It's All in Your Mind

The brain's central role in the progression of a chronic disease

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Faculty/Presenter Disclosure

- **Faculty/Presenter: Dr. Sarah High**

- **Relationships with commercial interests:**

I have received honoraria for speaking engagements from Bausch Health, Novo Nordisk, Obesity Canada, and the Canadian Collaborative Research Network.

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Potential for conflict of interest:
Products will be discussed during the presentation.

NovoNordisk may benefit from the sale of the following products:
- Liraglutide

Mitigating Potential Bias

Includes evidence based information related to obesity management but is not influenced by the sponsoring organizations

Program **OBJECTIVES**

1. Discover the complex **pathophysiology** of obesity
2. Understand the mechanisms through which the **brain defends the body against weight loss**
3. Establish the role of **pharmacological intervention** in a multi-modal treatment strategy
4. Discuss conversation-starter strategies to create an individualized, sustainable **treatment plan**

What words come to mind when you think OBESITY?

Chronic medical condition
Complex pathophysiology
Neurohormonal control
Medical treatments available

6 million

Canadians are living with this chronic disease.[1]

Obesity is a growing problem in Canada.

Worldwide, 2.8 million people per year die from overweight/ obesity[2].

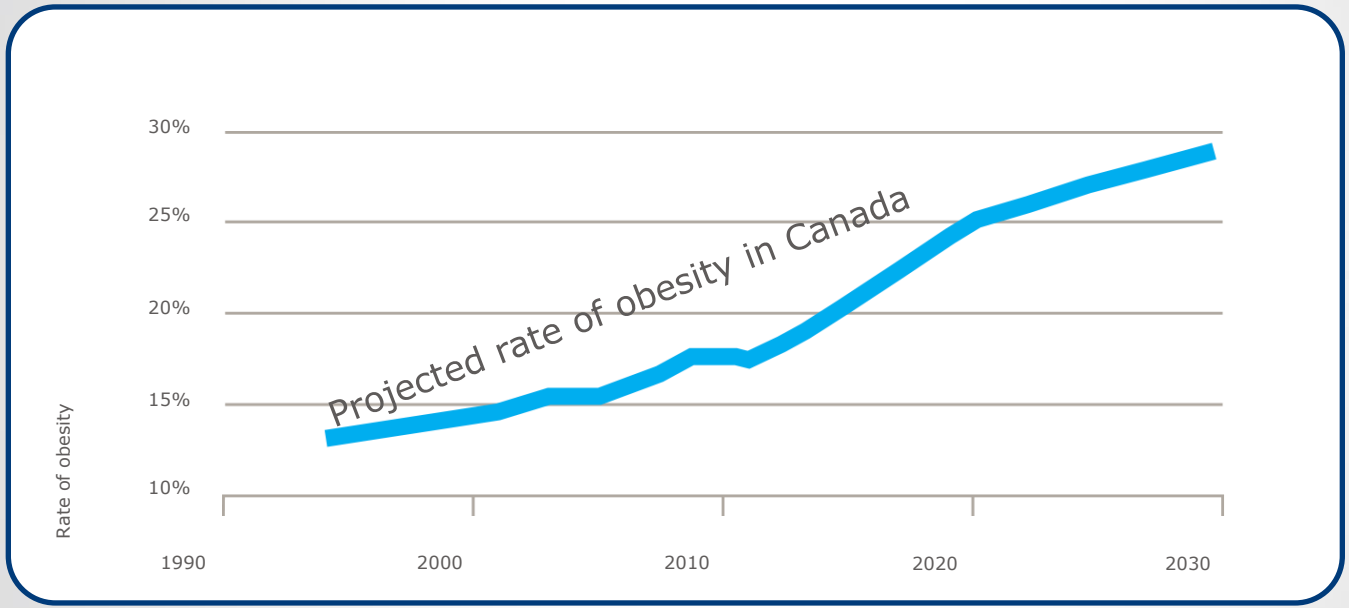
Sources: 1. Canadian Obesity Network. 2018. Understanding Obesity Available at: http://www.obesitycanada.ca/understanding-obesity;
2. WHO. 2017. 10 facts on obesity. Available at: http://www.who.int/features/factfiles/obesity/en/# 10 facts on obesity

Canadians living with obesity.

Sources: 1. Canadian Obesity Network. 2018. What is obesity?. Available at: http://www.obesitycanada.ca

Obesity

The prevalence continues to rise…



Source: Obesity Update 2017. Available: www.oecd.org/health/obesity-update.htm

Obesity is globally recognized as a chronic disease

shifting the perception of obesity from a lifestyle choice to a medical disease that requires research, treatment, and prevention.

Canadian Obesity Network

"Obesity is a chronic and often progressive condition not unlike diabetes or hypertension"[1]

Canadian Medical Association

"Obesity is a chronic disease requiring enhanced research, treatment and prevention efforts"[2]

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"[3]

World Health Organization

"Obesity is a chronic disease, prevalent in both developed and developing countries, and affecting children as well as adults"[4]

1. Canadian Obesity Network. 5As of Obesity Management. Downloaded from www.obesitynetwork.ca on November 17, 2014; 2. CMA Press Release (October 2015). Available at: https://www.cma.ca/En/Pages/cma-recognizes-obesity-as-a-disease.aspx; 3. AMA position statement. Available at: http://www.ama-assn.org/; 4. TOS Obesity as a Disease Writing Group. Obesity 2008;16:1161–77.

But first, what is obesity?

Photo credit: Canadian Obesity Network.

Obesity is…

a chronic medical condition characterized by accumulation of excess body fat causing impairment to health or function.

BMI 18.5-24.9
Normal

BMI 25.0-29.9
Overweight

BMI 30.0-34.9
Obesity Class I

BMI 35.0-39.9
Obesity Class II

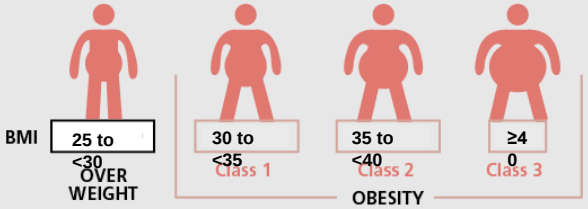
BMI >40.0
Obesity Class III

Body Mass Index (BMI) for adults: Overweight = BMI>25; Obesity = BMI >30

BMI is calculated by dividing a person's weight in kilograms by his or her height in metres squared (kg/m2).

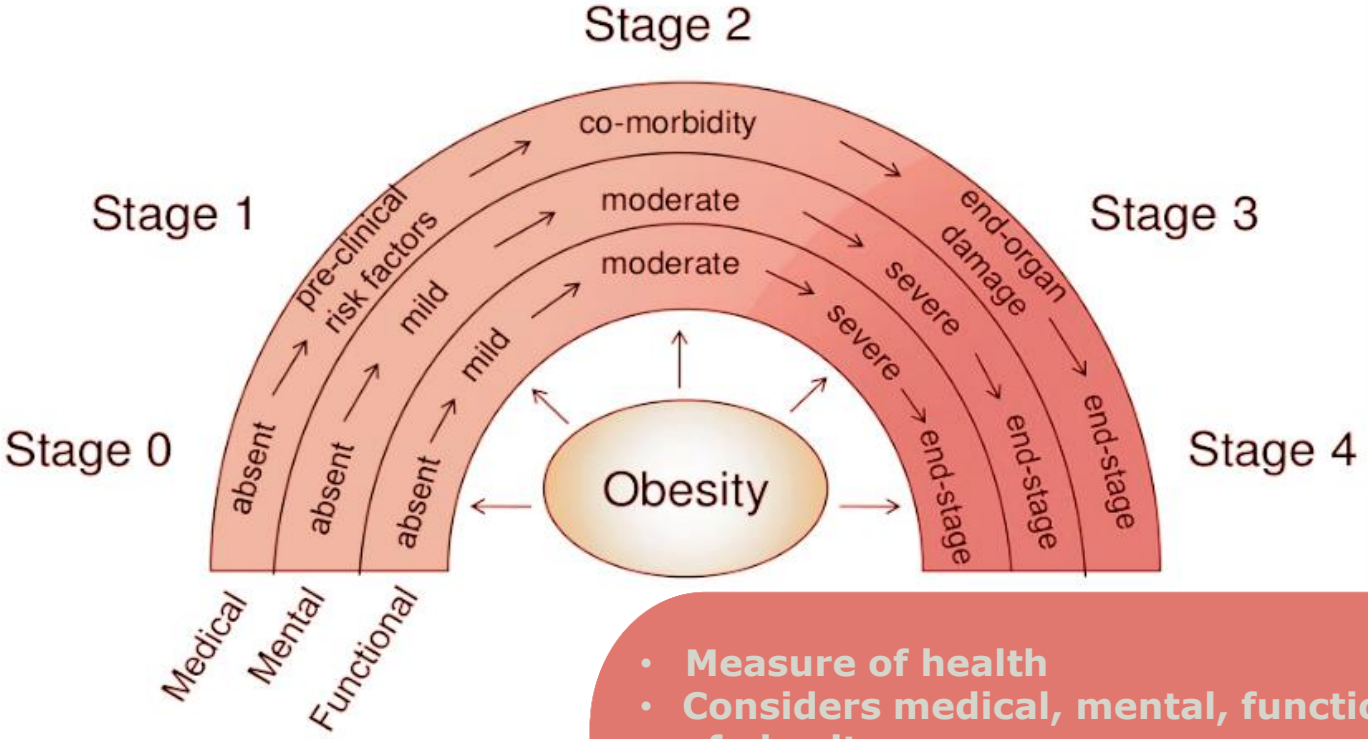
Source: 1. Canadian Obesity Network. 2018. How is obesity measured? Available:www.obesitycanada.ca

Obesity is more than numbers on the scale

			Additional considerations
Obesity, by definition:	**Measure height** **Measure weight** **Calculate BMI** **BMI = kg/m²**		• BMI does not consider body composition (muscle or fat distribution)
Abdominal adiposity:	**Measure waist circumference*** *** If BMI is >25 and ≤35 kg/m²**	European, Sub-Saharan African, Eastern Mediterranean and Middle Eastern (Arab) ♂ **94 cm** | ♀ **80 cm** South Asian, Chinese, Japanese, South and Central American ♂ **90 cm** | ♀ **80 cm**	• Waist circumference reflects visceral adiposity in adults • Associated with increased risk of CVD and other chronic diseases
Other weight-related health risks and comorbidities:	**Assess obesity-related health risks**	Diabetes: **FPG, A1C** Hypertension: **Blood pressure (BP)** Dyslipidemia: **Lipid profile** NAFLD: **ALT** *Other weight-related comorbidities*	• Obesity also strongly associated with psychiatric comorbidities, especially depression

ALT, al
Adapte

Edmonton Obesity Staging System (EOSS)



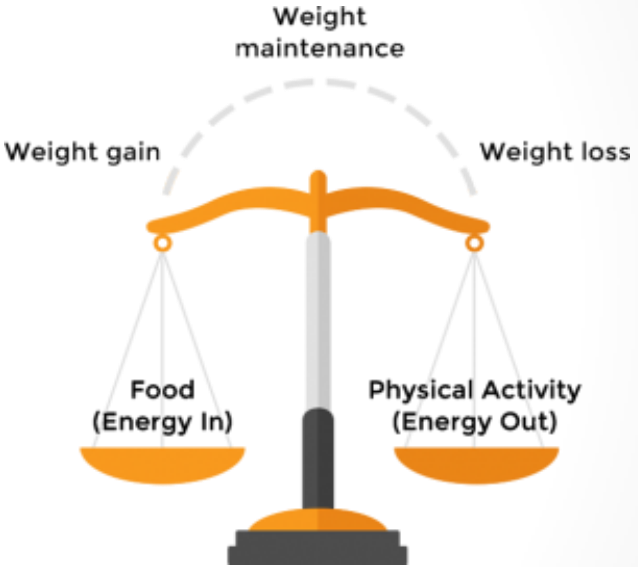
- **Measure of health**
- **Considers medical, mental, functional impact of obesity**
- **As a result, EOSS may be a better predictor of mortality compared to BMI alone**

Sharma AM, Kushner RF. *Int J Obes* (Lond). 2009;33:289-95.
Additional information at: http://www.ottawahospital.on.ca/wps/wcm/connect/1c3afc004699b6c3a604fe0fc4dadf18/Edmonton-obesity-staging-system-staging-tool.pdf?MOD=AJPERES

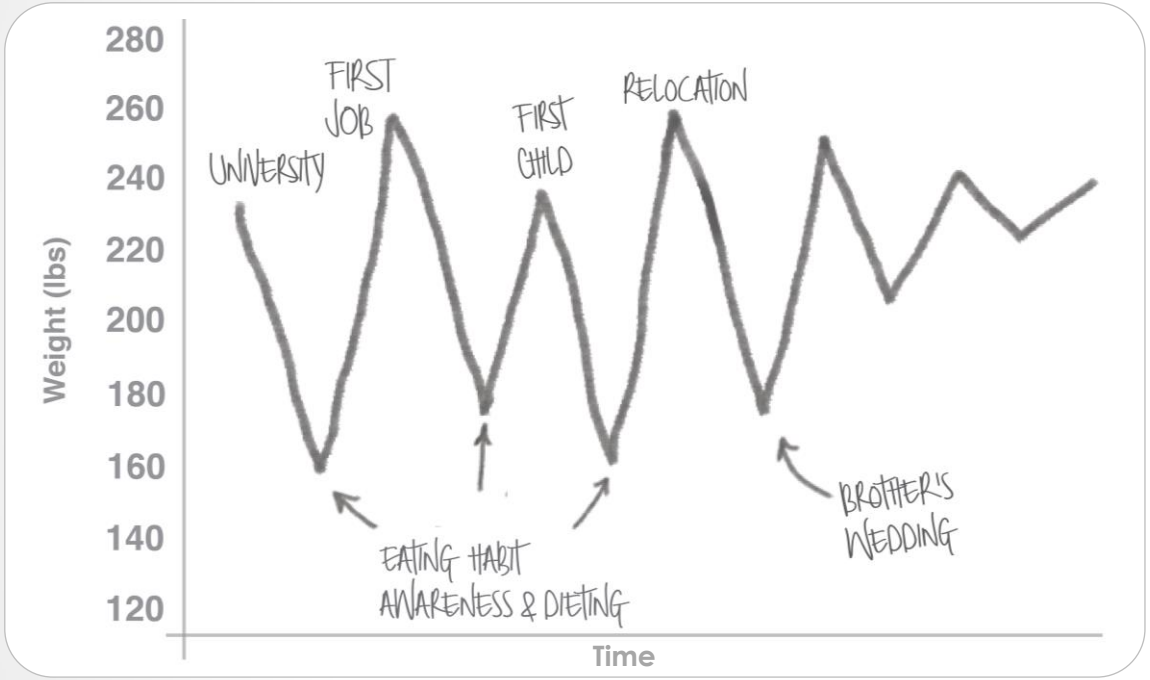
Old Paradigm

- Calories in, calories out
- Eat less, exercise more

"Bad patient"



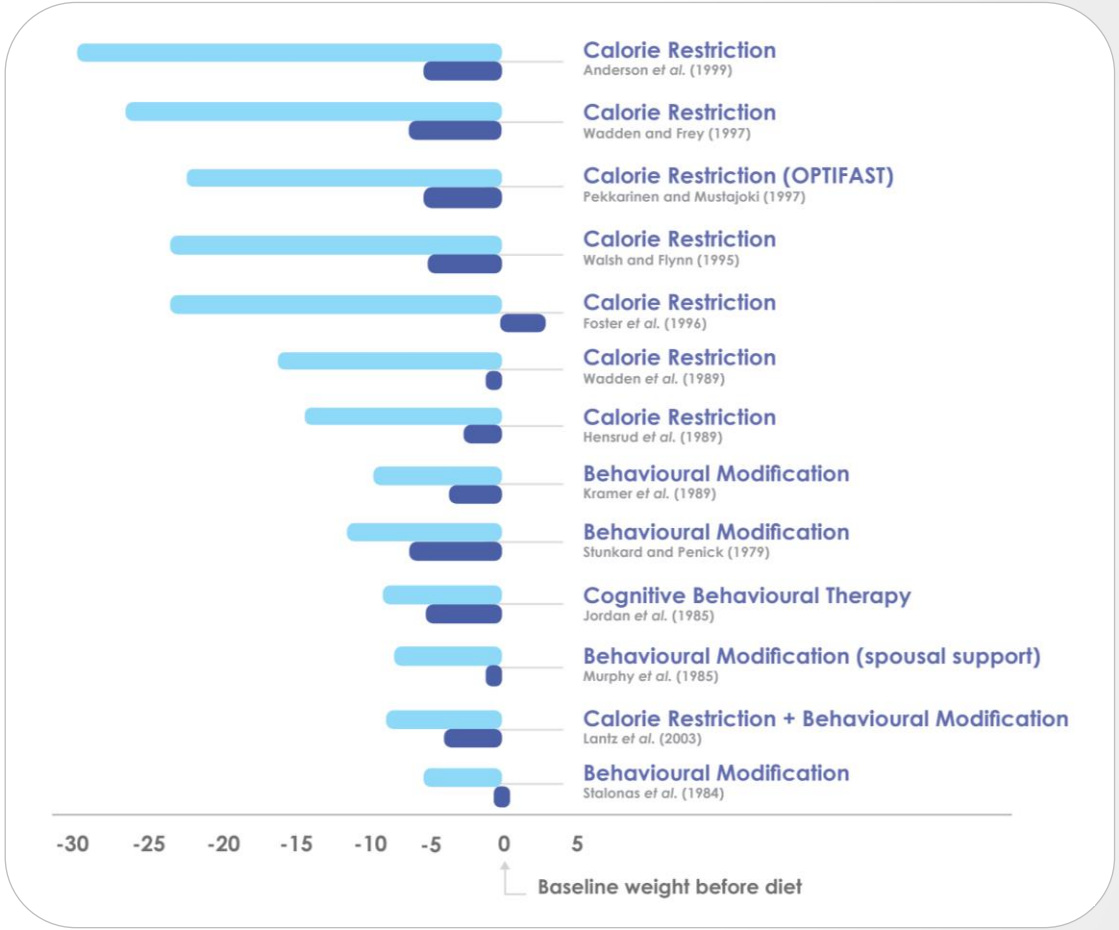
“Bad patient”



MICHAEL, 42

Patients asked to plot their weight over time with respect to life events.
Adapted from:
Kushner RF. *American Medical Association*. 2003.
Kushner RF *et al.* *American Diatetic Association*. 2009.
Kushner RF *et al. JAMA*. 2014;312(9):943-952.

Weight regain is the norm



Follow up range from 4 to 7 years.
Mann *et al. Am Psychol* 2007;62:220–33.

Adapted from Mann *et al*. 2007.

Lessons Learned from "THE BIGGEST LOSER"

"The Biggest Loser changed my life."

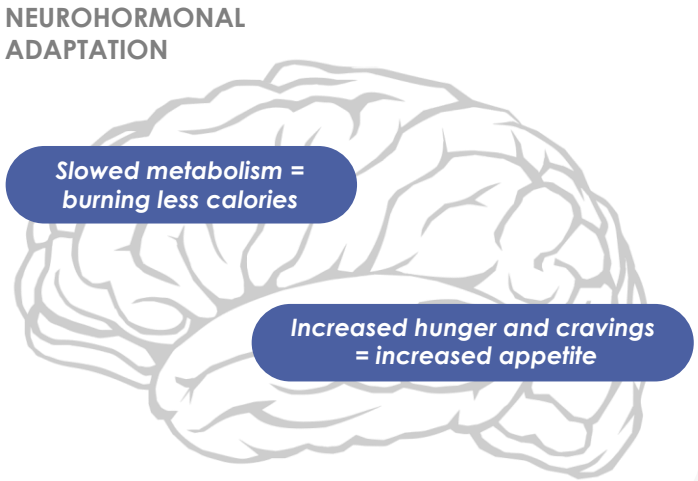
"But not the way that I thought it would."

cal = kilocalorie; lbs = pounds

Fothergill E *et al*. *Obesity*. 2016;24(8):1612-1619.

Figures adapted from Kolata G. *New York Times*. May 2, 2016.

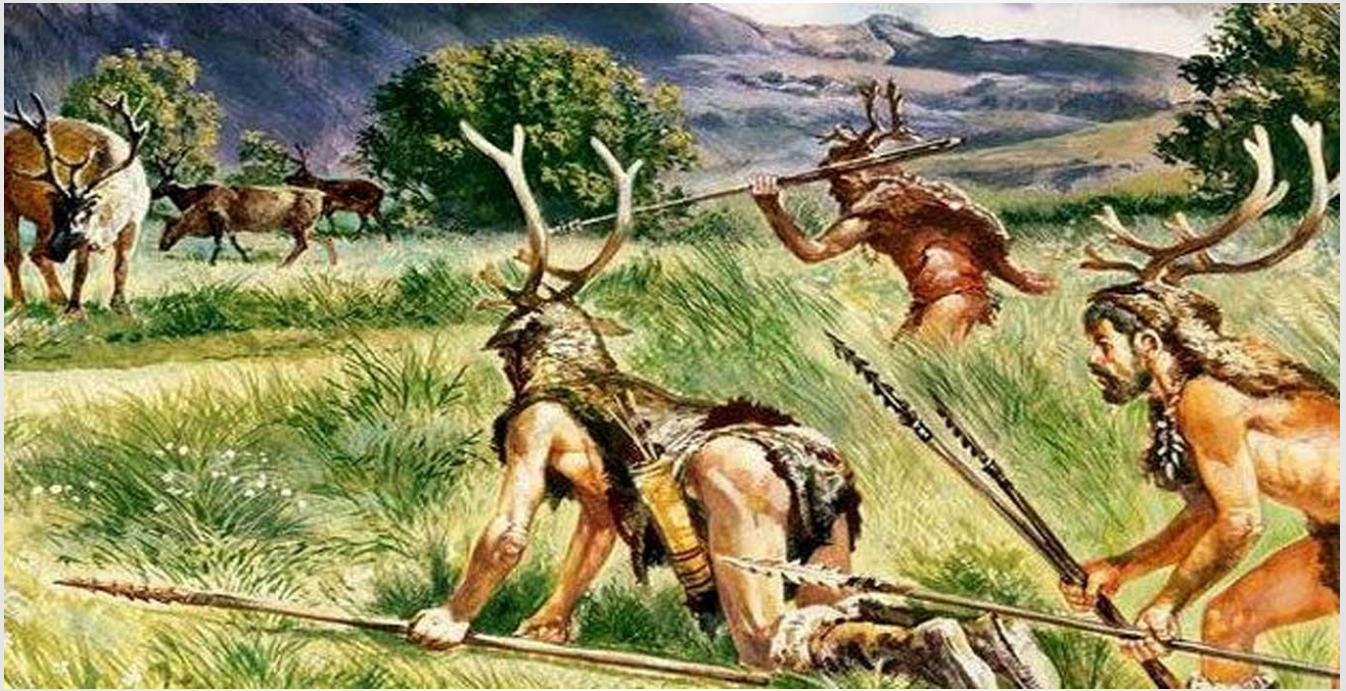
The brain is behind the yo-yo phenomenon of **WEIGHT LOSS AND GAIN**



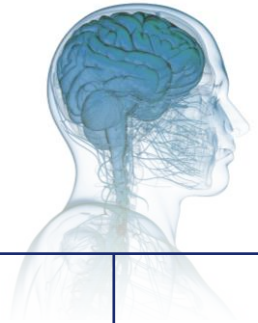
The brain is designed to defend the body against weight loss

Sumithran P *et al. N Engl J Med.* 2011;365(17):1597-604.
Fothergill E *et al.* Obesity. 2016;24(8):1612-1619.
Behary P and Miras AD. *Exp Physoil*. 2014;99(9):1121-1127.

Human bodies favour energy conservation, resulting in **calorie seeking and a desire for sedentariness**



The brain is the
APPETITE CONTROL CENTRE



Hypothalamus:
HOMEOSTATIC EATING
- *Energy balance*
- *Hunger*

Mesolimbic area:
HEDONIC EATING
- *Reward and pleasure*
- *Food cravings*

Frontal cortex:
EXECUTIVE FUNCTION
- *Decision-making*
- *Food selection*

Lutter M and Nestler EJ. *J Nutr*. 2009;139(3):629-632.

Homeostatic eating is **EATING FOR SURVIVAL**

HYPOTHALAMUS

HOMEOSTATIC EATING
- ***Energy balance***
- ***Hunger***

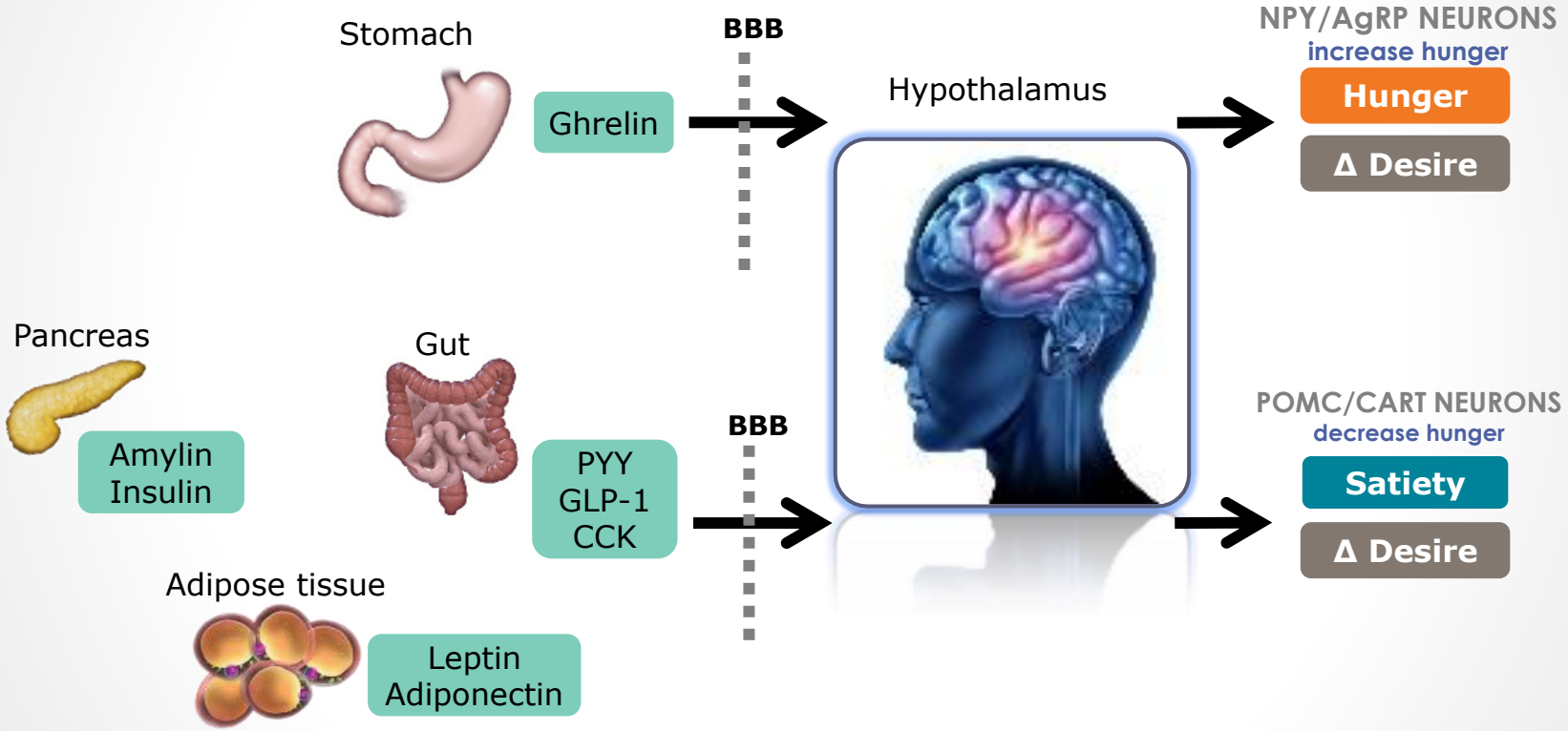
HEDONIC EATING
- ***Reward and pleasure***
- ***Food cravings***

EXECUTIVE FUNCTION
- ***Decision-making***
- ***Food selection***

I'M HUNGRY!

Lutter M and Nestler EJ. *J Nutr*. 2009;139(3):629-632.

Hunger, satiety and desire are regulated by peripheral hormones and integrated in the hypothalamus



BBB = blood-brain barrier; CCK = cholecystokinin; GLP-1 = glucagon-like peptide-1; PYY = peptide YY.
*the brain's reward circuitry, especially in the ventral tegmental area and nucleus accumbens. †especially the dorsolateral pre-frontal cortex. Suzuki K et al. *Exp Diabetes Res*. 2012;2012:824305; Berthoud HR. *Curr Opin Neurobiol*. 2011;21(6):888–896.

Postprandial suppression of ghrelin is lower in obesity

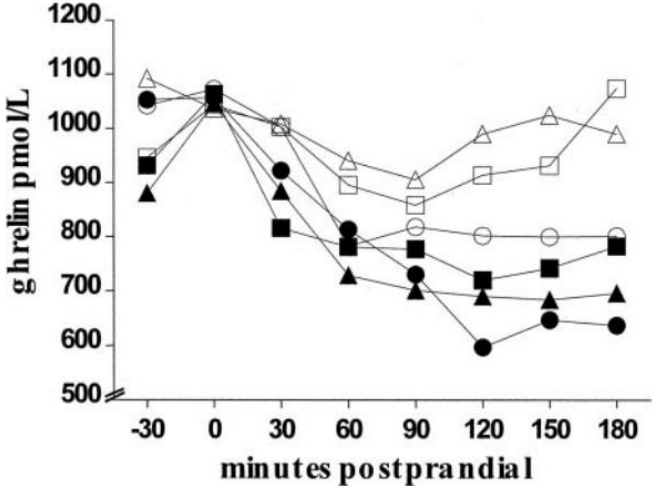


FIG. 1. Pre- and postprandial plasma ghrelin response in normal-weight subjects after 250 kcal (*open square*), 500 kcal (*open triangle*), and 1000 kcal (*open circle*) in 500 ml and 1000 kcal (*filled square*), 2000 kcal (*filled triangle*), and 3000 kcal (*filled circle*) in 900 ml.

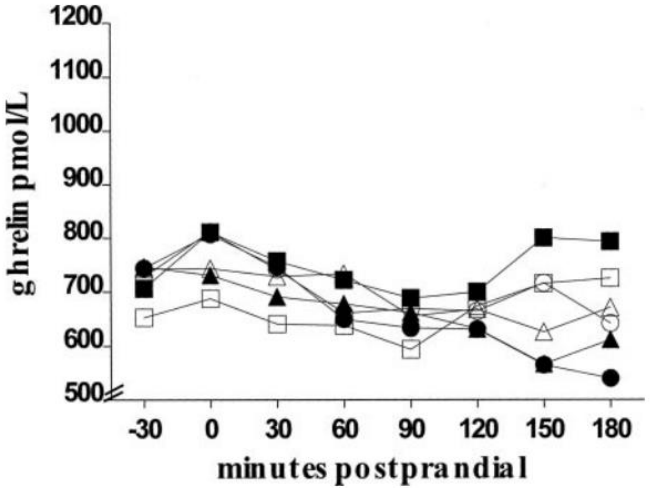


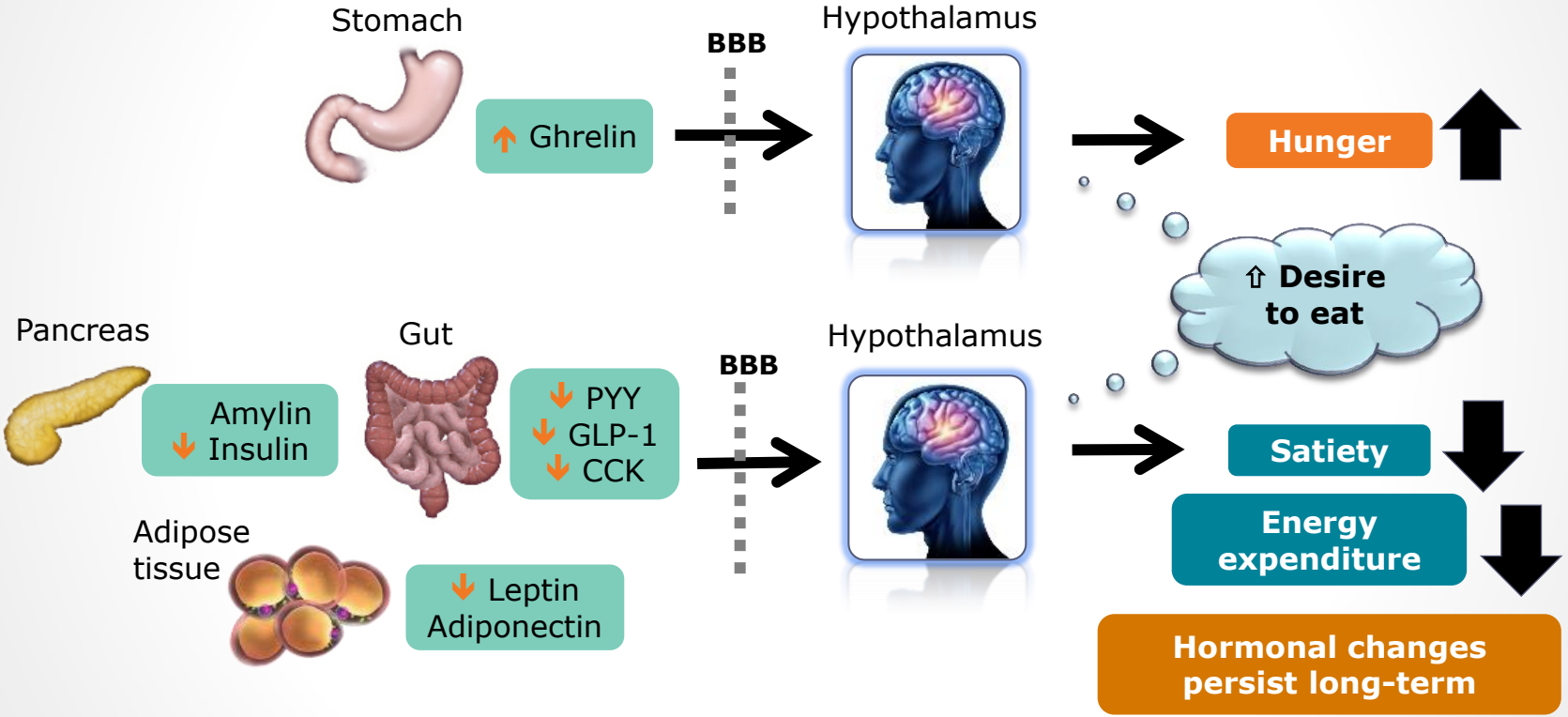
FIG. 3. Pre- and postprandial plasma ghrelin response in obese subjects after 250 kcal (*open square*), 500 kcal (*open triangle*), and 1000 kcal (*open circle*) in 500 ml and 1000 kcal (*filled square*), 2000 kcal (*filled triangle*), and 3000 kcal (*filled circle*) in 900 ml.

Le Roux et al. Ghrelin Suppression in Lean and Obese Subjects. J Clin Endocrinol Metab, February 2005, 90(2):1068 –1071

Leptin resistance and obesity

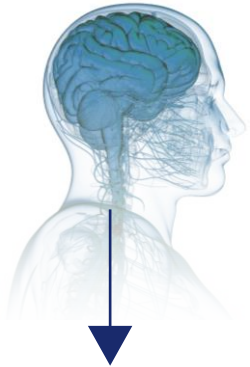
- Leptin is secreted primarily by adipocytes
- Leptin is present in serum in direct proportion to the amount of adipose tissue
- The primary role is to provide the CNS with a signal of energy (adipose) stores in the body
- Serum leptin in obesity is **high**
- ?? Leptin resistance

Following weight loss, physiologic and metabolic responses favour weight regain



BBB, blood-brain barrier; CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY. Suzuki K et al. *Exp Diabetes Res*. 2012;2012:824305; Schwartz A & Doucet É. *Obes Rev*. 2010;11:531–47. 2. Sumithran P et al. *N Engl J Med*. 2011;365:1597–1604.
3. Rosenbaum M et al. *Am J Physiol Regul Integr Comp Physiol*. 2003;285:R183–R92.

Hedonic eating is
EATING FOR PLEASURE



HOMEOSTATIC EATING
- *Energy balance*
- *Hunger*

HEDONIC EATING
- ***Reward and pleasure***
- ***Food cravings***

MESOLIMBIC SYSTEM

EXECUTIVE FUNCTION
- *Decision-making*
- *Food selection*

Lutter M and Nestler EJ. *J Nutr*. 2009;139(3):629-632.

Cravings are controlled by hedonic signaling associated with **THE SIGHT, SMELL, OR TASTE OF FOOD**

HEDONIC EATING

Mesolimbic system

DOPAMINE RECEPTORS
control the motivation to eat

OPIOID and CANNABINOID RECEPTORS
control the pleasure associated with food

WANTING

LIKING

AgRP = agouti-related peptide; CART = cocaine- and amphetamine-regulated transcript; CCK = cholecystokinin; GLP-1 = glucagon-like peptide 1; NPY = neuropeptide Y; POMC = proopiomelanocortin

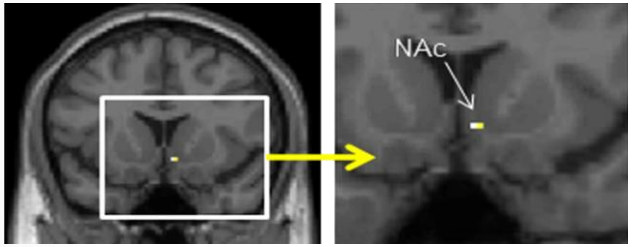
Lutter M and Nestler EJ. *J Nutr*. 2009;139(3):629-632. Mendieta-Zerón H *et al. Gen Comp Endocrinol*. 2008;155:481-495. Berridge KC *et al. The American psychologist.* 2016;71(8):670-679. Gibbons C and Blundell J. *Hamdan Medical Journal*. 2015;8:33-52.

Altered mesolimbic reward system activation in people with obesity

Fasted/Hungry State

Individuals with obesity have greater reward system activation

in response to pictures of high-calorie foods compared with lean individuals[1*]

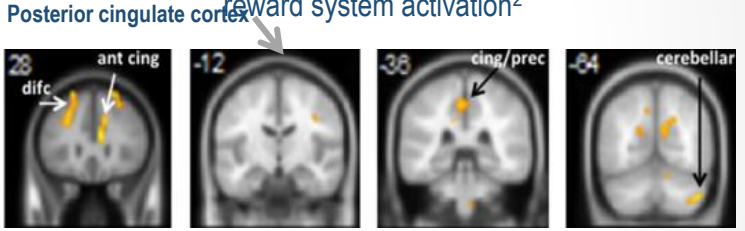


Nucleus accumbens

Fed/Satiated State

Individuals with obesity still show reward system activation following a meal

when exposed to food cues vs lean individuals who have reduced reward system activation[2*]



Anterior cingulate & dorsolateral frontal cortex

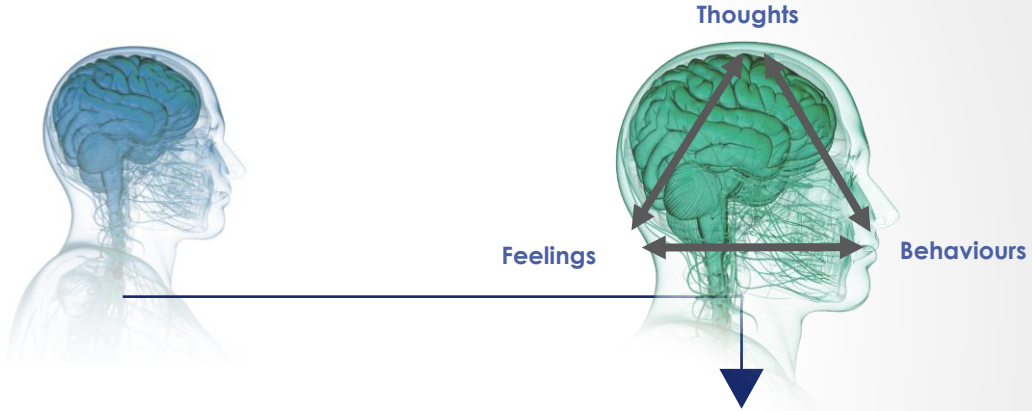
Posterior cingulate cortex

Cingulate & precuneus

Cerebellar

Figure on left adapted from Stoeckel et al,[1] © 2008, with permission from Elsevier. Figure on right adapted from Puzziferri et al,[2] © 2016 The Obesity Society, with permission from John Wiley and Sons.
Ant cing=anterior cingulate; Cing=cingulate; Dlfc=dorsolateral frontal cortex; fMRI=functional magnetic resonance imaging; NAc=nucleus accumbens; Prec=precuneus.

Executive function decides
WHETHER AND WHAT TO EAT



HOMEOSTATIC EATING
- *Energy balance*
- *Hunger*

HEDONIC EATING
- *Reward and pleasure*
- *Food cravings*

EXECUTIVE FUNCTION
- ***Decision-making***
- ***Food selection***

BEHAVIOURAL INTERVENTIONS
empower sustainable behaviours in controlling eating

Lutter M and Nestler EJ. *J Nutr*. 2009;139(3):629-632.

The pathophysiology of obesity is complex

Energy expenditure

Energy intake

Sociocultural

Pregnancy
Menopause
Race, sex, age

Genetics

Adipose tissue

Gut

Medications
& medical conditions

Psychological factors

Hedonic input:

Experienced palatability or pleasure

"Obesogenic" environment:

Highly palatable, energy-dense foods; physical inactivity

1. Woods SC, et al. *Int J Obes Relat Metab Disord*. 2002;26 Suppl 4:S8–S10; 2. Ludwig DS. *JAMA*. 2014;311:2167–2168; 3. Speliotes EK, et al. *Nat Genet*. 2010;42:937–948;
4. Garvey WT, et al. *Endocr Pract*. 2014;20:977–989; 5. Bray GA, and Ryan DH. *Ann NY Acad Sci*. 2014;1311:1-13.

New Paradigm

Obesity is a genetically conferred, environmentally-influenced, neurohormonally-controlled, behaviourally and socially-mediated complex chronic medical condition.

Obesity underlies three major types **OF CONSEQUENCES…**

BIOLOGICAL (METABOLIC)	STRUCTURAL (MECHANICAL)	PSYCHO-SOCIAL (MENTAL)
• Polycystic Ovary Syndrome • Infertility • Cancer • NAFLD • Hypertension • Dyslipidemia • Type 2 diabetes	• Osteoarthritis • Chronic pain • Sleep apnea	• Anxiety • Depression • Eating disorder • ADHD • Migraine • Stigma • Social exclusion • Alzheimer Dementia • Vascular Dementia

…leading to 200+ comorbidities

NAFLD = non-alcoholic fatty liver disease; ADHD = attention deficit hyperactivity disorder

Twells LK *et al. CMAJ Open*. 2014; 2(1):E18-26. Catenacci VA *et al. Clin Chest Med*. 2009;30(3):415-444. Calle EE *et al. N Engl J Med*. 2003;348(17):1625-1638. Bluher M. *Exp Clin Endocrinol Diabetes*. 2009;117(6):241-250. Luppino FS *et al. Arch Gen Psychiatry*. 2010;67:220-22. Ganz ML *et al. Diab & Met Syndr*. 2014;6(1):50. Rahmanian K *et al. Glob J Health Sci*. 2016;8(4): 95-101. Leenen FH *et al. Am J Hypertens*. 2010;23(9):1000-1006. Singh K *et al. Int J Biol Med Res*. 2011;2(3):824-828. Huang Y *et al. Atherosclerosis*. 2016;247:218-224. Pang Q *et al. World J Gastroenterol*. 2015;21(5):1650–1662. Dag ZO *et al. J Turk Ger Gynecol Assoc*. 2015; 16(2):111–117. Sallmen M *et al. Epidemiology*. 2006;17(5):520-523. Knight JA *et al. Ann Clin Lab Sci*. 2011;41(2):107-121. Hampel H *et al. Ann Intern Med*. 2005;143(3):199-211. Wosu AC *et al. ISRN Obes*. 2014;1-8. Willenberg T *et al. J Vasc Surg*. 2010;52(3):664-668. Vlajinac HD *et al. Eur J Vasc Endovasc Surg 2013*;45(3):293-298. Hashimoto Y *et al. J Phys Ther Sci*. 2017;29(6):978–983. Thom DH *et al. J Urol*. 2010;184(4):1394-1401.

Obesity

is associated with increased mortality

Each 5 kg/m^2 higher BMI gives ~40% higher mortality rate for ischemic heart disease, stroke, and other vascular diseases[1]

Sources: 1. Prospective Studies Collaboration. Lancet. 2009

Q. What weight loss target should be recommended to patients for health benefit?

A. 1-3%

B. 5-10%

C. 15-20%

D. To achieve a normal BMI of 24

E. To bring the BMI below 30

Modest weight loss of 5-10% confers significant clinical benefits

CONDITION	WEIGHT LOSS RESULTING IN THERAPEUTIC BENEFIT
Diabetes (prevention)	3-10%
Hypertension	5 to >15%
Dyslipidemia	3 to >15%
Hyperglycemia	3 to >15%
NAFLD	10%
Sleep apnea	10%
Osteoarthritis	5-10%
Stress incontinence	5-10%
Gastroesophageal reflex disease	5-10% in women; 10% in men
Polycystic ovary syndrome	5-15%

NAFLD = non-alcoholic fatty liver disease

Cefalu WT *et al. Diabetes Care*. 2015;38(8):1567-1582.

Starting the conversation

Patients with obesity face
STIGMA AND BIAS EVERY DAY

Negative comments or actions can impede successful weight management and may come from:


Family and friends


Colleagues


Strangers


HCPs

Patients who experience obesity bias from their HCPs may avoid clinical care and talking about weight or may be less adherent to their weight management plan

Fruh SM, et al. Obesity Stigma and Bias. J Nurse Pract. 2016;12(7):425-432; Phelan SM, et al. Impact of weight bias and stigma on quality of care and outcomes for patients with obesity. Obes Rev. 2015;16(4):319-326; Puhl RM, Heuer CA. The stigma of obesity: a review and update. Obesity. 2009;17(5):941-64; Canadian Obesity Network. 5As of Obesity Management [last accessed 2018 October 2018]. Available from: www.obesitynetwork.ca.

Let's use

PATIENT FIRST LANGUAGE

DO SAY

"Patients living with…"

- Increased weight
- Obesity
- Weight problems

DON'T SAY

"Obese patients"

- Obese
- Fat
- Morbidly obese

Enhancing the office setting to **OPTIMIZE OBESITY CARE**

Tips for setting up an office environment for obesity care:

Waiting room

- Sturdy, armless chairs
- Magazines and other reading materials that are weight sensitive and promote healthy living

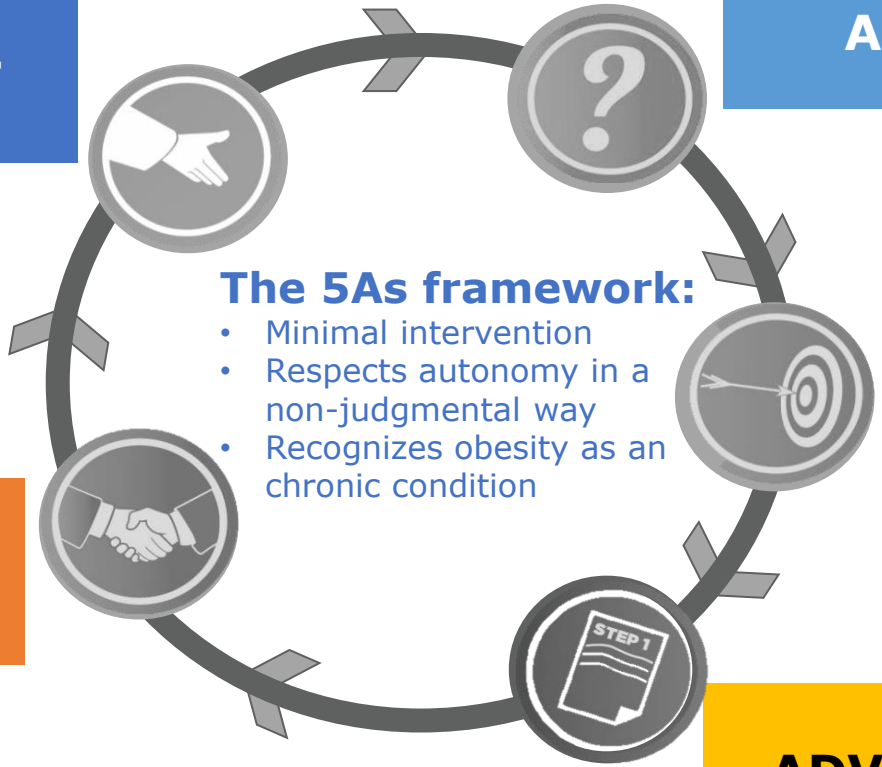
Examination rooms

- Scales with an adequately sized base and supportive handle bar that can measure >300 lbs (>137 kg)
- Extra large adult arm and thigh blood pressure cuffs
- Large-size gowns
- Adequately sized, sturdy examination tables

Office protocols

- Weigh patients in a private setting
- **Ask patient for permission to be weighed**

Starting the conversation: The 5As framework

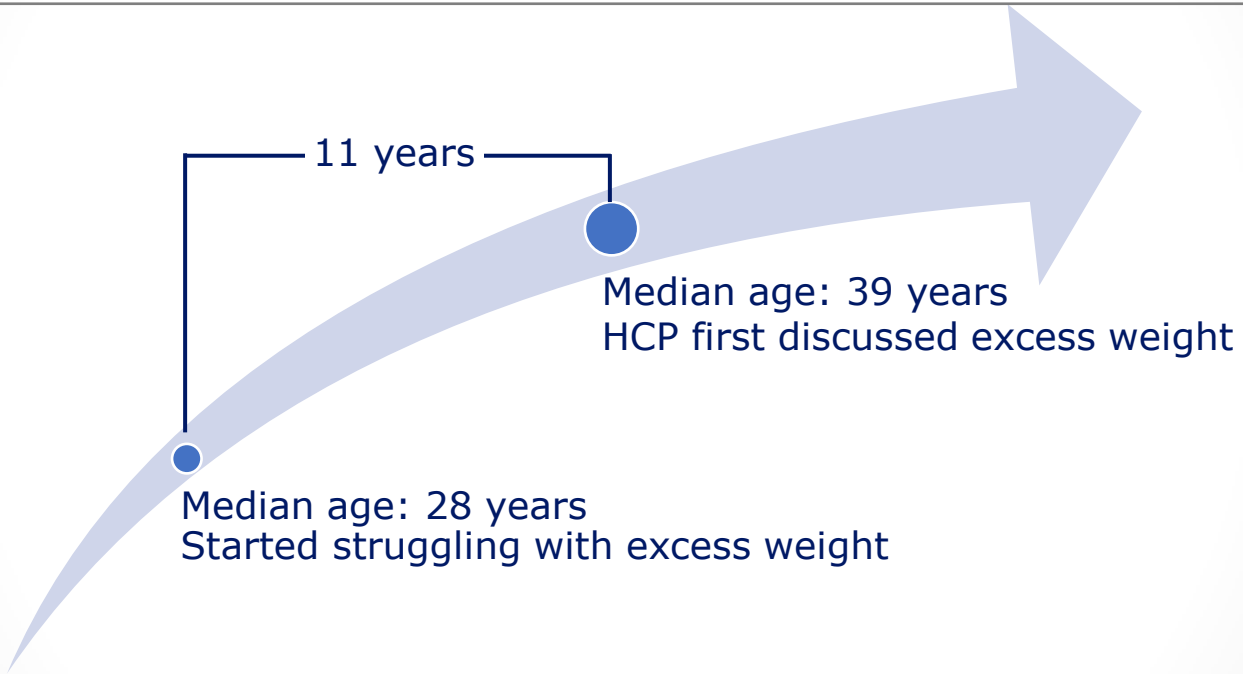


The 5As framework:

- Minimal intervention
- Respects autonomy in a non-judgmental way
- Recognizes obesity as an chronic condition

5As of obesity management. Canadian Obesity Network 2011. Accessed November 25, 2014 at http://www.obesitynetwork.ca/5As.

It takes over a decade for people living with obesity
TO DISCUSS WEIGHT WITH THEIR HCP



[All PwO] Q122A Approximately how old were you when you first remember struggling with excess weight or obesity?
[PwO has Discussed with HCP] Q122 Approximately how old were you when a healthcare provider first discussed your excess weight or recommended that you lose weight?

Based on total PwO (n=2000/1129). PwO, people with obesity; HCP, healthcare practitioner

1. Sharma AM *et al.* Presented at the Canadian Family Practice Nurses Association Biennial Meeting, 27–29 April 2018, Winnipeg, Canada

Q. What prevents patients from discussing weight with their HCPs?

A. Patients are too embarrassed to bring it up

B. Patients are not motivated to address their weight

C. Patients feel that it's their own responsibility to manage their weight

D. Patients do not believe they can lose weight

E. Patients are not interested in losing weight

What proportion of patients feel that weight loss is completely their own responsibility?

74 %

Sharma AM, et al. Perceptions of barriers to effective obesity management in Canada: results from the ACTION Study. Canadian Family Practice Nurses Association Biennial Meeting 2018; April 27–29, 2018; Winnipeg, Canada.

What proportion of HCPs feel that weight loss is completely the responsibility of the patient?

74 %

23 %

Sharma AM, et al. Perceptions of barriers to effective obesity management in Canada: results from the ACTION Study. Canadian Family Practice Nurses Association Biennial Meeting 2018; April 27–29, 2018; Winnipeg, Canada.

The ACTION Study Canada:

"I know what I need to do and I can lose weight if I really put my mind to it"

55%

Q. What is the average weight loss achieved over 1 year with diet and exercise?

A. 2-5%

B. 5-7%

C. 7-10%

D. 10-12%

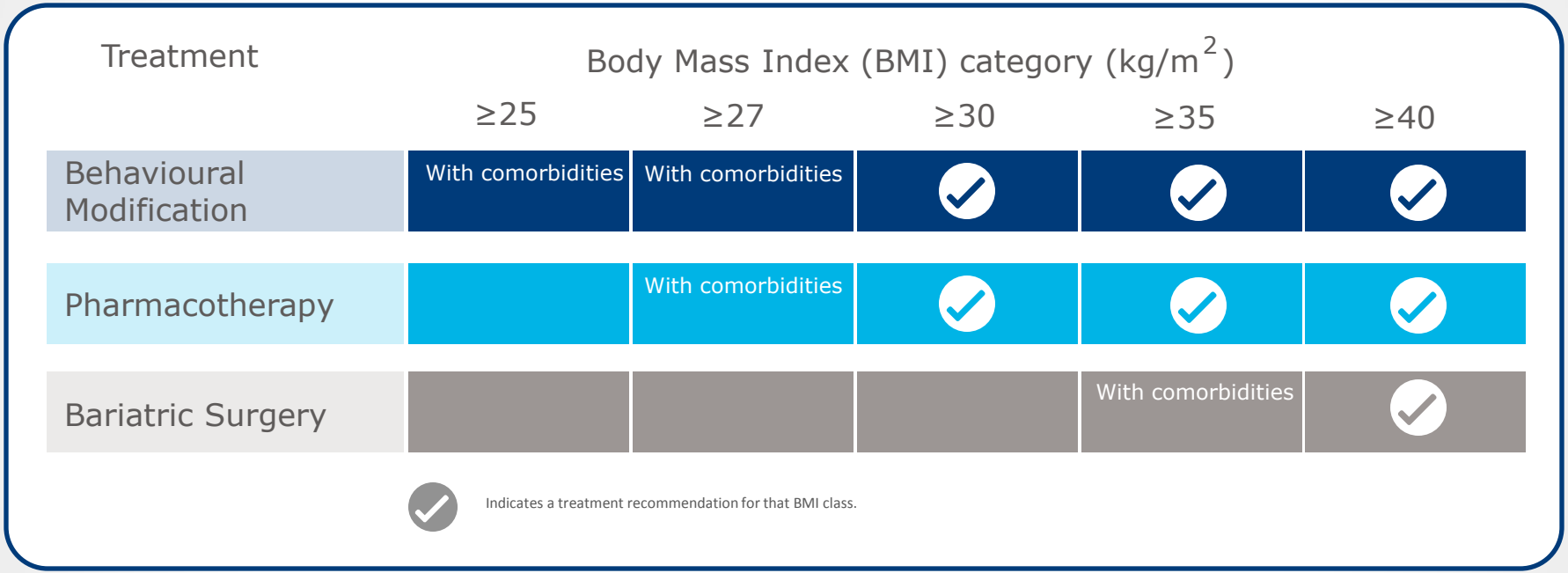
The ACTION Study Canada:

"I know what I need to do and I can lose weight if I really put my mind to it"

Only  reported maintaining ≥10% weight reduction for >1 year

Obesity management must change.

Guidelines



Source: Lau et al. CMAJ 2007;176(8 suppl):Online-1–117

Weight management requires a multi-modal approach

DIETARY COUNSELLING

PHYSICAL ACTIVITY

COGNITIVE BEHAVIOURAL THERAPY

MINDFULNESS

*Surgery is indicated in eligible patients with BMI >35 + weight-related comorbidity or BMI >40
†Pharmacology is indicated for BMI >27 + weight-related comorbidity or BMI >30

Lau, *et al. CMAJ*. 2007;176(8 suppl):Online-1-117.

Expectations for weight management

- Weight-loss advertisements can focus on **aesthetic weight loss** and unrealistic expectations

Long-term goals of obesity management are weight maintenance and prevention of weight regain

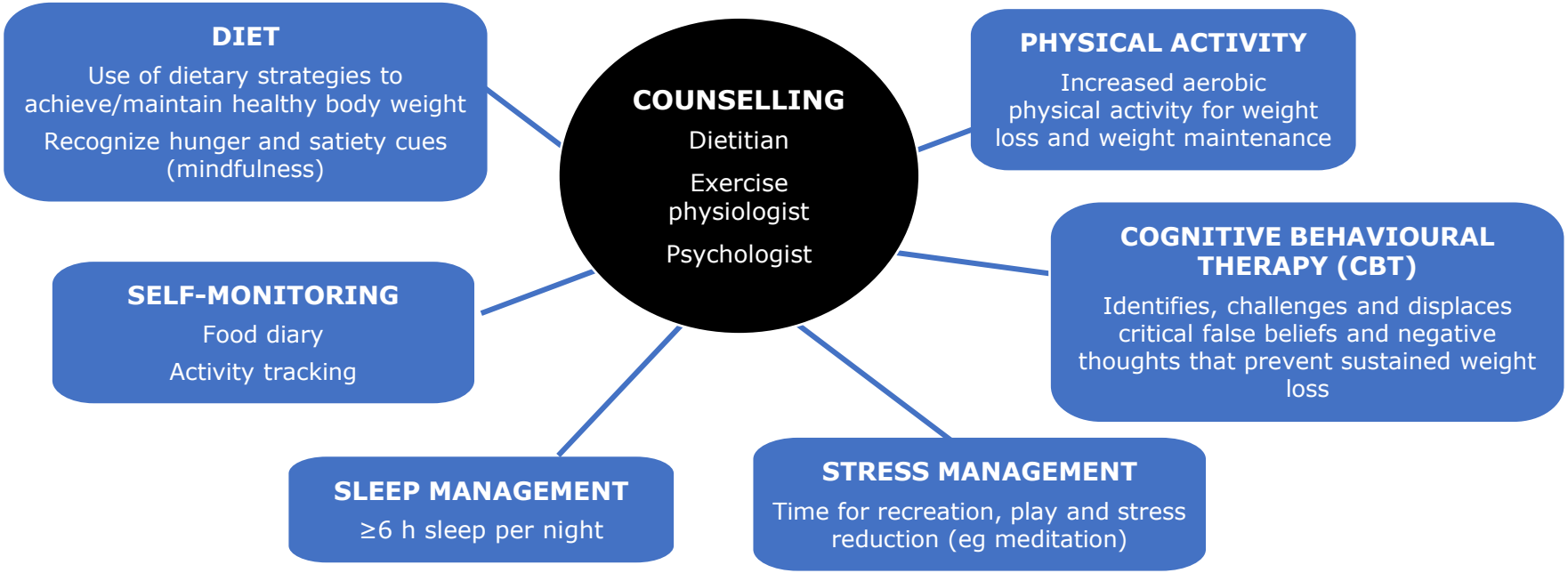
- **Long-term goal:**
  - Improved health and quality of life
- **Behavioural goals:**
  - Should be **SMART** (**s**pecific, **m**easurable, **a**chievable, **r**ewarding, **t**imely)

- Clarify patient-defined **values**

The 5As of obesity management. Canadian Obesity Network 2011. Accessed November 10, 2015 at http://www.obesitynetwork.ca/5As. Lau DCW, et al. CMAJ 2007;176(8 suppl):Online-1–117; Forman EM and Butryn ML. Effective Weight Loss: An Acceptance-Based Behavioural Approach, Clinician Guide: Oxford University Press; 2016.

Overview of recommended lifestyle modification

Guidelines recommend individualized behavioural interventions as the cornerstone of weight management

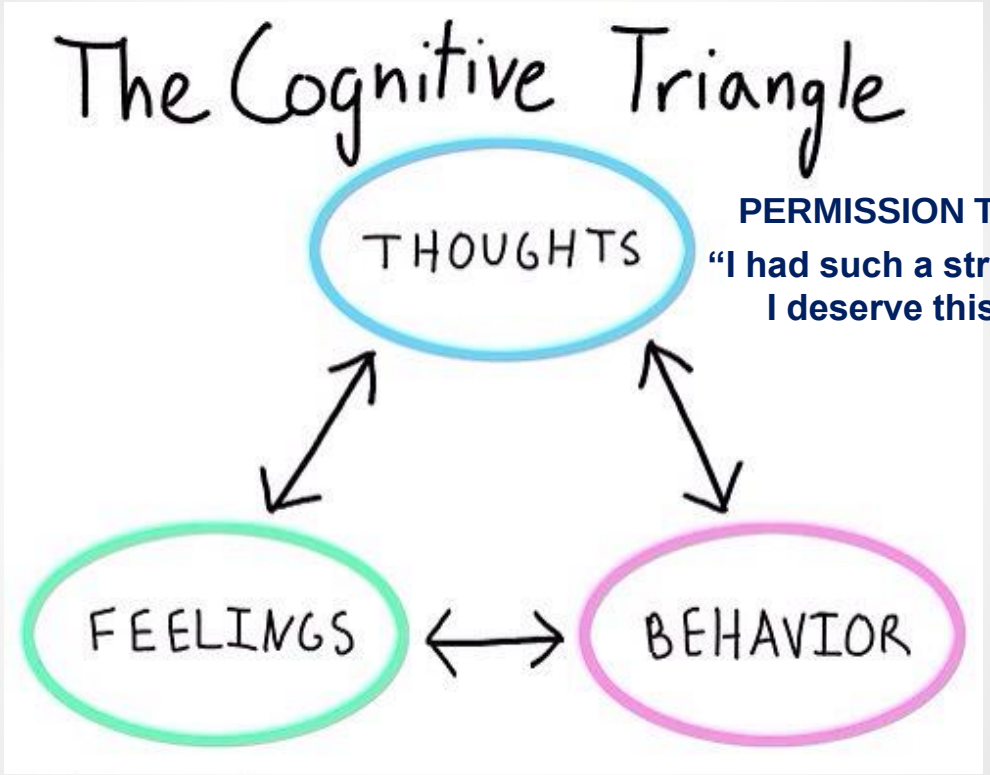


1. Lau DCW, et al. *CMAJ*. 2007;176(8 suppl):Online-1–117; 2. Jensen MD, et al. *Circulation*. 2014; 129:S102–38; 3. Gonzalez-Campoy JM, et al. *Endocr Pract*. 2013; 19 S3:1–82; 4. Tsigos C, et al. *Obesity Facts*. 2008;1:106–116.

Behavioural strategies commonly used

Strategy	Requirements
Self-monitoring	Monitoring of diet, physical activity, mood and weight
Stimulus control	Modifying external environment to make it more conductive to supporting behavior change goals
Core Values	Guide our decision making throughout life, different from goals (end-point). Health behaviours are often uncomfortable or unpleasant – what will make it worth it?
Self-reinforcement	Self-reward; end of day reflection and self-affirmation
Anticipating setbacks, Relapse prevention	Problem-solving solutions to cope with barriers or pre-identified high-risk situations
Goal setting	Behavioural goals, not weight goal. Specific, Measurable, Attainable, Realistic, Time-framed (SMART), regular monitoring and re-evaluation of goals
Cognitive restructuring	Challenging problematic thinking and emotions that hinder efforts and treatment adherence

Cognitive behavioural therapy



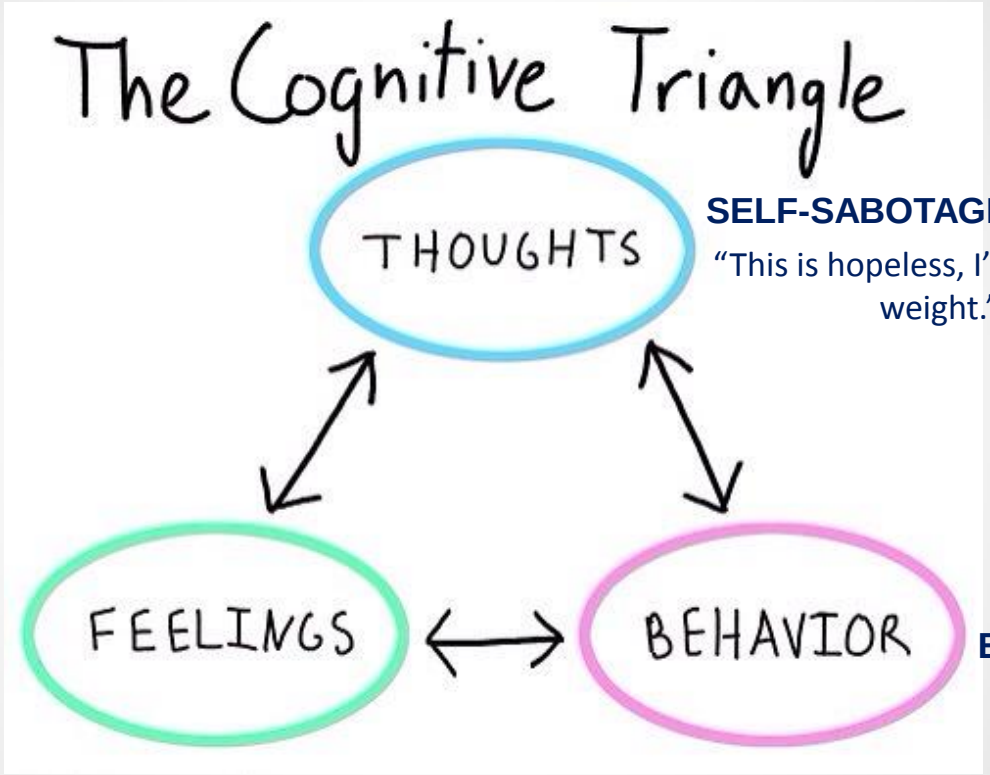
PERMISSION THOUGHT

“I had such a stressful day, I deserve this treat.”

Guilt

Impulse eating

Cognitive behavioural therapy



SELF-SABOTAGING THOUGHT

"This is hopeless, I'll never lose weight."

Sadness, **Hop**elessness

Emotional eating episode

Pharmacotherapy

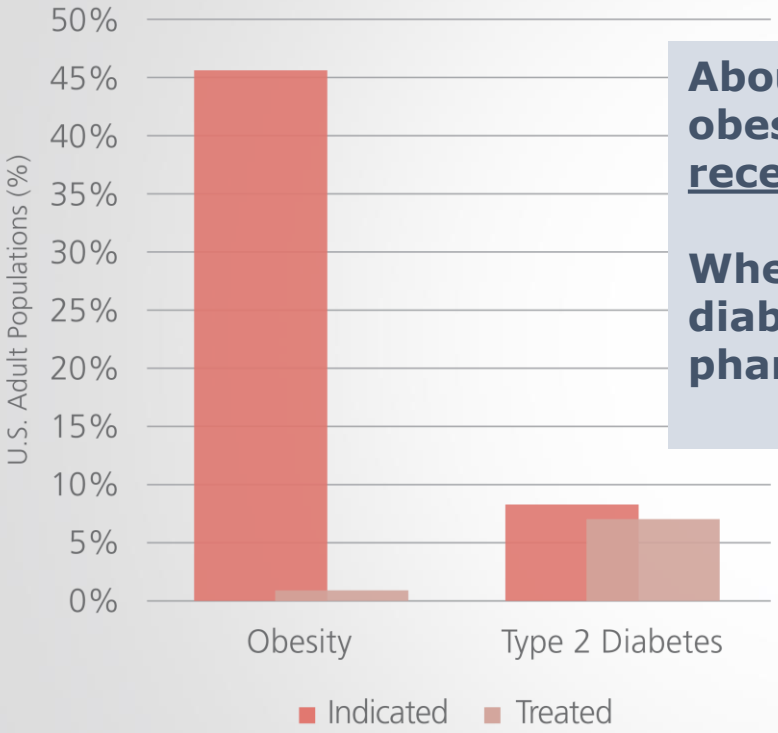
What proportion of patients and HCPs feel that prescription weight-loss medication is effective for weight-management ?

Patients

17 %

Sharma AM, et al. Perceptions of barriers to effective obesity management in Canada: results from the ACTION Study. Canadian Family Practice Nurses Association Biennial Meeting 2018; April 27–29, 2018; Winnipeg, Canada.

Low adoption of anti-obesity medications (AOM)



About 46% of adults are indicated for anti-obesity pharmacotherapy, but only 2% of them receive treatment

Whereas, 8.4% of adults are diagnosed with diabetes—86% receive antihyperglycemic pharmacotherapy

Thomas CE, et al. Low Adoption of Weight Loss Medications: A Comparison of Prescribing Patterns of Antiobesity Pharmacotherapies and SGLT2s. *Obesity* (Silver Spring). 2016;4(9):1955–1961.

Who is AOM **INDICATED FOR?**

Adult patients with an initial body mass index (BMI) of

- 30 kg/m^2 or greater (obesity), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia)

who are concurrently adopting a reduced-calorie diet and increased physical activity.

Contrave® (product monograph), February 12, 2018, Valeant Canada LP, Laval, QC.

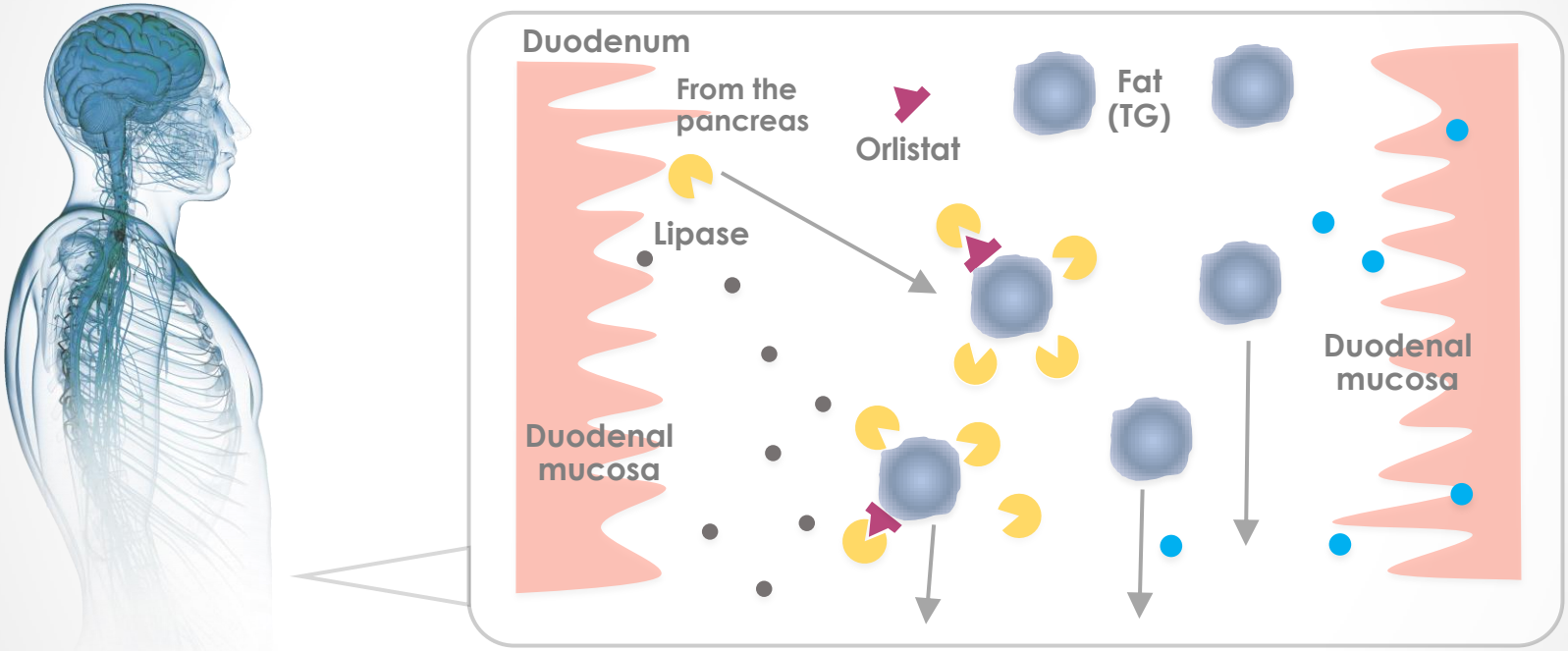
Anti-obesity medications available in Canada

DRUG (TRADE NAME)	HEALTH CANADA APPROVAL	MECHANISM OF ACTION	1-YEAR WEIGHT LOSS, PLACEBO-SUBTRACTED (ITT)	MAJOR SAFETY ISSUES	TOLERABILITY
Orlistat (Xenical)	1999	Gastrointestinal lipase inhibitor	~3%	Fat-soluble vitamin malabsorption	Fecal urgency, fecal incontinence, flatus with discharge, oily spotting
Liraglutide (Saxenda)	2015	GLP-1 receptor agonist	4.0-5.4%	Gallstones, acute pancreatitis	Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain, headache, fatigue, hypoglycemia, increased lipase
Naltrexone hydrochloride/ Bupropion hydrochloride (Contrave)	2018	Opioid receptor antagonist/ aminoketone antidepressant	3.3-4.8%	Use in controlled hypertension only	Nausea, vomiting, constipation, diarrhea, dizziness, dry mouth

GLP-1 = glucagon-like peptide 1

Xenical® (product monograph), September 27, 2017, Cheplapharm, Germany.
Saxenda® (product monograph), July 12, 2017, Novo Nordisk Canada Inc, Mississauga, ON.
Contrave® (product monograph), February 12, 2018, Valeant Canada LP; Laval, QC.

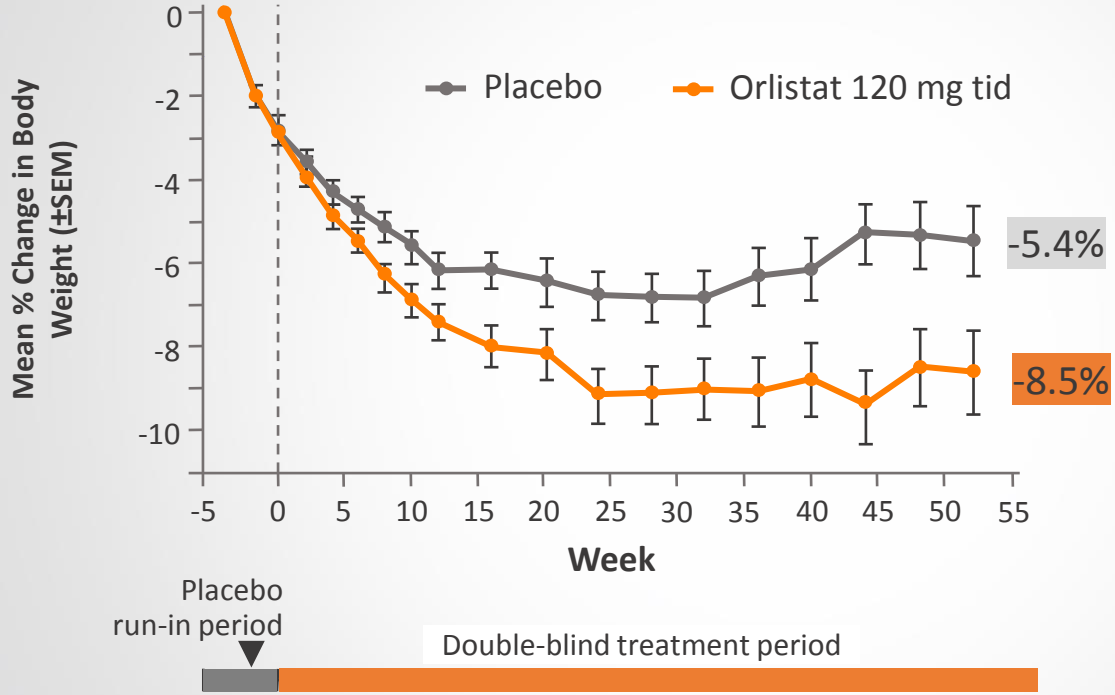
Orlistat:
A PANCREATIC & GASTRIC LIPASE INHIBITOR



TG = triglyceride

Heck AM *et al. Pharmacotherapy*. 2000;20(3):270-279.
Hadvary *et al. J Biol Chem*. 1991;266(4):2021-2027

Orlistat Efficacy
Phase 3 Study – BM14119C



Placebo-subtracted weight change:

-3.1%

ITT population
P = 0.016

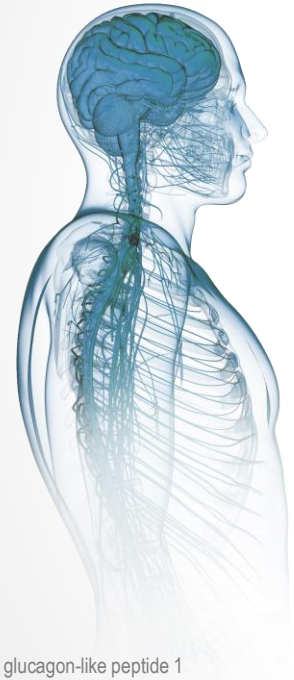
Finer et al, Int J Obesity, 2000;24(3):306-313

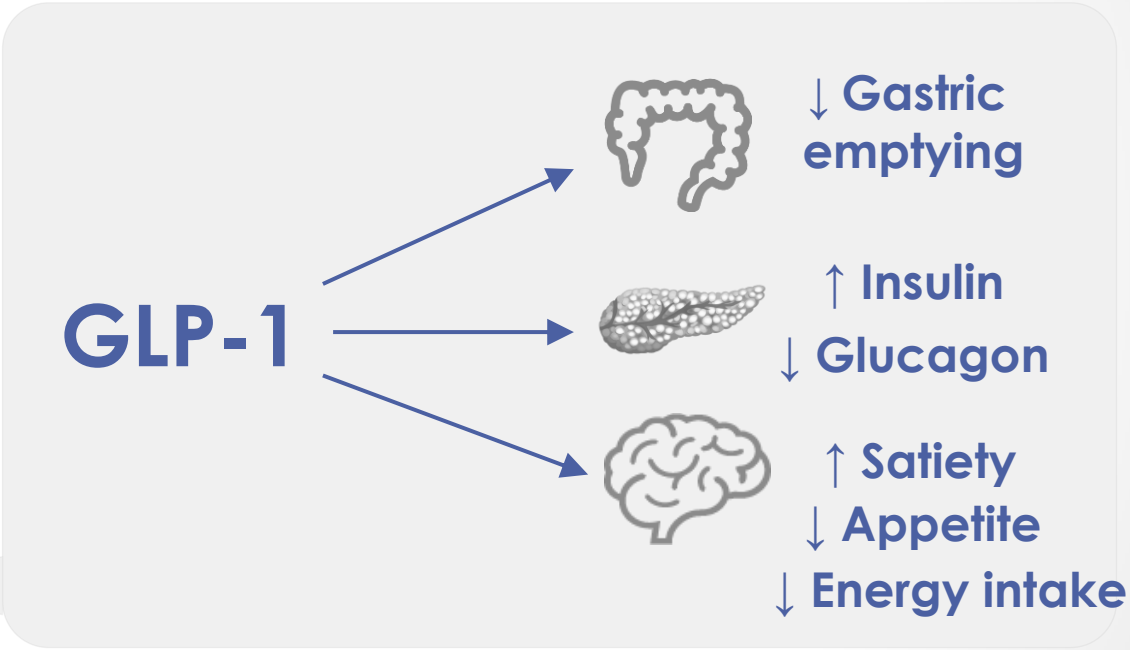
Orlistat:
SAFETY AND TOLERABILITY

ADVERSE EVENT (AE)	ORLISTAT n = 1,913 (%)	PLACEBO n = 1,466 (%)
Oily spotting	26.6	1.3
Flatus with discharge	23.9	1.4
Fecal urgency	22.1	6.7
Fatty/oily stool	20.0	2.9
Oily evacuation	11.9	0.8
Increased defecation	10.8	4.1
Fecal incontinence	7.7	0.9

Xenical® (product monograph), September 27, 2017, Cheplapharm, Germany.

Liraglutide: A GLP-1 receptor agonist
MIMICS THE EFFECTS OF THE HORMONE GLP-1

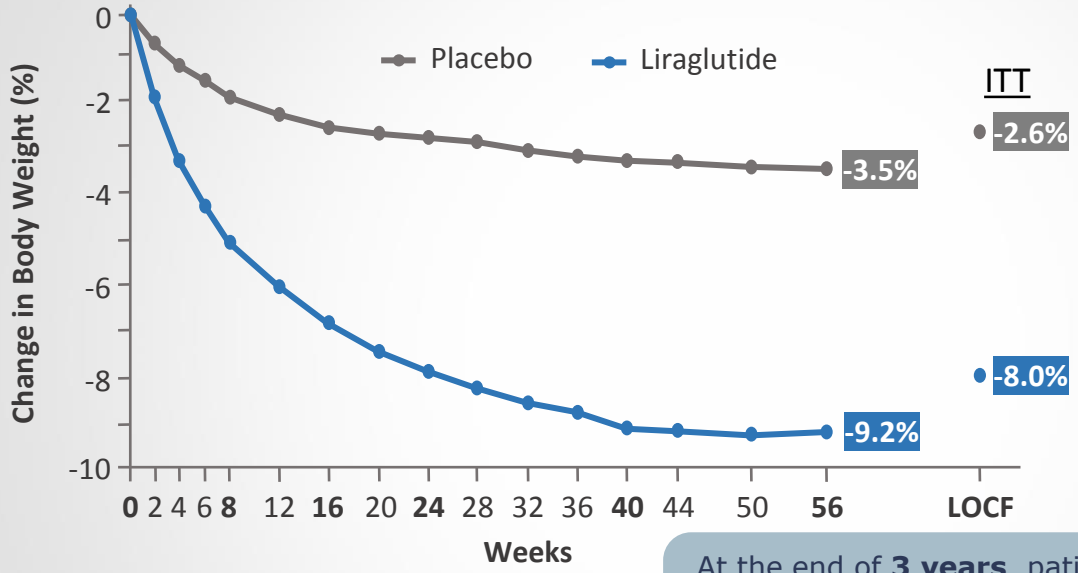




GLP-1 = glucagon-like peptide 1

Shaefer CF *et al*. *Postgrad Med*. 2015;127(8):818-826.
Baggio *et al*. *J Clin Invest*. 2014;124(10):4223-4226.

Liraglutide Efficacy
Phase 3 Study – SCALE 1



N	2437	2267	2152	2073		1910

Placebo-subtracted weight change:

-5.7%

ITT: -5.4%

ITT population
P < 0.0001

At the end of **3 years**, patients with **prediabetes** at baseline **progressed to type 2 diabetes**:

3% in the **liraglutide** group

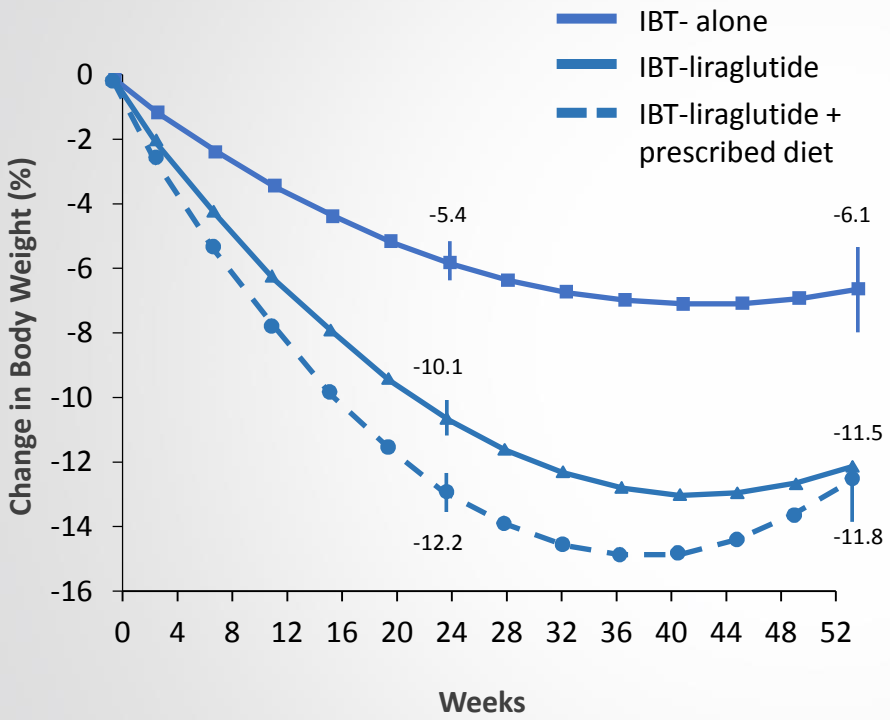
11% in the **placebo** group

80% relative risk reduction

(estimated cumulative incidence rates)

Saxenda® Product monograph, July 12, 2017, Novo Nordisk Canada Inc, Mississauga, ON.

Additive Benefits of Lifestyle Change and Pharmacologic Intervention:
Liraglutide Efficacy in Combination with Lifestyle Modification

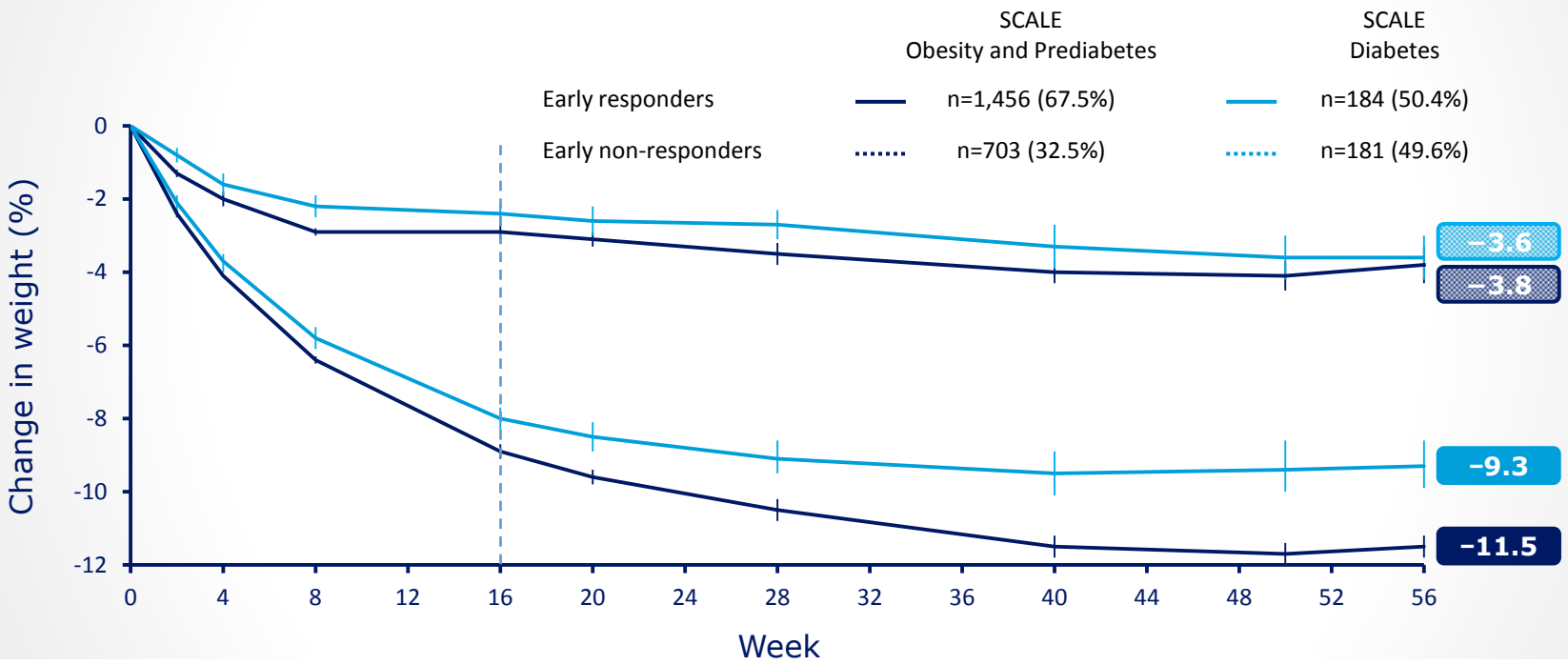


- 150 participants all received intensive behavioral therapy (IBT) and were randomized 1:1:1 to receive no additional treatment, liraglutide, or liraglutide and a prescribed meal replacement diet (1000–1200 kcal/d)

Wadden et al., Obesity. 2019; 27:75-86.

Week 56 weight loss in all patients vs. early responders

SCALE Obesity and Prediabetes and SCALE Diabetes: Week 56



Early responders, individuals who achieved ≥5% weight loss from baseline at 16 weeks; early non-responders, individuals who achieved <5% weight loss from baseline at 16 weeks. Week 56 completers, FAS, fasting visit data only. Line graphs are observed means (±95% CI). Red dashed line shows when early response was assessed. Early responder/early non-responder data are for Week 16 completers. CI, confidence interval; FAS, full analysis set

Blüher *et al. Diabetologia* 2015;58 (Suppl 1):S310 (Poster 645)

Liraglutide
SAFETY AND TOLERABILITY

ADVERSE EVENT (AE)	LIRAGLUTIDE n = 3,384 (%)	PLACEBO n = 1,941 (%)
Nausea	39.3	13.8
Diarrhea	20.9	9.9
Constipation	19.4	8.5
Vomiting	15.7	3.9
Dyspepsia	9.6	2.7
Abdominal pain	5.4	3.1
Upper abdominal pain	5.1	2.7
Decreased appetite	10.0	2.3
Fatigue	7.5	4.6
Dizziness	6.9	5.0
Increased lipase	5.3	2.2

Saxenda® (product monograph), July 12, 2017, Novo Nordisk Canada Inc, Mississauga, ON.

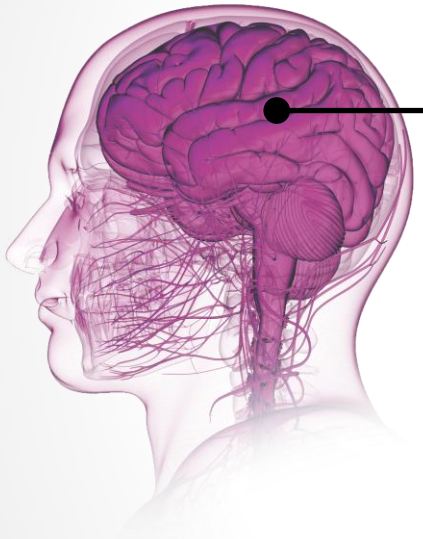
Liraglutide
ADMINISTRATION

- Once daily SC injection, usually evening
- Dose titration

0.6mg SC daily x 1 week,
1.2mg SC daily x 1 week,
1.8mg SC daily x 1 week,
2.4mg SC daily x 1 week,
3.0mg SC daily ongoing

- Side effects can be minimized by slower titration

Naltrexone and bupropion (Contrave) - MECHANISM OF ACTION



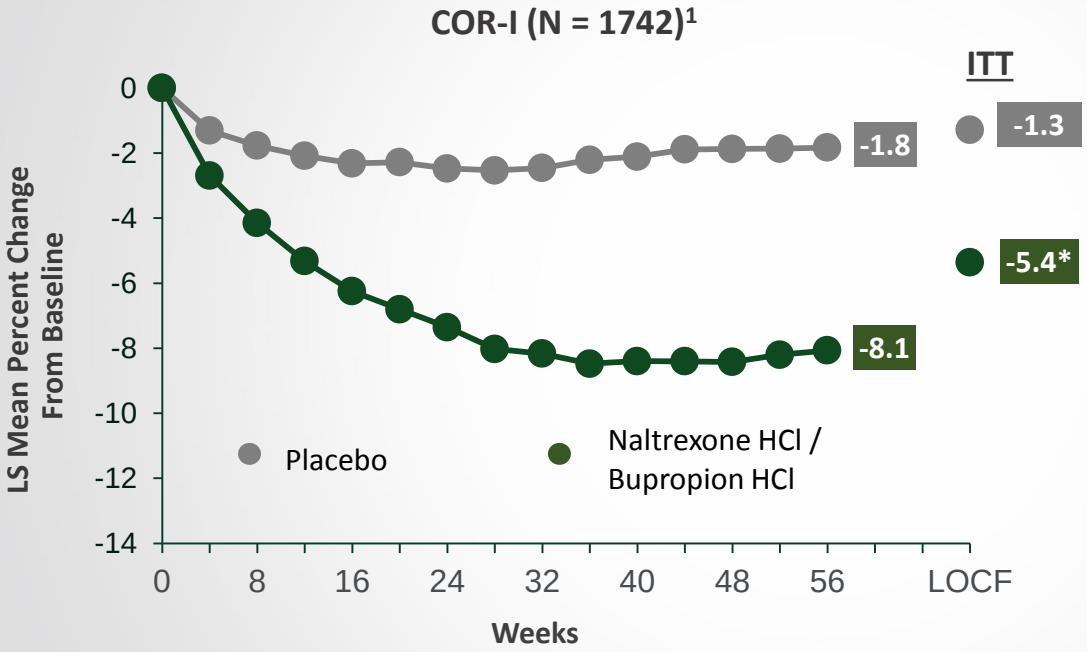
Bupropion HCl	Naltrexone HCl
• Dopamine and norepinephrine reuptake inhibitor • Dopaminergic effect controls motivation/drive to eat • Works on cravings and wanting food	• Opioid antagonist • Recall opioid receptor involvement in pleasure associated with food • Reduce rewarding aspect of food

Synergistic action in:

Hypothalamus	**Mesolimbic circuit**
Stimulates appetite-suppressing POMC neurons to reduce feelings of hunger	Modulates feelings of reward and craving

Apovian CM, et al. Obesity..2013;21:935-943

Naltrexone HCl / Bupropion HCl Efficacy Phase 3 Study – COR-I



Placebo-subtracted weight change:

-6.3%

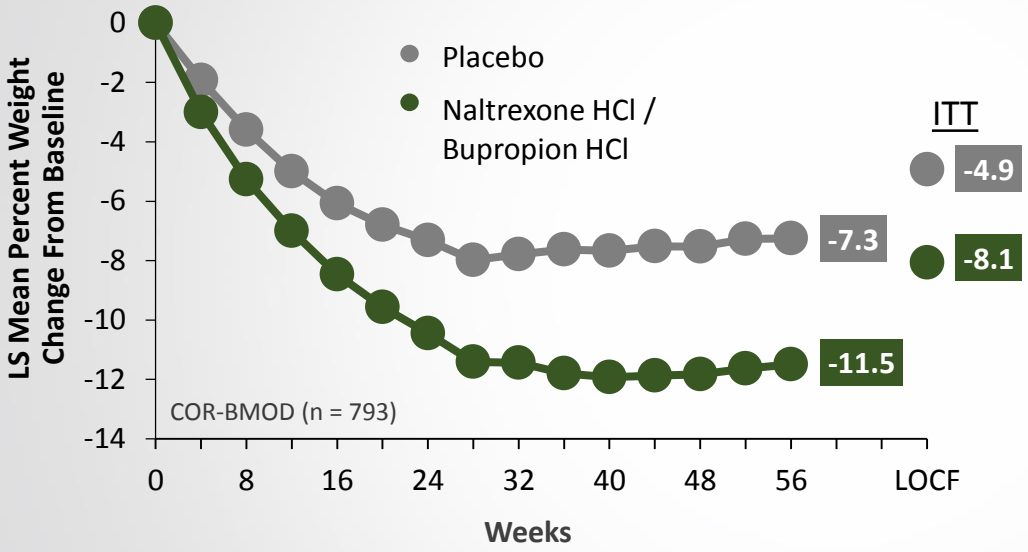
ITT: -4.1%

ITT population
P < 0.001

ITT = intent-to-treat

1. Contrave® Product monograph, February 12, 2018, Valeant Canada LP; Laval, QC
2. Apovian CM, et al. Obesity..2013;21:935-943

Additive Benefits of Lifestyle Change and Pharmacologic Intervention Naltrexone HCl / Bupropion HCl Efficacy in Combination with Lifestyle Change (COR-BMOD Study)



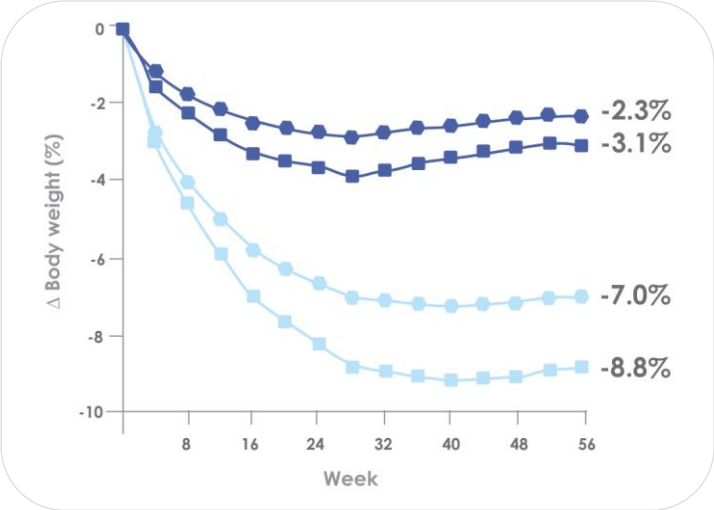
- 793 participants all received behavioural modification (BMOD) counselling and were randomized 3:1 to receive naltrexone HCl / bupropion HCl or placebo
- Mean weight loss was evident in both groups, and significantly higher in patients taking active treatment ($P < 0.001$)

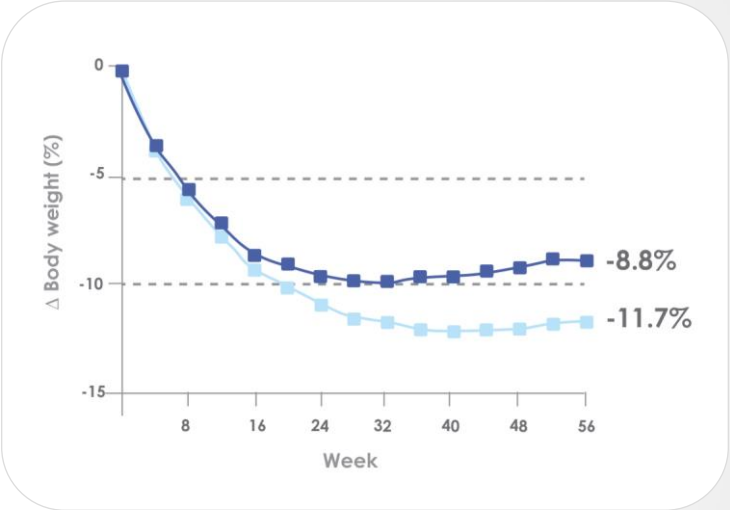
Wadden TA, et al. Obesity (Silver Spring). 2011; 19(1): 110–120.

Week 56 weight loss in
ALL PATIENTS VS. RESPONDERS

POOLED ANALYSIS

- COR-I
- COR-II
- COR-BMOD
- COR-DM





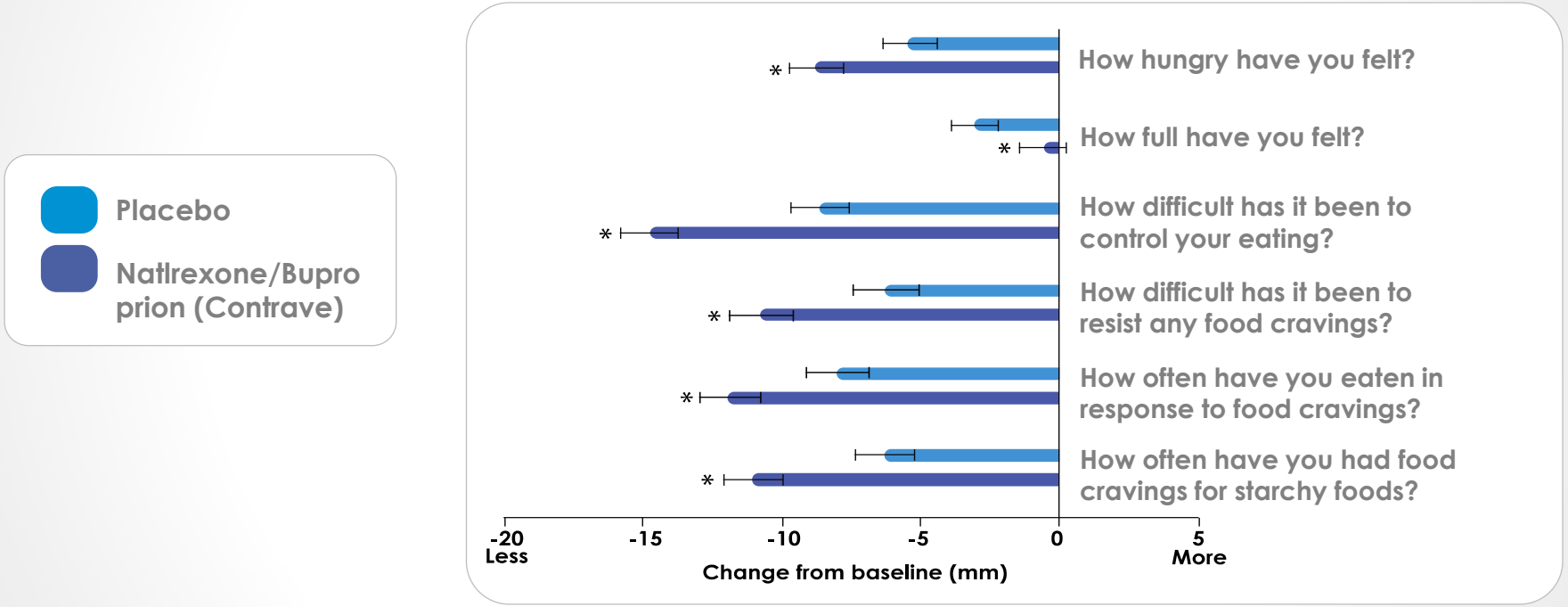
Placebo mITT-LOCF (n = 1319)
Contrave mITT-LOCF (n = 2023)
Placebo completer (n = 763)
Contrave completer (n = 1310)

Placebo responder completer (n = 763)
Contrave responder completer (n = 1310)

BMOD = behavioural modification; DM = type 2 diabetes mellitus; mITT-LOCF = participants with a baseline and at least one post-baseline weight measurement while on study treatment with last-observation-carried-forward imputation of missing data

Fujioka K *et al. Int J Obes.* 2016;40:1369-1375.
Gilder K *et al. International Conference on Obesity (poster).* 2016

COR-1 study: The effect of Naltrexone/Buproprion (Contrave) on food cravings per the CONTROL OF EATING QUESTIONNAIRE



Greenway FL *et al*. *Lancet*. 2010;376:595-605.

*$p<0.05$ (nominal values) compared to placebo group.
COR-1, a 56-week, placebo-controlled phase III study of patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) and at least one comorbidity (hypertension or dyslipidemia) randomized to naltrexone (16-50 mg/day) and/or bupropion (300-400 mg/day) or placebo plus a reduced-calorie diet, behavioural counselling, and increased physical activity.

Naltrexone/Bupropion
SAFETY AND TOLERABILITY

POOLED ANALYSIS

- COR-I
- COR-II
- COR-BMOD
- COR-DM

ADVERSE REACTION	CONTRAVE* n = 2,545 (%)	PLACEBO n = 1,515 (%)
Nausea	32.5	6.7
Constipation	19.2	7.2
Headache	17.6	10.4
Vomiting	10.7	2.9
Dizziness	9.9	3.4
Insomnia	9.2	5.9
Dry mouth	8.1	2.3
Diarrhea	7.1	5.2

BMOD = behavioural modification; DM = type 2 diabetes mellitus

*Contrave 32 mg/360 mg for up to 52 weeks (n=2,482) or a combination of naltrexone 32 mg and bupropion SR 400 mg/day (n=63) for up to 24 weeks

Contrave (product monograph), February 12, 2018, Valeant Canada LP, Laval, QC.

Naltrexone/Bupropion (Contrave)
Administration by dose escalation

Naltrexone/Buproprion (Contrave) dosing should be escalated over a 4-week period

	☀	☾
Week 1	1	
Week 2	1	1
Week 3	2	1
Week 4 + maintenance	2	2

Tablets should be taken by mouth in the morning and evening and should not be cut, chewed, or crushed.

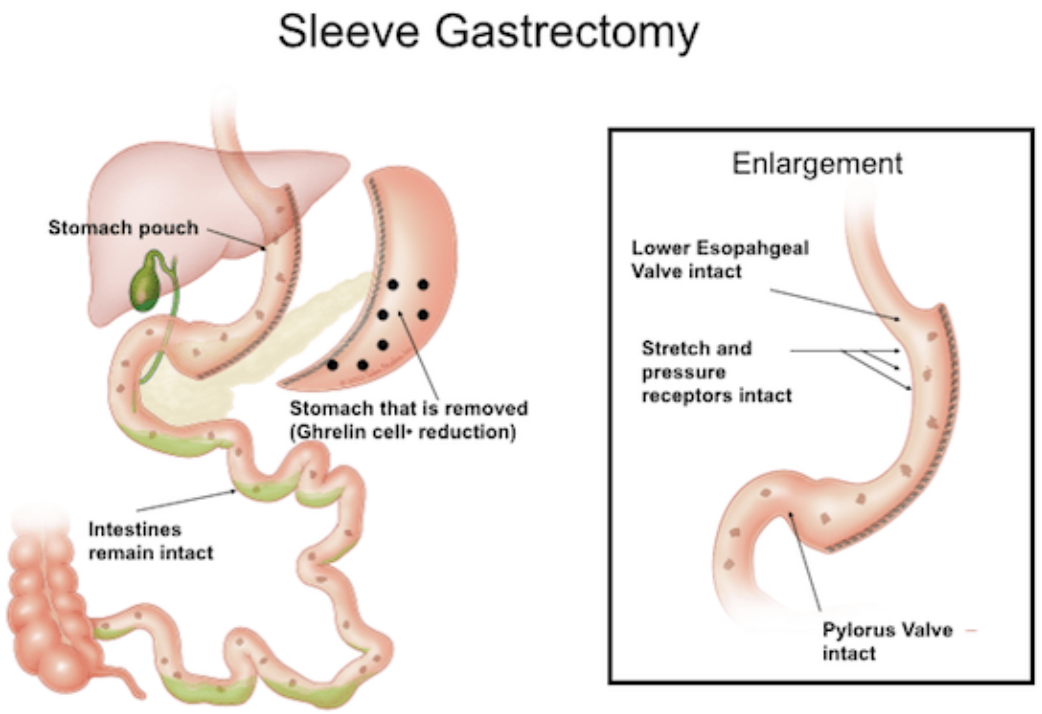
The dose escalation protocol was designed with the intent to allow patients to acclimate to Natrexone/Buproprion (Contrave) and to minimize the risk of seizure as well as mitigate the onset of transient nausea.

In clinical trials, Naltrexone/Buproprion (Contrave) was administered with meals; however, it should not be taken with a high-fat meal because of a resulting significant increase in bupropion and naltrexone systemic exposure.

Contrave® (product monograph), February 12, 2018, Valeant Canada LP, Laval, QC.

Bariatric surgery

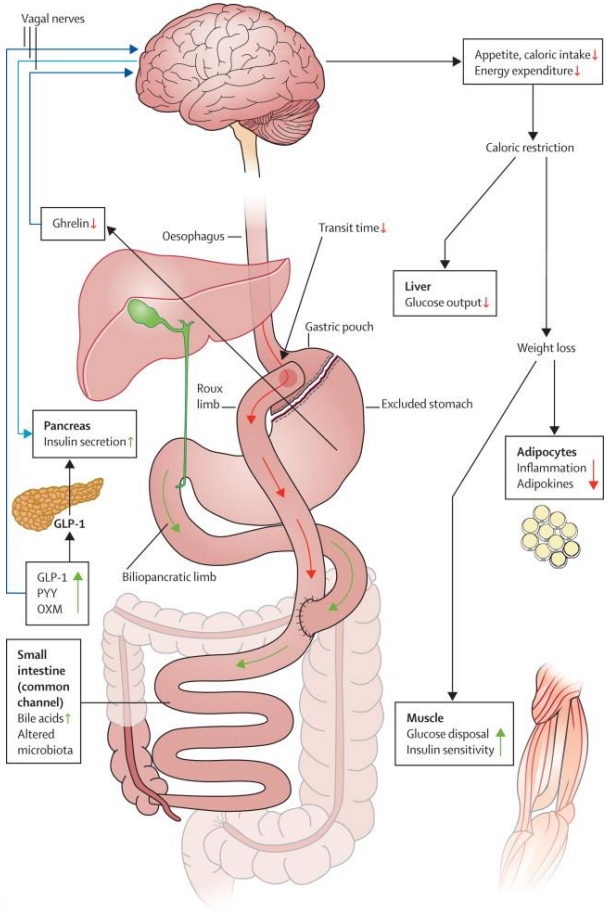
VERTICAL SLEEVE GASTRECTOMY



Restrictive,
Hormonal

↓ Ghrelin

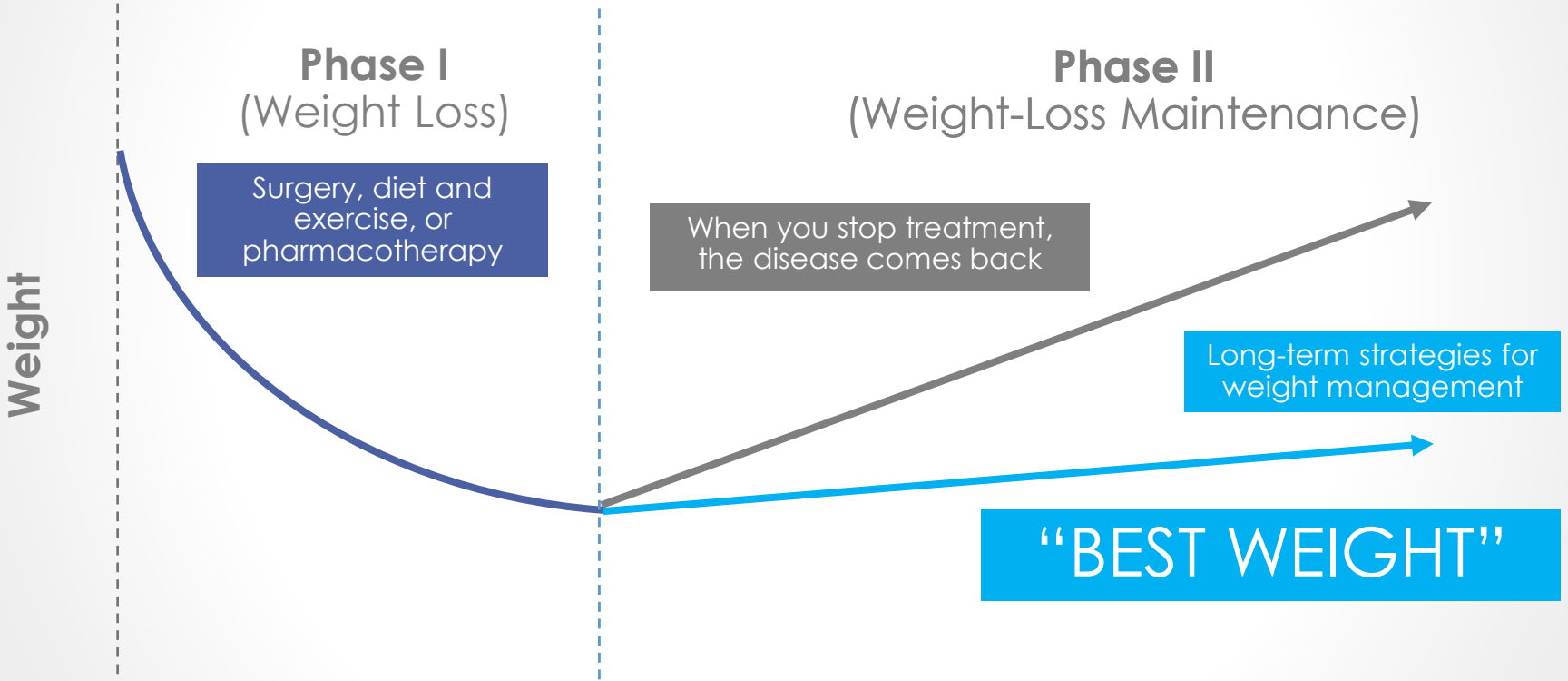
ROUX-EN-Y GASTRIC BYPASS



Restrictive,
Hormonal,
Malabsorptive

↑ GLP1

No single treatment
INTERVENTION IS A CURE

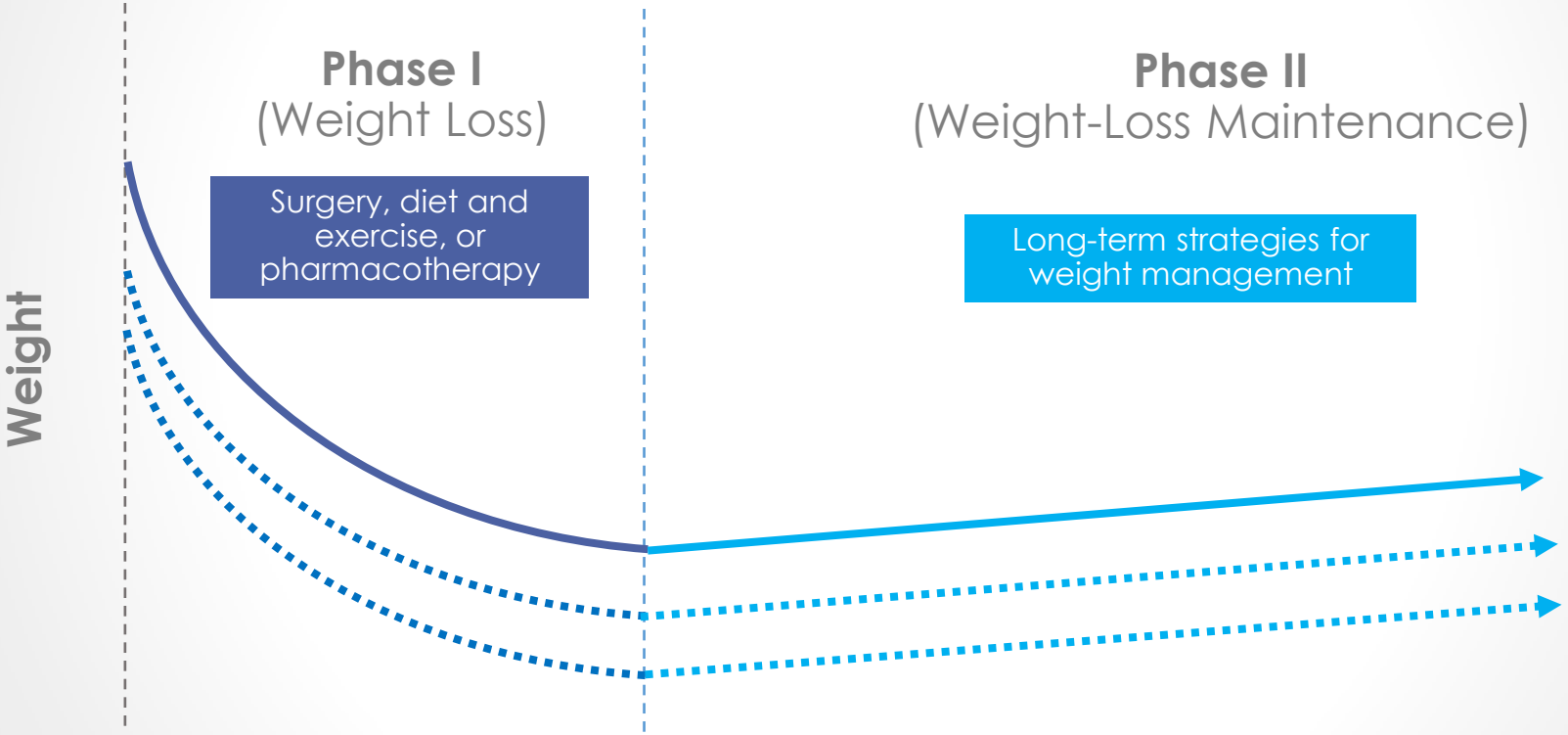


Ryan *et al. Arch Intern Med.* 2010 Jan 25;170(2):146-54. Golomb I *et al. Jama Surg.* 2015;150(11):1051-1057.

“Best Weight”

The weight that is achieved when one is living their healthiest lifestyle that they can truly enjoy and maintain longterm.

Treating early allows
STABILIZATION AT A LOWER SET POINT WEIGHT



Ryan *et al.* Arch Intern Med. 2010 Jan 25;170(2):146-54. Golomb I *et al*. Jama Surg. 2015;150(11):1051-1057.

KEY TAKE-AWAY MESSAGES

1

Obesity is a chronic medical condition with biologic maladaptation.

Alterations in brain circuits can disturb appetite regulation, cravings and eating behaviours, leading to obesity.

2

Early intervention ensures stabilization at a lower setpoint,
because once weight is increased the brain defends against weight loss.

3

Obesity requires a long-term treatment plan beyond simply “will power” or “eat less, move more”.

4

Evidence-based treatments should target the brain to bolster successful lifestyle changes and include: cognitive behavioural therapy, pharmacotherapy and sometimes surgery.

Thank you

For more information, please visit:

www.obesitycanada.ca

www.myweightwhattoknow.com

Photos provided courtesy of:

obesity canada