Medical Management and Practical Strategies

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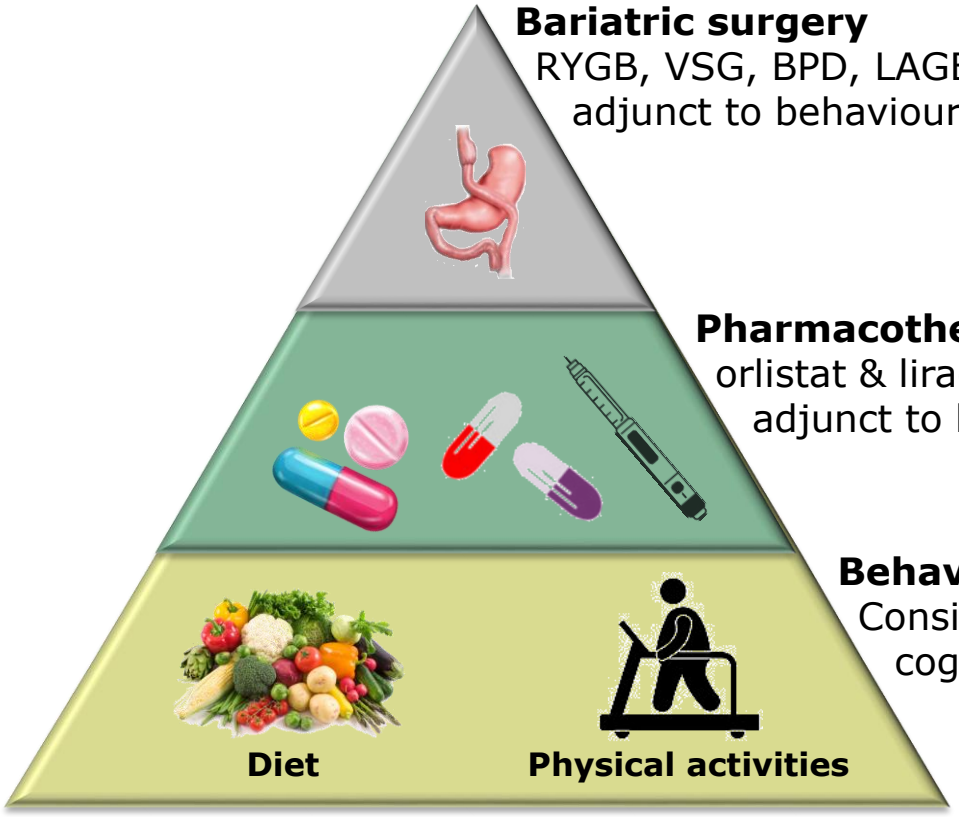
Three principal treatment modalities for obesity



Bariatric surgery
RYGB, VSG, BPD, LAGB;
adjunct to behavioural modifications

Pharmacotherapy
orlistat & liraglutide;
adjunct to behavioural modifications

Behavioural modifications
Consists of nutrition, physical activity, and cognitive-behavioural therapy

The choice of treatment depends on the evaluation of a patient's level of obesity and their risk of obesity-associated disease

BPD = biliopancreatic diversion; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass; VSG = vertical sleeve gastrectomy.

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

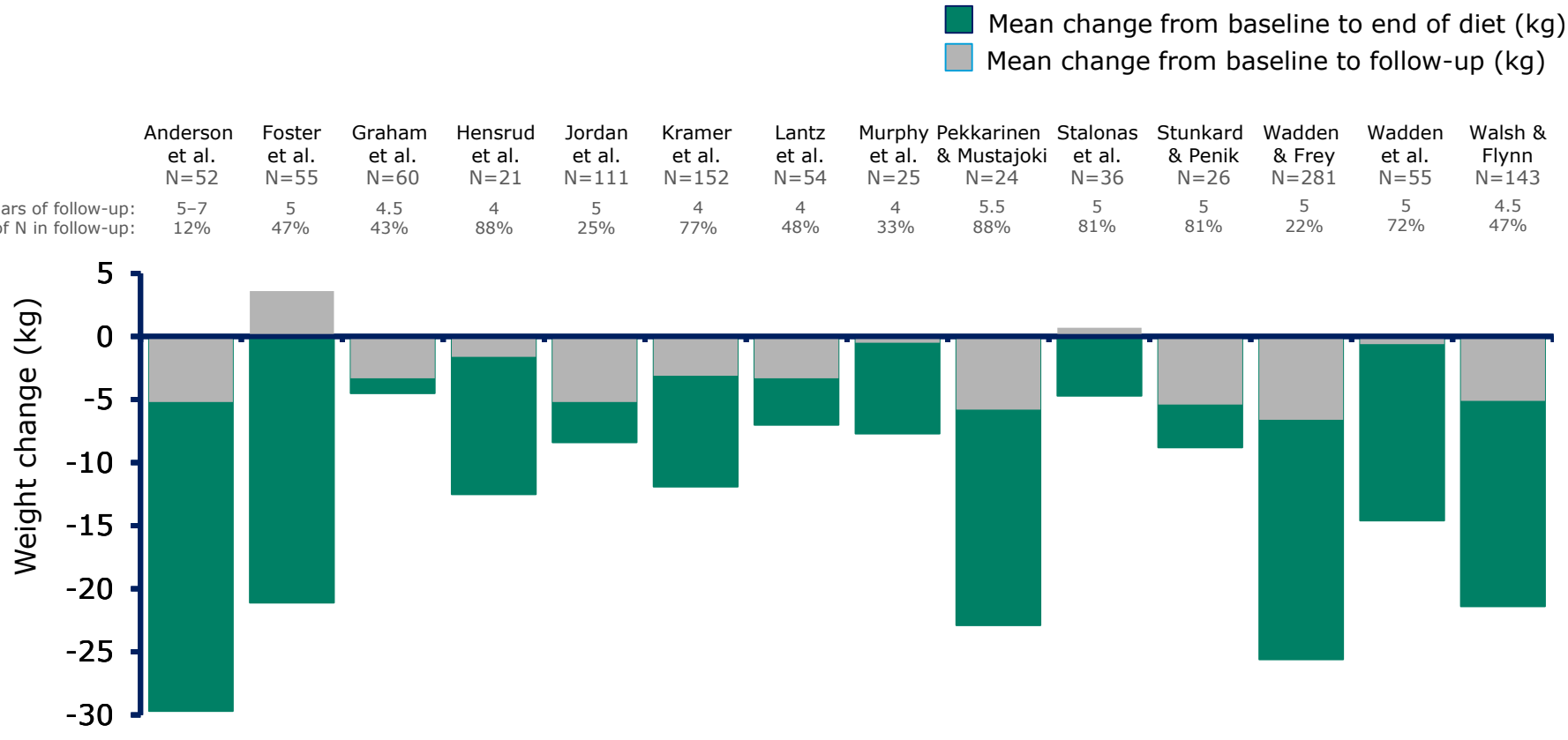
Canadian guidelines for the clinical management of obesity

Treatment	BMI category (kg/m²)				
	≥25	≥27	≥30	≥35	≥40
Behavioural modification Consists of nutrition, physical activity, and cognitive-behavioural therapy	With comorbidities	With comorbidities	✓	✓	✓
Pharmacotherapy Adjunct to behavioural modifications; consider if patient has not lost 0.5 kg per week by 3–6 months after behavioural changes		With comorbidities	✓	✓	✓
Bariatric surgery Consider if other weight loss attempts have failed. Requires lifelong medical monitoring				With comorbidities	✓

✓ Indicates a treatment recommendation for that BMI class. BMI, body mass index

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

Unintentional weight regain is common after diet-associated weight loss

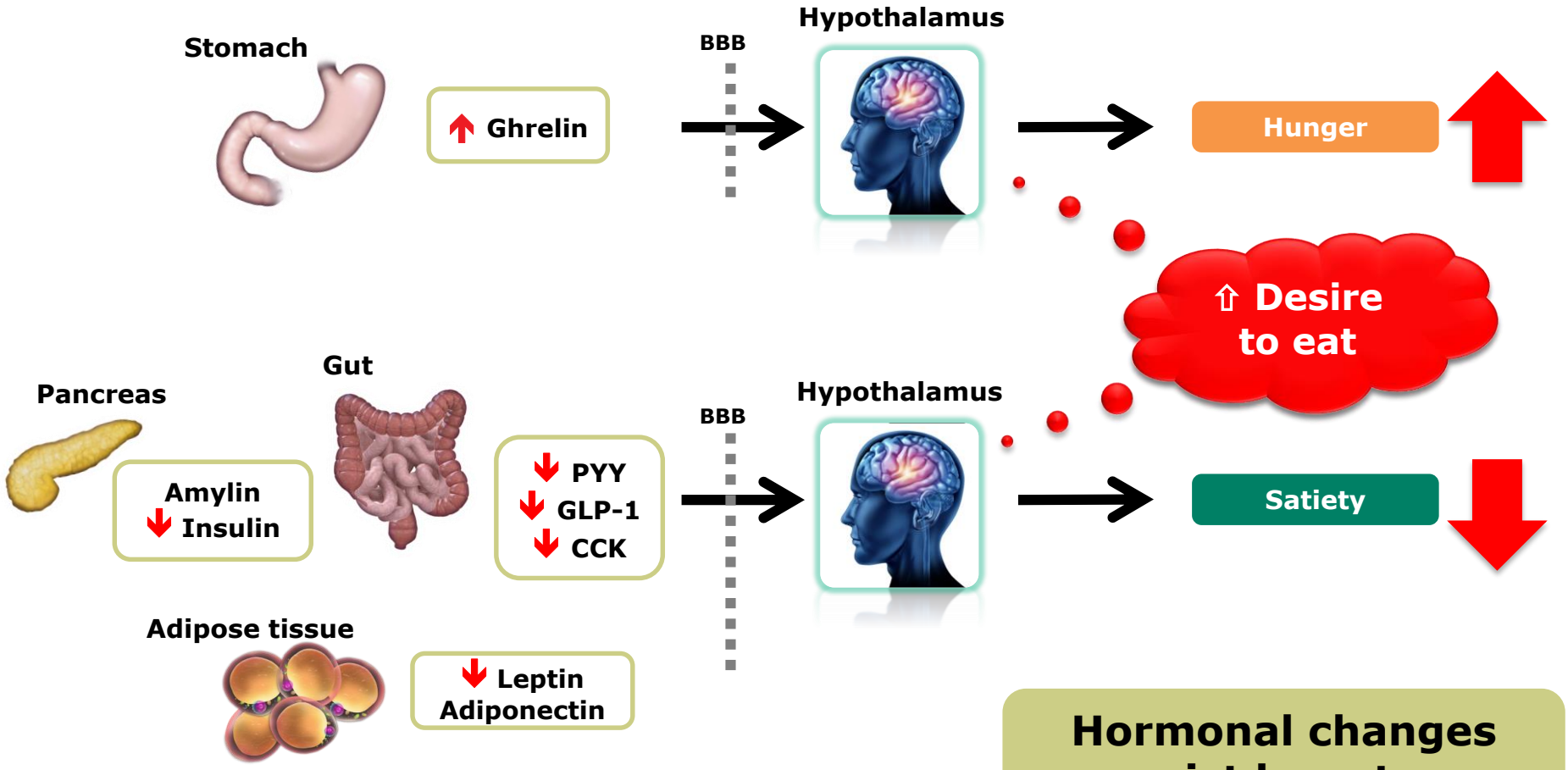


P-values not available

Follow up range from 4 to 7 years

Mann et al. Am Psychol 2007;62:220–33

Following weight loss, physiologic and metabolic responses favour weight regain

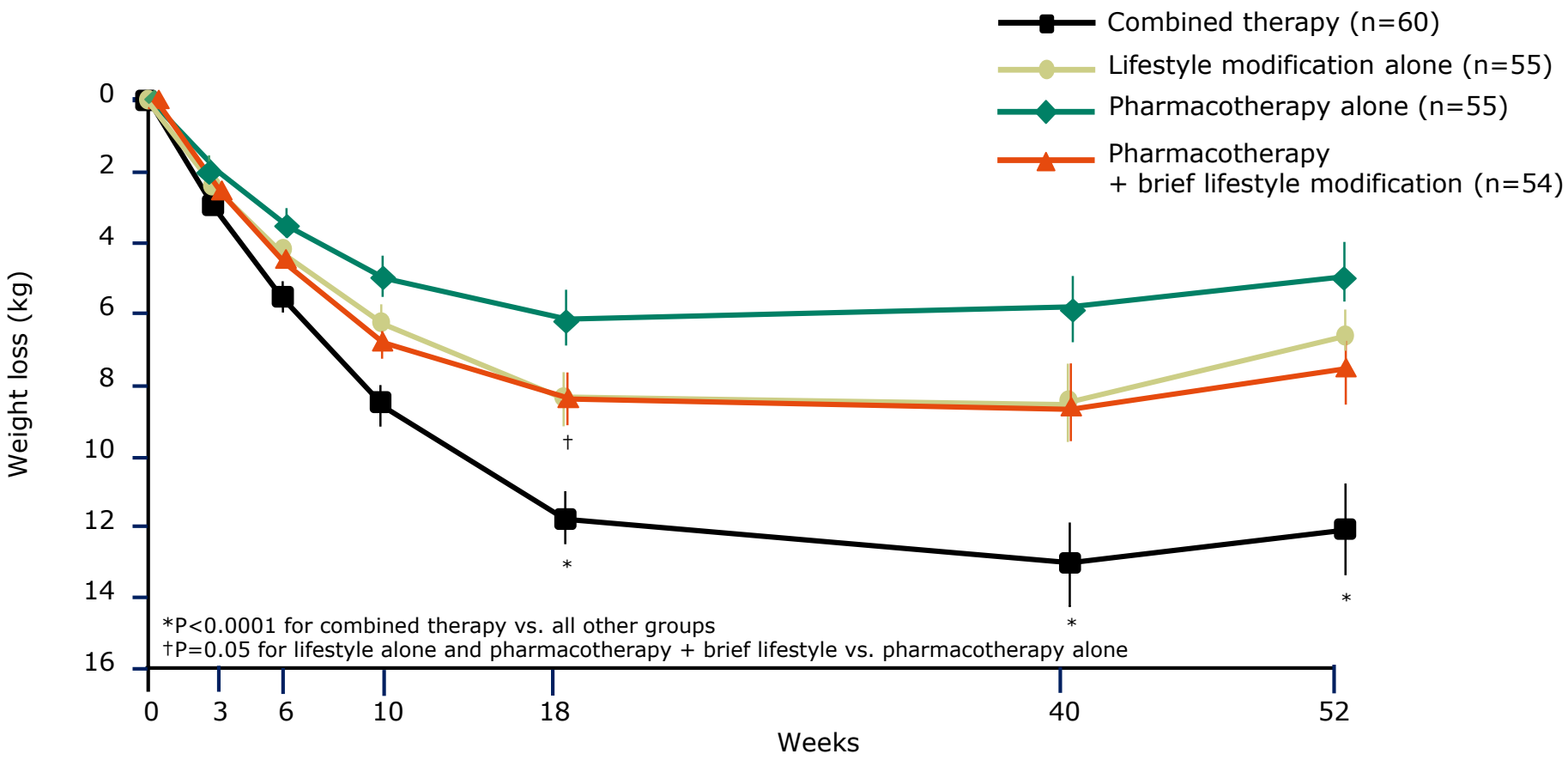


Hormonal changes persist long-term

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;365:1597–604. 3. Rosenbaum M et al. Am J Physiol Regul Integr Comp Physiol. 2003;285:R183–R92.

Pharmacotherapy, in addition to diet and exercise, can help patients achieve clinically relevant weight loss



Data are mean ± SE
Pharmacotherapy: sibutramine; Pharmacotherapy alone: Patients received a daily dose of 15 mg/day; Lifestyle modification alone: Patients attended 30 lifestyle counselling sessions; Pharmacotherapy + brief therapy: Patients were given sibutramine and received brief lifestyle counselling; Combined therapy: Patients received sibutramine and attended 30 lifestyle counselling sessions.

Wadden *et al. N Engl J Med* 2005;353:2111–20

Features of available pharmacotherapy options

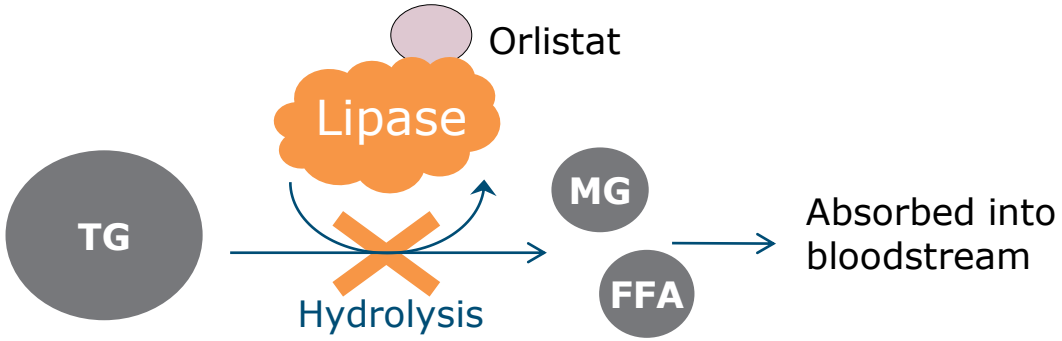
Feature	Orlistat (Xenical®)	Liraglutide (Saxenda®)
Drug class	Gastric and pancreatic lipase inhibitor	GLP-1 receptor agonist
Indication	**≥30 kg/m²** or **≥27 kg/m²** + comorbidity	**≥30 kg/m²** or **≥27 kg/m²** + comorbidity
Contra-indications	• Chronic malabsorption syndrome • Cholestasis	• Multiple Endocrine Neoplasia syndrome (MEN2), medullary thyroid cancer (MTC) • Pregnancy/breastfeeding
Most common adverse events	• Oily spotting, stool, evacuation • Flatus with discharge • Fecal urgency, increased defecation	• Nausea, vomiting, dyspepsia • Diarrhea, constipation • Abdominal pain

BMI, body mass index; GLP-1, glucagon-like peptide-1.

Orlistat Product Monograph, Hoffman-La Roche Limited., Jan, 2012; Liraglutide Product Monograph, Novo Nordisk Canada Inc., June, 2015.

Orlistat mechanism of action

- Reversible inhibitor of lipase
- Acts non-systemically in the lumen of the stomach and small intestine to inactivate lipases from hydrolyzing dietary fat
- Undigested triglycerides are not absorbed → subsequent caloric deficit results in weight loss
  - At the recommended dosage, orlistat inhibits dietary fat absorption by approximately 30%



FFA, free fatty acid; MG, monoglycerides; TG, triglycerides

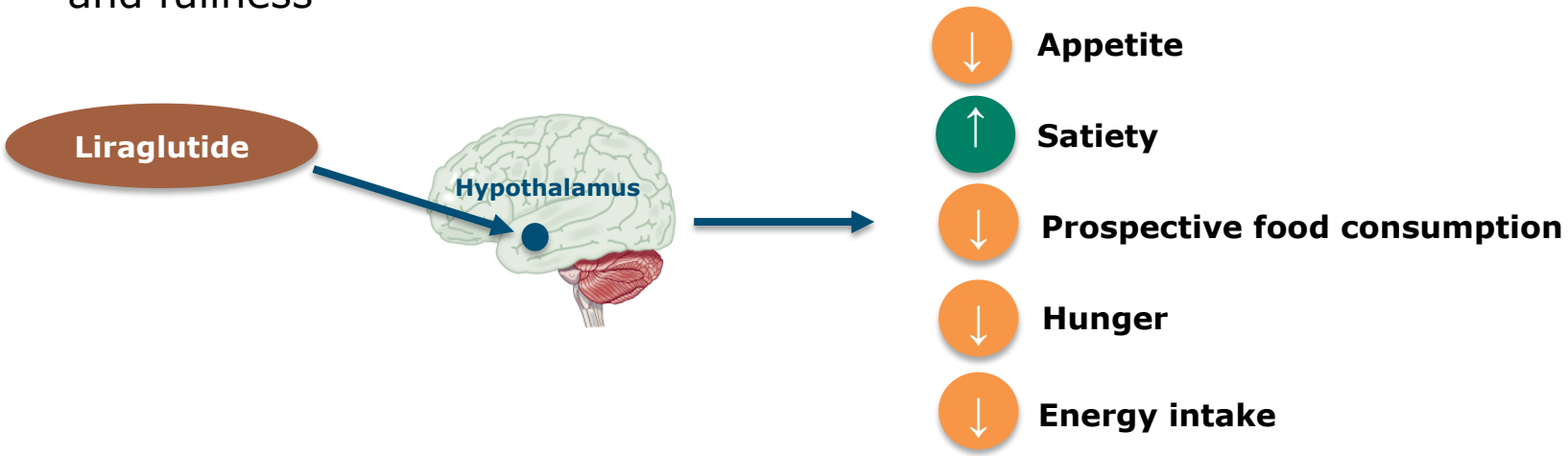
Orlistat Product Monograph, Hoffman-La Roche Limited., Jan, 2012.

Liraglutide mechanism of action

RECALL: Glucagon-like peptide-1 (GLP-1) is a physiologic regulator of appetite and food intake

- GLP-1 receptors are present in several areas of the brain involved in appetite regulation

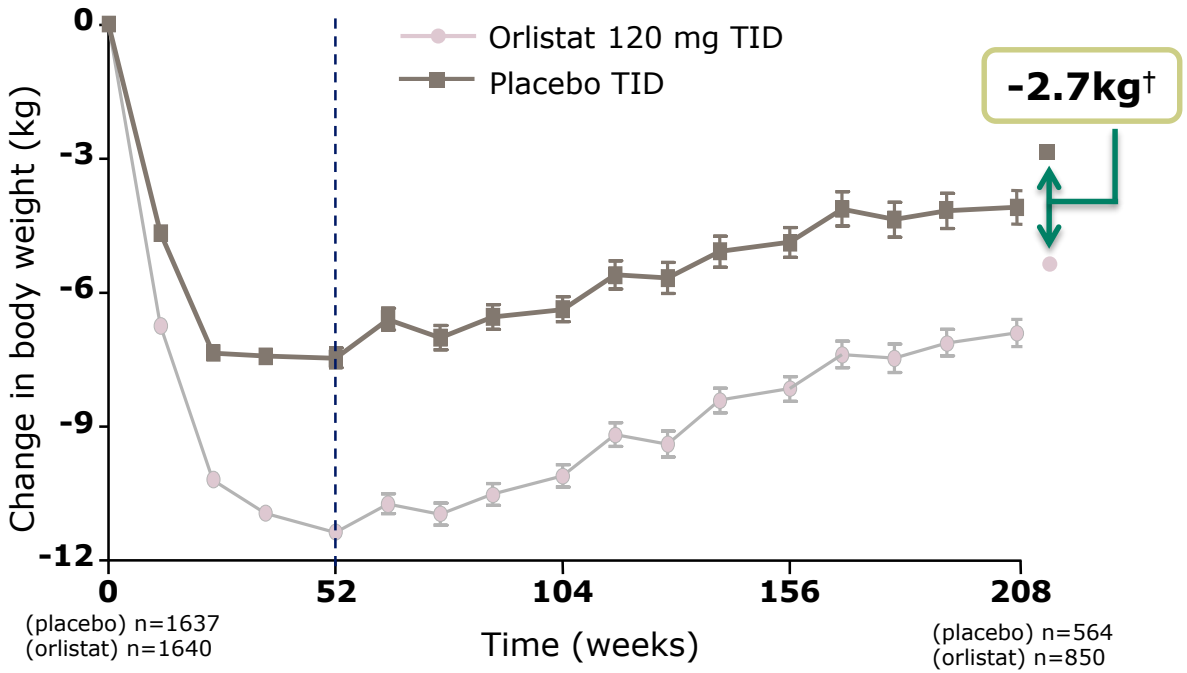
- Liraglutide is a human GLP-1 agonist with 97% homology to endogenous human GLP-1
  - Liraglutide signal is highly localized to the hypothalamus—accesses the arcuate nucleus (ARC) in the hypothalamus directly to mediate satiety and fullness



Liraglutide Product Monograph, Novo Nordisk Canada Inc., June, 2015; Secher A. J Clin Invest. 2014;124(10):4473-88.

Weight reductions with pharmacotherapy: Orlistat XENDOS trial

ORLISTAT TID[1,2]



YEAR 1

110.4–110.6 kg

-11.4 kg

vs. 7.5 kg* (completers)

≥5% weight loss
73%
vs. 45%*

>10% weight loss
41%
vs. 21%*

YEAR 4

110.4–110.6 kg

-6.9 kg

vs. -4.1 kg* (completers)

≥5% weight loss
44.8%
vs. 28.0%*

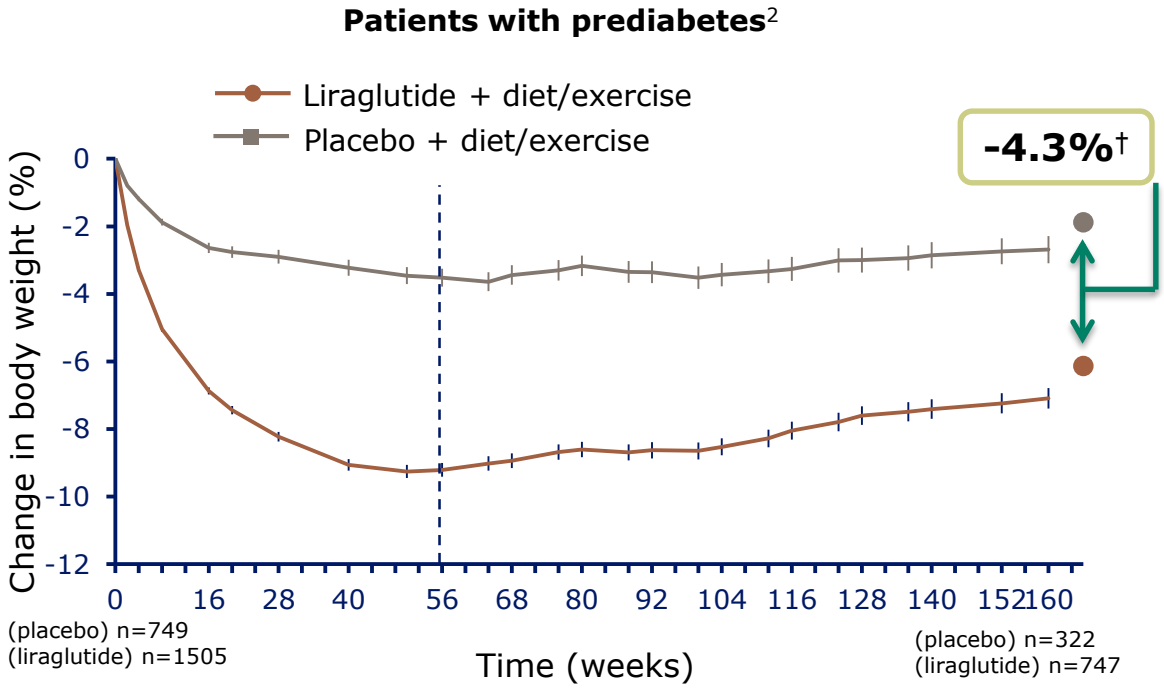
>10% weight loss
21%
vs. 10%*

*p<0.001; †p<0.001 by LOCF analysis (last observation carried forward)

1. Torgerson JS et al. Diabetes Care. 2004;27:155-61; 2. Orlistat Product Monograph. Hoffman-La Roche, Ltd. 2012

Weight reductions with pharmacotherapy: Liraglutide SCALE™ Obesity and Prediabetes trial

LIRAGLUTIDE 3 mg once daily



YEAR 1[1]

Patients with and without prediabetes (N=3731)‡

106.2 kg

-9.2%

vs. 3.5%* (completers)

≥5% weight loss
63.2%
vs. 27.1%*

>10% weight loss
33.1%
vs. 10.6%*

YEAR 3[2]

Patients with prediabetes (N=2254)

107.5–107.9 kg

-7.1%

vs. -2.7%§ (completers)

≥5% weight loss
49.6%
vs. 23.7%#

>10% weight loss
24.8%
vs. 9.9%#

*p<0.001; †p<0.0001 by LOCF analysis (last observation carried forward); ‡Weight loss was similar regardless of prediabetes status.[1]
#p<0.0001; §p-value not available.

1. Pi-Sunyer *et al. NEJM* 2015;373(1):11-22; 2. Le Roux C et al. Poster T-P-LB-3843 presented at Obesity Week. November 2–6, 2015.

RECALL: Obesity management is about improving health and well-being, and not simply reducing numbers on the scale

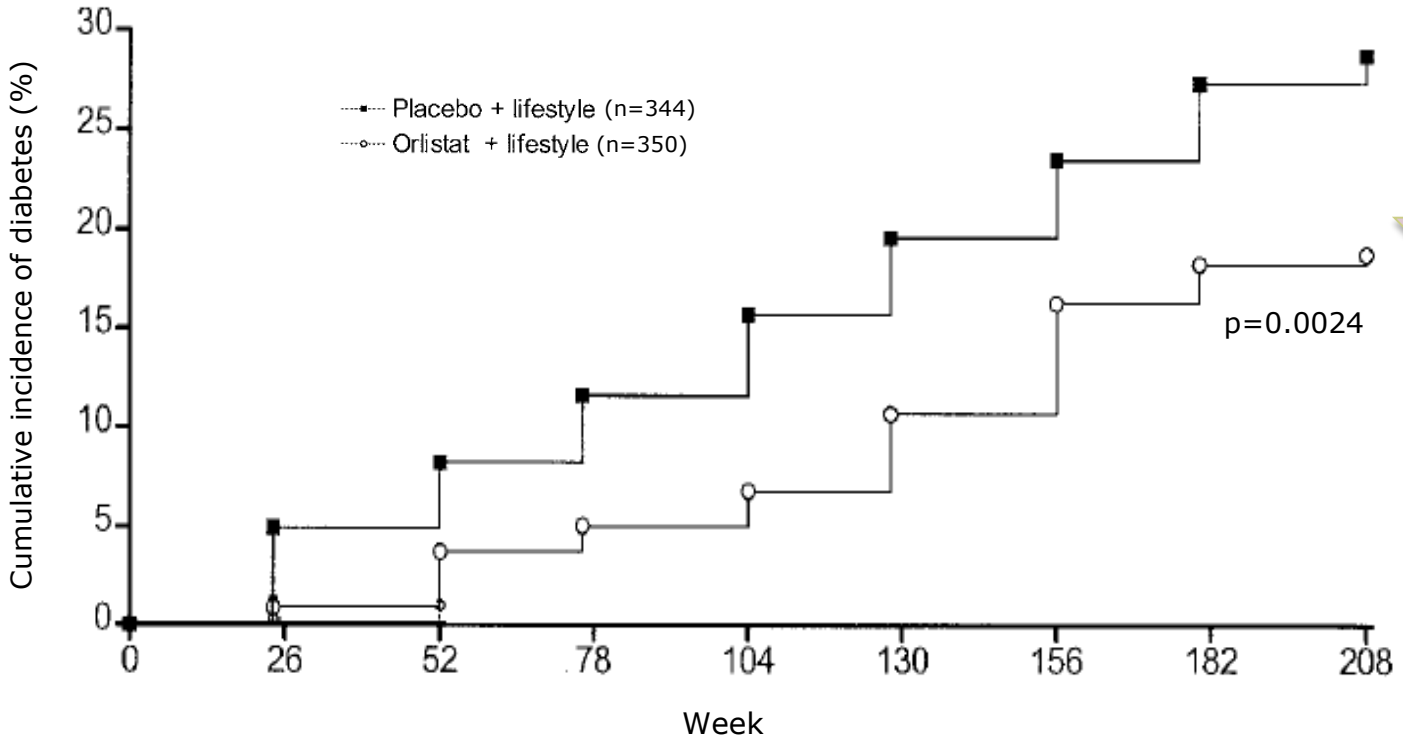
	Orlistat **XENDOS trial[1]**	**Liraglutide** **SCALE™ Obesity and Prediabetes trial[3]**
Waist circumference	✓	✓
Glycemic control		
OGTT or A1C	✓(OGTT)*	✓(A1C)*
Fasting plasma glucose (FPG)	✓	✓
Risk of developing type 2 diabetes	✓	✓
Lipids		
HDL cholesterol	✓	✓
LDL cholesterol	✓	✓
Total cholesterol	✓	✓
Triglycerides	ns	✓
Blood pressure		
Systolic blood pressure (SBP)	✓	✓
Diastolic blood pressure (DBP)	✓	✓
Health-related quality of life (HRQoL)	n/a	✓

ns, not significant; n/a, not assessed/reported; OGTT, oral glucose tolerance test. *Only OGTT was assessed in the orlistat trial. Change in A1C was assessed for the liraglutide trial.

1. Torgerson JS et al. Diabetes Care. 2004;27:155-61; 2. Orlistat Product Monograph. Hoffman-La Roche, Ltd. 2012; 3. Pi-Sunyer et al. NEJM 2015;373(1):11-22.

Reduced risk of developing type 2 diabetes with pharmacotherapy: Orlistat

ORLISTAT TID[1,2]



Relative risk reduction of developing type 2 diabetes:

-45.0%

Number needed to treat (**NNT**):
10 over 4 years

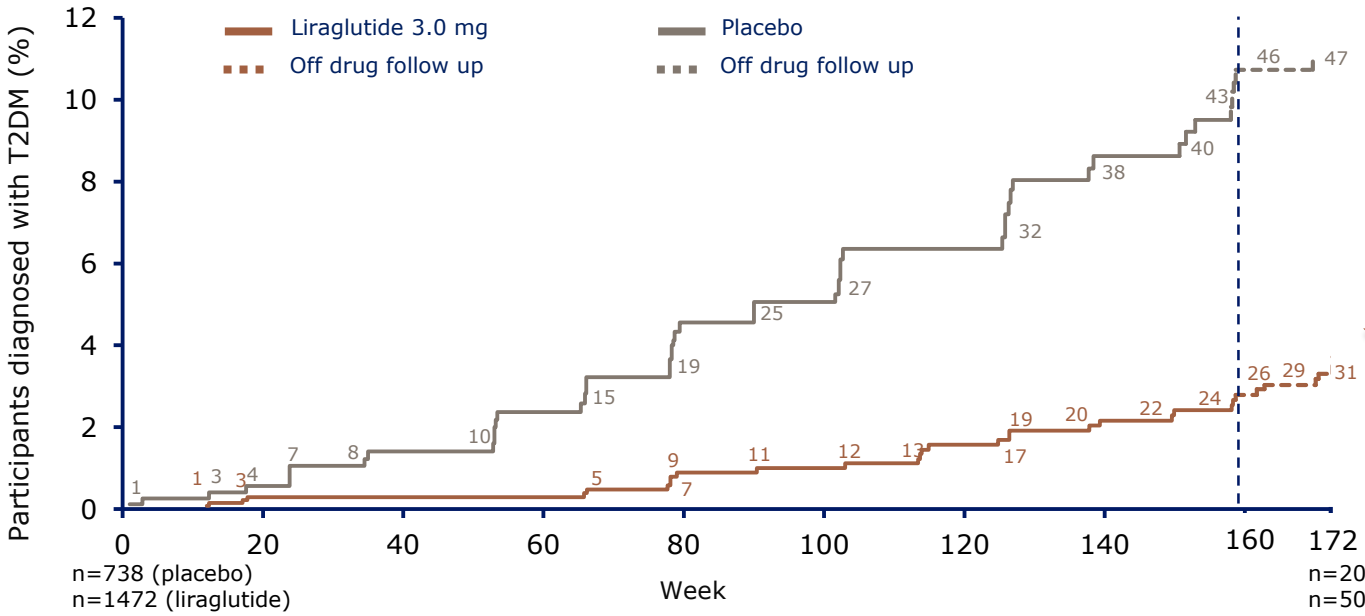
Mean age: 43.0–43.7 years;
All patients with IGT (FPG <6.7 mmol/L)

1. Torgerson JS et al. Diabetes Care. 2004;27:155-61; 2. Orlistat Product Monograph. Hoffman-La Roche, Ltd. 2012.

Reduced risk of developing type 2 diabetes with pharmacotherapy: Liraglutide

LIRAGLUTIDE 3 mg once daily[2]

Relative risk reduction of developing type 2 diabetes:



-79.3%

p<0.0001

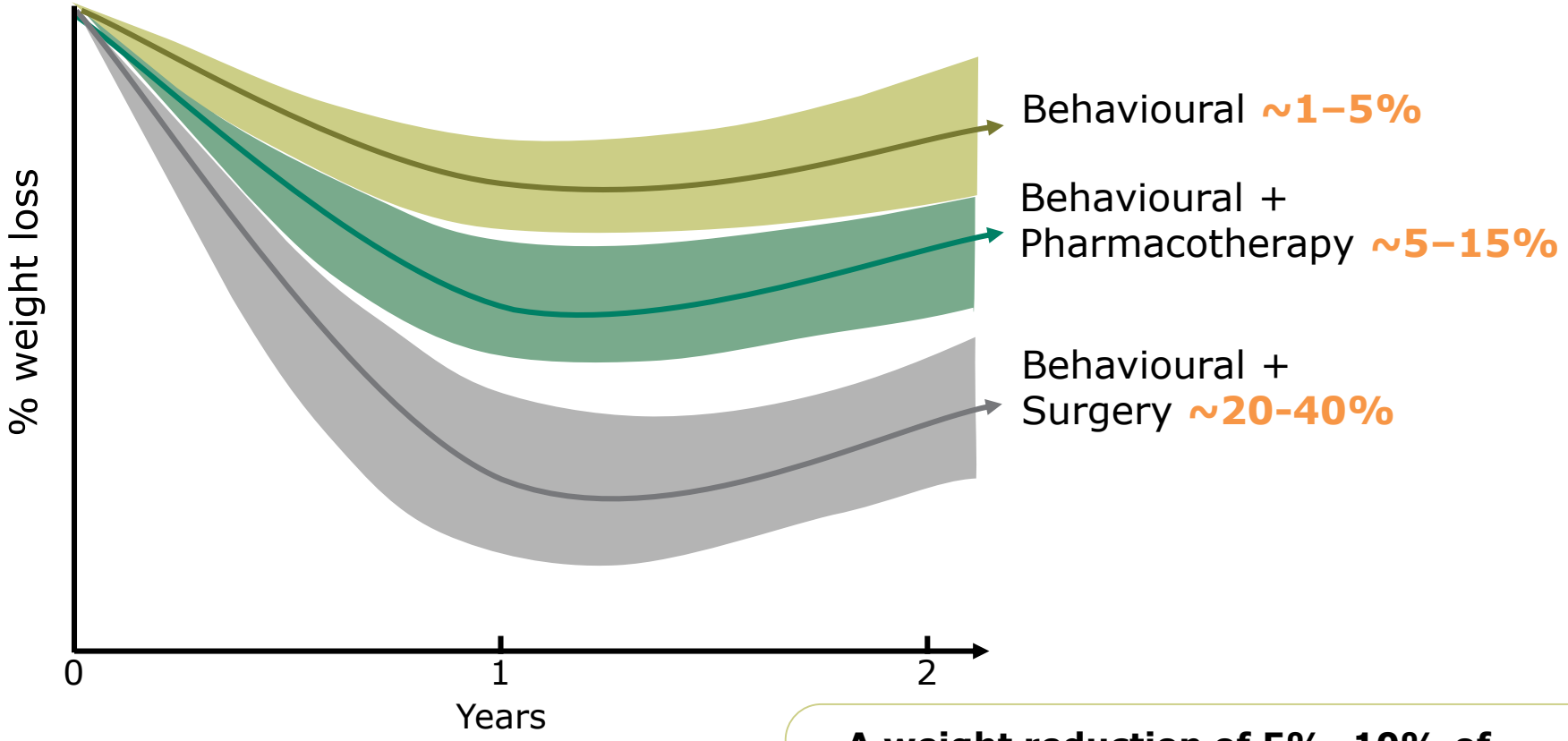
Number needed to treat (**NNT**): **14 over 3 years**

Time to onset of T2DM over 3 years was **2.7 times longer** with liraglutide vs. placebo

Mean age: 47.3–47.5 years;
All patients had prediabetes at baseline

1. Pi-Sunyer *et al. NEJM* 2015;373(1):11-22; 2. Le Roux C et al. Poster T-P-LB-3843 presented at Obesity Week. November 2–6, 2015.

Summary: Anticipated weight loss by treatment type



A weight reduction of 5%–10% of body weight is beneficial

Weight maintenance and prevention of weight regain are long-term goals

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

Practical Strategies

Practical tips for initiating pharmacotherapy: Orlistat

Dosage:

- **One 120 mg capsule TID** with each main meal

Ensure a **nutritionally balanced, mildly hypocaloric diet**

- Distribute daily intake of fat, carbohydrate and protein over three main meals
- Take a **multivitamin** at bedtime (away from orlistat dosing) that includes fat-soluble vitamins and β-carotene to ensure adequate nutrition

Minimizing side effects:

- Diet should contain ≤30% of calories from fat

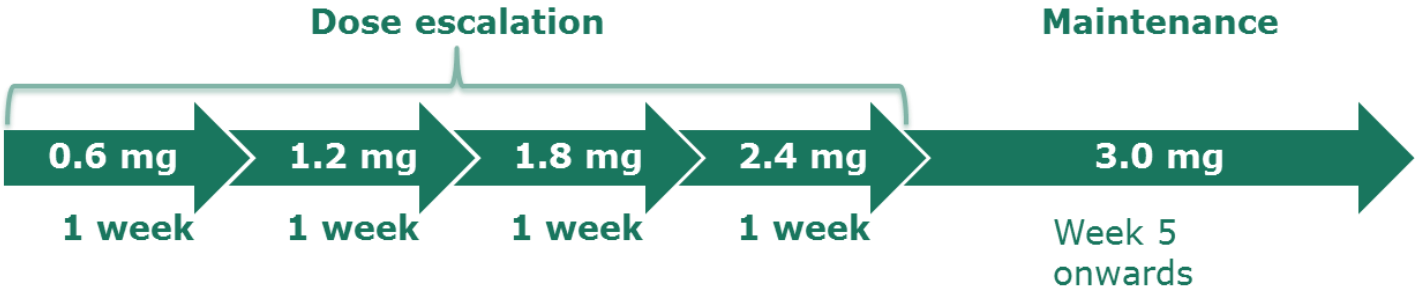
Practical tips for initiating pharmacotherapy: Liraglutide

Start with 0.6 mg/day; slowly increase to the maintenance dose of **3 mg/day**

Minimizing side effects:

- GI side effects are mostly mild to moderate and transient
- Counsel patients to:
  - Eat smaller meals
  - Stop eating when full
  - Avoid foods that make them feel sick
  - Delay dose escalation by up to 7 days:
    - The 0.6–2.4 mg doses are intended to reduce GI symptoms during dose escalation

Discontinue treatment if a patient has not lost ≥5% of their initial body weight after 12 weeks on the 3.0 mg/day dose

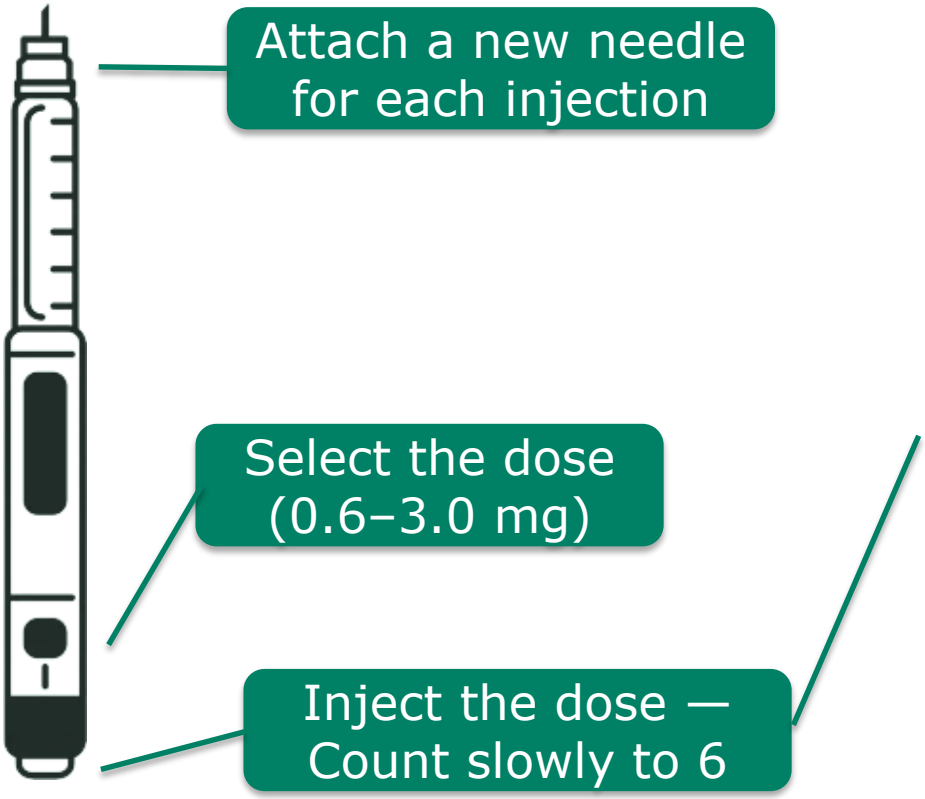


Liraglutide 3 mg should not be used with insulin (not been studied) or another GLP-1 receptor agonist.

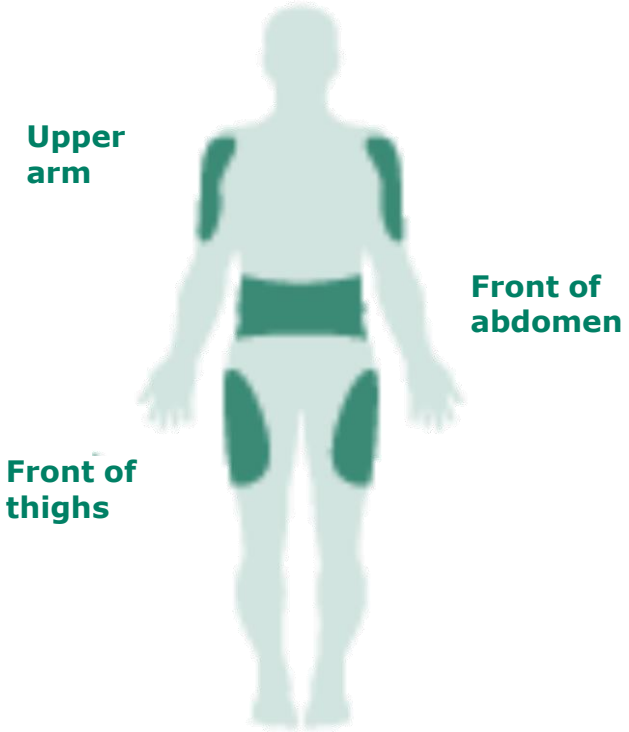
Saxenda® (liraglutide) Product Monograph. Novo Nordisk Canada Inc. 2015

Practical tips for initiating pharmacotherapy: Liraglutide

- Inject once a day, regardless of mealtime



Best places to inject include:



Have patients inject their first dose with you

Saxenda® (liraglutide) Product Monograph. Novo Nordisk Canada Inc. 2015

There is no quick fix

There is no medical or surgical invention that is stand alone/a quick fix

Education of this fact/Provision of a clear Limited Choice Diet is a key

Removal of trigger foods is key

Use of Saxenda is long likely long term. Taking it away is likely to increase the potential for old behaviors to return secondary to increased hunger/cravings/less GLP1.

Keeping busy is key

Journaling is a great tool (Retraining your brain—this is how I live now)

Talk to your patients about their weight

"Can we talk about your weight"?

"How long have you had challenges with your weight"? ,10, between 11 and 19 or >age 19

"How important is weight loss for you out of 10"

"How confident are you regarding creating behavior changes and sticking with them until you are 80"?

"What are your personal goals"/"What makes this meaningful"

"Do you know that your brain likes you at your highest possible weight and makes you feel very happy for a short time when eating trigger foods" "Swim against the current"

5-10%weight loss is Good!

Realistic weight loss targets are key.

5-10% is all that is needed to start to see medical benefits—glycemic changes, liver enzyme improvement, CRP improvement

In Hospital

Talk to patients about opportunities to change behaviors/weight loss

?Trial 1200 cal Diets (Halifax Obesity Network Website Diet Stages 3,4,5)

?Hand weights at the bedside

Physio consults

Air beds

Walkers, Wheechairs, trapeze….

Discharge plan

Your work with one patient likely affects far more

We need to not lose sight of the fact that this work affects families and populations!