

Weight Loss Drugs

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

October 2006



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Highlights

- ♦ 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. {e.g. ↓ progression to diabetes with orlistat in those with IGT}
- ♦ 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.

IGT= impaired glucose tolerance; OTC=over the counter products;
SK=Saskatchewan; NIHB=Indian Affairs

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.

FYI: Caloric Amounts of Common Beverages / Snacks⁴

Coke, 591ml	= 240Kcal	Donut	= 300Kcal	15g fat
Frappuccino Venti Starbucks	= 323Kcal	Mars Bar	= 294Kcal	11g fat
Slurpee, 1.18 litre ⁵	= 570Kcal	Fries, Supersized	= 570Kcal	28g fat
Big Gulp – Double ^{1,91}	= 800Kcal	Milkshake Triple Thick Lg	= 1160Kcal	28g fat

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

Meta-Analysis: Sibutramine or Orlistat at 1 year¹¹

Drug	Source	Population (Means if reported)	Mean Weight Change (95% CI)
Sibutramine 10-20mg/d n=1060	29 RCTs	age 34-54yr; 53-100% ♀	- 4.45kg (-5.3 to -3.6kg)
Orlistat 360mg/d n=4213	22 RCTs	age 48yr; 73% ♀; BMI=36.7	- 2.75kg (-3.3 to -2.2kg)

Sibutramine 10-15mg/d: NNT=3-5 for 1 year to achieve 5% weight loss, NNT=3-8 for 1 year to achieve 10% weight loss. Most trials excluded patients with CV disease (controlled HTN was allowed).¹²

Are Weight Loss Drugs Safe?

- Since 1997, 6 weight loss drugs have been removed from the market:
 - Fenfluramine in FEN-PHEN & dexfenfluramine (heart valve abnormalities, primary pulmonary HTN);
 - phenylpropranolamine (strokes in females);
 - phentermine IONAMIN, diethylpropion TENUATE, & mazindol SANOREX (discontinued by manufacturers; concerns with abuse and adverse events CNS & CV).²⁷
- Sibutramine** was temporarily suspended from the market in Italy, citing tachycardia, hypertension, arrhythmia & cardiac arrest.^{13,14} 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.¹⁵
- Orlistat** is minimally absorbed (<5%); however, tolerability due to GI adverse events is an issue.¹⁴ {Discontinuation GI, Lab ~2x vs placebo 8% vs 4%}.¹⁶ Absorption of fat soluble vitamins is decreased, yet remains within range (but a daily multivitamin is recommended). The FDA^{USA} is considering approving a 60mg strength for OTC sale.
- Long term safety has not yet been established. Adverse reaction reporting is encouraged. [AR-Link](#)

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 aging.

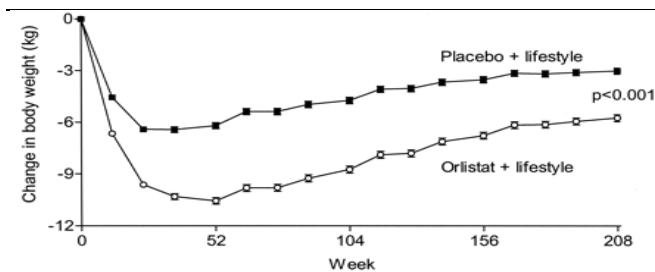


Figure 1: Weight loss during 4 years of treatment with orlistat + lifestyle versus placebo + lifestyle.¹⁶ (XENDOS: orlistat 120mg po tid)

Acknowledgements: Contributors & Reviewers: Dr. D. Blackburn (C. of Pharm, U. of S.; SHR-Risk Reduction Clinic), Dr. S. Mann (Regina-Endo), Dr. L. Salgado (Regina-GP), Dr. D. Lau (Calgary-Endo), Dr. A. Paus-Jensen (SHR-Int Med/Risk Reduction Clinic), Dr. T. Wilson (SHR), Dr. J. Taylor (C. of Pharm, U. of S.) & the RxFiles Advisory Committee. Prepared by: L. Kolodziejak MSc Candidate, L. Regier BSc BA, B. Jensen BSc
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Other Options

- For patients with impaired glucose tolerance (IGT), lifestyle changes decrease the risk of developing diabetes;¹⁷ DPP however lifestyle may be hard to maintain.¹⁸ STENO-2 Drugs such as metformin and acarbose may also be useful for IGT/weight loss.^{17,19} (Rosiglitazone ↓ progression to diabetes, but ↑HF, edema & wt.)^{DREAM 20}
- Metformin** is useful for obese patients with Type 2 diabetes (providing no contraindication) for its beneficial outcomes and weight loss potential.²¹
- Drugs known to decrease morbidity & mortality in patients with CV risk should be considered. (e.g. ASA, antihypertensives and statins).
- Drugs that should not be used for weight loss^{22,27}:
 - thyroid hormone: may cause bone loss & arrhythmias
 - amphetamines (eg. Adderal)
- New Drug: Rimonibant ACOMPLIA (Not yet in Canada)**
 - A cannabinoid (CB1) receptor blocker with favourable changes in weight (-6kg/1yr^{20mg} daily) and cardiometabolic risk factors (↓waist circumference ↓TG; ↑HDL). Side effects (e.g. nausea, anxiety, depression), a high drop-out rate^{>45%} and lack of clinical outcome trials warrant caution.^{23,24,25}

Quick Facts on Obesity

- The incidence of obesity is rising.
- In 2004, approximately 23% of adult Canadians were obese & 36% were overweight.²⁶
- Reducing weight by only 5-10% can reduce the risk of cardiovascular (CV) disease, diabetes & comorbidities.^{27,28}
- 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.²⁹ A measurement of **waist circumference** or the waist:hip ratio³⁰ is a better predictor of metabolically active visceral fat and disease risk.³¹
- “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.³²
- 1kg weight loss ⇒ ~1cm decrease in waist circumference
- Removal of adipose fat tissue via liposuction does not achieve metabolic benefits of weight loss.³³

Obesity Related Medical Complications^{32,31}

- 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

Trial	n=	Population (Means)	Mean Wt Loss (Intention-to-treat)
XENDOS¹⁶ (4yr): Orlistat 120mg po tid vs PI. (IGT subgroup -21%) {Diet: 800kcal/day deficit; counsel q2wk x6mo, then monthly; extra 1km walk/day}	3,305	Age 43 yrs, -55% ♀, BMI 37kg/m ² , Wt=110kg {↓ progression to diabetes repeat +ve test; NGT: NS 2.6% vs 2.7%; IGT 21%; NNT=17/ 4yrs 8.3% vs 14.2%} {↓BP, ↓LDL; SAE ^{15vs13%} ; NS}	@4yr: -2.8kg ^{-5.8 vs -3kg, p<0.001; 48 vs 65% drop-out; @1yr: -10.6 vs -6.2kg}
Hauptman et al.³⁴ (2yr): Orlistat 60mg tid vs 120mg tid vs PI	796	Age 43 yrs, -72% ♀, BMI 36kg/m ² , Wt=100kg	-2.9kg (±0.54) ^{60mg} vs -3.8kg (±0.57) ^{120mg} vs PI, p<0.001
Davidson et al.³⁵ (2yr) Orlistat 120mg tid vs PI; (60mg arm in 2nd yr)	880	Age 43 yrs, -84% ♀, BMI 36kg/m ² , Wt=101kg	@1yr: -2.9kg ^(-8.7kg vs -3.8kg) ; less wt regain in 2 nd yr
Rossner et al.³⁶ (2yr) Orlistat 60mg tid vs 120mg tid vs PI	718	Age 44 yrs, -80% ♀, BMI 35kg/m ² , Wt=97kg	@1yr: -3kg ^(-9.4kg vs -6.4kg) ; less wt regain in 2 nd yr
Sjostrom et al.³⁷ (2yr) Orlistat 120mg tid vs PI, 2nd yr eucaloric diet	743	Age 45yrs, -83% ♀, BMI 36kg/m ² , Wt=99kg	@1yr: -3.9kg ^(-10.3kg vs -6.1kg) ; wt regain >1kg in 2 nd yr
STORM³⁸ (2yr) Sibutramine 10mg/d for all x 6 month, then sibutramine 10-20mg vs PI {mean 13.5mg/d}	605	Age 40 yrs, 83% ♀, BMI 37kg/m ² , Wt=102kg (42% & 50% dropped out)	-4.0kg ^(95% CI 2.59-8.28) vs PI (p<0.001); dose ↑d for effect; {maintain 80% wt loss: 43% vs 16%}

HF=heart failure IGT=impaired glucose tolerance NGT=normal glucose tolerance NNT=number needed to treat for one person to benefit NS=not significant SAE=serious adverse events Wt=weight Topiramate: ~1 year (designed to be 2 yrs, but stopped early as drug re-formulated). N=854 (designed for 1282). % Weight loss (not in kg): placebo 1.7%, TPM 96mg/d 7%, TPM 192mg/d 9.1%, 256mg/d 9.7%.³⁹

All studies: •used lifestyle modifications; •had high attrition rates (~½) regardless of treatment; •initial weight loss often offset by partial weight regain.

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