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Pharmacotherapies for Overeating and Obesity

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Abstract

Obesity has become pandemic, and the annual cost in related illnesses and loss of productivity is already over $100 billion and rising. Research has shown that obesity can and does cause changes in behavior and in the brain itself that are very similar to changes caused by drugs of abuse. While food addiction is not the causal agent of all obesity, it is clear that many people no longer eat to survive, but instead survive to eat. This review considers the importance of the brain's reward system in food intake. The review also examines research developments and current treatments for obesity, including diet and exercise, psychotherapy, surgical interventions, and pharmacotherapies. Finally we discuss alterations in American society that are necessary for change to occur, and the difficulties therein.

Keywords: Obesity; Pharmacotherapies; Dopamine, Brain reward circuitry; Social change; Reward Deficiency Syndrome (RDS)

Abbreviations: ASAM: American Society of Addiction Medicine ; CBT- Cognitive Behavioral Therapy (CBT); CBT-gsh: Cognitive Behavioral Therapy guided self-help (CBT-gsh); dialectical DBT: Dialectical Behavioral Therapy; IPT: Interpersonal Therapy; RDS: Reward Deficiency Syndrome

Introduction

Food addiction may play a role in the obesity epidemic. Obesity has reached pandemic proportions and is rapidly surpassing smoking as the number one killer in the industrialized world, as well as costing an estimated $117 billion annually in related illnesses and loss of productivity [1-3]. As the number of persons diagnosed with obesity continues to rise every year, many people are seeking answers for why so many people struggle with these issues. While food addiction certainly does not explain all cases of obesity, the increased number of persons with interest in eating above that which is required for the basic energetic needs of survival, suggests that food intake is no longer simply for survival purposes [4]. It has been demonstrated that rats overeating sugar solution developed many behavioral and brain changes resembling the effects of drugs of abuse [5-7]. Also similar to drug addictions, the reward circuitry of the brain, especially the dopaminergic system, was found to be involved in animals overfed highly palatable foods [8-13].

Not all foods are currently implicated in the development of food addictions [14]. Foods that are thought to be addictive tend to be highly palatable and are rich in fats, sugars, salt, and are calorie dense [4]. Further, these foods often are comprised of synthetic combinations of ingredients that may make them more potentially addictive than traditional foods [15]. Beyond this, research has recently demonstrated that each of these nutrient elements affects specific neurotransmitter systems in the brain [6,16-18], providing the potential for targeted pharmacologic treatments [19,20]. With the soaring numbers of individuals affected with obesity, many of whom are children, it is important to seriously evaluate some of these new treatment modalities.

Reward system in food intake

Motivational abnormalities such as excessive overeating have been linked with changes in the mesocorticolimbic system of the brain, a complex and interrelated network with many functions, including food addiction [21]. Principal components of the mesocorticolimbic reward circuit consist of the amygdala, hippocampus, nucleus accumbens (ventral striatum), and ventral diencephalon (including the basal forebrain, ventral tegmentum, and hypothalamus), as well as cortical areas that provide modulating and oversight functions, such as the dorsolateral prefrontal, orbitofrontal, temporal pole, subcallosal, and cingulate cortices, parahippocampal gyri, and the insula. Dysfunctional eating may reflect an underlying addictive state.

Eating is essential for the survival of all living organisms [22], and even relatively brief durations of starvation, e.g., days, can lead to detrimental physical and psychological changes [23,24]. Therefore, eating behaviors are programed in the brain by powerful neural systems to ensure food-intake and to regulate caloric balance. These feeding behaviors are, however, controlled by more than homeostatic mechanisms. As it has been pointed out, "If feeding were controlled solely by homeostatic mechanisms, most of us would be at our ideal body weight, and people would consider feeding like breathing or elimination, a necessary but unexciting part of existence" [25]. The fact that this is not the case suggests that there is a role for the reward systems in the brain to promote motivational, hedonically-driven feeding. Thus, excessive food intake may be explained more by dysfunction in the reward circuitry than strictly dysfunction in the homeostatic mechanisms controlling feeding habits. Studies in human and nonhuman animals alike have supported the hypothesis that brain's reward circuitry may be dysregulated in cases of obesity, disordered eating, and more recently, food addiction [5-12,26].

Genetics may play a role in the underlying addictive feeding. As

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not everyone who is exposed to drugs becomes an addict, similarly, not every person exposed to high-risk foods goes on to compulsively over eat. The difference in susceptibility can be attributed, at least in part, to underlying genetic predispositions, specifically, down-regulation of dopamine D2 receptors [27-30]. One particular dopamine receptor genetic polymorphism, the TaqIA A1 allele, has been implicated specifically in obesity and substance use disorders through increases in reward sensitivity in the striatum by elevated dopamine activity levels [31-33]. It follows then, that new forms of treatment, largely pharmaceutical, would potentially target these genetic predispositions as a means of intervention. This paper outlines some of the existing modalities of treatment with emphasis on pharmacologic interventions.

Diet and exercise

Although obesity often is described as an imbalance between caloric intake and energy expenditure, diet and exercise alone are not enough to combat most cases of obesity. Nonetheless, there is a simplified view suggesting that obesity is the fault of the obese individual due to excessive consumption, inadequate activity, or a combination of the two, resulting in much of the stigma that is associated with this condition [34]. While decreased caloric consumption and increased physical activity can be effective in normalizing weight, these lifestyle modifications have proven very difficult to sustain [35]. Studies have found that when dieting, the rate of initial weight loss can be rapid and then slowly declines over time such that the point of maximum weight loss is typically around six months after the initiation of treatment. After this point weight regain typically begins and gradually increases until stabilizing at a point usually somewhat below baseline level [36]. This pattern seems to remain independent of the initial weight loss, and aggressive maintenance strategies have been able to slow, but not prevent the rate of regain over time [37]. Further, adherence to these maintenance strategies typically slows over time, thereby failing to prevent relapse [38], and the expenditure of time and money to implement these maintenance strategies generally renders them impractical to any large-scale, community-based intervention [39]. The failure of many of these lifestyle modifications to reduce obesity over the long term suggests that obesity may not be entirely a metabolic disorder, but likely has a neuropsychogenic component [35]. While food addiction certainly does not explain all cases of obesity, the prevalence of people who eat for reasons other than obtaining energy suggests that other factors may play a role in motivating and/or reinforcing feeding behaviors. With the rapidly increasing number of cases of obesity, it may be time to consider new ways of understanding and approaching this problem. Moreover, it is well-known that carrying the DRD2 A1 allele results in reduced energy expenditure but a higher requirement for food reinforcement [40].

Psychotherapy

The study of food addiction is relatively new, and specialized treatment approaches have not yet been developed. However, because of overlaps between binge eating, obesity, and food addiction, it is possible that strategies that are effective for treating binge eating and obesity also may prove helpful in the treatment of food addiction. Certain types of psychotherapy, including cognitive behavioral therapy (CBT), cognitive behavioral therapy with guided self-help (CBT-gsh), dialectical behavioral therapy (DBT), and interpersonal therapy (IPT), have shown success in the treatment of binge eating disorder [41,42]. Some have argued that the utility of these psychotherapeutic modalities in treating food addictions negates the idea of food as addictive and, therefore, nullifies the utility of pharmacotherapy targeting reward circuitry [43-45]. However, drug addictions are accepted as dysfunctions in the reward processes in the brain, and psychotherapy has been effectively utilized in the treatment of alcohol and narcotic addictions. Thus, the utility of therapy does not preclude the usefulness of pharmaceutical interventions aimed at addressing underlying brain dysfunction in food-addicted individuals. Some even have argued that obesity would best be understood as an impulse-control disorder, thereby requiring multimodal treatment to achieve success [46,47].

Psychotherapy also might help to address co-morbid psychiatric disorders that could be contributing to dysfunctional eating behaviors. For some, eating may have become an ingrained behavior that serves as a form of self-medication in response to negative emotional states such as depression, anxiety, loneliness, boredom, anger, and interpersonal conflict [48-52]. As such, the use of psychotherapy might be beneficial in effecting underlying psychopathology that may be, at least in part, driving the food addiction. If so, the role of behavior modification can be highlighted in conjunction with pharmacological interventions, for the treatment of food addictions. Thus, the need for multimodal treatment paradigms is underscored [53]. It should also be noted, however, that treatment of disordered eating can be a long and arduous process marked by alternating periods of relapse and recovery.

Because there are many studies that have established the role of dopaminergic genetics in binge eating and obesity in general, along with other notable brain substances and peptides, including leptin [54,55], pharmacological treatments also are considered adjunctive avenues of treatment (as discussed later).

Surgery

Given the high rates of relapse and limited efficacy of current obesity treatments, increasing numbers of obese individuals find themselves turning to bariatric surgery for treatment of obesity [56]. Initial weight-loss reported with this procedure is excellent, averaging 88 lbs [57]. Complication rates from this procedure, however, are high, ranging from 20-30%, as well as causing long-term health effects and nutrient deficiencies [58-60]. Also, similar to behavioral interventions, relapse rates are high ranging from 20.4-34.9% [61]. Further, there have been reports of a subset of bariatric surgical patients who, being less able to consume food in excess, later developed other addictive behaviors such as gambling, substance abuse, and impulsive spending [62,63], suggesting the addictive phenotype may be hard-wired in some cases of obesity.

Other surgical modalities have been investigated as possible means of treating obesity. It has long been known that lesions in the ventromedial hypothalamus produced obesity [64-68]. Scientists therefore attempted to use deep brain stimulation on this portion on the brain as a means of weight loss. Initial trials with nonhuman animals had seemed promising [69-73], but the translation to humans was more troublesome, with patients having regained all initial weight-loss by one year post-surgery [74-77]. To address these issues, neurosurgeons have discussed the possibility of instead targeting areas involved in other areas of the reward circuitry rather than the hypothalamus itself [78]. Specifically, interest has been expressed in targeting the nucleus accumbens, subgenual cingulate cortex, anterior insula, amygdala, and stria terminalis as potential locations for deep brain stimulation [78].

Given the current lack of long-term benefit, cost, and the significant risks, at this time, surgery is not an optimal treatment for food-addicted patients. Despite the type of surgery undertaken, in desperation for results, obese patients often undergo these expensive,

invasive procedures with high complication rates, long-term health impacts, and with high relapse rates, a far from ideal treatment. As a result, much attention today has shifted to developing better treatment options. Given the rise of obesity not only in the United States, but around the world [79], a number of pharmaceutical companies are looking to develop new treatments for obesity based upon knowledge about the addiction hypothesis [16] and Reward Deficiency Syndrome (RDS) [27].

Pharmacotherapies

The American Society of Addiction Medicine (ASAM) now recognizes addictions as a brain disorder [80], and as such, treatments aimed at addressing food addiction must address the dysfunctions at the level of the brain. It follows, then, that pharmaceuticals may be essential adjuncts to effective treatment of these disordered brain mechanisms. A number of excellent reviews have been written outlining the endogenous neurotransmitter involvement in food addicts, including papers on opiates [81,82], neuropeptide Y and leptin [83], cannabinoids [84], and dopamine [13,85,86]. Unsurprisingly, the use of pharmaceuticals has been suggested to modulate these brain areas, decrease craving, and negate pathologic drive for overconsumption [87,88].

Current pharmacologic treatments for obesity have failed to adequately address the problem. Despite the neurobiological linkage with satiety signals and noted elevated levels of leptin in obese individuals and food addicts, trials of pegylated recombinant human leptin targeting the homeostatic mechanisms of obesity have not succeeded [64,83,89-93]. Silbutramine, a mixed serotonin, norepinephrine, and dopamine reuptake inhibitor, had shown some promise of effecting weight loss, but was pulled off the market in 2010 due to concerns of increased risk of stroke and cardiovascular events [94,95]. Orlistat is currently the only pharmacologic therapy for obesity that is approved for long-term use (up to one year). It works by inhibiting absorption of fat in the gut and results in modest weight loss of an average of 6.4 pounds in the course of a year [94]. Phentermine and diethylpropion also are commonly provided for obesity, and similarly have had limited success [96]. Despite their use, these pharmaceuticals for obesity have failed to produce significant, enduring weight loss [97] and at best have provided only modest, short-term benefit [98].

Given the lack of utility of current treatments, new modalities currently are under investigation. Traditionally, obesity-related treatments have targeted hunger and eating behavior itself. Researchers now are interested in further characterizing the effects of various nutrients on the neurotransmitter systems of the brain, as these may provide for targeted interventions based on an individual's particular food preference [4]. Researchers also are interested in pharmacotherapeutic interventions aimed at reducing the reinforcing effects of highly palatable nutrients as a means of reducing body mass [15]. Indeed, a number of new treatments are in both Phase II and Phase III clinical trials, including: Contrave, Qnexa, and Lorcaserin, as well as investigating other novel pharmaceuticals [16]. The majority of these potential treatment options target the neuropathways and neurotransmitters discussed individually below [99].

Dopamine

Dopaminergic dysfunction is a common link between obesity and addiction. Obese individuals and those addicted to substances of abuse have decreased dopamine receptor D2 availability in the striatum of the brain [11,100]. In obese individuals, this level of decrease is proportional to the body mass index [87], which makes intuitive sense in a case of food addictions, as dopamine is the primary reward transmitter in the brain's reward circuitry [101]. Therefore, it has been postulated that food-addicted individuals are driven to eat either because they obtain a very high reward from the food itself (too much dopamine) or because they are not satisfied by normal amounts of food (too little dopamine) [9,32,78]. Thus, pharmaceuticals both targeting and inhibiting dopaminergic pathways are currently under investigation, including: raclopride, buprprion, and antipsychotics [102]. However, blocking dopaminergic function has met with enhanced suicide ideation as reviewed and rejected by the FDA when considering aproval of rimonabant [103,104].

Endorphins (endogenous opioid peptides that function as neurotransmitters)

Opioids have long been implicated in the reward circuitry of the brain and with pleasure derived from eating. As such, opioid antagonists have been shown to decrease short-term food intake and decrease the pleasurable nature of palatable foods, and have been long considered in weight loss therapy [105]. Studies suggest that opioid antagonists such as naloxone, naltrexone, and nalmefene may result in decreased caloric intake and thus have been suggested for use [106-119]. However, the results of clinical trials have been mixed, with a few suggesting that opioid antagonists failed to yield any significant effect in the treatment of obese binge eaters [120,121]. It has been suggested that these differences in findings may be explained by such things as varying dosing strategies, open-label *vs.* blind designs, and use of antagonists as a sole agent *vs.* augmentation strategy [122]. Given these findings, a double-blind placebo controlled dose-response trial in food addictions seems a logical future direction for this work. The use of agents that block opiate receptors (e.g., mu opiate receptor) may be helpful in the short term, however, caution for long-term use seems prudent, based on many studies [123].

Serotonin

Cravings may serve as an obstacle to treatment and may be controlled through serotonergic and dopaminergic agonists [124]. Similar to drug addicted persons, people with food addiction may also experience overpowering urges to eat specific foods, better known as cravings [125], especially in environments of dietary restrictions such as found in repetitive diets [126]. Unsurprisingly, food cravings have been implicated in snacking behavior, compliance with dietary restrictions, early dropout from weight-loss treatments, and overeating and bingeing in obese individuals [127-129]. It is these compulsive behaviors that serotonergic drugs are thought to modulate [130,131]. Thus, it likely comes as no surprise that various serotonergic drugs are under investigation as possible treatments for binge eating and food addiction, including fluoxetine, sertraline, sibutramine, fluvoxamine, desipramine, imipramine, and topiramate, with results demonstrating superiority of serotonergic drugs to placebo [132].

Glutamate and GABA

Increasing numbers of studies have also implicated the glutamate system in the regulation of food intake [133,134], as well as drug and alcohol abuse [135,136]. It has thus been hypothesized that compounds that decrease the function of the glutamate system may reduce food intake [137,138] As such, compounds such as acamprosate, an antagonist of the glutamate N-methyl-D-aspartate (NMDA) receptor and possible partial antagonist of mGluR5 function [139] has long been used in the maintenance of alcohol dependence under the presumed

action that it decreases cravings [140,141], and is being looked at as a potential medication in binge eating and food addictions as well [142-145]. It has been reported that acamprosate can reduce food cravings and associated weight gain in alcoholic patients [146], but results have been mixed as a standalone in binge eating disorder [147]. Similarly, topiramate, an antagonist of the glutamate kainate receptor has shown promise in addressing bulimia nervosa, binge eating disorder, as well as alcoholism [137,138,148-150]. Memantine, another NMDA antagonist, has been shown to reduce the consumption of highly palatable food [151] and has been shown to reduce binge eating in open-label trails [152,153]. Additionally, the mGluR5 antagonist MTEP has been shown to reduce binge eating [151]. Baclofen also is under investigation as a possible GABAnergic intervention [102]. There also are a number of GABAnergic drugs under investigation for various drug addictions that may in the future be tested in food addictions; however, their use has been questioned [154].

Cannabinoids

Cannabinoid receptors may serve as another potential target. Antagonism of the endocannabinoid receptors, specifically CB1 and CB2, has been suggested as a potential target in the battle against obesity. CB1 receptors are associated with motivational brain reward circuits involving the mesocorticolimbic dopamine system [155-157], and CB-1 receptor antagonism is believed to attenuate dopaminergic activation of the reward circuitry [158]. Given this correlation, it follows that much research has been aimed at the development of novel synthetic CB-1 receptor antagonists, as this is believed to have appetitive component [159,160]. The most famous example, rimonabant, a selective cannabinoid-1 receptor antagonist and CB-1 receptor inverse agonist, had shown promise resulting in an average drop of 11 pounds over the course of a year [94,161]. However, it was removed from the market in 2007 due to increased reports of anxiety, depression, aggression, psychosis, and increased suicidal thinking [162]. Nevertheless, there are other cannabinoid drugs currently under investigation including: dronabinol, nabilone, sativex, levonantradol, WIN55212-2, AM 251, AM4113, SR141716A, V24343, SR-147778, SLV319, MK-0364, and CP-945,598 [102,163-166]. Of these, nabilone, SR141716A, AM4113, V24343, SR-147778, SLV319, MK-0364, and CP-945,598 have been specifically targeted for obesity related issues [163,164,167].

As originally noted in 1948, addicts typically are able to function without symptoms of withdrawal and craving in an environment devoid of the substance to which the person is addicted, but upon returning to the environment associated with these addictive behaviors, the addict experiences marked feelings of withdrawal and craving [168]. Similar to drug cravings, food cravings can easily be triggered by exposure to sight, smell, or imagery of the craved food [169]. Given these trends, it is time to address some of the cultural aspects associated with these behaviors.

Society

As it stands, obesity and binge eating behaviors will continue to be a threat to global heath [170]. Therefore, it is essential to reevaluate the current food environment from many aspects, while taking into consideration both the individual's perspective and society as whole. Societal measures may, in fact, be required at this time, as dysfunctional eating behaviors affect not only the current generation, but also its offspring due to the effects that consuming certain highly palatable foods may have on the developing brain *in utero*.

Given that cultural influences often are driven by economic factors that lie outside the control of the individual, the topic of obesity cannot simply be relegated to the domain of personal responsibility. Rather, economic incentives that encourage people to make unhealthy food choices need to be re-evaluated on a larger scale. Indeed, any plan to combat the rise in obesity will need to address the economic, political, social, psychological, and biological factors that contribute to obesity, as well as factors such as taste, accessibility, convenience, cost, and level of promotion [79]. Moreover, it is important to closely re-evaluate the current state of food marketing. One study has found that food-addicted persons respond at an even higher level to food cues than their non-addicted counterparts [171]. This finding suggests that advertising cues may contribute, at least in part, to compulsive eating in at-risk persons. Further, societal changes such as reevaluating where government subsidies are allocated, taxation, publicly enforced well-care programs, and corporate driven employee well-being programs also may be needed to address the issues of disordered eating and obesity. While these efforts are not expected to cure obesity, binge eating, or food addiction, they may help to reduce their prevalence and aid prevention efforts.

Undertaking such actions as advertising, availability, and addressing public health and cost-related measures are not unreasonable. Indeed, each of these efforts has been used successfully in reducing alcohol and tobacco use [15]. Given the implications of obesity and the underlying cost in terms of health care dollars and human health, the utility of these efforts to reduce the rates of obesity would be profound [15]. Indeed, many researchers have argued the only realistic means of addressing this epidemic would be refocusing efforts on prevention, as well as changes in public health policy [172-175].

Conclusions

Recent research has uncovered both neurobiological and behavioral similarities between substance dependence and excess consumption of highly processed foods [18]. Observations of this nature have led some to propose the concept term food addiction and to postulate its role in the obesity epidemic. A better understanding of the food addiction paradigm and the underlying brain dysfunction may help develop better pharmaceutical therapies. There are a number of such therapies under investigation targeting neuropathways and neurotransmitters implicated in addiction, including: dopaminergic, opioid, GABAnergic, cannabinoid, serotonergic, and other novel treatment options.

However, these medications are not without risk; many carry significant side effects including increased risk for depression, anxiety, obsessive-compulsive disorder, seizures, suicide, confusion, or memory deficits [16]. Given the risks and side effects associated with these drugs, physicians need to exercise great care when considering whether to prescribe them as treatments, and to carefully select their population base prior to prescribing [16]. One alternative that offers new hope following additional rigorous research, is to consider gentle activation of dopamine D2 receptors, preventing dopamine D2 receptor down regulation [18,176].

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Conflict of Interest

Kenneth Blum, PhD, has been awarded a number of global patents for Obesity treatment compounds. Mark Gold, MD, has US patents pending related to obesity treatment compounds. No other author has any conflict to report.

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