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Pharmacological interventions for obesity: current and future targets

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Abstract

Purpose of review—Obesity in the United States has been on a constant rise since the Center for Disease Control and Prevention (CDC) began tracking it over 50 years ago. Despite focused attention on this epidemic, pharmacological treatments aimed at obesity are lacking. Here, we briefly give perspective on the central and peripheral mechanisms underlying feeding behaviors and describe the existing pharmacological treatments for obesity. With this lens, I suggest future targets for the treatment of obesity.

Recent findings—Given the development of genetic and molecular tools, understanding of how energy expenditure is modulated is becoming more nuanced. There is growing evidence for a link between obesity and addiction, which should be utilized in the development of new pharmacological treatments.

Summary—More focus is needed on identifying targets for anti-obesity pharmacology. In doing so, research should include intensive investigation of the brain's reward circuitry.

Keywords

obesity; pharmacology; addiction; dopamine

Introduction

In the United States, rates of obesity have nearly tripled since the Center for Disease Control and Prevention (CDC) first began tracking them in 1960 [1], with approximately 38% of adults meeting the qualifications for obesity [2]. It is among the leading causes of preventable, premature death, due to its high comorbidity with conditions such as cardiovascular disease, diabetes, some forms of cancer and stroke [3]. It has been estimated

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that obesity accounts for \$150 billion dollars alone of healthcare costs in the United States [4], as well as the economic burden of lost work days, lower productivity at work, mortality and permanent disability [5]. Given the great personal, societal and economic burden, obesity has taken center stage as a national health concern. However, despite focused efforts, obesity rates remain unaffected in the United States [1].

Previously, obesity was considered as a lifestyle or behavioral disorder, and as a result, most treatment has been reliant on lifestyle changes. However, recent understanding points to the complexity of the disease, which results from a variety of contributing factors, including behavior, genetics, development and environment. Weight loss based on behavioral changes can be difficult to achieve and more so to maintain, especially once the body has undergone adaptive biological responses [6]. The use of pharmacological agents has been suggested in combination with behavioral changes in individuals with obesity. However, there are very few pharmacological agents available to assist in weight loss efforts.

The control of energy intake and expenditure are complex facets and dependent on bidirectional interactions between the periphery and the brain. Understanding the mechanisms that regulate energy balance will allow for the identification of novel pharmacotherapy targets. The current review will briefly outline important brain regions and neuronal substrates regulating energy balance, discuss available pharmacological agents, and suggest future targets that could provide useful in the treatment of obesity.

Central pathways regulating energy Intake and expenditure

Energy expenditure is regulated by integrating signals from the central and peripheral nervous systems. The brain acts as a master coordinator of appetite and body weight. Early lesion studies indicated a two-pronged model for the regulation of ingestive behavior, with the lateral hypothalamus as a hunger center and the ventromedial hypothalamus as a satiety center [7]. Years of research have expanded on this model, identifying a number of unique brain regions, cell types and projection patterns which are strongly implicated in the regulation of feeding (Figure 1). While a complete discussion of the systems involved in feeding is beyond the scope of this review, I will briefly discuss circuitry that is relevant to current and proposed pharmacological interventions in obesity.

Current models of energy control are no longer confined to the lateral and the ventromedial hypothalamus, but also include the arcuate, dorsomedial, and the paraventricular nuclei. Of particular interest is the arcuate nucleus of the hypothalamus (ARC). The ARC is adjacent to the third ventricle, allowing for it to integrate endocrine and exogenous signals and relay information to the other hypothalamic nuclei [8, 9]. The ARC is heterogeneous, hosting a variety of cell types, which are classified by the neurotransmitters and neuropeptides they secrete. Agouti-related peptide (AgRP) neurons are known to drive food consumption, as injections of AgRP and the co-expressed neuropeptide Y lead to increased food intake [10, 11]. Further, targeted stimulation of AgRP neurons drives feeding in sated mice [12–15], while ablating the cells leads to rapid starvation [16, 17]. Pro-opiomelanocortin (POMC) neurons, which are comingled with AgRP neurons, have the opposite effect on food intake. Selective stimulation of POMC neurons has been shown to inhibit food intake and body

weight over a 24 h period via the melanocortin receptor, while acute injection of the melanocortin receptor agonist leads to more immediate effects on feeding [18]. While most research in the ARC has focused on the roles of the AgRP and POMC neurons, there are other cell populations that have been indicated in modulating feeding behaviors. For example, recently it was shown that activation of tyrosine hydroxylase (TH)-expressing neurons in the ARC can illicit feeding in sated mice [19]. The ongoing discovery of discrete cell populations sufficient in regulating feeding behaviors demands more research.

Rates of obesity suggest that food intake is not simply controlled by calculations of energy expenditure and homeostatic requirements. Factors, such as the hedonic properties of food, play an important role in regulating intake. It has been suggested that while the ARC circuitry directly controls homeostatic feeding, the lateral hypothalamus (LHA) might drive compulsive and/or hedonic feeding [20]. The LHA receives input from other hypothalamic nuclei that relay information from the periphery, including the ARC [21]. However, while early studies identified the LHA as a “feeding center”, a more complete picture includes the role of the LHA in motivation and reward. This stems from early studies where rodents reliably pressed for electrical self-stimulation of the LHA [22, 23], and has been confirmed with anatomical studies which show that LHA neurons have diverse efferent and afferent connections with reward circuitry.

While the LHA is molecularly heterogeneous, new genetic tools have allowed for the identification of several distinct populations of cells with direct effects on food intake and/or reward and aversion. Activation of LHA glutamatergic neurons inhibits feeding [24], while genetic deletion increases food intake [25]. Activation of LHA GABA neurons increases food consumption and food seeking [26, 27], seemingly opposing the actions of the glutamatergic cells. Interestingly, *in vivo* visualization of neuronal activity has determined that anatomically distinct GABA populations in the LHA are activated during food consumption and food seeking [26]. Further, activation of a subset of LHA GABA neurons expressing the neuropeptide galanin, leads to enhanced motivated feeding of palatable foods without affecting standard chow intake [28]. Complementing, it was found that selective activation of LHA GABAergic neurons, projecting to the ventral tegmental area (VTA) of the midbrain, promoted food consumption but not sucrose seeking [29]. Collectively these data suggest two subsets of LHA GABAergic neurons which mediate food-reward behavior or food consumption, respectively.

Orexin containing neurons in the LHA have also been identified as an important population in regulating feeding, with acute activation of LHA orexin neurons driving food seeking [30] and genetic removal of orexin decreasing food consumption [31]. A separate, distinct population of neurons expresses melanin-concentrating hormone (MCH) [32] or leptin receptors [33]. Like orexin, MCH-producing neurons regulate feeding and arousal, with intracerebroventricular injections of the peptide increasing feeding and body weight in rodents [34]. Further, genetic studies have shown that overexpression of MCH results in hyperphagia and obesity [35]. Orexin and MCH-producing cells and leptin-receptor cells all project to the VTA, where they influence reward seeking, and intake of palatable foods.

The VTA is a central component of the mesolimbic dopamine pathway, which is known as the brains' reward system. Within the mesolimbic circuitry, dopamine has long been implicated as a mediator of motivated and rewarding behaviors, such as food intake. This is evidenced by the fact that disruption of dopamine production leads to profound aphagia, as well as hypoactivity [36]. Further, aphagia resulting from genetic disruption of dopamine can be rescued by selective striatal restoration of dopamine synthesis [37]. Circulating feeding signals, such as leptin, insulin and ghrelin, can act directly on VTA dopamine neurons, either inhibiting (leptin and insulin) or stimulating (ghrelin) dopamine signaling in the ventral striatum [38]. Circulating signals, such as leptin, can also have indirect effects on midbrain dopamine neurons via lateral hypothalamic inputs [39].

The ingestion of palatable foods, such as sugar and fat, is known to increase striatal dopamine release in animal models [40, 41]. Further, the striatal dopaminergic system is altered in obese humans and animals. And while there is some controversy, it has been shown that the striatal dopamine D2 receptor availability is inversely correlated with body weight in humans and animal models [21, 42, 43]. Further, a viral knockdown of the D2 receptor or chronic blockade of the D2 receptor (via antipsychotics) leads to weight gain in animal models [43, 44].

In addition to the mesolimbic dopamine system, the serotonergic system plays an important role in regulating feeding. Pharmacological increases of serotonin availability, decreases food intake, while decreases have the opposite effect [45]. Consistent with these findings, genetic studies indicate that mice lacking certain serotonin receptors are hyperphagic and obese [46]. It has been suggested that serotonin is working predominantly through the ARC AgRP and POMC neurons to regulate feeding [47].

Peripheral pathways regulating energy Intake and expenditure

As already alluded to, gut-derived peptides are important relays of energy needs to the brain. They can do this by acting in the periphery, or in the brain itself. In the periphery, gut peptides bind with their designated receptors, effecting the vagal afferent discharge [48]. This leads to signaling of the brainstem (NTS), ultimately sending information to targeted brain regions. While some of these endocrine signals are short-term signals which are activated in proportion to the amount and composition of ingested food (such as ghrelin, glucose and glucagon-like peptide), other signals are responsible for longer-term energy needs. For example, leptin is produced by adipose tissue, and levels vary exponentially with fat mass in order to communicate levels of peripheral fat stores to the brain [49–51]. Leptin crosses the blood brain barrier, and acts centrally on receptors to affect appetite, thermogenesis, and a number of other actions. One target of leptin is the ARC POMC neurons, which in turn inhibit AgRP neurons, together signaling satiety [52]. In addition to promoting satiety, leptin has been shown to effect the incentive value of food through several proposed mechanisms [53, 54]. Leptin has been shown to act directly on receptors on midbrain dopamine neurons [53, 55, 56], as well as neurons in the LHA that project to the midbrain, ultimately decreasing feeding and body weight [33].

Ghrelin is the only known circulating hormone with strong orexigenic activity. Ghrelin is secreted by the stomach, peaking just before a meal and declining after [57]. It has effects on both the central and peripheral nervous system, and while it can cross the blood brain barrier to target brain centers involved in feeding, there is also evidence that ghrelin can be produced in the brain, in areas such as the ARC [58], where it is known to drive AgRP neurons. Ghrelin is also known to act on several brain regions that are linked to the hedonic aspects of food intake, including the VTA and the nucleus accumbens, where it may be regulating the rewarding aspects of food intake [59]. Unlike ghrelin, all other peripheral peptides, such as cholecystokinin (CCK), peptide YY (PYY) and Glucagon-like peptide 1, play a role in appetite suppression.

While all of the above peptides are important in regulating food intake and body weight, this list is not exhaustive. Peptides, such as insulin, also play an important role, peripherally and centrally, in regulating food intake, and are discussed in detail in the literature.

All of the above systems provide potential targets for the development of anti-obesity drugs. Further, understanding how exogenous compounds interact with the system is important in identifying potential pharmacological targets. For example, nicotine activates POMC neurons, leading to decreased food intake. Paradoxically, cannabis also activates POMC neurons, via the CB1 receptor (CB-1R), to induce feeding in a state of satiety [60]. Alcohol drives hunger via activation of AgRP, as well as increased levels of hypothalamic galanin mRNA [61, 62]. Amphetamine, and amphetamine-like derivatives, are also known to suppress hunger, through mechanisms that are not fully elucidated.

History of pharmacological treatments

While by no means the start of the use of pharmacological agents for weight loss, phentermine was the first approved by the US Food and Drug Administration (FDA) in 1959 for short term use. Clinically, the use of such drugs did not take off until the early 1990's, which correlates with a dramatic increase in the prevalence of obesity [63]. Phen-fen, the combination of phentermine, an amphetamine-like psychostimulant, and fenfluramine, a serotonin releasing agent [64], was most commonly used, until reports surfaced of valvular heart disease. As a result, fenfluramine, and the closely related dexfenfluramine, were taken off the market, leaving a dearth in pharmacological anti-obesity treatments [63].

It was not until recent years that the FDA has approved medications for the treatment of obesity and overeating disorders. See Table 1 for a comprehensive list of all FDA approved weight loss agents. With stricter guidelines, in order to gain FDA approval, the drug must show >5% weight loss over placebo, as well as a positive impact on a profile of related risk factors and disease markers [65]. If a clinically meaningful effect (>5% weight loss or >3% weight loss in patients with diabetes) is not achieved within three months of treatment, the drug should be stopped [66]. See Figure 2 for summary of weight loss of FDA approved drugs in clinical reports. Because of the effects of previous obesity-targeting drugs, new drugs must also show cardiovascular safety.

Available pharmacological treatments

In addition to **Phentermine** (available as both Phentermine hydrochloride and low-dose Phentermine), which is still prescribed as a short-term obesity treatment, there are 6 drugs that are FDA approved for obesity and overeating and can be used for long-term treatment. Weight loss on these medication ranges from 3-12% in a 12-month period. Obesity screening includes the calculation of body mass index (BMI), which is a ratio of weight to height. In 2015, the Endocrine Society Clinical Practice Guidelines on Pharmacological Management of Obesity were updated to indicate the use of pharmacological interventions to supplement diet, exercise and behavioral modification in patients presenting a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with a comorbidity [6]. Despite these recommendations, it has been estimated that only 2% of American adults who meet these guidelines receive pharmacological intervention [67].

Orlistat is a pancreatic lipase inhibitor, which leads to the malabsorption of fat by the intestines. It is the only FDA approved weight loss medication that is available over the counter, but its effects of weight loss are modest. It is also the only approved FDA approved weight loss drug that operates peripherally [68].

Lorcaserin, a selective 5-HT_{2C} serotonin receptor agonist, decreases food intake by increasing satiety. It has this effect through activation of hypothalamic POMC neurons [69]. It's potential cardiovascular impact is still under investigation, so while it has been approved in the US and Mexico, it has not yet gained approval in Europe.

Phentermine/topiramate is the first combination drug approved for weight loss. As previously mentioned, phentermine is an amphetamine analog that causes satiety through norepinephrine and dopaminergic antagonism. Topiramate is an anticonvulsant with known effects on GABA and glutamate signaling [70, 71]. However, the mechanism of action causing weight loss is unknown [72]. Taken together, phentermine/topiramate has the highest level of placebo-subtracted weight loss. However, it is also associated with a list of safety concerns including psychiatric morbidity and cardiovascular effects.

Bupropion/naltrexone is another combination treatment. Bupropion is a dopamine/norepinephrine reuptake inhibitor, which is clinically approved for depression and as a smoking cessation aid. Naltrexone is an opioid receptor antagonist which is clinically used to treat alcohol use disorder. This drug combination can lead an increase in blood pressure and heartrate, and therefore cannot be prescribed to individuals with cardiovascular disease, which often accompanies obesity [63].

Liraglutide is an analog of the human glucagon-like peptide-1 (GLP-1), and mimics the actions of endogenous GLP-1, which is released from the small intestines [73]. It peripherally regulates appetite through by increasing the release of insulin from the pancreas in the presence of glucose, as well as centrally through direct stimulation of hypothalamic POMC neurons. This medication must be administered via subcutaneous injection [74].

The most recent drug to gain approval in the treatment of overeating is **lisdexamfetamine dimesylate**, which was originally labeled for attention deficit hyperactivity disorder

(ADHD). Lisdexamfetamine dimesylate, a prodrug of dextroamphetamine, an amphetamine-class stimulant, is the first medication approved to treat Binge Eating Disorder (BED) [75]. While BED is not synonymous with obesity, approximately 30% of people seeking obesity treatment report some degree of binge eating and up to 10% of obesity treatment seekers meet clinical criteria for BED [76]. Therefore, by extension, treatment of overeating in BED does have effects on one form of obesogenic phenotype. It also highlights the fact that obesity is a heterogeneous disease and treatment must be customized to the individual patient.

Off-label drug use

There are a handful of medications that are prescribed for conditions other than obesity, that have the known side effect of weight loss. For example, exenatide, a GLP-1 receptor agonist used to treat diabetes, reduces appetite and induces satiety, in part, through hypothalamic mechanisms [77]. Zonisamide, which is approved for epilepsy treatment, has been used alone or in combination with bupropion, to effect weight loss by causing enhancement of dopamine and serotonin transmission [78, 79]. Unlike exenatide and zonisamide, most medications that fall under this category have unknown mechanisms of action. By determining the mechanisms of action, targeted treatments for weight loss can be developed.

Future targets for obesity treatment

While gut-derived peptides are a potential target for inducing satiety and ultimately effecting weight loss, the development of drugs based on these principles has been challenging due to short half-lives, gastrointestinal side effects which limit therapeutic use, and redundant neuronal and hormonal mechanisms [80]. That said, stable analogs, such as exenatide (GLP-1 receptor agonist), have been developed, and has been shown to cause weight loss in a diabetic population that is intrinsically unlinked to the common nausea experienced by the drug [81].

Given the unmet need for safe, efficacious anti-obesity treatments, it is necessary to look towards new treatment targets. A developing literature has identified the fact that certain instances of compulsive overeating have striking behavioral and neurobiological similarities to substance abuse disorder [82]. Drugs of abuse exert powerful effects on the brain's reward system, which evolutionarily developed to reinforce behaviors such as feeding. Seeing that drugs of abuse and food are processed, in part, through the same neural pathways, it has been suggested that a state of addictive-like eating can develop. It has been hypothesized that "food-addiction" can develop when highly palatable foods hyperstimulate the reward pathways, ultimately leading to overconsumption, weight gain and obesity [83]. By implementing the lens of addiction, novel, anti-obesity pharmaceutical targets may be identified.

The mesolimbic dopamine pathway plays an important role in the development and maintenance of substance abuse and excessive caloric intake. It has been well established that use of addictive substances causes an acute rise in striatal dopamine levels. Consumption of palatable foods, rich in fat and sugar, have also been shown to increase

striatal dopamine levels [40, 41]. Targeting the dopamine system to pharmacologically treat obesity is not a new concept. In the 1930's the psychostimulant, amphetamine, was prescribed for weight loss. It is also well established in the literature, that psychostimulants, which work, in part as dopamine agonists, suppress food intake [84]. The anorectic properties of stimulants are highly exploited in supplements marketed for weight loss, with estimates of more than 11% of adults in the United States using stimulant-containing, nonprescription weight-loss supplements [85]. The most common active ingredients in these supplements are amphetamine derivatives [86]. Despite the broad use of amphetamine drugs to curb appetite and reduce weight, the specific neuronal mechanisms underlying the effects on consummatory behaviors are not well understood.

While use of traditional stimulants is no longer medically condoned for weight loss because of their addiction potential, better understanding of the neuronal circuitry underlying stimulant-induced hypophagia can inform the development of safe pharmaceuticals targeting obesity. An example of this is lisdexamfetamine dimesylate, a prodrug of dextroamphetamine, an amphetamine class stimulant, which was recently approved for the treatment of binge eating disorder. Other drugs which target dopamine and other monoamines have been studied in the development of anti-obesity agents. And while they are effective and lead to weight loss, they have been withdrawn from development because of cardiovascular side effects [87]. One compound, tesofensine, a triple monoamine reuptake inhibitor, which is known to affect dopamine functioning, is currently in phase three clinical trials, scheduled for completion in 2019 [88].

In addition to the neurotransmitter dopamine, there are other anti-obesity targets within the dopamine circuitry, such as the dopamine D2 receptor (D2R). Extended use of drugs of abuse is associated with downregulation of striatal dopamine D2 receptor (D2R) availability [89]. It has been hypothesized that this decrease in receptor availability drives the need for more of the substance to derive the same level of reward [90]. It has been suggested that low D2 receptors are a cause and a consequence of addictive behaviors [91]. The animal literature indicates that low D2Rs confers vulnerability towards substance use, and chronic drug use further downregulates striatal D2Rs [92, 93]. Similar to individuals with a history of substance use disorder, individuals with obesity have a depletion in D2R availability [94], providing a novel target for future anti-obesity interventions. Further, it has been suggested that decreased D2R activity might be linked to the physical inactivity accompanying obesity [42]. It follows that targeting D2 receptors may lead to a dual-pronged outcome of decreased food intake and increased movement, effecting weight loss.

The development of the Yale Food Addiction Scale (YFAS), a psychometrically validated scale based on substance use disorder diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5), has allowed for the identification and operationalization of food addiction [95]. And while not all obese individuals meet YFAS criteria for food addiction, the prevalence of meeting diagnosis criteria is approximately 5 times more in overweight and obese populations than the general population [96]. Further, over 50% of individuals with BED meet diagnostic criterion on the YFAS [97]. Methylphenidate, a dopamine reuptake inhibitor, is known to suppress appetite and decrease food intake in obese and non-obese individuals. However, In a population of over-weight

and obese individuals meeting diagnostic criteria on the YFAS, methylphenidate failed to decrease consumption of preferred snack-foods, providing evidence of dopamine signaling differences compared to those not meeting YFAS diagnostic criteria [98]. This may suggest that treatment of obesity must be individually tailored based on individual obesity phenotypes.

Another target in the reward circuitry is cannabinoid system. The rewarding effects of cannabinoids are related to their ability to increase dopamine activity in the mesolimbic pathway via the CB-1 receptor [99]. The CB-1 receptor has also been identified as an important factor in the rewarding effects of morphine and heroin, both of which are drugs that act on brain opioid systems [100]. Cannabinoids also play an important role in modulating feeding. Over nutrition is known to activate the endocannabinoid system, resulting in hyperphagia, reduction in energy expenditure and ultimately, obesity. Conversely, CB-1 receptor antagonists suppress feeding and decrease weight [101]. Rimonabant, a CB-1 inverse agonist, was approved in several parts of the world as an anti-obesity drug, but withdrawn from the market due to psychiatric side effects [102]. Given the links between cannabinoids, the brain reward system, addiction and feeding, this is another potential pharmacological target that must be further explored.

Finally, the opioid system is a viable anti-obesity target within the reward circuitry. Naltrexone, an opioid antagonist, is already approved by the FDA for weight loss in the Naltrexone/Bupropion cocktail, Contrave. Interestingly, both drugs are individually approved for other indications, Bupropion, a dopamine/norepinephrine reuptake inhibitor, for smoking cessation and naltrexone to treat alcohol and opioid dependence [103]. This highlights two important concepts for moving forward with weight loss pharmacology: 1) combination treatments seem to be the most effective and 2) medications indicated in addiction treatment will likely be effective in promoting weight loss.

Conclusions

With obesity rates remaining to rise, the need to novel pharmacological interventions is crucial. Given the fact that obesity shares many behavioral and neurochemical similarities with addiction, exploring targets relevant to addiction might lead the way to new anti-obesity drugs. It is even possible that future drugs initially developed for addiction treatment will have profound effects on body weight and obesity. Because eating is central to survival, the ability to selectively target hedonic eating, while leaving homeostatic feeding untouched is the ultimate goal in curbing the obesity epidemic.

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Figure 1.

Simplified peripheral and central regulation of feeding and satiety. Peripheral signals from the intestine, stomach, pancreas and adipose tissue act directly on brain targets, or through vagal afferents via the Nucleus tractus solitarius (NTS). Aspects of the hypothalamus (HTH), such as the arcuate nucleus, integrate endocrine and exogenous signals and relay information to the other hypothalamic nuclei, such as the lateral hypothalamus. The lateral hypothalamus interacts more intimately with the brain's reward circuitry including the ventral tegmental area (VTA), ventral and dorsal striatum (vStr, dStr). Peptide YY (PYY); cholecystokinin (CCK); Glucagon-like peptide-1 (GLP-1)

Figure 2.

Reported weight loss in clinical studies of FDA approved pharmaceutical agents after 1 year of use. Mean drug reported weight loss (black bars) beyond placebo reported weight loss (open bars). [45][105–109]

Table 1

FDA approved pharmacology for obesity and eating disorders. ER extended release, SR sustained release [104].

Drug name	FDA Approval	Mechanism of Action	Notes
Orlistat	1999	Pancreas lipase Inhibitor	Available at a low dose over the counter
Lorcaserin	2012	5-HT _{2C} receptor agonist	
Phenramine/topirmate ER	2012	Centrally acting noradrenergic agent/GABA/GLUT modulator	
Naltrexone SR/bupropion SR	2014	Opioid receptor antagonist/dopamine and norepinephrine reuptake inhibitor	
Liraglutide	2014	GLP-1 receptor agonist	Drug is a daily injectable
Lisdexamfetamine dimesylate	2015	central nervous system stimulant	Specifically approved for binge eating disorder
FDA approved for short-term use—up to 12 weeks			
Phentermine	1959	centrally acting noradrenergic agent	
Benzphetamine Hydrochloride	1960	centrally acting noradrenergic agent	
Diethylpropion	1959	centrally acting noradrenergic agents	
Phendimetrazine	1959	centrally acting noradrenergic agent	
Phentermine	1959	centrally acting noradrenergic agent	