Horizons in the Pharmacotherapy of Obesity

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Abstract:

Obesity drugs have had a chequered history. In the recent past, only the low efficacy, pancreatic lipase inhibitor orlistat was available worldwide and it was little used. The 5HT$_{2C}$ agonist lorcaserin, and two combinations of old drugs have been approved in the United States but not in Europe. The diabetes drug liraglutide has been approved in both the US and Europe and seems likely to be most widely accepted. In view of regulators’ caution in approving obesity drugs, some (like beloranib) may initially be progressed for niche obesity markets. New drug targets have been identified in brown adipose tissue with the aim of not only activating thermogenesis but also increasing the capacity for thermogenesis in this tissue. Attempts are being made to match the efficacy of bariatric surgery by mimicking multiple gut hormones. Unapproved pharmacotherapies are tempting for some patients. Others remain optimistic about more conventional routes to pharmacotherapy.
Introduction

Obesity and the diseases with which it is associated are some of the most common health issues that we face today. There are a number of pharmacotherapies for the associated diseases, such as diabetes, cardiovascular diseases and some cancers, but pharmacotherapy is little used for obesity itself. I shall describe drugs and drug discovery approaches that offer new hope, whilst also highlighting some less conventional routes. Table 1 gives an approximate guide to the relative efficacy of drugs that are approved in some jurisdictions or under clinical investigation.

The first drugs for obesity increased metabolic rate, but most of those that followed interacted with central neurotransmitters and reduced energy intake. One, orlistat, reduces fat absorption. Today there is a focus on reducing energy intake by mimicking or opposing gut hormones, together with a renewed interest in therogenic drugs. Some experimental drugs act on peripheral metabolic pathways [1] but this will not be discussed here.

Disappointments past and present

From thyroid hormones in the 1890s and the uncoupling agent dinitrophenol in the 1930s, through amphetamines and related compounds in the second half of the 20th century, to sibutramine and rimonabant in the 21st, anti-obesity drugs have come and – when found to be unsafe – gone [2,3]. In many countries, until very recently, the only remaining drug was orlistat, which inhibits gastric and pancreatic lipases and thereby the digestion of fat. Orlistat was approved by the Food and Drug Administration (FDA) of the United States in 1999 and marketed in most countries under the name Xenical. Despite massive market potential, it made little headway until 2007 when the FDA approved a half-strength version for sale without a prescription. This was sold under the name alli. In 2007 alli had the largest market share of all obesity drugs (sibutramine and rimonabant were still available) but its sales were nevertheless below $260M in that year. The following year sales dropped by 50%. The approval of alli by the European Medicines Agency (EMA) in 2009 saw only a temporary recovery in sales.

The median duration of use of orlistat (as Xenical) in the United States between 2002 and 2011 was 48 days [4]. Only 10% and 2% of patients were still using it after one and two years respectively. Two other anti-obesity drugs, phentermine and sibutramine, fared little better, each with median durations of use of 60 days. (Phentermine should not be used for more than 84 days, but some patients take it for longer.) For comparison, the figure for captopril, which is used to treat hypertension, was 164 days. The short duration of use of orlistat is probably due to its gastrointestinal side-effects and limited efficacy. In meta-analyses of clinical trials, average weight loss with the higher dose of orlistat (as in Xenical) reaches only about 2.7 to 2.9 kg more than placebo [5,6] (Table 1). The lower dose elicited
weight loss relative to placebo of 0.8 kg [6]. A recent analysis that focussed on maintenance of weight loss after ≥5% weight loss before introducing orlistat, found weight loss over ≥ 12 months of 2.34 kg. The figure for the alli dose was 0.70 kg [7]. Weight loss in routine clinical practice may be less well maintained, or even insignificant after three years [8]. Another pancreatic lipase inhibitor, cetilistat (brand name Cametor or Oblean in Japan from Takeda) was approved in Japan in September 2013. It has not been launched in Japan, but is being sold by an Indian company [9]. It has similar efficacy to orlistat, but is claimed to show a reduced incidence of gastrointestinal side-effects [10,11].

In the United States, the amphetamine-related drugs benzphetamine, diethylpropion phendimetrazine and phentermine remain available for short-term use. Of these phentermine is prescribed most [4]. These drugs have not been available in Europe since 2000.

Two drugs were launched in the United State in 2012 and 2013: a combination of phentermine and the anti-convulsant topiramate (brand name Qsymia) by Vivus in September 2012, and the 5HT2C receptor agonist lorcaserin (brand name Belviq) by Arena and Eisai in June 2013 (though approved in 2012 by the FDA before Qsymia). These, like most other new drugs of the past 40 years are approved for long-term use, unlike the amphetamine-related drugs.

So far, Qsymia and Belviq have not revolutionised the pharmacotherapy of obesity. First, phentermine/topiramate has been rejected by the EMA on the grounds that its benefits do not outweigh its risks, while the new drug application for lorcaserin was withdrawn when it became clear that it would suffer a similar fate [12,13]. The different stances of the FDA and EMA and the particular focus of regulatory authorities on cardiovascular risk are discussed by Pucci & Finer [14]. A number of articles and letters have been published recently that question the value of these drugs, or support them provided they are discontinued in patients who do not achieve weight loss of at least 5 kg within 12 weeks [6,13]. Lorcaserin elicits average weight loss of about 3.2 kg more than placebo (better than orlistat but still poor) and there are worries about its preclinical safety and psychiatric risks. There is no evidence that it increases valvulopathy [15], which was the main cause of the demise of the 5HT releasers and reuptake inhibitors fenfluramine and dexfenfluramine. This may remain a concern in the minds of some regulators, however. The standard (ie middle) dose of phentermine/topiramate elicits greater weight loss (6.7 kg; Table1), but with one of its components, phentermine, unavailable in Europe owing to psychiatric and cardiovascular concerns, it is unsurprising that it was not approved [6,12]. CNS and gastrointestinal side-effects of topiramate add to these worries.

Second, even in the US, sales of Qsymia (phentermine/topiramate) and Belviq (lorcaserin) have been very low. In the third quarter of 2014, sales of Qsymia were about $12.5M [16]. At a cost of $500 per person per quarter, this corresponds to 25,000 patients, whereas there are about 83 million people in the United State with a BMI > 30 kg.m\(^{-2}\) [17]. One reason for
these limited sales is that many patients find the side-effects of Qsymia (paraesthesia; cognitive changes; dry mouth; depression) unacceptable [18]. In the same period sales of Belviq totalled $20M [19], which corresponds to about 37,000 patients. Thus less than one in a thousand of obese subjects in the United States were taking Qsymia or Belviq in the third quarter of 2014. Doubts as to whether the benefits outweigh the risks of these drugs are probably enhanced by previous failures of anti-obesity drugs.

Looking to the horizon, prospects for orlistat, phentermine/topiramate and lorcaserin seem poor, though some analysts are optimistic.

**Recent approvals**

The combination of the dopamine and noradrenaline reuptake inhibitor bupropion and the μ-opioid antagonist naltrexone is branded by its makers Orexigen as Contrave in the United States and MysiDba in Europe. Already launched in the United States in October 2014, it was recommended for approval in Europe in December 2014, despite the FDA being concerned about its cardiovascular effects [14]. The European Commission is being lobbied by a consortium of European consumer groups that is concerned by its cardiovascular safety [20]. This concern was being addressed in the “Light Study” demanded by the FDA. This study was due to continue to 2017, but has now been abandoned. A provisional evaluation in 2014 was key to the approval by the FDA [21]. The FDA objected to Orexigen releasing provisional data [22,23], which now appears to have given a misleading impression of cardiovascular safety. A new study is planned. Weight loss after a year’s treatment is 4 to 5 kg greater than for placebo [6,21]. Nausea is the most reported adverse event [24].

Liraglutide (Novo Nordisk), which is an analogue of glucagon-like peptide-1 (GLP-1), was approved by the FDA for the treatment of obesity in December 2014. A month later, it was recommended for approval by the EMA. These approvals always seemed likely because liraglutide has been widely used as a treatment for type 2 diabetes (under the brand name Victoza) since 2009 in Europe and 2010 in the United States. However, the dose level for use in obesity (under the brand name Saxenda) is 3 mg once daily, compared with a maximum dose of 1.8 mg for diabetes. Being a peptide, liraglutide is administered by subcutaneous injection [14,25]. This may restrict its widespread use in obesity and thereby mitigate the impact of any unforeseen risks. Weight loss in a 20-week trial in non-obese patients was 4.4 kg higher than in the placebo group [26]. A greater benefit (5.9 kg) was reported for a trial of weight maintenance following a 12-week low-calorie diet [27]. The mechanism of action of liraglutide endows it with anti-diabetic activity beyond what might be predicted from its anti-obesity activity. There is however some concern about a slight increase in heart rate. The clinical relevance of this is being addressed in a long term study [14]. A study in mice showed that injection of liraglutide in the ventromedial nucleus of the hypothalamus stimulates brown adipose tissue thermogenesis [28]. This response might be mediated by activation of the sympathetic nervous system, which might also be responsible for the increase in heart rate in humans.
The horizon for bupropion/naltrexone and liraglutide (as an anti-obesity drug) is unclear. Sales of bupropion/naltrexone have passed those of phentermine/topiramate in the United States, but cardiovascular safety is an unresolved issue. The outlook for liraglutide seems hopeful in the short-term, but in the longer term it may be challenged by GLP-1 receptor agonists that can be administered once a week, rather than once a day [29]. The first long-acting GLP-1 receptor agonist, a formulation of exenatide, does not, however, appear to be a contender. The once-weekly formulation of exenatide elicited weight loss from baseline of 2.4 kg over 24 weeks in type 2 diabetic subjects, which was not significantly greater than the effect (1.4 kg) of the twice daily formulation [30]. At the dose used to treat type 2 diabetes (1.8 mg), liraglutide (once daily) elicits average weight loss of about 2.7 kg compared to placebo [31].

Niche obesity markets

Regulators are understandably concerned about approving obesity drugs that could potentially be used by over half the adult population within their jurisdictions. A more cautious approach is to focus on a minor segment of the obese population. This would seem to fit with the recent announcement by the EMA of an adaptive licensing initiative, especially if the unmet need is serious, or there are reasons for adopting a compassionate approach [32]. As experience is gained with new drugs, their use might be extended to a larger patient population.

Beloranib and Prader-Willi syndrome

Zafgen Inc. are developing their methionine aminopeptidase inhibitor beloranib for the treatment of obesity in patients with the rare genetic disorder Prader-Willi syndrome. Beloranib is an analogue of the anti-microbial agent fumagillin. It was originally identified as an angiogenesis inhibitor [33]. A phase 3 clinical trial of beloranib in Prader-Willi Syndrome was announced in October 2014. A phase 2 trial in hypothalamic injury-associated obesity, which affects only about 500 patients each year has been completed [34]. Although not the target market, ‘normal’ obese patients treated for 12 weeks with beloranib at its highest dose level lost 10.5 kg more body weight than patients treated with placebo [35]. This is significantly more than most anti-obesity drugs have achieved (Table 1).

Metformin and anti-psychotic drug-induced weight gain

Metformin is an old drug and the first-line drug for the treatment of type 2 diabetes. It has been known for many years that metformin causes only a modest reduction in body weight in diabetic patients [36], though it appears to be at least as effective as orlistat at reducing waist circumference [37]. Recently, there have been reports of its effect on body weight in non-diabetic patients, including children [38]. Children are unlikely to be a niche market for a novel obesity drug, but metformin has also been studied in patients with mood disorders [39] and schizophrenia [40]. These patients include schizophrenic patients newly treated
with anti-psychotic drugs, notably olanzapine, that promote weight gain [41,42]. The body weight benefits achieved in some of these studies have been markedly greater than in type 2 diabetic patients. Thus a meta-analysis of fourteen studies in children showed a 1.38% decrease in BMI over 6 months compared to placebo [38], and a meta-analysis of twelve studies in olanzapine-treated patients showed a 5.02 kg difference in body weight gain between those treated with metformin and placebo [41].

In addition to metformin, mifepristone, amantadine, zonisamide and betahistine reduce anti-psychotic drug-induced weight gain [43,44,45]. Any novel drug that targets this market would preferably have advantages over these drugs, as they are approved for other indications.

Eating disorders

Binge eating disorder involves episodes of uncontrollable excessive eating without subsequent purging. A large proportion (85%) of those diagnosed are obese or overweight [46]. In January 2015, the FDA approved the amphetamine-like drug lisdexamfetamine for the treatment of binge eating disorder [47]. Lisdexamfetamine was already used for the treatment of attention deficit hyperactivity disorder. Weight loss in an 8-week study was 4.2 kg higher in subjects treated with lisdexamfetamine than in those treated with placebo [48]. Eleven- and twelve-week studies have recorded weight losses of between 5.2 and 6.25% [49]. The amphetamine-like nature and side-effects of lisdexamfetamine will raise concerns for the EMA.

A number of other drugs have been investigated for the treatment of binge eating disorder but few of these have been used as anti-obesity drugs. Two exceptions are topiramate [50] and sibutramine [51]. Regulatory authorities might feel more comfortable approving drugs for binge eating disorder, if they are less effective or ineffective in general obesity and therefore less likely to be used off-label. Studies in rodents indicate that the aldehyde dehydrogenase-2 inhibitor GS455534 and the orexin-1 receptor antagonist GSK1059865 selectively inhibit intake of palatable food [52,53]. Drugs that are unlikely to be approved for general obesity, however, would be less attractive to the pharmaceutical industry.

The other major eating disorder is bulimia nervosa, for which fluoxetine if the only drug approved by the FDA [54]. Fluoxetine is an SSRI antidepressant that causes some short-term weight loss [55]. Bulimia might offer another route to entry into the wider obesity market.

Post-bariatric surgery

Bariatric surgery is the most effective treatments for obesity [56] but regain of between 20 and 30% of the weight initially lost is common [57]. There is anecdotal evidence that topiramate reduces binge eating and weight regain following bariatric surgery [58]. Prevention of weight regain following bariatric surgery might offer a niche indication for the entry of a drug into the obesity market.
Phase 2 Clinical Trials and Novel targets

Among drugs in phase 2 clinical trials for obesity are compounds targeting melanocortin-4 receptor, the histamine H3 receptor, the intestinal microsomal transfer protein and the sodium-glucose cotransporter 2 (SGLT-2) [59]. SGLT-2 is the target of approved drugs for diabetes, which lower blood glucose (and body weight) by increasing renal glucose excretion. The SGLT-2 inhibitor canagliflozin caused weight loss over 12 weeks in non-diabetic obese subjects, but at the most effective dose this was only 1.6% greater than with placebo [60]. Thus, although like liraglutide there will be ample experience of SGLT-2 inhibitors from their use in diabetes, weight loss may prove insufficient for them to be used to treat obesity alone.

This rest of this section will address two high-profile areas for research into novel targets for anti-obesity drugs.

Brown adipose tissue

Brown adipose tissue contains uncoupling protein-1 (UCP-1). When UCP-1 is activated by fatty acids, brown adipose tissue burns fat without synthesising ATP. Brown adipocytes, including human brown adipocytes [61], express the β3-adrenoceptor (β3-adrenergic receptor). From the 1970s until about 2009 the prevailing view, despite some evidence to the contrary, was that brown adipose tissue is present in human neonates and infants but does not occur in significant amounts in adult humans. This partly explained why β3-adrenoceptor agonists performed poorly in clinical trials for obesity and type 2 diabetes, despite performing well in rodent models. Recent studies in which positron emission tomography combined with computed tomography is used to measure and localise the uptake of 18F-fluorodeoxyglucose glucose into tissues, together with surgical intervention to demonstrate that sites of high uptake have multilocular adipocytes that express UCP-1, have, however, demonstrated unequivocally that active brown adipose tissue is present in at least some adult humans [62].

These studies have led to a surge in interest in brown adipose tissue as a target for thermogenic anti-obesity drugs, spurred on by the recognition of a lineage of ‘beige’ or ‘brite’ adipocytes that derive from white adipocytes in response to certain stimuli, such as cold [63]. Unfortunately, there tends to be less functional brown adipose tissue in obese than in lean subjects. Therefore, it is important not only to acutely activate thermogenesis in brown adipocytes but also to increase their number and their capacity for thermogenesis [64]. Among the approaches being investigated are mimetics of irisin and fibroblast growth factor-21 [65,66], though recent work casts doubt on the role of irisin because many studies have used commercial ELISA kits to detect irisin that cross-react with other proteins [67].

If brown adipose tissue plays a significant role in adult humans, should β3-adrenoceptor agonists be reconsidered for the treatment of obesity and type 2 diabetes? In rodents
dogs [70] and rhesus monkeys [71] β3-adrenoceptor agonists not only activate thermogenesis but, when given repeatedly, they increase the capacity of brown fat to respond to acute activation. Moreover, in phaeochromocytoma, an adrenal medulla neuroendocrine tumour, over-secretion of noradrenaline and adrenaline causes a marked increase in brown adipose tissue mass in humans, associated with reduced body fat content [72,73].

The only β3-adrenoceptor agonist approved for use in humans is mirabegron, which is used in the treatment of overactive bladder. From 210 to 250 min after giving four times its therapeutic dose, it increased resting metabolic rate by 13% [74]. If this increase could be sustained over 24 hours, one would expect weight loss of 5 kg in the first year [75]. However, the subjects were twelve lean young men selected from fifteen candidates, the other three not showing detectable brown adipose tissue activation in response to cold. There is less active brown fat not only in obese than lean subjects, but also in old than in young subjects, emphasising the need to increase thermogenic capacity during chronic treatment with β3-adrenoceptor agonists.

**Mimicry of bariatric surgery**

Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy, the most effective bariatric surgery procedures, elicit mean weight loss of about 40 kg [76]. Weight loss cannot easily be explained in terms of malabsorption, raising the possibility that changes in gut hormones, signalling molecules released by gut microbiota, or neuronal signalling from the gut play a role [77]. Of these, gut hormones offer the most obvious targets for pharmacotherapy [78]. The GLP-1 receptor agonist liraglutide elicits far less weight loss than bariatric surgery (Table 1), and it has been hypothesised that no single gut hormone is dominant in mediating the effects of bariatric surgery. Therefore, compounds have been investigated in rodents that mimic two [78] or even three gut hormone receptors, such as a ‘trianagonist’ of the GLP-1, glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors [79].

Vertical sleeve gastrectomy causes weight loss and improves glucose tolerance in diet-induced obese mice, but these effects are substantially reduced in mice in which the farnesoid-x receptor (FXR), a bile acid receptor, is disrupted [80]. This suggests that FXR agonists should cause weight loss in diet-induced obese mice. Inconsistent results have been obtained with such compounds, however [81,82,83]. Recently, the gut-restricted FXR agonist fexaramine has been reported to reduce obesity and insulin resistance in mice. These effects are associated with browning of adipose tissue [84], which raises the possibility that fexaramine increases sympathetic activity.
Less conventional routes

Whilst regulators can ensure that only effective and safe drugs are available to patients through pharmacies, they can do little to prevent patients from taking substances that are classified as foods or easily obtained because they are approved for other uses. Some of these substances might be as effective as previously approved anti-obesity drugs, but without the backing of a pharmaceutical company it is difficult to evaluate them in large clinical trials. They might also, of course, be unsafe by the standards demanded of regulators for anti-obesity drugs.

Cold, capsaicin and nicotine

The recent interest in brown adipose tissue has led to a reappraisal of earlier work [85] on the benefit of reduced ambient temperature in the treatment of obesity [86]. Some fat loss was observed in a 6-week study [87]. However, skeletal muscle made a far greater contribution that brown adipose tissue to systemic glucose uptake in response to cold [88], raising the possibility that skeletal muscle might also make a greater contribution to cold-stimulated thermogenesis.

Reducing the ambient temperature is not a comfortable way to lose weight, and so capsinoids, which like cold activate the sympathetic nervous system, have been investigated as an alternative approach. They were ineffective in reducing body fat in a 6-week study [87], but reduced abdominal fat in a 12-week study [89].

Nicotine also raises sympathetic activity as well as reducing appetite [90]. This has led to speculation that e-cigarettes might have an anti-obesity effect. It is unclear, however, whether smoking normal cigarettes has a long-lasting anti-obesity effect [91] or whether nicotine patches reduce weight gain following smoking cessation [92]. Moreover, smoking increases the incidence of the metabolic syndrome [91].

Any treatment that activates the sympathetic nervous system is likely to have adverse cardiovascular effects. The cardiovascular effects of sibutramine that led to its withdrawal as an anti-obesity drug were linked to increased sympathetic activity [3], and the adverse cardiovascular effects of smoking may be due in large part to increased sympathetic activity [93]. The incidence of myocardial infarction increases in cold weather, again potentially due to increased sympathetic activity [94].

Testosterone

Weight loss in response to most anti-obesity drugs plateaus after about 6 months of treatment. By contrast, in recent studies restoration of testosterone levels to the
physiological range in obese hypogonadal men with and without type 2 diabetes caused weight loss that continued for five to six years, reaching 15 to 20% [95,96]. These were uncontrolled studies, but weight loss was so large that it is very unlikely that it can be attributed to a placebo effect. Moreover, weight loss has also been demonstrated in controlled studies of shorter duration. Markers of metabolic and cardiovascular health are improved in hypogonadic men [96,97] but not in men without hypogonadism [98]. However, some studies have suggested that testosterone might increase cardiovascular risk, and although these have been strongly criticised, the FDA has decided to review the risks associated with testosterone treatment [97,99]. For this and possibly commercial reasons, testosterone may never be approved for the treatment of obesity in hypogonadic men. This is a controversial area that requires further randomised clinical trials [100].

Conclusions

Very few patients are currently treated with anti-obesity drugs. Of recently approved drugs, liraglutide seems best placed to make an impact in both the United States and other markets. Some drugs may be targeted to niche obesity markets because they are more effective in these than in the general obese population, or because they present too large a risk to be released directly to a large number of patients. Pharmaceutical companies will continue to explore new drug targets as long as the large unmet medical need remains. Patients, meanwhile, will be tempted to explore unapproved and potentially risky pharmacotherapies.

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Compliance with Ethics Guidelines

Conflict of Interest Jonathan RS Arch declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.
Table 1 Average weight loss in response to pharmacotherapy: a approximate guide to relative efficacy. Studies are of 6 months or longer duration in obese subjects and weight loss is relative to the response to placebo and given in kg, unless indicated otherwise.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Other details</th>
<th>Weight loss</th>
<th>Reference/source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Xenical dose</td>
<td>2.7 – 2.9</td>
<td>[5,6]</td>
</tr>
<tr>
<td></td>
<td>alli dose</td>
<td>0.8</td>
<td>[6]</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td></td>
<td>3.2</td>
<td>[6]</td>
</tr>
<tr>
<td>Phentermine/topiramate</td>
<td>7.5/46 mg</td>
<td>6.7</td>
<td>[6,18]</td>
</tr>
<tr>
<td>Bupropion/naltrexone</td>
<td>360/32 mg</td>
<td>4 – 5</td>
<td>[6,21]</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>3 mg</td>
<td>4.4/5.9</td>
<td>[26,27]</td>
</tr>
<tr>
<td>Beloranib</td>
<td>12 week study</td>
<td>10.5</td>
<td>[35]</td>
</tr>
<tr>
<td>Metformin</td>
<td>Olanzapine-treated; 12 weeks</td>
<td>5.0</td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>1.38% BMI</td>
<td>[38]</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>11-12 weeks</td>
<td>3.1 – 4.9</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td>Placebo ‘did not reduce weight’</td>
<td>(5.2 – 6.25%)</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>5 to 6 years. No placebo.</td>
<td>17.5/21.5</td>
<td>[95,96]</td>
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References


9. Top 100 diet pills Cametor review. Available at http://top100dietpills.com/cametor-review/
Acessed April 14, 2015.


49. Citrome L (2015) Lisdexamfetamine for binge eating disorder in adults: a systematic review of the efficacy and safety profile for this newly approved indication - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? International Journal of Clinical Practice 69: 410-421. • Lisdexamfetamine has been approved for the treatment of binge eating disorder in the US.


**Prolonged effect of testosterone on body weight.**


**The testosterone debate.**