Editor's Choice

Weight management in obesity – past and present

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ABSTRACT

Aims: To describe the treatment of obesity from ancient times to present day. **Methods:** Articles reporting the development of anti-obesity therapies were identified through a search for 'anti-obesity' AND 'pharmacotherapy' AND 'development' within the title or abstract on PubMed and 'obesity' in ClinicalTrials.gov. Relevant articles and related literature were selected for inclusion. **Results:** Stone-age miniature obese female statuettes indicate the existence and cultural significance of obesity as long as 30,000 years ago. Records from Ancient Egyptian and Biblical eras through Greco-Roman to Medieval times indicate that obesity was present throughout the major periods of history, although peoples of previous centuries would probably have experienced overweight and obesity as exceptional rather than normal. Health risks of obesity were noted by the Greek physician Hippocrates (460–377 BCE) when the earliest anti-obesity recommendations on diet, exercise, lifestyle and use of emetics and cathartics were born. These recommendations remained largely unchanged until the early 20th century, when spreading urbanisation, increasingly sedentary jobs and greater availability of processed foods produced a sharp rise in obesity. This led to the need for new, more effective, ways to lose weight, to address comorbidities associated with obesity, and to attain the current cultural ideal of slimness. Drug companies of the 1940s and 1950s produced a series of anti-obesity pharmacotherapies in short succession, based largely on amphetamines. Increased regulation of drug development in the 1960s and new efficacy requirements for weight-loss drugs led to rapid reduction in anti-obesity therapies available by the early 1990s. **Conclusion:** In the last two decades, several new and emerging therapies have been approved or are in development to provide safe, long-term pharmacological agents for the treatment of obesity.

Review criteria
Articles reporting on the development of anti-obesity therapies from ancient times to the present day in human studies were identified through an English language search for 'anti-obesity' AND 'pharmacotherapy' AND 'development' within the title or abstract on PubMed and 'obesity' in ClinicalTrials.gov. Relevant articles and related literature were selected for inclusion.

Message for the clinic
The health risks of obesity have been noted since the time of Hippocrates, but treatments remained largely unchanged until the sharp rise in obesity in the 20th century created a growing need for effective therapies. Initial amphetamine-based therapies developed around the 1950s were discontinued due to safety issues, and it is only in the last 20 years that effective pharmacological agents with acceptable safety profiles have become available.

Background

Although the global obesity epidemic is a relatively new phenomenon, obesity *per se* is known to have existed tens of thousands of years ago, as evidenced by artefacts such as the Venus of Willendorf (1) and the Venus of Hohle Fels (2). The Neolithic period has also yielded numerous statuettes portraying obesity, notably the 'Mother Goddess' artefacts found in Anatolia (modern Turkey) and Malta (3,4). Studies of the reconstructed skin folds of royal mummies from ancient Egypt indicated that several were obese, including King Ramses III and Queen Inhapy (4). However, in contrast to today, obesity in centuries past was likely to be exceptional rather than normal. Within the last few decades, the increasing occurrence of obesity has led to progress towards pharmacological treatment options for weight loss. This article describes how obesity has been viewed over the centuries, and focuses on how treatments for weight loss have changed throughout these times.

Methods

A search was conducted in PubMed in May 2015 for articles in humans that related to anti-obesity therapies from ancient times to the present day. The search was conducted using the terms 'anti-obesity' AND 'pharmacotherapy' AND 'development'. The results were limited to English language studies in humans, which yielded 344 articles. Abstracts were reviewed and those reporting on the development of specific obesity pharmacotherapies were selected. Relevant articles and related literature were selected for inclusion in the review. Additional references were identified from the bibliography of selected

articles and subsequent publications, including Internet articles and book chapters identified by the author. Up to and including May 2015, Clinical Trials.gov was searched for the status of ongoing trials relating to anti-obesity pharmacotherapies, and updates on relevant compounds were added to the review.

Observations and attitudes to obesity from ancient times to now

There is evidence that obesity was present, (although rare) during Biblical times (around 3500 years ago) (5), and while today we understand that obesity is associated with elevated rates of diabetes, cardiovascular and metabolic disease and some musculoskeletal disorders and cancers (6,7), an appreciation of the dangers of obesity only began to be understood around 500 BCE. At this time, the Indian physician, surgeon and teacher Sushruta described the disease 'Madhu-meha', which caused 'a sweet taste and smell like that of honey' in patients. Sushruta wrote, somewhat prophetically, that 'Madhu-meha' was associated with either a congenital defect, whereby patients would be emaciated, suffer a dryness of the body, excess thirst and loss of appetite, or with an 'injudicious' diet, whereby symptoms would include 'obesity, voracity, gloss of the body and increased soporific tendency' (8), known today as type 1 and type 2 diabetes, respectively.

The Ancient Greeks were aware of obesity as a health risk, causing for instance irregular menses and infertility in women (4). Greek physician and teacher Hippocrates (460–377 BCE) based the workings of the human body on the four internal humours (9), noting that premature death was more common in people who were fat than lean. He wrote, 'it is very injurious to health to take in more food than the constitution will bear, when, at the same time, one uses no exercise to carry off this excess' (9). The prominent Roman physician, surgeon and philosopher Galen (129–200 CE) made reference to the polysarkos (morbidly obese) person, a description derived from poly (much) and sarka (flesh). A polysarkos 'cannot walk without sweating, cannot reach when sitting at the table because of the mass of his stomach, cannot breathe easily, cannot give birth, cannot clean himself' (10).

With the emergence of Christianity in Europe, the belief grew that illness was because of sin and was therefore punishment from God. During this period, obesity was common among the elite, and signified wealth (11); however, gluttony was considered one of the 'seven deadly sins' of the Catholic Church (12,13). In contrast to Europe, the Islamic empire of Southwest and Central Asia contributed greatly to medical progression during this time. Avicenna, a prominent figure of the Arabic medical tradition, referred to obesity and T2D in his early 12th-century medical encyclopaedia, describing 'the sweet taste of diabetic urine' (4).

By the 1700s in Europe, attitudes towards obesity started to change again, with Scottish physician George Cheyne advocating exercise, fresh air, the 'Waters of Bath' and abundant vegetables to curb obesity. Similarly, in the 1800s, Army physician John Rollo and Royal undertaker William Banting recommended low-carbohydrate, high-protein diets to curb obesity, embraced today by programmes such as the Atkins diet.

In modern times, even with the negative societal and medical opinions of obesity, the prevalence of obesity continues to rise: 600 million adults were classified as obese globally in 2014 (14). This may reflect behavioural changes, particularly the easy availability and consumption of high-calorie food, as well as an increasingly sedentary lifestyle.

Historical treatments for obesity

Recommendations for obesity treatment can be traced back to Ancient Greek and Roman times. Physicians around Hippocrates' time suggested that overweight individuals should 'reduce food and avoid drinking to fullness', and take regular exercise, particularly 'running during the night' and 'early-morning walks' (15).

Several also recommended emetics and cathartics – some of the earliest weight-loss drugs. Emetics including hellebore plants and honey water, were advised 'for the evacuation of the nourishment two or three times a month to all men and women'. Cathartics were composed, for example, of juice of scammony (bindweed), Cnidian berry and sea spurge. Mild laxatives included donkey milk with honey, wild parsley, dodder of thyme (*Cuscuta epithymum*) and honey water or sweet wine (15). The writings of Aelianus (170–235 CE) reported the use of perhaps the earliest sleep apnoea treatment, whereby physicians 'prepared very long, thin needles and pushed them through the hips and belly of [Ancient Greek statesman] Dionysius when he had fallen into a deep sleep' (16).

Galen recorded treatments for obesity that included strenuous running every morning followed by a warm bath, a light meal and more physical work (17). Sushruta recommended physical work and described additional remedies for obesity such as 'fasting, exercise and depletory measures' (8). In the 1620s, British doctor Tobias Venner first used the term 'obese' to describe people who were very overweight, and recommended bathing in the warm

springs of Bath 'to make slender such bodies as are too gross'. The modern era of pharmacotherapy arguably began in the late 19th century, when preparations of thyroid hormone, extracted for use in the treatment of hypothyroidism, were also prescribed as anti-obesity therapy, largely due to their thermogenic properties (18).

Early in the 20th century, obese individuals began to search for effective remedies, to reach the societal ideal of slimness; manufacturers preyed upon their naiveté with a vast range of quack remedies (19). 'Fatoff' was marketed for overweight and obesity, despite containing the ineffective ingredients 10% soap and 90% water (20). Likewise, the product 'Human-Ease', marketed as a cure for obesity and 'all known diseases' was later found to consist of 95% lard (20).

Anti-obesity pharmacotherapies in modern times

Dinitrophenol
Used in 1933 as one of the first anti-obesity therapy therapies, 2-4 dinitrophenol (DNP) was found to cause weight loss by uncoupling oxidative phosphorylation, leading to a heightened metabolic rate and increased fat metabolism (21). In its first year, DNP was used by 100,000 individuals in the USA alone (22). However, by 1938, toxic hyperthermic effects were noted and the drug was discontinued.

Amphetamines
In the 1940s and 1950s, amphetamines became the primary drugs for obesity treatment. Amphetamines act on hypothalamic receptors to release norepinephrine and, to a lesser extent, dopamine and serotonin, increasing central nervous system (CNS) activity and resting energy expenditure, and decreasing appetite and food intake, thus leading to weight reduction (23). From 1945 to 1962, the US Food and Drug Administration (FDA) approved several amphetamine-based drugs for treatment of obesity as an adjunct to diet and exercise. In 1944, one version of desoxyephedrine (methamphetamine), manufactured by Endo Products (Garden City, NY, USA) was approved for the treatment of obesity as an adjunct to lifestyle modification (24). However, in 1946, the FDA questioned the wisdom of prescribing this type of drug for weight loss beyond its original purpose of treating narcolepsy, mild depression, hay fever and chronic alcoholism, and the potential to cause harm by its addictive properties (24). Further supporting evidence was then presented in 1947 upon which the FDA confirmed the approval of the first version of desoxyephedrine from Endo Products,

as well as a second version from Abbott Laboratories (Abbott Park, IL, USA) (24).

To reduce the addictive potential of the amphetamine-based anti-obesity drugs, analogues were developed with varying dopamine and serotonin receptor specificities. In 1956, phenmetrazine, was developed by Ciba Geigy Corp. (Ardsley, NY, USA) (25) and was followed in 1959 bydiethylpropion (Merrell National Drug; Cincinnati, OH, USA) (26), benzphetamine (Upjohn, Kalamazoo, MI, USA) (24) and phendimetrazine (Averst, McKenna & Harrison Ltd., Montreal, QC, Canada) (27).

Another option for amphetamines in affecting weight loss in the 1950s was to combine them with a barbiturate, which acts as a CNS depressant by allosterically modifying and prolonging the action of the inhibitory neurotransmitter *gamma*-aminobutyric acid $(GABA)_A$ receptor, thus providing a solution to the frequent agitation associated with amphetamine use. Some of the best known combinations of the time (now discontinued) included a combination of dextroamphetamine and amobarbital [Smith, Kline and French (now GlaxoSmithKline), London, UK]; methamphetamine and pentobarbital (Abbott Laboratories; Abbott Park, IL, USA); and methamphetamine and phenobarbital (Robin Pharmaceuticals Ltd, Auckland, New Zealand) (28).

In 1959, phentermine, an important amphetamine analogue still in use today in the USA for short-term treatment of obesity, was developed by Strasenburgh Laboratories (Rochester, NY, USA). At clinical doses, phentermine causes dopamine and serotonin [5-hydroxytryptamine (5-HT)] neurotransmitter release, although to a lesser extent than norepinephrine release (29). Phentermine thus has a lower potential for addiction than other amphetamine-based therapies, shown in an intervention trial in which withdrawing phentermine from patients accustomed to long-term use for weight loss (up to 21 years) did not result in drug cravings (30).

In 1962, the Kefauver–Harris amendment to the US Food, Drug and Cosmetic Act was passed in Congress, mandating the provision of substantial evidence of efficacy for all new drug applications (NDAs) (31), which includes those of obesity. At the same time, obesity drugs approved prior to 1962 became subject to the 'Drug Efficacy Study', whereby the FDA called upon the National Research Council of the National Academy of Sciences to investigate efficacy and safety of previously approved drugs and categorise them as 'effective', 'effective but' (possibly efficacious, but other, more efficacious or safer drugs were available), 'probably effective', 'ineffective' or 'ineffective as a fixed combination' (32).

As a result of the Kefauver–Harris amendment, it was 1973 when the FDA finally approved the marketing of three amphetamine-based drugs for weight loss: fenfluramine (Robins Co., Richmond, VA, USA), mazindol (Sandoz Pharmaceuticals, East Hanover, NJ, USA) and chlorphentermine (Warner Chilcott, Morris Plains, NJ, USA) (24). However, safety concerns regarding the addictive potential of these drugs were never fully countered and, in 1977, all approved amphetamine-derived anti-obesity drugs were restricted to short-term use (a few weeks) and became subject to label warnings regarding the risk of addiction (24). Largely due to these further restrictions, the development and use of amphetamines for obesity treatment began to decline until 1992, when a weight-loss trial involving 121 patients treated with a combination of low-dose phentermine and fenfluramine demonstrated average weight loss of 15.9% from baseline over 34 weeks with no major safety concerns during a follow-up period of up to 4 years' treatment (33,34). These findings generated new and dramatic interest in amphetamines for weight loss and kick-started the 1990s 'Phen–Fen period'.

Meanwhile, the FDA published a landmark guideline in the mid-1990s stipulating that any newly developed weight-loss drug should be able to promote a statistically significant difference in weight loss from baseline of at least 5% compared with placebo after 1 year. Alternatively, the proportion of subjects who lose at least 5% of baseline body weight in the treatment group is at least 35%, is approximately twice the proportion in the placebo-treated group and the difference between groups is statistically significant (35). In Europe, the Council Regulation European Executive Committee also established the European Medicines Evaluation Agency (EMA) which re-established the Committee on Proprietary Medicinal Products to formulate the opinion of the EMA on questions regarding the submission of NDAs (36).

In 1996, an NDA in the USA for dexfenfluramine, an isomer of fenfluramine, was approved following a 52-week trial; however, safety concerns were present, because of animal studies linking dexfenfluramine to neurotoxicity (37) and human epidemiological studies linking it to primary pulmonary hypertension (38). Thus, with some reservation, and under tight control, dexfenfluramine was finally approved by the FDA in 1996, and only indicated for patients with body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27–30 kg/m^2 if comorbidities such as hypertension, T2D or dyslipidaemia were present (24). If weight loss of at least 1.8 kg did not occur in the first month, treatment was to be discontinued; prominent package labelling warned that taking the drug for longer than 3 months posed an increased risk for pulmonary hypertension.

Dexfenfluramine use became widespread, with up to 85,000 prescriptions being dispensed weekly after the first year of approval. However, 6 months later, a spate of unusual cases of left-sided heart-valve degeneration in patients using dexfenfluramine resulted in its rapid withdrawal and subsequent restriction of Phen–Fen use. An article published soon afterwards indicated an increased risk of valvular heart disease with both dexfenfluramine and fenfluramine use (39), leading to a large number of lawsuits arising over possible dexfenfluramine-associated valvulopathy deaths. These lawsuits were resolved with some of the largest litigation pay-outs ever seen in the pharmaceutical industry, with individual amounts of up to US$200,000 and a total value of ~US$14 billion (40).

Unlike fenfluramine and dexfenfluramine, phentermine was not withdrawn from the market at that time. Further to its initial approval in 1959, short- and long-acting forms of phentermine HCl were both approved in 1970 and are still in use today for short-term weight management only in countries where it is approved for use. A meta-analysis of six randomised trials lasting 2–24 weeks demonstrated that phentermine-treated patients lost an average of 6.3 kg of additional weight compared with a 2.8 kg weight loss with placebo (41). Currently marketed by Medeva Pharmaceuticals (Leatherhead, UK) and Gate Pharmaceuticals (North Wales, PA, USA), recent trials also indicate that phentermine can result in weight loss of up to 7.2–8.1 kg vs. 1.7–1.9 kg with placebo over 12–14 weeks with mild-to-moderate and transient dry mouth and insomnia as the most commonly reported adverse events (42,43).

Although phentermine is not highly addictive, it is still classed as a controlled substance (Schedule IV drug) and is only recommended for short-term use, thereby limiting its capabilities for clinically obese patients. Long-term use has only been approved when used in combination with other weight-loss medications.

Amphetamine derivatives

Sibutramine (Abbott Laboratories) was approved for weight loss in the USA and Canada in 1997, and in Europe in 1999. Unlike previous amphetamine-based drugs, sibutramine acts as a sympathomimetic, blocking neuronal uptake of any released serotonin and norepinephrine, thereby prolonging stimulation of peripheral beta-adrenergic receptors to induce satiety (44–46).

Sibutramine underwent several years' development in clinical trials, involving 46 studies and 9303 over-

weight or obese patients, 5812 (62%) of whom received sibutramine treatment. Trials reported consistently efficacious weight loss with a mean placebo-subtracted weight loss of 4.2 kg over 12 months (47). Safety concerns included elevations in systolic and diastolic blood pressure and heart rate, even in normotensive patients (48). Approval of sibutramine in 1997 was conditional on its clear contraindication in patients with history of coronary heart disease, stroke, congestive heart failure, arrhythmia or uncontrolled hypertension. Safety concerns over sibutramine post licensure were initially voiced in Belgium in 1999, where increased blood pressure and heart rate were reported in a substantial number of users. As a result of this, the EMA's Committee for Medicinal Products for Human Use (CHMP) reviewed the safety and efficacy of sibutramine, concluding that the marketing authorisation for sibutramine could be maintained, on condition that a clinical study should evaluate its impact on cardiovascular risk factors and 6-monthly Periodic Safety Update Reports (PSURs) would be available for review. An unusual number of adverse cardiovascular events with sibutramine were reported in Italy in 2002, leading to its temporary suspension there, followed by initiation of a large formal European safety study to fully assess its cardiovascular risk profile. As part of this ongoing safety assessment, the 5-year long SCOUT trial was started in 2005, which randomised 9804 subjects to sibutramine or placebo for a period of over 3 years. Unlike the previous phase II and III trials, SCOUT specifically enrolled subjects with cardiovascular disease, high risk of cardiovascular events, high BMI, cerebral vascular disease, peripheral artery disease or T2D with an additional cardiovascular risk factor, to increase the number of adverse events that caused cardiovascular harm (49). However, the expected rate of cardiovascular events (anticipated at ~7%) was not achieved; thus the trial was extended and restricted to three groups only: those with T2D alone, those with cardiovascular disease alone and those with both T2D and cardiovascular disease (highest risk group).

In sibutramine-treated patients, the overall hazard ratio (HR) for cardiovascular events was found to be significantly increased {1.16 [95% confidence interval (CI): 1.03–1.31; p = 0.02]}, although the increased risk of cardiovascular events was not significantly different when the three defined subject groups were considered individually [T2D alone, 1.01 (95% CI: 0.74–1.38), cardiovascular disease alone, 1.28 (95% CI: 0.92–1.78), T2D with cardiovascular disease, 1.18 (95% CI: 1.02–1.37)] (50). However, due to the overall potential risk factors associated with this drug, the FDA recommended that sibutramine be

withdrawn voluntarily from the US and Canadian markets, a request complied with by Abbott Laboratories in October 2010 (51).

Meanwhile, before the full results of the SCOUT trial were published, ongoing safety concerns regarding sibutramine in Europe resulted in the CHMP recommending that sibutramine be withdrawn and, from January 2010, its use across Europe was suspended (52).

A re-analysis of the SCOUT data (53) indicated that sibutramine significantly lowered the risk of cardiovascular events and mortality in patients who lost weight; increased cardiovascular risk was only observed in high-risk patients who did not lose weight but who were maintained on the drug only to fulfil the trial protocol. In the past few years, other safety concerns with sibutramine have also come to light, with some reports and case studies of neuropsychiatric disorders attributed to its use (54).

Non-amphetamine-based obesity drugs
Orlistat. Towards the end of the 1990s, non-amphetamine-based anti-obesity drugs were beginning to be developed. The first to market was orlistat (Roche, Basel, Switzerland), approved in Europe in 1998 and the USA in 1999 and still available today. Orlistat inhibits pancreatic lipase, reducing digestion and absorption of fats from the small intestine by ~30%. Clinical trials with orlistat (e.g. XENDOS) demonstrated significantly greater weight loss compared with placebo [5.8 kg vs. 3.0 kg; p < 0.001 (55)]; however, a meta-analysis of up to 15 trials with orlistat revealed an overall mean placebo-adjusted weight loss of only around 2.9 kg (2.9%) with up to 4 years' treatment (47). Only one safety concern has arisen with orlistat: its potential link with liver toxicity. However, a recent meta-analysis of orlistat use in the UK demonstrated no increased risk of liver toxicity (56). Gastrointestinal side effects such as abdominal pain and discomfort, oily or liquid stool and faecal urgency are very common (57); thus, long-term tolerability remains problematic.

Rimonabant. Rimonabant was developed and approved in Europe in 2006 (Sanofi, Paris, France) as an inverse agonist on the cannabinoid receptor CB1, thereby reducing appetite (58). Safety concerns during clinical trials included an increased frequency of psychiatric disorders, including depression, anxiety and suicidal ideation (59). The UK was the first country where rimonabant was marketed and, by 2008, the drug was available in 56 countries. Although an application was also submitted to the FDA, in June 2007 the US Endocrine and Metabolic Drugs Advisory Committee voted against its approval

in the USA, due to the review of a briefing document indicating safety concerns over its associated psychiatric disorders (60). Then, in October 2008, a statement from the EMA recommended suspension of all marketing authorisation of rimonabant for the same psychiatric risk associations, leading to its complete withdrawal in Europe (61) and, eventually, worldwide (62). It remains possible that rimonabant could have been used safely in obese patients without a history of these disorders; however, this hypothesis has yet to be addressed in clinical trials.

New and emerging therapies – 2010 and onwards

In the last few decades, it has become abundantly clear that the pathophysiology of obesity is complex, and new information regarding neuronal circuits that control food intake and their hormonal regulation has extended our understanding of energy homoeostasis (63). Each new signalling pathway discovered in the hypothalamus is a potential target for drug development in the treatment of obesity. However, as these central pathways are involved in myriad functions, it is somewhat unsurprising that some pharmacotherapies have ultimately failed due to unexpected side effects that may only identified during clinical trials and sometimes many years following drug approval. Yet despite many previous setbacks in the obesity drug development process, manufacturers in the last two decades have persisted in their efforts to develop new, safer and more tolerable anti-obesity medications. In the last 5 years, several therapies have emerged as potentially effective and safe new long-term weight-loss pharmacotherapies. Current EMA/FDA approved anti-obesity drugs are shown in Table 1.

Lorcaserin. The first of these is lorcaserin, which was approved in the USA in 2012 (Arena Pharmaceuticals, San Diego, CA, USA). Lorcaserin acts on the 5-hydroxytryptamine 2C (5-HT2C) receptor to cause the release of serotonin (5-HT) and inhibit the subsequent uptake of serotonin (64). As a result of its low specificity for the 5-HT2B receptor (~100 times lower than that of the 5-HT2C receptor) (65), lorcaserin carries a low risk of causing heart-valve abnormalities with long-term use (66). The FDA lists the side effects of lorcaserin as: serotonin syndrome or neuroleptic malignant syndrome-like reactions: headache, dizziness, fatigue, nausea; dry mouth; constipation and in diabetic patients: low blood sugar (hypoglycaemia), headache, back pain, cough and fatigue (67). Two 52-week, phase III trials reported that, in patients with a mean baseline weight of ~100 kg, lorcaserin therapy resulted in up to 6% weight loss (compared to 2–3% with placebo; $p = 0.001$). Rates of adverse events (AEs) and discontinuations due to AEs in both trials were generally low (6–7%), with the most common side effect being headaches (65,68); however, around a third of patients in total withdrew from one trial, and in the other trial the proportion of withdrawals rose to over 40%. Due to the previous high risk of valvulopathy with other serotonin receptor agonists (e.g. fenfluramine), echocardiogram studies were performed on all phase III trial participants, leading to the final assessment that lorcaserin did not cause cardiac valve tissue fibrosis (69). In Europe, an application was made for approval of lorcaserin by the EMA; however, the application was withdrawn in May 2013 (70) after the EMA stated that the weight-loss benefits of lorcaserin did not outweigh its risks, which included the potential to increase the frequency of psychiatric disorders and valvulopathy that were both observed in some patients during phase III trials.

Phentermine/extended-release topiramate. A combination therapy of phentermine and extended-release (ER) topiramate has been developed by Vivus (Mountain View, CA, USA). Although the exact mechanism

Table 1 Anti-obesity drugs that are currently approved, as of October 2015, by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA)

	Anti-obesity drug	EMA	FDA
Short-term use (a few weeks)	Bidiethylpropion	Approved	Approved
	Benzphetamine	Approved	Approved
	Phendimetrazine	Approved	Approved
	Phentermine	Approved	Approved
Long-term use	Orlistat	Approved	Approved
	Lorcaserin	Not approved	Approved
	Phentermine/extended-release topiramate	Not approved	Approved
	Naltrexone/bupropion	Approved	Approved
	Liraglutide	Approved	Approved

of action remains unknown, phentermine is believed to mediate the release of catecholamines (including noradrenaline and dopamine) in the hypothalamus, while topiramate strengthens the activity of the neurotransmitter gamma-aminobutyrate, modulates voltage-gated ion channels, and inhibits AMPA/kainite excitatory glutamate receptors and carbonic anhydrase (71, 72). Although originally declined for approval due to concerns over the increased risk of depression and cognitive-related disorders, as well as cardiovascular events, the drug was reconsidered and approved by the FDA for weight loss in 2012. Side effects reported by the FDA include tingling of hands and feet (paraesthesia), dizziness, altered taste sensation, insomnia, constipation and dry mouth (72). Key clinical trials that were instrumental in its approval include EQUATE, CONQUER, EQUIP and SEQUEL. The EQUATE trial, a 28-week, randomised, phase III study, compared the combination treatment of phentermine/topiramate (high and low dose) with the individual components alone (both high- and low-dose phentermine and high- and low-dose topiramate) (73). Weight loss was significantly greater in patients receiving the high-dose combination treatment compared with high doses of both compounds alone. CONQUER was a 56-week, randomised, double-blind, placebo-controlled, phase III trial in which two phentermine/ER topiramate treatment arms (15 mg and 7.5 mg) and one placebo arm were initiated in conjunction with a 500 kcal/day dietary deficit (74). In patients who completed 1 year of treatment, a reduction in body weight of 12.4% with phentermine 15.0 mg plus topiramate 92.0 mg and 9.6% with phentermine 7.5 mg plus topiramate 46.0 mg, compared with 1.6% in the placebo group was reported. Cardiovascular improvements were also observed (74). The similarly designed EQUIP trial comprised two phentermine/ER topiramate treatment arms (15 mg and 3.75 mg) and a placebo arm (75). From a mean baseline body weight of 115.2–118.5 kg, the majority of subjects (67%) in the 15 mg group lost at least 5% of baseline body weight and 47% lost at least 10% of body weight from baseline. In the 3.75 mg group, the corresponding proportions of patients achieving 5% and 10% body weight loss from baseline were 45% and 19%, respectively. Minimal improvements were reported in cardiovascular markers such as blood pressure and lipid profiles (75). Finally, the SEQUEL study, a 2-year extension trial of CONQUER, has been performed, which confirmed the consistency and durability of the CONQUER findings. Moreover, a 76% reduction in new-onset T2D in the maximum dose group was observed (76).

The most common adverse reactions to phentermine/topiramate in these trials were paraesthesia, dizziness, dysgeusia, insomnia, constipation and dry mouth, with no increased risk of severe cardiovascular events. The drug is contraindicated in pregnancy due to the topiramate-related increased risk of orofacial clefts; accordingly, a risk evaluation and mitigation (REM) strategy is required for this drug (77). In Europe, marketing authorisation for phentermine/topiramate has been refused by the EMA in both 2012 and 2013 due to safety concerns regarding long-term effects on the heart and blood vessels, and psychiatric and cognitive effects (78). As a result, Vivus is currently conducting a long-term cardiovascular outcomes study (Qsymia CardiovascuLAr morbIdity and Mortality, AQCLAIM) (79) in patients with established cardiovascular disease, before submitting a further application for marketing approval to the EMA.

Naltrexone/bupropion. Naltrexone/bupropion has been development by Orexigen Therapeutics (La Jolla, CA, USA). Although a relatively weak inhibitor of norepinephrine and dopamine uptake, bupropion stimulates hypothalamic pro-opiomelanocortin (POMC) neurons, leading to melanocortin receptor activation and induction of weight loss via appetite suppression and increased energy expenditure (80). Naltrexone acts as an antagonist of the opioid receptor that would normally induce a negative feedback-mediated repression of POMC activation, and thus acts synergistically to prolong the action of bupropion on metabolism.

An NDA for naltrexone/bupropion was submitted to the FDA in March 2010 (81), based on three phase III trials in patients without T2D that demonstrated a weight loss from baseline of between 6.1 and 9.3% and one phase III trial in patients with T2D showing a weight loss of up to 5% (80). The most frequent AEs reported include nausea, headache, constipation, dizziness, vomiting, insomnia and dry mouth, and the drug was not associated with increased risk of depression or suicidal ideation (82). The final approval of naltrexone/bupropion was significantly delayed by the FDA's decision in February 2011 to request that Orexigen conduct a large-scale study into the drug's long-term cardiovascular effects (81). Orexigen initiated the LIGHT study to meet this request, which was due to reach completion in 2017. An interim analysis of 25% of the enrolled patients was submitted to the FDA showing a reduction in the number of cardiovascular events in the naltrexone/bupropion arm. Based on the original NDA and additional cardiovascular data, the FDA approved naltrexone/bupropion in September 2014, with the requirement for ongoing post-marketing studies (83). Unfortunately, premature disclosure of

the confidential LIGHT interim results by Orexigen has led to the trial being halted by the executive steering committee (84). After the trial was stopped, further analysis by the data safety and monitoring board of the study that contained 50% of the enrolled patients has bought into question the data from the earlier time point and suggested that there was no statistical difference between the naltrexone/bupropion and placebo groups (84). The FDA has requested that a further cardiovascular risk study is conducted, with completion expected in 2022 (83).

Naltrexone/bupropion has also recently (March 2015) been approved by the EMA as an adjunct to a reduced calorie diet and increased physical activity for the management of weight in adult patients with a BMI of $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 in the presence of comorbidities (85).

Liraglutide. Liraglutide (1.2 mg and 1.8 mg) was developed by Novo Nordisk (Søborg, Denmark) to treat T2D. The liraglutide molecule, an analogue of human glucagon-like peptide (GLP)-1, has a half-life of 13 h, which greatly extends its activation of the GLP-1 receptor (the half-life of native GLP-1 is ~1.5 min), thereby increasing stimulation of glucose-dependent insulin secretion and exerting a heightened effect on glucagon suppression (86). Throughout the extensive Liraglutide Effect and Action in Diabetes (LEAD) trial programme and the additional 1860-Lira-DPP-4 inhibitor phase III trial, liraglutide demonstrated consistent efficacy in reducing HbA$_{1c}$ (changes ranged between 1.1% and 1.5%) and fasting plasma glucose (changes ranged between 0.4 mmol/L and 2.4 mmol/L) in trials of up to 52 weeks (87–93), leading to its approval (at doses up to 1.8 mg daily) for management of glycaemic control in adults with T2D by the EMA in July 2009 and the FDA in 2010 (86,94).

Native GLP-1 has central effects that regulate appetite and feeding centres in the brain (95); therefore, liraglutide may also have the potential to impact upon energy intake. A 5-week incomplete crossover trial with liraglutide demonstrated that liraglutide induced weight loss, most likely mediated by reducing appetite and decreasing food intake, as measured by appetite scores and post-prandial satiety and fullness ratings, and did not increase energy expenditure (96).

On the basis of this, a higher dose of liraglutide (3.0 mg daily), was tested in phase III clinical trials (the SCALE programme) to investigate the safety and efficacy of liraglutide 3.0 mg in weight management in obese patients both with and without T2D. The largest SCALE study, the Obesity and Predia-

betes trial, investigated the effects of liraglutide 3.0 mg in 3731 individuals with BMI $\geq$ 30 kg/m^2 or 27 kg/m^2 with additional comorbidities, with or without prediabetes, over 56 weeks (97). At week 56, individuals on liraglutide 3.0 mg had lost 8.0% (8.4 kg) of body weight compared with 2.6% (2.8 kg) on placebo [estimated treatment difference -5.4%, (5.6 kg), p < 0.001]. Other benefits in addition to weight loss were also observed including improvements in glycaemic control, blood pressure and lipids. Liraglutide 3.0 mg was generally well tolerated, with the most common AEs being nausea and diarrhoea during the first 4–8 weeks of treatment. The incidences of gallbladder disorders and pancreatitis were low, although events were reported more frequently with liraglutide 3.0 mg [3.1 events/100 patient-years of exposure (PYE) and 0.4 events per 100 patient-years at risk (PYR), respectively] than with placebo (1.4 events/100 PYE and < 0.1 events/100 PYR, respectively) (97).

On the basis of the phase III SCALE clinical trial programme, the FDA approved liraglutide 3.0 mg in December 2014 as an adjunct to a reduced-calorie diet and increased exercise in adult patients with a BMI of $\geq$ 30 kg/m^2, or $\geq$ 27 kg/m^2 in the presence of at least one weight-related comorbid condition (98). Similarly, the EMA has also now approved the use of liraglutide 3.0 mg for the same indication as of March 2015 (99). The most common side effects observed in patients treated with liraglutide 3.0 mg were reported by the FDA to include nausea, diarrhoea, constipation, vomiting, low blood sugar (hypoglycaemia) and decreased appetite (100). Liraglutide is the first once-daily GLP-1 analogue to be licensed for treatment of obesity in the USA and Europe; post-marketing surveillance studies are ongoing to assess the long-term safety of the drug in this indication (98,101).

Cetilistat. Cetilistat, first developed by UK-based Alizyme, is now under development by Norgine (Amsterdam, the Netherlands) and Takeda (Tokyo, Japan). This pharmacotherapy works in a manner similar to orlistat, by inhibiting pancreatic lipase (102). In a 12-week study, weight loss of 3.3–4.1 kg (placebo not available) was demonstrated, with the most common side effects reported as gastrointestinal-related (103,104). As a result of phase III data, cetilistat has been approved in Japan since September 2013; however, it has not yet been filed for approval in the USA and Europe (105).

Bupropion/zonisamide. Bupropion/zonisamide (a mitochondrial carbonic anhydrase inhibitor) is an

anti-obesity combination pharmacotherapy in development by Orexigen Therapeutics (71). Currently in phase II, preliminary findings in 18 patients have demonstrated a 7.2 kg weight loss with bupropion/zonisamide vs. 2.9 kg with zonisamide alone over 12 weeks (106), with the most frequent AEs cited as headache, nausea and insomnia. The most common AEs reported from phase II trials are reported to include headache, insomnia and nausea (107).

Belonarib. Belonarib is a first-in-class obesity therapy being developed by Zafgen that is administered subcutaneously and that acts via inhibition of methionine aminopeptidase 2 (MetAP2) (108).

In a 12-week, phase II study, participants receiving belonarib 0.6 mg, 1.2 mg or 2.4 mg lost 5.5 kg, 6.9 kg or 10.9 kg, respectively, compared to 0.4 kg in the placebo group (p < 0.001) (108). Belonarib was generally well tolerated, although more sleep disturbances and gastrointestinal AEs were reported in the belonarib group compared to the placebo groups. These events were generally mild-to-moderate in severity, transient and dose-related, although more participants receiving the highest dose of belonarib withdrew from the study due to these AEs (108). Further phase II and III trials are ongoing (109).

Nutritional supplements/'black market' pharmaceuticals
The Internet is awash with countless unapproved 'anti-obesity' therapeutics. Many of these contain drugs that are now known to be dangerous, for example, sibutramine, or chemicals that have never been tested in humans, for example, clenbuterol.

Needless to say, these therapeutic 'options' should be avoided.

Conclusions

As we have moved through history to the present day, obesity has changed from being a rare, and perhaps even revered, occurrence to a condition that is common in a large proportion of the population in the developed world. Pharmacotherapies can play an important role in the treatment of obesity, by providing a non-invasive therapy that can increase weight loss established by diet and exercise alone, and thus help in reducing the impact of comorbidities associated with obesity. The pharmacotherapy landscape has been in a state of flux for many decades and as our understanding of the pathogenesis of obesity increases, so does the number of potential novel targets for therapeutic intervention. Gut hormones may be especially promising candidates for future exploration due to relatively few non-specific side effects compared with centrally acting drugs. It is hoped that weight-loss drugs of the present and future will provide safer and more effective tools for the long-term management of obesity. However, as has been the case with many previously approved anti-obesity drugs, only time will tell.

Acknowledgements

References

1 Antl-Weiser W. The anthropomorphic figurines from Willendorf. *Wiss Mitt Niederösterr Landesmuseum* 2008; **19**: 19–30.

2 Conard NJ. A female figurine from the basal Aurignacian of Hohle Fels Cave in southwestern Germany. *Nature* 2009; **459**: 248–52.

3 Rich SA. Midwifery and neolithic Malta: interpreting and contextualizing two terracotta figurines. *J Appl Anthropol* 2008. http://www.omertaa.org/archive/omertaa0034.pdf (accessed 28 October 2015).

4 Bray GA. History of obesity. In: Williams G, Frühbeck G, eds. *Obesity: Science to Practice.* Oxford, UK: Wiley-Blackwell, 2009: 3–18.

5 Kingshouse. *Bible Health.* http://www.kingshouse.org/Biblehealth.htm (accessed 28 October 2015).

6 Martin-Rodriguez E, Guillen-Grima F, Martí A, Brugos-Larumbe A. Comorbidity associated with obesity in a large population: the APNA study. *Obes Res Clin Pract* 2015; **9**: 435–47.

7 Louie SM, Roberts LS, Nomura DK. Mechanisms linking obesity and cancer. *Biochim Biophys Acta* 2013; **1831**: 1499–508.

8 Dods RF. Understanding diabetes: a biochemical perspective. *ChemMedChem* 2013; **8**: 1415.

9 Wells JCK. *The Evolutionary Biology of Human Body Fatness: Thrift and Control.* Cambridge, UK: Cambridge University Press, 2009.

10 Papavramidou NS, Papavramidis ST, Christopoulou-Aletra H. Galen on obesity: etiology, effects, and treatment. *World J Surg* 2004; **28**: 631–5.

11 Bloomgarden ZT. Prevention of obesity and diabetes. *Diabetes Care* 2003; **26**: 3172–8.

12 Shipley O. *A Theory About sin in Relation to Some Facts of Daily Life, Lent Lectures on the 7 Deadly Sins.* Oxford: Oxford University Library collection, 1875.

13 Haslam DW, Haslam F. *Fat, Gluttony and Sloth. Obesity in Literature, Art and Medicine.* Liverpool, UK: Liverpool University Press, 2009.

14 WHO. *Obesity and Overweight.* http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed 27 October 2015).

15 Christopoulou-Aletra H, Papavramidou N. Methods used by the Hippocratic physicians for weight reduction. *World J Surg* 2004; **28**: 513–7.

16 Kryger MH. Sleep apnea. From the needles of Dionysius to continuous positive airway pressure. *Arch Internal Med* 1983; **143**: 2301–23.

17 Haslam D, Rigby N. A long look at obesity. *Lancet* 2010; **376**: 85–96.

18 Clapham JC, Arch JR. Thermogenic and metabolic antiobesity drugs: rationale and opportunities. *Diabetes Obes Metab* 2007; **3**: 259–75.

19 Museum of the Royal Pharmaceutical Society. *Developing Treatments: Obesity*, 2009. http://www.rpharms.com/museum-pdfs/obesity.pdf (accessed 28 October 2015).

20 Haslam D. *The Weight of Obsession. A Brief but Wide, History*, 2015. https://commonreader.wustl.edu/c/the-weight-of-obsession (accessed 28 October 2015).

21 Cutting WC, Mehrtens HG, Tainter ML. Actions and uses of dinitrophenol: promising metabolic applications. *J Am Med Assoc* 1933; **101**: 193–5.

22 Tainter M, Cutting WC, Stockton AB. Use of dinitophenol in nutritional disorders: a critical survey of clinical results. *Am J Public Health* 1934; **24**: 1045–53.

23 Heal DJ, Smith SL, Gosden J, Nutt DJ. Amphetamine, past and present – a pharmacological and clinical perspective. *J Psychopharmacol* 2013; **27**: 479–96.

24 Colman E. Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. *Ann Intern Med* 2005; **143**: 380–5.

25 Martel A. Preludin (phenmetrazine) in the treatment of obesity. *Can Med Assoc J* 1957; **76**: 117–20.

26 Cohen S. Diethylpropion (Tenuate): an infrequently abused anorectic. *Psychosomatics* 1977; **18**: 28–33.

27 le Riche WH, van Belle G. Study of phendimetrazine bitartrate as an appetite suppressant in relation to dosage, weight loss and side effects. *Can Med Assoc J* 1962; **87**: 29–31.

28 Rasmussen N. America's first amphetamine epidemic 1929–1971: a quantitative and qualitative retrospective with implications for the present. *Am J Public Health* 2008; **98**: 974–85.

29 Nelson DL, Gehlert DR. Central nervous system biogenic amine targets for control of appetite and energy expenditure. *Endocrine* 2006; **29**: 49–60.

30 Hendricks EJ, Srisurapanont M, Schmidt SL et al. Addiction potential of phentermine prescribed during long-term treatment of obesity. *Int J Obes* 2013; **38**: 292–8.

31 *Drug Amendments of 1962*. Pub L No. 87-781, 76 Stat 780, 1962. http://www.gpo.gov/fdsys/pkg/STATUTE-76/pdf/STATUTE-76-Pg780.pdf (accessed 28 October 2015).

32 United States Food and Drug Administration. *The Code of Federal Regulations of the United States of America: 201.200 Disclosures of Drug Efficacy Study Evaluations in Labeling and Advertising*. Washington, DC, USA: The Office of the Federal Register National Archives and Records Administration, 1999.

33 Weintraub M. Long-term weight control study I (weeks 0 to 34). *Clin Pharmacol Ther* 1992; **51**: 586–94.

34 Weintraub M. Long-term weight control study: conclusions. *Clin Pharmacol Ther* 1992; **51**: 642–6.

35 United States Food and Drug Administration. *Guidance for the Clinical Evaluation of Weight-Control Drugs*, 1996. http://www.fda.gov/ohrms/dockets/98fr/03d-0570-gdl0001.pdf. Superseded by 2007 guidance. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071612.pdf (accessed 28 October 2015).

36 EEC Council Regulations. *Council Regulation (EEC) No 2309/93 of 22 July 1993 Laying Down Community Procedures for the Authorization and Supervision of Medicinal Products for Human and Veterinary use and Establishing a European Agency for the Evaluation of Medicinal Products*, 1993. http://ec.europa.eu/health/files/eudralex/vol-1/reg_1993_2309/reg_1993_2309_bg.pdf (accessed 28 October 2015).

37 McCann U, Hatzidimitriou G, Ridenour A et al. Dexfenfluramine and serotonin neurotoxicity: further preclinical evidence that clinical caution is indicated. *Pharmacol Exp Ther* 1994; **269**: 792–8.

38 Kramer MS, Lane DA. Aminorex, dexfenfluramine, and primary pulmonary hypertension. *J Clin Epidemiol* 1998; **51**: 361–4.

39 Connolly HM, Crary JL, McGoon MD et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997; **337**: 581–8.

40 Morrow DJ. Fen-Phen Maker to Pay Billions In Settlement of Diet-Injury Cases. *The New York Times*, October 8, 1999. http://www.nytimes.com/1999/10/08/business/fen-phen-maker-to-pay-billions-in-settlement-of-diet-injury-cases.html (accessed 28 October 2015).

41 Haddock CK, Poston WS, Dill PL, Foreyt JP, Ericsson M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int J Obes Relat Metab Disord* 2002; **26**: 262–73.

42 Kim KK, Cho HJ, Kang HC et al. Effects on weight reduction and safety of short-term phentermine administration in Korean obese people. *Yonsei Med J* 2006; **47**: 614–25.

43 Kang JG, Park CY, Kang JH, Park YW, Park SW. Randomized controlled trial to investigate the effects of a newly developed formulation of phentermine diffuse-controlled release for obesity. *Diabetes Obes Metab* 2010; **12**: 876–82.

44 Saraç F, Pehlivan M, Celebi G, Saygili F, Yilmaz C, Kabalak T. Effects of sibutramine on thermogenesis in obese patients assessed via immersion calorimetry. *Adv Ther* 2006; **23**: 1016–29.

45 Halford JC, Boyland EJ, Cooper SJ et al. The effects of sibutramine on the microstructure of eating behaviour and energy expenditure in obese women. *J Psychopharmacol* 2010; **24**: 99–109.

46 Araújo JR, Martel F. Sibutramine effects on central mechanisms regulating energy homeostasis. *Curr Neuropharmacol* 2012; **10**: 49–52.

47 Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *BMJ* 2007; **335**: 1194–9.

48 Beaston P. *BPCA Executive Summary: Clinical Review for New Drug Application 20-632, SE5-021*, 2005. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM163209.pdf (accessed 28 October 2015).

49 James WP. The SCOUT study: risk–benefit profile of sibutramine in overweight high-risk cardiovascular patients. *Eur Heart J* 2005; **7**: L44–8.

50 James WP, Caterson ID, Coutinho W et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010; **363**: 905–17.

51 United States Food and Drug Administration. *Meridia (Sibutramine): Market Withdrawal Due to Risk of Serious Cardiovascular Events*, 2010. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm228830.htm (accessed 28 October 2015).

52 European Medicines Agency. *Questions and Answers on the Suspension of Medicines Containing Sibutramine*, 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sibutramine_107/WC500094238.pdf (accessed 28 October 2015).

53 Caterson ID, Finer N, Coutinho W et al. Maintained intentional weight loss reduces cardiovascular outcomes: results from the Sibutramine Cardiovascular OUTcomes (SCOUT) trial. *Diabetes Obes Metab* 2012; **14**: 523–30.

54 An H, Sohn H, Chung S. Phentermine, Sibutramine and affective disorders. *Clin Psychopharmacol Neurosci* 2013; **11**: 7–12.

55 Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; **27**: 155–61.

56 Douglas IJ, Langham J, Bhaskaran K, Brauer R, Smeeth L. Orlistat and the risk of acute liver injury: self controlled case series study in UK Clinical Practice Research Datalink. *BMJ* 2013; **346**: f1936.

57 Roche. *Xenical Summary of Product Characteristics*, 2013. http://www.medicines.org.uk/emc/document.aspx?documentid=1746 (accessed 28 October 2015).

58 Robson PJ. Therapeutic potential of cannabinoid medicines. *Drug Test Anal* 2014; **6**: 24–30.

59 Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A, Rothman RB. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* 2007; **370**: 1706–13.

60 United States Food and Drug Administration. *Briefing Document NDA 21-888 Zimulti (Rimonabant) Tablets, 20 mg*, 2007. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf (accessed 28 October 2015).

61 European Medicines Agency. *The European Medicines Agency Recommends Suspension of the Marketing Authorisation of Acomplia*, 2009. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000244.jsp (accessed 28 October 2015).

62 *Drugs.com. Accomplia*. http://www.drugs.com/acomplia.html (accessed 28 October 2015).

63 Richard D. Cognitive and autonomic determinants of energy homeostasis in obesity. *Nat Rev Endocrinol* 2015; **11**: 489–501.

64 United States Food and Drug Administration. *Lorcaserin Briefing Information: Endocrinologic and Metabolic Drugs Advisory Committee*, 2012. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm225628.htm (accessed 28 October 2015).

65 Smith SR, Weissman NJ, Anderson CM et al. ; Behavioral modification and lorcaserin for overweight and obesity management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010; **363**: 245–56.

66 Weissman NJ, Sanchez M, Koch GG, Smith SR, Shanahan WR, Anderson CM. Echocardiographic assessment of cardiac valvular regurgitation with lorcaserin from analysis of 3 phase 3 clinical trials. *Circ Cardiovasc Imaging* 2013; **6**: 560–7.

67 United States Food and Drug Administration. *FDA Approves Belviq to Treat Some Overweight or Obese Adults*, 2012. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm (accessed 28 October 2015).

68 Fidler MC, Sanchez M, Raether B et al. ; BLOS-SOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab* 2011; **96**: 3067–77.

69 Arena Pharmaceuticals. *Lorcaserin for Obesity Passes Major Safety Milestone. Month-12 Independent Echocardiographic Data Safety Monitoring Board Review Strengthens Lorcaserin's Emerging Cardiovascular Safety Profile*, 2008. http://invest.arenapharm.com/common/mobile/iphone/release detail.cfm?ReleaseID=320197&CompanyID=ARNA (accessed 28 October 2015).

70 European Medicines Agency. *Withdrawal of the Marketing Authorisation Application for Belviq (Lorcaserin)*, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2013/05/WC500143811.pdf (accessed 28 October 2015).

71 Scozzafava A, Supuran CT, Carta F. Antiobesity carbonic anhydrase inhibitors: a literature and patent review. *Expert Opin Ther Pat* 2013; **23**: 725–35.

72 Unites States Food and Drug Administration. *FDA Approves Weight-Management Drug Qsymia*, 2012. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312468.htm (accessed 28 October 2015).

73 Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity (Silver Spring)* 2013; **21**: 2163–71.

74 Gadde KM, Allison DB, Ryan DH et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomized, placebo-controlled, phase 3 trial. *Lancet* 2011; **377**: 1341–52.

75 Allison DB, Gadde KM, Garvey WT et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)* 2012; **20**: 330–42.

76 Garvey WT, Ryan DH, Look M et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr* 2012; **95**: 297–308.

77 Colman E, Golden J, Roberts M, Egan A, Weaver J, Rosebraugh C. The FDA's assessment of two drugs for chronic weight management. *N Engl J Med* 2012; **367**: 1577–9.

78 European Medicines Agency. *Refusal of the Marketing Authorisation for Qsiva (Phentermine/Topiramate)*, 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002350/WC500134085.pdf (assessed 28 October 2015).

79 EUDRACT. *A Qsymia™ CardiovascuLAr MorbIdity and Mortality (AQCLAIM) Study in Subjects With Documented Cardiovascular Disease*. http://www.clinicaltrialsregister.eu/ctr-search/search?query=AQCLAIM (accessed 28 October 2015).

80 Unites States Food and Drug Administration. *Contrave (Naltrexone 4 mg, 8 mg/Bupropion HCL 90 mg Extended Release Tablet) Briefing Document, NDA*

200063, 2010. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm235671.pdf (accessed 28 October 2015).

81 United States Food and Drug Administration. *Center for Drug Evaluation and Research. Application Number 200063Orig1s000*. Summary Review, 2014. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/200063Orig1s000SumR.pdf (accessed 28 October 2015).

82 Wadden TA, Foreyt JP, Foster GD et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity* 2011; **19**: 110–20.

83 Guettier J-MP. *Contrave NDA Approval Letter*, 2014. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/200063Orig1s000ltr.pdf (accessed 28 October 2015).

84 Cleveland Clinic. *Clinical Trial Testing Safety of Obesity Drug Contrave Halted; 50 Percent Interim Data Released by the Study's Executive Committee*. http://my.clevelandclinic.org/about-cleveland-clinic/newsroom/releases-videos-newsletters/2015-5-12-clinical-trial-testing-safety-of-obesity-drug-contrave-halted (accessed 28 October 2015).

85 European Medicines Agency. *Mysimba Summary of Product Characteristics*. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003687/WC500185580.pdf (accessed 28 October 2015).

86 European Medicines Agency. *Victoza Summary of Product Characteristics*. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf (accessed 28 October 2015).

87 Marre M, Shaw J, Brandle M et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med* 2009; **26**: 268–78.

88 Nauck M, Frid A, Hermansen K et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 2009; **32**: 84–90.

89 Garber A, Henry R, Ratner R et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; **373**: 473–81.

90 Zinman B, Gerich J, Buse JB et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 2009; **32**: 1224–30.

91 Russell-Jones D, Vaag A, Schmitz O et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia* 2009; **52**: 2046–55.

92 Buse JB, Rosenstock J, Sesti G et al. Liraglutide once a day versus exenatide twice a day for type 2

diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009; **374**: 39–47.

93 Pratley RE, Nauck M, Bailey T et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 2010; **375**: 1447–56.

94 United States Food and Drug Administration. *Highlights of Prescribing Information for Victoza® (Liraglutide Injection)*. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022341s023lbl.pdf (accessed 28 October 2015).

95 Turton MD, O'Shea D, Gunn I et al. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* 1996; **379**: 69–72.

96 van Can J, Sloth B, Jensen CB et al. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Int J Obes (Lond)* 2014; **38**: 784–93.

97 Pi-Sunyer X, Astrup A, Fujioka K et al. A randomized, controlled trial of 3.0 mg liraglutide in weight management. *N Engl J Med* 2015; **373**: 11–22.

98 Smith JP. *Saxenda NDA Approval Letter*, 2014. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/206321Orig1s000ltr.pdf (accessed 28 October 2015).

99 European Medicines Agency. *Saxenda Summary of Product Characteristics*, 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003780/WC500185786.pdf (accessed 28 October 2015).

100 United States Food and Drug Administration. *FDA Approves Weight-Management Drug Saxenda*, 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427913.htm (accessed 28 October 2015).

101 European Medicines Agency. *Assessment Report: Saxenda*, 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003780/WC500185788.pdf (accessed 28 October 2015).

102 Yamada Y, Kato T, Ogino H, Ashina S, Kato K. Cetilistat (ATL-962), a novel pancreatic lipase inhibitor, ameliorates body weight gain and improves lipid profiles in rats. *Horm Metab Res* 2008; **40**: 539–43.

103 Kopelman P, Bryson A, Hickling R et al. Cetilistat (ATL-962), a novel lipase inhibitor: a 12-week randomized, placebo-controlled study of weight reduction in obese patients. *Int J Obes (Lond)* 2007; **31**: 494–9.

104 Kopelman P, Groot Gde H, Rissanen A et al. Weight loss, HbA1c reduction, and tolerability of cetilistat in a randomized, placebo-controlled phase 2 trial in obese diabetics: comparison with orlistat (Xenical). *Obesity (Silver Spring)* 2010; **18**: 108–15.

105 Takeda. *Norgine and Takeda Announce the New Drug Application Approval of OBLEAN® Tablets 120 mg in Japan for the Treatment of Obesity With Complications*, 2013. http://www.takeda.com/news/2013/20130920_5991.html (accessed 28 October 2015).

106 Gadde KM, Yonish GM, Foust MS, Wagner HR. Combination therapy of zonisamide and bupropion for weight reduction in obese women: a preliminary, randomized, open-label study. *J Clin Psychiatr* 2007; **68**: 1226–9.

107 Orexigen. *Orexigen® Therapeutics Phase 2b Trial for Empatic™ Meets Primary Efficacy Endpoint Demonstrating Significantly Greater Weight Loss Versus Comparators in Obese Patients*, 2015. http://ir.orexigen.com/phoenix.zhtml?c = 207034&p=irol-newsArticle&ID=1336796 (accessed 28 October 2015).

108 Kim DD, Krishnarajah J, Lillioja S et al. Efficacy and safety of beloranib for weight loss in obese adults: a randomized controlled trial. *Diabetes Obes Metab* 2015; **17**: 566–72.

109 *An Efficacy and Safety Study of Beloranib in Obese Subjects With Type 2 Diabetes Mellitus.* https://clinicaltrials.gov/ct2/show/NCT02324491 (accessed 28 October 2015).