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.

# Canadian guidelines for the clinical management of obesity

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

✓ 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
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.
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.

## Features of available pharmacotherapy options

<table>
<thead>
<tr>
<th>Feature</th>
<th>Orlistat (Xenical®)</th>
<th>Liraglutide (Saxenda®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug class</strong></td>
<td>Gastric and pancreatic lipase inhibitor</td>
<td>GLP-1 receptor agonist</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>≥30 kg/m² or ≥27 kg/m² + comorbidity</td>
<td>≥30 kg/m² or ≥27 kg/m² + comorbidity</td>
</tr>
</tbody>
</table>
| **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 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
**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

![Diagram of Liraglutide action](image)

**Diagrams and Text:**
- **Appetite** ↓
- **Satiety** ↑
- **Prospective food consumption** ↓
- **Hunger** ↓
- **Energy intake** ↓

Weight reductions with pharmacotherapy: Orlistat XENDOS trial

**ORLISTAT TID**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Change in body weight (kg)</th>
<th>(placebo)</th>
<th>(orlistat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>110.4 – 110.6 kg</td>
<td>110.4 – 110.6 kg</td>
</tr>
<tr>
<td>52</td>
<td>-2.7 kg†</td>
<td>110.4 – 110.6 kg</td>
<td>110.4 – 110.6 kg</td>
</tr>
<tr>
<td>104</td>
<td></td>
<td>vs. 7.5 kg* (completers)</td>
<td>vs. -4.1 kg* (completers)</td>
</tr>
<tr>
<td>156</td>
<td></td>
<td>≥ 5% weight loss 73% vs. 45%*</td>
<td>≥ 5% weight loss 44.8% vs. 28.0%*</td>
</tr>
<tr>
<td>208</td>
<td></td>
<td>&gt; 10% weight loss 41% vs. 21%*</td>
<td>&gt; 10% weight loss 21% vs. 10%*</td>
</tr>
</tbody>
</table>

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

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

**LIRAGLUTIDE 3 mg once daily**

**Patients with prediabetes**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Change in body weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>-4.3%†</td>
</tr>
<tr>
<td>28</td>
<td>-5.1%†</td>
</tr>
<tr>
<td>40</td>
<td>-5.9%†</td>
</tr>
<tr>
<td>56</td>
<td>-6.6%†</td>
</tr>
<tr>
<td>68</td>
<td>-7.1%†</td>
</tr>
<tr>
<td>80</td>
<td>-7.6%†</td>
</tr>
<tr>
<td>92</td>
<td>-8.1%†</td>
</tr>
<tr>
<td>104</td>
<td>-8.5%†</td>
</tr>
<tr>
<td>116</td>
<td>-9.0%†</td>
</tr>
<tr>
<td>128</td>
<td>-9.2%†</td>
</tr>
<tr>
<td>140</td>
<td>-9.5%†</td>
</tr>
<tr>
<td>152</td>
<td>-9.8%†</td>
</tr>
<tr>
<td>160</td>
<td>-10.0%</td>
</tr>
</tbody>
</table>

* p<0.001; † p<0.0001 by LOCF analysis (last observation carried forward); ‡ Weight loss was similar regardless of prediabetes status.¹

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

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

Reduced risk of developing type 2 diabetes with pharmacotherapy: Orlistat

**ORLISTAT TID**

Relative risk reduction of developing type 2 diabetes:

- Cumulative incidence of diabetes (%)
  - Mean age: 43.0–43.7 years;
  - All patients with IGT (FPG <6.7 mmol/L)

- **Placebo + lifestyle (n=344)**
- **Orlistat + lifestyle (n=350)**

**Number needed to treat (NNT):**

10 over 4 years

Reduced risk of developing type 2 diabetes with pharmacotherapy: Liraglutide

**LIRAGLUTIDE 3 mg once daily**

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

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(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**

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

**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.

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:**

- Upper arm
- Front of abdomen
- Front of thighs

Attach a new needle for each injection

Select the dose (0.6–3.0 mg)

Inject the dose — Count slowly to 6

Have patients inject their first dose with you
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, Wheechnairs, 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!