Drug Saf (2014) ■: 1–15
DOI 10.1007/s40264-014-0210-7

REVIEW ARTICLE

Benefit-Risk Assessment ~~Of~~of Orlistat ~~In The~~in the Treatment ~~Of~~of Obesity

Priya Sumithran (✉) · Joseph Proietto

P. Sumithran (✉) · J. Proietto
~~University of Melbourne,~~ Department of Medicine (Austin ~~Health),~~Health), Heidelberg Repatriation ~~Hospital~~Hospital, University of Melbourne, Heidelberg, ~~Victoria~~VIC, 3081 Australia

Abstract Orlistat, an inhibitor of intestinal lipase, has been available for the treatment of obesity for nearly two decades. In conjunction with a hypocaloric diet, orlistat treatment results in a placebo-subtracted reduction in body weight of around 3 kg at ~~one year,~~1 year, and increases the likelihood of achieving clinically significant ~~(≥ 5%)~~(≥5 %) weight loss by around ~~20%.~~20 %. Orlistat-induced weight loss also confers modest improvements in systolic and diastolic blood pressure, ~~LDL~~low-density lipoprotein (LDL) cholesterol, glycemic parameters, and progression to diabetes in people with impaired glucose tolerance. Overall, it has a good safety profile, and serious adverse events (including reports of severe kidney and liver injury) are rare. However, a high rate of gastrointestinal side effects limits adherence to treatment.

Key Points

~~Orlistat inhibition of gastrointestinal lipase reduces the absorption of dietary fat by approximately 30%~~
In clinical trials, orlistat treatment in conjunction with a hypocaloric diet confers a modest additional weight loss of 3 kg at one year compared with placebo
Gastrointestinal side effects are commonly reported, but serious adverse events are rare

Introduction

Around the world, more than one third of adults are overweight, and more than ~~10%~~10 % are obese [1]. Excess weight is an independent risk factor for coronary artery disease, and is associated with an increased risk of cardiovascular risk factors including hypertension, dyslipidemia and type 2 ~~diabetes,~~diabetes mellitus (T2DM), as well as several other conditions such as osteoarthritis, non-alcoholic fatty liver disease, obstructive sleep apnoea, polycystic ovary ~~syndrome~~syndrome, and certain cancers [2]. Many of these risks are substantially reduced by intentional loss of ~~5–10%~~5–10 % of weight [3, 4]. The gastrointestinal lipase inhibitor orlistat has been available for the treatment of obesity since the late ~~1990 s.~~1990s. The purpose of this paper is to review the benefits and risks of orlistat, and its place in the management of obesity.

Literature ~~search methodology~~Search Methodology

A search of the MEDLINE database was performed in January 2014 using the term ~~"orlistat"~~'orlistat' and excluding articles not in English. The ~~U.S.~~US Food and Drug Administration (FDA) adverse event reporting system, European database of suspected

adverse drug reaction reports, and the Australian adverse drug reaction reporting system database were also searched for reports of adverse events in orlistat users. Articles returned were published between 1987 and 2013, and those reporting the use of orlistat for the treatment of obesity and related metabolic conditions ~~(eg~~(e.g., dyslipidemia), or reporting adverse events were reviewed. The reference lists of these articles were searched for additional relevant papers. As this manuscript relates to the risks and benefits of orlistat for the treatment of obesity, studies in which orlistat was used outside its approved therapeutic indication ~~(eg~~(e.g., for ~~binge-eating~~binge-eating disorder) were not reviewed.

Body ~~weight regulation, role~~Weight Regulation, Role of ~~pharmacotherapy~~Pharmacotherapy

Although most people can lose a substantial amount of weight through changes in diet and physical activity, the weight is usually regained over time [5]. Several circulating hormones play a role in appetite regulation, including the adipocyte hormone leptin, ghrelin, cholecystokinin (CCK), glucagon-like peptide 1 ~~(GLP-1)~~(GLP-1), and peptide YY (PYY) from the gastrointestinal tract, and insulin, ~~amylin~~amylin, and pancreatic polypeptide from the pancreas [6–13]. In the hypothalamus, signals from these peripheral hormones are integrated to regulate appetite and energy expenditure [14]. Diet-induced weight loss is accompanied by a number of compensatory changes, including reductions in circulating leptin and CCK, an increase in the orexigenic hormone ghrelin, an increase in subjective appetite and reduced energy expenditure, which collectively encourage weight regain [15, 16]. However, there are currently no non-surgical treatments available which counteract these physiological changes to assist people in maintaining weight loss. Studies involving the appetite-suppressing medications sibutramine and rimonabant (which have been withdrawn from the market due to adverse events [17, 18]) indicate that pharmacotherapy may be at least partially effective in facilitating maintenance of diet-induced weight loss [19, 20].

~~Orlistat—mode~~Orlistat—Mode of ~~action~~Action and ~~administration~~Administration

For dietary fats to be absorbed in the intestine, ingested triglyceride must be broken down by gastric and pancreatic lipases into absorbable free fatty acids and monoglycerides. Orlistat inactivates gastrointestinal lipase, thereby reducing the absorption of dietary fat [21]. It has minimal effect if dietary fat intake is very low (daily ~~intake < 45 g or < 20%~~intake < 45 g or < 20 % energy from fat), but otherwise, the percentage of dietary fat excreted with orlistat use increases in a dose-dependent manner, plateauing at around ~~30–35%~~30–35 % for dosages of ~~180–360 mg~~180–360 mg per day, compared with a normal fecal fat excretion of ~~5%~~5 % [22, 23].

When taken orally, orlistat is almost entirely excreted via the feces within ~~3–5 days~~3–5 days [24, 25]. There is minimal systemic absorption and no accumulation during at least ~~two years~~2 years of treatment [26].

Orlistat is indicated for the treatment of obesity ~~(BMI ≥ 30 kg/m~~(body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) in the presence of associated risk factors, in conjunction with a hypocaloric diet. It is available in most regions of the world, and is marketed as Xenical ® (Roche), in a ~~120 mg~~120-mg capsule which requires a prescription in most countries (an exception is Australia, where orlistat 120 mg became available from pharmacists without a prescription in 2004). A ~~60 mg~~60-mg capsule, marketed as Alli ~~(GlaxoSmithKline)~~® (GlaxoSmithKline), became available without a prescription in the ~~European Union~~EU and ~~United States~~US in 2007. The dosage of orlistat is ~~180 to 360 mg~~180–360 mg per day, in three divided doses during, or up to ~~one hour~~1 hour after each main meal. Patients should follow a ~~nutritionally balanced~~nutritionally balanced hypocaloric diet containing no more than ~~30%~~30 % calories from fat ~~(< 67 g~~(< 67 g fat per day for a ~~2000 kcal~~2,000 kcal diet), and the fat intake should be distributed evenly across each meal to ~~minimise~~minimize gastrointestinal adverse effects. If a meal does not contain fat, the dose of orlistat can be omitted. It is also advised that patients take a multivitamin supplement containing fat-soluble vitamins, administered at least ~~2 hours~~2 hours before or after administration of orlistat [27]. Orlistat is contraindicated in pregnancy and lactation, and in people with chronic malabsorption syndromes or cholestasis [27].

Benefits

In clinical studies, orlistat has been evaluated for the treatment of obesity, as well as several related conditions including dysglycemia, dyslipidemia, polycystic ovary syndrome, non-alcoholic steatohepatitis, and binge-eating disorder. This review will focus on ~~orlistat's~~the role of orlistat in obesity treatment, which is to date its only approved therapeutic indication.

Body ~~weight~~Weight

Numerous clinical studies have examined the efficacy and safety of orlistat for the treatment of obesity in conjunction with an energy-reduced diet, compared with placebo or an active comparator (usually sibutramine), and several meta-analyses have been undertaken. Two meta-analyses of randomized placebo-controlled trials conducted between 1997 and 2005 ~~with ≥ 12 months~~with ≥12 months follow-up [28, 29] included ~~12–16~~12–16 studies involving more than 10,000 adults, and were consistent in their conclusion that orlistat (usually at a dosage of 120 mg ~~tds)~~three times a day [tds]) induces a weight loss of around 3 kg in excess of placebo. In the Cochrane review undertaken by Padwal and ~~colleagues,~~colleagues [29], placebo-subtracted reductions in waist circumference of 2.1 cm ~~(95%~~(95 % CI ~~1.3 to 2.9, 9~~1.3–2.9, nine studies) and BMI of 1.1 kg/m^2 ~~(95%~~(95 % CI ~~0.7 to 1.4, 3~~0.7–1.4, three studies), and increases in the proportion of participants achieving ~~5% (21%~~5 % (21 % more than placebo, ~~90%~~90 % CI ~~18 to 24%,~~18–24, 14 studies) and ~~10%~~10 % weight loss ~~(12%~~(12 % more than placebo, ~~90%~~90 % CI ~~9 to 14%,~~9–14, 13 studies) with orlistat were also ~~reported [29].~~reported. Analyses restricted to include only people with ~~type 2 diabetes~~T2DM (5 studies) have found a slightly smaller placebo-subtracted weight reduction of ~~2.3 to 2.5 kg,~~2.3–2.5 kg, but the relative likelihood (compared with placebo) of orlistat users with diabetes achieving 5 and ~~10%~~10 % weight loss was not lower than in low-risk obese patients [29, 30].

Weight ~~loss maintenance~~Loss Maintenance

Weight maintenance after weight loss has been examined in several studies. In five 2-year ~~multicentre~~multicenter placebo-controlled studies, obese adults who were compliant with placebo administration during a 4-week lead-in period including a hypocaloric diet were then randomized to 52 weeks of treatment with orlistat (60 or 120 mg tds) or placebo along with a hypocaloric diet. At the end of the first year, the energy content of the diets were adjusted if required, to achieve weight maintenance rather than continuing weight loss. In participants randomized to receive orlistat 120 mg or placebo for ~~two years,~~2 years, greater proportions of patients maintained 5 and ~~10%~~10 % weight loss at the end of ~~two years~~2 years of treatment with orlistat 120 mg tds compared with placebo [26, 31–33]. In participants randomized to placebo treatment in the first year of the study, and re-randomized to receive either orlistat 120 mg tds or placebo in the second year, the initial weight loss of ~~6–9%~~6–9 % was maintained in those who subsequently received orlistat in the ~~2nd~~second year, whereas participants who received placebo in the ~~2nd~~second year regained around ~~30–40%~~30–40 % of initial weight loss [26, 34]. The potential of orlistat to assist with weight loss maintenance has also been examined in large ~~multicentre~~multicenter studies in which weight loss was induced by a hypocaloric or very-low-energy diet (VLED) and lifestyle modification program, followed by introduction of orlistat or placebo in participants who achieved the target initial weight loss [35, 36]. In the study by Hill and colleagues [35], ~~1313~~1,313 obese adults without diabetes undertook a ~~6 month~~6-month hypoenergetic diet ~~(4180 kJ/d deficit)/behavioural~~(4,180 kJ/day deficit)/behavioral modification/exercise, aiming for ~~0.5–1.0 kg~~0.5–1.0 kg per week. Those who ~~lost ≥ 8%~~lost ≥8 % of initial weight ~~(56%~~(56 % of starting participants) were randomly assigned to receive placebo, orlistat 30, 60 or 120 mg tds for 1 year. The mean initial weight loss was ~~10%~~10 % in all groups. After 12 months of pharmacotherapy, mean weight loss was greater, and weight regain less in those receiving orlistat 120 mg than placebo (weight loss 8.2 ~~vs. 6.4%~~vs 6.4 % compared with baseline; regain 32 ~~vs. 56%, p < 0.001).~~vs 56 %, $p < 0.001$). Nearly one quarter of participants receiving orlistat 120 mg did not regain, or continued to lose weight during the treatment period ~~(23.5% vs. 16.3%~~(23.5 vs 16.3 % of placebo-treated participants). In the study by Richelsen and co-workers [36], 383 adults with abdominal obesity ~~and ≥ 1~~and one or more of the following: impaired fasting glucose, diet-controlled ~~type 2 diabetes~~T2DM, or ~~dyslipidemia~~dyslipidemia, underwent an 8-week VLED. Those who ~~lost ≥ 5%~~lost ≥5 % of initial weight ~~(81%)~~(81 %) were randomized to orlistat 120 mg tds or placebo for 3 years, along with a 600 kcal deficit diet and exercise program. Mean weight loss during the VLED was 14 kg ~~(13%).~~(13 %). After 3 years, mean weight loss was greater, and regain less in participants who received orlistat compared with placebo (weight loss 8.3 ~~vs. 6.4%;~~vs 6.4 %; regain 32 ~~vs. 48%).~~vs 48 %). At 3 years, improvements in glycemia, lipids, and blood pressure were not different between groups, but significantly more patients in the placebo group developed T2DM (11 ~~vs. 5%, p = 0.04).~~vs 5 %, $p = 0.04$).

Blood ~~pressure~~Pressure

Two meta-analyses evaluating orlistat in 10 and 12 randomized clinical studies with ~~4–48 months~~4–48 months' follow-up ~~(3~~(three studies were included in both meta-analyses) conducted in a total of ~~5634–7718~~5,634–7,718 participants with and without risk factors for cardiovascular disease were consistent in their findings that participants using orlistat had greater reductions in systolic

and diastolic blood pressure of 1.9 and ~~1.5 mmHg respectively~~1.5 mmHg, respectively, than those taking placebo [37, 38]. Orlistat-treated participants lost ~~2.4 2.8 kg~~2.4–2.8 kg more than placebo-treated patients. In one of these meta-analyses, the beneficial effect of orlistat on blood pressure was not seen in the ~~3~~three studies examining only patients with diabetes [37]. In another more recent meta-analysis examining ~~31323~~3,132 people with hypertension from ~~4~~four randomized, double-blinded, placebo-controlled studies, participants using orlistat had ~~a~~ placebo-subtracted reductions in weight of 3.7 kg, systolic and diastolic blood pressures of ~~2.46 (95%~~2.46 mmHg (95 % CI ~~4.01, 0.90)~~4.01–0.90) and 1.92 mmHg ~~(2.99, 0.85)~~(95 % CI 2.99–0.85), respectively [39].

Lipids

Randomized, placebo-controlled studies have consistently found orlistat to have a beneficial effect on total and ~~LDL~~low-density lipoprotein (LDL) cholesterol. In meta-analyses of studies in people with and without dyslipidemia and ~~type 2 diabetes,~~T2DM, modest placebo-subtracted reductions in total ~~(0.27 0.38 mmol/L)~~(0.27–0.38 mmol/L) and LDL ~~(0.21 0.27 mmol/L)~~(0.21–0.27 mmol/L) cholesterol were seen in orlistat-treated patients [29, 38, 40]. An earlier meta-analysis of 15 studies in 10,995 people with and without obesity-related comorbidities found that a significant reduction in total cholesterol in orlistat-treated patients correlated with mean weight reduction ~~(r = 0.48; p < 0.05),~~($r = 0.48$; $p < 0.05$), but when a multiple linear regression analysis was performed adjusting for weight loss, the ~~%~~percentage reduction in total cholesterol correlated with orlistat treatment, suggesting a cholesterol-lowering effect of orlistat independent of weight loss [41]. In one study of 294 non-diabetic overweight or obese participants with untreated dyslipidemia included in this meta-analysis [42], patients randomly assigned to receive orlistat 120 mg tds for 24 weeks had placebo-subtracted reductions in total and LDL cholesterol of 8.4 and ~~10.0%~~10.0 %, respectively. In a subsequent 24-week open-label orlistat extension phase, mean ~~%~~percentage change in LDL was not related to weight change, and in all categories of ~~%~~percentage weight loss, the reduction in LDL remained significantly greater in patients treated with orlistat compared with placebo [42]. This is supported by another study in which 47 premenopausal obese non-diabetic women with previous gestational diabetes were randomized to receive orlistat 120 mg tds or placebo in addition to a hypocaloric diet, to achieve ~~8%~~8 % weight loss over ~~18 20 weeks~~18–20 weeks [43]. Reductions in weight, ~~%~~percentage body ~~fat~~fat, and fasting insulin were not different between groups, but LDL fell only in orlistat-treated participants ~~(by11%,~~(by 11 %, or 0.48 mmol/L, ~~p < 0.01).~~$p < 0.01$). Markers of endothelial function improved only in patients receiving orlistat, and correlated with the change in LDL [43]. This beneficial effect of orlistat on LDL beyond that expected with weight loss is likely to relate to the fact that orlistat reduces the absorption not only of dietary fat by ~~30%,~~30 %, but also of dietary cholesterol by ~~23%~~23 % [44]. Small studies have shown that when administered with a high-fat meal, orlistat reduces post-prandial lipemia [45, 46], and in a randomized study of 86 overweight non-diabetic adults with untreated hypercholesterolemia prescribed a low-fat hypocaloric diet, patients receiving orlistat for 6 months had equivalent reductions in total cholesterol, triglycerides, ~~LDL~~LDL, and small dense LDL particles compared with those treated with the lipid-lowering agent ezetimibe [47].

Although it has been estimated that every 1 kg of weight lost is associated with a reduction in triglycerides of 0.015 mmol/L [48], and orlistat treatment usually results in greater weight loss than placebo, a beneficial effect of orlistat on triglycerides has only variably been reported [29, 38, 40, 41]. In a study in which weight loss was equivalent in the orlistat- and placebo-treated participants, a significant reduction in triglycerides was seen only in the placebo group [43]. In general, no beneficial effect of orlistat on ~~HDL~~high-density lipoprotein (HDL) has been found [38, 41].

Glucose

Orlistat treatment is associated with modest improvements in glycemia in people with and without ~~type 2 diabetes.~~T2DM. A placebo-subtracted reduction in fasting glucose of 0.12 mmol/L ~~(95%~~(95 % CI ~~0.20 to 0.04)~~0.20–0.04) has been found in a meta-analysis of predominantly non-diabetic participants, and in people with diabetes, reductions in fasting glucose of 1.0 mmol/L ~~(95%~~(95 % CI ~~0.6 to 1.5)~~0.6–1.5) and HbA1c of ~~0.4% (95%~~0.4 % (95 % CI ~~0.2 to 0.6%)~~0.2–0.6 %) greater than placebo have been reported [29, 38]. Although some of this benefit is undoubtedly due to greater weight loss in orlistat-treated participants, a retrospective pooled analysis of ~~7~~seven trials in overweight or obese people with T2DM (total ~~n = 2250)~~$n = 2{,}250$) randomized to orlistat or placebo treatment found significantly greater improvements in fasting glucose and HbA1c in those taking orlistat compared with placebo even in the ~~10%~~10 % of orlistat-treated and ~~20%~~20 % of placebo-treated patients who ~~lost ≤ 1%~~lost ≤1 % of their starting weight after 1 year of treatment [49]. Suggested possible mechanisms include the reduced percentage of absorbed calories from fat, stimulation of GLP-1 release in the small intestine related to incomplete fat digestion,

reduction in post-prandial ~~NEFA levels~~non-esterified fatty acid (NEFA) levels, and reduction in visceral adipose tissue with orlistat [49].

Several randomized placebo-controlled trials ~~(n = 220–550)~~(n = 220–550) have shown that in people with ~~type 2 diabetes~~T2DM treated with oral hypoglycemic agents or insulin, the addition of orlistat is safe if blood glucose levels are monitored [50–54]. In these studies, the dosage of diabetes medications was adjusted depending on glycemic control following commencement of orlistat, and ~~although~~although, in most [50, 52–54], more participants taking orlistat compared with placebo required a reduction in the dosage of their diabetes medications, dose reductions tended to be small, and it was also fairly common for participants in both groups to require an escalation in their diabetes treatment. For example, in the largest study [53], mean reductions in daily insulin dosage for ~~orlistat~~orlistat- and placebo-treated patients were 8.1 ± 1.5 ~~vs.~~vs 1.6 ± 1.7 units (baseline dosage 71 ~~vs.~~vs 84 units). For sulfonylureas, the mean dose reduced by 7.8 ± 6.2 mg in the orlistat group, and increased by 1.3 ± 4.1 mg in the placebo group (baseline doses 61 and ~~68 mg~~68 mg, respectively). Changes in metformin dose were not significantly different between groups, ~~41%~~41 % of orlistat and ~~31%~~31 % of placebo-treated patients reduced or discontinued at least one medication, and 15 ~~vs. 32%~~vs 32 % had increased requirements for a diabetes medication. A greater proportion of orlistat-treated patients (16.9 ~~vs. 9.7%)~~vs 9.7 %) experienced an episode of hypoglycemia, of whom ~~3~~three (orlistat) and ~~1~~one (placebo) required medical intervention. In ~~2~~two studies [50, 52], rates of hypoglycemia were not mentioned, and in one [51~~]~~], rates of hypoglycemia (2/68 orlistat-treated and 4/60 placebo-treated patients) and medication changes were similar between groups.

Two studies have examined the effect of orlistat on progression to T2DM [55, 56]. In the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study [56], ~~3305~~3,305 obese participants with normal ~~(79%)~~(79 %) or impaired ~~(21%)~~ glucose tolerance (IGT) (21 %) were prospectively randomized to 4 years of treatment with orlistat 120 mg tds or placebo in addition to an energy-reduced diet and exercise advice. Both groups regained some of the initial weight loss between years 1 and 4, but end-of-study weight loss was significantly greater with orlistat (5.8 ~~vs.~~vs 3.0 kg, ~~p < 0.001).~~p < 0.001). Cumulative incidence of T2DM was significantly lower in the orlistat than the placebo group (overall 6.2 ~~vs. 9.0%, p = 0.003;~~vs 9.0 %, p = 0.003; baseline IGT 18.8 ~~vs. 28.8%, p = 0.002),~~vs 28.8 %, p = 0.002), indicating that in people with IGT who undertake a lifestyle intervention, addition of orlistat for 4 years would prevent the development of diabetes in one person for every ~~10~~ten treated. The rate of progression to T2DM in people with baseline normal glucose tolerance was very low ~~(< 3%~~(< 3 % over 4 years), and no difference was detected between orlistat and placebo groups. Attrition rates were ~~48%~~48 % for the orlistat and ~~66%~~66 % for the placebo group by the end of the study [56]. Heymsfield and colleagues [55] conducted a retrospective pooled analysis of a subgroup of patients assigned to receive ~~two years~~2 years of treatment with orlistat 120 mg tds or placebo from ~~3 multicentre RCTs [55].~~ three multicenter randomized controlled trials (RCTs). At ~~randomisation,~~randomization, the diagnostic criteria for T2DM and IGT were met by ~~5.3%~~5.3 and ~~18.7%~~18.7 % of orlistat-treated and ~~4.4%~~4.4 and ~~16.8%~~16.8 % of placebo-treated participants. Around two thirds of participants in each group completed the study. Among people with baseline normal glucose tolerance, progression to IGT (6.6 ~~vs. 10.8%)~~vs 10.8 %) or diabetes (0 ~~vs. 1.2%)~~vs 1.2 %) by the end of treatment had occurred in significantly fewer orlistat- than placebo-treated patients, and the effect of orlistat on 2-hour ~~OGTT~~oral glucose tolerance test (OGTT) glucose remained significant after adjusting for the difference in weight loss between orlistat and placebo groups. In people with IGT at ~~randomisation, 3.0%~~randomization, 3.0 % in the orlistat and ~~7.6%~~7.6 % in the placebo group progressed to diabetes, while ~~71.6%~~71.6 % of orlistat and ~~49.1%~~49.1 % of placebo participants reverted to normal glucose tolerance [55]. An analysis which combined data from these two studies found a hazard ratio of 0.44 ~~(95%~~(95 % CI ~~0.28 to 0.69)~~0.28–0.69) for the development of T2DM in orlistat-treated participants with IGT [57].

Use in ~~adolescents~~Adolescents

In obese ~~adolescents ≥ 12 years~~adolescents ≥12 years old, orlistat treatment is approved by the FDA, and is suggested in the UK NICE guidelines for the management of obesity if physical or severe psychological comorbidities are present [58]. A meta-analysis of ~~2~~two RCTs comparing orlistat 120 mg tds and placebo for ~~6–12 months~~6–12 months in obese ~~10–18yo (n = 573)~~10- to 18-year-olds (n = 573) found a significant placebo-subtracted reduction in BMI of 0.83 ~~(95%~~(95 % CI ~~0.47, 1.19),~~0.47–1.19), equating to a reduction of 0.24 BMI SD, or a weight loss of 2.3 kg [59]. The analysis was dominated by a study conducted in several US and Canadian sites involving 539 adolescents ~~(12–16yo,~~(aged 12–16 years, BMI ≥ 2U above ~~95th~~95th percentile, ~~25%~~25 % met ~~ATP~~Adult Treatment Panel [ATP] III criteria for metabolic syndrome) who underwent a 2-week placebo lead-in period, followed by 52 weeks of orlistat 120 mg tds or placebo in conjunction with a ~~40%~~40 % energy-reduced diet, ~~exercise~~exercise, and ~~behavioural~~behavioral therapy [60]. Attrition rate ~~(64–65%)~~(64–65 %) was not different between treatment groups. Orlistat-treated adolescents had greater mean changes in BMI (reduction of 0.55 ~~vs.~~vs gain of 0.31 kg/m^2, ~~p = 0.001),~~p = 0.001), waist cir-

cumference (reduction of 1.33 ~~vs.~~vs gain of 0.12 cm, ~~p < 0.05),~~$p < 0.05$), fat mass ~~(2401 vs.~~(2,401 vs 380 g loss, ~~p = 0.03)~~$p = 0.03$), and diastolic blood pressure (reduction of 0.51 ~~vs.~~vs gain of 1.30 mmHg, ~~p = 0.04)~~$p = 0.04$) than placebo. Changes in lipids, ~~glucose~~glucose, and systolic blood pressure were not significantly different between groups. All participants received a daily multivitamin, and there were no adverse changes in vitamins A, D, E or beta-carotene. Gastrointestinal adverse events were more common with orlistat treatment, affecting up to ~~50%~~50 % of participants, but leading to discontinuation in only ~~2%.~~2 %. There was no significant difference between groups in non-gastrointestinal adverse events.

Orlistat 60 mg tds ~~dose~~Dose

The dose of 60 mg tds available without prescription appears to have around ~~80%~~80 % of the efficacy of the 120 mg tds dose of orlistat, with no significant difference in the incidence of adverse events [61]. In a randomized, ~~double-blinded~~double-blinded, placebo-controlled study conducted in 131 overweight or mildly obese adults (BMI ~~25-35 kg/m~~25–35 kg/m^2), orlistat 60 mg tds along with a ~~500-kcal~~500-kcal reduced diet for 24 weeks induced statistically significant reductions in mean weight (6.6 ~~vs. 4.3%~~vs 4.3 % placebo), fat mass (13.6 ~~vs. 8.4%),~~vs 8.4 %), visceral adipose tissue ~~(15.7% vs. 9.4%),~~(15.7 vs 9.4 %), and fasting glucose (0.23 ~~vs.~~vs 0.11 mmol/L). A greater proportion of participants receiving orlistat compared with placebo ~~lost ≥ 5%~~lost ≥5 % of starting weight (57 ~~vs. 36%)~~vs 36 %) [62]. In another study in which participants received orlistat 60 mg or 120 mg tds or placebo, placebo-subtracted changes in weight loss, lipids, proportions of patients achieving 5 and ~~10%~~10 % weight loss, and adverse events were similar in the orlistat ~~60~~60-mg and ~~120-mg groups, however~~120-mg groups; however, the study was not powered to detect differences between the two dosages [33]. In the study by Hill and colleagues [35], in which participants ~~lost ≥ 8%~~lost ≥8 % of their starting weight over 6 months with a hypocaloric diet followed by orlistat 30, 60, 120 mg ~~tds~~tds, or placebo for 12 months, weight regain in the orlistat ~~60-mg~~60-mg group was not significantly different from placebo (53.3 ~~vs. 56.0%).~~vs 56.0 %). Fewer people in orlistat ~~60-mg (18.7%)~~60- (18.7 %) and ~~120-mg~~120-mg groups ~~(12.3%) re-gained > 75%~~(12.3 %) regained >75 % initial loss compared with orlistat 30 mg ~~(29.0%)~~(29.0 %) and placebo ~~(32.1%, p < 0.05).~~(32.1 %, $p < 0.05$). Significant reductions in total and LDL cholesterol were seen in the orlistat ~~60~~60- and ~~120-mg~~120-mg tds-treated patients compared with baseline and placebo [35]. In the study by Davidson and colleagues [31], patients who lost weight using orlistat 120 mg in the first year regained less weight when orlistat 120 mg tds compared with 60 mg tds was used in the second year (35 ~~vs. 51%, p < 0.001).~~vs 51 %, $p < 0.001$).

Treatment ~~adherence~~Adherence

It should be noted that clinical trials will generally overestimate the benefits of orlistat, as adherence to the medication and associated lifestyle prescription are likely to be higher than in a real-world setting. Furthermore, the majority of studies have included a ~~2-4-week~~2- to 4-week initial lead-in period, during which compliance with medication (placebo) is a requirement in order to continue into the ~~randomised~~randomized phase of the study. For example, in a meta-analysis of attrition from 16 randomized controlled orlistat trials of at least ~~one-year's~~1 year's duration, the overwhelming majority of which were pharmaceutical company-funded, total attrition at 1 year was reported to be lower with orlistat treatment than placebo (29 ~~vs. 35%, p < 0.05)~~vs 35 %, $p < 0.05$) [63]. Attrition from the orlistat group in studies without a lead-in period was ~~40%~~40 % [63]. In ~~4 multicentre~~four multicenter studies which included a 4-week placebo lead-in period ~~(≥ 75%~~(≥75 % compliance required) followed by 2 years of treatment with orlistat or ~~placebo~~placebo, attrition at 2 years was ~~37-55%~~37–55 % [26, 31–33]. In contrast, a population-based report without external funding of 17,000 users of orlistat found persistence with treatment ~~of < 50%~~of <50 % beyond the first prescription, ~~6%~~6 % at 1 year and ~~2%~~2 % at 2 years [64]. In an anonymous postal survey of prescribers of ~~1000~~1,000 randomly selected prescriptions for orlistat (789 respondents) in Sweden, more than half of patients either ~~lost < 5%~~lost <5 % or gained weight after ~~three months~~3 months of treatment [65].

Risks

Gastrointestinal ~~adverse events~~Adverse Events

In general, orlistat is a safe medication, and the reported frequency of overall adverse events (AEs) in clinical trials is similar to that in placebo-treated participants. The exception to this is gastrointestinal disturbances, which are by far the most commonly reported AEs among orlistat users, and include oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, abdominal

~~pain~~pain, and fecal incontinence. Their incidence increases with increasing dietary fat intake [22], and may be reduced by addition of psyllium fibre [66]. The frequency of gastrointestinal AEs also seems to improve over time. For example, in the XENDOS study [56], the proportion of patients with at least one gastrointestinal AE in the orlistat ~~vs.~~versus placebo group was 91 ~~vs. 65%~~versus 65 % at ~~one year,~~1 year, and 36 ~~vs. 23%~~versus 23 % after ~~four years~~4 years of treatment. For ~~orlistat~~orlistat- and placebo-treated participants respectively, withdrawals due to AEs (primarily gastrointestinal) or laboratory abnormalities occurred in ~~8%~~8 and ~~4%,~~4 %, serious AEs in 15 and ~~13%,~~13 %, and serious gastrointestinal AEs in ~~2%~~2 % of both groups. No deaths were attributed to the study medication.

In the meta-analysis of 16 studies by Padwal and colleagues [29~~], > 80%~~], > 80 % of orlistat-treated patients experienced at least one gastrointestinal AE, an absolute frequency of ~~24%~~24 % more than placebo-treated patients. The most commonly reported events (frequency of ~~15–30%~~15–30 % each) were fatty/oily stool, fecal urgency and oily spotting. In another meta-analysis of 29 studies of at least 6 months' duration [67], the relative risks and numbers needed to harm ~~(NNH)~~ for various gastrointestinal AEs were calculated as 3.40 and 1.5 for ~~diarrhoea,~~diarrhea, 3.10 and 6.5 for flatulence, and 1.48 and 25.8 for bloating, abdominal pain and dyspepsia. No increase in risk was found for headache, nausea/vomiting, gallbladder problems or mood changes [67].

The frequency of adverse events appears to be similar with the ~~60-mg,~~60-mg, compared ~~to 120-mg~~with the 120-mg dose: in the study by Smith and colleagues [62], treatment-related gastrointestinal AEs were judged to have occurred in 67 and ~~27%~~27 % of the orlistat and placebo ~~group~~groups, respectively, and ~~5%~~5 % of orlistat-treated participants (compared with 0 in the placebo group) discontinued due to AEs. There was no difference in the rate of non-gastrointestinal AEs.

~~Fat-soluble vitamins~~Fat-Soluble Vitamins

Because it reduces the absorption of dietary fat, orlistat use incurs a risk of reducing the absorption of fat-soluble vitamins, and people using orlistat are recommended to take a multivitamin supplement containing fat-soluble vitamins [27]. Several studies in the meta-analysis by Padwal and colleagues [29] reported reductions in vitamins A, D, ~~E~~E, and beta-carotene, but no study reported clinically significant vitamin deficiency, and patients were usually advised to take a daily ~~multivitamin [29].~~multivitamin. No change in B12 or folate levels ~~were~~was found after ~~three months~~3 months of orlistat treatment in another study [68].

Medication ~~interactions~~Interactions

Clinically relevant interactions occur between orlistat and a number of medications. Most notably, orlistat interferes with the absorption of some highly lipophilic medications, including cyclosporine, amiodarone, lamotrigine, efavirenz, and prodrugs whose hydrolysis is catalysed by lipases, such as dalcetrapib (now withdrawn from development) [69–73]. It is recommended that cyclosporine be taken at least ~~3 hours~~3 hours before or after orlistat, and that cyclosporine levels are monitored more frequently in people taking both medications [27~~],~~]. Closer monitoring of anticonvulsant drug levels may be required during co-administration with orlistat [71], and prescribers and patients should be aware of the possibility of a reduction in therapeutic effect of anticonvulsant medications and amiodarone [25]. There is a case report of a possible interaction with orlistat reducing the bioavailability of exogenous thyroxine [74], and in vitro data suggesting that orlistat inhibition of the activity of carboxylesterase-2, an enzyme involved in the metabolism and activation of the anticancer prodrug PPD, reduces the cytotoxic efficacy of PPD [75]. It is recommended that people treated with both thyroxine and orlistat administer the medications at least ~~4 hours~~4 hours apart, and be monitored for changes in thyroid function tests [27]. Orlistat treatment had no demonstrable effect on the pharmacokinetics of a single ~~30-mg~~30-mg dose of ~~warfarin, however~~warfarin; however, there is a case report of an increased ~~INR~~international normalized ratio (INR) in a patient on a previously stable dose of warfarin after commencement of orlistat treatment, and a plausible mechanism of interference with vitamin K intake or absorption [76, 77~~], therefore~~]; therefore, it is recommended that if orlistat is added in people taking a chronic stable dose of warfarin, changes in coagulation parameters are monitored closely [25, 27].

Orlistat appears not to interact in a clinically significant manner with the pharmacokinetics of glibenclamide (glyburide), metformin, frusemide, digoxin, nifedipine, captopril, losartan, atenolol, atorvastatin, simvastatin, combined oral contraceptive pills, ethanol, phenytoin, amitriptyline, fluoxetine, phentermine or psychotropic medications [70, 78–85].

Kidney ~~injury~~Injury

Since 2006, several case reports have appeared of acute kidney injury (AKI) in users of orlistat, almost all with other predisposing conditions such as diabetes [86–90]. The proposed mechanism is that unabsorbed dietary fat binds calcium in the gut lumen, thereby competitively inhibiting calcium binding of oxalate, an excess amount of which is then absorbed and deposited in the renal parenchyma [87]. In several of the reports, oxalate crystal deposition was found on renal biopsy [86–89], and increased urinary oxalate has been demonstrated in animals and humans taking orlistat [91, 92]. A 2011 analysis of a Canadian health insurance database identified 953 users of orlistat, of whom ~~99%~~99 % had medication-requiring diabetes and ~~78%~~78 % had hypertension [93]. In the year preceding orlistat prescription, ~~5~~five experienced AKI (the etiology of which could not be determined), compared with 18 ~~(p = 0.01)~~($p = 0.01$) in the year following commencement. A separate report documented no change in mean ~~eGFR~~estimated glomerular filtration rate (eGFR) over 12 months in 33 patients with stage ~~3–4 CKD~~3–4 chronic kidney disease treated with orlistat ~~for > 6 months,~~for > 6 months, although in 6 of the 33 ~~(18%),~~(18 %), eGFR fell ~~by > 10 ml/min~~ by > 10 mL/min during the 12 months following orlistat commencement [94]. In 2012, the FDA approved a safety label change for orlistat warning that some patients may develop increased levels of urinary oxalate, and that people at risk for renal insufficiency should have their renal function monitored.

Liver ~~injury~~Injury

In 2009, the FDA issued an early communication about an ongoing safety review of a possible link between orlistat and liver injury after ~~analysing~~analyzing 32 reports of serious liver injury, including ~~6~~six of liver failure, submitted to the FDA's adverse event reporting system between 1999 and 2008 [95]. The completed safety review identified 13 reports worldwide of severe liver injury (one of which related to the ~~60 mg~~60-mg dosage), including ~~2~~two deaths and ~~3~~three patients requiring liver ~~transplantation, and~~transplantation. This resulted in revised ~~labelling~~labeling for orlistat to include new safety information about cases of severe liver injury, although the FDA noted that (i) a causal relationship between orlistat and liver injury had not been ~~established, that~~established; (ii) in some of the 13 patients, other factors may have predisposed them to the development of liver ~~injury,~~injury; and ~~that~~(iii) an estimated 40 million people worldwide had used orlistat [96]. A population-based case series examining the electronic general practice records of 94,695 UK residents who had received a prescription for orlistat between 1999 and 2011 found a ~~1.5~~1.5- to 2-fold increase in risk of liver injury during the 90 days before, as well as the first 30 days after, commencement of orlistat treatment, but not from day 30 onwards, suggesting that the start of treatment coincided with a period of increased risk, but not a causal link with liver injury [97]. In this report, ~~99%~~99 % of events were of elevated ~~LFTs~~liver function tests or jaundice, with one case of hepatitis and no liver failure or necrosis. It is estimated that orlistat has been used by over 53 million people worldwide [98]. From 1997 to 2011, 21 cases worldwide were reported of severe liver toxicity in which orlistat 120 mg was considered a possible cause, and there were ~~9~~nine reports between 2007 and 2011 of liver failure in people using orlistat 60 mg [98]. In 2012, the Committee for Medicinal Products for Human Use (CHMP) of the ~~EMA~~European Medicines Agency (EMA) reviewed the available ~~data~~data, including post-marketing surveillance, data from the studies supporting marketing ~~authorisations,~~authorizations, population-based studies in the published literature, and data requested from the companies which market orlistat, and concluded that (i) there was no strong evidence that orlistat increased the risk of severe liver ~~injury,~~injury; (ii) the rate of severe liver reactions was lower than the expected background rate in the population of ~~users,~~users; (iii) other factors increased the risk of liver injury in the majority of ~~cases, that~~cases; (iv) there was no known mechanism by which it was expected to cause liver ~~disorders,~~disorders; but (v) there were very rare cases of serious liver injury for which orlistat could not be excluded as a possible cause. The CHMP considered that the benefits of orlistat continued to outweigh its risks, but that the product information for orlistat 60 mg should be updated to include ~~"hepatitis~~'hepatitis that may be ~~serious"~~serious' as a possible side effect (already contained in the product information for orlistat 120 mg) [98].

Other

Numerous case reports have been published documenting the occurrence of various adverse events (many with other predisposing factors) in people using orlistat, such as skin reactions ~~(> 180~~(> 180 reports including lichenoid drug eruptions, cutaneous leukocytoclastic vasculitis, oral aphthous ulcers), acute pancreatitis ~~(> 99~~(> 99 reports to FDA), gastro-oesophageal reflux, diabetic ketoacidosis in a person with T1DM, exacerbation of major depression in a person with bipolar disorder, ~~hypertension~~hypertension, and myopathy [99–109]. The Australian Therapeutic Goods Administration (TGA) database of adverse

events received 188 reports in users of orlistat between Jan 1998 and Nov 2013 [110]. The majority were gastrointestinal events, along with several reports of musculoskeletal problems such as arthralgia and myalgia, neurological disorders including headache and dizziness, 26 psychiatric reports (including depression, anxiety and psychosis), ~~2~~two reports of pancreatitis, and single case reports of arrhythmias and hematological disorders [110]. In the last 2 years, the FDA has approved updates to the ~~la-belling~~labeling for orlistat to include the adverse events of convulsions in people treated concomitantly with orlistat and anti-epileptic drugs, and lower gastrointestinal bleeding [27].

Effect on ~~gastrointestinal hormones~~Gastrointestinal Hormones

By reducing the absorption of dietary fat, orlistat may affect the release of gastrointestinal hormones in response to nutrient intake, thereby potentially affecting appetite. For example, the release of CCK, a hormone involved in satiation, gallbladder motility, and inhibition of gastric emptying, is largely stimulated by intraduodenal lipolysis of dietary fat to fatty acids [111]. Some studies have found reduced meal-stimulated release of CCK, ~~PYY~~PYY, and GLP-1, inhibition of gallbladder contraction, accelerated gastric emptying, reduced lipid-induced suppression of ghrelin, and increased appetite and energy intake after orlistat treatment [112–119].

However, other studies have found no effect of orlistat on CCK release, gallbladder motility, gastric emptying, appetite or eating ~~behaviour~~behavior [120–125], and given that orlistat is generally associated with improved weight outcomes compared with placebo, it seems unlikely that any alteration in gut hormones leads to clinically significant hyperphagia in the majority of patients.

Summary and ~~conclusions~~Conclusions

A summary of the benefits and risks of orlistat treatment is presented in Table 1. In conjunction with a hypocaloric diet, orlistat treatment results in modest reductions in body weight and waist circumference in obese people with and without complications related to excess weight, and increases the likelihood of achieving clinically significant ~~(≥ 5%)~~(≥5 %) weight loss. Orlistat-induced weight loss also brings about modest improvements in cardiovascular risk factors including blood pressure, LDL cholesterol, glycemia and progression to diabetes in those at high risk. Overall, it is a safe treatment and serious adverse events, such as severe acute kidney or liver injury, are rare. However, significant clinical benefits are likely to occur in only a minority of patients, as adherence to treatment is very poor outside the clinical trial setting, likely in part due to a high rate of disagreeable gastrointestinal side effects. Furthermore, although weight maintenance after weight loss is improved compared with placebo, weight regain remains problematic, as orlistat does not counteract the compensatory physiological adaptations to weight loss which encourage regain.

In many countries, orlistat is the only medication available for long-term use in obesity treatment. In the US, two other agents have become available in recent years: lorcaserin ~~(Belviq,~~(Belviq®, a selective serotonin 5HT-2c receptor agonist), and the combination of phentermine plus topiramate ~~(Qsymia).~~(Qsymia®). Although they have not been compared directly in head-to-head studies, ~~one year~~1-year placebo-subtracted weight loss ~~(≈ 3%)~~(≈3 %) and proportions of patients achieving ~~5%~~5 % weight loss with orlistat seem comparable to that of lorcaserin, and lower than that achieved with the highest dose of phentermine/topiramate (weight ~~loss ≈ 9%)~~loss ≈9 %) [126~~], and unlike~~]. Unlike orlistat, both newer agents have the advantage of reducing hunger. However, adverse events associated with these agents are potentially more worrisome than those associated with orlistat. These include teratogenicity and increase in heart rate with phentermine/topiramate, serotonin or neuroleptic malignant syndrome-like reactions (if co-administered with serotonergic or antidopaminergic medications) and possible valvular heart disease with lorcaserin, and mood and cognitive changes with both agents. ~~Therefore~~Therefore, in countries where these alternative medications are an option for long-term weight management, the risks and benefits of each treatment must be weighed ~~for~~up on an individual basis, and orlistat may be ~~favoured~~favored in patients with cardiovascular disease or mood disorders.

It is worth noting that although orlistat treatment lowers weight and cardiovascular risk factors, no study has demonstrated a reduction in cardiovascular events or mortality with orlistat (or any weight loss medication).

Orlistat inhibition of gastrointestinal lipase reduces the absorption of dietary fat by approximately 30 %.
In clinical trials, orlistat treatment in conjunction with a hypocaloric diet confers a modest additional weight loss of 3 kg at 1 year compared with placebo.
Gastrointestinal side effects are commonly reported, but serious adverse events are rare.

~~Acknowledgements~~**Acknowledgments** No sources of funding were used to assist in the preparation of this manuscript. Priya Sumithran and Joseph Proietto have no conflicts of interest that are directly relevant to the content of this review.

References

1. Obesity and overweight. World Health ~~Organisation.~~Organisation. 2010. http://www.who.int/mediacentre/factsheets/fs311/en/index.html.
2. National Health and Medical Research Council. Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults. 2013.
3. Williamson D, Pamuk E, Thun M, et al. Prospective study of intentional weight loss and mortality in never-smoking overweight US white women aged ~~40–64 years.~~40–64 years. Am J Epidemiol. 1995;141:1128–41.
4. Jung RT. Obesity as a disease. Br Med Bull. 1997;53:307–21.
5. Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr. 2014;99:14–23.
6. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372:425–32.
7. Wren AM, Seal LJ, Cohen MA, et al. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab. 2001;86:5992–5.
8. Moran TH, Kinzig KP. Gastrointestinal satiety signals II. Cholecystokinin. Am J Physiol Gastrointest Liver Physiol. 2004;286:G183–8.
9. Gutzwiller JP, Goke B, Drewe J, et al. Glucagon-like peptide-1: a potent regulator of food intake in humans. Gut. 1999;44:81–6.
10. Batterham RL, Cowley MA, Small CJ, et al. Gut hormone PYY[3-36] physiologically inhibits food intake. Nature. 2002;418:650–4.
11. Rezek M. The role of insulin in the glucostatic control of food intake. Can J Physiol Pharmacol. 1976;54:650–65.
12. Morley JE, Flood JF. Amylin decreases food intake in mice. Peptides. 1991;12:865–9.
13. Batterham RL, le Roux CW, Cohen MA, et al. Pancreatic polypeptide reduces appetite and food intake in humans. J Clin Endocrinol Metab. 2003;88:3989–92.
14. Schwartz MW, Woods SC, Porte D Jr, et al. Central nervous system control of food intake. Nature. 2000;404:661–71.
15. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. ~~New~~N Engl J Med. 2011;365:1597–604.
16. Rosenbaum M, Hirsch J, Gallagher DA, et al. Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. Am J Clin Nutr. 2008;88:906–12.
17. US Food and Drug ~~Administration~~Administration. 2010. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm228812.htm.
18. European Medicines ~~Agency~~Agency. 2009. http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/11/WC500012189.pdf.
19. Apfelbaum M, Vague P, Ziegler O, et al. Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. Am J Med. 1999;106:179–84.
20. Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA. 2006;295:761–75.
21. Hogan S, Fleury A, Hadvary P, et al. Studies on the antiobesity activity of tetrahydrolipstatin, a potent and selective inhibitor of pancreatic lipase. Int J Obes. 1987;11(Suppl 3):35–42.
22. Hauptman J, Jeunet F, Hartmann D. Initial studies in humans with the novel gastrointestinal lipase inhibitor Ro 18-0647 (tetrahydrolipstatin). Am J Clin Nutr. 1992;55(Suppl):309S–13S.
23. Zhi J, Melia A, Guerciolini R, et al. Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. Clin Pharmacol Ther. 1994;56:82–5.
24. Zhi J, Melia A, Funk C, et al. Metabolic profiles of minimally absorbed orlistat in obese/overweight volunteers. J Clin Pharmacol. 1996;36:1006–11.
25. Roche 2012. Xenical Product Information. http://www.roche-australia.com/content/dam/internet/corporate/roche/en_AU/files/miscellaneous/xenical-pi.pdf.

26. Sjöstrom L, Rissanen A, Andersen T, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. Lancet. 1998;352:167–73.
27. US Food and Drug ~~Administration~~Administration. 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020766s033lbl.pdf.
28. Franz M, VanWormer J, Crain L, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc. 2007;107:1755–67.
29. Padwal R, Rucker D, Li ~~S~~S, et al. Long-term pharmacotherapy for obesity and overweight (review). Cochrane Database Syst ~~Rev~~Rev. 2003; CD004094.
30. Hutton B, Fergusson D. Changes in body weight and serum lipid profile in obese patients treated with orlistat in addition to a hypocaloric diet: a systematic review of randomized clinical trials. Am J Clin Nutr. 2004;80:1461–8.
31. Davidson M, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat. JAMA. 1999;281:235–42.
32. Rössner S, Sjöstrom L, Noack R, et al. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. Obes Res. 2000;8:49–61.
33. Hauptman J, Lucas C, Boldrin M, et al. Orlistat in the long-term treatment of obesity in primary care settings. Arch Fam Med. 2000;9:160–7.
34. Karhunen L, Franssila-Kallunki A, Rissanen P, et al. Effect of orlistat treatment on body composition and resting energy expenditure during a two-year weight-reduction programme in obese Finns. Int J Obes. 2000;24:1567–72.
35. Hill J, Hauptman J, Anderson J, et al. Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a ~~1-y~~1-year study. Am J Clin Nutr. 1999;69:1108–16.
36. Richelsen B, Tonstad S, Rössner S, et al. Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients. Diabetes Care. 2007;30:27–32.
37. Johansson K, Sundström J, Neovius K, et al. Long-term changes in blood pressure following orlistat and sibutramine treatment: a meta-analysis. Obes Rev. 2010;11:777–91.
38. Zhou Y-H, Ma X-Q, Wu C, et al. Effect of anti-obesity drug on cardiovascular risk factors: a systematic review and meta-analysis of randomized controlled trials. PLoS ~~ONE.~~One. 2012;7:e39062.
39. Siebenhofer A, Jeitler K, Horvath ~~K~~K, et al. Long-term effects of weight-reducing drugs in hypertensive patients. Cochrane Database Syst ~~Rev~~Rev. 2013; CD007654.
40. Norris S, Zhang X, Avenell A, et al. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. Arch Intern Med. 2004;164:1395–404.
41. Mannucci E, Dicembrini I, Rotella F, et al. Orlistat and sibutramine beyond weight loss. ~~Nutrition, Metabolism and Cardiovascular Diseases.~~Nutr Metab Cardiovasc Dis. 2008;18:342–8.
42. Muls E, Kolanowski J, Scheen A, et al. The effects of orlistat on weight and on serum lipids in obese patients with hypercholesterolemia: a randomized, double-blind, placebo-controlled, multicentre study. Int J Obes. 2001;25:1713–21.
43. Bergholm R, Tiikkainen M, Vehkavaara S, et al. Lowering of LDL cholesterol rather than moderate weight loss improves endothelium-dependent vasodilatation in obese women with previous gestational diabetes. Diabetes Care. 2003;26:1667–72.
44. Mittendorfer B, Ostlund R, Patterson B, et al. Orlistat inhibits dietary cholesterol absorption. Obes Res. 2001;9:599–604.
45. Suter P, Marmier G, Veya-Linder C, et al. Effect of orlistat on postprandial lipemia, NMR lipoprotein subclass profiles and particle size. Atherosclerosis. 2005;180:127–35.
46. Gabriel F, Samson C, Abejuela Z, et al. Postprandial effect of orlistat on the peaking of lipid level after sequential high fat meals. Int J Endocrinol Metab. 2012;10:458–63.
47. Nakou E, Filippatos T, Georgoula M, et al. The effect of orlistat and ezetimibe, alone or in combination, on serum LDL and small dense LDL cholesterol levels in overweight and obese patients with hypercholesterolaemia. Curr Med Res Opin. 2008;24:1919–29.
48. Dattilo A, Kris-Etherton P. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr. 1992;56:320–8.
49. Jacob S, Rabbia M, Meier M, et al. Orlistat 120 mg improves glycaemic control in type 2 diabetic patients with or without concurrent weight loss. ~~Diab~~Diabetes Obes Metab. 2009;11:361–71.
50. Berne C, et al. A randomized study of orlistat in combination with a weight management programme in obese patients with ~~Type~~type 2 diabetes treated with metformin. Diabet Med. 2005;22:612–8.
51. Hanefeld M, Sachse G. The effects of orlistat on body weight and glycaemic control in overweight patients with type 2 diabetes: a randomized, placebo-controlled trial. ~~Diab~~Diabetes Obes Metab. 2002;4:415–23.
52. Hollander P, Elbein S, Hirsch I, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. ~~Diab~~Diabetes Care. 1998;21:1288–94.

53. Kelley D, Bray G, Pi-Sunyer F, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes. ~~Diab~~Diabetes Care. 2002;25:1033–41.
54. Miles J, Leiter L, Hollander P, et al. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. ~~Diab~~Diabetes Care. 2002;25:1123–8.
55. Heymsfield S, Segal K, Hauptman J, et al. Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. Arch Intern Med. 2000;160:1321–6.
56. Torgerson J, Hauptman J, Boldrin M, et al. XENical in the prevention of diabetes in obese subjects (XENDOS) study. Diabetes Care. 2004;27:155–61.
57. Gillies C, Abrams K, Lambert P, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ. 2007;334:299–307.
58. National Institute for Health and Clinical Excellence. Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43; 2006.
59. Viner R, Hsia Y, Tomsic T, et al. Efficacy and safety of anti-obesity drugs in children and adolescents: systematic review and meta-analysis. Obes Rev. 2010;11:593–602.
60. Chanoine J-P, Hampl S, Jensen C, et al. Effect of orlistat on weight and body composition in obese adolescents. JAMA. 2005;293:2873–83.
61. Van Gaal L, Broom J, Enzi G, et al. Efficacy and tolerability of orlistat in the treatment of obesity: a 6-month dose-ranging study. Eur J Clin Pharmacol. 1998;54:125–32.
62. Smith S, Stenlof K, Greenway F, et al. ~~orlistat~~Orlistat 60 mg reduces visceral adipose tissue: a 24-week randomized, placebo-controlled, multicentre trial. Obesity. 2011;19:1796–803.
63. Fabricatore A, Wadden T, Moore R, et al. Attrition from randomized controlled trials of pharmacological weight loss agents: a systematic review and analysis. Obes Rev. 2009;10:333–41.
64. Padwal R, Kezouh A, Levine M, et al. Long-term persistence with orlistat and sibutramine in a population-based cohort. Int J Obes. 2007;31:1567–70.
65. Beerman B, Melander H, Säwe J, et al. Incorrect use and limited weight reduction of orlistat (Xenical) in clinical practice. Eur J Clin Pharmacol. 2001;57:309–11.
66. Cavaliere H, Floriano I, Medeiros-Neto G. Gastrointestinal side effects of orlistat may be prevented by concomitant prescription of natural fibers (psyllium mucilloid). Int J Obes. 2001;25:1095–9.
67. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med. 2005;142:532–46.
68. Holecki M, Zahorska-Markiewicz B, Nieszporek T, et al. The influence of a 3-month weight-reduction therapy with Orlistat on serum vitamin B12 and folic acid concentration in obese women. Int J Obes. 2006;30:1017–8.
69. Colman E, Fossler M. Reduction in blood cyclosporine concentrations by orlistat. N Engl J Med. 2000;342:1141–2.
70. Zhi J, Moore R, Kanitra L, et al. Effects of orlistat, a lipase inhibitor, on the pharmacokinetics of three highly lipophilic drugs (amiodarone, fluoxetine, and simvastatin) in healthy volunteers. J Clin Pharm. 2003;43:428–35.
71. Bigham S, McGuigan C, MacDonald B, et al. Reduced absorption of lipophilic anti-epileptic medications when used concomitantly with the anti-obesity drug orlistat. Epilepsia. 2006;47:2207.
72. Kent S. Loss of control of HIV viremia associated with the fat malabsorption drug orlistat. AIDS ~~Research and Human~~Res Hum Retroviruses. 2012;28:961–2.
73. Bentley D, Young A-M, Rowell L, et al. Evidence of a drug-drug interaction linked to inhibition of ester hydrolysis by orlistat. J Cardiovasc Pharmacol. 2012;60:390–6.
74. Madhava K, Hartley A. Hypothyroidism in thyroid carcinoma follow-up: orlistat may inhibit the absorption of thyroxine. Clin Oncol. 2005;17:492–3.
75. Xiao D, Shi D, Yang D, et al. Carboxylesterase-2 is a highly sensitive target of the antiobesity agent orlistat with profound implications in the activation of anticancer prodrugs. Biochem Pharmacol. 2013;85:439–47.
76. Zhi J, Melia A, Guerciolini R, et al. The effect of orlistat on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. J Clin Pharmacol. 1996;36(7):659–66.
77. MacWalter R, Fraser H, Armstrong K. Orlistat enhances warfarin effect. Ann Pharmacotherapy. 2003;37:510–2.
78. Zhi J, Melia A, Koss-Twardy S, et al. The influence of orlistat on the pharmacokinetics and pharmacodynamics of glyburide in healthy volunteers. J Clin Pharmacol. 1995;35:521–5.
79. Melia A, Mulligan T, Zhi J. The effect of orlistat on the pharmacokinetics of phenytoin in healthy volunteers. J Clin Pharmacol. 1996;36:654–8.
80. Melia A, Zhi J, Koss-Twardy S, et al. The influence of reduced dietary fat absorption induced by orlistat on the pharmacokinetics of digoxin in healthy volunteers. J Clin Pharmacol. 1995;35:840–3.

81. Zhi J, Moore R, Kanitra L, et al. Pharmacokinetic evaluation of the possible interaction between selected concomitant medications and orlistat at steady state in healthy subjects. J Clin Pharmacol. 2002;42:1011–9.
82. Weber C, Tam Y, Schmidtke-Schrezenmeier G, et al. Effect of the lipase inhibitor orlistat on the pharmacokinetics of four different antihypertensive drugs in healthy volunteers. Eur J Clin Pharmacol. 1996;51:87–90.
83. Hartmann D, Güzelhan C, Zuiderwijk P, et al. Lack of interaction between orlistat and oral contraceptives. Eur J Clin Pharmacol. 1996;50:421–4.
84. Melia A, Zhi J, Zelasko R, et al. The interaction of the lipase inhibitor orlistat with ethanol in healthy volunteers. Eur J Clin Pharmacol. 1998;54:773–7.
85. Hilger E, Quiner S, Ginzei I, et al. The effect of orlistat on plasma levels of psychotropic drugs in patients with long-term psychopharmacotherapy. J Clin Psychopharmacol. 2002;22:68–70.
86. Karamadoukis L, Shivashankar G, Ludeman L, et al. An unusual complication of treatment with orlistat. Clin Nephrol. 2009;4:430–2.
87. Courtney A, O'Rourke D, Maxwell A. Rapidly progressive renal failure associated with successful pharmacotherapy for obesity. Nephrol Dial Transplant. 2007;22:621–3.
88. Singh A, Sarkar S, Gaber L, et al. Acute oxalate nephropathy associated with orlistat, a gastrointestinal lipase inhibitor. Am J Kidney Dis. 2006;49:153.
89. Kwan T, Chadban S, Mckenzie P, et al. Acute oxalate nephropathy secondary to orlistat-induced enteric hyperoxaluria. Nephrology. 2013;18:241–2.
90. Coutinho ~~A and~~A, Glancey G. Orlistat, an under-recognised cause of progressive renal impairment. Nephrol Dial ~~Transplant 2013;28(Suppl. 4):iv172–4.~~Transplant. 2013;28(Suppl 4):iv172–4.
91. Ferraz R, Tiselius H, Heiberg I. Fat malabsorption induced by gastrointestinal lipase inhibitor leads to an increase in urinary oxalate excretion. Kidney ~~International.~~Int. 2004;66:676–82.
92. Sarica K, Akarsu E, Erturhan S, et al. Evaluation of urinary oxalate levels in patients receiving gastrointestinal lipase inhibitor. Obesity. 2008;16:1579–84.
93. Weir M, Beyea M, Gomes T, et al. Orlistat and acute kidney injury: an analysis of 953 patients. Arch Intern Med. 2011;171:703–4.
94. MacLaughlin H, Macdougall I. Rapidly progressive renal failure associated with successful pharmacotherapy for obesity. Nephrol Dial Transplant. 2007;22:2403–5.
95. US Food and Drug Administration. 2009. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm180025.htm.
96. US Food and Drug ~~Administration~~Administration. 2010. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213038.htm.
97. Douglas I, Langham J, Bhaskaran K, et al. Orlistat and the risk of acute liver injury: self-controlled case series study in UK Clinical Practice Research Datalink. BMJ. 2013;346:f1936.
98. European Medicines ~~Agency~~Agency. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Orlistat_31/WC500122883.pdf.
99. Sergeant A, Milne G, Shaffrali F. Lichenoid eruption associated with orlistat. Br J Dermatol. 2006;154:1020–1.
100. US Food and Drug ~~Administration~~Administration. 2006. http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4201S1_05_FDA-Golden.ppt.
101. Gonzalez-Gay M, Garcia-Porua C, Lueiro M, et al. Orlistat-induced cutaneous leukocytoclastic vasculitis. Arthritis ~~& Rheumatism.~~Rheum. 2002;47:566–7.
102. Sheikh-Taha M, Ghosn S, Zeitoun A. Oral aphthous ulcers associated with orlistat. Am J ~~Health Syst~~Health Syst Pharm. 2012;69:1462–4.
103. Ahmad F, Mahmud S. Acute pancreatitis following orlistat therapy: report of two cases. J Pancreas. 2010;11:61–3.
104. Napier S, Thomas M. 36 year old man presenting with pancreatitis and a history of recent commencement of orlistat case report. Nutr J. 2006;5:19.
105. Buyukhatipoglu H. A possibly overlooked side effect of orlistat: gastroesophageal reflux disease. J ~~National~~Natl Med Assoc. 2008;100:1207.

106. Azar S, Zantout M. Diabetic ketoacidosis associated with orlistat treatment. Diabetes Care. 2001;24:602.

107. Benazzi F. Depression induced by orlistat (Xenical). ~~Canadian~~Can J Psychiatry. 2000;45:87.

108. Persson M, Vitols S, Yue Q. Orlistat associated with hypertension. BMJ. 2000;321:87.

109. Ringman J, Mozaffar T. Myopathy associated with chronic orlistat consumption: a case report. ~~Neuromuse Disorders.~~Neuromuscul Disord. 2008;18:410–2.

110. Australian Government Department of Health Therapeutic Goods Administration Database of Adverse Event Notifications. http://www.tga.gov.au/DAEN/daen-entry.aspx. Accessed April 2014.

111. Degen L, Matzinger D, Drewe J, et al. Role of free fatty acids in regulating gastric emptying and gallbladder contraction. Digestion. 2006;74:131–9.

112. Ellrichmann M, Ritter P, Otte J, et al. Orlistat reduces gallbladder emptying by inhibition of CCK release in response to a test meal. ~~Regulatory Peptides.~~Regul Pept. 2007;139:136–40.

113. Ellrichmann M, Kapelle M, Ritter P, et al. Orlistat inhibition of intestinal lipase acutely increases appetite and attenuates postprandial glucagon-like peptide-1-(7-36)-amide-1, cholecystokinin, and peptide YY concentrations. J Clin Endocrinol Metab. 2008;93:3995–8.

114. Borovicka J, Schwizer W, Guttmann G, et al. Role of lipase in the regulation of postprandial gastric acid secretion and emptying of fat in humans: a study with orlistat, a highly specific lipase inhibitor. Gut. 2000;46:774–81.

115. Mathus-Vliegen E, ~~van~~Van Ierland-van Leeuwen M, Terpstra A. Lipase inhibition by orlistat: effects on gall-bladder kinetics and cholecystokinin release in obesity. Aliment Pharmacol ~~Ther 2004;19:601–11.~~Ther. 2004;19:601–11.

116. O'Donovan D, Feinle-Bisset C, Wishart J, et al. Lipase inhibition attenuates the acute inhibitory effects of oral fat on food intake in healthy subjects. Br J Nutr. 2003;90:849–52.

117. Pilichiewicz A, O'Donovan D, Feinle C, et al. Effect of lipase inhibition on gastric emptying of, and the glycemic and incretin responses to, an oil/aqueous drink in type 2 diabetes mellitus. J Clin Endocrinol Metab. 2003;88:3829–34.

118. Feinle-Bisset C, Patterson M, Ghatei M, et al. Fat digestion is required for suppression of ghrelin and stimulation of peptide YY and pancreatic polypeptide secretion by intraduodenal lipid. Am J Physiol Endocrinol Metab. 2005;289:E948–53.

119. Tai K, Hammond A, Wishart J, et al. Carbohydrate and fat digestion is necessary for maximal suppression of total plasma ghrelin in healthy adults. Appetite. 2010;55:407–12.

120. Goedecke J, Barsdorf M, Beglinger C, et al. Effects of lipase inhibitor (orlistat) on cholecystokinin and appetite in response to a high-fat meal. Int J Obes. 2003;27:1479–85.

121. Froehlich F, Hartmann D, Guezelhan C, et al. Influence of orlistat on the regulation of gallbladder contraction in man. ~~Digestive Diseases and Sciences.~~Dig Dis Sci. 1996;41:2404–8.

122. Trouillot T, Pace D, McKinley C, et al. Orlistat maintains biliary lipid composition and hepatobiliary function in obese subjects undergoing moderate weight loss. Am J Gastroenterol. 2001;96:1888–94.

123. Kocelak P, Zahorska-Markiewicz B, Jonderko K, et al. Long-term effects of lipase inhibition by orlistat on gastric emptying and orocecal transit time of a solid meal. J Gastroenterol. 2008;43:609–17.

124. Svendsen M, Rissanen A, Richelsen B, et al. Effect of orlistat on eating behavior among participants in a 3-year weight maintenance trial. Obesity. 2008;16:327–33.

125. Svendsen M, Helgeland M, Tonstad S. The long-term influence of orlistat on dietary intake in obese subjects with components of metabolic syndrome. J Hum Nutr Diet. 2009;22:55–63.

126. Yanovski S, Yanovski J. Long-term drug treatment for obesity: a systematic and clinical review. JAMA. 2014;311:74–86.