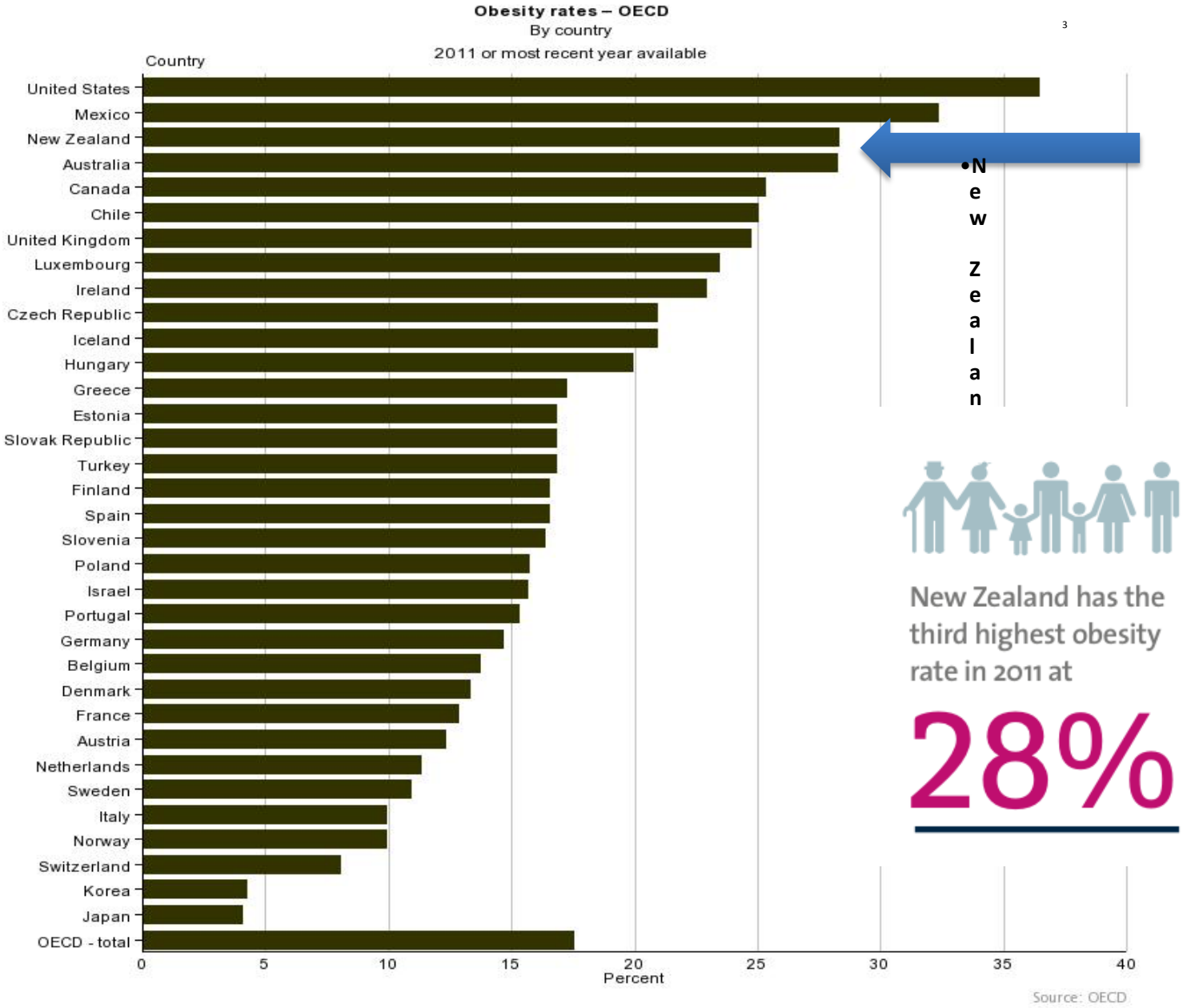
Medical management of obesity

Dr Ole Schmiedel, MRCP MD FRACP

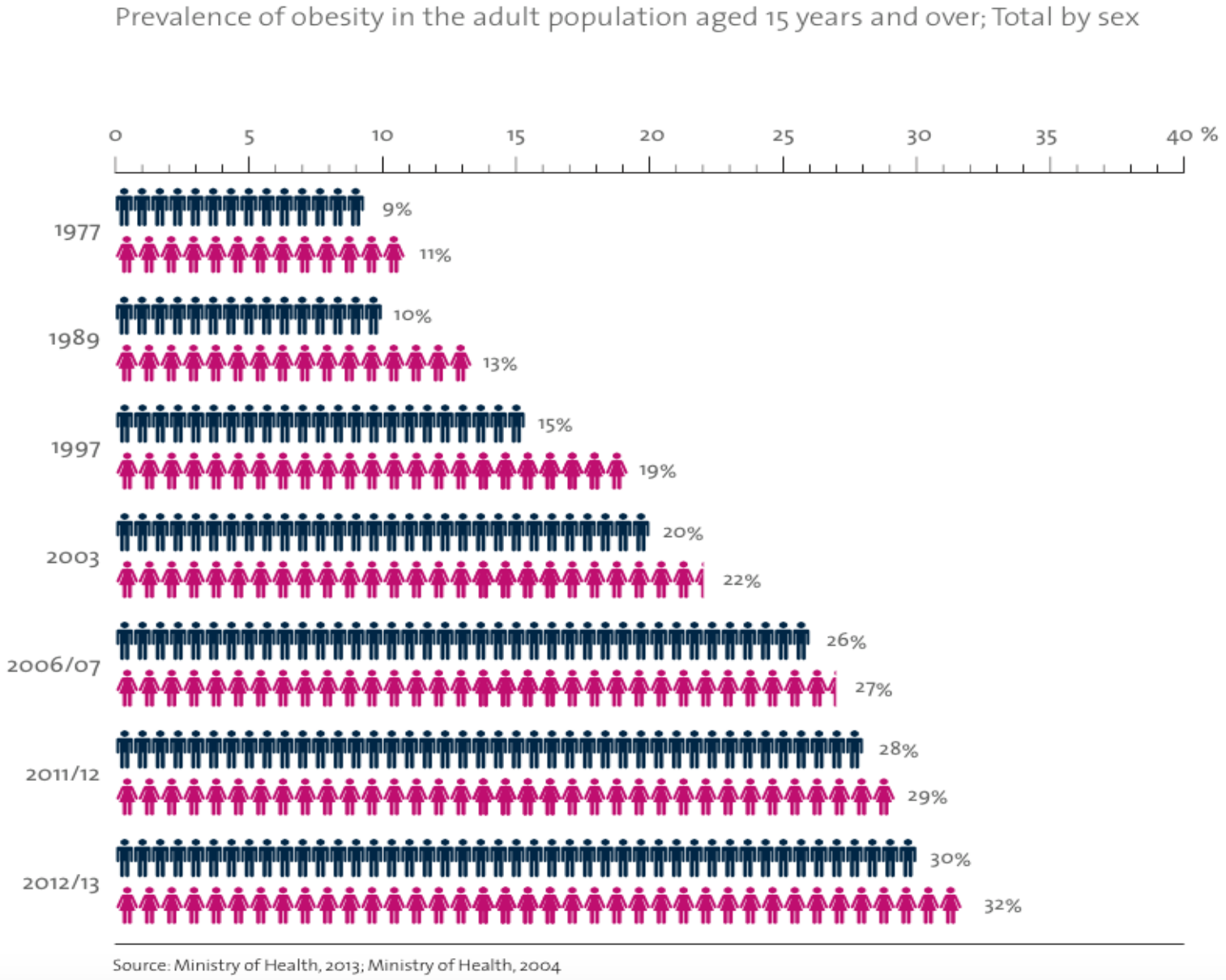
Physician and Endocrinologist

SCD Auckland Diabetes Centre

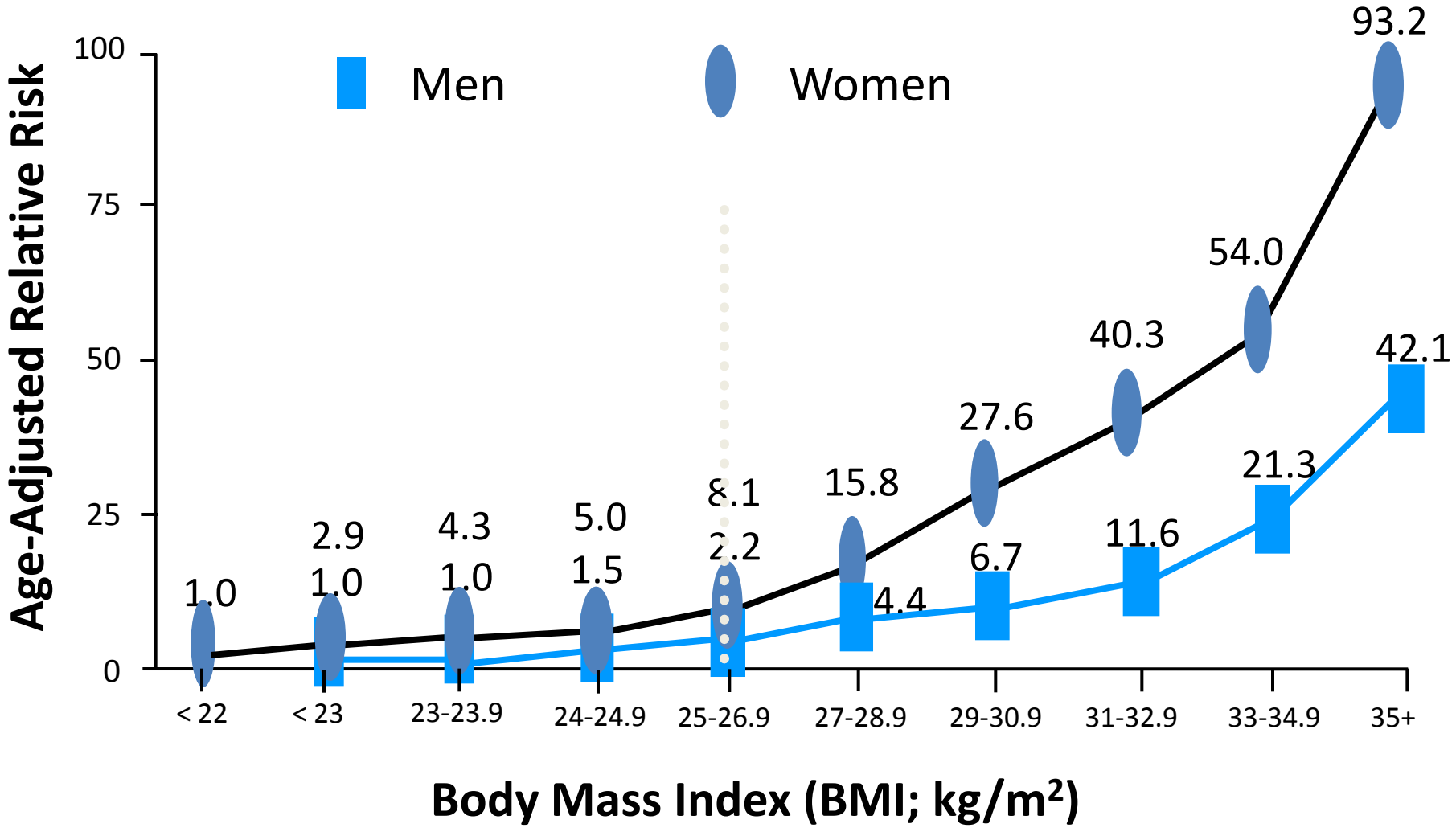
You are fully aware of:



You are fully aware of:



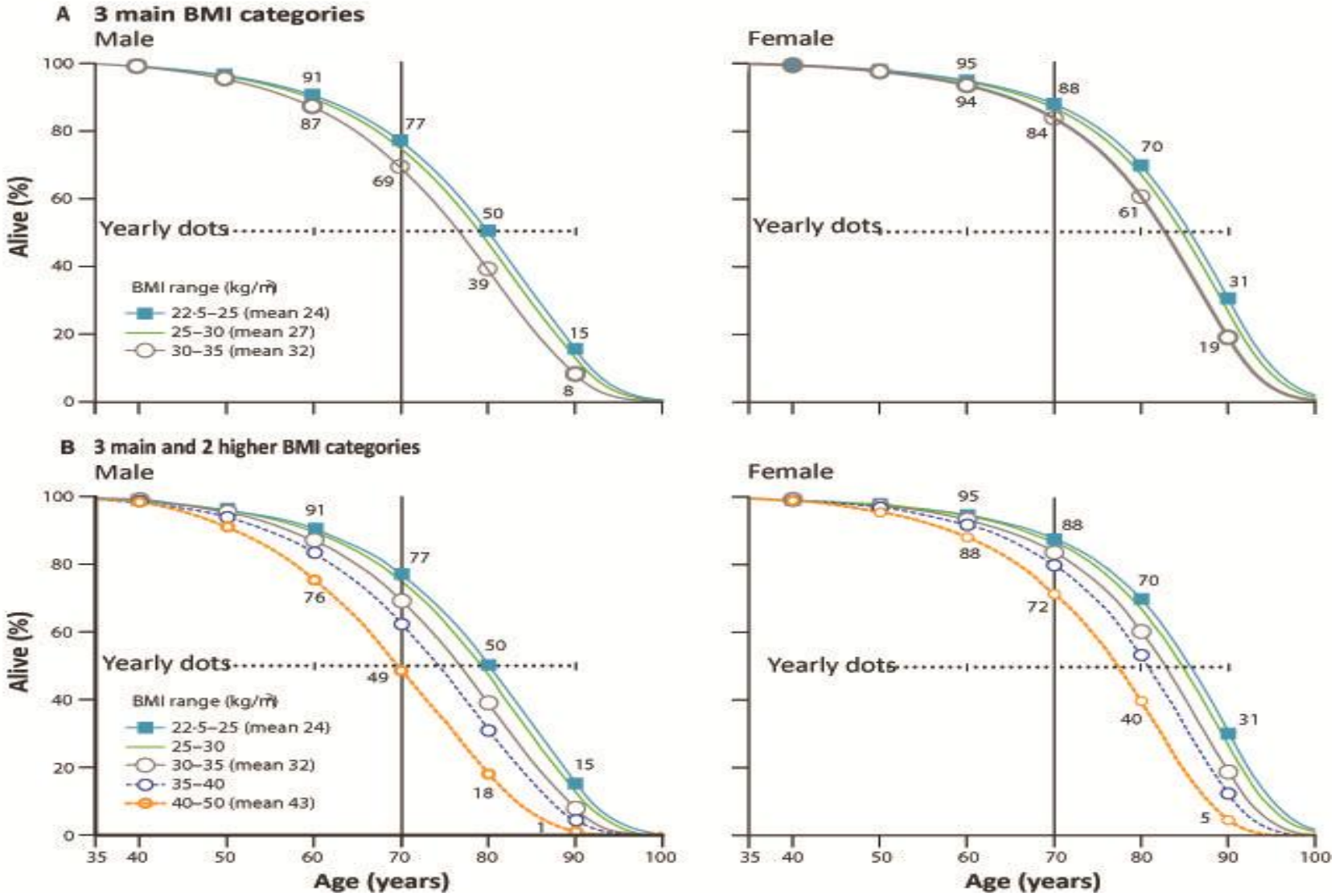
Relationship Between BMI and Risk for Type 2 Diabetes



Chan J, et al. *Diabetes Care.* 1994;17:961-969.

Colditz G, et al. *Ann Intern Med.* 1995;122:481-486.

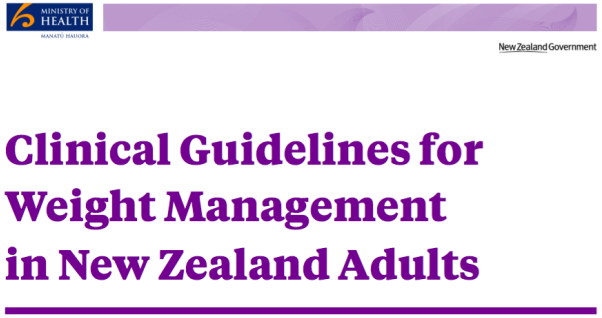
Effect of BMI on Lifespan



Prospective Studies Collaboration. *Lancet*. 2009;373:1083-1096.

All Healthcare Professionals Play a Role

- Monitor for change in weight by noting weight trajectory over time
- Provide dietary, physical activity, and lifestyle counseling to “at-risk” patients
- Pharmacologic and surgical treatment when indicated



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Myths, Presumptions, and Facts about Obesity

Krista Casazza, Ph.D., R.D., Kevin R. Fontaine, Ph.D., Arne Astrup, M.D., Ph.D., Leann L. Birch, Ph.D., Andrew W. Brown, Ph.D., Michelle M. Bohan Brown, Ph.D., Nefertiti Durant, M.D., M.P.H., Gareth Dutton, Ph.D., E. Michael Foster, Ph.D., Steven B. Heymsfield, M.D., Kerry McIver, M.S., Tapan Mehta, M.S., Nir Menachemi, Ph.D., P.K. Newby, Sc.D., M.P.H., Russell Pate, Ph.D., Barbara J. Rolls, Ph.D., Bisakha Sen, Ph.D., Daniel L. Smith, Jr., Ph.D., Diana M. Thomas, Ph.D., and David B. Allison, Ph.D.

What is obesity?

- An epidemic ?
- Lifestyle choice ?
- A disease ?
- A chronic condition that can lead to disease(s) ?

Obesity is subject to strong heritability (40–70%).
point mutations and single nucleotide polymorphisms
Environmental changes interacting with genetic susceptibility
inappropriate to take the **judgmental attitude** that obesity is merely a **lifestyle choice and a self-inflicted problem**.

You might be interested in knowing that:

Obesity Increasingly Becoming Officially Recognized as a Disease

Obesity Medicine Association

"…a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences"

OBESITY SOCIETY
Research. Education. Action.

"…obesity is a serious chronic disease with extensive and well-defined pathologies, including illness and death."

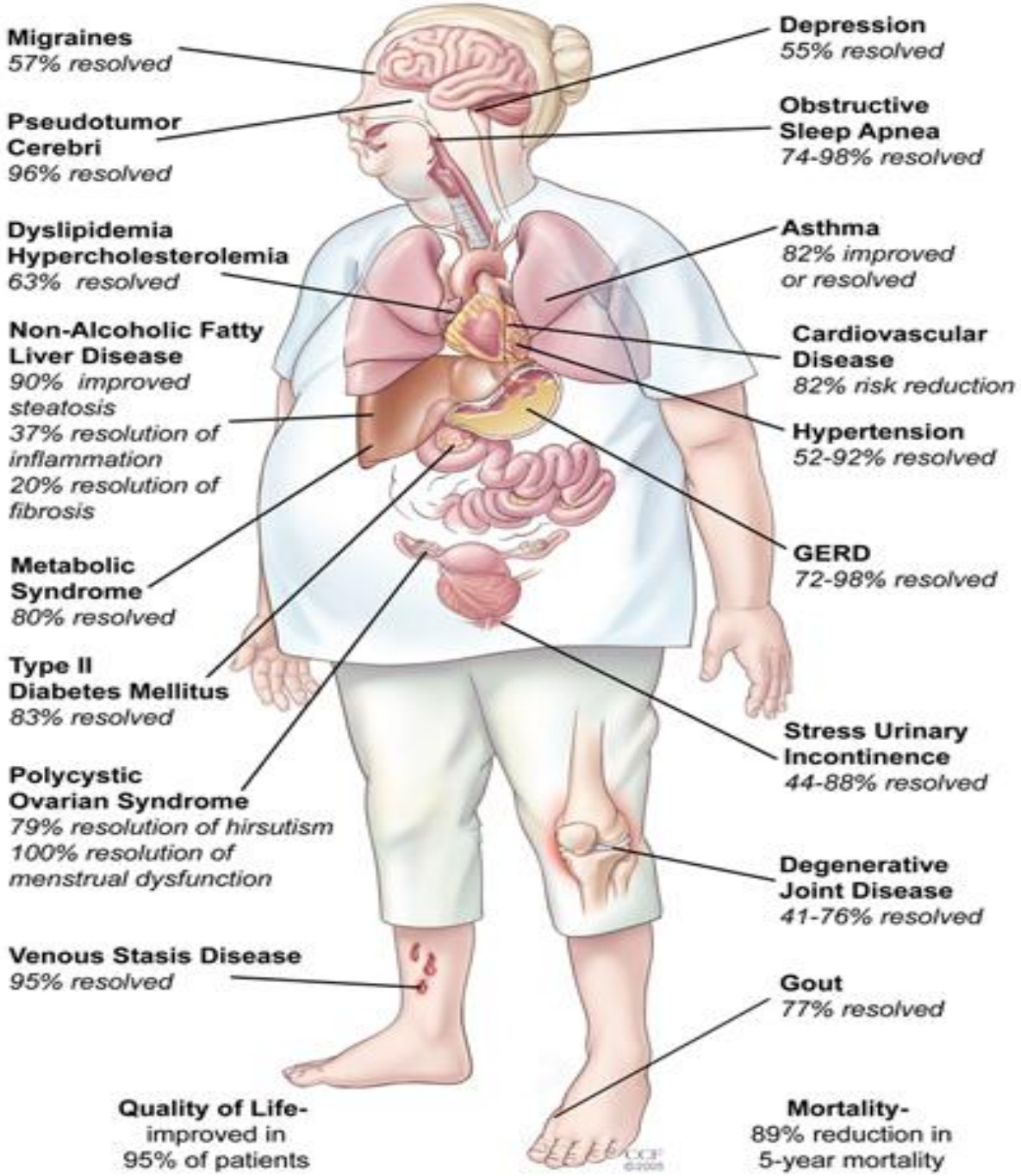
AMA AMERICAN MEDICAL ASSOCIATION

"Recognizing obesity as a disease will help change the way the medical community tackles this complex issue that affects approximately one in three Americans" [2]

World Health Organization

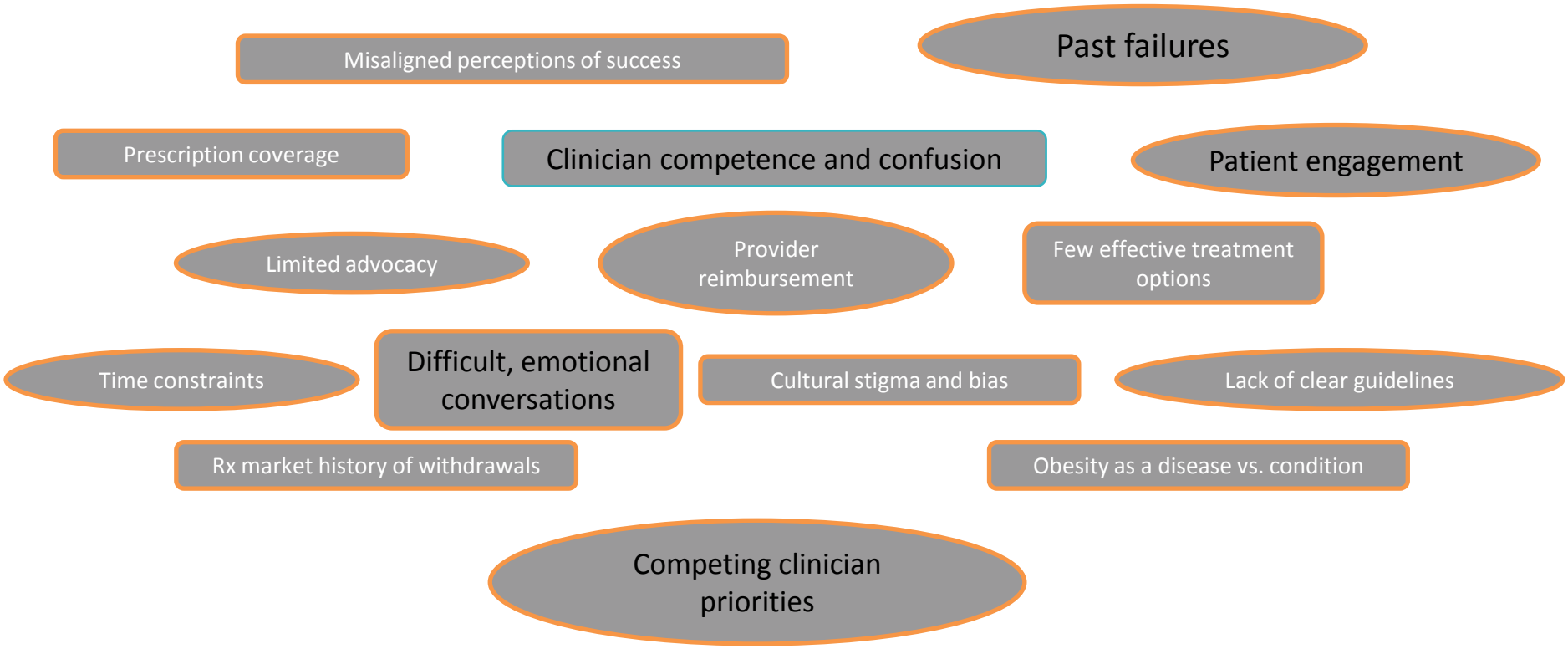
"Obesity is a chronic disease, prevalent in both developed and developing countries, and affecting children as well as adults" [3]

Mechanick JI et al. *Endocr Pract.* 2012;18:642–648. **2.** AMA position statement. At: http://www.ama-assn.org. Accessed Oct 2014. **3.** WHO. Obesity and overweight. At: http://www.who.int/dietphysicalactivity/media/en/gsfs_obesity.pdf. Accessed Oct 2014. **4.** US Food and Drug Administration. Federal Register. 2000;65(4):1000-1050.


Migraines
57% resolved
Pseudotumor Cerebri
96% resolved
Dyslipidemia
Hypercholesterolemia
63% resolved
Non-Alcoholic Fatty Liver Disease
90% improved steatosis
37% resolution of inflammation
20% resolution of fibrosis
Metabolic Syndrome
80% resolved
Type II Diabetes Mellitus
83% resolved
Polycystic Ovarian Syndrome
79% resolution of hirsutism
100% resolution of menstrual dysfunction
Venous Stasis Disease
95% resolved
Quality of Life-
improved in 95% of patients
Depression
55% resolved
Obstructive Sleep Apnea
74-98% resolved
Asthma
82% improved or resolved
Cardiovascular Disease
82% risk reduction
Hypertension
52-92% resolved
GERD
72-98% resolved
Stress Urinary Incontinence
44-88% resolved
Degenerative Joint Disease
41-76% resolved
Gout
77% resolved
Mortality-
89% reduction in 5-year mortality

HOWEVER - Why is it so difficult?

What are the barriers and challenges ?



STOP Obesity Alliance. Available at: www.stopobesityalliance.org/wp-content/assets/2010/03/STOP-Obesity-Alliance-Primary-Care-Paper-FINAL.pdf. Forman-Hoffman V et al. *BMC Family Practice*. 2006;7:35.

How to do it?

BRITISH OBESITY & METABOLIC SURGERY SOCIETY

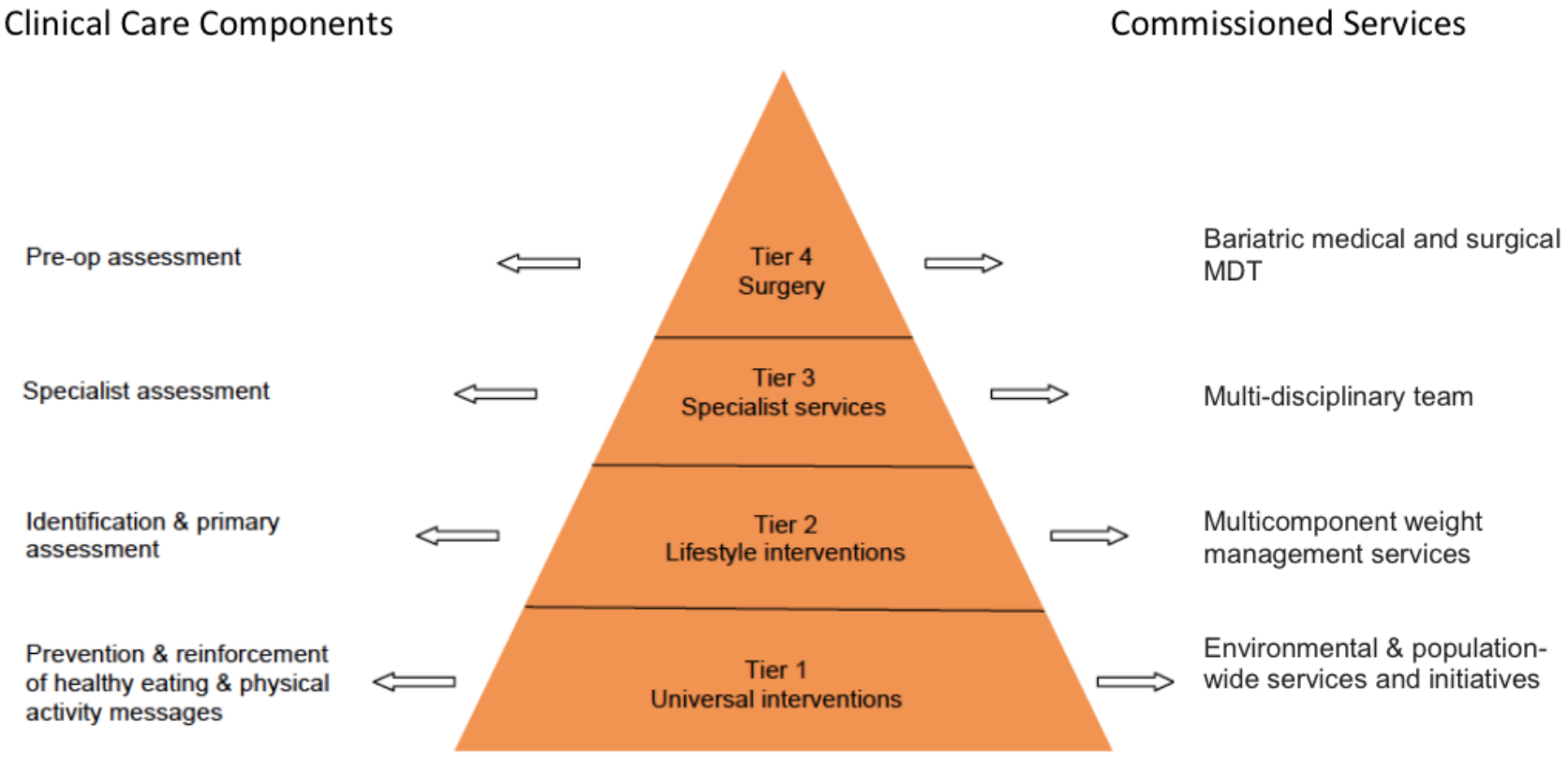
RCS ADVANCING SURGICAL STANDARDS

2014

Commissioning guide:

Weight assessment and management clinics (tier 3)

1 High Value Care Pathway for weight assessment and management clinics [c]



A clinicians **diagnosis**

- Obesity = a disease / condition
- Chronic + relapsing
- Complex – **genetic – behavioral – hormonal**
- Related to environments (political/society)
- Multiple comorbidities + direct consequences (metabolic and bio-mechanic and psychological)

- *Endocrinologists / diabetes specialist have a role in managing obesity*

Diets alone don't work ? (if you want to gain weight go on a diet)

MWMC

- Assessment steps
  - Detailed patient self- assessment
  - Comprehensive medical assessment
  - Comprehensive dietitian assessment
  - Specific laboratory & other investigations
  - MDM approach and proactive treatment planning

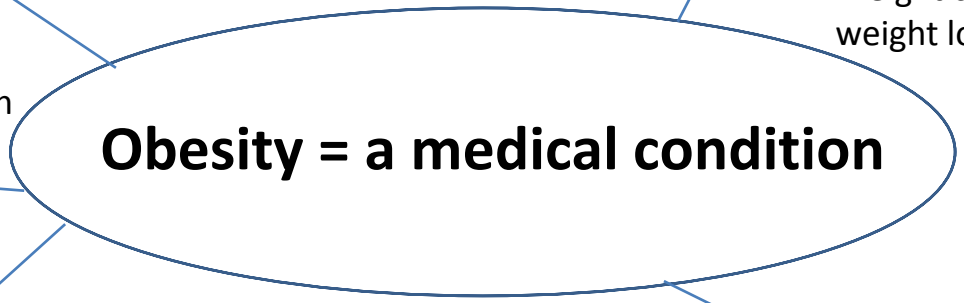
- AIM:
  - Predictors of success (likelihood of success)
  - Treatment and management plan
    - Decision - which dietary approach
    - Decision - whether and which medication to change / to use
    - Frequency and duration of follow up
    - Exercise prescription

Multi- modal and comprehensive assessment

Medical
- Medications leading to weight gain
- Medical conditions associated with weight gain (rare)
- Complicating / limiting medical conditions
- Hormonal problems

Genetic and epigenetic
- Mono and polygenic obesity
- Family history
- GDM, weight gain in pregnancy
- Weight gain in infancy (trajectory)
- Weight cycling (time of sustained weight loss)

Weight history
- causes and timely
- associations for weight gain
- success in previous attempts

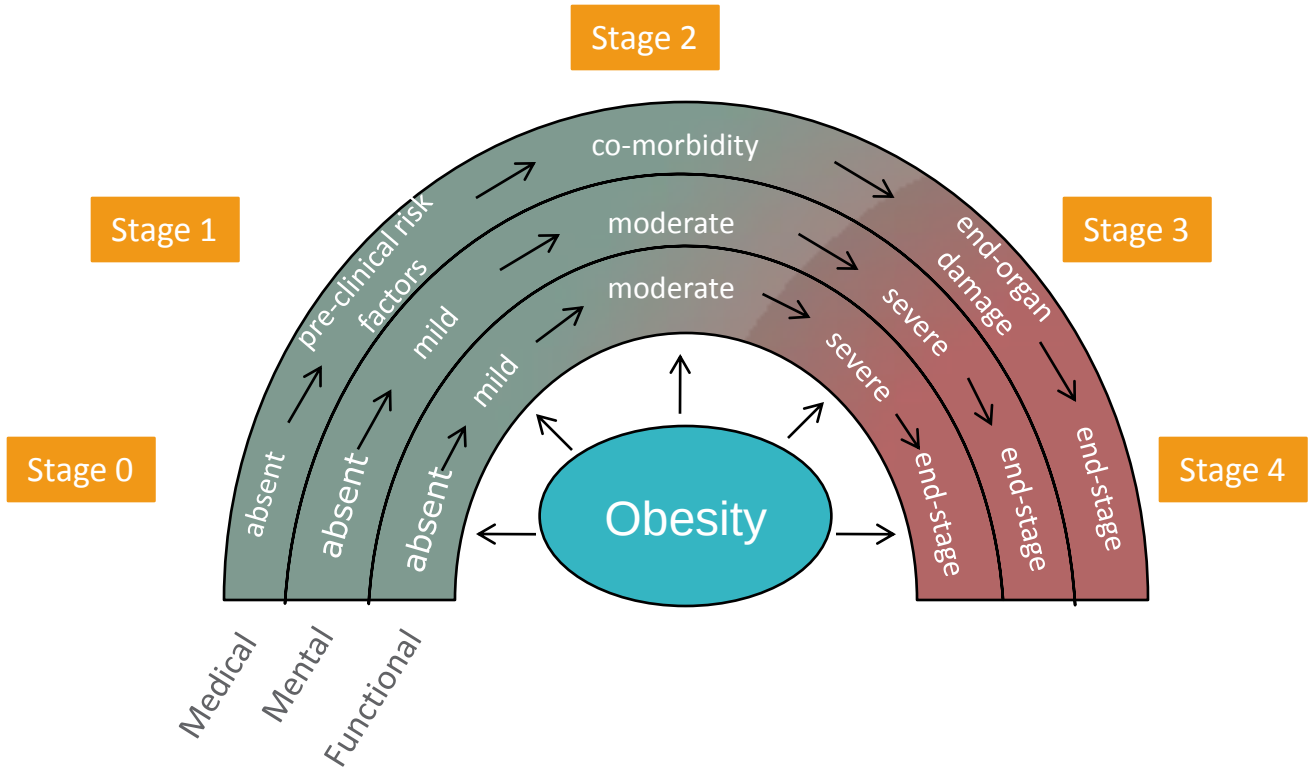


Individual / behavioral
- Motivation and readiness
- Anxiety and depression
- Self-reliance and confidence
- Eating habits and pattern (feasters, emotional eaters, constant cravers)
- Diet preferences
- Exercise ability
- Conflicting demands

Environmental
- Food- access and quality
- Family environment
- Transport
- Work support
- Toxins (endocrine disruptors)

Obesogenic environments

Complications: The Edmonton Obesity Staging System (EOSS) for Assessing RISK



Sharma AM et al. Int J Obes. 2009

EOSS: EDMONTON OBESITY STAGING SYSTEM - *Staging Tool*

STAGE 0

- **NO** sign of obesity-related risk factors
- **NO** physical symptoms
- **NO** psychological symptoms
- **NO** functional limitations

Case Example:
Physically active female with a BMI of 32 kg/m², no risk factors, no physical symptoms, no self-esteem issues, and no functional limitations.

Class I, Stage 0 Obesity

EOSS Score

WHO Obesity Classfication

STAGE 1

- Patient has obesity-related **SUBCLINICAL** risk factors (borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.)

- OR -

- **MILD** physical symptoms - patient currently not requiring medical treatment for comorbidities (dyspnea on moderate exertion, occasional aches/pains, fatigue, etc.)

- OR -

- **MILD** obesity-related psychological symptoms and/or mild impairment of well-being (quality of life not impacted)

Case Example:
38 year old female with a BMI of 59.2 kg/m², borderline hypertension, mild lower back pain, and knee pain. Patient does not require any medical intervention.

Class III, Stage 1 Obesity

WHO CLASSIFICATION OF WEIGHT STATUS (**BMI kg/m²**)

Obese Class I ..... 30 - 34.9
Obese Class II ..... 35 - 39.9
Obese Class III ..... ≥40

Stage 0 / Stage 1 Obesity

Patient ***does not meet clinical criteria for admission*** at this time.
Please refer to primary care for further preventative treatment options.

STAGE 2

- Patient has **ESTABLISHED** obesity-related comorbidities requiring medical intervention (HTN, Type 2 Diabetes, sleep apnea, PCOS, osteoarthritis, reflux disease)

- OR -

- **MODERATE** obesity-related psychological symptoms (depression, eating disorders, anxiety disorder)

- OR -

- **MODERATE** functional limitations in daily activities (quality of life is beginning to be impacted)

Case Example:
32 year old male with a BMI of 36 kg/m² who has primary hypertension and obstructive sleep apnea.

Class II, Stage 2 Obesity

STAGE 3

- Patient has **significant** obesity-related end-organ damage (myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis)

- OR -

- **SIGNIFICANT** obesity-related psychological symptoms (major depression, suicide ideation)

- OR -

- **SIGNIFICANT** functional limitations (eg: unable to work or complete routine activities, reduced mobility)
- **SIGNIFICANT** impairment of well-being (quality of life is significantly impacted)

Case Example:
49 year old female with a BMI of 67 kg/m² diagnosed with sleep apnea, CV disease, GERD, and suffered from stroke. Patient's mobility is significantly limited due to osteoarthritis and gout.

Class III, Stage 3 Obesity

STAGE 4

- **SEVERE** (potential end stage) from obesity-related comorbidities

- OR -

- **SEVERELY** disabling psychological symptoms

- OR -

- **SEVERE** functional limitations

Case Example:
45 year old female with a BMI of 54 kg/m² who is in a wheel chair because of disabling arthritis, severe hyperpnea, and anxiety disorder.

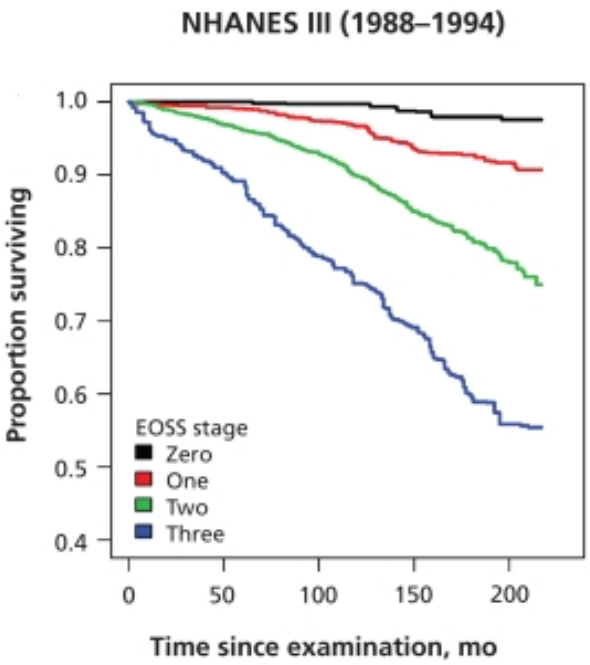
Class III, Stage 4 Obesity

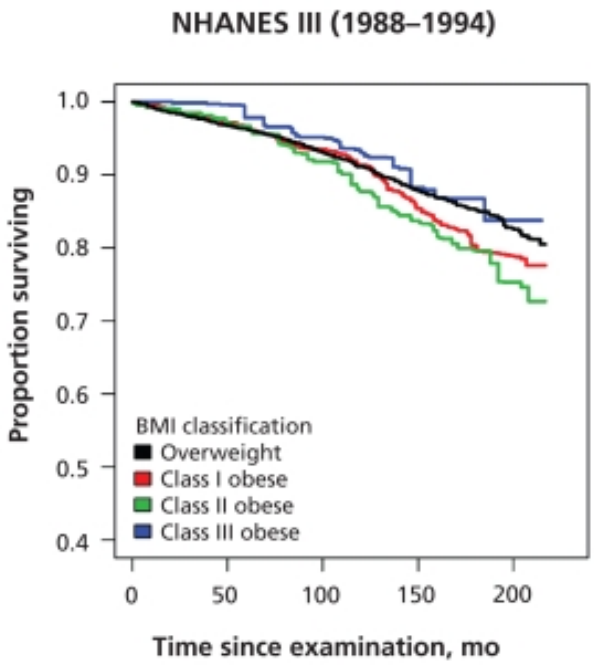
Alberta Health Services

UNIVERSITY OF ALBERTA

Sharma AM & Kushner RF, *Int J Obes* 2009

Edmonton Staging System Can Predict Mortality Better than BMI





Padwal R et al. CMAJ. 2011

Sustainability – need appropriate long-term planning and management

The NEW ENGLAND JOURNAL of MEDICINE

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

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.

Conclusions

- One year after initial weight reduction, levels of the circulating mediators of appetite that encourage weight regain after diet-induced weight loss do **not** revert to the levels recorded before weight loss
- Long-term strategies to counteract this change may be needed to prevent obesity relapse

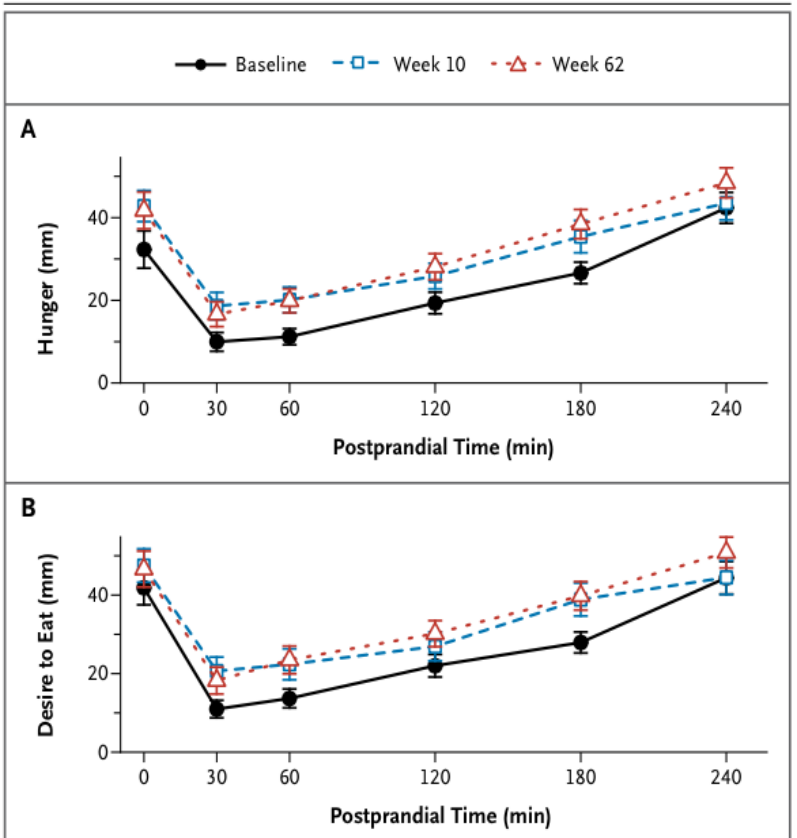
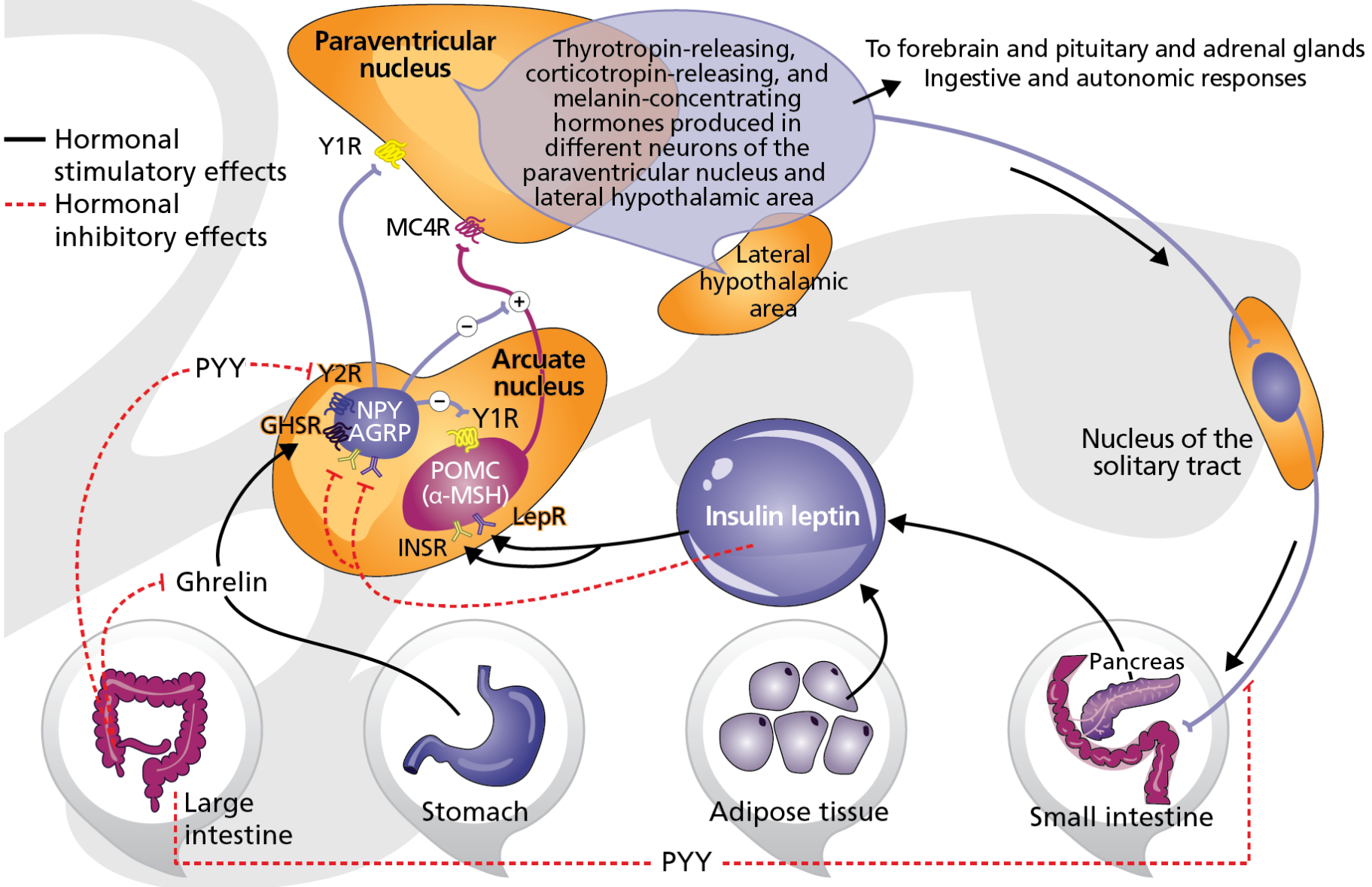


Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.

Ratings were based on a visual-analogue scale ranging from 0 to 100 mm. Higher numbers indicate greater hunger or desire.

Obesity = a brain disease - Control Over Appetite Regulation



AGRP: agouti-related peptide; α-MSH: α-melanocyte-stimulating hormone; GHSR: growth hormone secretagogue receptor; INSR: insulin receptor; LepR: leptin receptor; MC4R: melanocortin-4 receptor; NPY: neuropeptide Y; POMC: proopiomelanocortin; PYY: peptide YY; Y1R; neuropeptide Y1 receptor; Y2R: neuropeptide Y2 receptor. Apovian CM, Aronne LJ, Bessesen D et al. *J Clin Endocrinol Metab*. 2015;100:342-362.

What Does Comprehensive Medical Obesity Treatment Include?

Nutrition

Physical Activity

Behavior

Medication

SPECIAL FEATURE

Clinical Practice Guideline

Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

Caroline M. Apovian, Louis J. Aronne, Daniel H. Bessesen, Marie E. McDonnell, M. Hassan Murad, Uberto Pagotto, Donna H. Ryan, and Christopher D. Still

Boston University School of Medicine and Boston Medical Center (C.M.A.), Boston, Massachusetts 02118; Weill-Cornell Medical College (L.J.A.), New York, New York 10065; Denver Health Medical Center (D.H.B.), Denver, Colorado 80204; Brigham and Women's Hospital (M.E.M.), Boston, Massachusetts 02115; Mayo Clinic, Division of Preventative Medicine (M.H.M.), Rochester, Minnesota 55905; Alma Mater University of Bologna (U.P.), S. Orsola-Malpighi Hospital Endocrinology Unit, 40138 Bologna, Italy; Pennington Biomedical Research Center (D.H.R.), Baton Rouge, Louisiana 70808; and Geisinger Health Care System (C.D.S.), Danville, Pennsylvania 17822

Objective: To formulate clinical practice guidelines for the pharmacological management of obesity.

Conclusions:

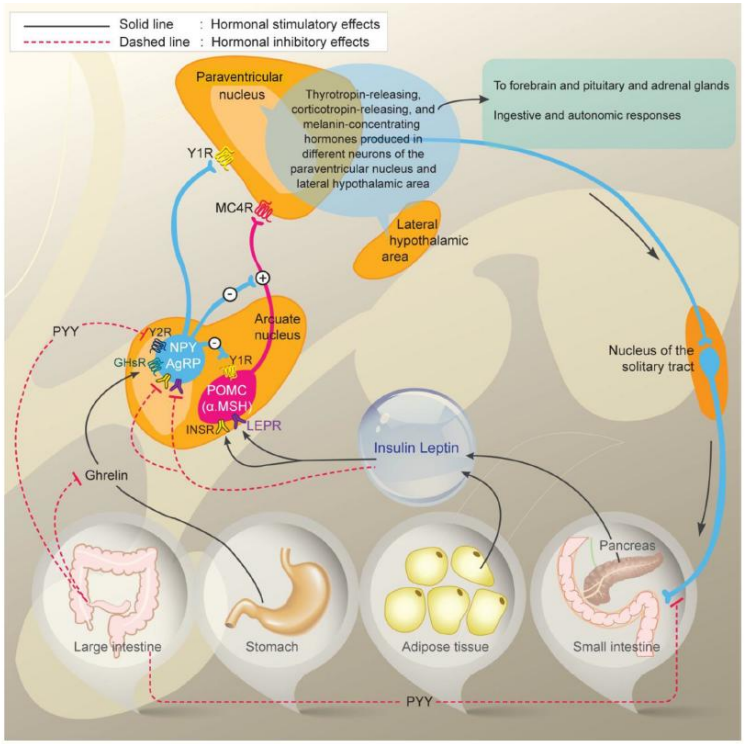
1. Medications for **chronic** weight management can be useful adjuncts

2. Many medications for diabetes, depression, and chronic diseases have weight effects

3. Knowledgeable prescribing - can aid in the prevention and management of obesity and improve health

Which medication is *the odd one out* – **not** causing weight gain?

1. Atenolol
2. Sulphonylureas
3. Pioglitazone
4. Estrogens
5. Gabapentin
6. Amitriptyline
7. Bupropion
8. Paroxetine
9. Antihistamines
10. Sodium valproate



Medications for weight- management

General:

1. As part of combined approach
2. Aim – reduce co-morbidities
3. Prevent weight regain / stabalize weightloss

Weight loss medications:

- Orlistat
- Phentermine
- **Lorcaserin (camellia study)**
- **Phentermine + Topiramate (Quesima)**
- **Naltrexone + Bupropion**

Diabetes medications:

- GLP4 (Exenatide and Liraglutide)
- Metformin
- SGLT2 inhibitors (dapaglifozin)

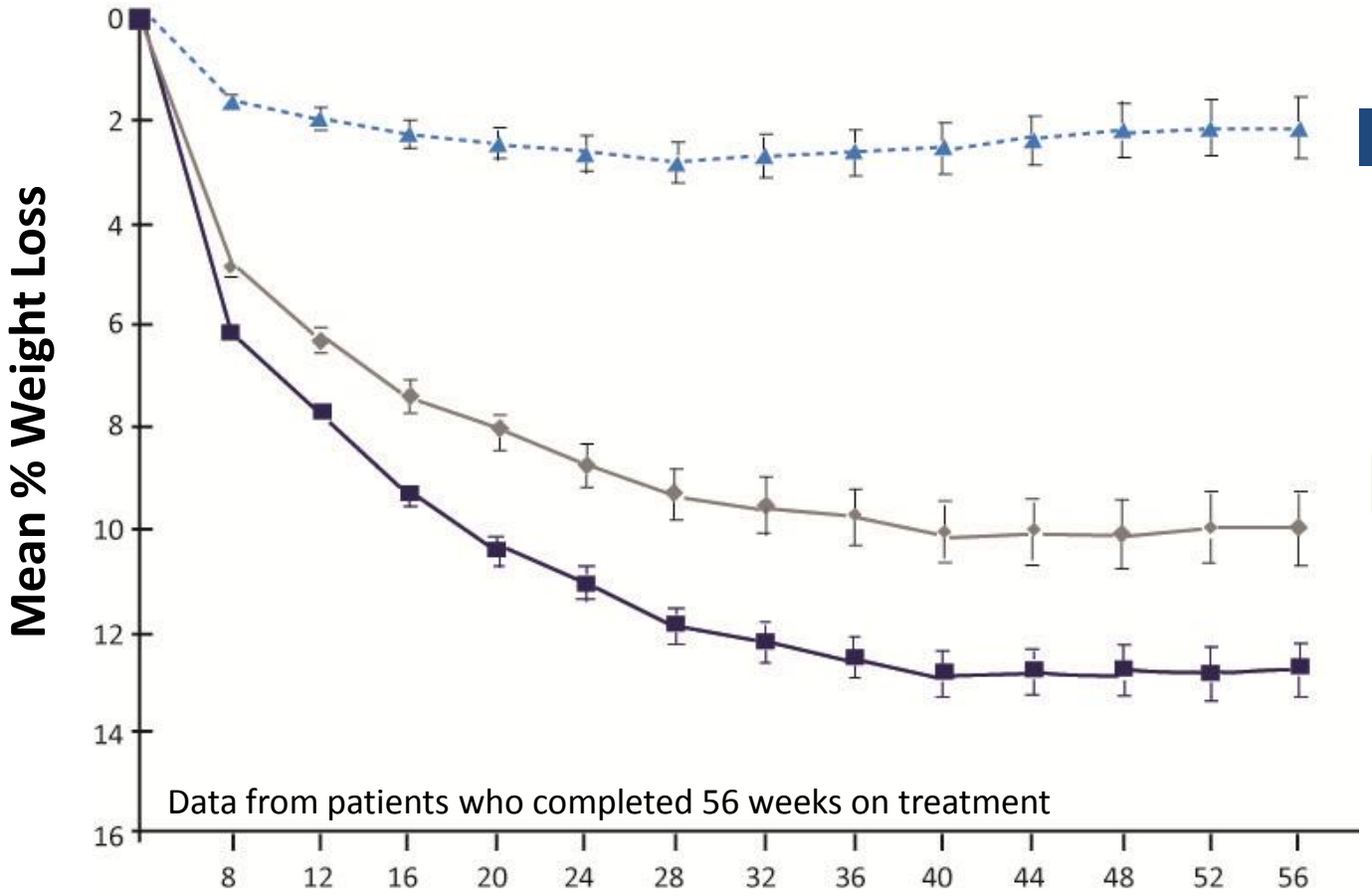
Newer Antiobesity Medications

Agent	Mechanism of Action	Approval Date
Lorcaserin[a]	• Selective serotonin receptor agonist (5-HT_{2C})	2012
Phentermine/ Topiramate ER[b]	• Sympathomimetic • Anticonvulsant (GABA receptor modulator, carbonic anhydrase inhibitor, glutamate antagonist)	2012
Naltrexone SR/ Bupropion SR[c]	• Opioid receptor antagonist • Dopamine/noradrenaline reuptake inhibitor	09/10/2014
Liraglutide 3.0 mg[d]	• GLP-1 receptor agonist	12/23/2014

a. Belviq® PI 2012.[12] b. Qsymia® PI 2014[9]; c. CONTRAVE® PI[10]; d. Saxenda® PI.[11]

CONQUER: Weight Loss Over Time

(Phentermine / Topiramate)

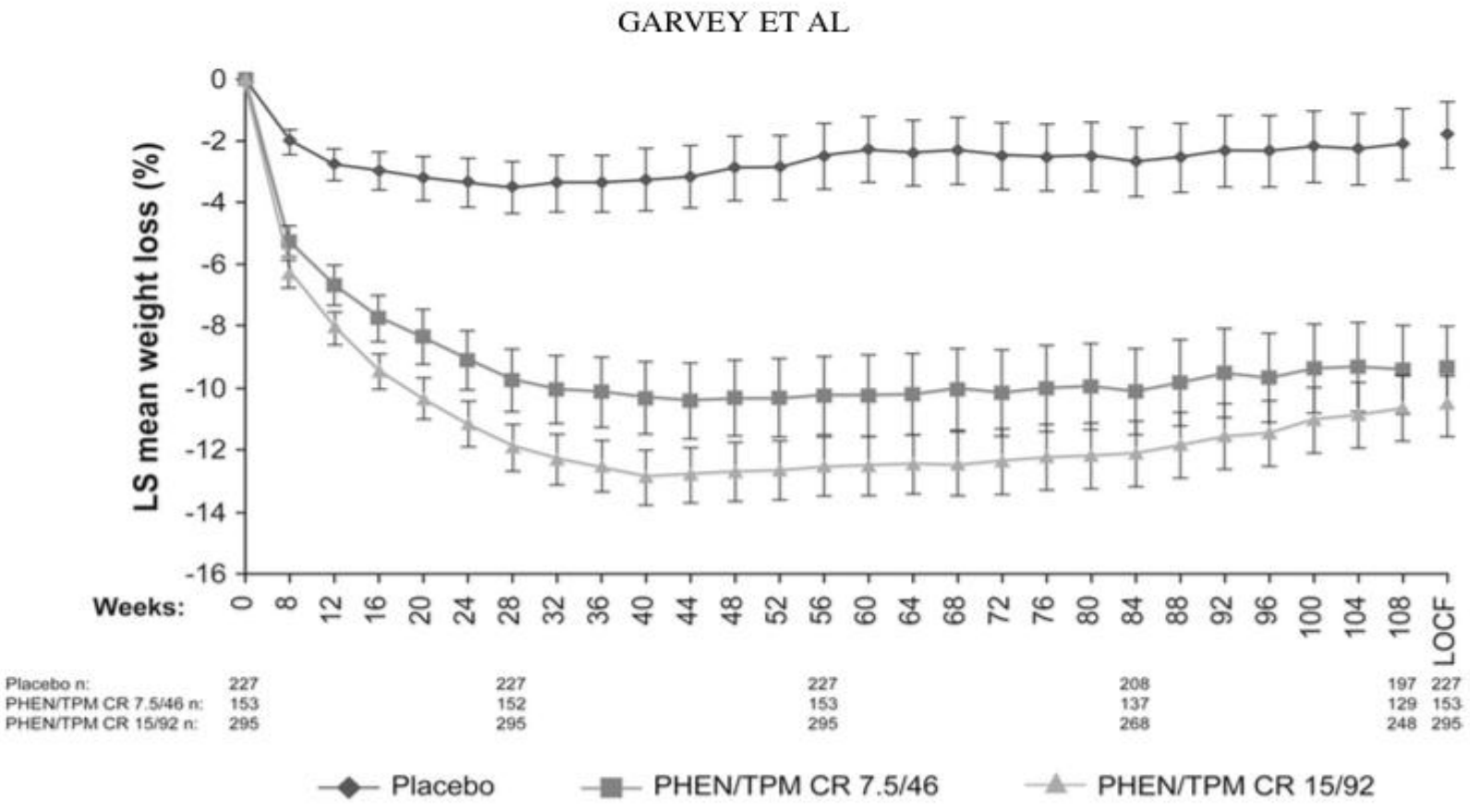


Patients	Placebo	Mid	Full
Completers (% of randomized)	564 (57%)	344 (69%)*	634 (64%)*

*Statistically greater number of patients completing study on combination drug vs placebo, $P < .0001$

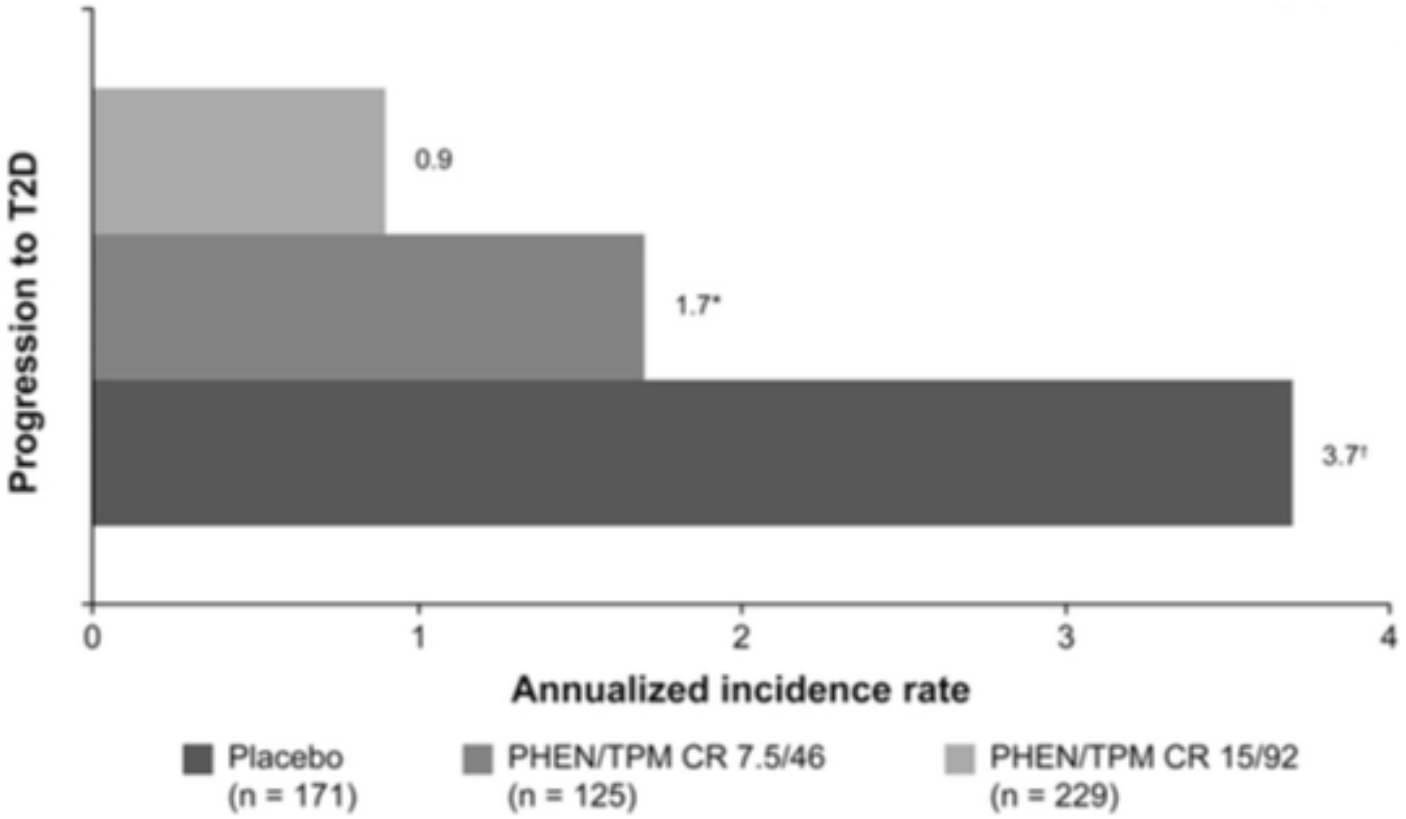
Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study[1–3]

W Timothy Garvey, Donna H Ryan, Michelle Look, Kishore M Gadde, David B Allison, Craig A Peterson, Michael Schwiers, Wesley W Day, and Charles H Bowden



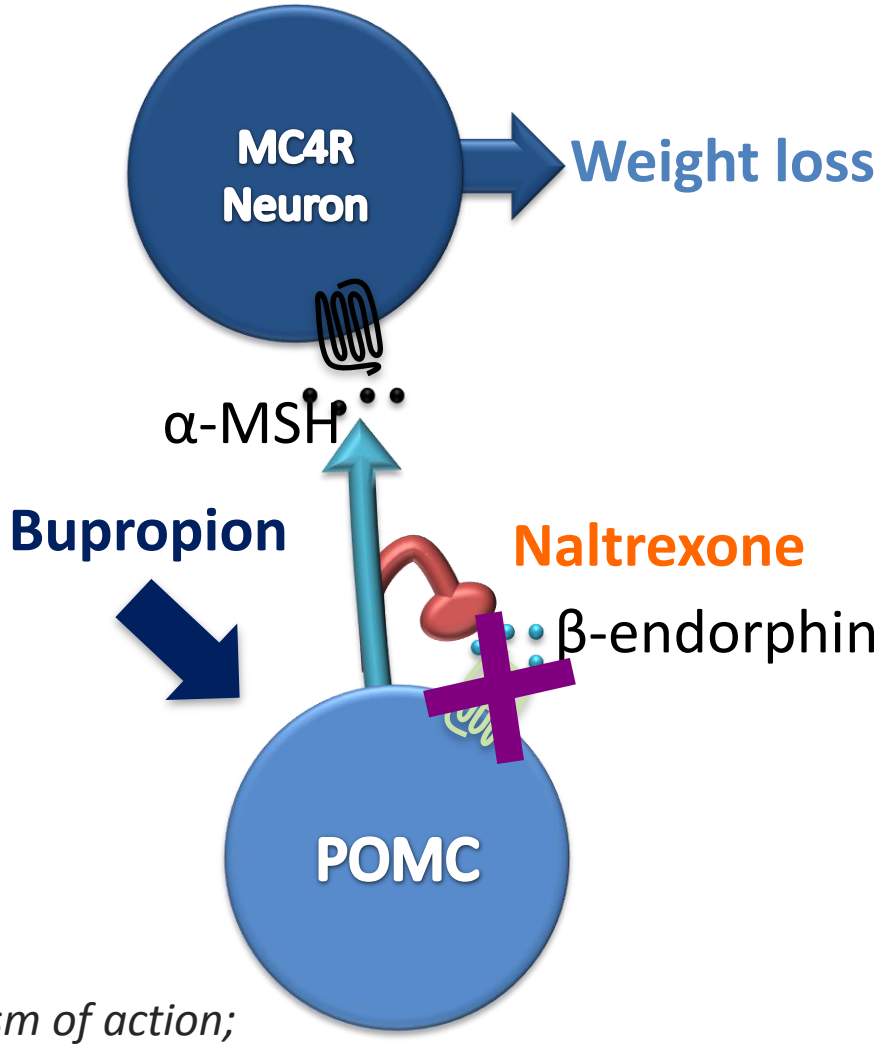
Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study[1–3]

W Timothy Garvey, Donna H Ryan, Michelle Look, Kishore M Gadde, David B Allison, Craig A Peterson, Michael Schwiers, Wesley W Day, and Charles H Bowden



Naltrexone and Bupropion Rationally Designed Around MOA to Initiate and Sustain Weight Loss

- Obesity: complex pathways to defend body weight
- evidence for drug synergy
  - Naltrexone/bupropion synergistic increase in POMC activity
  - Decrease in food intake and body weight

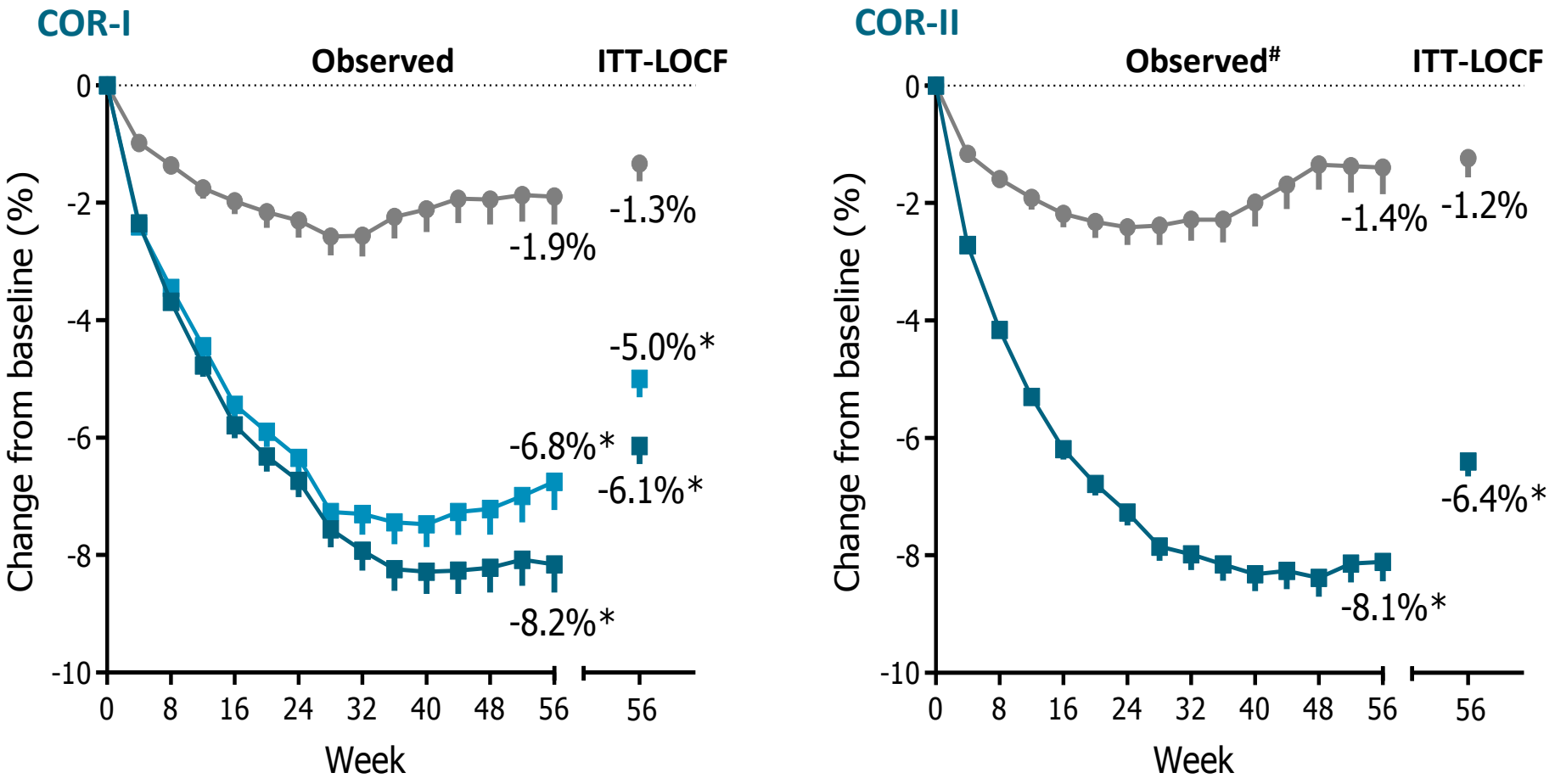


MC4R = melanocortin-4 receptor; MOA = mechanism of action; MSH = melanocyte-stimulating hormone; POMC = proopiomelanocortin

Greenway FL, et al. *Obesity*. 2009;17:30-39.

COR-I, II: Body Weight, Change From Baseline

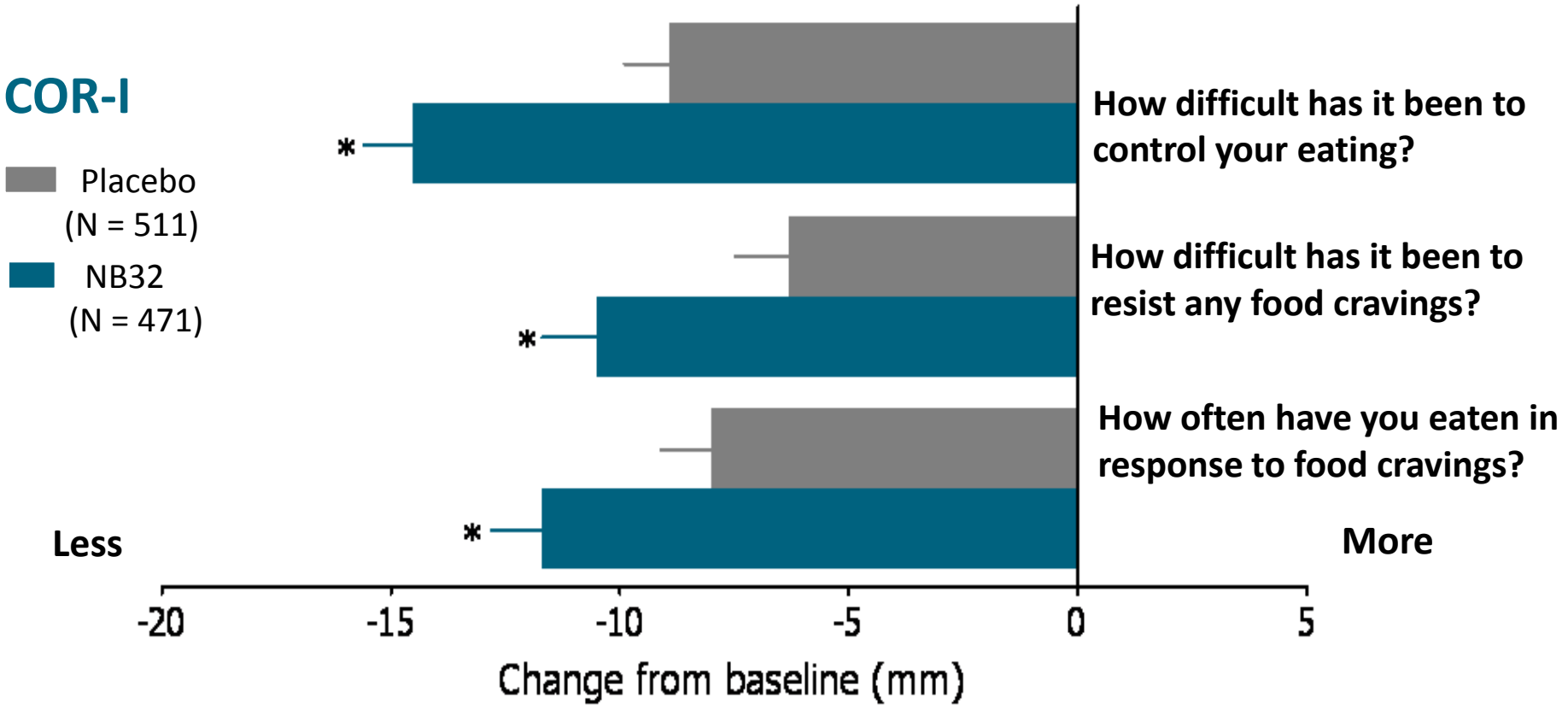
Placebo (N=511) NB16 (N=471) NB32 (N=471) Placebo (N=456) NB32 (N=702)



Completers: Placebo (N = 290): -1.8% , NB16 (N = 284): -6.7%*
NB32 (N = 296): -8.1%*

Completers: Placebo (N = 267): -1.4%
NB32 (N = 434): -8.2%*

COR-I: Improvements in Control of Eating



Drug Tolerability

Orlistat[a]	Lorcaserin[b]	Phentermine/ Topiramate ER[c]	Naltrexone SR/ Bupropion SR[d]	Liraglutide 3.0 mg[e]
• Steatorrhea symptoms	• Headache • Dizziness • Fatigue	• Paresthesias • Dysgeusia • Dizziness • Dry mouth	• Nausea • Vomiting • Headache • Dizziness • Insomnia	• Nausea • Vomiting • Diarrhea • Constipation • Dyspepsia • Abdominal pain

a. Xenical PI 2013[5]; b. Belviq® PI 2012[12];c. Qsymia® PI 2014[9]; d. CONTRAVE PI 2014[10]; e. Saxenda PI 2015.[11]

Diabetes and Obesity

- Lean et al, Lancet, 2017 Dec 4, *Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial*

- Taylor R et. al, *Beating type 2 diabetes into remission, BMJ* 2017, 13 September 2017

- Deborah A. Hutcheon, December 2017, *Short Term Preoperative Weight Loss and Postoperative Outcomes in Bariatric Surgery*

MINISTRY OF HEALTH
MANATŪ HAUORA

New Zealand Government

Clinical Guidelines for Weight Management in New Zealand Adults

Conclusion

1. Obesity is a complex condition
2. Physicians and endocrinologists need to take charge of the *medical management*
3. Evidence based, well developed concepts (international and national guidelines)
4. All aspects need to be integrated (MDT)
5. Long-term sustainability
6. Before and after bariatric surgery

Back-up slides

MINISTRY OF HEALTH
MANATŪ HAUORA

New Zealand Government

Clinical Guidelines for Weight Management in New Zealand Adults

Clinical Guidelines for Weight Management in New Zealand Adults

Evidence shows that poor diet, excess weight and physical inactivity are three major modifiable risk factors that contribute to early death, illness and disability in New Zealanders. Identifying and supporting people who require help with weight management will help empower them to 'live well, stay well, and get well', consistent with the New Zealand Health Strategy (Ministry of Health 2016b).

Health practitioners working in community and primary health care settings are often the first point of contact with the health system. They are well placed to identify whether an adult is overweight or obese, support them to attain and maintain a healthy weight, and coordinate referral to specialist services if required.

This limited update of the *Clinical Guidelines for Weight Management in New Zealand Adults* will equip health practitioners with the most up-to-date tools to monitor, assess manage and support overweight and obese adults to attain and maintain a healthy weight. The aim of the guidance is to improve health outcomes and equity of health outcomes for those with excess weight.

The guidance is our interpretation of key international evidence for the New Zealand context. We encourage health practitioners and others to use this information as the basis for helping New Zealand adults to attain and maintain a healthy weight.

Chai Chuah
Director-General of Health

Referral to specialist services

Consider referring overweight or obese people to a specialist or specialist services if:

- they consider that a specialist needs to assess the underlying cause of a person's overweight or obesity
- the person has complex comorbidities or needs that the practitioner cannot adequately manage
- conventional treatment has been unsuccessful
- the practitioner considers that specialist interventions (eg, a very low-energy diet) may be necessary [NICE 2006 (amended 2014)].

Consider referring people to a dietitian for specialist nutrition or dietary advice if they have food allergies, or have been unsuccessful in their attempts to alter their eating/drinking behaviours.

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Background - assess whether intensive weight management within routine primary care would achieve remission of type 2 diabetes.

Methods

open-label, cluster-randomised trial (DiRECT) at 49 primary care practices in Scotland and England.

Practices were randomly assigned (1:1) to provide either a weight management programme (intervention) or best-practice care by guidelines (control)

individuals aged 20–65 years who had been diagnosed with type 2 diabetes within the past 6 years, had a body-mass index of 27–45 kg/m2, and were not receiving insulin.

The intervention comprised withdrawal of antidiabetic and antihypertensive drugs, total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks), and structured support for long-term weight loss maintenance.

Co-primary outcomes were weight loss of 15 kg or more, and remission of diabetes, defined as glycated haemoglobin (HbA1c) of less than 6·5% (<48 mmol/mol) after at least 2 months off all antidiabetic medications, from baseline to 12 months.

Findings

At 12 months, we recorded weight loss of 15 kg or more in 36 (24%) participants in the intervention group and no participants in the control group (p<0·0001).

Diabetes remission was achieved in 68 **(46%)** participants in the intervention group and six (4%) participants in the control group (odds ratio 19·7, 95% CI 7·8–49·8; p<0·0001).

Mean bodyweight fell by 10·0 kg (SD 8·0) in the intervention group and 1·0 kg (3·7) in the control group (adjusted difference −8·8 kg, 95% CI −10·3 to −7·3; p<0·0001).

Interpretation

Our findings show that, at 12 months, almost half of participants achieved remission to a non-diabetic state and off antidiabetic drugs. Remission of type 2 diabetes is a practical target for primary care

Short Term Preoperative Weight Loss and Postoperative Outcomes in Bariatric Surgery

Background

Preoperative weight loss is often encouraged before undergoing weight loss surgery. Controversy remains as to its effect on postoperative outcomes.

The aim of this study was to determine what impact short-term preoperative excess weight loss (EWL) has on postoperative outcomes in patients undergoing primary vertical sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB).

Study Design

All patients who underwent SG (n = 167) or RYGB (n = 188) between 2014 and 2016 and who completed our **program-recommended low calorie diet (LCD) for 4 weeks immediately preceding surgery** were included. These patients (N = 355) were then divided into 2 cohorts and analyzed according to those who achieved ≥8% EWL (n = 224) during the 4-week LCD period and those who did not (n = 131). Primary endpoints included percent excess weight loss (% EWL) at 1, 3, 6, and 12 months postoperatively.

Results

Patients achieving ≥8% EWL preoperatively experienced a greater % EWL at postoperative month 3 (42.3 vs 36.1 %, $p < 0.001$), month 6 (56.0 % vs 47.5 %, $p < 0.001$), and month 12 (65.1 vs 55.7 %, $p = 0.003$).

Median operative duration and mean hospital length of stay (1.8 days vs 2.1 days; $p = 0.006$) were also less in patients achieving ≥8% EWL. No significant differences in follow-up, readmission, or reoperation rates were seen. Linear regression analysis revealed that patients who achieved ≥8% EWL during the 4-week LCD lost 7.5% more excess weight at postoperative month 12.

Conclusions

Based on these data, preoperative weight loss of ≥8% excess weight, while following a 4-week LCD, is associated with a significantly greater rate of postoperative EWL over 1 year, as well as shorter operative duration and hospital length of stay.

Phentermine / Topiramate (Qysmia™)
(FDA 2012)

Evidence:

- **Longer term data (2 years)**
- **3 large RCT's & post-marketing surveillance**

Phentermine: centrally acting, noradrenaline release (1959) (low dose 3.75-15mg)

- works via **suppression of appetite**
- adverse effects: insomnia, CV, blood pressure & HR

Topiramate: an anticonvulsant and for migraine prophylaxis (low dose 16-92mg)

- Clinical trials - lead to and maintain weight loss
- Theoretically, a lower dose combination of these two drugs may lead to fewer side effects while still producing significant weight loss

Safety concerns:

- potential for **teratogenicity**
- elevations in resting heart rate (sympathomimetic effects of phentermine)
- **glaucoma**
- psychiatric and cognitive adverse effects

CONQUER trial

Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults

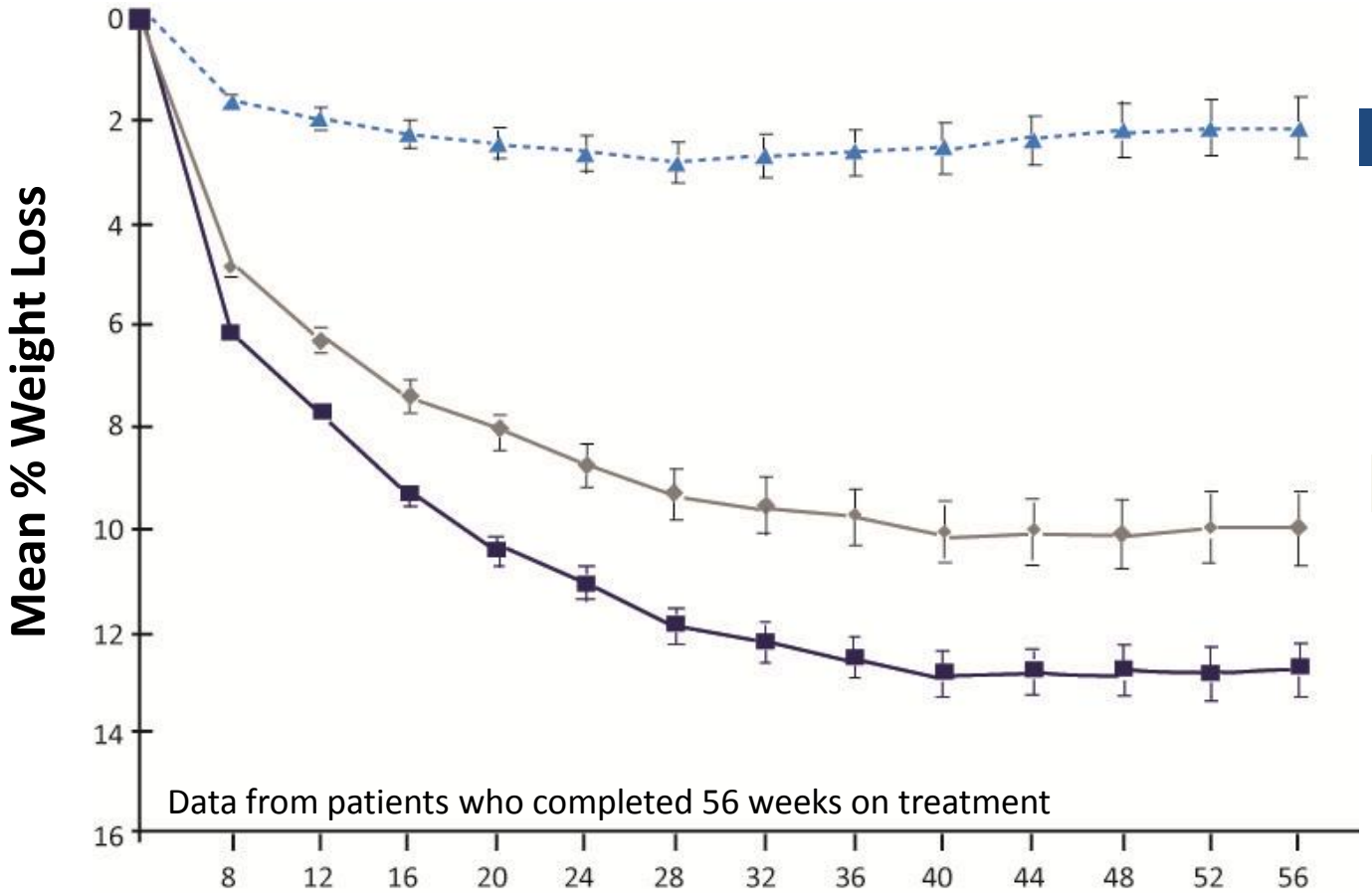
- large two year phase 3 double-blind, placebo controlled study - 2487 overweight and obese patients (BMI 27–45 kg/m2)
- at least two obesity related comorbidities, including hypertension, dyslipidaemia, type 2 diabetes (16%) and pre-diabetes (45%)

- Participants in CONQUER did not only lose a significant amount of weight versus placebo (10.2kg vs 1.4kg), but they also experienced significant improvements in cardio-metabolic risk factors, and required significantly fewer medications to manage hypertension and type 2 diabetes than those receiving placebo

- Furthermore, there was less progression from pre-diabetes to diabetes versus placebo within one year (4.4% vs 9%)

- The two-year continuation of the CONQUER trial, SEQUEL, which also included a continuation of the lifestyle intervention, showed sustained weight loss versus placebo (10.5% vs 1.8%) and maintained improvements in cardio-metabolic disease parameters.34

CONQUER: Weight Loss Over Time
(Completer Population)



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

*Statistically greater number of patients completing study on combination drug vs placebo, $P < .0001$

ARTICLES
INTERVENTION AND PREVENTION

nature publishing group
Open

Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP)

David B. Allison[1,2], Kishore M. Gadde[3], William Timothy Garvey[2,4], Craig A. Peterson[5], Michael L. Schwiers[6], Thomas Najarian[5], Peter Y. Tam[5], Barbara Troupin[5] and Wesley W. Day[5]

Controlled-Release Phentermine/Topiramate in Severely Obese adults: a Randomized Controlled Trial (EQUIP)

- A 56-week randomized controlled trial
- safety and efficacy of a controlled-release combination of phentermine and topiramate (PHEN/TPM CR) for weight loss (WL) and metabolic improvements

- (BMI ≥ 35 kg/m2) were randomized to placebo, PHEN/TPM CR 3.75/23 mg, or PHEN/TPM CR 15/92 mg, added to a reduced-energy diet

- Primary end points were percent WL and proportions of patients achieving 5% WL

- Secondary end points included waist circumference (WC), systolic and diastolic blood pressure (BP), fasting glucose, and lipid measures.

Controlled-Release Phentermine/Topiramate in Severely Obese adults: a Randomized Controlled Trial (EQUIP)

Results:

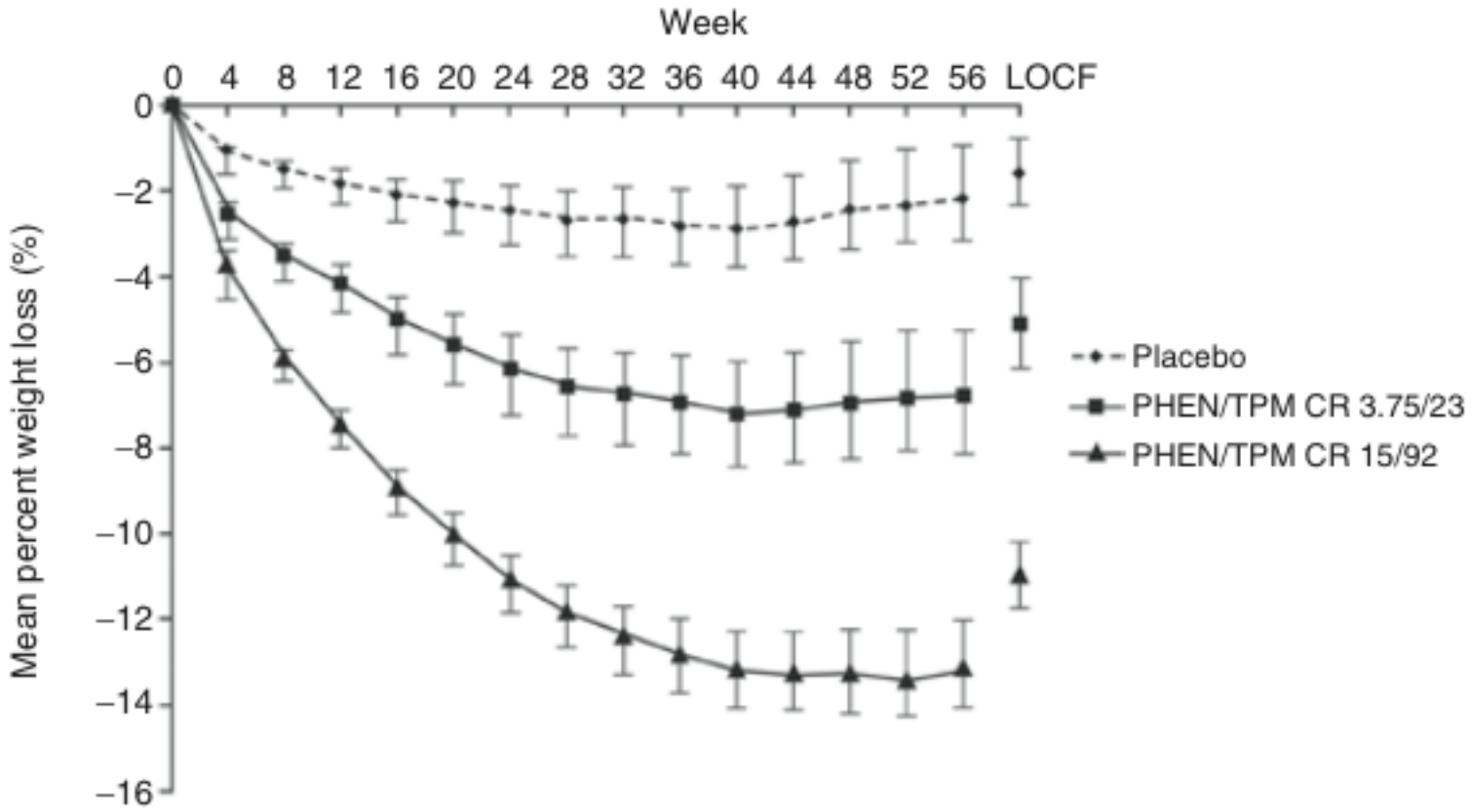
In the primary analysis patients in the placebo, 3.75/23, and 15/92 groups lost 1.6%, 5.1%, and **10.9%** of baseline body weight (BW), respectively, at 56 weeks($P < 0.0001$).

In categorical analysis, 17.3% of placebo patients, 44.9% of 3.75/23 patients, and 66.7% of 15/92 patients, lost at least 5% of baseline BW at 56 weeks ($P < 0.0001$).

The 15/92 group had significantly greater changes relative to placebo for WC, **systolic and diastolic BP, fasting glucose, triglycerides, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL).**

- The most common adverse events were paresthesia, dry mouth, constipation, dysgeusia, and insomnia
- no evidence of serious adverse events induced by treatment
- Dropout rate from the study was 47.1% for placebo patients, 39.0% for 3.75/23 patients, and 33.6% of 15/92 patients

n					
Placebo	498	362	303	279	498
3.75/23	234	190	165	149	234
15/92	498	416	372	348	498

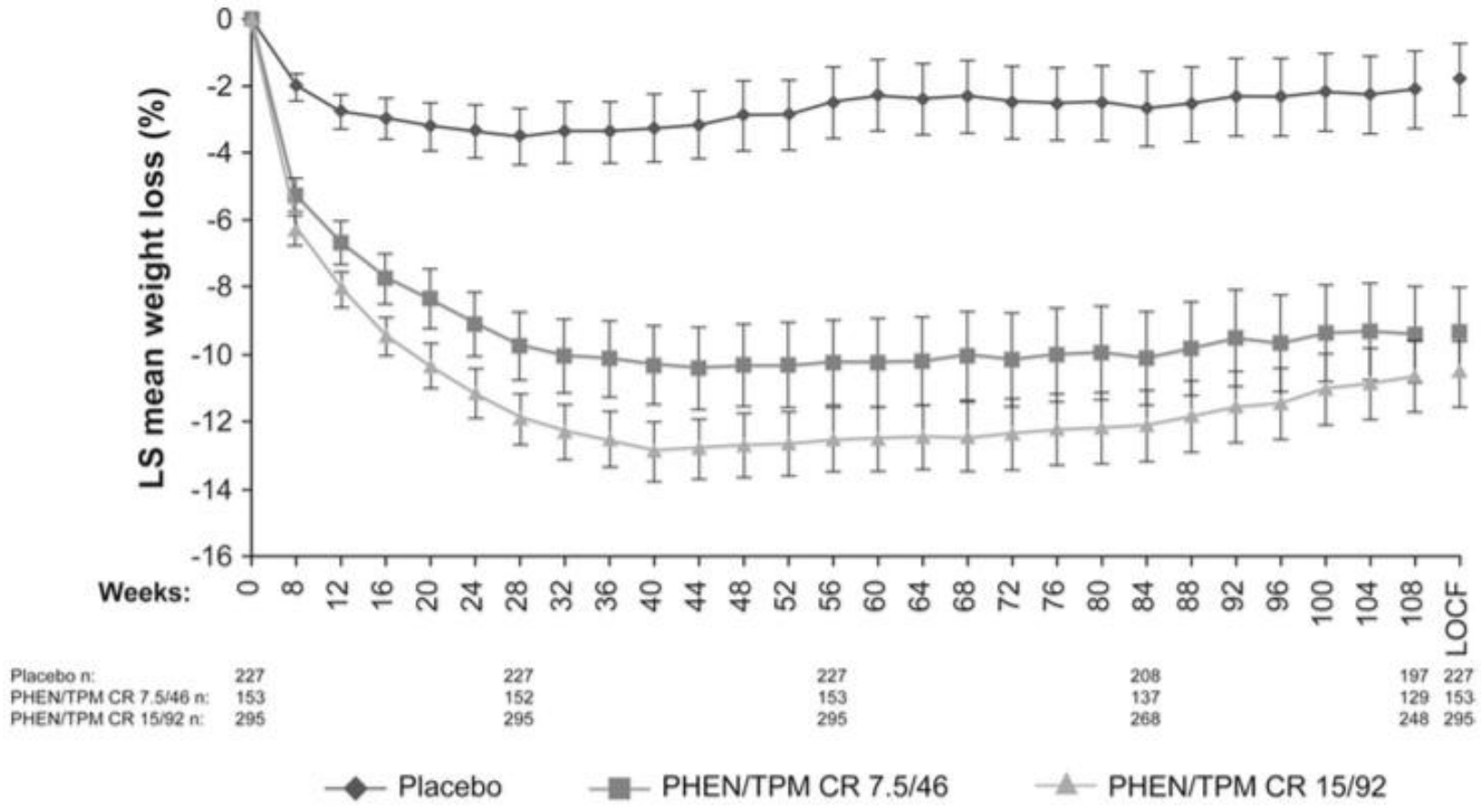


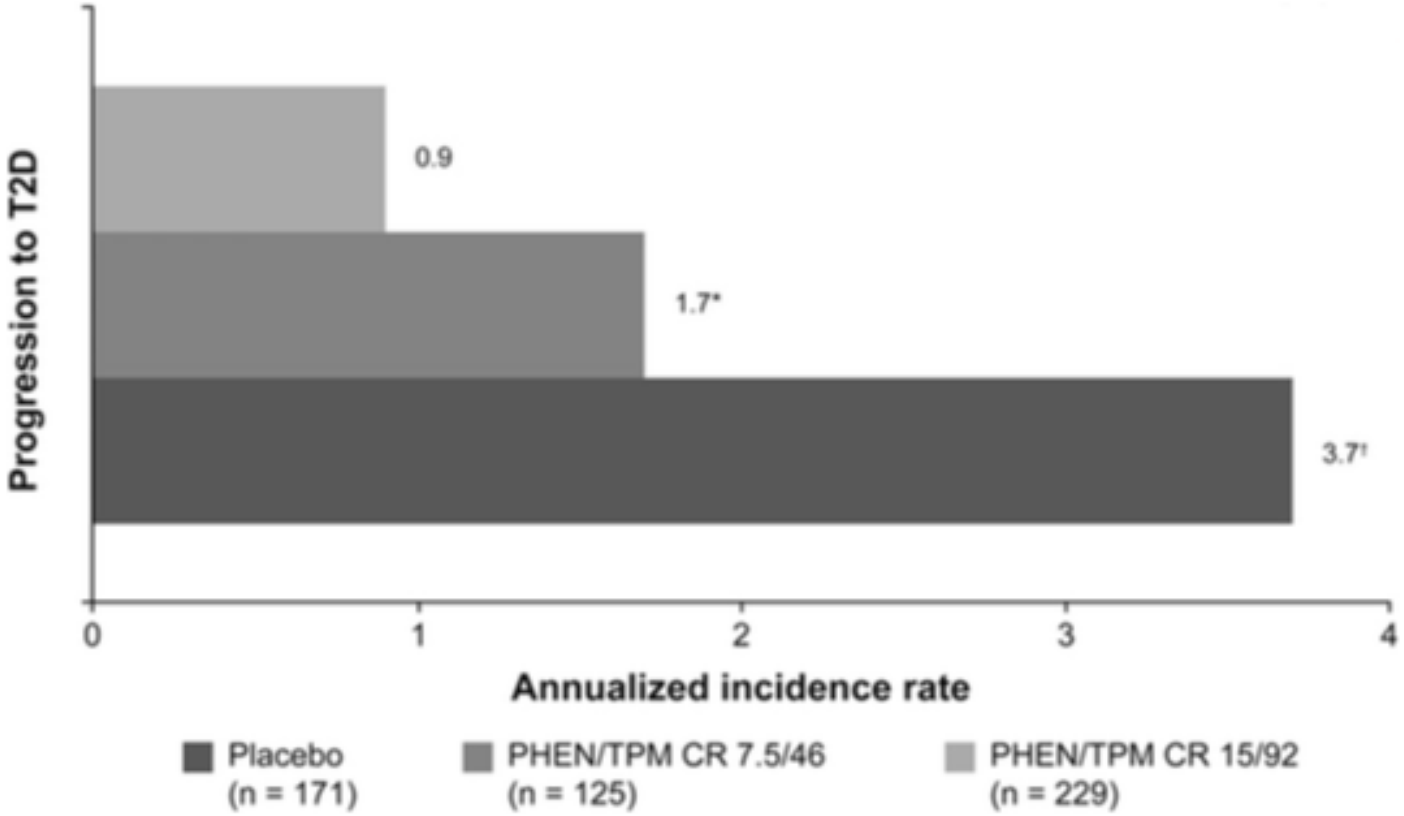
Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study[1–3]

W Timothy Garvey, Donna H Ryan, Michelle Look, Kishore M Gadde, David B Allison, Craig A Peterson, Michael Schwiers, Wesley W Day, and Charles H Bowden

This study evaluated the long-term efficacy and safety of PHEN/TPM CR in overweight and obese subjects with cardio-metabolic disease.

GARVEY ET AL


LS mean weight loss (%)
0
-2
-4
-6
-8
-10
-12
-14
-16
Weeks:
0 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104 108 LOCF
Placebo n: 227 227 227 208 197 227
PHEN/TPM CR 7.5/46 n: 153 152 153 137 129 153
PHEN/TPM CR 15/92 n: 295 295 295 268 248 295
Placebo
PHEN/TPM CR 7.5/46
PHEN/TPM CR 15/92


Progression to T2D
0.9
1.7*
3.7†
0
1
2
3
4
Annualized incidence rate
Placebo
(n = 171)
PHEN/TPM CR 7.5/46
(n = 125)
PHEN/TPM CR 15/92
(n = 229)

Health Benefits of Weight Loss

- Improvement in glycemic control
- Reduction in[a]
  - Diabetes medications
  - Hypertension medications
  - Lipid-lowering medications
- Improvement in
  - Urinary stress incontinence[b]
  - Sexual function[c]
  - Mobility[d]
  - Measures of pain[d]
  - Quality of life

a. Look AHEAD Research Group, et al. *Diabetes Care*. 2007;30:1374-1383[26]; b. Phelan S, et al. *J Urol*. 2012;187:939-944[28]; c. Wing RR, et al. *Diabetes Care*. 2013;36:2937-2944[29]; d. Rejeski WJ, et al. *N Engl J Med*. 2012;366:1209-1217.[30]

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Background - assess whether intensive weight management within routine primary care would achieve remission of type 2 diabetes.

Methods

open-label, cluster-randomised trial (DiRECT) at 49 primary care practices in Scotland and England.

Practices were randomly assigned (1:1) to provide either a weight management programme (intervention) or best-practice care by guidelines (control)

individuals aged 20–65 years who had been diagnosed with type 2 diabetes within the past 6 years, had a body-mass index of 27–45 kg/m2, and were not receiving insulin.

The intervention comprised withdrawal of antidiabetic and antihypertensive drugs, total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks), and structured support for long-term weight loss maintenance.

Co-primary outcomes were weight loss of 15 kg or more, and remission of diabetes, defined as glycated haemoglobin (HbA1c) of less than 6·5% (<48 mmol/mol) after at least 2 months off all antidiabetic medications, from baseline to 12 months.

Findings

At 12 months, we recorded weight loss of 15 kg or more in 36 (24%) participants in the intervention group and no participants in the control group (p<0·0001).

Diabetes remission was achieved in 68 **(46%)** participants in the intervention group and six (4%) participants in the control group (odds ratio 19·7, 95% CI 7·8–49·8; p<0·0001).

Mean bodyweight fell by 10·0 kg (SD 8·0) in the intervention group and 1·0 kg (3·7) in the control group (adjusted difference −8·8 kg, 95% CI −10·3 to −7·3; p<0·0001).

Interpretation

Our findings show that, at 12 months, almost half of participants achieved remission to a non-diabetic state and off antidiabetic drugs. Remission of type 2 diabetes is a practical target for primary care

Short Term Preoperative Weight Loss and Postoperative Outcomes in Bariatric Surgery

Background

Preoperative weight loss is often encouraged before undergoing weight loss surgery. Controversy remains as to its effect on postoperative outcomes.

The aim of this study was to determine what impact short-term preoperative excess weight loss (EWL) has on postoperative outcomes in patients undergoing primary vertical sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB).

Study Design

All patients who underwent SG (n = 167) or RYGB (n = 188) between 2014 and 2016 and who completed our **program-recommended low calorie diet (LCD) for 4 weeks immediately preceding surgery** were included. These patients (N = 355) were then divided into 2 cohorts and analyzed according to those who achieved ≥8% EWL (n = 224) during the 4-week LCD period and those who did not (n = 131). Primary endpoints included percent excess weight loss (% EWL) at 1, 3, 6, and 12 months postoperatively.

Results

Patients achieving ≥8% EWL preoperatively experienced a greater % EWL at postoperative month 3 (42.3 vs 36.1 %, $p < 0.001$), month 6 (56.0 % vs 47.5 %, $p < 0.001$), and month 12 (65.1 vs 55.7 %, $p = 0.003$).

Median operative duration and mean hospital length of stay (1.8 days vs 2.1 days; $p = 0.006$) were also less in patients achieving ≥8% EWL. No significant differences in follow-up, readmission, or reoperation rates were seen. Linear regression analysis revealed that patients who achieved ≥8% EWL during the 4-week LCD lost 7.5% more excess weight at postoperative month 12.

Conclusions

Based on these data, preoperative weight loss of ≥8% excess weight, while following a 4-week LCD, is associated with a significantly greater rate of postoperative EWL over 1 year, as well as shorter operative duration and hospital length of stay.