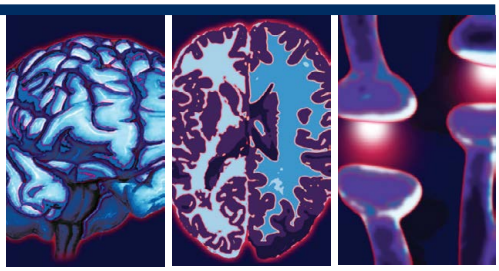
Mini Review



The Problem of Eating Disorders and Comorbid Psychostimulants Abuse: A Mini Review

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ABSTRACT

Comorbidity between substance use disorders (SUD) and eating disorders (ED) is extremely frequent in clinical practice, probably because they share similar psychopathological and neurophysiologic pathway. In particular, even if the amphetamine and other psychostimulants use and abuse may be relatively common among patients affected with ED, the problem of abuse is often unrecognized and the current knowledge of this phenomenon is relatively low in the existing literature. Therefore, the aim of this mini-review was to provide a brief update on this topic. The results of this review pointed out that ED in comorbidity with psychostimulants abuse showed worst prognosis compared to ED alone and no definitive and well-established treatment in comorbid ED–SUD is so far available. Stimulants use and misuse seem to be preferred in anorexia with purging behavior or binge eating disorder. Thus, everyone who is managing patients with ED should always investigate a possible psychostimulant use or abuse in such subjects in order to formulate a correct and clear diagnosis and provide tailored "dual-diagnosis" treatments.

Keywords

Psychostimulants, Eating disorders, Substance use disorders, Anorexia, Amphetamines, Bulimia, Binge

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List of Abbreviations

ED: Eating Disorders; BN Bulimia Nervosa; AN: Anorexia Nervosa; SUD: Substance Use Disorders; MDMA: 3,4-Methylenedioxy methamphetamine; ADHD: Attention Deficit Hyperactivity Disorder; VMAT-2: Vesicular Monoamine Transporter-2; DAT: Dopamine Transporter; SU: Substance Users; NAC: Nucleus Accumbens; DA: dopamine; AA: Ach Acetylcholine; NA: Noradrenaline; 5HT: Serotonin; VTA: Ventral Tegmental Area; mPFC: Medial Prefrontal Cortex; MSN: Medium Spiny Neurons; 5HIAA: 5-Hydroxyindoleacetic Acid; CRF: Cephalorachidian Fluid; PNS: Peripheral Nervous System; AVS: Anterior Ventral Striatum; CPP: Conditioned Place Preference; MA: Methamphetamine; PSLW: Postsurgical Loss Weight; OC: Obsessive-Compulsive; DAT: Dopamine Transporter; LSD: Lysergic Acid; PCP: Phencyclidine; R: Restrictive; B/P: Binge Purging; BED: Binge Eating Disorder; ASI: Addiction Severity Index

Introduction

Substance Use Disorders (SUD) and Eating Disorders (ED) are demonstrated to be often in comorbidity [1] Up to 50% of individuals with ED abused alcohol or illegal drugs, a rate five times higher than the general population [2] and up to 35% of individuals who abused or were dependent on alcohol or other drugs have also had ED, a rate 11 times greater than the general population. [3] The substances most frequently abused by persons with ED or with sub-clinical symptoms may include alcohol, laxatives, emetics, diuretics, amphetamines, heroin, and cocaine [4,5]. ED are frequently reported among patients with SUD [6-12], particularly in adolescents [13,14]. However, a comorbid SUD-ED represented an important burden on clinical outcomes, and validated management is so far available. An addictive personality shows a vulnerability to SUD and a range of additive behavioral patterns [15-20]. Wolfe exposed several theories regarding a common etiology as well as a consequential etiology between both disorders [21].

A common etiology supports a shared base (i.e. vulnerability [22-24], neurobiology [25-27] and environment [28-31]) whilst most consequential theories affirm that ED occur before SUD [32] (i.e., self-medication [33-35] and food deprivation leading to an addiction [36,37]). However, none of these theories seem to be sufficiently supported by the literature [38-40]. According to the National Center on Addiction and Substance, about 50% of ED women are also affected by a SUD, and 35% of patients with SUD own an ED [41] Several studies reported a specific preference towards psychostimulants among ED patients [42-45]. Psychostimulants are psychoactive substances able to enhance the activity of the Nervous System (SN), by specifically acting on dopaminergic (DA) system, a common target in the ED.

The present narrative mini-review aimed to provide an updated review concerning the relationship between ED and psychostimulants abuse (particularly, amphetamine, khat, and cocaine) in animal models and clinical settings, to better elicit the clinical as well as therapeutic implications of a comorbid psychostimulants abuse and ED. This updated review may be useful as the existing evidences in the current literature are relatively sparse and few and, to date; only out-of-date reviews have investigated this topic. Moreover, even if narrative, we tried to use the methods of a systematic review to strengthen the evidences.

Methods

The following keywords have been used on Pubmed/Medline on October 2016 eating disord* [title/abstract] AND substance abus* [title/abstract]" with 5 years of time limitation; "[bulimia] AND [amphetamine]", "[Anorexia nervosa] AND [psychostimulant]", "anorexia nervosa AND cocaine", "[eating disorders] AND [substance abuse] AND psychostimulant"; "bulimia [abstract/Title] AND cocaine [abstract/title]"; "bulimia [title/abstract] AND amphetamine [title/abstract]"; "Eating disord* [title/abstract] AND substance abus* [title/abstract]". Hand-searched papers were collected. Inclusion criteria comprise comorbidity between SUD and ED. Both human and animal studies have been included. Clinical and nonclinical samples have been here considered, both adults and adolescents. Axis II and Axis I were included. Comorbid patient's samples were preferred, but also only ED and SUD clinical samples have been here considered.

Neurobiology and Psychopharmacology of Psychostimulants in Ed

It has been reported that about 50%-80% of the risk of developing Anorexia Nervosa (AN) and

Bulimia Nervosa (BN) is determined by genetic burden [46,47]. Avena and al [48] concluded that there are specific alterations involving DA, serotoninergic (5HT), acetylcholine (Ach) and opioid system in binge animal models. Umber et al. [49] explored the neurobiology of BN, by underlining its similarities with SUD.

According to Klenowski et al., acute and chronic consume of sucrose may cause a specific pattern of neural modeling in NAC shell and MSN [50]. An upregulation of μ- opioid receptors is present during abstinence from purgers as well as non-purgers bulimic patients have low β- endorphin levels [51,52]. Moreover, 5HIAA levels are low in CRF of BN subjects [53,54].

Insulin receptors are demonstrated to be present in VTA promoting DAT activity [55-57] with a decreased sensitivity to DA similar to opiate abusers [58]. Moreover, purging behavior may lead to insulin decrease. [59] Repeated amphetamine administration also increases 5-HT1AY binding affinity in rodents [60]. Also, 5HT facilitates DA release in NAc and striatum. [61,62]

Amphetamine, Khat, and cocaine are psychostimulants enhancing NAC activity via stimulation of monoamine firing inhibiting DA, NA, 5HT reuptake by blocking the reuptake of DA from the synaptic fissure; they enhance the neuronal firing. [63] It has a powerful stimulant effect on SNC by provoking motor hyperactivity, loquacity, sense of grandiosity, anxiety, delusions, hostility and psychomotor agitation and "punding" a stereotyped and purposeless complex motor behavior [64]. Libido is increased, while appetite and sleep needs are inhibited [65-68]. Contextually, bronchodilation, pulmonary vasoconstriction, an increased heart rate, vasodilation in skeletal muscles and hyperglycemia may also be present while gastrointestinal activity is inhibited. [69,70]

The substrates are the vesicular monoamine transporter-2 (VMAT-2) and the dopamine transporter (DAT) [71]. The VMAT2 is a critical mediator of dopamine dynamics in the neuronal terminal and exchanges DA from neuronal cytosol to synaptic vesicles against the gradient. [72] It has an H+ ATPase pump that creates a proton gradient across the vesicular membrane with an inner vesicular Ph=5.5, driving cytosolic monoamines (DA, NA, 5-HT, histamine) into small synaptic and dense core vesicles. Amphetamine alkalizes vesicles by blocking VMAT [73]. By preventing the accumulation of dopamine in the neuronal cytosol, VMAT2 also counters intracellular dopamine toxicity [74]. Increasing evidence suggests that amphetamine-related psychostimulants may exert their effects increasing the non-exocytotic release of DA in several brain areas through direct interaction with VMAT-2 with a neuronal nitric oxide synthase-dependent oxidation of VMAT-2 determining a long-term decrease in VMAT-2 protein and function [75]. Individuals with cocaine-induced mood disorders showed a greater loss of VMAT-2 that may reflect an impairment of striatal DA fibers of human cocaine users, which could play a role in causing disordered mood and motivational processes in more severely dependent patients. Therefore, the VMAT2 could be a valuable marker in the clinical study of cocaine neurotoxicity [76]. Chronic use of methamphetamine (MA) has been associated with cardiovascular problems [77], immune system depression, and also to malnourishment [78,79], all probably mediated by impairment in VMAT-2 system.

Kaye et al. [80] found imaging data confirming that BN exposes to SUD while AN is protective [81]. Probably BN and SUD share D_2 receptors abnormalities. AN has an enhanced inhibitory function over consummatory drive due to dorsal executive hyperactivity while BN shows a decreased dorsal activity [82].

Some recent studies [83,84] showed that diet might modulate the impulsivity. Rats maintained in high-fat diet exert increased motor impulsivity and a higher score in premature responding, by demonstrating that a chronic diet with high fatty acid may reduce their inhibitory ability. Puhl et al. [85] demonstrated that BED rat models consume more quantity and more frequently cocaine. According to these authors, binging behavior may enhance the risk of addiction [85]. Davis et al. [86] investigated the influence of diet in modulating psychostimulant reward. This study reported that chronic consumption of a high-fat diet might decrease the amplitude of amphetamine reward. Findings demonstrated that animals consuming a high-fat diet, exhibit a decreased dopamine turnover in the mesolimbic system, a lower appetite for amphetamine and sucrose [86]. Liu et al. [87] demonstrated that food restriction might enhance the drug reward magnitude. Zheng et al. [88] studied the modulation of the rewarding effects of d-psychostimulants, by demonstrating a persistent Conditional Place Preference (CPP) in rats.

Studies Focusing On Epidemiological Data about the Comorbidity Ed-Sud

A study [89] recruiting 248 subjects who underwent bariatric surgery intervention, reported that low distress tolerance more likely leads to emotional eating, SUD an unsuccessful weight maintenance.

Killeen et al. [90] investigated 122 women from four substance abuse treatment sites who participated in a multi-site clinical trial through the National Institute of Drug Abuse Clinical Trials Network (NIDA CTN) in order to evaluate the relationships between ED, SUD and PTSD. A correlation between addictive symptoms severity (measured with the Addiction Severity Index, ASI), ED and use of opiates was more likely present in patients with comorbid SUD and PTSD. These findings suggested a strong relationship between addiction severity, use of certain drugs of abuse and eating disorder symptoms, particularly those involving weight and shape concerns in women with comorbid PTSD and SUD [91]. King et al. [92] evaluated 2348 subjects who underwent Roux-en-Y gastric bypass and laparoscopic adjustable gastric band. They found that, in adults with severe obesity, undergoing Roux-en-Y gastric bypass was associated with increased risk of incident alcohol abuse, illicit drug use (including cocaine), and SUD treatment. Therefore, patients considering bariatric surgery should be informed of risk factors for postsurgery SUD. Additionally, alcohol and SUD evaluation, and referral for treatment should be combined in both pre- and postoperative care. Brewerton et al. [93] examined age of first binge and its clinical correlates using data extracted from the National Women's Study (n=3,006) and participants who endorsed ever binge eating (n=707) were divided into two groups: (1) child-adolescent onset (CO) - age of first binge <18 years, and (2) adult onset (AO) - age of first binge ≥ 18 years. They reported that AO binge eating was more than twice as common as CO binge eating in women, but CO binge eating was associated with higher rates of lifetime BN, greater severity of BN, and higher rates of victimization, PTSD, and substance abuse (including cocaine and other psychostimulants).

Czarlinski et al. [94] evaluated 39 women residing in Oxford Houses (a network of over 1,300 non-profit communal-living homes for men and women in recovery for drug and/or alcohol use problems.) located throughout the USA and found that young adult and middle-aged women in recovery from an SUD appear to be at a high risk for developing a BED. Thus, this may serve to demonstrate to clinicians treating these subjects the need to be aware of the risk and occurrence of such eating-related problems. Interestingly, the score of body image self-efficacy gets higher with rehabilitation treatment.

Glasner-Edwards et al. [95] studied 526 methamphetamine dependent adults who participated in the Methamphetamine (MA) Treatment Project, a randomized, controlled trial of psychosocial treatments for MA dependence and found that comorbid BN was observed in more than 2% of MA users, a prevalence rate consistent with U.S. population, but than AN. Moreover, individuals with BN and MA dependence suffered declines in functioning over time in several domains, including psychiatric, family and employment, relative to those without BN.

Stock et al. [96] evaluated 95 female adolescents with ED. Restricting patients took fewer drugs than purging and healthy controls. Purging patients had similar pattern compared to the control group, even though they more likely preferred stimulants, LSD and PCP. In another study [97] has been reported that bulimic adolescent patients took more substances of abuse (amphetamine included) compared to anorexic patients. A sample of parents [98] of twin-born (1323 man and 1384 woman) show that woman with the amphetamine use disorder were more likely to have AN. In a population of adult female twins, both in BED and AN group, stimulants represented the second most prevalent substances of abuse after the cannabis [99]. Root et al. [100] evaluated 1327 SUD female twins in 4 groups (anorexia, bulimia, anorexia-bulimia, binge eating disorder group) and a healthy control group without ED. Psychostimulants, alcohol, diet pills and polyabuse are more significantly assumed by anorexic-bulimic group rather than other groups. The AN-BN purging subtype is more frequently related to stimulant use compared to the anorexic group with restrictive behavior. Moreover, AN subtype comparisons revealed that stimulants were the only illicit substances more frequently reported in the ANBP (anorexia nervosa bingeing – purging type) group compared to the RAN (restrictive anorexia nervosa) group.

Dunn et al. [101] conducted a temporal examination of the associations among

disordered eating behaviors, substance use, and use-related negative consequences in female college students, a population at high risk for developing ED-SUD, and found that associations were more evident for alcohol use than for drug use, with concurrent relations between alcohol use and both vomiting and fasting, and that temporal findings suggested that alcohol use more often preceded disordered eating behaviors than the reverse. However, amongst female college students with ED-SUD, the laxative use was positively correlated with both amphetamine and alcohol use. It is noteworthy that Stock concluded that restrictive behavior might negatively correlate with alcohol, tobacco, and cannabis use. Moreover, strong associations have been reported between the risk for an ED and psychostimulants [97-99]. Interestingly, Corstorphine et al. investigated a sample of 102 individuals who met strict criteria for an eating disorder, and who were interviewed regarding trauma history and comorbid impulsive behaviours [102,103]. They found that a reported history of childhood trauma was associated with a higher number of impulsive behaviours and with the presence of multi-impulsivity. In particular, the childhood sexual abuse was particularly important in ED subjects, and was associated with self-cutting, alcohol abuse, and substance abuse (more often psychostimulants such as amphetamines and cocaine and other substances such as cannabis and ketamine). Therefore, a childhood trauma may predispose individuals to develop both ED and psychostimulants abuse and this should be always investigated in such subjects.

Studies Focusing On Clinical Data about the Comorbidity Ed-Sud

■ Cocaine

Methylphenidate 54 mgr, quetiapine, and lamotrigine were used in a case of BN and cocaine [104]. It has been suggested that both trait and state binge eating may predispose individuals towards cocaine craving [105]. Walfish et al. [106] assessed tha incidence of BN in 100 consecutive adult women entering a residential substance misuse treatment program utilizing DSM-III-R self-report data. Fourteen percent of the clients were diagnosed as having a concomitant eating disorder, seven times the community prevalence rate. Moreover, they reported that cocaine was the first drug abused by BN patients and cocaine addicts had the highest rate of bulimia, while opioid addicts had the lowest. In a sample of 259 cocaine abusers, 32% of subjects showed comorbidity with AN, BN or both AN-BN [107].

In another study, Jean et al. [108] showed that nucleus accumbens (NAC) produced the same protein (CART) both in case of food restriction and both in case of $5HT_4$ receptors psychostimulants stimulation. NAC-5-HTR_4 overexpression upregulated NAC-CART, causing anorexia and hyperactivity.

■ Amphetamine

Fioravanti et al. [109] evaluated 102 ED patients at baseline, after a CBT, at 3 and 6 year follow-up. Regarding cocaine or amphetamine abuse, they reported no significant reduction in Emotional Eating Scale (EES) in a sample of ED patients. A significant decrease of EES total score was observed in AN-B/P and BN patients. The Authors concluded that ED patients with a history of cocaine or amphetamine abuse may represent a sub-population of patients with lasting dysfunctional mood modulatory mechanisms. The use of psychostimulants has been proposed as a therapeutic solution in BN and comorbid ADHD and, recently, a retrospective study described 6 case reports of outpatients with BN who were prescribed a psychostimulant specifically for their bulimia nervosa with significant reductions in the number of binge/purge days per month [110].

Cortese et al. [111] supposed that the impulsivity determined by ADHD may lead to BN. According to some authors [112,113], the lack of inhibitory control and immediate reward seeking predispose subjects affected by ADHD to an ED, particularly BN. Moreover, dopaminergic system disruption, also reported in BN, may lead to lower dopaminergic tone (via D_4 and D_2 receptors) [114]. In general, the 'appetite' for psychostimulants may explain the therapeutic rationale of psychostimulants uses for the treatment of BN. Several studies demonstrated the benefits of psychostimulant use in BN patients [115] and the data are most convincing concerning methylphenidate [116-119].

Curran et al. [120], comparing 73 ecstasy users with five healthy controls, demonstrated that ecstasy users had significantly higher scores on 4 out of 11 EDI (Eating Disorder Inventory) sub-scales: bulimia, impulse dysregulation, social insecurity, and interpersonal distrust. Ecstasy

users more likely reported that ecstasy may aid the weight loss. However, a following study reported that cocaine and amphetamines use represented the first abused substances in ED sample [121].

■ Cathinones

Chronic abuse of synthetic cathinones may have dangerous effects on the central nervous system and may cause acute psychosis, hypomania, paranoid ideation, and ED symptoms, similar to the effects of other better-known amphetamine-type stimulants [122].

Khat may determine a weight loss in 1 month, by reducing the appetite via the increase of DA and NA in the hypothalamus, as well as via the reduction of neuropeptide Y [122].

Moreover, it may increase T4, and T3 levels causing xerostomia [123] and hyperthermia [124,125].

Conclusions

Bulimia sorely occurs in SUD [126-128] and traumatic development [129]. Psychostimulants are preferred for their slimming and euphoriant effect properties [130,131] Correlations between ED and SUD have been found in purging traits and in ANBN. Compulsivity and impulsivity are in part responsible for the higher prevalence of SUD amongst the purging subtype of AN and BN. Despite ED have been traditionally considered 'cultural diseases', recent findings demonstrated the existence of specific biochemical alterations involving NAC and mPFC as well as DA system. In AN, DA system may be altered, and food restriction makes more palatable the cocaine and amphetamine effects. ED and SUD share alterations of the reward system, impulse control but the authors debated the consistency of the relationship between the addiction and the overeating. To date, there are no data concerning the use of novel psychoactive substances (NPS) in ED [132-135].

However, despite the available data, the clinical guidelines are absent. The samples were inadequate and very homogeneous: samples were mainly composed of woman and adolescent or young woman. Probably, difficulties of matching for sex and age and also finding samples without personality disorders comorbidity were consistent. All considered, further studies are needed to further clarify this important and clinically relevant topic.

In conclusion, the link between ED and SUD is often ignored, to the disadvantage of our patients. Recognizing that where there is ED, there's often SUD, and vice-versa, and offering concurrent, multidisciplinary and tailored "dual diagnosis" care, may help some of our severe patients get on the road to recovery sooner and stay there for life.

Conflict of Interest

The authors declare no conflicts of interest.

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