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Safety and tolerability of new-generation anti-obesity medications: a narrative review

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Abstract

The prevalence of obesity and associated comorbidities is rising. Despite their weight-loss efficacy, new generation anti-obesity medications are only prescribed to a minority of adults with obesity, possibly, which in part may be due to safety concerns. This review presents detailed safety profiles for orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion and liraglutide 3.0 mg, and discusses the associated risk–benefit profiles. Two anti-obesity medications presented safety issues that warranted further discussion; phentermine/topiramate (fetal toxicity) and liraglutide 3.0 mg (risk of gallstone disease and mild, acute pancreatitis), whereas the adverse events associated with orlistat, lorcaserin, and naltrexone/bupropion were mostly transient tolerability issues. The difficulties surrounding the objective determination of risk–benefit for anti-obesity medications is discussed. The need for more long-term data, thorough patient assessment, individualization of pharmacological interventions and adherence to stopping rules to maximize risk–benefit are highlighted. Overall, the majority of new generation anti-obesity medications present encouraging tolerability profiles; however, in some cases a lack of long-term clinical trials confounds the accurate determination of risk–benefit.

Keywords

Anti-obesity drugs; liraglutide; orlistat; lorcaserin; phentermine/ topiramate; naltrexone/ bupropion

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Declaration of interest

DKP has participated in speakers bureaux for AstraZeneca, Boehringer Ingelheim, MannKind Corporation, Merck, Novo Nordisk, and Sanofi; and has been a consultant/advisor to Eli Lilly & Co, Regeneron, Sanofi, and The Medicines Company. FCS has been a consultant/advisor to Novo Nordisk. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

1. Introduction

Roughly, 20% of people within the World Health Organization (WHO) European Region are living with obesity [1]. In the USA, conservative estimates predict that the percentage of adults with obesity will reach 42% in 2030 [2], an increase from 36% in 2014 [3]. Obesity is thought to cost the European Union (EU) €1 billion per annum [4], and in 2006, the annual medical costs for individuals with obesity in the USA were \$1429 higher than for individuals of normal weight [5]. This disparity is primarily the result of the cost of treating obesity-related comorbidities [6] such as type 2 diabetes (T2D), coronary heart disease, and obstructive sleep apnea (OSA), all of which occur at a greater rate with overweight and obesity [7].

In clinical studies, weight loss of around 5–10% due to lifestyle intervention in the form of diet and exercise – the first-line treatment for obesity – can result in a reduced risk of T2D, cardiovascular disease, and OSA [8–10]. However, weight regain following weight lost through diet and exercise is estimated to approach 50% after only 1 year [11].

Currently, the majority of guidelines recommend pharma-cotherapy as the second-line treatment for obesity, with bariatric devices and surgery as third- and fourth-line treatments, respectively. The European Association for the Study of Obesity [12], The Obesity Society [13], and the American Association of Clinical Endocrinologists [14] guidelines all recommend bariatric surgery for individuals with a body mass index (BMI) 40 or 35 kg/m² with obesity-related comorbidities. Although the risk of major adverse outcomes with bariatric surgery are low [15], factors including patient and physician perceptions, lack of resources, and cost burden all act as barriers to utilization [16].

Anti-obesity medications (AOMs) increase the likelihood of achieving clinically meaningful (5%) weight loss when used as an adjunct to lifestyle intervention [17], and decrease the likelihood of weight regain post-bariatric surgery [18]. Pharmacological intervention as adjunct to diet and exercise is indicated for individuals with a BMI 30 or 27 kg/m² with at least one obesity-related comorbidity [19], providing greater availability to people with overweight and obesity. In 2011, only 2% of adults with obesity in the USA were pre-scribed AOMs [19]. More recent data from the USA show that in 2015, despite the higher prevalence of obesity compared with diabetes, the number of prescriptions for new-generation AOMs was increasing far slower (5154 new prescriptions per month) than for new anti-diabetes medications (25,259 per month for sodium/glucose cotransporter 2 inhibitors alone) [20]. It is possible that historic concerns of serious adverse events, exemplified by the high-profile market withdrawals of fenfluramine (due to concerns over valvular heart disease [21]), sibutramine (due to increased risk for stroke and myocardial infarction [22]), and rimonabant (withdrawn from Europe due to concerns over severe mood disorders [23]; never approved in the USA), may continue to discourage some clinicians from prescribing and individuals from taking AOMs [24]. Plausibly, additional patient-barriers may include the higher costs associated with newer AOMs compared with old-generation AOMs and, for liraglutide, the requirement for subcutaneous injection.

Reviews to date have had a broad focus, briefly covering the mechanisms of action, efficacy, and safety of AOMs simultaneously. This review will profile, in detail, the safety of all AOMs currently marketed in the EU and the USA for chronic weight management, and in the context of the health risks of obesity itself, discuss and interpret the clinical data.

2. Methodology

At the time of writing, this review covers all AOMs approved for long-term use in the EU and USA. For each AOM, safety data have been taken from the phase 3 trials featured in the relevant United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) applications for drug approval. FDA and EMA reports that contain additional analyses of safety data have also been included where appropriate. A PubMed search for key terms (including obesity, overweight, pharmacology and the trade names of the respective AOMs) was performed in January 2017, in order to capture more recent clinical or post-marketing trial data, not featured in the regulatory agency approval applications or safety reports. An overview of the clinical safety data identified for each AOM is shown in Table 1 [25–45].

3. Safety profiles

Following the market withdrawal of the serotonergic drugs fenfluramine and dexfenfluramine, all classes of new-generation AOM are subject to detailed investigation of potential cardiovascular safety issues. The regulatory requirements and hence the clinical data generated for regulatory approval therefore differ between the old- and new-generation AOMs.

3.1. Orlistat (Xenical®, Roche, Basel, Switzerland; Alli®, GlaxoSmithKline, Brentford, UK)

Orlistat is an old-generation AOM, with the prescription dose (Xenical®, 120 mg) approved in the EU in 1998 and the over-the-counter dose (Alli®, 60 mg) approved in 2010. Generic formulations are also authorized nationally in different EU member states [46]. In the USA, Xenical® was approved in 1999 and Alli® in 2007. Approval was granted without the requirement of a long-term safety trial [47]. Unlike other AOMs on the market, orlistat works not through affecting appetite, but by reducing calorie absorption [48].

Orlistat prevents the hydrolysis of triglycerides in the gut through inhibition of pancreatic lipase, resulting in decreased triglyceride (and thus calorie) absorption in the gut, leading to an overall caloric intake reduction [48]. Treatment-related adverse events reflect this mechanism of action and include fatty/oily stools, fecal incontinence, and increased defecation [48]. In XENDOS, the largest clinical trial of orlistat ($n = 3304$), 91% of individuals experienced at least one gastrointestinal event with orlistat and 8% of individuals withdrew from the study due to adverse events [25].

Decreased triglyceride absorption in the gut poses several risks. First, in XENDOS, a significant decrease in the absorption of vitamins A, D, E, and K was observed [25]. Thus, the supplementation of diet with concomitant multivitamins and beta-carotene is advised for individuals taking orlistat. Second, the presence of excess fat in the colon has raised

concerns regarding a potential increased risk of colorectal cancer. In animal models, orlistat has been associated with an increase in aberrant crypt foci [49]; clusters of apoptosis-resistant, neoplastic, premalignant colonic lesions. However, analysis of pooled data from phase 3 and 4 studies of at least 6 months' duration ($n = 3571$ orlistat patients; 3396 on placebo) found no significant difference in the risk of colon cancer between orlistat and placebo [50]. Although this pooled analysis was underpowered to detect relevant risk (only four events of colon or rectal carcinoma were identified), a subsequent retrospective matched cohort study has drawn similar conclusions [51].

3.2. Phentermine/topiramate extended-release (ER) (Qsymia®; Vivus Inc. Campbell, CA, USA)

A new-generation AOM, rejected in the EU, but approved in 2012 for use in the USA, phentermine/topiramate ER is a combination of two drugs, formulated to release slowly in order to improve tolerability. Phentermine monotherapy has been approved in the USA since 1959 as a short-term (i.e. a few weeks) appetite suppressant [52]. Phentermine suppresses appetite by increasing norepinephrine concentration in the central nervous system, and topiramate is an anticonvulsant used to treat epilepsy, partial onset seizures, and migraines. The weight-loss mechanisms of topiramate are yet to be elucidated [53].

Available in two approved doses (phentermine 7.5 mg/ topiramate 46 mg and phentermine 15 mg/topiramate 92 mg), dose escalation is covered in instructions to prescribers and indicates that medication should be stopped if weight-loss thresholds are not achieved within a given time frame at a given dose [54]. Each drug carries separate risks that should be accounted for when phentermine/topiramate ER is prescribed [55].

EQUIP [27] (randomized $n = 241$ to phentermine 3.75 mg plus topiramate 23.0 mg; $n = 512$ to phentermine 15.0 mg plus topiramate 92.0 mg; and $n = 514$ to placebo) and CONQUER [26] (randomized $n = 498$ to phentermine 7.5 mg plus topiramate 46.0 mg; $n = 995$ to phentermine 15.0 mg plus topiramate 92.0 mg; and $n = 994$ to placebo) were the two key phase 3 trials for phentermine/topiramate ER. Common adverse events in these trials included dry mouth, insomnia, dysgeusia, and paresthesia. Across the four phase 3 clinical trials conducted for phentermine/topiramate ER, the rates of trial withdrawal due to adverse events ranged from 4.4% to 19% [26–29].

Because phentermine is a sympathomimetic [55] agent with a similar pharmacology profile to amphetamines, it has the potential to increase both heart rate and blood pressure. Data from two of the phase 3 trials and from one extension trial have indicated a small increase in heart rate with phentermine/topiramate ER in individuals prescribed the highest dose (15 mg phentermine/96 mg topiramate) when compared with placebo [26–28]. No significant difference in rates of major adverse cardiovascular events (MACE) were observed between phentermine/topiramate ER and placebo [56]. However, the individual trials were not sufficiently powered to detect meaningful differences in cardiovascular safety. The EMA rejected the drug citing a lack of evidence for long-term cardiovascular safety, concerns over psychiatric and cognitive adverse events, and abuse potential [57]. The FDA, however, granted approval on the condition that a cardiovascular out-comes trial (AQCLAIM) was undertaken [58]. In 2015 Vivus Inc. indicated that they were in discussion with the FDA

regarding possible cost-saving alternatives to AQCLAIM and therefore the cardiovascular outcomes trial may not run to completion [59].

Phentermine/topiramate ER is contraindicated in pregnancy [54] due to the known toxicity of topiramate to the fetus, which, when compared with a nonexposed individual, doubles the risk of children being born with oral clefts [30]. As a result, a Risk Evaluation Mitigation Strategy (REMS) factsheet has been produced to educate physicians and females of reproductive age about the potential risks and benefits associated with phentermine/topiramate ER [55]. In addition, females of reproductive age require negative pregnancy tests before starting treatment and monthly during treatment.

Overall, topiramate monotherapy has a favorable adverse event profile [60]. However, the therapy has several neuropsychiatric warnings. Some antiepileptic drugs, including topiramate, have been associated with an increased risk of suicidal ideation when compared with placebo [56]. Topiramate monotherapy has also been linked with visual adverse events, including myopia, glaucoma, and increased intraocular pressure; however, the incidence is relatively low [60]. In the two largest clinical trials for phentermine/topiramate ER, anxiety, depression, and irritability were all more common with the highest dose when compared with placebo [26,27].

Furthermore, topiramate monotherapy is associated with metabolic acidosis at higher doses. A reduction in serum bicarbonate has been observed during the clinical trials of phentermine/topiramate ER, reaching the nadir at around week 4 of treatment [54]. In the majority of individuals, levels of serum bicarbonate were corrected by week 56; however, it is suggested that serum bicarbonate and other electrolytes should be measured before and during treatment [54].

3.3. Lorcaserin (Belviq®, Belviq XR®; Arena Pharmaceuticals, Zofingen, Switzerland)

Lorcaserin, a new-generation AOM, is another member of the serotonergic drug class. Lorcaserin, however, selectively targets the serotonin-2C receptor (influencing appetite), rather than the serotonin-2B receptors [53] (safety data from AOM therapies now withdrawn, reveal that 2B receptor activation can increase risk of valvulopathy) [61]. Despite the selective activation of the 2C receptor, echocardiograms were required in all three of the lorcaserin phase 3 trials, BLOOM, BLOSSOM, and BLOOM-DM [32–34]. Pooled echocardiographic data in patients with FDA-defined valvulopathy at baseline demonstrated lorcaserin did not worsen patients' condition following 1 year of treatment [62]. However, data from these trials did not sufficiently power the analysis to test between treatment groups [62], and as a result, valvulopathy is a key secondary end point in the ongoing cardiovascular outcomes trial, CAMELLIA-TIMI. The trial, designed to evaluate the incidence of MACE, recently completed a prespecified interim safety analysis and will continue until expected completion in 2018 [63].

In placebo-controlled trials of at least 1 year's duration ($n = 3451$ lorcaserin; $n = 3437$ placebo), the most common adverse reactions occurring in 5% of patients without diabetes were headache, dizziness, fatigue, nausea, dry mouth, and constipation; and in patients with diabetes, the most common adverse reactions were hypoglycemia, headache, back pain,

cough, and fatigue [32–34,64]. In BLOOM-DM, the most commonly reported adverse event was headache, occurring more frequently with lorcaserin than with placebo [34]. Symptomatic hypoglycemia was more common with lorcaserin than with placebo, but there were no reported events of serious hypoglycemia (defined as an episode in which the individual experienced a loss of consciousness, confusion or treatment with a parenteral agent). In the three phase 3 clinical trials with lorcaserin, rates of withdrawal due to adverse events in individuals prescribed the drug twice daily ranged from 7.1% to 8.6% [32–34].

While efficacy was considered modest, the EMA concluded that it did not outweigh potential risks (concerns were raised regarding tumors, psychiatric disorders, and valvulopathy) and rejected approval for use in the EU [65]. The FDA, however, approved the 10 mg twice-daily dose in 2012 for use in the USA. Subsequently, a 20 mg, ER, once-daily version of lorcaserin has also been approved by the FDA, following the determination of bioequivalence to the twice-daily 10 mg dose [66].

3.4. Naltrexone/bupropion (Contrave®, Mysimba®; Orexigen Therapeutics, La Jolla, CA, USA)

Naltrexone/bupropion (32 mg/360 mg), a new-generation AOM, has been marketed in the USA since approval in 2014 as Contrave® and in the EU since 2015 as Mysimba®. Both naltrexone and bupropion are used independently for separate indications and as such, the safety profiles of both have been extensively studied. Naltrexone (an opioid receptor antagonist) monotherapy is indicated for treatment of alcohol and opioid dependence, while bupropion (a norepinephrine–dopamine reuptake inhibitor and nicotinic acetylcholine receptor antagonist) monotherapy is indicated for treatment of depression and smoking cessation [67]. Bupropion monotherapy is known to produce substantial weight loss, whereas naltrexone is associated with negligible weight-loss effects. However, together naltrexone has a synergistic effect when combined with bupropion [67]. Bupropion acts to stimulate the arcuate nucleus-based pro-opiomelanocortin (POMC) neurons that release alpha-melanocyte-stimulating hormone (α -MSH), initiating a decrease in food intake and energy expenditure. However, naltrexone blocks the mu-opioid receptor, disrupting the binding of beta-endorphins usually responsible for providing inhibitory feedback and limiting the release of α -MSH. This action is suggested to facilitate a more potent and longer-lasting activation of POMC neurons, suppressing appetite to a greater extent than naltrexone and bupropion independently further facilitating weight loss [68].

Similar to phentermine and sibutramine, bupropion has sympathomimetic effects, raising concerns over its cardiovascular safety [67]. In the four phase 3 clinical trials conducted with naltrexone/bupropion, greater decreases in blood pressure were observed with placebo than with naltrexone/bupropion, despite an inferior weight loss with placebo [35,36]. It is likely that potential blood pressure improvement as a result of weight reduction with naltrexone/bupropion was offset by the noradrenergic action of bupropion, which can increase blood pressure and heart rate [67]. The LIGHT study, a cardiovascular outcomes trial for naltrexone/bupropion, was stopped in March 2015 due to the premature release of interim results and the subsequent risk for the introduction of bias [39]. Despite early termination, a MACE analysis was performed with 50% of the MACE required to meet the original power

requirements [39]. Unfortunately, despite previous reports of a significantly lower incidence of MACE with naltrexone/bupropion vs. placebo (following the 25% interim analysis), the 50% interim analysis indicated the MACE-reduction with naltrexone/bupropion was nonsignificant [39]. As a consequence of the early termination, the investigators reported it was no longer possible to perform the prespecified primary analysis (non-inferiority for MACE) and a new cardiovascular outcomes trial is now required by the regulatory agencies due to the early termination [39].

In an analysis of five double-blind placebo controlled trials ($n = 3239$ naltrexone/bupropion; 1515 patients, placebo), common adverse events that occurred in 5% of the patients and at least twice as often as placebo included nausea, constipation, vomiting, dizziness, and dry mouth [69]. In the four phase 3 clinical trials with naltrexone/bupropion, trial withdrawal due to adverse events ranged from 19.2% to 29.3% [35–38]. With placebo, 12.9% of individuals experienced a psychiatric-related adverse event compared with 17.6% with naltrexone/bupropion [70]. In all trials, there were no differences between the active treatment and placebo groups with regards to suicide or suicide attempts [69]. Pooled data from the four main phase 3 trials showed three reports of suicidal ideation with placebo and one with naltrexone/bupropion [70].

There is an increased risk of seizures with naltrexone/bupropion, due to the role of bupropion in lowering seizure threshold [67]. Across all trials, there was one incidence of a seizure with naltrexone/bupropion and none with placebo [36]. Previous history of seizures was an exclusion criterion for all the phase 3 trials which may explain the low incidence across the studies [67].

3.5. Liraglutide 3.0 mg (Saxenda®; Novo Nordisk, Bagsvaerd, Denmark)

Liraglutide, a new-generation AOM, is an analog of glucagon-like peptide-1 (GLP-1), an endogenous gut hormone that binds to and activates GLP-1 receptors in the central nervous system. GLP-1 receptor agonists stimulate anorexigenic POMC/CART neurons and indirectly inhibit orexigenic neurons expressing neuropeptide Y and agouti-related peptide, via GABA-dependent signaling, leading to a reduction in energy intake [71]. Liraglutide is available in the USA and EU at a 3.0-mg dose (Saxenda®; Novo Nordisk) for weight management, that offers greater efficacy for weight loss than the 1.8 mg indicated dose for improvement of glycemic control in patients with T2D (Victoza®; Novo Nordisk) [72].

Four phase 3 trials have been published with liraglutide 3.0 mg (the SCALE trials), and in each trial, more adverse events were reported in individuals receiving liraglutide than in those receiving placebo [40,42–44]. The greater rate of adverse events was primarily driven by an increase in gastrointestinal events, including nausea, constipation, diarrhea, and vomiting, but most events were mild or moderate in severity [40,42–44]. Nausea and vomiting – the most common adverse events – occurred mostly during dose escalation (i.e. within the first 4 weeks), and were transient in nature. Trial withdrawal due to adverse events with liraglutide ranged from 8.4% to 11.4% across the SCALE trials [40,42–44], and was greater in the liraglutide arms than placebo arms in three of the four trials [40,42–44]. These withdrawal rates in the liraglutide arms were largely driven by mild-to-moderate gastrointestinal adverse events.

The GLP-1 receptor agonists class of drugs is associated with an increase in heart rate of around 2–3 bpm [73]. The cardiovascular safety of liraglutide 1.8 mg was assessed during the LEADER trial [45]. In the primary composite outcome (first occurrence of either cardiovascular death, nonfatal myocardial infarction or non-fatal stroke), individuals treated with liraglutide 1.8 mg were at a lower risk than individuals treated with a placebo (liraglutide 3.0 mg was not assessed in LEADER) [45]. Individuals treated with liraglutide 1.8 mg were found to be at lower risk of death from cardiovascular events, death from any cause, and microvascular events when compared with placebo. LEADER also demonstrated beneficial reductions in the cardiovascular risk factors such as blood pressure and bodyweight with liraglutide compared with placebo [45]. The SCALE Diabetes trial reported no significant difference in heart rate occurring over 56 weeks with two doses of liraglutide (1.8 and 3.0 mg, $p = 0.69$) [42] and, due to the similarities in exposure with these doses, the regulatory authorities have accepted that findings from LEADER are relevant to the cardiovascular safety of liraglutide 3.0 mg. In June 2017, the EMA approved an update of the EU Saxenda® label to include MACE data from the LEADER trial [74].

Cholelithiasis and acute cholecystitis were more common over 56 weeks with liraglutide than with placebo in SCALE Obesity and Prediabetes (the largest clinical trial [$N = 3731$] with liraglutide 3.0 mg) [40]. Observations from the same trial over 3 years reveal slightly higher numbers and rates of gallbladder-related events with liraglutide ($n = 74/1501$, 5%) than with placebo ($n = 13/747$, 2%) [40]. It is important to note however, that rapid weight loss, as observed with liraglutide vs. placebo, is associated with an increased risk for gallbladder disease owing to impaired bile acid secretion, impaired intestinal motility, and a reduction in gallbladder emptying [75]. A mechanistic study is currently underway with the aim of investigating the effects of liraglutide on gallbladder emptying in people with overweight and obesity (NCT02717858).

The absolute number and incidence of pancreatitis adverse events that occurred with liraglutide over 3 years in SCALE Obesity and Prediabetes was low, and only slightly higher than the background rate with placebo (liraglutide: $n = 12/1501$, 0.7%; placebo: $n = 2/747$, 0.3%) [41] and the events were mainly graded as mild (revised Atlantic criteria) [76]. In this trial, increases in mean levels of amylase and lipase were evident with liraglutide from baseline to week 56 [40]. Two additional cases of acute pancreatitis were observed with liraglutide in years 2 and 3 of the trial, from a total 1505 participants in the liraglutide arm [41]. However, few participants had a level three-times the upper limit of normal for these enzymes, and a pooled analysis of phase 3 data demonstrates such elevations do not positively predict the occurrence of pancreatitis [77].

There were no significant differences in the rates of both benign and malignant neoplasms reported with liraglutide when compared with placebo in SCALE Obesity and Prediabetes. GLP-1 receptor agonists can cause thyroid C-cell hyperplasia and calcitonin release in mice [78]. The GLP-1 receptor is frequently expressed in C-cells in rodents, but expression is very rare or absent in healthy human C-cells. Cases of medullary thyroid C-cell carcinoma (MTC) have been reported in patients receiving liraglutide in the post-marketing period; however, the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined [79]. There have been no reports of MTC with liraglutide in the SCALE

trials or the LEADER study; however, these trials were not sufficiently powered to determine the effect of the drug on cancer risk [40,42–45]. Despite this, treatment with liraglutide 3.0 mg is contraindicated in individuals with a personal or family history of MTC [79].

Confirmed hypoglycemia (plasma glucose; <3.1 mmol/L [56 mg/dL]) occurred more often with liraglutide 3.0 mg than with placebo in SCALE Diabetes (randomized $n = 423$, liraglutide 3.0 mg; $n = 211$, liraglutide 1.8 mg; $n = 212$, placebo; all individuals with overweight/obesity and T2D), over 58 weeks [42]. There were no differences in the frequency of severe hypoglycemia (hypoglycemia for which assistance was required from a third party) between the two treatment arms and more episodes occurred in participants with background sulfonylurea or insulin use.

To date, the overall safety data for liraglutide are reassuring, with no new safety signals emerging from the 3-year SCALE Obesity and Prediabetes trial [41].

4. Discussion

4.1. Safety concerns with phentermine/topiramate and liraglutide 3.0 mg

Overweight and obesity are associated with a greater risk of developing T2D, dyslipidemia, hypertension, kidney failure, and death from all causes [80,81]. Therefore, to determine the risk–benefit profile of AOMs, data must be reviewed in the context of the risks associated with obesity itself.

In this review, two AOMs present safety concerns that warrant further attention. First, phentermine/topiramate is associated with fetal toxicity and contraindicated in pregnancy. Consequently, a REMS factsheet has been produced to mitigate this risk. While phentermine/topiramate may be appropriate for the majority of individuals with obesity, the risk of phentermine/topiramate treatment during pregnancy, as with all AOMs, far outweighs the benefits of weight loss.

Second, there is a slight increase in the risk of both gallstone disease and acute pancreatitis associated with liraglutide 3.0 mg. However, it is important to note that obesity itself is a risk factor for these conditions. As obesity and related metabolic comorbidities progress, so too does the risk of developing gallstone disease. A recent meta-analysis showed that the relative risk of symptomatic gallstone disease was increased with obesity, with a hazard ratio (HR) for individuals with a mean BMI of 32.5 kg/m^2 of 2.87 (95% confidence interval [CI]: 2.35–3.49) when compared with individuals with a mean BMI of 20.9 kg/m^2 ($p < 0.001$) [82]. Furthermore, there is an increased risk of developing cholelithiasis with rapid weight loss, even without exposure to AOMs [83]. However, it is important to note that despite a slightly higher rate of gallbladder-related events with liraglutide 3.0 mg compared with placebo in the SCALE Obesity and Prediabetes trial, the mean weight lost with liraglutide was also greater and thus may have been a confounding factor [40,41].

Hong et al. showed that individuals with obesity are at an increased risk of acute pancreatitis (HR: 1.34, 95% CI: 1.07–1.68) and increased severity of the disease (HR: 1.82, 95% CI:

1.44–2.30), when compared with individuals without obesity [84]. Therefore, it is possible that individuals in clinical weight management trials are already at risk of both pancreatitis and gallstone development, due to excess body weight at study entry and/or the conditions may be exacerbated through excess body weight if pancreatitis/gallstones begin to develop. The assessment of AOM risk–benefit must account for benefits associated with weight loss, as weight loss is associated with many, varied health benefits (including lower T2D risk [10], lower rates of cardiovascular mortality [85], lower blood pressure [86], and improvements in OSA [9]). Given that gallstones and pancreatic disease are risks of obesity and not just risks of liraglutide 3.0 mg, over-all, a favorable risk–benefit profile for liraglutide may be inferred.

4.2. Tolerability issues with orlistat, lorcaserin, and naltrexone/bupropion

Adverse events with orlistat, lorcaserin, and naltrexone/bupropion were primarily issues of tolerability rather than safety. By considering participant discontinuation rates for each study drug, we can infer the tolerability of these drugs in the context of their perceived efficacy. For all AOMs, the average trial with-drawal rate due to adverse events was around 10%, with the exception of naltrexone/bupropion, which was 24.5%. In general, these withdrawal rates represent an encouraging tolerability profile for the new-generation AOMs (with the exception of naltrexone/bupropion), in the context of perceived efficacy. However, to assess the tolerability profile of each drug fully, individual adherence studies would be required.

4.3. Long-term data are required for the determination of the risk–benefit

It is widely held that there is positive correlation between percentage of body weight lost and health benefits for individuals with obesity, and indeed the FDA efficacy bench marks for AOMs reflect this (the achievement of 5% weight loss and statistical differences between active and placebo groups form the basis of these criteria) [87]. However, although initial improvements in cardiovascular and metabolic markers of health become apparent relatively quickly following weight loss, these may not tip the balance toward a favorable risk–benefit profile for a drug. Time to improvement in more complex comorbidities such as T2D and OSA may take longer to manifest and an unfavorable risk–benefit profile may be concluded before the benefits of weight loss become evident. Similarly, serious adverse events may also take longer to appear. Adverse events that can occur more frequently with some AOMs (e.g. nausea with liraglutide or orlistat) are mild and transient in nature, which should be accounted for when considering the risk–benefit profile. Conversely, the identification of serious, long-term adverse events such as cancers and cardiovascular risk factors that would undoubtedly push a drug toward an unfavorable risk–benefit profile may take longer to manifest. This reinforces the need for long-term safety data and the requirement for long-duration clinical trials with new-generation AOMs. New-generation AOMs should also be subject to post-authorization studies that evaluate their safety under real-world conditions. Although randomized control trials are the gold standard for demonstrating efficacy, they use strict inclusion and exclusion criteria that can limit the generalizability of safety data to clinical practice [88].

4.4. BMI alone may not be the most useful means to determine efficacy

When considering the risk–benefit profile of an AOM, the widespread use of the WHO BMI-based classification of weight status may not be the most useful system to identify those individuals most likely to benefit from treatment, or to effectively monitor/assess treatment effects, as BMI alone may not reflect genuine clinical need/benefit. The Edmonton Obesity Staging System categorizes health risk based on not only BMI but also the presence of symptoms, risk factors, and comorbidities associated with obesity [89]. For an individual presenting with stage 0 (WHO class I) obesity, where there are no signs of obesity-related risk factors besides a BMI ≥ 30 kg/m², and the risk of taking a given AOMs may outweigh the risks of having obesity. For an individual presenting with stage 4 obesity (WHO class III; BMI ≥ 40 kg/m²) with severe functional limitations and obesity-related comorbidities, the risk of taking an AOM may not outweigh the risks associated with obesity [90].

4.5. Patient preference can affect the risk–benefit profile

One potential limitation of this analysis is the subjective nature of risk–benefit determination. For one individual, the adverse events associated with AOM use may be of negligible importance; to others, they may lead to treatment discontinuation. In this sense, it is important to determine the risk–benefit profile of a given drug on an individual, patient-by-patient basis. Indeed, patient preferences regarding tolerability issues will influence adherence/discontinuation and thus affect the risk–benefit profile, as poor adherence or discontinuation will negate treatment benefits. It follows that, in addition to the evaluation of weight loss in the individual patient, physicians should consult the patient regarding their preference of adverse event profile that is associated with a given AOM.

4.6. Stopping rules avoid unnecessary exposure and improve the risk–benefit ratio

Just as there is a range in the severity of obesity and obesity-related comorbidities, there is a range of weight-loss responses to AOMs. The prescribing information of most AOMs discussed in this article suggest that individuals should discontinue treatment if weight loss does not exceed 5% after 12 weeks (the exceptions being liraglutide 3.0 mg in the USA, which suggests 4% after 16 weeks; naltrexone/bupropion in the EU which suggests 5% after 16 weeks; and orlistat, which provides no recommendations in the USA but uses the 5% after 16 weeks stopping rule in the EU). Use of AOMs should be personalized and account for the response observed in the individual; if an individual does not experience a clinically beneficial level of weight loss, unnecessary exposure to a given drug should be limited and an alternative approach and/or drug should be considered.

5. Conclusion

In conclusion, pharmacotherapy as adjunct to diet and exercise can result in clinically meaningful weight loss and help improve many obesity-related comorbidities. Based on clinical data derived from trials that were mainly of relatively short duration, and in the context of the health risks associated with obesity itself, approved AOMs offer a safe and tolerable adjunct to life-style interventions for the majority of individuals with obesity. Additional, long-term, safety-specific trials as well as post-marketing surveillance are required to establish the long-term safety of AOMs. Clinicians can take a number of steps to

ensure that patients minimize the risks and maximize the benefits when considering AOMs. On one hand, patient preference regarding potential adverse event profiles and delivery vehicle (oral vs. injectable) can help minimize poor adherence/treatment discontinuation. On the other hand, in depth patient-assessments that go beyond BMI and the implementation of stopping rules will help target AOMs to those individuals most likely to benefit and to limit use to those that experience a clinically beneficial response. Thus, the risks of prescribing can be reduced, and an optimal risk–benefit profile can be achieved for each individual that receives treatment with a new-generation AOM or orlistat.

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Table 1.

A summary of the anti-obesity medications currently marketed in the USA.

Drug (trade name)	FDA approval	EMA approval	Phase 3 clinical trial [Ref]	Trial length	Mechanism of action	Major safety issues	Tolerability
Orlistat (Xenical®, Alii®)	Yes	Yes	XENDOS [23]	4 years	Gastrointestinal lipase inhibitor	n/a	Gastrointestinal steatorrhea
Phentermine/ topiramate extended-release (Qsymia®)	Yes	No	CONQUER [24]	56 weeks	Sympathomimetic amine with anorectic effect/mechanism unknown	Fetal toxicity	Dry mouth, insomnia, dysgeusia, paresthesia
Lorcaserin (Belviq®, Belviq XR®)	Yes	No	EQUIP [25]	56 weeks			
			SEQUEL [26]	52-week extension			
			EQUATE [27]	24 weeks			
			FORTRESS [28]	n/a			
			SLEEP [29]	28 weeks			
			BLOOM [30]	2 years		Serotonin 2C receptor agonist	Headache, dizziness, nausea, fatigue
			BLOSSOM [31]	52 weeks			
			BLOOM-DM [32]	52 weeks		Opioid receptor antagonist/aminoketone antidepressant	Nausea, constipation, vomiting, dizziness, dry mouth
		Yes	COR-I [33]	56 weeks			
			COR-II [34]	56 weeks			
Naltrexone/bupropion (Contrave® Mysimba®)	Yes	Yes	COR-BMOD [35]	56 weeks			
			COR-Diabetes [36]	56 weeks			
			LIGHT [37]	n/a			
			SCALE Obesity and Prediabetes [38]	56 weeks		GLP-1 receptor agonist	Nausea, constipation, diarrhea, vomiting, abdominal pain
			SCALE Obesity and Prediabetes – 3 years [39]	172 weeks			
			SCALE Diabetes [40]	56 weeks			
			SCALE Maintenance [41]	56 weeks			
			SCALE Sleep Apnea [42]	56 weeks			
			LEADER ^a [43]	32 weeks			
				42–60 months			

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^aLEADER was completed using liraglutide doses up to 1.8 mg.

FDA : Food and Drug Administration; EMA : European Medicines Agency; n/a: not applicable.

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