Weight Loss Drugs
Weighing modest long-term weight loss against safety and cost.

October 2006

Weight Loss Management

- Obesity is a chronic condition requiring a long-term management plan.
- Goals should be individualized and include weight loss, blood pressure, blood glucose, and lipids.1
- Suggested initial goal: 5-10% weight loss in 6 mo.2
- Lifestyle & behavioural modifications, such as diet & exercise, are the cornerstone of therapy. A multidisciplinary approach is ideal.3,27
- Assess patients for their risk of obesity-related health risks, weight history, previous weight loss attempts, and current medications that may cause weight gain (e.g. antipsychotics, antidepressants, diabetic medications, anticonvulsants & steroids).3,28
- Whenever possible, consider choosing drugs with lower potential to cause weight gain. (See bottom notes on Weight Loss Agents Comparison Chart.)

Encourage activity and limit the Slurpees!

DAILY ACTIVITY IDEAS: Walk 10,000+ steps; Take the stairs. 6x10min activity bursts.

<table>
<thead>
<tr>
<th>Caloric Amounts of Common Beverages / Snacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coke, 59ml= 240Kcal</td>
</tr>
<tr>
<td>Frappuccino 16oz= 323Kcal</td>
</tr>
<tr>
<td>Slurpee, 1.18 litre= 570Kcal</td>
</tr>
<tr>
<td>Big Gulp – Double 1.9l= 800Kcal</td>
</tr>
<tr>
<td>Donut = 300Kcal</td>
</tr>
<tr>
<td>Mars Bar = 294Kcal</td>
</tr>
<tr>
<td>Fries, Supersized = 570Kcal</td>
</tr>
<tr>
<td>Milkshake Triple Thick Lie = 1160Kcal</td>
</tr>
</tbody>
</table>

Consider opportunities to identify & modify lifestyle choices in children & adolescents!

Therapy Options

Lifestyle & behavioural modifications:
- Lifestyle interventions are recommended for all overweight patients.1,28 They should be continued even if medication or surgery options are used.28
  - E.g. Consider membership at a suitable gym e.g. Curves
  - Limit computer & TV “screen-time” for kids

Drug therapy:
- The role of weight loss drugs is of some debate. Limited long-term effectiveness and risks must be weighed against the complications associated with obesity such as diabetes and heart disease.
- A 6 month trial of diet, exercise & behavioural therapy is recommended prior to considering drug therapy.32 Drug therapy may be considered in select patients: obese patients (BMI ≥30kg/m²) or those with a BMI ≥27 kg/m² + 1 risk factor (diabetes, hypertension, hyperlipidemia, coronary artery disease or sleep apnea). Safety, efficacy and overall costs should be considered.

Surgery (e.g. Roux-en-Y gastric bypass or duodenal switch6):
- Surgery may be considered in select patients (obesity class III (BMI 40 kg/m²) or obesity class II (BMI 35-39.9 kg/m²) + ≥1 severe obesity related medical complications).
- Mortality rates (generally between 0.1%-1.1%) vary with surgery type and experience of centre.7,27,28

Do Weight Loss Drugs Work?
- In the short term, weight loss drugs may provide a modest reduction in body weight (<5kg at 1 year; See Table 1).1 Whether long-term outcome benefits will result is yet to be established.27
- Sibutramine & Orlistat have been shown to reduce and, to some extent, maintain weight loss.2 {No additional benefit when agents combined.}8,9,10
- Drug therapy alone is insufficient as trials also included lifestyle modification co-interventions.11
- Weight regain is common upon discontinuation.

Table 1

<table>
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<tr>
<th>Drug</th>
<th>Meta-Analysis: Sibutramine or Orlistat at 1 year</th>
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<td>Source</td>
<td>Population (Means if reported)</td>
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<tr>
<td>Sibutramine 10-20mg/d (n=290)</td>
<td>29 RCTs age 34-54yr; 53-100%</td>
</tr>
<tr>
<td>Orlistat 360mg/d (n=412)</td>
<td>22 RCTs age 48yr; 73% Y; BMI 36.7</td>
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Sibutramine 10-20mg/d NNT=3.5 for 1 year to achieve 5% weight loss, NNT=3.4 for 1 year to achieve 10% weight loss. Most trials excluded patients with CV disease (controlled HTN was allowed).12

Notes:
1. IGT= impaired glucose tolerance; OTC=over the counter products; SK=Saskatchewan; NIHB=Indian Affairs
2. SK = Saskatchewan; NIHB = Indian Affairs
3. Mean Weight Change (95% CI)

Highlight:
- Obesity and its’ associated comorbidities is increasing.
- Weight loss drugs provide a modest reduction in body weight (<5kg at 1 year); weight regain is common.
- Improvements in metabolic risk factors may be seen.
- Long-term efficacy, safety and outcome data is lacking.
- Prescription, herbal and OTC agents used for weight loss are expensive. The 2 drugs with official weight loss indications, Sibutramine MERIDIA and Orlistat XENICAL, cost >$120 per month. (Neither are currently covered by the SK formulary or NIHB.)
- Consider cardiovascular risk reduction strategies such as lifestyle interventions and drugs such as ASA, antihypertensives and statins if indicated.
- Minimizing weight gain may be a consideration when choosing drugs within certain therapeutic classes.
### Are Weight Loss Drugs Safe?

- Since 1997, 6 weight loss drugs have been removed from the market:
  - Fenfluramine and dexfenfluramine (heart valve abnormalities, primary pulmonary HTN);
  - phenylpropanolamine (strokes in females);
  - phentermine, diethylpropion, & mazindol (discontinued by manufacturers; concerns with abuse and adverse events)

- **Sibutramine** was temporarily suspended from the market in Italy, citing tachycardia, hypertension, arrhythmia & cardiac arrest. 
  - An increase in BP of 1-3mmHg & heart rate of 4-5 beats/min can result from sibutramine use; however it is unclear if any increase in cardiovascular risk is offset by the reduction in body weight.

- **Orlistat** is minimally absorbed (<5%); however, tolerability due to GI adverse events is an issue.
  - Absorption of fat soluble vitamins is decreased, yet remains within range (but a daily multivitamin is recommended). The FDA is considering approving a 60mg strength for OTC sale.

- Long term safety has not yet been established. Adverse reaction reporting is encouraged.

### Weight Regain With Continued Therapy

- There generally appears to be a trend towards partial weight regain despite continued therapy. (e.g. orlistat, XENDOS trial - Figure 1). This may be due in part to the natural history of weight regain.

### Quick Facts on Obesity

- The incidence of obesity is rising. 
- In 2004, approximately 23% of adult Canadians were obese & 36% were overweight.
- Reducing weight by only 5-10% can reduce the risk of cardiovascular (CV) disease, diabetes & comorbidities.
- There is debate as to whether Body Mass Index (BMI) is the best risk predictor for obesity as it does not take into account fat-free mass, or the abdominal fat shown to contribute to CV risk.
- A measurement of waist circumference or the waist:hip ratio is a better predictor of metabolically active visceral fat and disease risk.
- “1lb (0.45kg) = 3500 calories”. Reducing energy intake or increasing energy expenditure by 500 calories/day will result in losing about 1lb (½ kg) in one week.
- 1kg weight loss (~1cm decrease in waist circumference.
- Removal of adipose tissue via liposuction does not achieve metabolic benefits of weight loss.

### Other Options

- For patients with impaired glucose tolerance (IGT), lifestyle changes decrease the risk of developing diabetes. 
  - **Metformin** drugs such as metformin and acarbose may also be useful for IGT/weight loss. 
  - Rosiglitazone progression to diabetes, but TFG, edema & wt.

- Drugs known to decrease morbidity & mortality in patients with CV risk should be considered. (e.g. ASA, antihypertensives and statins).

### Obesity Related Medical Complications

Obese patients have an increased risk for:
- hypertension, Type 2 diabetes, gall bladder disease, sleep apnea & hyperlipidemia (>3x risk)
- CAD, knee osteoporosis, & gout (2-3x risk)
- breast, endometrial & colon cancer (1-2x risk)
- low back pain, cancer, infertility & surgical risk (1-2x risk)

The relationship between comorbidities & obesity is stronger in individuals <55 years. After age 74, there is no longer an association between increased BMI & mortality.

### Table 2: Weight Loss Drug Trials (RCT) of ≥24 months: Orlistat or Sibutramine

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