CASE REPORT

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Pilot clinical observations between food and drug seeking derived from fifty cases attending an eating disorder clinic

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Background: The reward deficiency syndrome hypothesis posits that genes are responsible for reward dependence and related behaviors. There is evidence that both bulimia and anorexia nervosa, especially in women, have been linked to a lifetime history of substance use disorder (SUD). There are difficulties in accepting food as an addiction similar to drugs; however, increasingly neuroimaging studies favor such an assertion. *Case presentations:* We are reporting the evidence of comorbidity of eating disorders with SUD found within these case presentations. We show 50 case reports derived from two independent treatment centers in Florida that suggest the commonality between food and drug addictions. In an attempt to provide data from this cohort, many participants did not adequately respond to our questionnaire. *Discussion:* We propose that dopamine agonist therapy may be of common benefit. Failure in the past may reside in too powerful D2 agonist activity leading to D2 receptor downregulation, while the new methodology may cause a reduction of "dopamine resistance" by inducing "dopamine homeostasis." While this is not a definitive study, it does provide some additional clinical evidence that these two addictions are not mutually exclusive. *Conclusion:* Certainly, it is our position that there is an overlap between food- and drug-seeking behavior. We propose that the studies focused on an effort to produce natural activation of dopaminergic reward circuitry as a type of common therapy may certainly be reasonable. Additional research is warranted.

Keywords: food and drug addictions, commonality, dopamine pathways, reward deficiency syndrome, eating disorder

INTRODUCTION

The concept that food and drugs have common neurobiological and neurogenetic mechanisms has been pioneered first by Hoebel (1985) over 25 years ago and introduced into the media and mainstream America by Gold and Avena (2013) and Avena's group (Murray, Tulloch, Chen, & Avena, 2015).

Research has revealed that obesity results in changes in both behaviors and brain structures quite similar to the changes observed in drug addiction. However, addiction to food is not the cause of all cases of obesity. Can it be assumed that a large group of individuals no longer eat to survive, but rather survive to eat? This article considers the importance of the brain's reward system in food intake the "thrifty gene hypothesis" (survival gene related to famine and fat metabolism) and as such the commonality between food and drug addictions (Prentice, Hennig, & Fulford, 2008; Speakman, 2006).

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Certain overlaps in the brain circuitry activation by food and drug intake suggest that different types of reinforces (natural and artificial) activate a number of the same neural systems (Hernandez & Hoebel, 1990; Hoebel, 1985; Kelley et al., 2002; Le Magnen, 1988; Volkow & Wise, 2005; Wise, Fotuhi, & Colle, 1989). In fact, there are several regions of the brain involved in the reinforcement of both feeding and drug intake (Baldo, Pratt, & Kelley, 2010; Kalivas & Volkow, 2005; Koob & Le Moal, 2005; Mogenson & Yang, 1991), and a number of neurotransmitters, as well as hormones, have been studied in these related brain areas (Baldo et al., 2010; Schoffelmeer, Wardeh, & Vanderschuren, 2001; Simpson et al., 2012; Spangler et al., 2004; Stein & Belluzzi, 1979).

An objective of this article is to support these commonality theories, as proposed by Avena, Murray, and Gold (2013) and Blum et al. (1996). In clinical situations, treatment of both food and drug addictions typically appears to present with reciprocal comorbidity and this common comorbidity deserves intensive investigation.

This pilot data from patients attending an outpatient eating disorder program may offer an opportunity for exploration of both inheritable traits and the environmental, genetic expression involved in eating disorders and comorbid drug addiction. Here, we present 50 cases of patients attending an outpatient eating disorder program in North Miami Beach, FL.

CASE PRESENTATIONS

Methods

Procedure. Observational data from case histories from 50 subjects attending an eating disorder program at "A new Beginning PA," North Miami Beach, FL, and Ocean Breeze Recovery Program, Pompano Beach, FL, have been investigated.

Each patient was interviewed by a clinician using a number of intake instruments including DSM-5 criteria and a structured interview, with duration of at least 1 hr. Each patient was asked for their demographics, their name, age, the location of residence, marital status (single, divorced, married, widowed, in a relationship, or living with a partner), their ethnicity, and their religion to be recorded. A detailed assessment for eating disorder and substance abuse history was made. The eating disorder assessment included the onset of the eating disorder (childhood or adult) and classification/diagnosis of the eating disorder: Compulsive eating (binge eating or grazing), night eating, and bulimia-purging (i.e., self-induced vomiting, laxative abuse, diuretics, overexercising, restricting, or anorexia). The duration of symptoms, frequency of substance (food, sugar, laxatives, and diuretics), and body image (experiencing body dysmorphia) and whether they were stimulated to eat more food after eating sugar and/or flour products were assessed. Family history of eating disorders including any relatives who had, in the past or present, eating disorders, other addictions, and mood disorders was noted. Their current weight and body mass index (BMI), highest weight as an adult if adult onset, or highest weight as a child/adolescent and lowest weight in adulthood, and diets and methods of weight loss or weight gain if attempting to control weight were noted. A history of any bariatric surgeries (gastric bypass, lap band, sleeve) and any suicidal attempts due to weight/food issues was taken. In addition, it is critical to note that the term "eating disorders" included all of the categories stated above including anorexia nervosa.

The substance abuse history had listed every category and specific names of each drug in DSM 5. The instrument was the same as the eating disorders/food addiction history (including all demographics noted above). In addition, a history of suicidal attempts with drugs was taken, and drug overdoses (frequency and names of the drugs used to overdose) and the number of treatment modalities attended, completed and/or left Against Medical Advice were recorded.

Participants. The resultant information was self-reported with input from the treatment facility staff. All the subjects were adults, reported ages ranged between 20 and 61 years; other demographic information is listed in Table 1.

Ethics. The study procedures were carried out in accordance with the Declaration of Helsinki. The Institutional Review Board of the PATH Foundation NY approved this study concerning obesity research. All subjects were informed about the study and all provided informed consent.

Results

Within the case study group, BMI of 4 subjects was normal (18.5–24.9), BMI of 9 subjects was overweight (25–29.9), and BMI of 37 was obese (30 or greater).

Physical characteristics including height and weight were used to determine the BMI. Other information including a recent food history; drug history; surgical procedures; prior diagnosis; family history of eating disorders; family history of addiction to psychoactive substances, and highest and lowest weights were recorded. The percentages of the characteristics recorded in Table 2 are broken down in the list as follows:

– *Food history breakdown:* 3 sugar (6%), 25 flour/sugar (50%), and 22 no response (44%).

Table 1. Demographics of the studied cohort

Characteristics	*N* (%)	Total *N* (%)
Gender	30 (60) Males	50 (100)
	20 (40) Females	
Race	43 (86) Caucasians	50 (100)
	6 (12) African-Americans	
	1 (2) Hispanic	
Marital status	18 (36) Single	50 (100)
	12 (24) Married	
	12 (24) Divorced	
	2 (4) Separated	
	6 (12) No response	

Table 2. Results of interviews and clinical instruments for the entire studied cohort

Pt No.	BMI	Drug history	Family eating disorders	Family drug history	Highest weight lb (kg)/age	Lowest weight lb (kg)/age
1	36	Opiates, benzodiazepines, alcohol	Yes	No		
2	43.4	Opiates, nicotine	Yes	Yes	350 (158.8)/53	200 (90.7)/27
3	27.4	Alcohol, nicotine, benzodiazepines, pot	Yes	Yes	210 (95.3)/30	92 (42.7)/20
4	29.1	Alcohol	Yes	Yes	250 (113.4)/50	160 (72.6)/53
5	24.8	Alcohol	Yes	Yes	326 (147.9)/22	160 (72.6)/28
6	30.7	Alcohol, cocaine, heroin, benzodiazepines	Yes	Yes	230 (104)/15	132 (59.8)/15
7	38.3	Opiates	Yes	No	299 (135.6)/35	170 (77.1)/24
8	31.7	Alcohol	Yes	Yes	254 (115.2)/33	145 (65.8)/34
9	39.1	Alcohol, opiates	Yes	Yes	300 (136)/32	165 (74.8)/33
10	32.3	Opiates	NR	NR		
11	36.3	Polysubstance	NR	NR		
12	31.3	Cocaine	NR	NR		
13	29.8	Sedative hypnotics	NR	NR		
14	27	Alcohol	NR	NR		
15	29.9	Alcohol	NR	NR		
16	34.4	Alcohol	NR	NR		
17	29.1	Alcohol	NR	NR		
18	32.8	Polysubstance	NR	NR		
19	31.1	Alcohol	NR	NR		
20	39.6	Alcohol	NR	NR		
21	32.6	Cocaine	NR	NR		
22	38.4	Opiates	NR	NR		
23	31.4	Alcohol	NR	NR		
24	28.1	Alcohol	NR	NR		
25	36.5	Polysubstance	NR	NR		
26	34.3	Opiates	NR	NR		
27	39.1	Alcohol, benzodiazepines, nicotine, pot	Yes	Yes	260 (117.9)/28	113 (51.3)/19
28	30.4	Alcohol, crack, nicotine	NR	Yes	210 (95.3)/46	140 (63.5)/37
29	53.8	Heroin, benzodiazepines, crack, nicotine	Yes	Yes	290 (131.5)/20	210 (95.3)/22
30	30.9	Alcohol, cocaine, heroin, benzodiazepines, mushrooms, nicotine	NR	NR	235 (106.6)/15	168 (76.2)/18
31	32.5	Crystal meth, cocaine, alcohol, pot, nicotine	Yes	NR	280 (127)/32	170 (77.1)/32
32	41.5	Heroin	Yes	Yes	305 (138.3)/16	200 (90.7)/17
33	33	Alcohol	NR	NR	232 (105.2)/20	175 (79.4)/18
34	27.5	Alcohol	Yes	NR	303 (137.4)/49	190 (86.2)/50
35	22.8	Alcohol	Yes	Yes	289 (131)/40	178 (80.7)/60
36	24.8	Opiates, cocaine, nicotine	Yes	Yes	180 (81.6)/17	120 (54.4)/17
37	22.1	Opiates, crack	Yes	Yes	138 (62.6)/19	89 (40.4)/16
38	35.4	Opiates	Yes	NR	225 (102)/24	140 (63.5)/21
39	41.5	Alcohol, nicotine	Yes	NR	300 (136)/39	185 (83.9)/20
40	26	Alcohol, benzodiazepines	NR	NR	267 (121.1)/40	155 (70.3)/40
41	33.2	Fastest, nicotine, opiates, cocaine, crack, alcohol	Yes	Yes	250 (113.4)/19	189 (85.7)/17
42	38.2	Alcohol, crystal meth	Yes	NR	230 (104.3)/39	135 (61.2)/25
43	42.2	Nicotine, cocaine, crack alcohol	Yes	NR	280 (127)/34	210 (95.3)/18
44	36	Alcohol	NR	NR	302 (137)/39	218 (98.9)/41
45	42.7	Opiates, pot, nicotine, hallucinogens	NR	NR	325 (147.4)/21	230 (104.3)/17
46	32.8	Alcohol, nicotine	Yes	NR	215 (97.5)/45	189 (85.7)/30
47	32.7	Alcohol, opiates	NR	Yes	260 (117.9)/31	195 (88.5)/19
48	31.5	Benzodiazepines, opiates, nicotine, pot, cocaine, crack	NR	NR	235 (106.6)/22	190 (86.2)/19
49	34.7	Crystal meth, opiates	NR	Yes	270 (122.5)/42	190 (86.2)/22
50	50.2	Opiates, crack	NR	NR		

Note. NR = none reported; opiates = non-heroin opiates and opioids; pot = marijuana; crack = crack cocaine.

– *Drug history breakdown:* 8 benzodiazepines (16%), 16 opiates meaning non-heroin opiates and opioids (32%), 14 nicotine (28%), 5 pot meaning marijuana (10%), 9 cocaine (18%), 7 crack meaning crack cocaine (14%), 30 alcohol (60%), 3 crystal meth meaning methamphetamine (6%), 4 heroin (8%), 1 hallucinogens (2%), 3 polysubstance (6%), 1 sedative (2%), 1 hypnotics (2%), 1 mushrooms (2%), and 1 fastest (2%).
– *Averages for height:* Males 69.6 in. (176.7 cm), 11 values were missing and females 64.1 in. (162.8 cm), 6 values were missing.

- *Averages for weight:* Males 236.4 lb (107.2 kg), 11 values were missing and females 206.2 lb (93.5 kg), 6 values were missing.
- *Prior diagnosis breakdown:* 3 eating disorder NOS (6%), 6 bulimia (12%), 6 diabetes (12%), and 35 no response (70%).
- *Average BMI:* 33.9 for males and 33.7 for females (see Table 2).
- *Surgical history breakdown:* 8 gastric bypass (16%), 3 lap band (6%), and 39 no response (78%). Family history of eating disorders breakdown: 23 yes (46%) and 27 no response (54%).
- *Family drug history breakdown:* 17 yes (34%), 2 no (4%), and 31 no response (62%).

In this observational pilot study, any meaningful statistical analysis of the data regarding the family history of SUD was prevented with 62% of the current patients who either did not want to respond or did not know their family history of SUD; however, 17 of 24 cohort families whose drug taking history was available and all of the people in the eating disordered cohort had a comorbid drug history.

DISCUSSION

We have reviewed 50 case reports that indicate an explicit relationship between food and drug seeking. The evidence from this pilot experiment on human subjects helps the scientific community to question the requirement for separate treatment methods for two distinct but frequently coexisting abnormal seeking behaviors.

Many articles have examined research developments and current treatments for obesity, including diet and exercise, psychotherapy, surgical interventions, and pharmacotherapies (Blum et al., 2011; Michaelides, Thanos, Volkow, & Wang, 2012; Volkow & Baler, 2015). Overeating may have important neurochemical links to drug abuse, although, less is known about other eating disorders like bulimia and anorexia (Jordan et al., 2003). There is an evidence that substance use disorder (SUD) has been linked to both bulimia and anorexia nervosa, especially in young women (Mann et al., 2014). Some other clinical issues merit attention and provide information that shed light on the commonality concept of food and drug comorbidities. For example, after several years of effective bariatric surgeries, which used to treat obese patients, clinicians now report that some patients are substituting compulsive overeating with other compulsive behaviors. These behaviors involve decreased dopamine (DA) type 2 receptors (DRD2) and include alcoholism, gambling, drugs, compulsive shopping, and exercise (Cuellar-Barboza et al., 2015; Dunn et al., 2010). Previously, evidence from psychiatric genetic animal and human studies associating compulsive overeating and other compulsive behaviors was explored to elucidate the process of addiction transfer. Potentially because of neurochemical similarities, overeating and obesity may act protectively by decreasing drug reward (Hodgkins, Frost-Pineda, & Gold, 2007). Similar to the process of opiate withdrawal, in animal sugar addiction withdrawal models, imbalances occur in neurotransmitters, such as acetylcholine and DA (Avena, Potenza, & Gold, 2015; Gold & Avena, 2013). In addition, several animal neuroimaging studies have reinforced the link between food craving and drug craving (Avena & Bocarsly, 2012).

Common intricate molecular neurobiological mechanisms related to both food and drug addictions

Tomasi et al. (2015) reported that in comparison to neutral cues, food and cocaine cues increasingly engaged cerebellum, orbitofrontal, inferior frontal, and premotor cortices and insula and disengaged cuneus and default mode network (DMN). Importantly, these functional magnetic resonance imaging (fMRI) signals were proportional to striatal D2/D3 receptors. Surprisingly, cocaine and food cues also deactivated ventral striatum and hypothalamus suggesting deficiency. Moreover, compared to food cues, cocaine cues produced lower activation in insula and postcentral gyrus, and less deactivation in hypothalamus and DMN regions. In addition, activation in cortical regions and cerebellum increased in proportion to the valence of the cues, and activation to food cues in somatosensory and orbitofrontal cortices also increased in proportion to body mass. As expected, longer exposure to cocaine was associated with lower activation to both cues in occipital cortex and cerebellum, which could reflect the decreases in D2/D3 receptors associated with chronicity (Tomasi et al., 2015).

The authors suggested that these findings show that cocaine cues activate similar, though not identical, pathways to those activated by food cues and that striatal D2/D3 receptors modulate these responses, suggesting that chronic cocaine exposure might influence brain sensitivity not just to drugs but also to food cues (Tomasi et al., 2015).

The term "reward deficiency syndrome" (RDS) was coined to describe the genetic determinants that predict addiction. The predictive value of being a carrier of the DRD2 Taq A1 allele, which may cause future RDS behaviors, was 74% (Blum, Wood, Braverman, Chen, & Sheridan, 1995). People with the DRD2 Taq A1 allele carry a reduced number of D2 receptors and, therefore, have reduced DA function. In addition, RDS is polygenetic, which involves a cascade of reward genes. The deficiency concept of DA may not be the only way to gain weight and there is also an evidence for a DA surfeit theory (Yokum, Gearhardt, Harris, Brownell, & Stice, 2014). However, DA function disruptions, in particular, may predispose people to obesity and other addictive disorders. A family history of alcoholism is considered to be a substantial obesity risk factor (Pach et al., 2014). Thus, we hypothesize that RDS is the cause of replacing food addiction with other addictive behaviors and may describe this recent phenomenon of addiction transfer that is common following bariatric surgery.

Research into the neuroscience of glucose and cocaine treatments have shown that treatment for both food and psychoactive substance misuse should include DA agonist therapy inducing dopamine release as opposed to present antagonistic DA therapy (Adler et al., 2000).

Several molecular and metabolic processes involved in the interaction of dopaminergic system and glucose may

provide possible common therapeutic targets for both food and drug addictions. They include

- in the mesolimbic structure, the enkephalinergic neurons are found close to the vicinity of glucose receptors;
- highly concentrated glucose triggers the calcium channel to activate DA P12 cell release;
- a significant connection between blood glucose and cerebrospinal fluid levels of homovanillic acid, the DA metabolite; and
- in pharmacological doses, the glucose analog, 2-deoxyglucose (2DG), is related to improved DA yields and produces acute glucoprivation.

Stress-induced cocaine-seeking behavior involves the discharge of neuropeptides corticotropin-releasing factor (CRF) and orexin-A in the ventral tegmental area (VTA). There is a support for pharmacologically important connections between CRF and orexin-A that are dependent on the oligomerization of orexin OX1 receptors (OX1R) and CRF1 receptor (CRF1R). CRF1R–OX1R heteromers are like the channels of an adverse crosstalk between orexin-A and CRF as exhibited in rat VTA and transfected cells, where it considerably regulates dendritic DA discharge. The cocaine target 1 receptor (1R) also links with the CRF1R–OX1R heteromer. Cocaine binding to the 1R–CRF1R–OX1R complex supports a long-standing disturbance of the orexin-A–CRF negative crosstalk. It is within this mechanism that cocaine sensitizes VTA cells to the stimulatory effects of both CRF and orexin-A, hence offering a mechanism by which stress produces cocaine seeking (Navarro et al., 2015). The RDS model of etiology holds very well for a variety of chemical (drugs and food) and behavioral seeking that can result in addiction.

Dopamine function deregulation is a significant cause of addictive behaviors, like drug, alcohol, and food addictions. Dopamine and other reward neurotransmitters are also a part of a largely dispersed neural network responsible for regulation of eating behavior, affecting both homeostatic and hedonic mechanisms (Berridge & Kringelbach, 2015; Li, Zuo, Yu, Ping, & Cui, 2015). Considering this, the dopaminergic and opioidergic mechanisms are especially involved in palatable food modulation, and opioid antagonists weaken drug cravings and palatable food appetite. Therefore, palatable food cravings could be contemplated as a type of DA-opioid-related addiction. Though there are at least five dopaminergic receptors, the D1 and D2 have been most associated with reward according to the research (Li et al., 2015).

Interestingly, McCutcheon (2015) suggested that post-ingestive mechanisms occurring from nutrients in the gut could impact food consumption and behavioral conditioning. The physiological processes essential to these mechanisms are multifaceted and are thought to join in mesolimbic DA signaling to translate post-ingestive sensing of nutrients that have a reinforcement reward value.

Currently, there are three chief families of opioid receptors (μ, κ, and δ), of which the μ-receptors are most involved in reward. The cases that show common phenotype between food and drug addictions suggest a common therapeutic target (Karlsson et al., 2015). They found that low μ-opiate receptor availability results in increased feeding behavior. Similarly, dopaminergic agonists reduce appetite (Frank, 2014) while DA antagonists, especially at D2 loci, increase ingestive behavior (Liu et al., 2012). Have we hatched the common phenotype egg and should we consider common treatment for these two seemingly diverse substances?

Obese versus lean humans have less striatal D2 receptors and show fewer striatal reactions to palatable food intake (Stice, Yokum, Blum, & Bohon, 2010). These findings align with the idea that those who have hypofunctioning reward circuitry are inclined to overeat, to satisfy a reward deficit. Also, decreases in striatal response to food intake forecasts weight gain in the future for those at genetic risk for lowered signaling of DA-based reward circuitry, particularly in adolescents (Stice et al., 2010). There is also an alternate possibility that a surfeit of DA may also cause weight gain (Stice & Yokum, 2014). However, animal studies specify that palatable food intake causes downregulation of D2 receptors, decreased D2 sensitivity, and reduced reward sensitivity, suggesting that overeating may denote diminished striatal responsivity. Stice and Yokum (2014) and Stice et al. (2010) examined whether or not overeating causes decreased striatal responsivity to palatable food intake in humans utilizing repeated measures of fMRI. Outcomes specified that females who gained weight during a 6-month period showed a decline in striatal response to palatable food ingestion compared to females who had stable weight. Together, these results imply that low sensitivity to reward heightens the risk for overeating and additionally, overeating may diminish the responsivity of reward circuitry in a feed-forward manner, specifically in DRD2 A1 allele carriers (Carpenter, Wong, Li, Noble, & Heber, 2013).

Neuroimaging studies have revealed that psychoactive substances, palatable foods, and anticipated behaviors, such as gambling and sex, affect brain structures that activate reward circuitry and may not be unidirectional. Psychoactive substances boost DA signaling and sensitize mesolimbic mechanisms that have been developed to modulate the incentive salience of reward processing (Laricchiuta, Musella, Rossi, & Centonze, 2014). Drugs of abuse are willingly self-administered. Either directly or indirectly, they heighten the dopaminergic synaptic function in the nucleus accumbens and fuel brain reward circuitry functioning (creating the "high" that drug users pursue). Though initially thought to determine the setting of hedonic tone, the functions of dopaminergic circuitry are now understood to be more intricate, coding for attention, reward expectancy, disconfirmation of reward expectancy, and incentive motivation. Elevated stress levels, along with dopaminergic gene polymorphisms and additional neurotransmitter genetic variants, may have an aggregate effect on the susceptibility to both food and drug addictions involving epigenetic effects (Wright et al., 2015). Recently, Badgaiyan, Sinha, Sajjad, and Wack (2015) clearly showed that dopaminergic tone at rest is reduced in attention-deficit/hyperactivity disorder. This work suggests that subjects presenting with comorbid aberrant seeking behavior may share a common rubric displaying a hypodopaminergic trait/state.

Food and drug comorbidities observed – 50 case series

Understanding these common intricate molecular neurobiological mechanisms related to both food and drug addictions is underscored by this 50 case series, showing that 100% of patients attending an eating disorder clinic had previous psychoactive substance misuse history both in the present and in the past. However, due to unknown factors like adoption, the information on family history needs to be more intensely investigated in this cohort or a larger cohort in future studies. However, showing that 48% of the patients did have a family history of eating disorders seems important and provides some information regarding genetic inheritability. Our finding of 34% having a known family history of psychoactive substance misuse also seems to be important in terms of psychoactive substance addiction inheritability.

Limitations

This is a small observational pilot study with only demographic information and without meaningful statistics to support the main theme of this article. A much larger cohort with non-eating disorder controls must be evaluated in future studies. Also, we did not characterize the type of psychoactive substance misuse in terms of severity, which is important in terms of genetic commonality (Gold & Avena, 2013; Hoebel, 1985; Tomasi et al., 2015; Volkow & Wise, 2005). We are indeed encouraged, however, since all 50 subjects who entered an eating disorder clinic had comorbid SUD or at least aberrant seeking behavior history.

Future perspectives

This study found that subjects who entered an eating disorder clinic had comorbid substance-use-seeking behavior. Many theories supported by scientific neurochemical and genetic studies offer sound evidence that food addiction and psychoactive drug addiction are similar (Hadad & Knackstedt, 2014) in spite of arguments to counter this notion (Ziauddeen & Fletcher, 2013). Genetic and epigenetic impairments of the brain reward circuitry, which cause hypodopaminergic functioning, define RDS (Blum et al., 2011). RDS involves neurotransmitter exchanges and produces abnormal craving behaviors. Animal and human fMRI studies reinforce the hypothesis that several similar brain circuits are disturbed during drug addiction and obesity, which involves DA-modulated reward circuits in habitual eating (Blum, Liu, Shriner, & Gold, 2011).

Recognizing the role of DNA and polymorphic links to brain reward circuitry has steered us to an innovative treatment for addiction, which is important to psychiatry in the genomics era. This approach may offer support to those who suffer from RDS. Studies have indicated that assessing established reward gene and polymorphism panels permits the stratification of genetic risk for RDS. The panel named the "Genetic Addiction Risk Score (GARS™)" is a diagnostic instrument for genetic predispositions to RDS. Clinical groups using this test would have the advantage of being able to detect from an early age of those at risk for both food and drug addiction liabilities (Blum et al., 2012; Gold, Blum, Oscar-Berman, & Braverman, 2014).

The current failure of DA D2 agonists in clinical use is due to chronic downregulation of the D2 receptors' targets. Less potent D2 agonists that may upregulate D2 receptors have had some clinical success (Burris, Fausing, & Molinoff, 1998). Thus, approaches aimed at DA function improvements, rather than treatments that block DA function may better treat food- and drug-seeking behavior. The significant role that genes play in reward dependence and associated behaviors including food and drug addictions is emphasized by the role of DA.

Schulte, Avena, and Gearhardt (2015) reported that processed foods, high in fat and glucose, were most frequently associated with addictive-like eating behaviors. Moreover, processing was a large, positive predictor for whether a food was associated with problematic, addictive-like eating behaviors. In their model, fat and glucose were large, positive predictors of problematic food ratings. This underscores the need to restrict these foods during recovery from both food and drug addictions.

CONCLUSION

Based on this, pilot case series finding focus on natural activation of dopaminergic reward circuitry as a type of common therapy may certainly be parsimonious (Field et al., 2014; Holderness, Brooks-Gunn, & Warren, 1994; Hudson, Weiss, Pope, McElroy, & Mirin, 1992; Kendler et al., 1995). While this study may not answer the definitive question as to the true relationship between food and drugs of abuse, it does extend the view of a commonality rather than non-commonality. Additional research in this regard is warranted especially further neuroimaging studies to unravel the current mysteries involved in eating disorder like anorexia and bulimia, and any links to common mechanisms to drug-seeking behavior.

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Authors' contribution: The original idea to perform this trial was based on a previous clinical observation by MSG. The final design of the study was developed by HB-C, JG, and KB. The execution of the clinical data retrieval was obtained by HB-C. The basic write up of each case was developed by MAM and KB. The initial writing of the manuscript was executed by KB and KD. The interpretation of the data was imputed by KB, RDB, MSG, ERB, ML, MF, and KD. The development of the tables was executed by MAM and KD. The literature review was performed by KB, MSG, RDB, ERB, and MF. All authors approved the final draft of the revised manuscript.

Conflict of interest: KB, PhD, holds US and Foreign patents issued and pending on KB220Z and receives royalties based on its commercialization from various sources. He is also an officer and stock holder of IGENE, LLC, Victory Nutrition, RDSolutions, Inc., and is a paid consultant of Dominion Diagnostics, LLC, and Malibu Recovery Center. He is a member of the scientific advisory board of Dominion Diagnostics, LLC. MSG is a paid consultant for Rivermend LLC, New York, NY. ERB owns Total Health Nutrients and JG distributes nutritional supplements to the recovery marketplace based in-part on Blum's patents. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript part from those disclosed, ERB and MF.

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REFERENCES

Adler, C. M., Elman, I., Weisenfeld, N., Kestler, L., Pickar, D., & Breier, A. (2000). Effects of acute metabolic stress on striatal dopamine release in healthy volunteers. *Neuropsychopharmacology, 22*(5), 545–550. doi:10.1016/S0893-133X(99)00153-0

Avena, N. M., & Bocarsly, M. E. (2012). Dysregulation of brain reward systems in eating disorders: Neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. *Neuropharmacology, 63*(1), 87–96. doi:10.1016/j.neuropharm.2011.11.010

Avena, N. M., Murray, S., & Gold, M. S. (2013). Comparing the effects of food restriction and overeating on brain reward systems. *Experimental Gerontology, 48*(10), 1062–1067. doi:10.1016/j.exger.2013.03.006

Avena, N. M., Potenza, M. N., & Gold, M. S. (2015). Why are we consuming so much sugar despite knowing too much can harm us? *JAMA Internal Medicine, 175*(1), 145–146. doi:10.1001/jamainternmed.2014.6968

Badgaiyan, R. D., Sinha, S., Sajjad, M., & Wack, D. S. (2015). Attenuated tonic and enhanced phasic release of dopamine in attention deficit hyperactivity disorder. *PLoS One, 10*(9), e0137326. doi:10.1371/journal.pone.0137326

Baldo, B. A., Pratt, W. E., & Kelley, A. E. (2010). Frontiers in neuroscience: Control of fat intake by striatal opioids. In J. P. Montmayeur & J. le Coutre (Eds.), *Fat detection: Taste, texture, and post ingestive effects.* Boca Raton, FL: CRC Press/Taylor & Francis.

Berridge, K. C., & Kringelbach, M. L. (2015). Pleasure systems in the brain. *Neuron, 86*(3), 646–664. doi:10.1016/j.neuron.2015.02.018

Blum, K., Bailey, J., Gonzalez, A. M., Oscar-Berman, M., Liu, Y., Giordano, J., Braverman, E., & Gold, M. (2011). Neurogenetics of reward deficiency syndrome (RDS) as the root cause of "addiction transfer": A new phenomenon common after bariatric surgery. *Journal of Genetic Syndromes & Gene Therapy, 2012*(1), S2-001. doi:10.4172/2157-7412.s2-001

Blum, K., Braverman, E. R., Wood, R. C., Gill, J., Li, C., Chen, T. J., Taub, M., Montgomery, A. R., Sheridan, P. J., & Cull, J. G. (1996). Increased prevalence of the Taq I A1 allele of the dopamine receptor gene (DRD2) in obesity with comorbid substance use disorder: A preliminary report. *Pharmacogenetics, 6*(4), 297–305. doi:10.1097/00008571-199608000-00003

Blum, K., Liu, Y., Shriner, R., & Gold, M. S. (2011). Reward circuitry dopaminergic activation regulates food and drug craving behavior. *Current Pharmaceutical Design, 17*(12), 1158–1167. doi:10.2174/138161211795656819

Blum, K., Oscar-Berman, M., Giordano, J., Downs, B., Simpatico, T., Han, D., & Femino, J. (2012). Neurogenetic impairments of brain reward circuitry links to reward deficiency syndrome (RDS): Potential nutrigenomic induced dopaminergic activation. *Journal of Genetic Syndromes & Gene Therapy, 3*(4), 1000e115. doi:10.4172/2157-7412.1000e115

Blum, K., Wood, R. C., Braverman, E. R., Chen, T. J., & Sheridan, P. J. (1995). The D2 dopamine receptor gene as a predictor of compulsive disease: Bayes' theorem. *Functional Neurology, 10*(1), 37–44.

Burris, K. D., Fausing, S. M., & Molinoff, P. B. (1998). Regulation of D2 and D3 receptors in transfected cells by agonists and antagonists. *Advances in Pharmacology, 42*, 443–446. doi:10.1016/S1054-3589(08)60783-8

Carpenter, C. L., Wong, A. M., Li, Z., Noble, E. P., & Heber, D. (2013). Association of dopamine D2 receptor and leptin receptor genes with clinically severe obesity. *Obesity (Silver Spring), 21*(9), E467–E473. doi:10.1002/oby.20202

Cuellar-Barboza, A. B., Frye, M. A., Grothe, K., Prieto, M. L., Schneekloth, T. D., Loukianova, L. L., Hall-Flavin, D. K., Clark, M. M., Karpyak, V. M., Miller, J. D., & Abulseoud, O. A. (2015). Change in consumption patterns for treatment-seeking patients with alcohol use disorder post-bariatric surgery. *Journal of Psychosomatic Research, 78*(3), 199–204. doi:10.1016/j.jpsychores.2014.06.019

Dunn, J. P., Cowan, R. L., Volkow, N. D., Feurer, I. D., Li, R., Williams, D. B., Kessler, R. M., & Abumrad, N. N. (2010). Decreased dopamine type 2 receptor availability after bariatric surgery: Preliminary findings. *Brain Research, 1350*, 123–130. doi:10.1016/j.brainres.2010.03.064

Field, A. E., Sonneville, K. R., Crosby, R. D., Swanson, S. A., Eddy, K. T., Camargo, C. A., Jr., Horton, N. J., & Micali, N. (2014). Prospective associations of concerns about physique and the development of obesity, binge drinking, and drug use among adolescent boys and young adult men. *JAMA Pediatrics, 168*(1), 34–39. doi:10.1001/jamapediatrics.2013.2915

Frank, G. K. (2014). Could dopamine agonists aid in drug development for anorexia nervosa? *Frontiers in Nutrition, 1,* 19. doi:10.3389/fnut.2014.00019

Gold, M. S., & Avena, N. M. (2013). Animal models lead the way to further understanding food addiction as well as providing evidence that drugs used successfully in addictions can be successful in treating overeating. *Biological Psychiatry, 74*(7), e11. doi:10.1016/j.biopsych.2013.04.022

Gold, M. S., Blum, K., Oscar-Berman, M., & Braverman, E. R. (2014). Low dopamine function in attention deficit/hyperactivity disorder: Should genotyping signify early diagnosis in children? *Postgraduate Medicine, 126*(1), 153–177. doi:10.3810/pgm.2014.01.2735

Hadad, N. A., & Knackstedt, L. A. (2014). Addicted to palatable foods: Comparing the neurobiology of Bulimia Nervosa to that of drug addiction. *Psychopharmacology (Berlin), 231*(9), 1897–1912. doi:10.1007/s00213-014-3461-1

Hernandez, L., & Hoebel, B. G. (1990). Feeding can enhance dopamine turnover in the prefrontal cortex. *Brain Research Bulletin, 25*(6), 975–979. doi:10.1016/0361-9230(90)90197-8.

Hodgkins, C., Frost-Pineda, K., & Gold, M. S. (2007). Weight gain during substance abuse treatment: The dual problem of addiction and overeating in an adolescent population. *Journal of Addictive Diseases, 26*(Suppl 1), 41–50. doi:10.1300/J069v26S01_05

Hoebel, B. G. (1985). Brain neurotransmitters in food and drug reward. *American Journal of Clinical Nutrition, 42*(Suppl 5), 1133–1150.

Holderness, C. C., Brooks-Gunn, J., & Warren, M. P. (1994). Co-morbidity of eating disorders and substance abuse review of the literature. *International Journal of Eating Disorders, 16*(1), 1–34. doi:10.1002/1098-108X(199407)16:1<1::AID-EAT2260160102>3.0.CO;2-T

Hudson, J. I., Weiss, R. D., Pope, H. G., Jr., McElroy, S. K., & Mirin, S. M. (1992). Eating disorders in hospitalized substance abusers. *American Journal of Drug and Alcohol Abuse, 18*(1), 75–85. doi:10.3109/00952999209001613

Jordan, J., Joyce, P. R., Carter, F. A., Horn, J., McIntosh, V. V., Luty, S. E., McKenzie, J. M., Mulder, R. T., & Bulik, C. M. (2003). Anxiety and psychoactive substance use disorder comorbidity in anorexia nervosa or depression. *International Journal of Eating Disorders, 34*(2), 211–219. doi:10.1002/eat.10177

Kalivas, P. W., & Volkow, N. D. (2005). The neural basis of addiction: A pathology of motivation and choice. *American Journal of Psychiatry, 162*(8), 1403–1413. doi:10.1176/appi.ajp.162.8.1403

Karlsson, H. K., Tuominen, L., Tuulari, J. J., Hirvonen, J., Parkkola, R., Helin, S., Salminen, P., Nuutila, P., & Nummenmaa, L. (2015). Obesity is associated with decreased μ-opioid but unaltered dopamine D2 receptor availability in the brain. *Journal of Neuroscience, 35*(9), 3959–3965. doi:10.1523/JNEUROSCI.4744-14.2015

Kelley, A. E., Bakshi, V. P., Haber, S. N., Steininger, T. L., Will, M. J., & Zhang, M. (2002). Opioid modulation of taste hedonics within the ventral striatum. *Physiology & Behavior, 76*(3), 365–377. doi:10.1016/S0031-9384(02)00751-5

Kendler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1995). The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry, 52*(5), 374–383. doi:10.1001/archpsyc.1995.03950170048007

Koob, G. F., & Le Moal, M. (2005). Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. *Nature Neuroscience, 8*(11), 1442–1444. doi:10.1038/nn1105-1442

Laricchiuta, D., Musella, A., Rossi, S., & Centonze, D. (2014). Behavioral and electrophysiological effects of endocannabinoid and dopaminergic systems on salient stimuli. *Frontiers in Behavioral Neuroscience, 8*, 183. doi:10.3389/fnbeh.2014.00183

Le Magnen, J. (1988). Control of eating behaviour. *Baillière s Clinical Gastroenterology, 2*(1), 169–182. doi:10.1016/0950-3528(88)90026-7

Li, Y., Zuo, Y., Yu, P., Ping, X., & Cui, C. (2015). Role of basolateral amygdala dopamine D2 receptors in impulsive choice in acute cocaine-treated rats. *Behavioural Brain Research, 287*, 187–195. doi:10.1016/j.bbr.2015.03.039

Liu, Y. Y., Liu, T. Y., Qu, W. M., Hong, Z. Y., Urade, Y., & Huang, Z. L. (2012). Dopamine is involved in food-anticipatory activity in mice. *Journal of Biological Rhythms, 27*(5), 398–409. doi:10.1177/0748730412455913

Mann, A. P., Accurso, E. C., Stiles-Shields, C., Capra, L., Labuschagne, Z., Karnik, N. S., & Le Grange, D. (2014). Factors associated with substance use in adolescents with eating disorders. *Journal of Adolescent Health, 55*(2), 182–187. doi:10.1016/j.jadohealth.2014.01.015

McCutcheon, J. E. (2015). The role of dopamine in the pursuit of nutritional value. *Physiology & Behavior, 152*(Pt. B), 408–415. doi:10.1016/j.physbeh.2015.05.003

Michaelides, M., Thanos, P. K., Volkow, N. D., & Wang, G. J. (2012). Dopamine-related frontostriatal abnormalities in obesity and binge-eating disorder: Emerging evidence for developmental psychopathology. *International Review of Psychiatry, 24*(3), 211–218. doi:10.3109/09540261.2012.679918

Mogenson, G. J., & Yang, C. R. (1991). The contribution of basal forebrain to limbic-motor integration and the mediation of motivation to action. *Advances in Experimental Medicine and Biology, 295,* 267–290. doi:10.1007/978-1-4757-0145-6

Murray, S. M., Tulloch, A. J., Chen, E. Y., & Avena, N. M. (2015). Insights revealed by rodent models of sugar binge eating. *CNS Spectrums, 20*(6), 530–536. doi:10.1017/S1092852915000656

Navarro, G., Quiroz, C., Moreno-Delgado, D., Sierakowiak, A., McDowell, K., Moreno, E., Rea, W., Cai, N. S., Aguinaga, D., Howell, L. A., Hausch, F., Cortés, A., Mallol, J., Casadó, V., Lluís, C., Canela, E. I., Ferré, S., & McCormick, P. J. (2015). Orexin-corticotropin-releasing factor receptor heteromers in the ventral tegmental area as targets for cocaine. *Journal of Neuroscience, 35*(17), 6639–6653. doi:10.1523/JNEUROSCI.4364-14.2015

Pach, D., Radomska, M., Groszek, B., Hydzik, P., Gilis-Januszewska, A., & Pach, J. (2014). Abnormal glucose metabolism in men with alcohol withdrawal syndrome. *Przeglad Lekarski, 71*(9), 469–474.

Prentice, A. M., Hennig, B. J., & Fulford, A. J. (2008). Evolutionary origins of the obesity epidemic: Natural selection of thrifty genes or genetic drift following predation release? *International Journal of Obesity (London), 32*(11), 1607–1610. doi:10.1038/ijo.2008.147

Schoffelmeer, A. N., Wardeh, G., & Vanderschuren, L. J. (2001). Morphine acutely and persistently attenuates nonvesicular GABA release in rat nucleus accumbens. *Synapse, 42*(2), 87–94. doi:10.1002/syn.1104

Schulte, E. M., Avena, N. M., & Gearhardt, A. N. (2015). Which foods may be addictive? The roles of processing, fat content, and glycemic load. *PLoS One, 10*(2), e0117959. doi:10.1371/journal.pone.0117959

Simpson, N., Maffei, A., Freeby, M., Burroughs, S., Freyberg, Z., Javitch, J., Leibel, R. L., & Harris, P. E. (2012). Dopamine-mediated autocrine inhibitory circuit regulating human insulin secretion in vitro. *Molecular Endocrinology, 26*(10), 1757–1772. doi:10.1210/me.2012-1101

Spangler, R., Wittkowski, K. M., Goddard, N. L., Avena, N. M., Hoebel, B. G., & Leibowitz, S. F. (2004). Opiate-like effects of sugar on gene expression in reward areas of the rat brain. *Molecular Brain Research, 124*(2), 134–142. doi:10.1016/j.molbrainres.2004.02.013

Speakman, J. R. (2006). Thrifty genes for obesity and the metabolic syndrome – Time to call off the search? *Diabetes & Vascular Disease Research, 3*(1), 7–11. doi:10.3132/dvdr.2006.010

Stein, L., & Belluzzi, J. D. (1979). Brain endorphins: Possible role in reward and memory formation. *Federation Proceedings, 38*(11), 2468–2472.

Stice, E., & Yokum, S. (2014). Brain reward region responsivity of adolescents with and without parental substance use disorders. *Psychology of Addictive Behaviors, 28*(3), 805–815. doi:10.1037/a0034460

Stice, E., Yokum, S., Blum, K., & Bohon, C. (2010). Weight gain is associated with reduced striatal response to palatable food. *Journal of Neuroscience, 30*(39), 13105–13109. doi:10.1523/JNEUROSCI.2105-10.2010

Tomasi, D., Wang, G. J., Wang, R., Caparelli, E. C., Logan, J., & Volkow, N. D. (2015). Overlapping patterns of brain activation to food and cocaine cues in cocaine abusers: Association to striatal D2/D3 receptors. *Human Brain Mapping, 36*(1), 120–136. doi:10.1002/hbm.22617

Volkow, N. D., & Baler, R. D. (2015). NOW vs LATER brain circuits: Implications for obesity and addiction. *Trends in Neuroscience, 38*(6), 345–352. doi:10.1016/j.tins.2015.04.002

Volkow, N. D., & Wise, R. A. (2005). How can drug addiction help us understand obesity? *Nature Neuroscience, 8*(5), 555–560. doi:10.1038/nn1452

Wise, R. A., Fotuhi, M., & Colle, L. M. (1989). Facilitation of feeding by nucleus accumbens amphetamine injections: Latency and speed measures. *Pharmacology Biochemistry and Behavior, 32*(3), 769–772. doi:10.1016/0091-3057(89)90031-2

Wright, K. N., Hollis, F., Duclot, F., Dossat, A. M., Strong, C. E., Francis, T. C., Mercer, R., Feng, J., Dietz, D. M., Lobo, M. K., Nestler, E. J., & Kabbaj, M. (2015). Methyl supplementation attenuates cocaine-seeking behaviors and cocaine-induced c-Fos activation in a DNA methylation-dependent manner. *Journal of Neuroscience, 35*(23), 8948–8958. doi:10.1523/JNEUROSCI.5227-14.2015

Yokum, S., Gearhardt, A. N., Harris, J. L., Brownell, K. D., & Stice, E. (2014). Individual differences in striatum activity to food commercials predict weight gain in adolescents. *Obesity (Silver Spring), 22*(12), 2544–2551. doi:10.1002/oby.20882

Ziauddeen, H., & Fletcher, P. C. (2013). Is food addiction a valid and useful concept? *Obesity Reviews, 14*(1), 19–28. doi:10.1111/obr.2013.14.issue-1