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Review

Medical management of obesity in Scandinavia 2016

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ABSTRACT

Background: Preventive efforts with improved diet and more exercise have at best decelerated increasing prevalence of overweight and obesity in Scandinavia, and the complications call for more effective treatments. This review is an overview of dietary supplements, medical devices (for oral use), and pharmacological treatments approved in Scandinavian countries.
Interventions: One dietary fibre supplement, glucomannan, may produce a weight loss of 0.8 kg over 3 months, but a recent meta-analysis questioned efficacy. Cactus fig and white bean extracts, oral compounds that increase satiety by a fiber effect in the stomach and inhibit either fat or carbohydrate absorption, result in weight losses of ~2–3% over 3–6 months, and are generally well tolerated. The pharmaceutical compound orlistat (a lipase inhibitor) produces weight loss of 1–2% with low-dose (over-the-counter) and 3% with high-dose (prescription), with a long-term reduction in risk of type 2 diabetes (T2D). The GLP-agonist liraglutide enhances satiety and produces weight loss of 5–7% over 6 months to 2 years, reducing comorbidities. A naltrexone/bupropion combination produces 3–5% weight loss, and reduces risk of T2D. A class of sodium-glucose co-transporter type 2 (SGLT2) inhibitor approved for the management of T2D also produces a weight loss (2–4% over 3–6 months) by increased excretion of urinary glucose.
Conclusion: The available non-pharmacological agents produce clinically relevant weight loss, but studies are small and adverse effects are not well established. Studies of pharmacological agents that use combinations to assess additive effects on weight loss and maintenance are lacking.

Obesity is an increasing health challenge at the global level, and the Scandinavian countries are no exception. About 15–25% of the adult population can be classified as obese (BMI > 30 kg/m^2), and the majority of the population is overweight (BMI > 25 kg/m^2), which causes numerous comorbidities, disability, and reduced life expectancy. While prevention of weight gain, overweight and obesity is preferred, there are only early indications of a leveling off of the increase in prevalence, and a large part of the obese population is seeking treatment. Many obese individuals manage to lose weight by following various diet and exercise programs, commercial weight loss plans, and using meal replacements, but there is an increasing demand for adjunct therapy that can enhance initial weight loss efforts and improve long term weight loss maintenance. Bariatric surgery is an option for morbidly obese patients, but the majority of obese subjects do not fulfill the criteria for such surgical interventions. For some patients this gap may be bridged with dietary supplements, medical devices, and pharmacological compounds. The purpose of this review is to provide an update on the management options available in Scandinavia, and present a brief assessment of efficacy and safety, and clinical directions for choices for the individual patient.

When previously approved pharmaceutical agents such as sibutramine and rimonabant were withdrawn from the market due to potential serious adverse effects, only orlistat and amfepramone were left. However, in 2015 two new compounds were approved in the EU for weight reduction: liraglutide 3 mg (Saxenda®), and naltrexone/bupropion (Mysimba®). We therefore present a brief updated summary of the use of orlistat and amfepramone, and a section on the two novel compounds. Furthermore for patients with S, the GLP-1 analogues and SGLT2 inhibitors are available,

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providing both glucose control and weight loss. Moreover, a number of dietary supplements and medical devices have been approved for weight control, and these products are also reviewed. We have included products available in at least two Scandinavian countries.

1. Pharmaceutical compounds

1.1. Orlistat (Xenical®, Alli®)

Orlistat has withstood the test of time, remaining the only approved therapy in Europe since 1998 for long-term treatment of obesity. Orlistat potently and selectively inhibits gastric and intestinal lipase, reducing intestinal fat absorption. While orlistat's inhibition of intestinal fat absorption is minimal when dietary fat intake is very low, the proportion of fat excretion increases in a dose-dependent manner with increasing dietary fat, reaching a plateau of about 30% with the usual dose of 120 mg three times daily (Hauptman et al., 1992). In addition, orlistat may increase glucagon-like peptide 1 secretion (Damci et al., 2004).

1.1.1. Weight loss efficacy

In a meta-analysis of 16 randomized, placebo-controlled trials of ≥1 year orlistat reduced body weight by 2.9 kg (95% confidence interval [CI] 2.5–3.2 kg) compared with placebo (Rucker et al., 2007). In a recent systematic review of studies with at least 50 participants per group and at least 50% retention, an intention-to-treat analysis found that orlistat gave a 3.4 kg greater weight loss (3.1% of initial weight) than placebo (Yanovski and Yanovski, 2014). Two trials of orlistat 60 mg three times daily found a 2.5 kg greater weight loss than with placebo at 12 months (Yanovski and Yanovski, 2014). In patients with T2D, the difference between orlistat and placebo was about 2 kg (Norris et al., 2005; Jacob et al., 2009).

1.1.2. Weight maintenance

In a trial in 3304 participants most of the weight loss difference at 1 year (11.4 kg for orlistat versus 7.5 kg for placebo) was preserved in those that completed all four years of the study (6.9 kg for orlistat versus 4.1 kg for placebo) (Torgerson et al., 2004). Other trials have looked specifically at orlistat as a weight maintenance treatment following weight loss induced by orlistat, conventional dieting or a very low energy diet (VLED). In one trial orlistat administered for three years after VLED significantly reduced weight regain compared to placebo (4.6 kg versus 7.0 kg) (Richelsen et al., 2007). A meta-analysis found that orlistat effectively maintained weight loss at 12 months, with a difference of 1.8 kg (95% CI 1.06 to 2.54) compared to placebo (Dombrowski et al., 2014).

1.1.3. Glycemic control in T2D

In a retrospective analysis involving 2550 overweight or obese patients with T2D, participants treated with orlistat for 6–12 months had significantly larger decreases in HbA1c compared to placebo (−0.74% vs. −0.31%) (Jacob et al., 2009).

1.1.4. Prevention of T2D

In a 4-year randomized, controlled trial, orlistat added to lifestyle changes resulted in a 37.3% reduction in the incidence of T2D (Torgerson et al., 2004). Pooled data from three studies has indicated that orlistat prevented progression to diabetic status in subjects with impaired glucose tolerance (Heymsfield et al., 2000).

1.1.5. Cardiovascular risk factors

Orlistat improves most cardiovascular risk factors. Reductions in visceral fat (Tiikkainen et al., 2004), LDL cholesterol (Muls et al., 2001) and glycemia (Jacob et al., 2009), and improved insulin sensitivity (Kelley et al., 2004), appear in part to be independent of weight loss. In patients with hypertension, orlistat improved systolic blood pressure by −2.5 mm Hg (95% CI, 4.0 to −0.9 mmHg) and diastolic blood pressure by −1.9 mm Hg (95% CI −3.0–0.9 mmHg) (Siebenhofer et al., 2013). A recent meta-analysis found that orlistat increased adiponectin and reduced leptin and C-reactive protein (Derosa et al., 2015).

1.1.6. Safety and tolerability

Gastrointestinal effects including oily spotting, flatus with discharge, fecal urgency and steatorrhea are common, though they tend to subside as patients learn to adjust fat intake. The risk ratio for discontinuation of orlistat compared to placebo due to adverse events in randomized controlled trials was 1.59 (95% CI, 1.21–2.08), with a number need to harm of 39 (95% CI, 25–83) (Johansson et al., 2009). Rare cases of liver injury have been reported. However, the UK Clinical Practice Research Datalink found no evidence of an increased risk of liver injury (Douglas et al., 2013). Orlistat interferes with the absorption of several drugs and fat-soluble vitamins (Filippatos et al., 2008) and may cause acute kidney injury (Kwan et al., 2013).

1.1.7. Clinical use

Orlistat is indicated for the treatment of obesity (BMI ≥30 kg/m^2) or overweight (BMI 27–29.9 kg/m^2) with associated risk factors, in conjunction with a modestly fat-reduced diet. Attrition rates are high, mostly due to high cost and side effects (Padwal et al., 2007), as well as difficulty in complying with dietary recommendations (Svendsen et al., 2009) and the popularity of low carbohydrate diets. A study suggested that a low-carbohydrate ketogenic diet leads to similar weight loss as orlistat combined with a low fat diet (Yancy et al., 2010). Beneficial long-term effects of orlistat on cardiovascular disease parameters have not been demonstrated.

1.2. Amfepramone

Amfepramone (diethylpropion) is approved in the EU for treatment of obesity for short durations (4–6 weeks and no longer than 3 months) under various brand names (Anorex®, Dobesin®, Regenon® etc.). The drug is closely related to amphetamines and possesses some of the same CNS stimulant properties and abuse potential, and has been associated with serious cases of primary pulmonary hypertension. In 1999 the Committee for Proprietary Medicinal Products (CPMP) recommended a stop to the use of amfepramone for obesity treatment and a stop to the sale of this drug in EU countries. In the Scandinavian countries it is available only in Denmark, but its use cannot be recommended.

1.3. Liraglutide 3 mg (Saxenda®)

GLP-1 is an endogenous hormone released from L-cells in the small intestine in response to the presence of food (peptides and monoglycerates), and it acts both as an incretin that stimulates the postprandial release of insulin, and as a satiety hormone. It is cleared from the bloodstream within minutes, but injectable agonists have been developed that can be given once daily, or even only once weekly, and a number of such agents have been approved for the management of T2D (e.g. exenatide, liraglutide). GLP-1 agonists in dosages used for treatment of T2D have been found to produce a small weight loss (Wang et al., 2014). Liraglutide is used in the doses 1.2 and 1.8 mg daily for T2D (Victoza®), but higher dosages are required for a clinically relevant weight loss in obese patients (i.e. 3 mg).