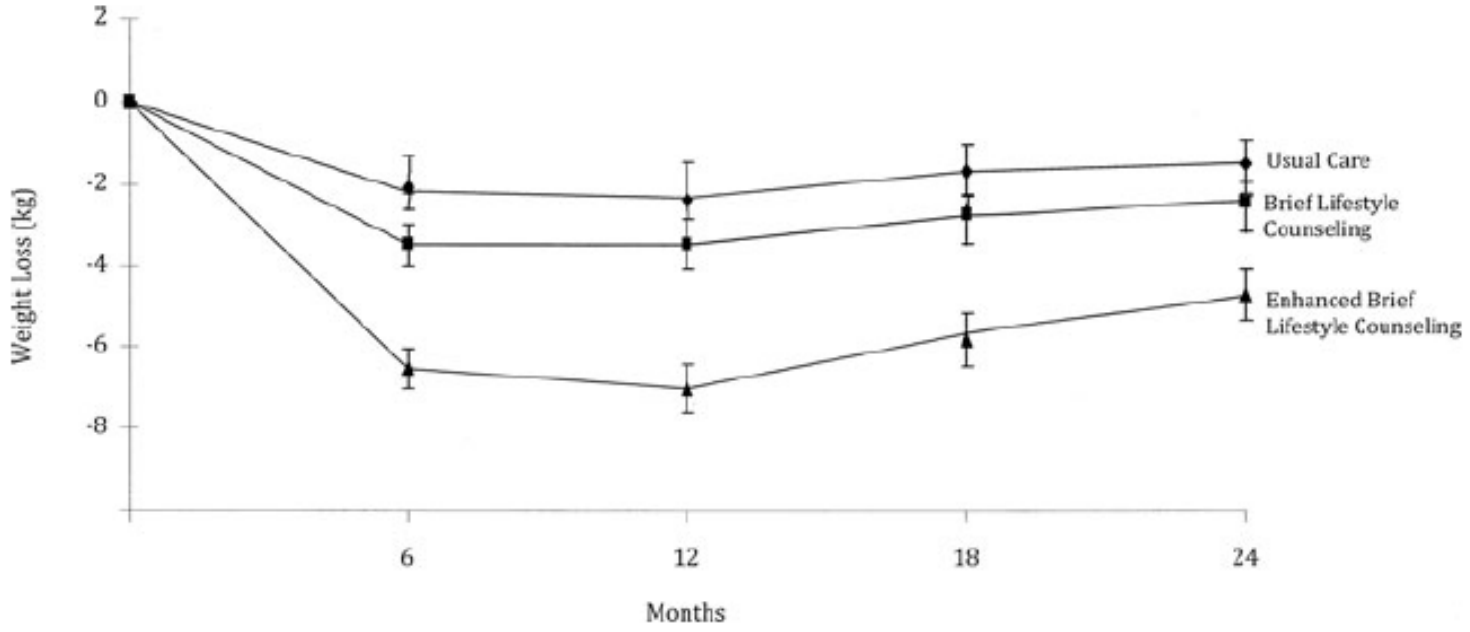
Weight Loss is Hard to Achieve[1]

Primary care setting, comparing usual care with:
Brief lifestyle counselling (quarterly GP visits with medical assistant counselling)
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	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	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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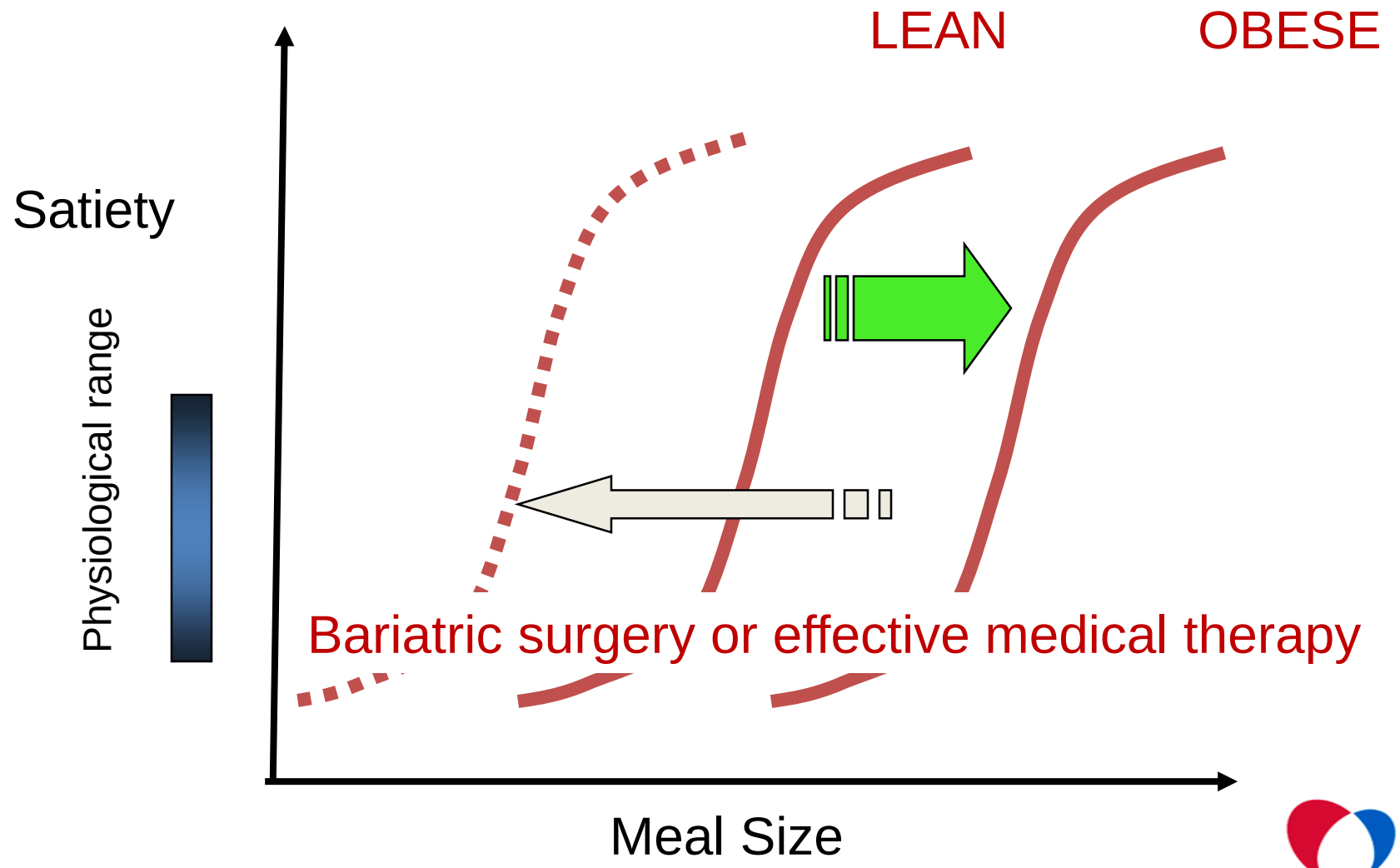
Dose response curve
"A change in regulation"



Per Carel Le Roux

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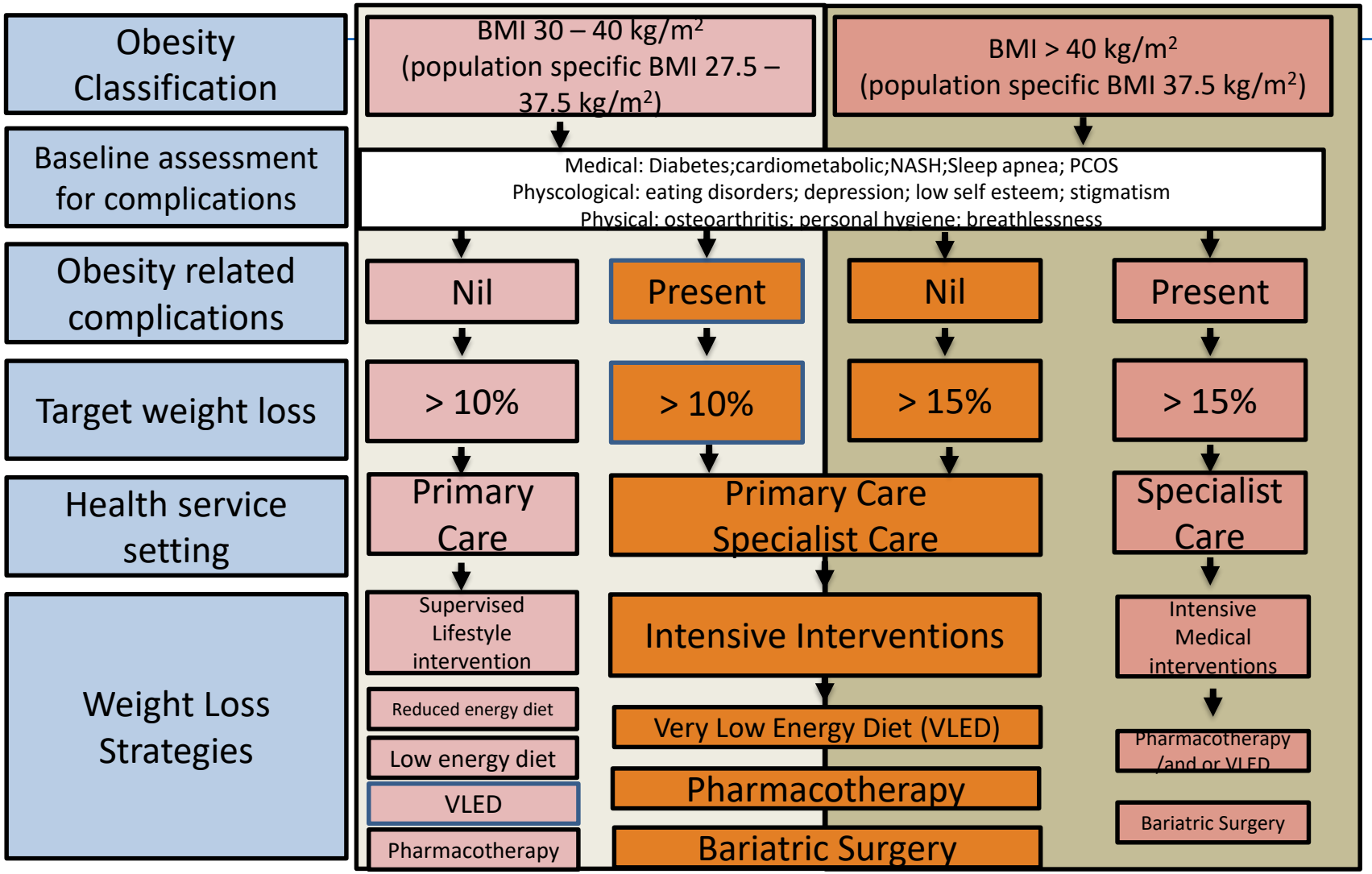
The Australian Diabetes Society Obesity Treatment Algorithm[1]



Developed in conjunction with ANZOS and representatives from RACGP

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

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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.

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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

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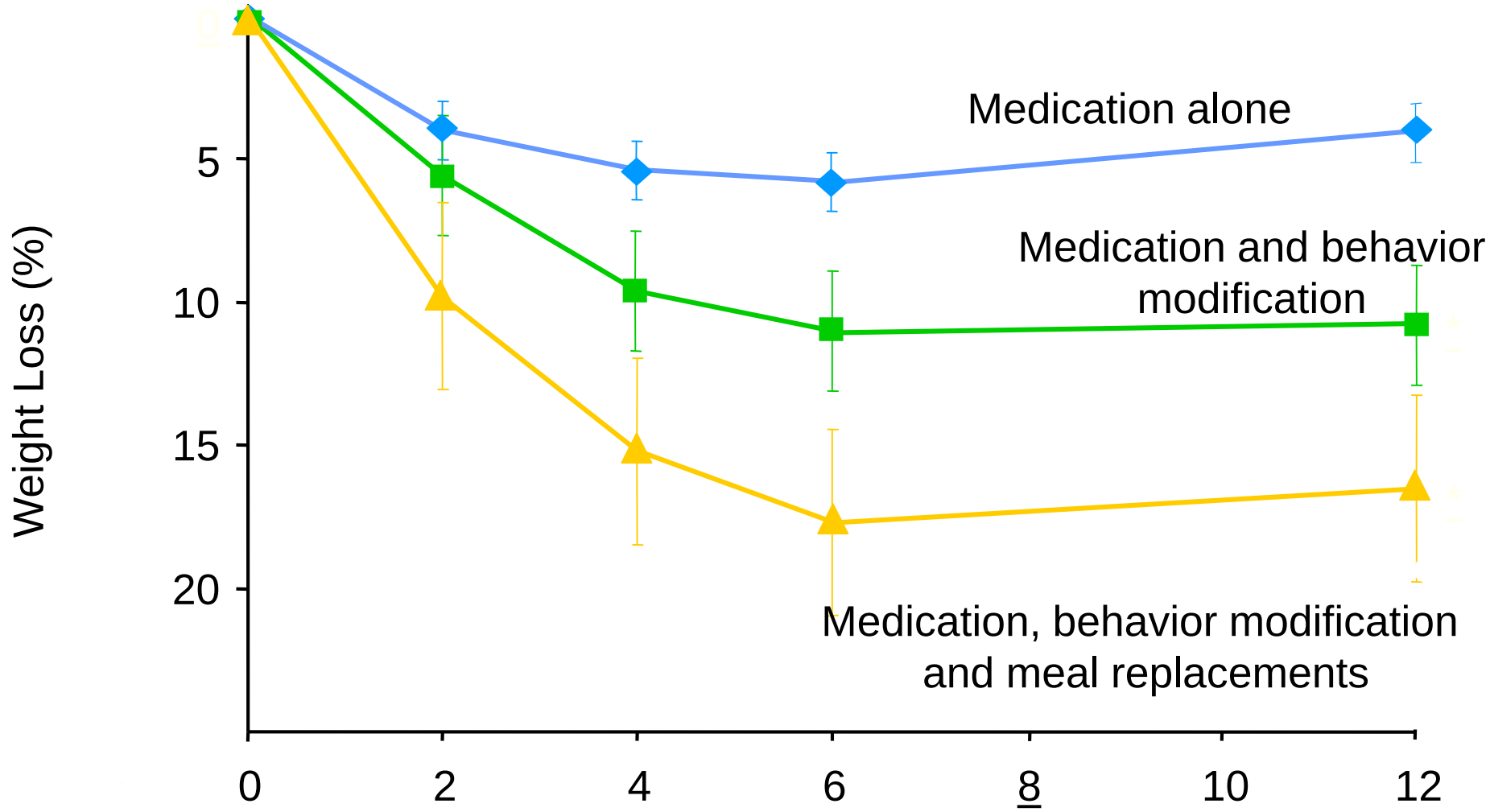
Additive Effects of Behavior and Meal Replacement Therapy With Pharmacotherapy for Obesity



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

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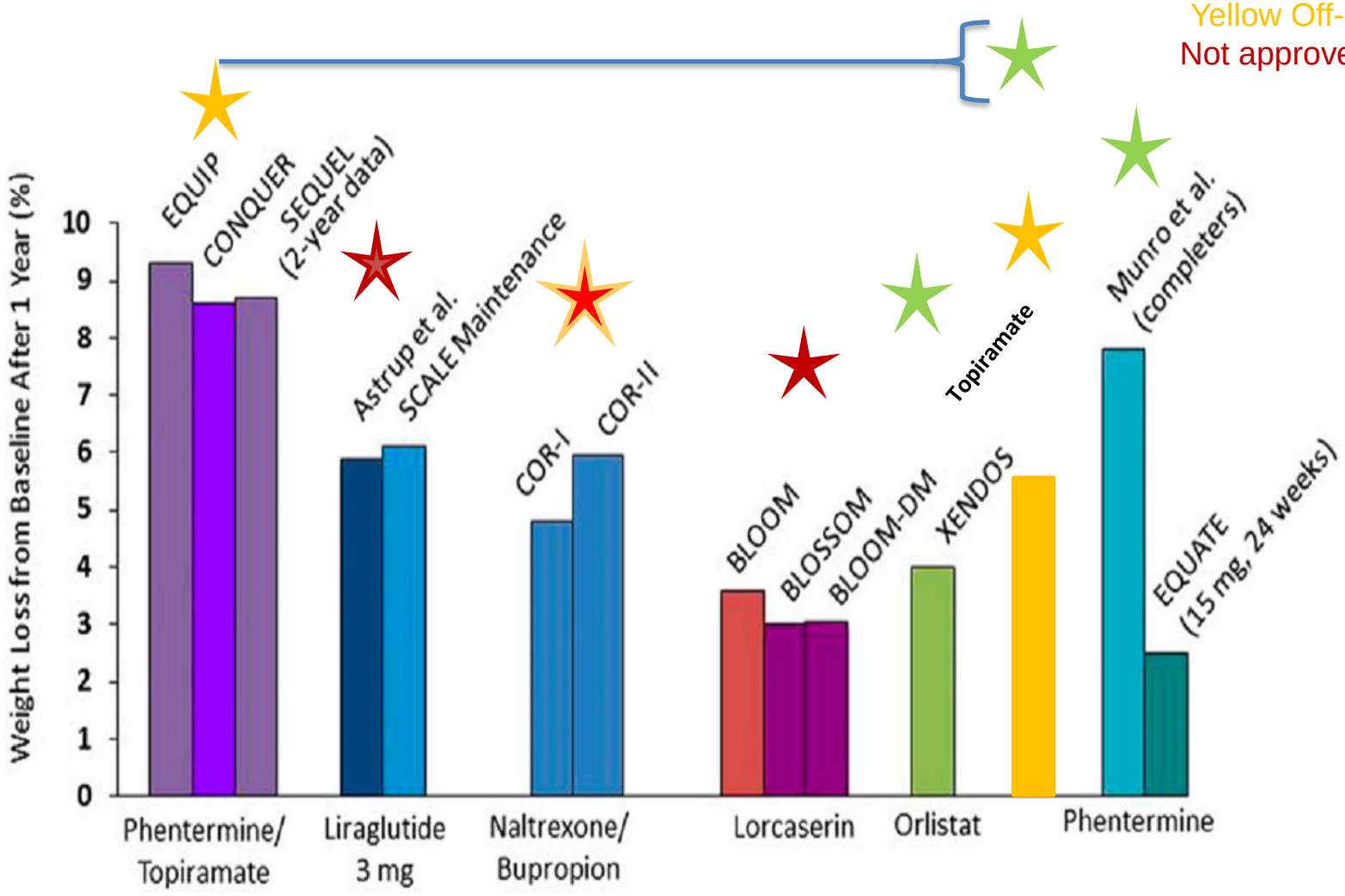
Comparison of weight loss medications at 1-year (placebo subtracted – ITT – LOCF)

In weight loss studies % and kg loss is similar

Green approved
Yellow Off-label
Not approved yet



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I am going to focus on the use of the 5 drugs we have available in Australia today

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

Topiramate (Off label)

Naltrexone-Bupropion (Contrave Off label NZ)

How to use them?

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Orlistat
120mgs tds (oral)

ACTION

Inhibits intestinal lipase - reduces fat absorption by 30%.

EVIDENCE

In a one-year clinical study, weight loss of 9 kg was reported in the orlistat group, compared with 5-6kg for the placebo-treated group

XENDOS (XENical) in the Prevention of Diabetes in Obese Subjects) study, at four years, it reduced the risk of developing diabetes by 37.3% compared with the lifestyle intervention alone

. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27(1):155–61.

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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.

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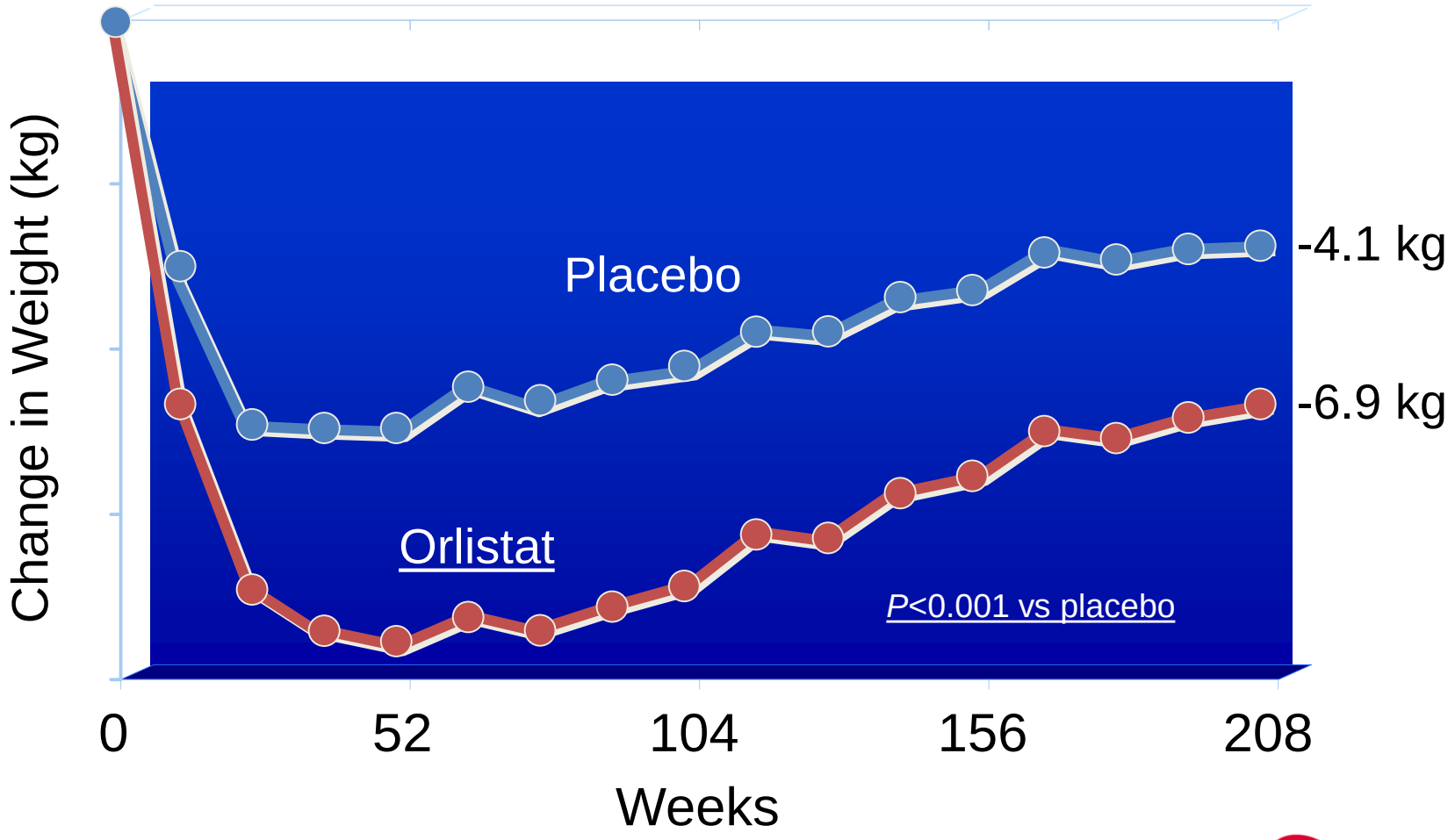
Effect of Long-term Orlistat Therapy on Body Weight



Torgenson et al. Diabetes Care 2004;27:155

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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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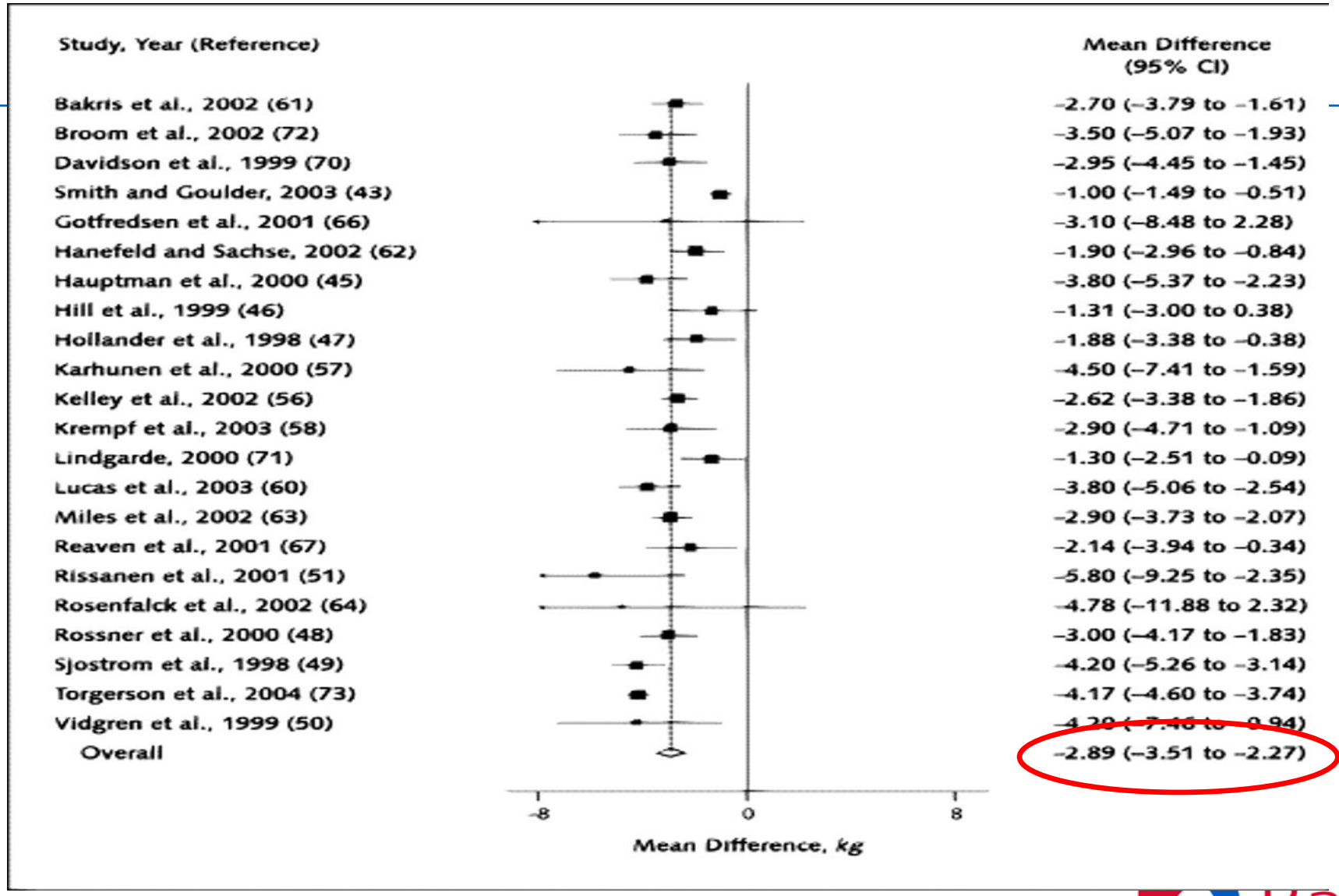
Weight loss with orlistat versus placebo at 12 months



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

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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.

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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”

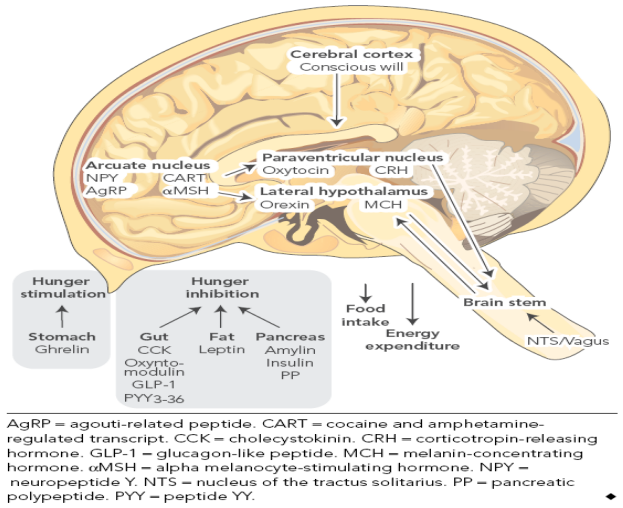
“I don’t graze all day and night”

“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).



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.

3 - Factor eating questionnaire

Improved cognitive restraint

Lower levels disinhibition

Reduced hunger

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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

ACTION

Phentermine is a sympathomimetic amine with significant anorectic activity in animal models.

It's appetite suppressant effect is generally considered to be exerted through the hypothalamus, but it is not certain that this is the only effect related to weight loss.

EVIDENCE

Differences in weight loss at 6 months of 3.6 – 4.5 kg or %WL for phentermine-treated patients vs placebo

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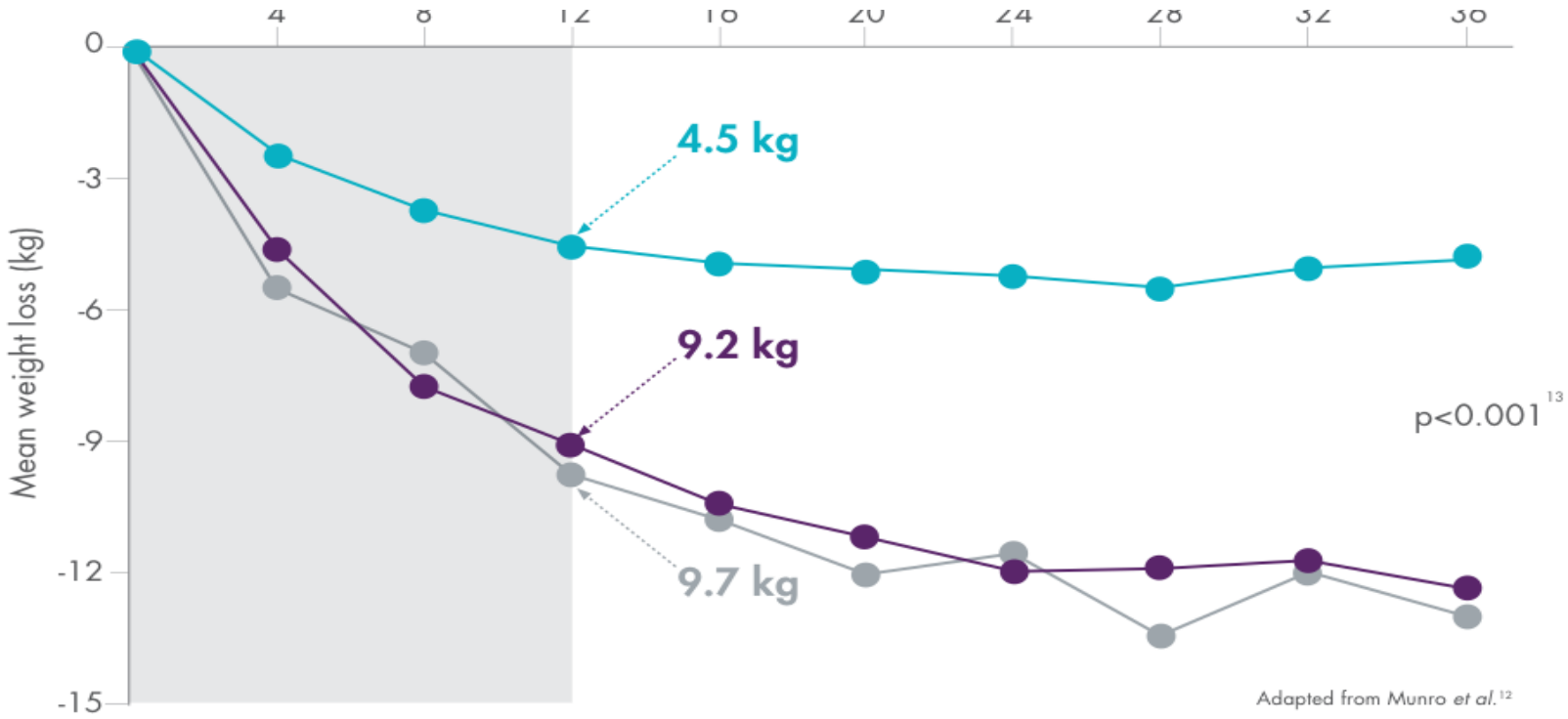
Comparison of Continuous and Intermittent Anorectic Therapy in Obesity

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.

Brit. med. J., 1968, **1**, 352–354



- Placebo once-daily (continuous regimen) + 1,000 Cal/day dietary advice, n=25
- Duromine™ 30 mg once-daily (continuous regimen) + 1,000 Cal/day dietary advice, n=17
- Duromine™ 30 mg once-daily for 4 weeks alternating with placebo once-daily for 4 weeks (alternate regimen) + 1,000 Cal/day dietary advice, n=22

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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

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 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

Titrate dose to effectiveness

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

I recommend taking the dose in the morning

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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

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Topiramate

Approved TGA for seizures in 1996

Approved TGA 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

Start low and go slow

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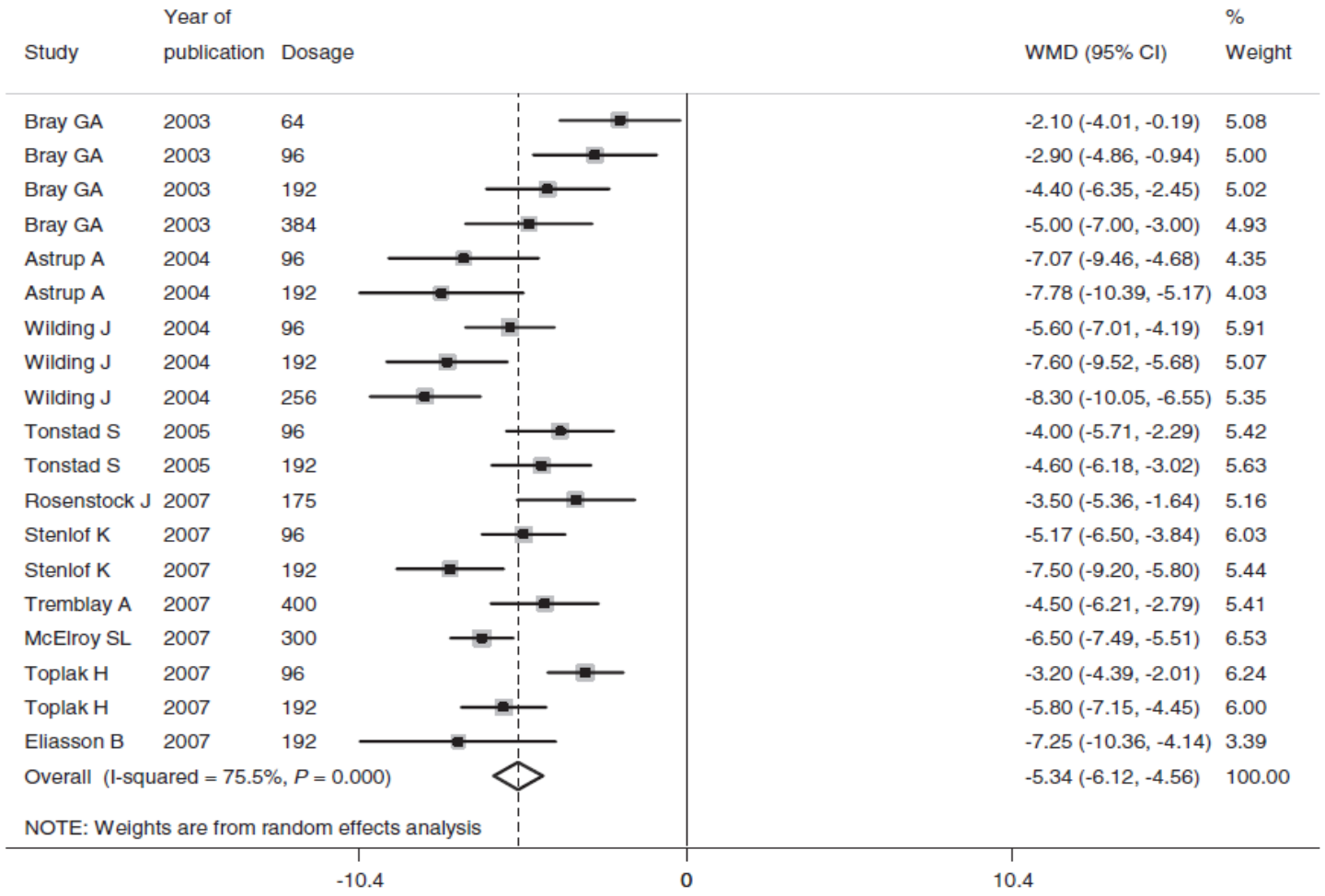
Meta-analysis of Topirimate RCTs

Weight loss 5.3% greater than placebo



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

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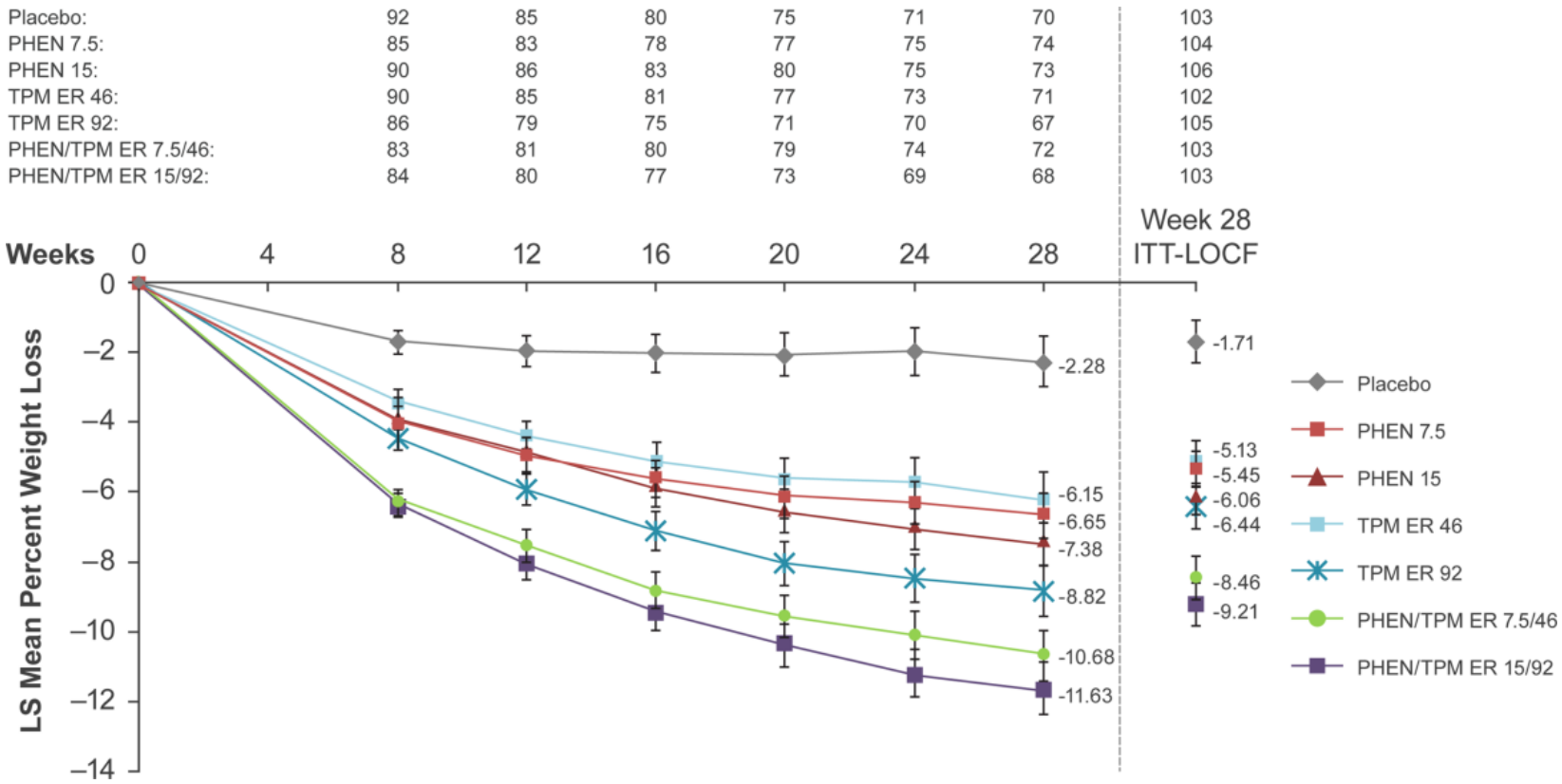
Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults



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)

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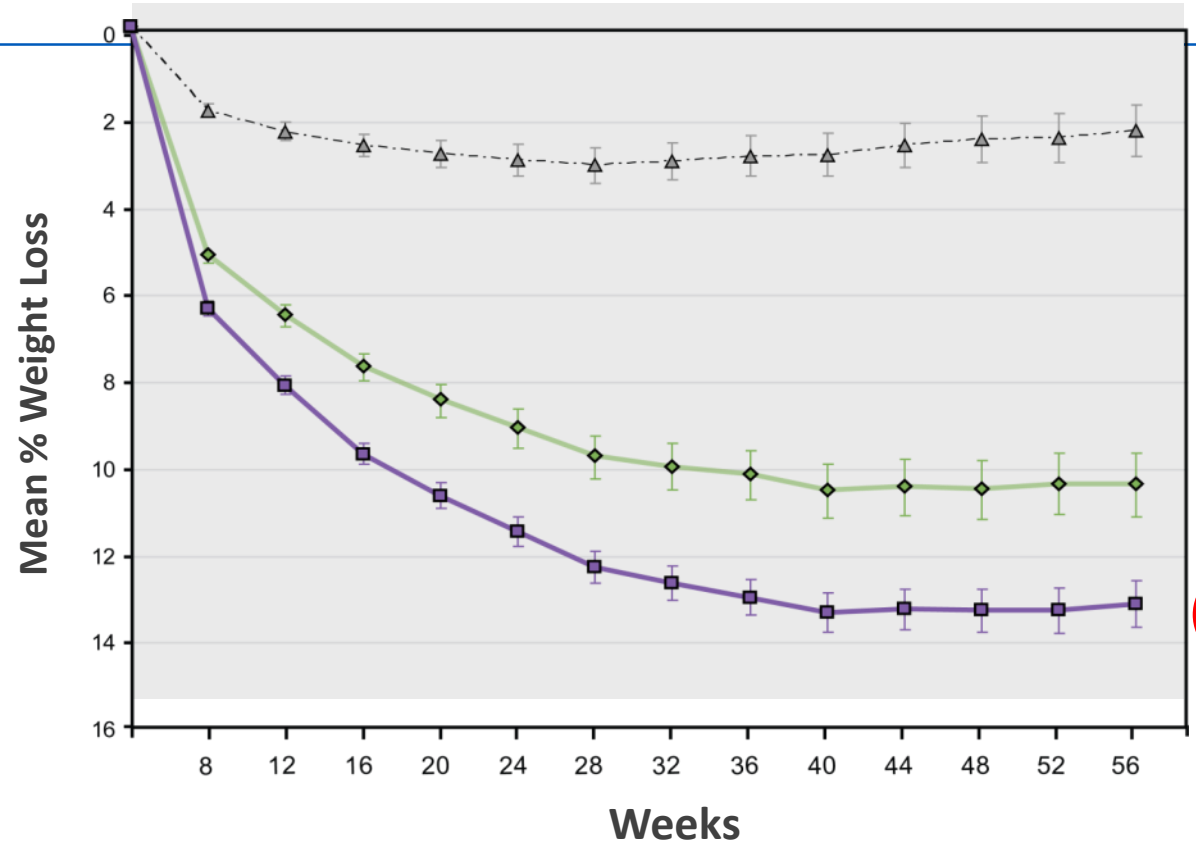
Qsymia : Weight Loss Over Time
(Completer Population)



Placebo
-2.4%, 6 lbs

Qsymia Mid
-10.5%, 24 lbs

Qsymia Full
-13.2%, 30 lbs

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*

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

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Using Topiramate Alone

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

Stay at 25 mg/day at least 2 weeks

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.

I recommend taking the dose at night

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VLCD program < 800 kcal/ day
Very Low Calorie Diets

Average VLCD (replacing 3 meals/day) typically provides:

Energy:	1.9 – 2.6 MJ/day
Carbohydrate:	45 – 60g carbohydrate distributed evenly throughout the day
Protein:	50 – 60g protein/day

VLCD are designed to meet 100% daily recommendations for vitamins, minerals, trace elements and essential fatty acids. VLCDs are designed to promote ketosis – using fat stores for energy in preference to carbohydrate, while providing nutritional adequacy with a reduced kilojoule intake.

The production of ketones reduces hunger.

Therefore any additional food (i.e. allowed foods) should be very low / no carbohydrate.

Foods containing carbohydrate should be re-introduced in a structured way during transitional phases of management.

VLCD program < 800 kcal/ day
Very Low Calorie Diets

Indications and contraindications:
Incredibly safe: In both the short and long terms
Rapid weight loss is not associated with rapid weight regain[1]
Use of VLEDs generates long-term clinically meaningful weight loss[2]

Adults with:

- BMI >30kg/m2
- BMI >27kg/m2 with medical complications and risks

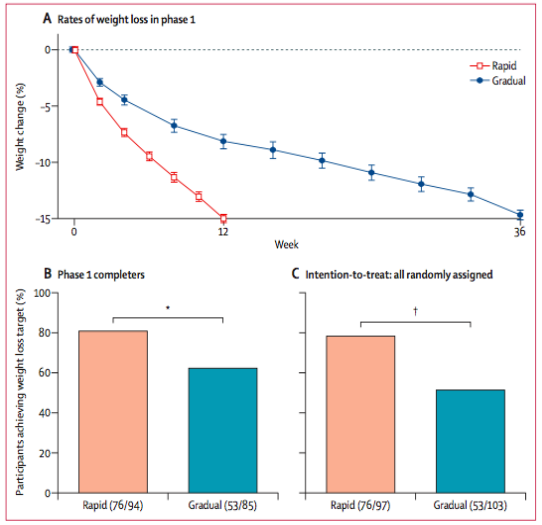


Figure 2: Rate of weight loss during phase 1 for successful participants (mean % change, 95% CI)
Successful participants were those who achieved at least 12·5% weight loss from baseline to end of phase 1.
*p=0·009. †p=0·0001.

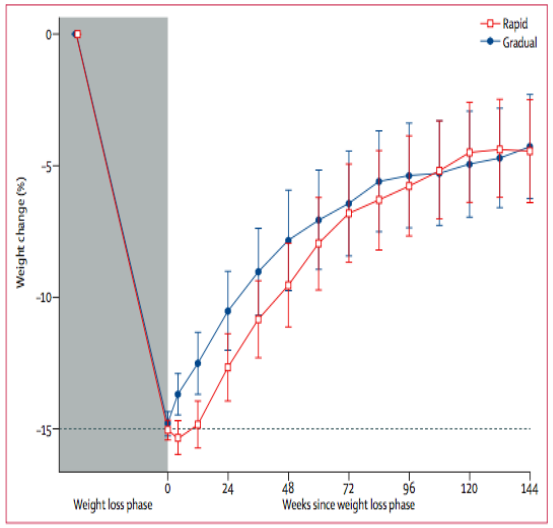
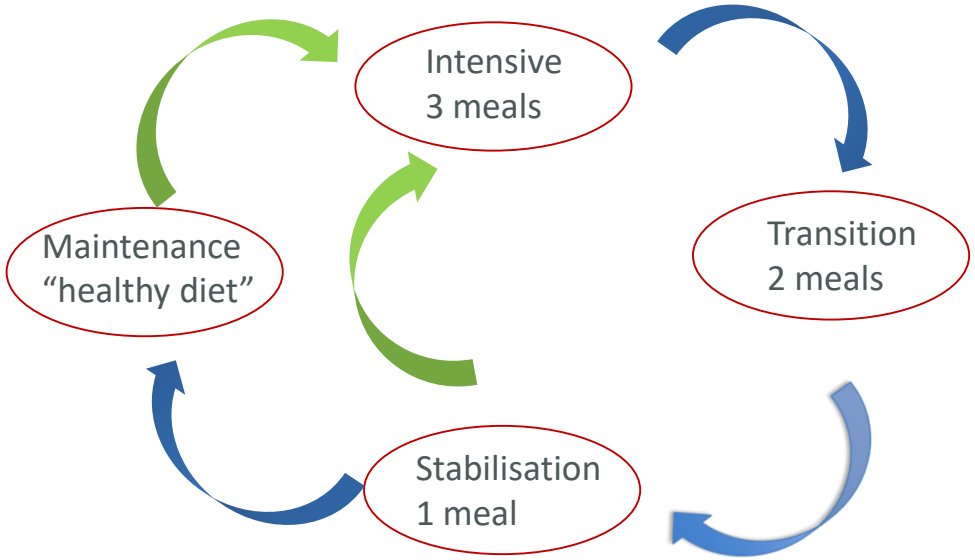


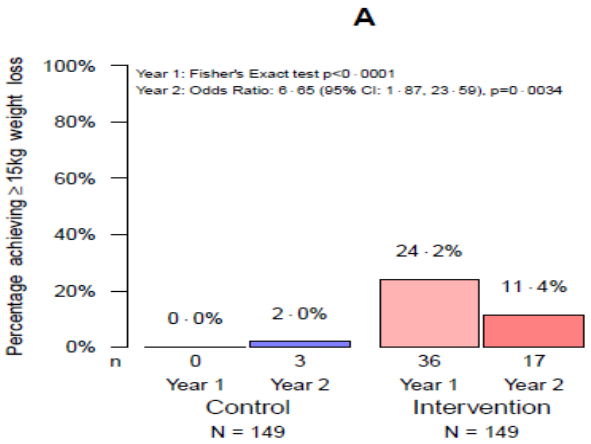
Figure 3: Mean weight change (% change, 95% CI) during phase 2 for study completers (n=61 in rapid weight loss and n=43 in gradual weight loss group)

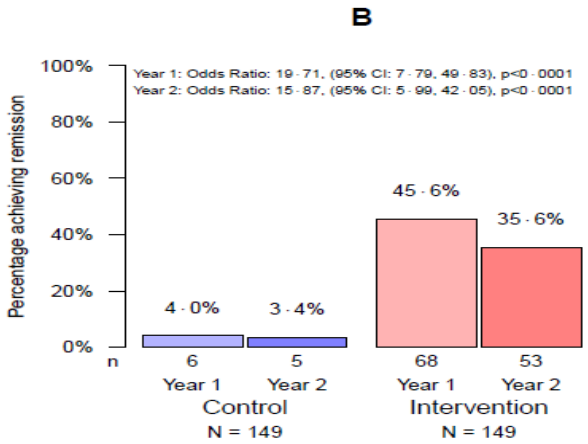


1. Purcell K, *et al. Lancet Diabetes Endocrinol* 2014;2:954–62.
2. Anderson JW, *et al. Am J Clin Nutr* 2001;74:579–84.

Two-year results of the DiRECT trial

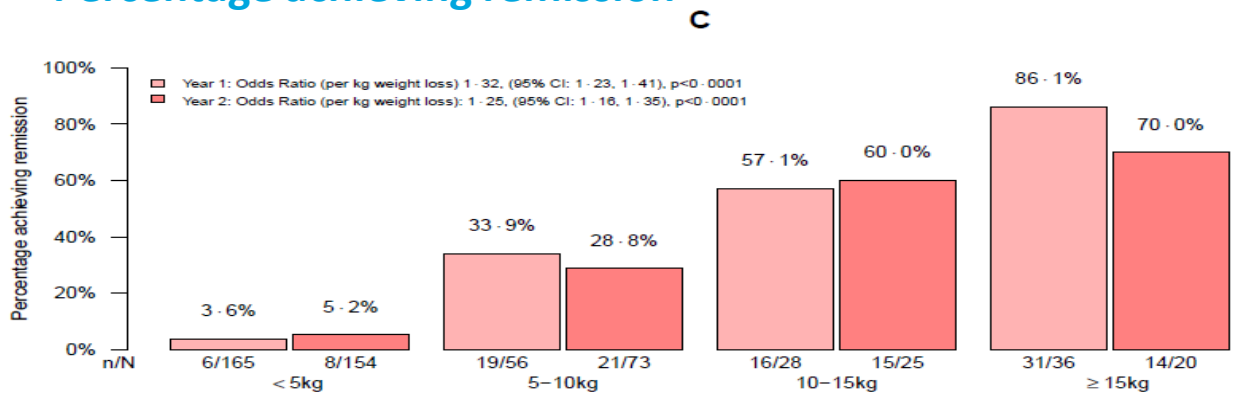
15% weight loss





Remission of diabetes

Percentage achieving remission



DiRECT: Diabetes REmission Clinical Trial

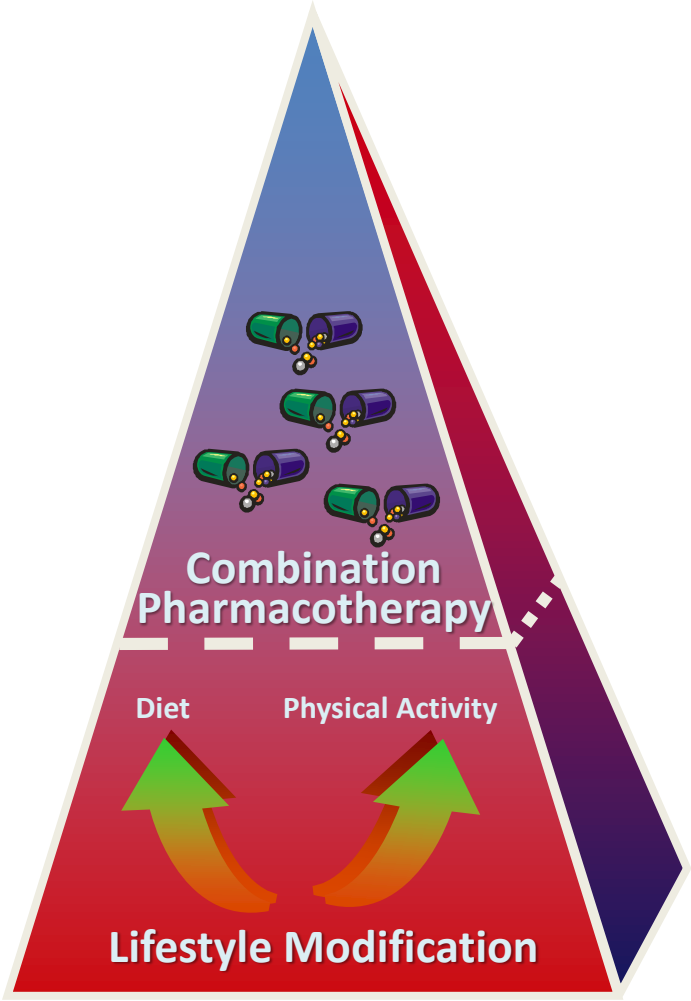
Lean MEJ *et al. Lancet Diabetes Endocrinol* 2019;7:344–55.

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



Adapted from source: www.obesityonline.org

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