From Disordered Eating to Addiction

The ''Food Drug'' in Bulimia Nervosa

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Abstract: The high prevalence of substance abuse in individuals with bulimia nervosa (BN) and the pervasive symptom substitution in many types of drug addiction suggest that a number of substances—including food—can impair an individual's self-control, even in the presence of negative consequences. Nonetheless, the neurobiological similarities between BN and drug addiction are not clearly established. This review explores how the specific eating patterns seen in BN (binge eating and purging, with intermittent dietary restriction) are particularly addictive and differentiate BN from other eating disorders and obesity. A number of peripheral and central biological aberrations seen in BN may result in altered reward sensitivity in these individuals, particularly through effects on the dopaminergic system. Neurobiological findings support the notion that BN is an addictive disorder, which has treatment implications for therapy and pharmacological manipulations.

Key Words: addiction, substance abuse, bulimia nervosa, eating disorders, dopamine, reward

(*J Clin Psychopharmacol* 2012;32: 376–389)

Eating disorder research has generally focused on familial and environmental factors that contribute to the psychopathology in bulimia nervosa (BN). Whereas the development of BN has been linked to past sexual abuse,[1] weak social attachment,[2] low self-esteem,[3,4] and a desire to lose weight,[5,6] less is known about the neurobiological factors that contribute to the maintenance of these maladaptive behaviors that persist despite adverse consequences.

The cardinal symptom of BN is binge eating—that is, the rapid consumption of an objectively large amount of food in a discrete period accompanied by a sense of lack of control or feeling that one cannot either restrain from eating or stop once started (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [*DSM-IV-TR*]). Bingeing, in turn, is followed by a compensatory "purging" behavior such as self-induced vomiting. This cycle can occur anywhere from several times weekly to numerous times a day in what can be viewed as a psychological addiction to the binge and purge.[7]

Initially, the purging behavior may be motivated by a desire to lose weight. However, the purging that follows the binge in BN rarely results in significant (if any) weight loss. Studies have shown that reductions in binge eating, purging, and food restriction after treatment do not result in significant changes (ie, weight gain) in body mass index, as one might expect.[8,9] On the contrary, higher frequency of purging actually predicts greater weight loss during treatment when the behavior is stopped.[8] Purging may attenuate the magnitude of weight gain caused by repeated bingeing, but results from other studies support the notion that dieting behaviors do not maintain BN behaviors.[10] Thus, although sociocultural pressures to be thin may initiate bulimic behaviors, other factors must contribute to the maintenance of BN when weight loss is not accomplished. It is plausible that neurobiological substrates affected in drug addiction perpetuate the binge-purge cycle in BN.

Substance abuse disorders are commonly coincident with BN. Between 30% and 50% of individuals with BN abuse or are dependent on alcohol or drugs[11–17] compared with approximately 9% in the general population.[18] Up to 35% of individuals who abuse or are dependent on alcohol or drugs also have an eating disorder,[12,13,19,20] compared with about 1.6% in the general population.[21]

Bulimia nervosa and drug addiction both exhibit mood-altering effects, environmental cueing, reinforcement, craving, compulsion, and loss of control.[22] The high prevalence of substance abuse in individuals with BN and the pervasive symptom substitution in many types of addiction suggest that a number of substances—including food—have the capacity to impair an individual's inhibitory regulation and control over certain behaviors, even in the presence of negative consequences. Still, the potentially addictive properties of food in the specific eating patterns of BN are not fully understood. Behavioral and epidemiological similarities between BN and drug addiction have been described,[22,23] but only 1 study has directly explored neurological reward substrates in persons with BN.[24]

Defining Addiction

Drug "addiction" is a condition characterized by compulsive drug intake, craving, and seeking, despite negative consequences associated with drug use. The *DSM-IV-TR* classifies addiction in terms of substance abuse or substance dependence (SD). Substance dependence may be considered a more severe form of addiction, and as such, diagnostic criteria are more stringent (Table 1).

Even using the more conservative criteria, BN meets the definition for an addiction disorder. Although only 3 of these criteria are required for a diagnosis of SD, BN putatively possesses all 7 criteria. Tolerance and withdrawal (criteria 1 and 2) will be discussed in the next section in the context of possible neurobiological changes. Criterion 3 describing that "the substance" is taken in larger amounts than intended is true for BN. During a meal, individuals with BN may try to eat smaller portions, but end up eating much larger amounts than intended, transitioning them into a binge.[25] Although many seek treatment, more than 50% end up in relapse,[26,27] consistent with "unsuccessful efforts to cut down or control substance use" (criterion 4). Indeed, loss of control when trying to moderate eating is a key feature of BN.[28] The subsequent binge-purge cycle can take up to several hours and is repeated multiple times a day for some

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Received March 13, 2011; accepted after revision December 19, 2011.

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Funding was provided through the Shader Family Fellowship awarded from the Shader Family Research and Education Fund at Tufts University.

ISSN: 0271-0749
DOI: 10.1097/JCP.0b013e318252464f

TABLE 1. Diagnostic Criteria for Substance Dependence, American Psychiatric Association (*DSM-IV-TR*)

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by 3 (or more) of the following, occurring any time in the same 12-mo period:

(1) Tolerance, as defined by either of the following:
  (*a*) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect *or*
  (*b*) Markedly diminished effect with continued use of the same amount of the substance

(2) Withdrawal, as manifested by either of the following:
  (*a*) The characteristic withdrawal syndrome for the substance *or*
  (*b*) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms

(3) The substance is often taken in larger amounts or over a longer period than intended.

(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use.

(5) A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.

(6) Important social, occupational, or recreational activities are given up or reduced because of substance use.

(7) The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance (for example, current cocaine use despite recognition of cocaine-induced depression or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

individuals, clearly fulfilling the time requirement (criterion 5) for SD.[29] The amount of time (and money) dedicated to bulimic behavior (obtaining binge foods, finding a secretive place to consume and purge the food, and recovering from the postpurge hypoglycemia) significantly impacts other activities, estranges social relationships, and diminishes job performance,[7,30] pursuant to criterion 6 for SD. Moreover, both bulimics and substance abusers compulsively engage in these maladaptive behaviors even in the presence of injurious physical consequences. In BN, these consequences include (but are not limited to) gastroesophageal reflux disorder, tooth decay, renal failure, cardiac arrhythmia, and even death.[31–33] Despite knowledge of the consequences of the disorder, individuals with BN persist in the binge-purge cycle, fulfilling criterion 7 for SD.

NEUROBIOLOGY OF BULIMIA NERVOSA AND LINKS TO ADDICTION

Reinforcement

The mesolimbic dopaminergic system is centrally involved in the acute positive effects of a number of rewarding stimuli, including drugs of abuse.[34–36] Microdialysis and positron emission tomography (PET) studies show that illicit drugs increase extracellular dopamine (DA) preferentially in the ventral striatum—particularly in the nucleus accumbens (NAc) area—in rats, nonhuman primates, and humans.[37,38] As such, increased DA release could be a crucial mechanism for reinforcement of rewarding stimuli.[35,39,40] The subjective perception of pleasure varies among individuals based on the degree of dopaminergic activity the stimulus/drug evokes, with greater DA release associated with a more euphoric "high."[41] In the study of Volkow et al,[41] the intensity of the "high" induced by methylphenidate was significantly correlated with the levels of released DA. Thus, the subjects who reported the most intense "high" were those who had the greatest increase of DA release.

In principle, food should have similar properties of reinforcement if bulimic behavior (ie, binge eating) belongs within the framework of addiction. Food does release DA in the NAc.[42–46] Palatable food (high-sugar or sugar/fat) in particular causes even greater DA release.[47] In fact, orosensory properties of sweet foods alone can invoke this reward effect. For example, rats that are fed saccharine, an artificial sweetener[48] or are "sham fed" sucrose using gastric cannulas to empty stomach contents[42] still exhibit significant rises in accumbens DA despite the lack of postingestive effects or macronutrient absorption. Hajnal et al[43] demonstrated the same effect of sweet taste on NAc DA when rats obtain sucrose by merely licking. These findings indicate that sweet taste alone is enough for reinforcement, which has important implications for BN in which macronutrient absorption is attenuated because of purging.

Moreover, accumbens DA increases as a function of sucrose solution concentration, with the sweetest solution evoking the greatest overflow of DA.[43,49] This suggests that "sweeter" foods are more reinforcing. Individuals with BN appear to have a heightened subjective response to sweet taste[50,51] and frequently claim to crave sweets.[52–54] Given the reinforcing properties of sweet taste, BN individuals might be predisposed to repetitive use (and in turn, heightened reinforcement) of high-sugar binges. In fact, women with BN have reported popular binge foods to be sweet desserts, such as cake and ice cream, and have a heightened preference for sweets as compared with nonbingeing controls.[54–56]

A possible difference between drugs of abuse and food is that drugs (ie, opiates, cocaine, methamphetamine) can increase extracellular DA with every administration,[57,58] whereas food-induced increases in DA usually wane with additional intake of the same substance.[59,60] However, sweet foods can persistently increase accumbens DA in a fashion similar to addictive drugs using an intermittent eating pattern.[61,62] This feeding paradigm has been shown to create dependency,[62] as indicated by withdrawal signs such as teeth chattering and fear sensitivity. Other feeding models used as controls included ad libitum feeding with chow, intermittent feeding (12-hour access/12-hour deprivation) with chow, and ad libitum feeding with chow and sucrose solution.[61] All 3 control groups underwent 12-hour deprivation before feeding on testing days to control for any effects of energy depletion on microdialysis samples. Only the intermittent-sucrose-feeding group showed persistent increase in DA as demonstrated on day 21 of testing, whereas the control groups showed a blunting in DA response compared with day 1. This feeding schedule is consistent with the eating patterns seen in BN where individuals restrict intake early in the day and then binge later in the evening, usually on palatable foods high in sucrose.[63,64]

Food-induced DA release is not isolated to the NAc. In vivo monitoring studies in rats have demonstrated that increases in DA efflux occur in other "reward centers," such as the ventral tegmental area (VTA) and medial prefrontal cortex (MPFC).[65–67] The MPFC has been implicated in the acute reinforcing effects of drugs of abuse. Dopamine levels in the MPFC increase in response to administration of addictive drugs[68,69] or presentation of conditioned stimuli associated with such drugs.[70,71] Of interest, BN individuals show significant MPFC activation in response to cues associated with their putative drug of abuse, namely, food.[72] Healthy controls and individuals with anorexia nervosa (AN) do not display the same activations. Moreover, in an [^{11}C]raclopride-binding study, Small et al[73] reported that the amount of DA released in the dorsal striatum correlates with food pleasantness.

Palatable foods may also produce reinforcement through the opioid system. Like drugs of abuse,[39,74–76] food (especially sweet/high fat) is associated with the release of endogenous opioids.[62,77–81] Moreover, palatable food can activate opioid receptors in the VTA and further stimulate DA-releasing cells in the NAc.[45] The effects on consumption of palatable food,[82] as well as food-induced DA release in the accumbens, were attenuated by the opioid receptor antagonists, naltrexone[83] and LY255582.[82] In tests of individual preferences in rats, high saccharin preference is associated with higher intake of intravenous morphine and alcohol, 2 drugs that exert direct effects on the opioid system.[84,85]

Given the similar neural substrates of acute reward in drugs of abuse and palatable foods, such reinforcement could induce compulsive bingeing and, ultimately, "binge dependence" in individuals with BN. In addition to the reinforcing properties of the binge, purging may also reinforce BN behavior in an addictive manner. Specifically, vomiting may acutely increase endogenous opioids in BN individuals.[86] Moreover, the rise in acetylcholine (ACh) in the NAc during a meal is significantly reduced in sham-feeding rats.[42] Increased Ach is involved in the satiation process when DA rises during food intake,[87] and a blunted Ach response may heighten sensitivity to the increases in accumbens DA released while eating. Thus, purging may strengthen the rewarding dopaminergic release from binge eating. Taken together, the intermittent dietary restriction, followed by binge eating and purging of palatable foods, may result in neurobiological changes consistent with drug addiction in individuals with BN.

Dependence, Tolerance, and Withdrawal

Even though the reinforcing effects of drugs may initiate drug-taking behavior, repeated drug use often continues despite negative consequences, possibly because of long-term, neuromodulatory effects that persist beyond the "high" after acute administration. Chronic administration of drugs of abuse, such as cocaine, alcohol, and heroin, alters brain substrates of reward.[88–90] Likewise, repetitive bingeing on sucrose, interspersed with dietary restriction, can cause long-term neurobiological changes in experimental animals similar to those seen in long-term drug users.[62,81,91,92]

With drugs of abuse, terminal regions of the mesolimbic DA system adapt by increasing D1 receptor binding with stimulants, decreasing D2 receptor sensitivity with opiates, and increasing μ-opioid receptor binding with both.[93–95] Similarly, in "sugar-dependent" rats, food restriction followed by access to palatable food increases (ie, sensitizes) μ-opioid and D1 receptor binding and decreases D2 receptor binding in limbic regions.[62,81,92] Other neurochemical changes reminiscent of drugs of abuse, such as increases in D3 receptor mRNA,[96,97] also occur in sucrose-bingeing rats with intermittent access.[91] Moreover, rats maintained on a food deprivation/refeeding schedule are more responsive to the hyperphagic effects of the κ-opioid agonist, butorphanol, suggesting that this pattern of binge eating may modulate the endogenous opioid system.[98,99] A decrease in enkephalin gene expression in the NAc occurs in rats given restricted access to highly palatable food for 2 weeks.[100] Chronic treatment with morphine produces a similar down-regulation of enkephalin gene expression,[101,102] and ethanol also decreases enkephalin expression when given to rats chronically.[103]

Behavioral measures in these animals also indicate that palatable food has addiction potential similar to drugs of abuse. Animals sensitized to a particular drug of abuse will often show an increased locomotor response to a different drug of the same class ("cross-sensitization").[104–106] Importantly, drug cross-sensitization is also seen with palatable food, suggesting that both stimuli act on common neural circuitry.[107–110] Amphetamine-sensitized rats showed sugar-induced hyperactivity and sugar hyperphagia.[107] Conversely, sugar-dependent rats have a heightened sensitivity to amphetamine.[109] Cross-sensitization also occurs with alcohol, whereby sugar-dependent rats show enhanced intake of unsweetened ethanol.[108]

Drug dependence is also marked by tolerance, in which the response to a drug decreases with repeated exposure such that larger doses are required to achieve the same effect.[111] This phenomenon may be due to decreased responsiveness of molecular mediators.[112] Tolerance is a key characteristic of all drug addictions[113] and also occurs in sugar-dependent rats.[61,81] Bulimia nervosa individuals also report increases in binge size from onset of their disorder, and tolerance may be responsible for escalating intake. These individuals use larger quantities of sweeteners and prefer more intensely sweet samples than do nonbingers,[50,54,56] perhaps indicating decreased sensitivity to sweet taste.

Another hallmark of drug addiction is the withdrawal phenomenon. Abstinence from drugs of abuse induces neurochemical changes, such as decreases in striatal D1 and D2 receptor mRNA,[102] decreased extracellular DA in the NAc,[115,116] and an increase in accumbens ACh.[117] Similarly, sugar-dependent rats show a significant increase in extracellular ACh and a significant decrease in DA release in the NAc shell as compared with control groups during 36-h food deprivation.[118] This alteration in DA/ACh balance in the NAc is seen during withdrawal from drugs such as morphine, nicotine, and alcohol.[119–121] It would be interesting to see if similar changes occur when only palatable food is withheld while still allowing access to regular chow during the "deprivation" period.

Acute abstinence from drugs of abuse also causes behavioral and psychological withdrawal symptoms. In murine models of addiction, these symptoms include increased fear sensitivity and anxiety (as measured by reduced time on the exposed arm of an elevated plus maze), ultrasonic vocalization, paw shakes, and teeth chattering.[122–126] When food deprived for 24 hours, intermittent-sucrose-feeding rats also show somatic signs of withdrawal, including teeth chattering and paw shakes, and increased anxiety.[62,127,128] Control rats fed chow ad libitum do not experience these symptoms upon food deprivation. Furthermore, withdrawal symptoms can be induced pharmacologically in sugar-dependent animals using the opioid antagonist naloxone, indicating alterations in the opioid system in sugar dependence.[62] Individuals with BN also display signs of drug withdrawal, such as increased anxiety, sleep disturbance, and craving during abstinence from bingeing.[129,130] There are consistent reports of headaches, irritability, anxiety, and flulike symptoms among heavy sugar consumers who become abstinent.[113,131] Given that relapse among drug users often occurs to avoid unpleasant withdrawal symptoms, the high relapse rate among individuals with BN suggests a role for withdrawal symptoms in precipitating relapse.

Craving

In the substance abuse literature, craving has been described as an intense desire to use a drug.[132,133] Food craving is commonly defined as an intense desire to eat a specific food.[132,134,135] Similar to substance abuse in drug addiction, binge eating in BN is commonly precipitated by cravings.[136–138] Food cravings are not necessarily a product of nutrient deficit or dietary restraint.[139–145] Significantly, bingeing in BN has been associated with lower levels of hunger[137] However, food cravings are greater in individuals known to have high tendencies to

temporarily restrain their diets but lose control and binge eat versus individuals who are successful dieters as demonstrated by increased craving prevalence in BN subjects versus AN subjects.[145,146]

Based on studies of cue-induced drug craving,[147–150] Pelchat and colleagues[151] used functional magnetic resonance imaging (fMRI) to measure whether food cravings could evoke similar activations in the brain. The hippocampus, insula, and caudate, areas that are also activated during drug craving,[149,152–154] showed food craving–specific activation. Another fMRI study using photo cues of common binge foods (eg, cake, chocolate, pizza) demonstrated that individuals with BN recruit the medial orbitofrontal cortex and the anterior cingulate instead of the inferior parietal lobule and the left cerebellum, which were activated in the healthy comparison group.[72] Addiction-like cue reactivity has been described in BN,[155,156] and studies in drug addiction also show anterior cingulate and orbitofrontal activations related to craving.[148–150,157] Notably, repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex, which activates the underlying cortex, but inhibits more remote areas, including the anterior cingulate,[158] has been shown to reduce both drug[159–162] and food[163–165] craving.

Craving for drugs is elicited not only by the memory of the pleasurable effects of drugs,[166–168] but also by the memory of the aversive effects of drug abstinence, and may be an indicator of withdrawal.[169,170] Similarly, food cravings are associated with negative affect in BN and may initiate bingeing as a means of obtaining relief from the aversive state.[137,171–174] A multidimensional model of craving in BN may include negative-affect–driven craving (and subsequent binge eating) as well as positive reinforcement.

Dopamine and Reward Sensitivity in BN

A number of clinical and genetic studies indicate that individuals with BN may have aberrant DA activity. Frequently bingeing (14×/wk) BN patients have reduced levels of the DA metabolite homovanillic acid (HVA) in cerebrospinal fluid (CSF) and decreased plasma HVA concentrations.[175] Studies of peripheral DA metabolites support these findings for frequently (1×/d) bingeing patients.[176,177] However, after treatment and normalization of eating behaviors, HVA concentrations in recovered bulimics are similar to healthy controls with no eating disorder history.[175] Therefore, these lower levels could be a state-dependent phenomenon, possibly resulting from down-regulation of an overstimulated DA system during binge eating.

Aberrations in the DA transporter (DAT) have been described in individuals with BN. The disorder is associated with the short *s* allele of the DAT gene,[178] conferring lower transporter binding.[179] This short *s* allele polymorphism is also significantly associated with substance abuse disorders.[180,181] Based on single-photon emission computed tomography, subjects with BN have reduced striatal DAT availability compared with healthy controls.[182] However, peripheral levels of DAT are significantly higher in individuals with BN compared with healthy controls.[183] This could reflect a difference in central versus peripheral DA signaling. Alternatively, levels of DAT may up-regulate as the illness progresses to compensate for repeated DA surges during years of bingeing.

Peripherally, individuals with BN have been shown to have reduced D2 receptor gene subscript, which may be indicative of central receptor levels.[183] Individuals with lower levels of D2 receptors may be hyporesponsive to reward, consistent with the "reward deficiency syndrome."[184,185] On the other hand, lower receptor density could result in excessive DA release in response to reward in susceptible individuals. Along these lines, individuals with BN could putatively have heightened sensitivity to food reward. Interestingly, reward sensitivity in BN significantly correlates with the average weekly frequency of purge, with individuals purging more often having heightened sensitivity.[186]

Functional magnetic resonance imaging in BN also indicates altered reward processing in these individuals.[24] In a "guessing game" protocol, which is known to activate the anterior ventral striatum with a differential response to positive and negative feedback (monetary win/loss) in healthy volunteers,[187] BN subjects fail to show this differential response, suggesting an impaired ability to correctly attribute reward significance to a stimulus.[24]

Peripheral Hormones

Dopaminergic function and reward sensitivity in patients with BN may be indirectly altered through systemic signals, such as ghrelin and insulin, in individuals with BN. These homeostatic regulators of food intake may also be implicated in hedonic eating and reward functioning. Insulin receptors are present in reward centers of the brain (ie, VTA),[188] and insulin increases mRNA levels and synaptic activity of DAT both in vivo and in vitro.[189,190] This suggests that increased insulin may decrease DA signaling, and an attenuated insulin response could enhance DA transmission, perhaps augmenting reward sensitivity to DA-releasing agents such as palatable food and drugs. Bulimia nervosa patients who binge/purge frequently have a blunted insulin response to an oral glucose challenge[191] and decreased insulin sensitivity[191A] similar to heroine addicted subjects.[192] With a diminished insulin response, food intake in BN may result in greater acute DA release, thereby enhancing reward sensitivity to food and strengthening the reinforcing properties of binge eating. Bulimia nervosa subjects also have diminished insulin production after purging,[192A] which may further reinforce the maladaptive behaviors.

On the other hand, some investigators have described an exaggerated insulin response to a glucose challenge in purging BN individuals[191,193] similar to that seen in alcoholics.[194] If increased insulin results in diminished DA activity, this supports the "reward deficiency" hypothesis whereby reward-seeking behaviors (ie, binge eating) compensate for low DA.[185,195] These two theories may be reconciled by recognizing that both ends of the reward sensitivity spectrum could predispose an individual to addiction.

Another peripheral hormone altered in individuals with BN is ghrelin. This molecule enhances appetite and increases food intake[196,197] and is negatively associated with body mass index, with obese individuals having lower circulating levels.[198,199] Ghrelin levels generally increase before meals (cephalic phase) and decrease afterward (postprandial). In individuals with acute BN, basal ghrelin levels are higher than normal,[200–202A] the cephalic ghrelin response at the onset of a meal is significantly greater than that in healthy individuals,[203] and the postprandial ghrelin suppression is attenuated.[200,204] These differences are not confounded by differences in body weight, and the greater cephalic ghrelin response positively correlates with the severity of patients' illness.[203] Individuals with binge-eating disorder (BED) (even without comorbid obesity) have lower than normal circulating levels of ghrelin at baseline and postprandially,[205–208] highlighting that the binge eating in BN may be marked by distinct biological patterns.

The increased ghrelin response in BN is linked to the mesolimbic reward circuitry crucial to addiction. Ghrelin can increase NAc DA levels[209,210] and increase DA neuronal activity in the VTA.[211] Both central and peripheral delivery of ghrelin significantly increases the amount of work an animal is willing

to do to obtain sucrose reward, suggesting a role for the ghrelin system in the modulation of incentive motivation and reinforcing properties of sweet foods.[212] The enhanced ghrelin activity seen in BN during food intake could therefore heighten the rewarding effect of binge eating in these individuals.

Opioids and Serotonin

Individuals with BN have lower levels of β-endorphin, the endogenous opioid,[213] and μ-opioid receptor binding.[214] The insular cortex is repeatedly implicated in other reward-driven behaviors, including drug abuse[149] and gambling.[215] This downregulation could be a compensatory response to repeated bingeing. In cocaine-dependent[216] and alcohol-dependent[217] subjects, drug abstinence is associated with an up-regulation of μ-opioid receptor binding that is proportional to drug craving. Bulimia nervosa individuals could experience a similar phenomenon while abstaining from the binge-purge cycle for periods of time.

Opioid antagonists (ie, naloxone, naltrexone) reduce binge eating in this population,[218–223] with apparently selective suppression of ingestion of highly palatable foods (ie, common "binge" foods).[223–225] In 1 study, the difference was significant only in BN subjects as compared with nonbingeing controls, whether lean or obese.[223] Opioid antagonists are also effective in treating other addiction disorders such as alcohol dependence,[226–230] nicotine/tobacco dependence,[231,232] and heroine withdrawal.[233–235] Nevertheless, as with substance abuse disorders, naltrexone is not effective for all individuals with BN.[236]

Bulimia nervosa is also marked by serotonergic dysfunction in ill patients, as manifested by a blunted neuroendocrine response to a single administration of a serotoninergic agonist.[237–242] Levels of 5-hydroxyindoleacetic acid, a major serotonin metabolite, are reduced in the CSF of bulimic individuals, but only for frequently bingeing (ie, twice daily) patients, indicating that disease severity may be a factor in altered neurobiology.[175,242]

Imaging studies indicate increased 5-HT_{1A} receptor binding in patients with active BN.[243] Repeated amphetamine administration also increases 5-HT_{1A}–binding affinity in rodents,[244] possibly because of functional interactions between the dopaminergic and serotonergic systems. Serotonin may facilitate DA release, particularly in reward centers, such as the NAc and striatum.[245–250] Therefore, serotonin disturbances seen in BN may alter reward sensitivity through their effects on mesolimbic DA pathways. As such, selective serotonin reuptake inhibitors (SSRIs), the first-line drug therapy for BN,[251] may act by modulating DA. If SSRIs enhance DA neurotransmission, they may augment hyporesponsiveness to reward.

Even after treatment and remission of symptoms, a number of serotonin alterations persist in the absence of medication. The increased 5-HT_{1A} receptor binding seen in active BN also persists in patients recovered from BN.[252,253] Positron emission tomography imaging with [^{18}F]altanserin shows significant differences in 5-HT_{2A} receptor binding, most pronounced in the medial orbital frontal cortex, between women recovered from BN and controls with no eating disorder history.[254] Orbitofrontal alterations have also been linked to drug addiction.[255] Furthermore, recovered BN subjects have elevated CSF concentrations of 5-hydroxyindoleacetic acid[256] and evidence of reduced 5-HT transporter function.[257] However, other studies suggest that serotonin aberrations may normalize after bulimic behaviors remit.[258]

IMPLICATIONS FOR TREATMENT

Redefining BN within the framework of addiction has implications for treatment approaches and insurance coverage. Currently, cognitive behavioral therapy, in conjunction with antidepressant (SSRI) medication, is the customary treatment approach, but it is not uniformly effective. Programs targeted at addiction models, or pharmacological treatments with dopaminergic effects, might prove more beneficial. Case reports suggest that dopaminergic agonists, such as methylphenidate, attenuate bulimic symptoms without impacting body weight,[259–262] but controlled clinical trials are not available. As a DAT blocker, methylphenidate could be a particularly effective pharmacological intervention based on biological aberrations in DAT that researchers have demonstrated in BN.[178,182,183] Another alternative treatment approach could incorporate repetitive transcranial magnetic stimulation, which has been shown to reduce drug craving[159–162] and food craving,[163–165] although more research is needed as data are conflicting.[163,263]

Davis and Carter[113] have suggested that BN individuals may benefit from a behavioral strategy—adopted from drug abuse therapy—known as "cue exposure with response prevention" (CERP).[264] This approach aims to extinguish the association between conditioned food stimuli (ie, pleasant sight or smell of food) and the unconditioned stimuli, which serves as a positive reinforcer (ie, eating). Patients are exposed to food cues, but the response (eating) is prevented. This treatment has been shown successful in reducing cravings in small-scale studies with binge eaters[264] and with substance abusers.[265] However, more recent research on food craving suggests that negative affect cravings are more defining of BN than cue-dependent cravings.[145] Thus, modifying the CERP technique to elicit cravings by means other than mere food exposure and include manipulations able to modulate affective states may be more helpful to extinguish cravings relative to binge eating in BN.

Other variations of CERP involve exposure to small amounts of "binge" foods, but subsequent bingeing and purging are prevented.[266] However, this exposure-with-response-prevention paradigm does not seem to enhance cognitive behavioral therapy,[267] and some studies suggest that it may even have a deleterious effect on treatment outcome.[268] This may reflect the notion of "priming," in which the initial ingestion of a drug actually increases craving for the drug.[269,270] Likewise, binges can be triggered by small amounts of palatable (high-sugar/fat) foods.[271,272] Thus, from an addiction perspective, avoiding "trigger" foods altogether may be a more favorable approach.[113]

Insurance coverage may also be impacted by classifying BN as a form of SD. Inpatient coverage is routinely granted for chemical dependency, but not for BN. Those plans that do offer some coverage put a cap on the length of stay at 15 to 30 days, whereas recommended treatment stays are longer. Furthermore, the percentage covered for BN is much less than that for drug dependency. The average out-of-pocket cost for residential treatment programs for eating disorders was $6692 per week in 1996,[273] whereas costs for residential chemical dependency treatment averaged only $370 per week in 2008.[274] Thus, recognizing BN as an addiction disorder may result in more affordable treatment coverage.

IS ALL DISORDERED EATING "ADDICTIVE"?

Although eating in general stimulates reward pathways, so does music,[275] humor,[276] attractive faces,[276] being in love,[277] winning a prize,[278] and other "pleasant" stimuli. Therefore, the general statement that "food is addictive" is erroneous. It is the compulsive bingeing pattern seen in BN that has the ability to confer addictive potential to food substances, particularly sweet-tasting substances. Recently, there has been a surge in research

articles and media reports arguing that obesity may be a form of addiction.[279–285] The support for this argument largely comes from animal models of binge eating. However, most obese individuals are not classic binge eaters. Among obese individuals seeking weight loss treatment, only 1.3% to 30.1% of them have BED.[286–291] Obesity is usually associated with overconsumption, but intake may increase chronically throughout the day in the absence of marked bingeing. Furthermore, studies have shown that obese individuals do not have the heightened response to sweet taste as seen in BN. Although preference for high-fat food may be increased in obesity,[292] taste preferences for sweet are equivalent to or lower than those of normal-weight subjects,[293–300] making it unlikely that obese individuals suffer from "sugar addiction" as popular culture purports.

For individuals with BED, patterns of food consumption may more closely resemble an addictive disorder than that in obese individuals. However, the binge eating seen in BED is not typically followed by dietary restriction as it is in BN.[301,302] Rada and colleagues[61] have demonstrated that this pattern of binge eating (with rats given ad libitum access to sugar or chow) results in a blunted DA response that is typical of food and other natural rewards, but not of drugs of abuse. Only the sucrose-bingeing rats with intermittent access displayed recurrent DA release, even after several weeks of sucrose exposure.[61] Furthermore, greater DA release is seen when larger quantities of food are ingested,[303] and individuals with BN report significantly greater binge sizes than those with BED.[304,305] Binges in BN and BED differ not only in quantifiable calories ingested, but also in patterns of food selection, with bulimics prioritizing dessert and carbohydrate foods first, whereas BED subjects consume more meat.[136,306] In rodents, the presence of sweet taste in binge foods may be crucial to developing dependence, as fat-bingeing rats do not develop opiate-like withdrawal after naloxone administration.[118,307]

Individuals with BN demonstrate more severe psychopathology than those with BED,[302,308] and thus, the bingeing in these disorders may represent a continuum of clinical severity. This distinction may be analogous to differences in those who abuse alcohol versus those who are alcohol-dependent. The significant link between comorbid drug/alcohol addiction and BN does not seem to be present for BED,[309,310] nor are there robust neurobiological aberrations in BED to the extent seen in BN.[205,206,242] It is plausible that individuals with BN have distinct neurochemical permutations that put them at a greater risk for addiction than individuals with BED. This increased risk in BN may explain why nondrug rewards, such as palatable foods, have the capacity to highjack reward circuitry and transform disordered eating into addiction in these individuals.

FUTURE DIRECTIONS

Most of the aforementioned clinical studies are cross-sectional and thus do not address the question of whether biological differences in BN patients preceded or developed subsequent to the onset of the subjects' disorders. More longitudinal studies are needed. Furthermore, grouping purging versus nonpurging bulimics into 1 cohort may mask the emergence of distinct subtypes of BN. Because some evidence suggests that individuals with BN are hyporesponsive to reward, whereas other lines of research implicate a hypersensitive reward circuitry, it is plausible that BN may reflect 2 distinct disease states. Future studies could address this distinction by analyzing neurobiological findings as a function of reward sensitivity and determine whether the presence of purging predicts these differences. Bulimia nervosa individuals who purge may have significantly larger binge sizes,[304] and this could be manifested in differences in neurobiology.

Although PET studies looking at DA receptor binding have been performed in individuals with AN and obesity, none exists for individuals with BN. Plausibly, differences in reward functioning and hedonic evaluation of food would be reflected in either higher or lower receptor densities. Along these lines, fMRI of BN individuals during a palatable food challenge (where the food is actually ingested) would likely result in differential activation of limbic structures as compared with healthy, weight-matched controls. Degree of activation could also be correlated with subjective ratings of food pleasantness and individual scores on the reward sensitivity scale to better delineate between hypo– versus hyper–reward functioning.

CONCLUSIONS

Bulimia nervosa individuals clearly possess propensities for addiction as demonstrated by the significant association between bulimia and substance abuse.[11–16,17,311,312] Evidence of a common mechanism mediating the reinforcing properties of drugs and natural rewards supports the notion that certain eating patterns can impact behavioral and neurobiological substrates in a manner similar to addictive substances. These eating patterns are seen in BN (intermittent restriction, bingeing, purging). Although substance abuse is associated with a number of eating disorders, this association is greatest for BN and AN-BP,[13,313–316] highlighting the importance of the binge-purge pattern. Moreover, severe bingeing is consistently linked to alcohol use,[19,317,318] whereas purging behaviors predict the use of many substances including alcohol, cocaine, cigarettes, stimulants, and amphetamines.[317–322] Taken together, it is plausible that individuals with BN suffer from a form of food addiction. Recognizing BN as an addictive disorder has important ramifications for understanding of the disease process and development of new therapeutic treatment targets.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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