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## Exploring the Nexus of Binge Eating Disorder (BED), New Psychoactive Substances (NPS), and Misuse of Pharmaceuticals: Charting a Path Forward

**Keywords:** semaglutide, glucagon-like peptide-1 (GLP-1) agonists, binge eating disorder (BED), New Psychoactive Substances (NPS), drug misuse, drug abuse, pharmacovigilance, image- and performance- enhancing drugs (IPEDs)

Although a new diagnosis in the Fifth Edition of the Diagnostic and Statistic Manual of Mental Disorders (DSM-5) and the Eleventh Revision of the International Classification of Diseases (ICD-11), together with anorexia nervosa and bulimia nervosa, binge-eating disorder (BED) is an integral component of eating disorders (ED). These serious mental health conditions are generally characterized by abnormal eating behaviors and a distorted body image. In particular, BED is characterized by recurrent episodes of excessive food intake and a feeling of loss of control during these episodes [1]. Comorbidity between substance use disorders (SUD) and BED is highly prevalent in clinical practice, with symptomatology overlap, and likely due to shared psychopathological and neurophysiological pathways [2-3]. Shared traits might involve mechanisms related to the consumption of larger amounts of food/substances than planned, an inability to decrease their use despite concerted efforts, and continued drug use/food bingeing despite persistent negative consequences [3]. Individuals with ED might misuse substances to manage their emotions, control their weight, or improve their perception of their body image. Due to an overlapping pathophysiology, binge-eating behaviours might occur for similar reasons [4]. Moreover, substance use can exacerbate the symptoms and complications associated with BED, making it crucial to address both issues simultaneously in treatment. The development of excessive food consumption and SUD often involves a combination of factors, including *psychological factors*, such as emotional regulation, reward and pleasure, cravings and compulsions; *physiological factors*, such as drug-related neurochemical imbalance, hormonal imbalance involving leptin or ghrelin [4], and genetic predisposition; and *social and environmental factors*.

The use of substances for image enhancement refers to the consumption of certain products to enhance physical appearance or achieve a certain aesthetic or performance ideal. The desire to look good or meet perceived societal standards of beauty and prowess can lead individuals to turn to various substances. Use, misuse and abuse of stimulants, including amphetamine-type substances and cocaine, may be relatively common among patients affected by BED, as they can suppress appetite and increase metabolism, which may lead some individuals to use them as a means to control or reduce weight [2]; however, these clients may also be involved in polysubstance misuse/abuse with molecules such as alcohol, e.g., 'drunkorexia' is characterised by using extreme weight control methods to compensate for planned binge drinking [5]. Moreover, over the last couple of decades, the current drug abuse scenario has seen the emergence of New/Novel/Emerging Psychoactive Substances (NPS) [6-7], also known as "research chemicals", "smart/designer drugs" or "legal highs"; these molecules refer to a wide range of substances created to mimic the effects of illegal drugs, like marijuana, cocaine, or amphetamines, which are being designed to specifically bypass both current and evolving legal regulations whilst slightly altering the molecules' chemical composition. Individuals, especially young adults (14 to 25 years old) may ingest stimulating NPS for recreational purposes, e.g., seeking euphoria, altered perception, and increased energy, or enhancing academic performance. Among NPS, synthetic cathinones, a class of amphetamine analogs, are typically associated with effects (e.g., increased alertness, increased energy, and euphoria) similar to a wide range of other stimulants: MDMA/ecstasy; other amphetamine-type stimulants; and/or cocaine. Their trajectory of

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misuse intake may not only lead to acute psychosis, hypomania, paranoid ideation, but also disordered eating symptoms. In fact, due to their stimulant nature, they might also suppress appetite. This occurs because of the increased dopamine and norepinephrine levels in the hypothalamus, as well as by decreasing neuropeptide Y, resulting in reduced appetite and hence weight [8]. Conversely, a range of prescribed/over-the-counter (OTC) pharmaceuticals have recently been misused, causing significant public health concerns in many parts of the world [8]. Inappropriate or non-medical use of these pharmaceuticals may be associated with: intake of large dosages; long-term ingestion; use for purposes other than those intended and/or without a prescription; and/or combining them with other substances [9-11]. Factors that have contributed to the development of prescription drug misuse include insufficient regulation and monitoring of prescription drug prescribing, inadequate patient education about the risks and appropriate use of medications, and the availability of prescription drugs through illicit channels, such as online pharmacies and diversion. Commonly misused prescription drugs include not only opioids (such as oxycodone and hydrocodone), sedatives and tranquilizers (such as benzodiazepines), but also stimulants (such as amphetamines), which are particularly attractive to ED vulnerable subjects [10-12]. In this context, the occurrence of drug abuse and misuse, particularly for the purpose of weight loss, has been extensively documented in the literature; individuals having greater body image concerns had higher ED symptomatology and appeared more likely to use illicit drugs, and laxatives, diet pills and diuretics [13]. The pharmacological group of Image- and Performance- Enhancing Drugs (IPEDs) includes a wide range of substances, from various pharmacological categories, which are misused to enhance physical performance or alter one's appearance, similar to the misuse of slimming products. Many different molecules have been abused as weight loss agents, particularly those classified as sympathomimetic agents such as amphetamine/methamphetamine drugs, ecstasy, and cocaine [14]. Other extreme methods of slimming practices have involved the use of  $\beta$ -2 agonists like clenbuterol [9], and diuretics [10-11]. These substances are frequently misused and abused by individuals who are non-obese and who may suffer from body dysmorphia, with the intention of enhancing their appearance [14] and achieving significant weight loss.

Recently, there has been significant media coverage and discussion regarding the potential misuse of semaglutide and other GLP-1 (glucagon-like peptide-1) analogues; these substances mimic the action of the endogenous hormone GLP-1, which is released in response to food intake. Due to their roles in promoting insulin secretion, inhibiting glucagon secretion, and delaying gastric emptying, these medications are commonly prescribed for specific medical conditions such as type 2 diabetes and obesity. Conversely, central effects on the brain's appetite centers affecting appetite regulation and promoting feelings of fullness could be driving the reported levels of potential misuse in healthy non-obese individuals due to unrealistic ideals of physical attractiveness [15]. Several studies have been conducted to evaluate the potential therapeutic effects of GLP-1 agonists on BED and other EDs, showing, not only benefits in terms of weight loss and improvements in metabolic parameters, but also promising results by decreasing the frequency and severity of binge episodes, ultimately influencing brain regions involved in reward and appetite regulation [16]. Furthermore, the acquisition of medications from unauthorized or rogue websites might facilitate this phenomenon. From this perspective, semaglutide holds the potential to be misused as both a weight loss drug and an IPED. In March 2023, the National Agency for the Safety of Medicines and Health Products (ANSM) announced an increased level of surveillance for semaglutide due to the concerns surrounding its misuse. ANSM had been receiving alerts since September 2022, including reports of forged prescriptions and off-label use of semaglutide for weight loss in individuals without diabetes [18]. Additionally, there have been videos on social media promoting semaglutide as a weight-loss treatment [17]. A recent pharmacovigilance study [19] compared the signals of misuse and abuse associated with semaglutide and other GLP-1 receptor agonists, such as albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, tirzepatide, as well as the phentermine-topiramate combination. The study analyzed the Food and Drug Administration's FDA Adverse Events Reporting System (FAERS) dataset from January 2018 to December 2022. During

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this period, a total of 31,542 Adverse Event Reports (AERs) related to these selected molecules were submitted to FAERS, with dulaglutide accounting for the majority (n = 11,858; 37.6%) and semaglutide following closely (n = 8,249; 26.1%). When comparing semaglutide with the other molecules, the respective Proportional Reporting Ratio (PRR) values for the AERs related to "drug abuse," "drug withdrawal syndrome," "prescription drug used without a prescription," and "intentional product use issue" were found to be 4.05, 4.05, 3.60, and 1.80 (all p < 0.01), indicating a higher association of these adverse events with semaglutide compared to the other analyzed molecules.

Effective pharmacological treatments in psychiatric disorders, especially complex and challenging conditions including EDs, are needed. With an addiction perspective to BED treatment, interventions should focus on mitigating the effects of food triggering the reward system in a manner that makes it more challenging for vulnerable people to moderate their intake. Psychotherapy and behavioural interventions play critical roles in the management of these conditions; in addition, although limited by a warning for abuse and dependence, lisdexamfetamine is the only medication currently approved by the US Food and Drug Administration for BED [3]. Self-medication is a worldwide phenomenon that highlights the active role individuals play in managing their own healthcare. It refers to the act of choosing and using substances to treat self-diagnosed symptoms and ailments without consulting a healthcare professional [20]. However, self-medication comes with inherent risks, including the potential for adverse effects and misuse. Thus, monitoring the possibility of misuse of pharmaceuticals, e.g., semaglutide, and the use of NPS is important for several reasons. Specifically, these include both *safety*, related to adverse effects and potential harm to individuals; and *public health concerns*. With regard to the latter, identifying emerging drug trends and patterns of use can guide regulatory decisions, public health interventions, and educational campaigns to address and prevent misuse. Moreover, assessing the effectiveness of existing regulations is needed to make the necessary adjustments to ensure patient safety and medications' appropriate use. To monitor drug trends, including NPS and 'pharming' issues, online resources have proven to be effective; to this respect; internet fora and social media platforms, such as Reddit, Twitter, and YouTube, are valuable sources for analyzing both drug trends and harm reduction practices [21-22].

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FS was a member of the UK Advisory Council on the Misuse of Drugs (ACMD; 2011–2019) and is currently a member of the (European Medicines Agency (EMA) Advisory Board (Psychiatry).

JMC is a member of the ACMD's Novel Psychoactive Substances and Technical Committees.

The views and opinions expressed here are solely those of the authors; they do not necessarily reflect the views of their employers, the ACMD or EMA.

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#### Expert opinion (200-500 words)

- Comorbidity between substance use disorders (SUD) and eating disorders (ED) is indeed highly prevalent in clinical practice, and this can be attributed to shared psychopathological and neurophysiological pathways. While substance abuse may not directly cause eating disorders, individuals with ED often turn to substance misuse as a coping mechanism for dealing with their emotions, managing weight, or enhancing their body image. However, substance use can further exacerbate the symptoms and complications associated with ED.
- In the current landscape of drug abuse, there has been a rise in the use of New Psychoactive Substances (NPS), commonly referred to as "research chemicals", "smart/designer drugs" or "legal highs." Some individuals use NPS recreationally, seeking experiences of euphoria, altered perceptions, or increased energy. Of particular concern are synthetic cathinones, which are a type of NPS that bear resemblance to the effects of other well-known amphetamine-type stimulants. Chronic abuse of synthetic cathinones can have detrimental effects on the central nervous system, leading to conditions such as acute psychosis, hypomania, paranoid ideation, and even disordered eating's symptoms. These substances can induce weight loss by suppressing appetite through increased dopamine and norepinephrine levels in the hypothalamus, while reducing neuropeptide Y levels. In parallel to the misuse of NPS, the misuse of pharmaceuticals has also emerged as a significant public health issue worldwide. This refers to the inappropriate or non-medical use of prescription or over-the-counter medications in ways not intended by medical professionals. Examples of pharmaceutical misuse include taking higher doses, prolonging usage beyond recommended durations, using medications without a prescription, or combining them with other substances.
- Semaglutide is a medication prescribed for certain medical conditions such as type 2 diabetes and obesity. Recently media are increasingly reporting cases when semaglutide was used by Hollywood stars without medical supervision or for the sole purpose of weight loss, which may be considered a misuse issue, leading to adverse effects, risks to health, and may not produce the desired weight loss results.
- Monitoring and addressing the misuse of both NPS and pharmaceuticals are crucial for public health and safety. Investigations can provide valuable insights into the pharmacodynamics of these medications, including their interactions with various

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receptors. By better understanding their mechanisms of action, we can identify any potential risks or adverse effects associated with their misuse or abuse. One important aspect to investigate is the availability of GLP-1 receptor agonists from rogue websites. Unauthorized online sources can pose a significant risk as they may provide counterfeit or substandard medications, increasing the potential for harm. Monitoring the online market for these drugs and identifying sources that engage in illicit activities can help prevent their misuse and protect public health. Epidemiological studies play a crucial role in understanding the characteristics of potential misuse and abuse of GLP-1 receptor agonists. These studies can be designed to investigate patterns, risk factors, and potential consequences associated with their misuse in both the general population and vulnerable populations. By identifying specific demographics or populations at higher risk, targeted interventions and prevention strategies can be developed to address their needs and ensure safe use of these medications. In addition to investigating the misuse and abuse of NPS and pharmaceuticals, it is essential to raise awareness among healthcare professionals, patients, and the general public about their potential risks and inappropriate use. Providing education and resources can help promote responsible prescribing and usage practices, ultimately reducing the likelihood of misuse and abuse.

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