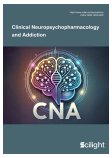
Scilight

Clinical Neuropsychopharmacology and Addiction

https://www.sciltp.com/journals/cna



Case Report

Semaglutide for Craving Reduction in a Cocaine Dependent Patient: A Case Report

Alessandro Matteo Sileoni [1,*], Elena Teresa Turco [1], Francesco Semeraro [2], Clara Cavallotto [2], Alessio Mosca [2], Stefania Chiappini [1] and Giovanni Martinotti [2]

[1] School of Medicine, UniCamillus International Medical School University, Via di S. Alessandro 8, 00131 Rome, Italy
[2] Department of Neuroscience, Imaging, Clinical Science, University G.d'Annunzio of Chieti-Pescara, 66100 Chieti, Italy
* Correspondence: alessandromatteo.sileoni@gmail.com

How To Cite: Sileoni, A.M.; Turco, E.T.; Semeraro, F.; et al. Semaglutide for Craving Reduction in a Cocaine Dependent Patient: A Case Report. *Clinical Neuropsychopharmacology and Addiction* **2025**, *1*(1), 3.

Received: 14 May 2025
Revised: 28 May 2025
Accepted: 5 June 2025
Published: 9 June 2025

Abstract: Semaglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist approved for type 2 diabetes and obesity, has demonstrated the ability to reduce drug-seeking behaviors in animal models. We report the case of a 33-year-old woman with severe Cocaine Use Disorder (CUD) and comorbid borderline personality disorder, who also presented with recurrent binge-eating episodes. While continuing the psychopharmacological interventions, an off-label oral semaglutide was initiated (starting and maintaining dose 3 mg daily). Baseline assessments included the Cocaine Craving Questionnaire (CCQ), Barratt Impulsiveness Scale (BIS-11), Eating Disorder Inventory (EDI), Hamilton Depression Rating Scale (HDRS), and Hamilton Anxiety Rating Scale (HARS). At one and three months, repeat evaluations revealed a pronounced decline in cocaine craving, with CCQ subscale scores (Reward, Relief, Obsessive) falling by more than 75%. Impulsivity measured by BIS-11 decreased from 80 at baseline to 33 at three months. Binge-eating behaviors remitted completely, as evidenced by normalization of EDI scores. Depressive symptoms improved modestly (HDRS from 9 to 7), and anxiety symptoms decreased substantially (HARS from 11 to 4). The patient tolerated semaglutide well, reporting no adverse effects. This single-case observation suggests that GLP-1 receptor agonism as add-on to a psychopharmacological treatment may alleviate core features of substance use disorders—craving, impulsivity, and associated affective dysregulation—while also addressing metabolic comorbidities. Potential mechanisms include modulation of mesolimbic dopamine pathways and enhancement of satiety signals, which together may reduce the reinforcing properties of cocaine.

Keywords: Semaglutide; GLP-1 receptor agonist; cocaine use disorder (CUD); metabolic comorbidity; reward pathway; substance use disorder

1. Introduction

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist originally developed for the treatment of type 2 diabetes and obesity [1]. It mimics the gut-derived incretin hormone GLP-1 by enhancing insulin secretion, inhibiting glucagon, slowing gastric emptying, and promoting satiety. GLP-1 is an incretin hormone and satiation factor that is released predominantly from L cells of the small intestine and neurons in the nucleus tractus solitarius (NTS) of the caudal brainstem which modulates hunger and food cravings [2]. Semaglutide has been approved by the European Medicines Agency (EMA) for obese and diabetic type 2 patients who cannot take metformin, available as a solution for injection in prefilled pens and can only be obtained with a prescription. It has to be injected under the skin of the belly, the thigh or the upper arm. The starting dose is 0.25 mg once a week, if needed

the dose has a maximum threshold of 1 mg once a week [3]. GLP-1 receptors are widely expressed in brain regions associated with reward processing, such as the nucleus accumbens (NAc) and the ventral tegmental area (VTA), suggesting a possible neuromodulatory effect on substance use and compulsive behaviors [4–6]. Indeed, semaglutide has recently gained attention for its potential role in modulating craving and addictive behaviors [7,8]. Preclinical studies have shown that GLP-1 receptor agonists can reduce drug-seeking behaviors in animal models of addiction [9], including cocaine, alcohol, and opioids, by altering dopaminergic signaling in the mesolimbic pathway [10]. Despite a GLP-1 agonists' misuse has been reported [4], clinical data on semaglutide's effect on craving are still emerging, with early studies suggesting potential benefits in reducing food cravings and appetite, which may extend to substance-related cravings.

In this manuscript we aim to present one clinical case involving a patient with substance use disorder who benefitted from semaglutide, originally prescribed for metabolic indications. The objective is to assess whether semaglutide contributes to improvements in substance use disorder, specifically by reducing craving and supporting sustained abstinence from substances.

2. Materials and Methods

The patient was selected among those hospitalized in the psychiatric clinical center Villa Maria Pia, which is a territorial intensive psychiatric treatment facility located in Rome (Italy) and dedicated to patients in a post-acute condition as well as a socio-rehabilitative facility with high socio-healthcare assistance intensity. Our patient was admitted in the clinic as a routine adult patient actively using cocaine and exhibiting a diagnosis of insulin resistance and diabetes mellitus, requiring treatment with subcutaneous 0.25 mg semaglutide. At the admission she was evaluated by both psychiatrists and clinical psychologists who conducted psychological assessments at baseline and followed up at 1 and 3 months using standardized instruments such as the Hamilton Depression Rating Scale (HDRS), the Hamilton Anxiety Rating Scale (HARS), the Cocaine Craving Questionnaire (CCQ), the Barratt Impulsiveness Scale (BIS11), and the Eating Disorder Inventory (EDI). Metabolic parameters, including abdominal circumference, blood pressure, fasting blood glucose, triglyceride levels, and HDL cholesterol, were monitored at the same time points as the psychodiagnostic assessments.

3. Case Report

Our patient is a 33-year-old female diagnosed with Cocaine Use Disorder (CUD) and Borderline Personality Disorder (BPD). She had her first psychiatric symptoms at the age of 20 while abusing cocaine (daily intake of 5 to 6 g), with self-harm thoughts and behaviors, and a binge eating disorder. She has been prescribed several anti-depressive treatments as well as a psychotherapeutic program without reaching any significant therapeutic benefit, leading the patient to interrupt both treatments relapsing into abuse of cocaine. Over the years, despite several periods of hospitalization and several rehabilitation treatments for her addiction, there was not any significant improvement. In July 2020, after the consumption of crack cocaine, the patient attempted suicide by jumping out of a window, resulting in multiple physical traumas (fractures of the ribs, sternum, vertebrae, hips, and wrist as well as internal organ injuries). Following this accident, the patient was admitted to a hospital, where she received emergency care. After a long hospitalization, and despite the psychopharmacological treatment, she continued showing persistent negativism, marked social withdrawal and a progressive decline in personal and social functioning. At that time, she was on oral treatment with aripiprazole 20 mg/day, lamotrigine 200 mg/day, chlorpromazine 100 mg/day, and duloxetine 60 mg/day.

Recently, in December 2023, she was brought to our clinical center by local police authorities following a "state of psychomotor agitation with aggressiveness". Her treatment was then adjusted to include oral treatzvalproic acid 600 mg/day, levomepromazine at a dosage of 100 mg daily, duloxetine 60 mg daily, topiramate 150 mg/day, and lorazepam 2.5 mg/day (Figure 1).

At the admission, the first psychodiagnostic evaluation was:

- The HDRS yielded a score of 9/52, indicating her depressive symptomatology;
- The HARS produced a score of 11/56, suggesting a low level of anxiety;
- CCQ scores recorded were 14/21 on the Reward Craving subscale, 17/21 on the Relief Craving subscale and 15/21 on the Obsessive Craving subscale;
- The BIS-11 obtained a total score of 80/120; For the purpose of this analysis, only the BIS-11 total score is presented. This decision was based on the study's principal focus on global impulsivity and to ensure consistency with our primary research objectives.
- The EDI score was taken in consideration due to history of binge eating disorder that with the semaglutide assumption yielded a score of 10.

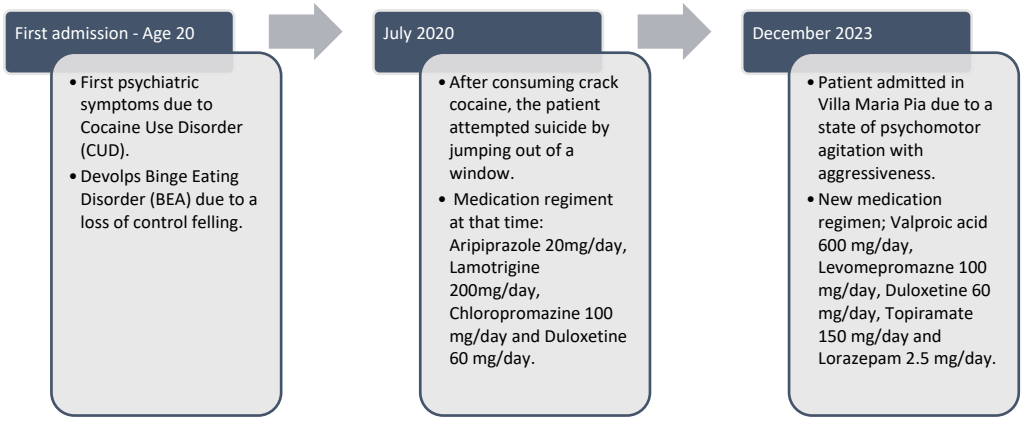


Figure 1. Brief summary of patient's life and treatment.

After the first assessment, the patient was evaluated at 1 month (T1) and at 3 months (T2). It revealed a decrease in craving, depressive and anxiety symptoms and in binge behaviors. As a result, the patient's general condition significantly improved, ameliorating her functioning in key areas of life (Table 1, Figure 2)

Table 1. Results from Questionnaires and Scales.

Questionnaire/Scale	T0	T1 (after 1 month)	T2 (after 3 months)
Cocaine Craving Questionnaire (CCQ)—Reward Craving	14	5	3
Cocaine Craving Questionnaire (CCQ)—Relief Craving	17	5	3
Cocaine Craving Questionnaire (CCQ)—Obsessive Craving	15	5	2
Hamilton Depression Rating Scale (HDRS)	9	13	8
Hamilton Anxiety Rating Scale (HARS)	11	5	3
Barratt Impulsiveness Scale (BIS)	80	46	33
Eating Disorders Inventory (EDI-2)	10	7	2

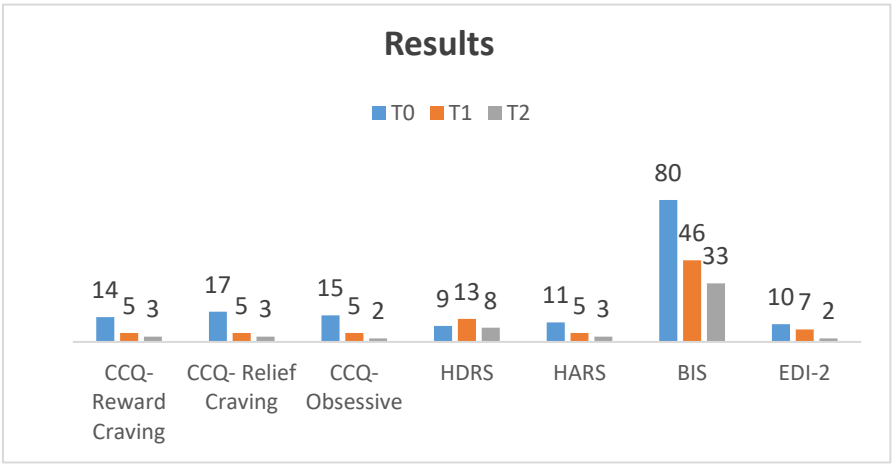


Figure 2. Interviews scores in different time periods.

4. Discussion

This case highlights semaglutide efficacy as add-on therapy during the treatment of CUD. Indeed, there was a marked reduction in cocaine craving reaching a 50% decrease in the patient's CCQ-Brief score, thus showing the efficacy of GLP-1 in both reducing of cocaine craving and the drug seeking. Therefore, given the nearly 50% reduction across all CCQ subscales the data suggest a broad effect of GLP-1 receptor agonism on overall craving, rather than a subtype-specific response. This uniform decrease implies that GLP-1 agonists may modulate core neurobiological processes shared across craving dimensions, such as dopaminergic signaling.

While the lack of differential improvement limits conclusions about subtype-specific efficacy, there are integrating findings from substance use literature [11] which could refine future hypotheses by identifying whether

the mesolimbic reward pathway is linked to specific craving subtypes and thereby is more susceptible to GLP-1-mediated modulation.

The physiology behind this phenomenon is possibly related to the intersection between the mesolimbic dopaminergic pathway and central GLP-1 circuits. Indeed, GLP-1 neurons in the brainstem send monosynaptic projections to the VTA and NAc thus the activation of GLP-1 receptors in these regions suppresses motivated intake of palatable foods, therefore remarking the parallel drug-seeking reduction [12]. In these reward circuits, GLP1 signaling modulates the hedonic and motivational value of food and drugs. Indeed, preclinical studies show that GLP-1R agonists reduce the reinforcing effects of addictive drugs, and specifically, cocaine's reinforcing effects depend on phasic mesolimbic dopamine signaling [13]. The neuroreceptors GLP-1Rs in the VTA are localized primarily on GABAergic interneurons; the GLP-1RA treatment increases VTA GABA neuron activity and concurrently suppresses dopamine neuron firing (Figure 3),

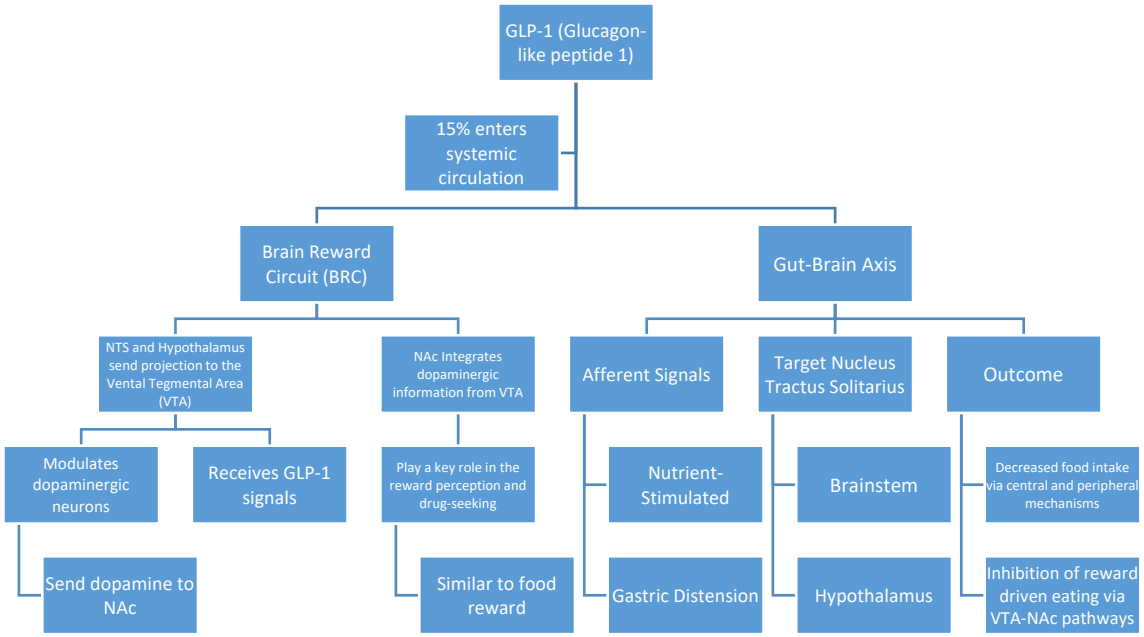


Figure 3. Summary of the process regarding the reward system and GLP-1 function involving the VTA (Ventral Tegmental Area) and NAc (Nucleus Accumbens).

Thereby attenuating cocaine-seeking behavior, apart for reducing the desire of food and eventual abnormal eating conduct and behaviors [14]. Moreover, semaglutide has been shown to have a good tolerability profile, indeed no adverse effects were reported. However, given that impulsivity is frequently associated with dysregulation within these identical reward pathways, which are characterized by difficulties in delayed gratification or the manifestation of compulsive behaviors driven by immediate rewards. It follows that a substance directly modulating these neural regions could, if misused, potentially interact with or exacerbate pre-existing impulsive tendencies [4].

Overall, this case report is the first one available in the literature reporting the use if semaglutide in a patient with a diagnosis of borderline personality disorder, co-occurring with cocaine use. Previously, a case report of a 54-year-old patient diagnosed with chronic CUD and obesity alone was reported. The treatment with semaglutide resulted with a patient's significant weight loss and reduction in cocaine cravings suggesting that semaglutide offers an effective approach to address both issues simultaneously [15]. In conclusion these neurobiological effects translate to meaningful clinical outcomes, suggesting semaglutide potential benefits on substance use disorders.

Despite the promising results of this case, they may be interpreted with caution and its limitations must be acknowledged. Firstly, even if the results of the study are encouraging to quantifying signs of drug addiction and rehabilitation as GLP-1 modulate the response to addictive drugs, they can't be generalised to a larger number of patients without further research due to its limitation to differentiate the reasons of addiction. A pharmacovigilance approach focused on the detection, assessment, deep understanding and prevention of adverse effects must be assessed in order to understand the concomitant drug assumption and other confounding factors such as comorbidities, routes of administration and treatment adherence. Although the GLP-1 agonist reduced cocaine consumption, the GLP-1 receptor must still be addressed as a confounding factor. Therefore, the use of semaglutide to treat CUD is still experimental and further research is needed to support its preclinical evidence: approaching

this type of treatment requires caution and is strongly recommended to perform it alongside behavioural therapy. Overall, due the preliminary nature of this study, it can only confirm the effect of semaglutide in this case report indeed further longitudinal studies are required to assess the long term effects and safety of semaglutide, including its potential side effects.

5. Conclusions

In conclusion, the overlap between GLP-1–mediated metabolic regulation and mesolimbic reward pathways provides a valuable scientific rationale for investigating semaglutide as an adjunct in cocaine and drug abuse disorders. However, evidence to date remains limited to preclinical models and isolated clinical observations. Rigorous, placebo-controlled trials and mechanistic human studies as these will help elucidate semaglutide's safety, optimal dosing, and therapeutic utility in addiction medicine.

Author Contributions

G.M., S.C.: conceptualization, methodology; A.M.S., S.C.: data curation, writing—original draft preparation; G.M., S.C.: supervision; A.M., C.C., E.T.T., F.S.: data collection, clinical assessment; G.M.: writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data supporting the findings of this study are available upon reasonable request from the corresponding author. Due to ethical and privacy considerations, some data cannot be shared publicly. However, de-identified data may be made available to qualified researchers upon request, in accordance with institutional and legal guidelines.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Shi, I.; Khan, S.S.; Yeh, R.W.; et al. Semaglutide Eligibility Across All Current Indications for US Adults. *JAMA Cardiol.* **2025**, *10*, 96–98. https://doi.org/10.1001/jamacardio.2024.4657.
2. Drucker, D.J. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell Metab.* **2018**, *27*, 740–756. https://doi.org/10.1016/j.cmet.2018.03.001.
3. EMA Statement on Ongoing Review of GLP-1 Receptor Agonists (EMA, 2023). Available online: www.ema.europa.eu/en/news/ema-statement-ongoing-review-glp-1-receptor-agonists (accessed on 10 May 2025).
4. Chiappini, S.; Papanti Pelletier, G.D.; Vickers-Smith, R.; et al. Exploring the nexus of binge eating disorder (BED), New Psychoactive Substances (NPS), and misuse of pharmaceuticals: Charting a path forward. *Expert. Opin. Pharmacother.* **2023**, *24*, 1915–1918. https://doi.org/10.1080/14656566.2023.2271389.
5. Eren-Yazicioglu, C.Y.; Yigit, A.; Dogruoz, R.E.; et al. Can GLP-1 Be a Target for Reward System Related Disorders? A Qualitative Synthesis and Systematic Review Analysis of Studies on Palatable Food, Drugs of Abuse, and Alcohol. *Front. Behav. Neurosci.* **2021**, *14*, 614884. https://doi.org/10.3389/fnbeh.2020.614884.
6. Klausen, M.K.; Thomsen, M.; Wortwein, G.; et al. The role of glucagon-like peptide 1 (GLP-1) in addictive disorders. *Br. J. Pharmacol.* **2022**, *179*, 625–641. https://doi.org/10.1111/bph.15677.
7. Arillotta, D.; Floresta, G.; Papanti Pelletier, G.D.; et al. Exploring the Potential Impact of GLP-1 Receptor Agonists on Substance Use, Compulsive Behavior, and Libido: Insights from Social Media Using a Mixed-Methods Approach. *Brain Sci.* **2024**, *14*, 617. https://doi.org/10.3390/brainsci14060617.
8. Hendershot, C.S.; Bremmer, M.P.; Paladino, M.B.; et al. Once-Weekly Semaglutide in Adults with Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* **2025**, *12*, e244789. https://doi.org/10.1001/jamapsychiatry.2024.4789.

9. Bruns Vi, N.; Tressler, E.H.; Vendruscolo, L.F.; et al. IUPHAR review—Glucagon-like peptide-1 (GLP-1) and substance use disorders: An emerging pharmacotherapeutic target. *Pharmacol. Res.* **2024**, *207*, 107312. https://doi.org/10.1016/j.phrs.2024.107312.
10. Jerlhag, E. The therapeutic potential of glucagon-like peptide-1 for persons with addictions based on findings from preclinical and clinical studies. *Front. Pharmacol.* **2023**, *14*, 1063033. https://doi.org/10.3389/fphar.2023.1063033.
11. Di Nicola, M.; Pepe, M.; Montanari, S.; et al. Predictors of polysubstance use in patients with severe alcohol use disorder: The role of reward craving. *J. Psychiatr. Res.* **2023**, *165*, 290–297. https://doi.org/10.1016/j.jpsychires.2023.07.041.
12. Castro, D.C.; Bruchas, M.R. A Motivational and Neuropeptidergic Hub: Anatomical and Functional Diversity within the Nucleus Accumbens Shell. *Neuron* **2019**, *102*, 529–552. https://doi.org/10.1016/j.neuron.2019.03.003.
13. Lewis, R.G.; Florio, E.; Punzo, D.; et al. The Brain's Reward System in Health and Disease. *Adv. Exp. Med. Biol.* **2021**, *1344*, 57–69. https://doi.org/10.1007/978-3-030-81147-1_4.
14. Hsu, T.M.; McCutcheon, J.E.; Roitman, M.F. Parallels and Overlap: The Integration of Homeostatic Signals by Mesolimbic Dopamine Neurons. *Front. Psychiatry* **2018**, *9*, 410.
15. Romeo, V.M. Use of semaglutide in a 54-year-old patient with Cocaine Use Disorder (CUD) and weight loss: A case report. *J. Med. Case Rep.* **2025**, *19*, 57. https://doi.org/10.1186/s13256-025-05049-w.