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The Neurobiology of Binge-Eating Disorder Differs from Obesity: Implications for Differential Therapeutics

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Abstract

Purpose: Emerging work shows divergence in the neurobiologies of binge-eating disorder (BED) and obesity despite their frequent co-occurrence. This review highlights specific distinguishing aspects of BED, including elevated impulsivity and compulsivity possibly involving the mesocorticolimbic dopamine system, and discusses implications for differential therapeutics for BED.

Methods: This narrative review describes epidemiological, clinical, genetic, and preclinical differences between BED and obesity. Subsequently, this review discusses human neuroimaging work showing differences in executive functioning, reward processing, and emotion reactivity in BED as compared to obesity. Finally, based on the neurobiology of BED, this review identifies existing and novel therapeutic agents that may be most promising given their specific targets based on putative mechanisms of action relevant specifically to BED.

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Conflicts of Interest

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Findings: BED is characterized by elevated impulsivity and compulsivity compared to obesity, which is reflected in divergent neurobiological characteristics and effective pharmacotherapies. Therapeutic agents that influence both reward and executive function systems may be especially effective for BED.

Implications: Greater attention to impulsivity-/compulsivity-related, reward-related, and emotion-reactivity-related processes may enhance conceptualization and treatment approaches for patients with BED. Consideration of these distinguishing characteristics and processes could have implications for more targeted pharmacological treatment research and interventions.

Keywords

binge-eating disorder; eating disorders; obesity; impulsive behavior; compulsive behavior; neurobiology; pharmacology

Many people struggle to regulate their eating, including those with binge-eating disorder (BED) and those with obesity. BED is a psychiatric illness characterized by frequent episodes of consuming an objectively large amount of food in a short period of time with a subjective sense of loss of control during eating without subsequent compensatory behaviors[1]. Obesity is a physical condition defined by elevated body mass index (BMI). Obesity and BED have high rates of comorbidity, with more than half of individuals with BED also meeting BMI criteria for overweight or obesity[2, 3]. Conversely, BED is highly prevalent in obese populations, especially in individuals participating in treatments targeting weight loss[4, 5].

Given frequent co-occurrence between BED and obesity, and some shared behavioral features of overeating behaviors, the emerging treatment literature for BED has been influenced by the obesity field[6]. Indeed, some early interventions attempted for BED included treatments from the obesity literature including, for example, very-low-calorie-diets (VLCDs), multiple behavioral weight-loss methods, and weight-loss medications[7–9]. Until recently, there were no approved pharmacological treatments for BED[10–12], and clinicians have needed to rely on off-label use of pharmacotherapy involving agents developed specifically for other medical (e.g., obesity, seizure disorders) or psychiatric (e.g., depression) conditions[13–15].

While the few weight-loss medications from the obesity literature tested to date have shown some potential to enhance weight loss in patients with BED, they have generally not reduced binge eating[16–18]. One potential explanation for this is that BED may represent a distinct phenotype of obesity because of its unique neurobiological characteristics[19–24]. As compared to obesity, BED may involve greater impulsivity and compulsivity, possibly involving the mesocorticolimbic dopamine system[20, 25–27]. Accordingly, targeting impulsivity, compulsivity, or other features of BED may be important to treatment outcomes and have implications for differential therapeutics for BED.

Methods

This narrative review examines the neurobiology of BED as compared to obesity, with a focus on how such differences may influence pharmacotherapy treatment for BED. First, we review neurobiological systems involved in BED and obesity. Second, we discuss epidemiological, clinical, genetic, and preclinical evidence for differences between BED and obesity. Third, we review human brain imaging work suggesting divergent impulsivity/compulsivity, reward-related, and emotion-related neurobiological processes in BED and obesity. Then, we consider whether specific therapeutic agents may be beneficial for individuals with BED. We review pharmacotherapies for BED, with a focus on their mechanisms of action and related effects on weight and binge eating. Finally, we discuss how future targeted pharmacological research may help to further establish differential therapeutics for BED.

Neurobiology of Eating and Binge Eating.

Substantial research has investigated neurobiological processes underlying eating behaviors. Complex interacting systems involving physiological and neural substrates for hunger and satiety, including both homeostatic/appetitive and hedonic/reward-based processes, have been implicated in eating[28]. In the human brain, proposed reward circuitry includes the ventral striatum (VS), palladium, amygdala, thalamus, and midbrain neurons, and this circuit interacts with frontoparietal control systems that help to regulate appetitive responding[29]. Multiple neurotransmitters and neuropeptides may influence these processes, including dopamine, serotonin, opioids, orexigenic peptides, glutamate, and endocannabinoids[29]. Disruptions to this circuitry may promote the development of obesity[28] and/or eating disorders[30, 31].

The neurobiology of BED is an active area of recent investigation. Emerging work has suggested that BED is characterized by elevated sensitivity to food reward coupled with increased impulsivity and compulsivity[20, 25–27, 32]. Impulsivity is a multifaceted construct characterized by “actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation that often results in undesirable consequences”[33]. In contrast, compulsivity is characterized by “perseverative behaviors that have no obvious relationship to an overall goal and often result in undesirable consequences”[33]. Impulsivity and compulsivity may reflect failures of “top-down” cognitive control, possibly mediated in part via interactions between prefrontal circuits and those that promote behavioral engagement like the mesocorticolimbic system[32–34]. A transition from impulsive, reward-driven behaviors to compulsive, habit-driven behaviors has been hypothesized to be related to both substance use disorders (SUD) and binge eating[30, 35]. Indeed, the degree to which eating is reported as similar to SUD (i.e., “food addiction” or addictive-like eating) may be an indicator of greater BED severity[36–39]. Accordingly, impulsivity-related and compulsivity-related processes may underlie BED to a greater extent than obesity[20, 25–27, 32].

Epidemiological and Clinical Differences Between Obesity and BED.

Obesity is a physical condition that affects much of the population, whereas BED is a psychiatric illness (i.e., a specific eating disorder) involving recurrent episodes of loss of control while overeating (which, as reviewed below, is distinct from overeating *per se*). Obesity is highly prevalent, with current findings estimating that >66% of the United States adult population is overweight or obese[40, 41]. In comparison, BED, despite being the most prevalent eating disorder, affects only ~1–3% of the United States adult population[2, 3, 42]. Obesity is strongly associated with increased risk for morbidity and mortality[43], and some research suggests that BED may further increase risk or lead to poorer outcomes for some conditions[3, 44–46]. For example, elevated rates of psychiatric conditions[44, 47–49], impaired social functioning[44, 50, 51], and diabetes[46, 52, 53] have been observed in individuals with BED. Across epidemiological, community, and clinical samples, individuals with BED show higher levels of body image concerns and psychological distress compared to those with obesity and without BED[54–57]. Notably, treatment outcomes for individuals with BED are poorer than individuals with obesity alone, including worse diabetes-related complications[46, 52], less weight loss[58–60], and poorer outcomes following bariatric surgery among those with “loss-of-control” eating[61]. Accordingly, despite significant overlap, BED likely represent a distinct, more severe phenotype within a broader obesity spectrum.

The etiology and behavioral presentation of BED diverges from that of obesity. The hypothesized etiology of BED is related to risk/maintenance factors for eating-related psychopathology (e.g., body-image disturbance, dietary restraint, negative mood) which may be associated with diminished control over eating[62]. In contrast, the etiology of obesity is related to caloric imbalance, without necessarily-associated impairments in control over eating[63]. Although individuals with obesity may also show problematic eating and overeating behaviors, BED is defined based on recurring binge-eating behaviors involving perceived loss-of-control whereas obesity is not. Laboratory and ecological momentary assessment (EMA) studies suggest differences in binge eating in BED and obesity[64, 65]. In laboratory studies, compared to overweight controls, individuals with BED consumed more calories[66, 67] and ate larger amounts of food when prompted to “lose control”[68, 69]. This finding contrasts with research with bulimia nervosa, where patients were observed to eat large amounts when prompted to “lose control” and eat less ad libitum[68]. Outside of the laboratory, EMA studies showed more binge eating[70, 71, c.f. 72] and greater distress about binge eating[70–72] in individuals with BED compared to overweight controls. Consistently, the experience of binge eating is not reported as pleasant[73] and results in increased overall negative affect[74]. Nonetheless, overweight controls in these studies also reported experiences of overeating and loss-of-control over eating[70–72]. Accordingly, the frequency and severity of binge eating observed in BED may suggest a more problematic, compulsive pattern that leads to significant distress and could be more closely related to difficulties with impulse control than observed in obesity.

Genetics of BED and Obesity.

Genetic studies suggest BED may be distinct from obesity. BED has been found to be moderately heritable (~45%;[75, 76]) and aggregate in families separately from obesity[77].

Additionally, preliminary research suggests that individuals with BED and obesity may differ with respect to candidate genes, including variants associated with dopaminergic and serotonergic functions[78].

Several genetic polymorphisms may be enriched in BED relative to obesity. Several genes investigated in BED are related to D2 receptors (D2Rs; e.g., *DRD2/ANKK1*) and their polymorphisms (e.g., Taq1A). These genetic polymorphisms have been associated with dopamine function, sensitivity to reward, and SUDs[79]. Fewer individuals with BED (relative to obesity alone) had the A1 allele of Taq1A (associated with decreased reward sensitivity[80]). Additionally, compared to weight-matched individuals, those with BED were more likely to be homozygous for the A2 allele of the Taq1A polymorphism and homozygous for the T genotype of the C957T marker (associated with increased reward sensitivity[81]). Compared to obese individuals without BED, those with BED had a higher multi-locus genetic profile on dopaminergic genes, suggesting possibly greater dopamine signaling and response to reward among those with BED[82, 83]. Together, this work suggests that obese individuals with BED may be genetically distinct from those with obesity alone, possibly related to hypersensitivity to reward. However, further work is needed to substantiate this, particularly given linkage disequilibrium between *DRD2* and *ANKK1* and nearby genes, and findings suggesting in comparison to other nearby genes, *DRD2* may be less closely linked to disorders characterized by poor impulse control[84, 85].

Other studies suggest potential genetic differences between individuals with BED and those with obesity. For example, serotonergic involvement in eating disorders has been widely investigated[78]. One study reported that the LL genotype and L allele of the serotonin transporter gene were more common in individuals with BED compared to lean individuals[86]. Other investigations suggest possible involvement of ghrelin[87], mu-opioid receptor[80], brain-derived neurotrophic-factor[88], *CLOCK*[89], and endocannabinoid[90] genes in BED. However, this work has not been widely replicated, nor have genome-wide association studies with genome-wide significant findings been reported for BED[91].

Animal Models of BED and Obesity.

Preclinical models of BED and obesity examine neurobiological effects of different environmental exposures related to the hypothesized etiologies of each condition[92]. These models find differing neurobiological characteristics associated with excess weight and binge eating in animals. In preclinical models of obesity, animals are fed a cafeteria-style diet with free access to palatable food[93, 94]. Under these conditions, animals gain weight gradually and show heightened sensitivity to palatable food[93]. Obese rats with lentivirus knockout of D2Rs engage in compulsive eating, but not when naturally exposed to palatable foods[94]. In contrast, there are multiple preclinical models of binge eating that involve intermittent access to palatable foods[92]. Unlike animals with cafeteria-style diets, these animals do not always show an increase in weight but do show differing in neurobiological characteristics, including reduced D2R density and enhanced mu-opioid receptor binding[92, 95]. Compulsive-like eating in these rats is modulated through VS projections in the mesocorticolimbic system[96].

Overall, animal models suggest that BED may be a more severe condition along an obesity spectrum. Animal models of obesity show that exposure to hyper-palatable foods leads to dopamine-related changes associated with heightened sensitivity to reward. In contrast, animal models of binge eating with intermittent access to food lead to arguably broader structural and metabolic changes. Accordingly, BED may be characterized by a greater degree of alteration to the mesocorticolimbic system than obesity.

Human Brain Studies of BED and Obesity.

Recent work in human neuroimaging has facilitated investigation of divergent neurobiological aspects of BED and obesity. PET (positron emission tomography) can use radioactive materials to measure receptor availability, and functional magnetic resonance imaging (fMRI) permits investigation of neurobiological correlates of cognitive processes. Such work helps to distinguish between neurobiological features of BED and obesity, including potential differences in receptor availability and neural correlates of psychological processes related to these conditions. Specifically, recent work has examined executive functioning (and related impulsivity/compulsivity), reward processing, and emotional reactivity in individuals with BED compared to obesity.

Receptor Availability.

In line with genetic and preclinical work, there may be differences in dopamine, serotonin, and mu-opioid receptor availabilities in individuals with BED as compared to obesity. Nonetheless, PET studies often have not found consistent differences in humans. In individuals with obesity, there are mixed findings, with some studies finding lower striatal D2/3R availability[97, 98] and others unaltered D2/3R availability[99, 100]. A study using a D3R-preferring ligand observed increased D2/3R receptor availability in people with obesity in D3-enriched brain regions including the substantia nigra/ventral tegmental area, VS, and pallidum[101]. No prior work has compared D2/3R availability in individuals with BED and obesity compared to those with obesity alone, although a [^{11}C]raclopride study suggested that methylphenidate increased food-related dopamine release in individuals with BED compared to those without[102]. Serotonin transporter binding may be related to BMI[103], but findings are mixed in BED. One small study found reduced serotonin transporter binding in obese women with BED compared to obese women without BED[104], whereas another study found enhanced serotonin transporter binding in individuals with BED compared to controls[105]. Other work has suggested that individuals with obesity show reduced mu-opioid availability[100], which increases with weight change[106]. Mu-opioid receptor availability was found to be similar in obese individuals with and without BED[107]. Additional research involving larger samples may help to clarify these seemingly mixed findings.

Executive Functioning and Impulsivity/Compulsivity.

Executive functions are cognitive processes that underlie control of behavior, including attentional control, inhibitory control, and cognitive flexibility[108]. Interactions between prefrontal cortical and subcortical systems underlie these processes[29, 108, 109]. Difficulties in implementation of cognitive control may reflect imbalances between these systems, which may contribute to impulsive and compulsive behaviors[32–34, 108, 109].

Some executive function deficits have been observed in individuals with obesity[110–112]. Genetic factors may link obesity with brain and cognitive measures associated with executive function[113]. BED and obesity also share differences in neurobehavioral circuitry with other conditions characterized by executive functioning deficits, including attention-deficit/hyperactivity disorder (ADHD)[114].

Individuals with BED may experience poorer executive functioning than those with obesity, but evidence is mixed. Individuals with BED have been reported to perform worse on executive function batteries including measures of inhibitory control, attention, and cognitive flexibility[115–119]. However, there have been inconsistent findings, with some studies not reporting differences between individuals with BED and those with obesity alone[110, 119, 120]. A recent review and meta-analysis found that individuals with BED performed worse on working memory tasks compared to obese individuals but did not suggest other performance deficits[119]. These mixed results may reflect small samples and different measures across studies.

Despite potentially-conflicting behavioral findings, recent neuroimaging work has begun to investigate divergence in executive functioning in individuals with BED and obesity as compared to those with only obesity. Individuals with obesity and BED showed hypoactivity in brain regions associated with impulse control during a cognitive control task, including the ventromedial prefrontal cortex (vmPFC), inferior frontal gyrus (IFG) and insula, compared to obese and lean individuals[121]. Individuals with BED compared to overweight individuals have shown reduced recruitment of prefrontal brain systems during a food go/no-go task[122]. Compared to overweight individuals, those with BED have also shown more difficulty with response inhibition in behavioral tasks with food stimuli[115, 123]. Together, this work suggests that there are likely differences in the recruitment of prefrontal brain systems in individuals with BED as compared to obesity. This work is consistent with the hypothesis that impaired cognitive control may differentiate between BED and obesity.

Reward Processing and Food Reward.

Mesocorticolimbic pathways are involved in incentive salience and reward processing[124]. Aberrant reward processing, in general and in the context of food, has been implicated in obesity and BED[20, 25, 26, 125]. Theoretical models suggest that hyposensitivity to general rewards (reduced incentive salience) combined with hypersensitivity to food rewards (increased incentive salience) may precipitate overeating and/or binge eating[62, 126].

Studies have compared individuals with BED and obesity during reward-related functional tasks. Individuals with BED have shown alterations in general reward processing during fMRI. For example, relative to lean individuals, obese individuals showed increased reward-related activity during anticipatory phases of a monetary reward task[127]. However, compared to obese individuals, obese individuals with BED demonstrated hypoactivation in reward-related brain regions during anticipatory reward/loss processing[127]. Such differences in reward-related brain activity in individuals with BED related prospectively to treatment outcomes[128] and resonate with findings from people with other disorders characterized by poor impulse control (e.g., SUDs, gambling disorder)[129]. Additionally, compared to BMI-matched individuals, those with BED showed impaired behavioral adaptation during a

reward learning task, including reduced activation associated with reward prediction error[130]. These results indicate a generalized pattern of diminished frontostriatal processing of non-food rewards in individuals with BED.

In the context of food, individuals with BED showed heightened reward-related reactivity compared to overweight controls[19, 20]. In neuroimaging studies, individuals with BED showed increased activation in reward-processing areas of the brain when shown food stimuli[131–133]. Studies using electroencephalography (EEG) have also found enhanced responses to food in individuals who binge eat compared to controls[134, 135]. Patterns of brain activation in the VS while viewing food stimuli in individuals with BED and obesity are dissociable from those in individuals with obesity only[136]. Further, dopamine signaling in the presence of food cues is stronger in BED compared to obesity. A [^{11}C]raclopride PET study investigated dopamine response in the presence of food vs. neutral stimuli in the presence of oral methylphenidate (which blocks the dopamine transporter and increases dopamine signaling)[102]. Obese individuals with BED as compared to those without showed greater dopamine release in the caudate when exposed to food stimuli after methylphenidate[102]. Dopamine release was correlated with binge eating severity, but not BMI[102]. Collectively, this research suggests that individuals with BED have heightened neurobiological responses to food reward compared to individuals with obesity alone.

Emotional Reactivity.

Emotional reactivity, defined as the intensity and duration of emotions in response to stimuli[137], is involved in eating-related psychopathology[138, 139]. Greater reported negative emotion is associated with subsequent binge eating[140] in individuals with BED and not in overweight individuals without BED[139]. Further, greater negative emotion is associated with increased impulsivity[34], perhaps via sensitization of the mesocorticolimbic system[141]. Accordingly, neurobiological differences in emotional reactivity may differentiate individuals with BED from those with obesity.

In general, individuals with BED report more frequent and severe daily negative affect than obese, overweight, or lean individuals[142]. Compared to controls, individuals with BED have greater reactivity to stress[143] and report more severe depression and anxiety symptoms[45, 131, 144]. A recent review found evidence that individuals with BED show heightened responses to stress, including differences in cortisol, ghrelin, and cardiovascular measures[138]. For example, obese women with BED had a greater increase in negative affect and blood pressure than obese women without BED after the Trier Social Stress Task[143].

Heightened emotional reactivity can reduce cognitive control and increase food-related reactivity in individuals with BED. Emotional distress may sensitize the brain's reward system to food[141] and its predictive cues[145]. Inducing negative affect increases activation in reward-related brain regions in chronic dieters shown food cues[146]. Similarly, under stress, reported desire to binge eat, the reinforcement value of food, and cortisol levels increase in people who binge eat[147–149]. Compared to controls and after an acute stressor, individuals with BED symptoms showed reduced inhibitory-control-related brain activity in response to food stimuli[150]. Further, following this acute stressor and exposure to food cues, individuals with BED ate more high calorie foods ad-libitum than controls[150]. Accordingly, binge eating

may be precipitated by the effects of emotional reactivity on mesocorticolimbic brain systems, particularly in individuals with BED, and this possibility warrants additional direct study.

Pharmacological Treatment for BED and Obesity: Differential Therapeutics

Accumulating evidence of divergent neurobiological processes in BED and obesity may have implications for informing and refining pharmacological research and treatment for BED. To date, nearly all of the pharmacological treatment literature for BED has included testing off-label medications based on their effects on obesity and other medical or psychiatric disorders[13–15]. Several previous reviews have detailed pharmacological treatment outcome findings for BED[13–15, 26, 151, 152]. Briefly, except for randomized clinical trials (RCTs) testing lisdexamfetamine dimesylate (LDX) that led to FDA approval for "moderate-to-severe" BED (but not obesity)[10–12], RCTs have generally been relatively small, of short duration, and without follow-up periods, and have produced mixed findings, which at best, despite being significantly superior to placebo, have generally been modest in their clinical effects. Additionally, several pharmacological agents have shown promise in preclinical studies, only to encounter significant problems in application to humans, including severe side effects and high rates of adverse events.

Here, we review studies testing pharmacological agents with putative mechanisms of action conceptually relevant to neurobiological factors highlighted in this review as potentially specific to BED. First, we review the application of stimulant, opioid antagonist, and serotonergic pharmacological agents to BED, with a focus on effects on impulsivity/compulsivity, reward-related, and emotion-related neurobiological processes. Subsequently, we discuss emerging evidence for novel agents for BED that may influence these processes. Consideration of these distinguishing characteristics and processes in BED could have implications for more targeted pharmacological research and treatment.

Stimulant Medications: Dual Effects on Executive Function and Food Reward.

Stimulants have been used to treat obesity and, more recently, BED. Stimulants act on the reward system by increasing catecholamine availability via reversing transport systems[153, 154], which results in appetite suppression associated with elevated extracellular dopamine in the VS[155] and, importantly, dose-related improvements in executive functioning[156]. Appetite-suppressant effects of stimulant medications led to their early applications for weight loss in patients with obesity; for example, amphetamines were used to reduce appetite beginning in the 1930s and the first stimulant to be FDA-approved for treating obesity was methamphetamine in 1947. Paralleling applications for obesity, their well-established effects on executive functioning led to widespread and long-standing use for treating ADHD in children, adolescents, and adults, with consistent findings of improvements in attentional and cognitive control[157].

Stimulant medications may be especially effective for individuals with BED because of dual effects on reward and executive function systems. Indeed, the only FDA-approved pharmacotherapy for BED is LDX, a d-amphetamine prodrug[158]. In preclinical models of binge eating, following administration of LDX, rats stopped compulsively eating

chocolate[159] and reduced "binge-eating-related" impulsive choices[160]. In humans, RCTs found that LDX reduced binge eating and impulsivity/compulsivity symptoms[10–12, 161]. Notably, there is a strong correlation between compulsivity symptoms and severity/frequency of binge eating episodes observed in LDX trials[162]. Further, in individuals with BED, changes in prefrontal brain systems associated with LDX treatment were related to treatment outcome[163]. Specifically, reductions in brain activation in the vmPFC and thalamus while viewing food pictures after LDX correlated with reductions in binge eating and compulsivity symptoms[163]. Research investigating short-term and long-term effects of LDX, alone and in combination with cognitive behavioral therapy, is ongoing[164, 165].

Research has recently tested dasotraline, an agent that inhibits dopamine and norepinephrine transporters with stimulant effects[166], for treating BED[167, 168]. Both the flexible-dose[168] and fixed-dose[167] RCTs found significantly greater reductions in binge eating and associated compulsivity symptoms versus placebo. However, the manufacturer of dastroline has withdrawn their application for FDA review for approval for BED, eliminating this potential option.

Opioid Antagonists: Effects on Food Reward.

Opioid-based agents used in the treatment of SUD have recently been applied to eating and eating disorders[169]. Opioid receptors, particularly mu-opioid receptors, interact with the mesocorticolimbic dopamine system, which may underlie addictive properties of opioid receptor agonists and effects of opioids on appetitive behaviors including eating[170]. Opioid antagonists, including naltrexone, reduce craving for and consumption of substances of abuse[171] and are thought to also reduce craving for food[170]. These agents were first applied to obesity following case studies reporting reduced weight in individuals with SUD treated with naltrexone[172]. In lean individuals, naltrexone results in ~20% reduction in food intake, which is associated with lower ratings of food pleasantness[173]. Nonetheless, monotherapy opioid antagonists neither consistently reduced food intake or weight in obese individuals[174, 175, c.f. 176] nor reduced binge eating in humans[169, 177, 178].

Combining opioid-based agents (which may target food reward) with complementary agents may improve the efficacy of pharmacotherapy for eating and binge eating. Specifically, the combination of naltrexone+bupropion, an FDA-approved weight-loss medication, seems conceptually relevant for BED given a number of findings that follow.

Bupropion, a selective reuptake inhibitor of dopamine and norepinephrine, has been found to be effective for smoking cessation[179, 180] and to reduce cravings for various substances[181]. Although some reports suggest reduced food cravings and weight loss with bupropion[182], the literature is mixed. In a RCT with overweight women with BED, bupropion did not significantly reduce binge eating nor food cravings relative to placebo, although patients receiving bupropion lost significantly more weight than those on placebo[183]. Some preliminary work suggests that bupropion may be associated with improvements in executive function[184, 185] which, as reviewed above, seems related to disordered eating.

Importantly, bupropion is thought to work synergistically with other agents[180, 186; for review,187] which stimulated a series of large-scale RCTs demonstrating the

efficacy of combined naltrexone+bupropion for weight-loss[186, 188, 189; for review,190] and subsequent FDA approval for obesity. Preliminary research suggests that naltrexone +bupropion may reduce food cue reactivity and enhance cognitive control[191]. Preliminary open-label trials of naltrexone+bupropion reported reductions in binge eating in adolescents with eating disorders[192] and in individuals with self-reported depressive and binge-eating symptoms[193]. One pilot placebo-controlled double-blind RCT reported preliminary findings that naltrexone+bupropion showed promise relative to placebo for reducing weight in patients with BED; the observed trends for binge-eating reductions, although not statistically significant, suggested the need for larger-scale and adequately-powered RCT[194]. There are two ongoing NIH-funded RCTs testing naltrexone+bupropion, alone and in combination with behavioral treatment, for BED[195, 196], which were designed to examine potential mechanisms (e.g., changes in impulsivity/compulsivity) in addition to testing the short- and longer-term effects of this agent.

Serotonergic Agents: Effects on Emotion Reactivity?

Serotonergic agents, long-prescribed for anxiety and mood-related psychiatric conditions, have historically been tested for obesity, given animal research indicating that serotonin influences eating by modulating satiety[197–201]. Overall, these agents produced very modest weight loss in patients with obesity[202] and those effects were poorly maintained[16, 203, 204]. This broad class of agents has, quite unfortunately, had a troubled history when applied to obesity, with several serotonergic drugs receiving FDA approval only to be subsequently withdrawn from the market due to emergent safety concerns. Medications with such concerns include sibutramine (for cardiovascular complications[205]), fenfluramine (for pulmonary hypertension[205]), and most recently lorcaserin (for cancer risk[206]).

Despite poor results for treatment of obesity, serotonergic agents were initially thought to hold promise for BED for several reasons. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is the sole FDA-approved medication for bulimia nervosa (another eating disorder characterized by recurrent binge eating) following a series of RCTs demonstrating efficacy relative to placebo[207–209]. Additionally, SSRIs have been found to reduce emotional reactivity[210] and symptoms of obsessive-compulsive disorder[211]. However, RCTs for serotonergic agents have consistently showed weak to non-significant effects in RCTs with BED for both binge eating and weight outcomes[15, 212]. Despite the suggestion that SSRIs could reduce emotional reactivity that may precipitate or maintain binge eating, individuals with greater depressive symptoms showed poorer outcomes on fluoxetine than in cognitive behavioral therapy[213], and depressive symptoms did not predict response to fluoxetine in patients with bulimia nervosa[214]. Accordingly, although individuals with BED may show heightened emotional reactivity, serotonergic agents are likely not effective as either stand-alone treatments or as additive treatments for BED[212, 213, see 18.]

Novel Therapeutic Agents.

Early, emerging work has tested novel therapeutic agents that may reduce eating and binge eating. Some of these agents influence neurobiological processes that may be relatively specific to BED, including impulsivity. However, several agents tested in preclinical settings have encountered challenges, including significant side effects, when translated to humans.

Thus, this brief overview is offered preliminarily and should be considered cautiously given the early stages of the research.

Orexin Receptor Antagonists.—Recent preclinical work has investigated the effects of orexin-based agents[215–217] on impulsive behavior and binge eating. In animals, selective OX1 receptor antagonists (SB-334867 and GSK1059865) reduced palatable food eating[217, 218] and a dual OX1/OX2 receptor antagonist (SB-649868) reduced binge eating[219]. In rats, OX1 receptor antagonists reduced impulsive behavior under baseline and cocaine conditions[220, 221, c.f. 222]. Given effects on impulsive behavior in animals, an important next step will be to determine whether these agents influence impulsive behavior and binge eating in humans.

Endocannabinoid Antagonists.—The endocannabinoid system modulates the transmission of other neurotransmitters in mesocorticolimbic pathways[223]. CB1 receptor inverse agonists or antagonists (SR141716A, AM 251 and rimonabant) decreased eating and weight in rodents[224–228], decreased food consumption in primates[229], reduced binge eating in animals[226, 230, 231], and reduced impulsivity during delay discounting tasks in overweight rats[232, 233]. However, in humans, despite preliminary effects on weight[234–237] and binge eating[238], CB1 receptor agonists had clear and significant side effects. These agents are not approved for use in humans because of concerns that the therapeutic dose and dose that generates seizures are similar, and concerns about psychiatric side effects, including severe depression[237].

Glutamatergic Agents.—Glutamatergic pharmacotherapies modulate mesocorticolimbic pathways[239] and are involved in eating[240–244]. For example, topiramate, an anticonvulsant, reduces binge eating and weight compared to placebo[15, 245, 246]. Notably, a double-blind RCT found that topiramate was superior to placebo for enhancing CBT outcomes for both binge eating and weight[247], which has not been shown for any other pharmacological agent tested to date for BED. It has been posited that topiramate may target impulsivity and therefore be especially effective for individuals with greater impulsivity and SUDs[248], and this might also account for some of its effects in patients with BED. Despite these promising findings for BED, topiramate is associated with high rates of adverse events and dropout (e.g., 28–68% dropout; [245, 249 , 250]) and this limits its wider use.

Novel glutamatergic agents are being tested for BED. Memantine is an NDMA receptor antagonist that is FDA-approved for treatment of Alzheimer's disease and has been used off-label for psychiatric disorders, including SUDs and BED. Very early and preliminary uncontrolled reports suggest that memantine may reduce binge eating in humans[251, 252], as shown in animal models[253–255]. However, animal work found that memantine increased impulsive choice[256, 257], potentially limiting efficacy for BED.

GABA Receptor Agonists.—$GABA_B$ receptors are found on GABA and dopamine neurons in the mesocorticolimbic system[258, 259]. Preliminary trials of baclofen, a GABA agonist used to treat muscle spasms, showed reductions in body weight in ten obese subjects[260] and reduced binge eating and food craving in a total of twenty-two individuals

with BED in two early pilot studies[261, 262]. Baclofen generates sedation in humans and has not been shown to reduce impulsivity, limiting its clinical utility for BED.

Conclusions & Future Directions

BED and obesity often co-occur and clinicians have employed similar behavioral and pharmacological treatment approaches to treat these conditions. However, given emerging evidence of divergent neurobiological characteristics of BED as compared to obesity, adopting a neurobiologically-informed, mechanism-focused approach to selecting pharmacological treatment for BED may prove to be advantageous. Indeed, pharmacotherapies that target both impulsivity/compulsivity and reward processing, such as LDX, have been shown to be effective for BED. Increased attention to the effects of pharmacological treatments on neurobiological processes related to BED, including impulsivity/compulsivity, reward processing, and emotional reactivity, may be relevant to enriching treatment conceptualizations and prescriptions, and for informing treatment research. Future work should investigate changes in impulsivity, compulsivity, and reward and emotion processing in preclinical and human trials of pharmacotherapies for BED. Such contributions could improve BED treatment and contribute to broader, transdiagnostic approaches to conceptualizing BED and other forms of impulsivity-related and compulsivity-related psychopathologies.

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