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Review

Naltrexone/bupropion for obesity: An investigational combination pharmacotherapy for weight loss

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ABSTRACT

The mechanism of action of the combination therapy, naltrexone/bupropion (NB), for obesity has not been fully described to date. Weight loss attempts rarely result in long-term success. This is likely a result of complex interactions among multiple peripheral and CNS systems that defend against weight loss, and may explain the overwhelming lack of effective obesity treatments. NB is an investigational combination therapy for obesity that was developed based on evidence that obesity involves alterations in the hypothalamic melanocortin system as well as brain reward systems that influence food craving and mood. Naltrexone and bupropion both have actions in these brain regions that may cause them to influence food intake, food craving, and other aspects of eating behavior that affect body weight. We review the individual actions of naltrexone and bupropion in brain hypothalamic and reward systems, and describe the current in vitro, in vivo, and clinical evidence for how NB influences food intake and produces weight loss.

Contents

Abbreviations: AgRP, agouti-related peptide; α-MSH, α-melanocyte stimulating hormone; CNS, central nervous system; COR, Contrave Obesity Research; DIO, diet-induced obese; fMRI, functional magnetic resonance imaging; MC4R, melanocortin-4 receptor; MOP-R, μ-opioid receptor; NB, naltrexone/bupropion combination; NB16, 16 mg/day naltrexone sustained-release (SR) plus 360 mg/day bupropion SR; NB32, 32 mg/day naltrexone sustained-release (SR) plus 360 mg/day bupropion SR; NB48, 48 mg/day naltrexone sustained-release (SR) plus 360 mg/day bupropion SR; POMC, pro-opiomelanocortin; VTA, ventral tegmental area.

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1. Overview of obesity and current obesity pharmacotherapies

Obesity increases the risk for diabetes, cardiovascular disease, osteoarthritis, cancer, and early mortality [1]. Since the mid 1970s, the incidence of adult obesity has doubled, while the incidence of overweight/obesity in children, adolescents and young adults has tripled [2,3]. Currently, 36% of adults and 17% of children in the United States are considered obese [4,5]. This has occurred in spite of public health advice about the benefits of exercise and reducing caloric intake. The increasing prevalence of obesity and its comorbidities has been predicted to account for 16–18% of US health care costs by 2030 [6] and to initiate the first decrease in life expectancy in modern history [7]. Behavioral interventions such as diet and exercise are the most common treatments for weight loss, but many overweight and obese individuals are unable to achieve moderate weight loss with behavioral intervention alone [8]. The increase in the prevalence of obesity is a clear indication of the failure of behavioral intervention to produce sustained and meaningful weight loss in today's obesogenic environment, and highlights the need for additional methods of weight loss.

Obesity is generally regarded as a chronic disease requiring continuous intervention to maintain ideal body weight [8,9]. Of the few treatments available for obesity, bariatric surgery is the most effective, resulting in weight loss of about 25% at 2 years post-surgery and improvements in many cardiometabolic risk factors [10,11]. Common limitations of bariatric surgery include peri- and post-operative complications, cost, and access. Bariatric surgery is associated with a 7.3% peri-operative complication rate, a 1.6–3.5% incidence of serious complications, conversions and reoperations, weight regain, and recurrent binge-eating [10,12].

Pharmacological treatments for obesity offer a less invasive alternative to bariatric surgery but the field has been hampered by few treatment options, limited efficacy, and uncertainty about the safety of long-term use in the general population. In recent years, the high-profile withdrawal of obesity drugs (e.g., sibutramine) from the market due to safety issues has left physicians with few treatment options, increased concern about the safety of pharmacotherapy options, and caused confusion about how to effectively manage obesity. Recent approval of 2 new obesity drugs by the FDA in 2012 increased the total to 3 FDA-approved long-term pharmacological treatments for obesity: orlistat, lorcaserin, and the combination of phentermine and topiramate [13]. Orlistat is a lipase inhibitor that reduces the body's ability to absorb fat from food. Weight loss with orlistat is modest, ranging from 2% to 4% greater than placebo [14–17]. Lorcaserin is a serotonin receptor (5-HT_{2C}) agonist that causes selective activation of CNS serotonin receptors. It was designed to avoid the side effect of serotonin-associated valvulopathy previously seen with non-selective serotonin-receptor agonists such as fenfluramine. At 1 year, placebo-subtracted weight loss with lorcaserin is about 3% in the intent-to-treat population or 4% in study completers (study participants who remained on drug for the duration of the study) [18–20]. Phentermine has been approved for short-term obesity treatment since 1959, and topiramate is an anticonvulsant that has shown weight-loss effects [21]. Various doses of phentermine/topiramate produced placebo-subtracted weight loss of 4–9% after 1 year of treatment in the intent-to-treat population or 5–12% in study completers [22–24].

With the exception of orlistat, which has a clear peripheral mechanism of action, lorcaserin and phentermine/topiramate are presumed to produce weight loss via actions in the brain, though the exact mechanisms are unknown [25]. They are presumed to reduce food intake by influencing appetite or eating behavior, though they may also have other effects that contribute to weight loss. Many physiological processes that reduce appetite also reciprocally regulate energy expenditure, although this has not been formally assessed in humans with any of the therapies discussed here.

2. Obesity and the brain

Body weight is influenced by energy intake and expenditure, both of which are regulated by the brain [26]. Brain systems that balance energy intake and expenditure are biased toward weight conservation in most individuals. This appears to make evolutionary sense, as weight conservation would protect against food shortage. Weight loss is often associated with reduced energy expenditure [27], requiring a greater reduction in caloric intake in order to maintain reduced body fat. Additionally, the intrinsic reward value of food often promotes consumption of more calories than necessary, resulting in weight gain over time [26].

Obesity is associated with alterations in neural signaling. Differences in neural responses to hunger and satiation are documented in obese vs. lean individuals [28] and women appear to exhibit lower cognitive control of brain responses to food stimuli than men [29]. Persistence of abnormal neural responses to a meal in formerly obese individuals, a group at high risk for relapse, indicates that a tendency to obesity may involve areas of the brain that control complex aspects of eating behavior including anticipation and reward, chemosensory perception, autonomic control of digestion, and memory [30]. Weight loss is also associated with increases in neural activity in brain regions involved in reward processing and valuation of food stimuli, as well as decreased activity in regions involved in restraint in response to food [31,32]. These changes likely drive the delayed satiation, decreased perception of caloric intake, and increased hunger observed after a 10% weight loss [33]. Furthermore, dieting is associated with increases in food preoccupation and food craving [34,35]. Consequently, significant and sustained weight loss in overweight or obese individuals is often accomplished by significant increases in dietary restraint or eating control [36,37]. Considering the broad availability of aggressively marketed, highly palatable food in developed countries, obesity drugs that reduce hedonic feeding behavior may be especially helpful [38,39]. Some of the currently available obesity therapies are thought to produce weight loss by influencing reward-mediated eating behavior through a variety of CNS mechanisms, though further study is needed [39].

2.1. Brain regions that influence energy balance

2.1.1. The hypothalamic melanocortin system

The melanocortin system in the hypothalamus (Fig. 1) is a fundamental component of CNS regulation of homeostatic energy

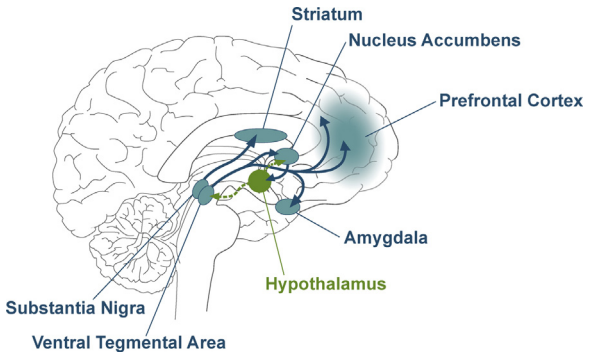

Fig. 1. Homeostatic (hypothalamus) and hedonic (reward system) regulation of energy balance. The hypothalamus (green) is important for regulation of homeostatic energy balance, while the reward system (blue) is important for processing the rewarding aspects of food and food-related stimuli. The reward system includes dopamine pathways that originate in the ventral tegmental area (VTA) or substantia nigra and project to regions including the striatum (movement, reward salience), nucleus accumbens (reward, addiction), prefrontal cortex (decision making, executive function), and amygdala (memory, emotion). The hypothalamus consists of cells that detect and integrate information related to energy state, such as glucose, leptin, and insulin. The lateral hypothalamus projects to the VTA, and also receives input from regions such as the nucleus accumbens. These connections are important for integrating the rewarding and homeostatic aspects of food seeking, avoidance, and other aspects of eating behavior. (For interpretation of the references to color in this legend, the reader is referred to the web version of the article.)

balance [40]. Cells in this brain region detect and integrate blood-borne and neural signals that relay information concerning energy availability to influence food intake and energy expenditure. Two key cell populations in the melanocortin system reside in the arcuate nucleus of the hypothalamus: pro-opiomelanocortin (POMC) cells and agouti-related peptide (AgRP) cells. These cells produce peptides that competitively bind to the melanocortin-4 receptor (MC4R) [41–44]. POMC cells produce α-melanocyte stimulating hormone (α-MSH), an MC4R agonist. Stimulation of the MC4R by α-MSH produces an overall anorexic effect, increasing energy expenditure and decreasing appetite in both animals and humans [45,46]. Conversely, AgRP is an MC4R antagonist that competitively blocks α-MSH, resulting in increased food intake and energy conservation [47].

Signals that stimulate POMC cells (such as leptin, an adipose tissue-derived hormone that can reduce food intake and body weight) generally produce an anorexic effect [48,49], whereas signals that stimulate AgRP cells (such as ghrelin, a hunger-stimulating hormone produced in the stomach), reduce energy expenditure and increase appetite [40,50–52]. Therefore, agents that stimulate POMC activity have been developed as possible obesity therapies, though few agents have been successful. One reason for the lack of success thus far may be that the melanocortin system is equipped with feedback mechanisms that limit sustained stimulation of POMC cells.

The endogenous opioid, β-endorphin, is produced from the POMC precursor peptide and is released from POMC cells along with α-MSH [53,54]. POMC cells are inhibited by opioids such as β-endorphin via stimulation of the μ-opioid receptor [55]. Thus, β-endorphin is thought to act as an autoinhibitor of POMC neurons [48,56]. Mice that develop obesity and insulin resistance through chronic maintenance on a high-fat diet [57] have increased hypothalamic β-endorphin [58]. It is possible that this increase in β-endorphin, coupled with decreased sensitivity to anorexic signals [59], contributes to the development of obesity. In normal weight animals, blockade of the μ-opioid receptor results in increased POMC activity [48]. Thus, blocking β-endorphin-mediated autoinhibition of POMC neurons with a μ-opioid antagonist may block this counter-regulatory pathway and facilitate weight loss in obesity.

2.1.2. The reward system

The mesocorticolimbic dopamine system (reward system) originates in the midbrain and projects to forebrain areas including the ventral striatum, prefrontal cortex and amygdala (Fig. 1) [60,61]. The reward system plays a central role in regulation of eating behavior by mediating the rewarding effects of pleasurable stimuli (food, sex and drugs of abuse) and governs reward-directed behavior [26,39,60,62,63].

In the reward system, dopamine and opioid systems facilitate feeding in an interdependent manner [64]. Dopamine release in the ventral striatum mediates the association between food and the positive experience of eating that food, which drives the degree of 'wanting' or desire for certain foods [65]. Dopamine also regulates the activity required for food seeking behavior [66]. In contrast, striatal opioids modulate the 'liking', or pleasurable feeling of rewarding stimuli [67,68]. In other words, whereas opioids convey the reward sensation of palatable foods, dopamine regulates the reward value of food and how hard we are willing to work to obtain that reward.

The availability of highly palatable food increases reward-based or hedonic feeding in humans and animals [69] and individual differences in the neurophysiology of the reward system have been identified that may explain why certain individuals are at greater risk for weight gain [70,71]. Furthermore, the reward system can undergo neuro-adaptations in response to chronic exposure to rewarding stimuli and it appears that similar changes occur in obesity [72,73]. In animals and humans, obesity is associated with alterations in striatal dopamine signaling [70,74–78]. Physiological signals like leptin were originally thought to act primarily in the hypothalamus; however, they also influence activity of dopamine cells in the reward system [79–83]. In obesity, the sensitivity of the reward system to signals such as leptin may be impaired [84,85].

3. Individual effects of naltrexone and bupropion on energy balance

The naltrexone/bupropion combination (NB) is an investigational obesity therapy that was developed to target neural pathways that regulate homeostatic food intake and energy expenditure [86,87] as well as hedonic eating behavior and decision making [35]. Preclinical and clinical studies with naltrexone and bupropion indicate that these agents may act in homeostatic and reward pathways to influence food intake and body weight [88].

3.1. Naltrexone

Naltrexone is an opioid antagonist with a high affinity for the μ-opioid receptor. Approved for treatment of alcoholism and opioid addiction [89–91], naltrexone influences eating behavior in animals. The hypothalamic melanocortin and reward systems contain opioid neurons [92,93], hence naltrexone activity may influence food intake and body weight via these dual systems.

Although there are several opioid receptors, genetic and pharmacological preclinical studies implicate the μ-opioid receptor in eating behavior. Mice engineered to lack the μ-opioid receptor are resistant to obesity induced by a high fat diet [94]. Chronic administration of naltrexone increases POMC mRNA [95]; this would be expected to restore activity of POMC neurons and melanocortin satiety systems [96,97]. These results are consistent with the hypothesis that naltrexone blocks β-endorphin action

at the μ-opioid receptor, thus preventing autoinhibition of POMC neurons.

Studies in animals indicate that acute naltrexone administration influences activity of the reward system and hedonic eating behavior. Systemic naltrexone prevents the increase in dopamine in the nucleus accumbens caused by food ingestion and also reduces food intake [98], food seeking, and binge-like eating [99,100]. Direct injection of naltrexone into the reward system (nucleus accumbens and ventral tegmental area) can reduce preference for highly palatable foods, especially foods that are high in fat and sugar [101–104], as well as expression of flavor preference [105,106], preference for palatable diets following periods of abstention [107], and binge-like eating [100]. Naltrexone produces a more profound reduction in food intake in animals in which endogenous opioid systems have been modified by chronic intake of a high fat diet [108,109].

Human studies also demonstrate that opioids can influence ingestive behavior by modulating subjective palatability. Consistent with the role of opioids in the rewarding aspects of eating, naltrexone reduces the subjective pleasantness, or liking, of certain foods (especially palatable foods); this effect is independent of nausea, a common side effect of naltrexone [110,111]. However, early reports that naltrexone monotherapy reduces food intake [112] and body weight [113] were largely unsubstantiated by subsequent placebo-controlled double-blind studies across a range of doses (50–300 mg/day) [114–117]. Although one study found that weight loss was significant in obese women when results were analyzed by sex [118], this finding has not been replicated. Thus, despite promising preclinical data, naltrexone monotherapy-mediated blockade of opioid neurotransmission is insufficient to produce reliable decreases in food intake in humans.

3.2. Bupropion

Bupropion is an atypical antidepressant currently approved as an aid in smoking cessation and for the treatment of depression and seasonal affective disorder [119–121]. Bupropion inhibits reuptake of the catecholamines dopamine and norepinephrine, and is a weak nicotinic acetylcholine receptor antagonist [122]. By blocking the removal of synaptic dopamine and norepinephrine, acute peripheral treatment with bupropion produces transient changes in extracellular dopamine and norepinephrine concentrations in the brain [123,124] and may also alter the activity of the neurons that release dopamine and norepinephrine [119,125].

Activity of the melanocortin system is influenced by both dopamine and norepinephrine [126,127], and reduced dopaminergic tone in the hypothalamus is associated with various elements of obesity [128]. Thus, the hypothalamic melanocortin system is a potential site of bupropion action. Indeed, bupropion stimulates activity of POMC cells in vitro [117] and increases α-MSH secretion (Billes & Cowley, unpublished observations). In addition, bupropion's antidepressant effects and efficacy as a smoking cessation aid are consistent with actions in the reward system [129].

Bupropion reduces short-term food intake in lean and obese rodent models and increases energy expenditure by increasing heat production [130–136], although the overall effect of bupropion on body weight in animals is modest [133]. In humans, weight loss is a common side effect of bupropion use for the treatment of depression [121]. In overweight and obese adults, bupropion (300–400 mg/day) for up to 6 months resulted in modest placebo-subtracted weight loss of 2–4% (by intent-to-treat analysis) and 3–5% in study completers [116,117,137–139]. The effect of bupropion on caloric intake in humans has never been studied directly. Early reports indicating no effect of bupropion on food intake were not designed to address this issue and further study is warranted [140,141].

4. Preclinical studies with the naltrexone/bupropion combination

4.1. Naltrexone/bupropion action in the melanocortin system

The combination of naltrexone and bupropion was originally developed based on in vitro studies in the mouse hypothalamus. Cowley and colleagues demonstrated that bupropion acutely increases activity of POMC cells that express enhanced green fluorescent protein (POMC-EGFP) [117]. It was hypothesized that the μ-opioid receptor, which mediates autoinhibition of POMC cells by β-endorphin [48,56], limits the effect of bupropion on increasing POMC activity, resulting in the modest effects of bupropion monotherapy on weight loss and caloric intake described in Section 3.2. Blockade of the μ-opioid receptor with naltrexone alone gradually increases POMC activity; however, simultaneous application of bupropion and naltrexone produces a larger increase in POMC activity (Fig. 2) [117]. Thus, the naltrexone/bupropion combination is thought to do the following: stimulate POMC cells (bupropion) while also removing the natural β-endorphin "brake" on POMC cells (naltrexone) (Fig. 3). These electrophysiological studies were the basis for further investigation of the naltrexone/bupropion combination in vivo.

4.2. Naltrexone/bupropion action in the reward system

Injection of bupropion alone or naltrexone alone directly into the reward system is sufficient to reduce food intake in hungry mice [142]. However direct injection of naltrexone and bupropion produces a synergistic (greater than additive) reduction in food intake (Fig. 4) [142], indicating that naltrexone and bupropion each have independent and complementary actions in the reward system.

4.3. Systemic effects of naltrexone/bupropion

As discussed, systemic administration of either naltrexone or bupropion produces a dose-dependent reduction in food intake in fasted normal weight (lean) mice [117,134] and rats [136]. Coadministration of naltrexone and bupropion produces a greater reduction in food intake that is comparable to the added effects of each drug [117,136]. In mice that are obese after long-term maintenance on a high-fat diet (diet-induced obese [DIO] mice), systemic naltrexone and bupropion each reduce food intake independently, and the combination produces a synergistic decrease in food intake [117]. In DIO rats, combined administration of naltrexone and bupropion also reduces food intake and body weight and results in loss of fat mass [136].

4.4. Summary of preclinical studies

Preclinical studies demonstrate that naltrexone and bupropion have independent actions in 2 brain regions that influence energy balance. In the melanocortin system, bupropion stimulates activity of POMC cells and this action is amplified by the addition of naltrexone, which blocks the endogenous opioid-mediated brake (Fig. 3). These effects are consistent with reduced food intake, increased energy expenditure, and weight loss over time. Additionally, naltrexone and bupropion act directly in the reward system to produce a synergistic effect on food intake; these actions likely influence the relative reward value of food and the activity required for food consumption. Finally, the acute effects of the naltrexone/bupropion combination on food intake are maintained in an obese rodent model.

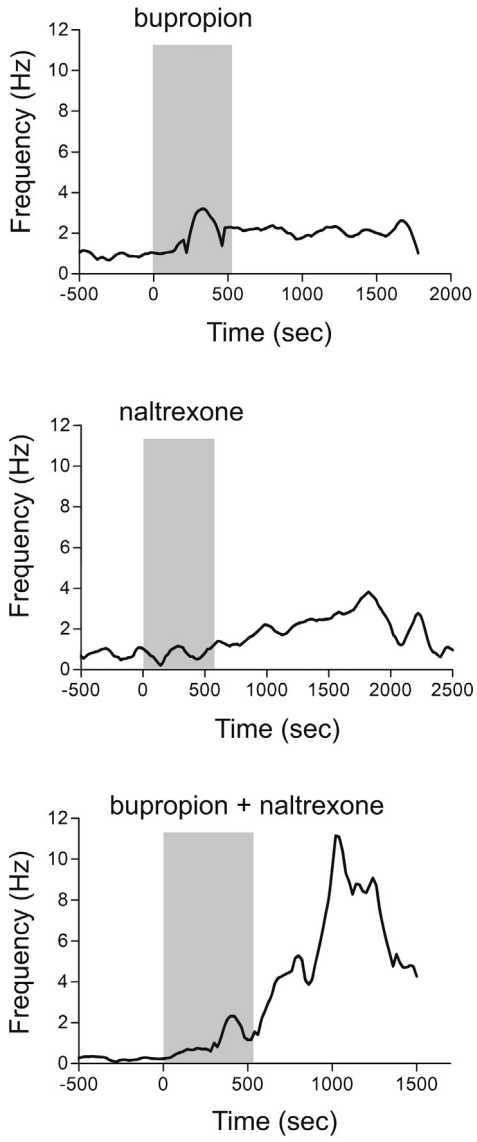

Fig. 2. Effect of naltrexone and bupropion on activity of POMC cells. Application of bupropion (10 μmol/L), naltrexone (1 μmol/L) and naltrexone (1 μmol/L) + bupropion (10 μmol/L) to mouse hypothalamic slices containing arcuate POMC-EGFP cells. Combined application of naltrexone and bupropion was associated with a transient increase POMC cell activity. Shading indicates duration of drug application.

Figure adapted from Greenway et al. [117]. Author retains copyright.

5. Clinical studies with the naltrexone/bupropion combination

Initial Phase 2 clinical studies compared the naltrexone/bupropion combination (NB) with naltrexone or bupropion monotherapy or placebo for weight loss in obese subjects for up to 24 and 48 weeks [116,117]. These studies demonstrated that the NB combination produced greater weight loss than would be expected based on the individual monotherapies. In the larger dose-ranging study that led to Phase 3 dose selection, NB-treated subjects had more than twice as much weight loss as those in the bupropion monotherapy group [116]. In addition, NB was associated with corresponding reductions in abdominal (visceral) and total body fat [143]. The results of these early clinical studies are consistent with preclinical findings showing a greater than additive acute effect of the two monotherapies on activity of POMC cells and inhibition of food intake.

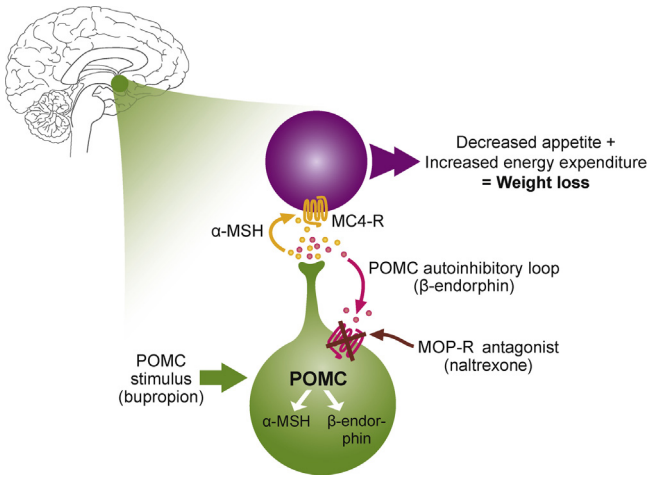

Fig. 3. Mechanism for naltrexone/bupropion action in the hypothalamic melanocortin system. The hypothalamus contains cells that produce pro-opiomelanocortin (POMC). In these cells, POMC is cleaved into peptides including α-melanocyte stimulating hormone (α-MSH) and β-endorphin, which are co-released from POMC cells. α-MSH stimulates the melanocortin-4 receptor (MC4R), which leads to decreased food intake, increased energy expenditure and weight loss. β-Endorphin binds to the inhibitory μ-opioid receptor (MOP-R) on POMC cells and acts like a brake to reduce activity of POMC cells. Bupropion stimulates activity of POMC cells, increasing POMC production and release of α-MSH and β-endorphin. Naltrexone blocks the MOP-R and prevents the β-endorphin-mediated feedback autoinhibition of POMC cells. Together, the naltrexone/bupropion combination produces a greater increase in POMC activity than either drug alone. This increased POMC activity is thought to contribute to weight loss in humans.

Subsequent Phase 3 studies extended Phase 2 findings by demonstrating that weight loss with a fixed combination of 32 mg/day naltrexone sustained-release (SR) plus 360 mg/day bupropion SR (NB32) occurred as early as Week 4 and was sustained for at least 56 weeks [144–147]. In the Contrave Obesity Research (COR) clinical studies (Table 1), overweight and obese subjects were treated with NB32 or placebo for 56 weeks.

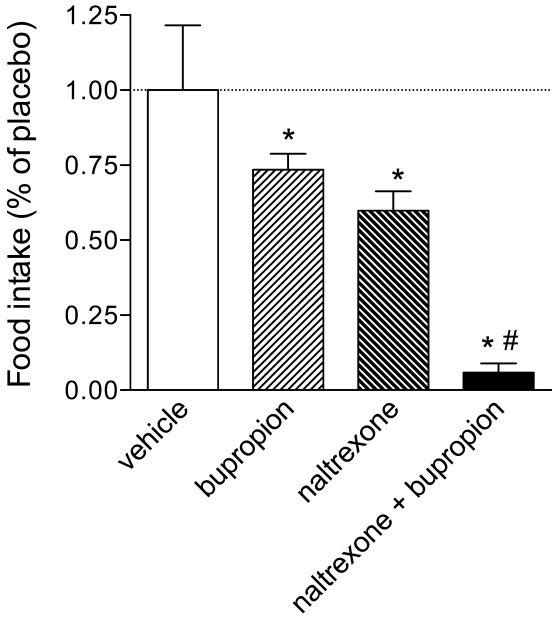

Fig. 4. Synergistic effect of intra-VTA naltrexone/bupropion on food intake in animals. Effect of intra-VTA injection of vehicle control, bupropion (1 μg), naltrexone (1 μg), or naltrexone (1 μg)/bupropion (1 μg) on 1-h food intake in mice fasted overnight. Data are mean (SD). $^{*}p < 0.01$ compared to vehicle. $^{\#}p = 0.0025$ for an interaction between bupropion and naltrexone.

Figure adapted from Sinnayah et al. [142].

Table 1
Weight loss with NB32 in Phase 3 trials in subjects who completed 56 weeks of treatment.

Trial	Study description	Randomized subjects, *N*	Proportion of subjects in completer population[a] (%)	Weight loss[a] (%)		Subjects with ≥5% weight loss[a] (%)		Subjects with ≥10% weight loss[a] (%)	
				NB32	Placebo	NB32	Placebo	NB32	Placebo
COR-I	56 weeks of NB32 or placebo in overweight and obese adults[b]	1742	50%	8.1 ± 0.5*	1.8 ± 0.5	62%*	23%	34%*	11%
COR-II	56 weeks of NB32 or placebo in overweight and obese adults[b]	1496	54%	8.2 ± 0.4*	1.4 ± 0.5	65%*	22%	39%*	8%
COR-BMOD	56 weeks of NB32 or placebo plus intensive lifestyle modification in overweight and obese adults[b]	793	51%	11.5 ± 0.6*	7.3 ± 0.9	80%*	60%	55%*	30%
COR-DM	56 weeks of NB32 or placebo in overweight and obese adults with type 2 diabetes	505	54%	5.9 ± 0.5*	2.2 ± 0.6	53%*	24%	26%*	8%

NB32: 32 mg/day naltrexone sustained-release (SR) plus 360 mg/day bupropion SR. The COR-I study also included another treatment group with a lower dose of naltrexone, NB16 (16 mg/day naltrexone SR plus 360 mg/day bupropion SR; data not shown). In the COR-II study, subjects were maintained on NB32 until weeks 28–44, when subjects who did not maintain at least 5% weight loss were re-randomized to either NB32 or a higher dose of naltrexone, NB48 (48 mg/day naltrexone SR plus 360 mg/day bupropion SR). NB32 includes all NB32 treatment groups in the 4 COR studies (data for participants in the COR-II study re-randomized to NB32 were double-weighted and participants re-randomized to NB48 were excluded). In the COR-BMOD study, subjects in both the NB32 and placebo treatment groups received intensive lifestyle modification.

[a] For subjects who completed 56 weeks of treatment and who were included in the completers analysis.

[b] Includes BMI between 30 and 45 or BMI between 27 and 45 and controlled hypertension and/or dyslipidemia.

* $p < 0.01$ for NB32 vs. placebo.

5.1. Efficacy

The COR-I study tested the effect of NB32 and a lower dose of naltrexone/bupropion, NB16 (16 mg/day naltrexone SR plus 360 mg bupropion SR) compared to placebo [144]. The COR-II study was similar to the COR-I study, except that NB32-treated subjects who did not maintain at least 5% weight loss were re-randomized to either NB32 or a higher dose of naltrexone, NB48 (48 mg/day naltrexone SR plus 360 mg/day bupropion SR), to test if increasing the dose of naltrexone would result in additional weight loss [146]. Subjects who were re-randomized to NB48 exhibited similar weight loss as those who continued to take NB32, thus, NB48 was not investigated further. Weight loss in subjects treated with NB32 for 56 weeks (study completers) was similar in COR-I and COR-II, ranging from 8.1% to 8.2% compared to placebo weight loss of 1.4–1.8% in study completers (Table 1 and Fig. 5). Weight loss in the intent-to-treat population using the last-observation-carried-forward (LOCF) method was 6.1% and 6.4% with NB32 compared to 1.2% and 1.3% with placebo. In both studies, a greater proportion of NB-treated subjects lost at least 5% or 10% of their baseline bodyweight. Compared to placebo, NB32-treatment was associated with larger improvements in cardiometatoblic risk factors such as waist circumferences, lipids, and insulin resistance, as well as weight-related quality of life.

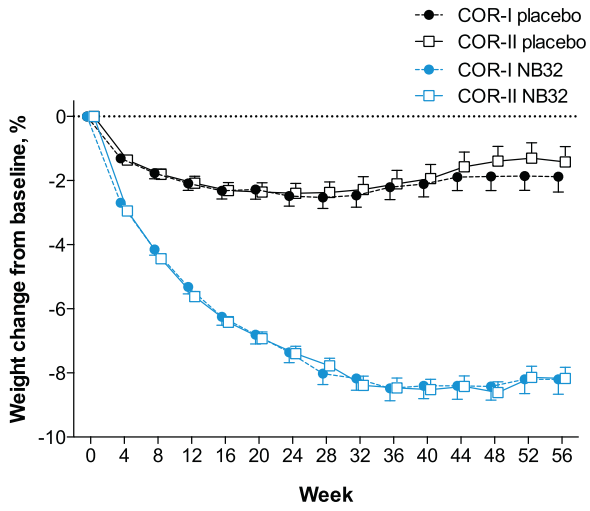

Fig. 5. Weight loss with NB32 in COR-I and COR-II. Mean (SEM) body weight by visit among subjects who completed 56 weeks of treatment in the COR-I and COR-II studies. Data for participants in the COR-II study re-randomized to NB32 were double-weighted and participants re-randomized to NB48 were excluded.

The COR-BMOD study tested the effects of combining NB32 or placebo with an intensive behavior modification program designed for weight loss (Table 1) [145]. NB32 resulted in weight loss in addition to that produced by the intensive behavior modification program alone (placebo), as well as improvements in obesity-related risk factors. The fourth COR study, COR-DM, was conducted to test the effect of NB32 in patients with type 2 diabetes mellitus who were not taking any diabetes medication or who were taking a stable dose of oral diabetes medications (e.g., metformin, sulfonylureas, or thiazolidinediones, or DPP-4 inhibitors) [147]. NB32 resulted in greater weight loss than placebo, regardless of concurrent diabetes medication.

The effect of NB32 on smoking cessation and major depressive disorder in overweight and obese adults has also been investigated in two small open-label studies. In overweight and obese smokers, 24 weeks of open-label NB32 was associated with decreased nicotine use and the absence of weight gain, a common side effect of smoking cessation [148]. Another study evaluating open-label NB32 for 24 weeks in overweight and obese women with major depressive disorder demonstrated that NB32 was associated with weight loss and improvements in multiple measures of depressive symptoms [149]. These findings are consistent with the efficacy of bupropion in treating depression and as an aid in smoking cessation. They illustrate the potential for NB to produce weight loss or prevent weight gain in specific populations that warrants further study.

5.2. Control of eating

Preclinical data and an understanding of the CNS pathways that are likely influenced by NB32 treatment suggest that improvement in reward-based eating and craving-related behavior may be at least partially responsible for the weight loss observed with NB32.

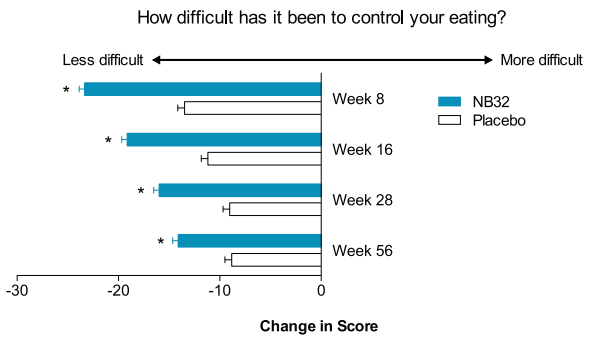

Fig. 6. Effect of NB32 on control of eating. Mean (SEM) change in CoEQ question 19, "Generally, how difficult has it been to control your eating?" from baseline to Week 8 through 56 for the intent-to-treat population using the last-observation-carried-forward method. NB32 includes all NB32 treatment groups in the 4 COR studies, and subjects who were switched from NB32 to NB48 in the COR-II study. $^{*}p < 0.05$ vs. placebo.

Indeed, subject-reported outcome data from the COR studies indicates that NB32 may influence appetite and food cravings.

The Control of Eating Questionnaire (CoEQ) was administered in all COR studies. The CoEQ consists of a series of 20 visual analog scales [150] designed to assess various aspects of appetite, food craving, eating behavior and mood [151]. In particular, the control of eating measure (CoEQ 19: Generally, how difficult has it been to control your eating?) was a pre-specified secondary endpoint in 3 of the 4 COR studies. In all 4 COR studies, NB32-treated subjects reported improved ability to control their eating (CoEQ 19) compared to placebo [88,144–146,152]. In an integrated analysis of all 4 COR studies, NB32 was associated with significant improvement in CoEQ 19 compared to placebo at all time points measured, including the earliest measure at Week 8 (Fig. 6). Additionally, improvement in CoEQ19 at Week 8 was positively correlated with weight loss at the end of the studies [152]. NB32 was also associated with improvements in other measures, including the increased ability to resist food cravings as well as reduced incidence and strength of food cravings.

Though preliminary results from the CoEQ suggest overall improvement in the general frequency, intensity, and ability to resist food cravings, no treatment differences were observed with respect to craving of specific types of food, which were assessed by the Food Craving Inventory [153]. These results are a reminder of the complexity of measuring food intake in humans; many psychological and physiological factors influence responses in a given population during a weight loss study [35,39].

An fMRI study compared the effects of 4 weeks of treatment with NB32 or placebo on brain activity in response to food images in fasted overweight and obese women [154]. Compared to placebo, NB32 was associated with reduced hypothalamic activation and increased activation of forebrain regions (dorsal anterior cingulate, superior frontal, posterior insula, hippocampal, and superior parietal regions) involved in self control, awareness, memory, and sensory processing. The forebrain regions identified in this study interact with the reward system to regulate eating behavior and are implicated in obesity [155]. Brain imaging studies in humans show that hypothalamic activation in response to food cues is increased during the fasted state, and that this activation is attenuated after overfeeding in lean [156], but not overweight, obese [157], or weight-reduced individuals [158]. Although the mechanism for these changes in brain activity requires further study, these results suggest that NB32 may restore the impaired hypothalamic response to satiety in obese individuals and improve forebrain control of behavior in response to food cues.

5.3. Safety

Adverse events with NB32 are consistent with the individual actions of bupropion and naltrexone. The most common adverse events are nausea, constipation, headache, and vomiting [144–147]. Generally, adverse events associated with NB32 are mild to moderate in severity, occur early in treatment during dose escalation, and do not result in study discontinuation. The most common adverse event, nausea, is likely a result of local actions of naltrexone in the gastrointestinal tract where opioids influence gastrointestinal motility [91,159]; however, a low incidence of nausea is also associated with bupropion [121]. Consistent with the known adverse effects of metformin [160], nausea occurred more frequently in patients with type 2 diabetes who were taking metformin [147].

Small increases in mean blood pressure and pulse rate have also been reported with NB32 [144–147]. These effects are consistent with the known hemodynamic effects of bupropion [121] and may be attributable to noradrenergic effects. Mean increases in systolic and diastolic blood pressure of approximately 1 mm Hg from baseline occurred during the first 8 weeks of treatment with NB32. After 12 weeks, mean blood pressure in NB32-treated subjects returned to baseline. By Week 56, both placebo and NB32 groups exhibited a small decrease from baseline in mean blood pressure; the reduction was slightly greater in the placebo group. Greater weight loss was associated with greater decreases in mean blood pressure for both NB32 and placebo, although the reduction in blood pressure was less with NB32 than with placebo in subjects with similar weight loss. A mean increase in pulse rate of 1.5–2.5 beats per minute has also been documented with NB32. The cardiovascular impact of these sympathomimetic effects of NB32 is currently being investigated in a trial designed to assess the occurrence of major adverse cardiovascular events for NB32 compared to placebo [161].

Antidepressants are associated with rare occurrences of psychiatric symptoms during treatment and after drug cessation [121]. Because NB32 contains an antidepressant, depressive and anxiety symptoms, as well as serious psychiatric events, were evaluated in all the COR studies. No differences were observed with NB32 compared to placebo [144–147]. In addition, the COR-I study compared the effects of sudden vs. tapered cessation of NB32 or placebo and found no difference in the incidence of adverse events, psychiatric adverse events, or depressive and anxiety symptoms compared to placebo (unpublished data on file at Orexigen Therapeutics, Inc.).

6. Long-term pharmacotherapy for obesity in the United States

Obesity is a chronic condition that requires long-term treatment to reduce and maintain a lower body weight [13]. Although lifestyle intervention is the ideal and safest way to reduce body weight, most individuals do not achieve clinically meaningful weight loss with diet and exercise alone [162]. Furthermore, weight regain after lifestyle intervention or cessation of obesity medications is common [17,19,163] and patients who stop taking obesity medications will likely experience at least some weight regain without further intervention. Thus, obesity medications facilitate weight loss and maintenance, which may yield long-term improvements in obesity-related comorbidities such as diabetes and cardiovascular disease.

Weight loss with NB32 in the COR-I and COR-II studies was comparable to the three obesity pharmacotherapies currently available for long-term use in the United States: orlistat, lorcaserin, and phentermine/topiramate [13,144,146]. All these agents increase the likelihood that overweight and obese patients will achieve

clinically meaningful weight loss of at least 5% and at least 10% after 1 year of treatment.

Similar to NB32, lorcaserin and phentermine/topiramate are believed to act primarily in the CNS and each has been reported to reduce appetite, which may contribute to weight loss efficacy [20,25]. Some of the most common adverse events with lorcaserin (headache, dizziness, fatigue, nausea) [18–20] and phentermine/topiramate (paresthesia, dizziness, dysgeusia, insomnia) [22–24] are consistent with a central mechanism of action. Many of these adverse events resolve with continued use. In contrast, the gastrointestinal adverse events that occur with orlistat are due to a peripheral mechanism of action, and usually resolve with reducing fat intake [13–17,164].

Despite the increasing rate of obesity and poor success rate of lifestyle intervention for weight loss, utilization of obesity pharmacotherapies is low. Persistence rates for orlistat and sibutramine (withdrawn from the market in 2010 due to increased risk of cardiovascular events) were less than 10% for 1 year and 2% for 2 years [165]. In 2011, an estimated 2.7 million individuals were taking obesity drugs in the United States [166]. This low utilization of obesity medications, combined with the recent approval of lorcaserin and phentermine/topiramate, means that the long-term effects of current obesity medications are largely unknown. Because of the heterogeneity of obesity, multiple treatment options will enable care providers and patients to maximize weight loss while minimizing safety and tolerability issues. As more obesity therapies become available, obesity medications may become increasingly utilized and improve our understanding of the mechanism of action and long-term effects of these drugs.

7. Summary

The limited success of obesity medications to date can most likely be attributed to the complexity of brain pathways that regulate hunger, food craving and eating behavior. We are only beginning to understand the powerful influence of factors such as mood and emotion on eating behavior and body weight. In today's environment where foods that are high in fat and sugar are readily available, neural pathways regulating hedonic drives are sure to play a role in weight regain and to limit weight loss attempts. Preclinical studies show that the naltrexone/bupropion combination acts in hypothalamic brain regions that regulate appetite and energy expenditure, while also influencing eating behavior that is mediated by the reward system. The weight loss produced by NB in humans is likely attributed to these dual actions. In clinical studies, a consistently substantial proportion of overweight and obese subjects responded to NB32 treatment with at least 5% or 10% weight loss. These treatment responders are likely those who would benefit most from NB treatment in clinical practice.

Conflict of interest

All authors had final decision of report content, interpretation of data, and the decision to submit the report for publication. SKB, of August Scientific Medical Writing, received financial compensation from Orexigen Therapeutics, Inc. for writing the report. SKB is a former employee of Orexigen Therapeutics, Inc. MAC is a founder and former employee of Orexigen Therapeutics, Inc., is currently a Director of Verva Pharmaceuticals, Ltd., and is a consultant to Novo Nordisk A/S, Johnson and Johnson, Inc., and 5 Prime Therapeutics, Inc. PS has no conflict of interest. The Sponsor (Orexigen Therapeutics, Inc.) provided data from the COR studies and feedback on the manuscript.

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References

[1] Haslam DW, James WP. Obesity. Lancet 2005;366:1197–209.
[2] Ogden CL, Carroll MD, McDowell MA, Flegal KM. Obesity among adults in the United States – no change since 2003–04: NCHS data brief no 1. Hyattsville, MD: National Center for Health Statistics; 2007.
[3] Health, United States. With special feature on the health of young adults. Hyattsville, MD: Centers for Disease Control and Prevention, National Center for Health Statistics; 2008.
[4] Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among us children and adolescents, 1999–2010. J Am Med Assoc 2012;307:483–90.
[5] Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among us adults, 1999–2010. J Am Med Assoc 2012;307:491–7.
[6] Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. Obesity (Silver Spring, MD) 2008;16:2323–30.
[7] Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 2005;352:1138–45.
[8] Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American college of cardiology/American heart association task force on practice guidelines and the obesity society. Circulation 2013 [Epub ahead of print].
[9] Appolinario JC, Bueno JR, Coutinho W. Psychotropic drugs in the treatment of obesity: what promise. CNS Drugs 2004;18:629–51.
[10] Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. Cochrane Database Syst Rev 2009:CD003641.
[11] Ioannides-Demos LL, Piccenna L, McNeil JJ. Pharmacotherapies for obesity: past, current, and future therapies. J Obes 2011;2011:179674.
[12] Birkmeyer NJ, Dimick JB, Share D, Hawasli A, English WJ, Genaw J, et al. Hospital complication rates with bariatric surgery in Michigan. J Am Med Assoc 2010;304:435–42.
[13] Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. J Am Med Assoc 2014;311:74–86.
[14] Prescribing information: Xenical (orlistat) capsules. USA: Genentech Inc.; 2013.
[15] Rossner S, Sjostrom L, Noack R, Meinders AE, Noseda G. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European orlistat obesity studygroup. Obes Res 2000;8:49–61.
[16] Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European multicentre orlistat studygroup. Lancet 1998;352:167–72.
[17] Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. J Am Med Assoc 1999;281:235–42.
[18] Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, et al. 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.
[19] Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010;363:245–56.
[20] Prescribing information: Belviq (lorcaserin hydrochloride) tablets. Eisai Inc.; 2012.
[21] Bray GA. Why do we need drugs to treat the patient with obesity? Obesity 2013;21:893–9.
[22] Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (conquer): a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:1341–52.
[23] Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (equip). Obesity 2012;20:330–42.
[24] Prescribing information: Qsymia (phentermine and topiramate extended-release) tablets. Vivus, Inc.; 2013.
[25] Witkamp RF. Current and future drug targets in weight management. Pharm Res 2011;28:1792–818.
[26] Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. Nature 2006;443:289–95.
[27] Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med 1995;332:621–8.

[28] Del Parigi A, Gautier JF, Chen K, Salbe AD, Ravussin E, Reiman E, et al. Mapping the brain responses to hunger and satiation in humans using positron emission tomography. Ann N Y Acad Sci 2002;967:389–97.
[29] Wang GJ, Volkow ND, Telang F, Jayne M, Ma Y, Pradhan K, et al. Evidence of gender differences in the ability to inhibit brain activation elicited by food stimulation. Proc Natl Acad Sci U S A 2009;106:1249–54.
[30] DelParigi A, Chen K, Salbe AD, Hill JO, Wing RR, Reiman EM, et al. Persistence of abnormal neural responses to a meal in postobese individuals. Int J Obes Relat Metab Disord 2004;28:370–7.
[31] Hinkle W, Cordell M, Leibel R, Rosenbaum M, Hirsch J. Effects of reduced weight maintenance and leptin repletion on functional connectivity of the hypothalamus in obese humans. PLoS One 2013;8:e59114.
[32] Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. J Clin Invest 2008;118:2583–91.
[33] Rosenbaum M, Kissileff HR, Mayer LE, Hirsch J, Leibel RL. Energy intake in weight-reduced humans. Brain Res 2010;1350:95–102.
[34] Pelchat ML. Food cravings in young and elderly adults. Appetite 1997;28:103–13.
[35] Hill AJ. The psychology of food craving. Proc Nutr Soc 2007;66:277–85.
[36] DelParigi A, Chen K, Salbe AD, Hill JO, Wing RR, Reiman EM, et al. Successful dieters have increased neural activity in cortical areas involved in the control of behavior. Int J Obes (Lond) 2007;31:440–8.
[37] Vogels N, Westerterp KR, Posthumus DL, Rutters F, Westerterp-Plantenga MS. Daily physical activity counts vs. structured activity counts in lean and overweight Dutch children. Physiol Behav 2007;92:611–6.
[38] Wang GJ, Volkow ND, Fowler JS. The role of dopamine in motivation for food in humans: implications for obesity. Expert Opin Ther Targets 2002;6:601–9.
[39] Halford JC, Boyland EJ, Blundell JE, Kirkham TC, Harrold JA. Pharmacological management of appetite expression in obesity. Nat Rev Endocrinol 2010;6:255–69.
[40] Cone RD. Anatomy and regulation of the central melanocortin system. Nat Neurosci 2005;8:571–8.
[41] Cowley MA, Cone RD, Enriori P, Louiselle I, Williams SM, Evans AE. Electrophysiological actions of peripheral hormones on melanocortin neurons. Ann N Y Acad Sci 2003;994:175–86.
[42] Lu D, Willard D, Patel IR, Kadwell S, Overton L, Kost T, et al. Agouti protein is an antagonist of the melanocyte-stimulating-hormone receptor. Nature 1994;371:799–802.
[43] Fan W, Boston BA, Kesterson RA, Hruby VJ, Cone RD. Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. Nature 1997;385:165–8.
[44] Broberger C, Johansen J, Johansson C, Schalling M, Hokfelt T. The neuropeptide y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. Proc Natl Acad Sci U S A 1998;95:15043–8.
[45] Brady LS, Smith MA, Gold PW, Herkenham M. Altered expression of hypothalamic neuropeptide mrnas in food-restricted and food-deprived rats. Neuroendocrinology 1990;52:441–7.
[46] Fan W, Voss-Andreae A, Cao WH, Morrison SF. Regulation of thermogenesis by the central melanocortin system. Peptides 2005;26:1800–13.
[47] Mizuno TM, Mobbs CV. Hypothalamic agouti-related protein messenger ribonucleic acid is inhibited by leptin and stimulated by fasting. Endocrinology 1999;140:814–7.
[48] Cowley MA, Smart JL, Rubinstein M, Cerdan MG, Diano S, Horvath TL, et al. Leptin activates anorexigenic pomc neurons through a neural network in the arcuate nucleus. Nature 2001;411:480–4.
[49] Elias CF, Aschkenasi C, Lee C, Kelly J, Ahima RS, Bjorbaek C, et al. Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. Neuron 1999;23:775–86.
[50] Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999;402:656–60.
[51] Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev 2007;8:21–34.
[52] Cowley MA, Pronchuk N, Fan W, Dinulescu DM, Colmers WF, Cone RD. Integration of NPY, AGRP, and melanocortin signals in the hypothalamic paraventricular nucleus: evidence of a cellular basis for the adipostat. Neuron 1999;24:155–63.
[53] Cone RD. Studies on the physiological functions of the melanocortin system. Endocr Rev 2006;27:736–49.
[54] Liotta AS, Advis JP, Krause JE, McKelvy JF, Krieger DT. Demonstration of in vivo synthesis of pro-opiomelanocortin-, beta-endorphin-, and alpha-melanotropin-like species in the adult rat brain. J Neurosci 1984;4:956–65.
[55] Pennock RL, Hentges ST. Differential expression and sensitivity of presynaptic and postsynaptic opioid receptors regulating hypothalamic proopiomelanocortin neurons. J Neurosci 2011;31:281–8.
[56] Kelly MJ, Loose MD, Ronnekleiv OK. Opioids hyperpolarize beta-endorphin neurons via mu-receptor activation of a potassium conductance. Neuroendocrinology 1990;52:268–75.
[57] Burcelin R, Crivelli V, Dacosta A, Roy-Tirelli A, Thorens B. Heterogeneous metabolic adaptation of c57bl/6j mice to high-fat diet. Am J Physiol Endocrinol Metab 2002;282:E834–42.
[58] Dum J, Gramsch C, Herz A. Activation of hypothalamic beta-endorphin pools by reward induced by highly palatable food. Pharmacol Biochem Behav 1983;18:443–7.
[59] Enriori PJ, Evans AE, Sinnayah P, Jobst EE, Tonelli-Lemos L, Billes SK, et al. Diet-induced obesity causes severe but reversible leptin resistance in arcuate melanocortin neurons. Cell Metab 2007;5:181–94.
[60] Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci 2002;22:3306–11.
[61] Kelley AE. Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. Neurosci Biobehav Rev 2004;27:765–76.
[62] Wise RA. Brain reward circuitry: insights from unsensed incentives. Neuron 2002;36:229–40.
[63] Pierce RC, Kumaresan V. The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? Neurosci Biobehav Rev 2006;30:215–38.
[64] Finlayson G, King N, Blundell JE. Liking vs. wanting food: importance for human appetite control and weight regulation. Neurosci Biobehav Rev 2007;31:987–1002.
[65] Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience. Brain Res Brain Res Rev 1998;28:309–69.
[66] Baldo BA, Kelley AE. Discrete neurochemical coding of distinguishable motivational processes: insights from nucleus accumbens control of feeding. Psychopharmacology (Berl) 2007;191:439–59.
[67] Glass MJ, Billington CJ, Levine AS. Opioids and food intake: distributed functional neural pathways. Neuropeptides 1999;33:360–8.
[68] Will MJ, Franzblau EB, Kelley AE. Nucleus accumbens mu-opioids regulate intake of a high-fat diet via activation of a distributed brain network. J Neurosci 2003;23:2882–8.
[69] Saper CB, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. Neuron 2002;36:199–211.
[70] Stice E, Spoor S, Ng J, Zald DH. Relation of obesity to consummatory and anticipatory food reward. Physiol Behav 2009;97:551–60.
[71] Small DM. Individual differences in the neurophysiology of reward and the obesity epidemic. Int J Obes (Lond) 2009;33(Suppl. 2):S44–8.
[72] Volkow ND, Wise RA. How can drug addiction help us understand obesity. Nat Neurosci 2005;8:555–60.
[73] Avena NM, Rada P, Hoebel BG. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev 2008;32:20–39.
[74] Stice E, Spoor S, Bohon C, Small DM. Relation between obesity and blunted striatal response to food is moderated by taqia a1 allele. Science (New York, NY) 2008;322:449–52.
[75] Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. Lancet 2001;357:354–7.
[76] Wang GJ, Volkow ND, Thanos PK, Fowler JS. Similarity between obesity and drug addiction as assessed by neurofunctional imaging: a concept review. J Addict Dis 2004;23:39–53.
[77] Fetissov SO, Meguid MM, Sato T, Zhang LH. Expression of dopaminergic receptors in the hypothalamus of lean and obese zucker rats and food intake. Am J Physiol Regul Integr Comp Physiol 2002;283:R905–10.
[78] Huang XF, Yu Y, Zavitsanou K, Han M, Storlien L. Differential expression of dopamine d2 and d4 receptor and tyrosine hydroxylase MRNA in mice prone, or resistant, to chronic high-fat diet-induced obesity. Brain Res Mol Brain Res 2005;135:150–61.
[79] Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Leptin regulates striatal regions and human eating behavior. Science (New York, NY) 2007;317:1355.
[80] Malik S, McGlone F, Bedrossian D, Dagher A. Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab 2008;7:400–9.
[81] Figlewicz DP, Evans SB, Murphy J, Hoen M, Baskin DG. Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. Brain Res 2003;964:107–15.
[82] Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB, et al. Leptin receptor signaling in midbrain dopamine neurons regulates feeding. Neuron 2006;51:801–10.
[83] Batterham RL, ffytche DH, Rosenthal JM, Zelaya FO, Barker GJ, Withers DJ, et al. PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. Nature 2007;450:106–9.
[84] Thanos PK, Michaelides M, Gispert JD, Pascau J, Soto-Montenegro ML, Desco M, et al. Differences in response to food stimuli in a rat model of obesity: in-vivo assessment of brain glucose metabolism. Int J Obes (Lond) 2008;32:1171–9.
[85] Berthoud HR. Interactions between the cognitive and metabolic brain in the control of food intake. Physiol Behav 2007;91:486–98.
[86] Horvath TL. The hardship of obesity: a soft-wired hypothalamus. Nat Neurosci 2005;8:561–5.
[87] Major GC, Doucet E, Trayhurn P, Astrup A, Tremblay A. Clinical significance of adaptive thermogenesis. Int J Obes (Lond) 2007;31:204–12.
[88] Billes SK, Greenway FL. Combination therapy with naltrexone and bupropion for obesity. Expert Opin Pharmacother 2011;12:1813–26.
[89] Anton RF. Naltrexone for the management of alcohol dependence. N Engl J Med 2008;359:715–21.

[90] Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review. Addiction 2006;101:491–503.
[91] Prescribing information: Revia (naltrexone hydrochloride) tablets. Duramed Pharmaceuticals, Inc.; 2013.
[92] Watson SJ, Akil H, Richard CWr, Barchas JD. Evidence for two separate opiate peptide neuronal systems. Nature 1978;275:226–8.
[93] Reece AS. Hypothalamic opioid-melanocortin appetitive balance and addictive craving. Med Hypotheses 2011;76:132–7.
[94] Tabarin A, Diz-Chaves Y, Carmona Mdel C, Catargi B, Zorrilla EP, Roberts AJ, et al. Resistance to diet-induced obesity in mu-opioid receptor-deficient mice: evidence for a thrifty gene. Diabetes 2005;54:3510–6.
[95] Bronstein DM, Day NC, Gutstein HB, Trujillo KA, Akil H. Pre- and posttranslational regulation of beta-endorphin biosynthesis in the CNS: effects of chronic naltrexone treatment. J Neurochem 1993;60:40–9.
[96] Carr KD, Park TH, Zhang Y, Stone EA. Neuroanatomical patterns of fos-like immunoreactivity induced by naltrexone in food-restricted and ad libitum fed rats. Brain Res 1998;779:26–32.
[97] Olszewski PK, Wirth MM, Grace MK, Levine AS, Giraudo SQ. Evidence of interactions between melanocortin and opioid systems in regulation of feeding. Neuroreport 2001;12:1727–30.
[98] Taber MT, Zernig G, Fibiger HC. Opioid receptor modulation of feeding-evoked dopamine release in the rat nucleus accumbens. Brain Res 1998;785:24–30.
[99] Giuliano C, Robbins TW, Nathan PJ, Bullmore ET, Everitt BJ. Inhibition of opioid transmission at the mu-opioid receptor prevents both food seeking and binge-like eating. Neuropsychopharmacology 2012;37:2643–52.
[100] Blasio A, Steardo L, Sabino V, Cottone P. Opioid system in the medial prefrontal cortex mediates binge-like eating. Addict Biol 2013, http://dx.doi.org/10.1111/adb.12033.
[101] Taha SA, Norsted E, Lee LS, Lang PD, Lee BS, Woolley JD, et al. Endogenous opioids encode relative taste preference. Eur J Neurosci 2006;24:1220–6.
[102] Kelley AE, Bless EP, Swanson CJ. Investigation of the effects of opiate antagonists infused into the nucleus accumbens on feeding and sucrose drinking in rats. J Pharmacol Exp Ther 1996;278:1499–507.
[103] Zhang M, Gosnell BA, Kelley AE. Intake of high-fat food is selectively enhanced by mu opioid receptor stimulation within the nucleus accumbens. J Pharmacol Exp Ther 1998;285:908–14.
[104] Shin AC, Pistell PJ, Phifer CB, Berthoud HR. Reversible suppression of food reward behavior by chronic mu-opioid receptor antagonism in the nucleus accumbens. Neuroscience 2010;170:580–8.
[105] Woolley JD, Lee BS, Fields HL. Nucleus accumbens opioids regulate flavor-based preferences in food consumption. Neuroscience 2006;143:309–17.
[106] Bonacchi KB, Ackroff K, Touzani K, Bodnar RJ, Sclafani A. Opioid mediation of starch and sugar preference in the rat. Pharmacol Biochem Behav 2010:1–8.
[107] Levine AS, Grace MK, Cleary JP, Billington CJ. Naltrexone infusion inhibits the development of preference for a high-sucrose diet. Am J Physiol Regul Integr Comp Physiol 2002;283:R1149–54.
[108] Apfelbaum M, Mandenoff A. Naltrexone suppresses hyperphagia induced in the rat by a highly palatable diet. Pharmacol Biochem Behav 1981;15:89–91.
[109] Kanarek RB, Mathes WF, Heisler LK, Lima RP, Monfared LS. Prior exposure to palatable solutions enhances the effects of naltrexone on food intake in rats. Pharmacol Biochem Behav 1997;57:377–81.
[110] Yeomans MR, Gray RW. Selective effects of naltrexone on food pleasantness and intake. Physiol Behav 1996;60:439–46.
[111] Yeomans MR, Gray RW. Opioid peptides and the control of human ingestive behaviour. Neurosci Biobehav Rev 2002;26:713–28.
[112] Hollister LE, Johnson K, Boukhabza D, Gillespie HK. Aversive effects of naltrexone in subjects not dependent on opiates. Drug Alcohol Depend 1981;8:37–41.
[113] Sternbach HA, Annitto W, Pottash AL, Gold MS. Anorexic effects of naltrexone in man. Lancet 1982;1:388–9.
[114] Maggio CA, Presta E, Bracco EF, Vasselli JR, Kissileff HR, Pfohl DN, et al. Naltrexone and human eating behavior: a dose-ranging inpatient trial in moderately obese men. Brain Res Bull 1985;14:657–61.
[115] Malcolm R, O'Neil PM, Sexauer JD, Riddle FE, Currey HS, Counts C. A controlled trial of naltrexone in obese humans. Int J Obes 1985;9:347–53.
[116] Greenway FL, Dunayevich E, Tollefson G, Erickson J, Guttadauria M, Fujioka K, et al. Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. J Clin Endocrinol Metab 2009;94:4898–906.
[117] Greenway FL, Whitehouse MJ, Guttadauria M, Anderson JW, Atkinson RL, Fujioka K, et al. Rational design of a combination medication for the treatment of obesity. Obesity (Silver Spring, MD) 2009;17:30–9.
[118] Atkinson RL, Berke LK, Drake CR, Bibbs ML, Williams FL, Kaiser DL. Effects of long-term therapy with naltrexone on body weight in obesity. Clin Pharmacol Ther 1985;38:419–22.
[119] Ascher JA, Cole JO, Colin JN, Feighner JP, Ferris RM, Fibiger HC, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995;56:395–401.
[120] Foley KF, DeSanty KP, Kast RE. Bupropion: pharmacology and therapeutic applications. Expert Rev Neurother 2006;6:1249–65.
[121] Prescribing information: Wellbutrin (bupropion hydrochloride) tablets. GlaxoSmithKline; 2013.
[122] Gadde KM, Xiong GL. Bupropion for weight reduction. Expert Rev Neurother 2007;7:17–24.
[123] Nomikos GG, Damsma G, Wenkstern D, Fibiger HC. Effects of chronic bupropion on interstitial concentrations of dopamine in rat nucleus accumbens and striatum. Neuropsychopharmacology 1992;7:7–14.
[124] Roitman MF, Wescott S, Cone JJ, McLane MP, Wolfe HR. Msi-1436 reduces acute food intake without affecting dopamine transporter activity. Pharmacol Biochem Behav 2010;97:138–43.
[125] Paladini CA, Robinson S, Morikawa H, Williams JT, Palmiter RD. Dopamine controls the firing pattern of dopamine neurons via a network feedback mechanism. Proc Natl Acad Sci U S A 2003;100:2866–71.
[126] Khan ZU, Gutierrez A, Martin R, Penafiel A, Rivera A, De La Calle A. Differential regional and cellular distribution of dopamine d2-like receptors: an immunocytochemical study of subtype-specific antibodies in rat and human brain. J Comp Neurol 1998;402:353–71.
[127] Fraley GS, Ritter S. Immunolesion of norepinephrine and epinephrine afferents to medial hypothalamus alters basal and 2-deoxy-D-glucose-induced neuropeptide y and agouti gene-related protein messenger ribonucleic acid expression in the arcuate nucleus. Endocrinology 2003;144:75–83.
[128] Pijl H. Reduced dopaminergic tone in hypothalamic neural circuits: expression of a thrifty genotype underlying the metabolic syndrome. Eur J Pharmacol 2003;480:125–31.
[129] Nestler EJ, Carlezon Jr WA. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry 2006;59:1151–9.
[130] Liu YL, Connoley IP, Harrison J, Heal DJ, Stock MJ. Comparison of the thermogenic and hypophagic effects of sibutramine's metabolite 2 and other monoamine reuptake inhibitors. Eur J Pharmacol 2002;452:49–56.
[131] Liu YL, Connoley IP, Heal DJ, Stock MJ. Pharmacological characterisation of the thermogenic effect of bupropion. Eur J Pharmacol 2004;498:219–25.
[132] Hasegawa H, Meeusen R, Sarre S, Diltoer M, Piacentini MF, Michotte Y. Acute dopamine/norepinephrine reuptake inhibition increases brain and core temperature in rats. J Appl Physiol 2005;99:1397–401.
[133] Billes SK, Cowley MA. Catecholamine reuptake inhibition causes weight loss by increasing locomotor activity and thermogenesis. Neuropsychopharmacology 2008;33:1287–97.
[134] Billes SK, Cowley MA. Inhibition of dopamine and norepinephrine reuptake produces additive effects on energy balance in lean and obese mice. Neuropsychopharmacology 2007;32:822–34.
[135] Zarrindast MR, Hosseini-Nia T. Anorectic and behavioural effects of bupropion. Gen Pharmacol 1988;19:201–4.
[136] Wright FL, Rodgers RJ. Acute behavioural effects of bupropion and naltrexone, alone and in combination, in non-deprived male rats presented with palatable mash. Psychopharmacology (Berl) 2013;228:291–307.
[137] Anderson JW, Greenway FL, Fujioka K, Gadde KM, McKenney J, O'Neil PM. Bupropion sr enhances weight loss: a 48-week double-blind, placebo-controlled trial. Obes Res 2002;10:633–41.
[138] Jain AK, Kaplan RA, Gadde KM, Wadden TA, Allison DB, Brewer ER, et al. Bupropion SR vs Placebo for weight loss in obese patients with depressive symptoms. Obes Res 2002;10:1049–56.
[139] Gadde KM, Parker CB, Maner LG, Wagner 2nd HR, Logue EJ, Drezner MK, et al. Bupropion for weight loss: an investigation of efficacy and tolerability in overweight and obese women. Obes Res 2001;9:544–51.
[140] Harto-Truax N, Stern WC, Miller LL, Sato TL, Cato AE. Effects of bupropion on body weight. J Clin Psychiatry 1983;44:183–6.
[141] Griffith JD, Carranza J, Griffith C, Miller LL, Bupropion. Clinical assay for amphetamine-like abuse potential. J Clin Psychiatry 1983;44:206–8.
[142] Sinnayah P, Wallingford N, Evans A, Cowley MA. Bupropion and naltrexone interact synergistically to decrease food intake in mice. In: Presented at the North American association for the study of obesity annual scientific meeting. 2007.
[143] Smith SR, Fujioka K, Gupta AK, Billes SK, Burns C, Kim D, et al. Combination therapy with naltrexone and bupropion for obesity reduces total and visceral adiposity. Diabetes Obes Metab 2013;15:863–6.
[144] Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (cor-i): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2010;376:595–605.
[145] Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, 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.
[146] Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring, MD) 2013;21:935–43.
[147] Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes Care 2013;36:4022–9.
[148] Wilcox CS, Oskooilar N, Erickson JS, Billes SK, Katz BB, Tollefson G, et al. An open-label study of naltrexone and bupropion combination therapy for smoking cessation in overweight and obese subjects. Addict Behav 2010;35:229–34.
[149] McElroy SL, Guerdjikova AI, Kim DD, Burns C, Harris-Collazo R, Landbloom R, et al. Naltrexone/bupropion combination therapy in overweight or obese patients with major depressive disorder: results of a pilot study. Prim Care Companion CNS Disord 2013:15.
[150] Flint A, Raben A, Blundell JE, Astrup A. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. Int J Obes Relat Metab Disord 2000;24:38–48.

[151] Hill AJ, Weaver CF, Blundell JE. Food craving, dietary restraint and mood. Appetite 1991;17:187–97.
[152] Fujioka K, Walsh B, Burns C, Klassen P. Early improvement in control of eating is associated with long-term weight loss – integrated analysis of four phase 3 trials of combination naltrexone/bupropion treatment. In: American Diabetes Association 73rd Scientific Session. 2013.
[153] White MA, Whisenhunt BL, Williamson DA, Greenway FL, Netemeyer RG. Development and validation of the food-craving inventory. Obes Res 2002;10:107–14.
[154] Wang GJ, Tomasi D, Volkow ND, Wang R, Telang F, Caparelli EC, et al. Effect of combined naltrexone and bupropion therapy on the brain's reactivity to food cues. Int J Obes 2013, http://dx.doi.org/10.1038/ijo.2013.145.
[155] Michaelides M, Thanos PK, Volkow ND, Wang GJ. Translational neuroimaging in drug addiction and obesity. ILAR J 2012;53:59–68.
[156] Cornier MA, Von Kaenel SS, Bessesen DH, Tregellas JR. Effects of overfeeding on the neuronal response to visual food cues. Am J Clin Nutr 2007;86:965–71.
[157] Fletcher PC, Napolitano A, Skeggs A, Miller SR, Delafont B, Cambridge VC, et al. Distinct modulatory effects of satiety and sibutramine on brain responses to food images in humans: a double dissociation across hypothalamus, amygdala, and ventral striatum. J Neurosci 2010;30:14346–55.
[158] Cornier MA, Salzberg AK, Endly DC, Bessesen DH, Rojas DC, Tregellas JR. The effects of overfeeding on the neuronal response to visual food cues in thin and reduced-obese individuals. PLoS One 2009;4:e6310.
[159] Holzer P. Opioid receptors in the gastrointestinal tract. Regul Pept 2009;155:11–7.
[160] Bailey CJ, Turner RC. Metformin. N Engl J Med 1996;334:574–9.
[161] Clinicaltrials.Gov identifier: Nct01601704. Cardiovascular outcomes study of naltrexone SR/bupropion SR in overweight and obese subjects with cardiovascular risk factors (the light study). Orexigen Therapeutics; 2012.
[162] Wadden TA, Volger S, Tsai AG, Sarwer DB, Berkowitz RI, Diewald LK, et al. Managing obesity in primary care practice: an overview with perspective from the power-up study. Int J Obes (Lond) 2013;37(Suppl. 1): S3–11.
[163] Sarwer DB, von Sydow Green A, Vetter ML, Wadden TA. Behavior therapy for obesity: where are we now? Curr Opin Endocrinol Diab Obes 2009;16:347–52.
[164] Torgerson JS, Hauptman J, Boldrin MN, Sjostrom 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.
[165] Padwal R, Kezouh A, Levine M, Etminan M. Long-term persistence with orlistat and sibutramine in a population-based cohort. Int J Obes (Lond) 2007;31:1567–70.
[166] Hampp C, Kang EM, Borders-Hemphill V. Use of prescription antiobesity drugs in the United States. Pharmacotherapy 2013;33:1299–307.