Feasibility of exenatide, a GLP-1R agonist, for treating cocaine use disorder: A case series study

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Protocol Title:	Feasibility of exenatide, a GLP-1R agonist, for treating cocaine use disorder: A case series study
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Study Coordinator:	Jessica Vincent, QA Manager
Population:	N = 4, male/female, 18-60 years old
Study Site:	UTHealth Center for Neurobehavioral Research on Addiction (CNRA)
Study Duration:	12 months
Subject Duration:	7 weeks

General Information

Cocaine use continues to be a significant public health problem with limited treatment options and no approved pharmacotherapies. Glucagon-like peptide 1 (GLP-1) receptors are located in brain areas important for reward and, as such, appear to play a significant role in modulating addictive-like behaviors and drug use (Eren-Yazicioglu et al. 2020). Extended-release exenatide is a GLP-1 receptor agonist approved by the FDA for the treatment of type 2 diabetes. In preclinical studies, exenatide reduces cocaine-seeking and cocaine-taking behavior (Brunchmann et al. 2019). The effect of extended-release exenatide on cocaine use in patients with a cocaine use disorder (CUD) has not yet been investigated. We propose a series of four case studies to collect preliminary data on the feasibility, safety, and clinical effects of exenatide in treatment-seeking patients with CUD.

Background Information

The U.S. is facing a re-emergence of cocaine as an epidemic drug, indicated by increases in availability, use, and overdose deaths following a previous period of decline (Maxwell 2020). Although significant strides have been made in medication development for the treatment of cocaine use disorder (CUD), no FDA-approved pharmacotherapies are currently available. NIDA's current strategic plan prioritizes efforts to accelerate CUD medication development by rigorously testing novel molecular targets based on a translational research approach. Emerging evidence supports the potential clinical utility of glucagon-like peptide 1 (GLP-1) receptor stimulation for the treatment of substance use disorders, including CUD.

GLP-1 is an incretin hormone that promotes insulin secretion from pancreatic beta cells. Current evidence shows that GLP-1 receptors are widely expressed in areas of the mesolimbic dopaminergic pathway where they regulate the rewarding value of food and drugs of abuse, including cocaine. Preclinical literature suggests that activation of GLP-1 receptors reduces the rewarding effects of cocaine and cocaine self-administration (e.g., Hernandez et al. 2018; Hernandez et al. 2019). In the human laboratory, acute cocaine administration decreases GLP-1 concentrations, with changes associated with subjective reinforcing responses to cocaine ("feeling high, anxious") (Bouhlal et al. 2017). Thus, there is compelling evidence to hypothesize that exenatide treatment will decrease

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cocaine use in individuals with CUD. In preparation for conducting a full-scale efficacy trial, the goal of the current proposal is to collect preliminary feasibility, safety, and clinical data on the effects of exenatide in series of four case studies.

Study Objectives

1. To evaluate the feasibility of using exenatide as a treatment for CUD. Primary outcome will be treatment completion, measured as attendance at the end-of-treatment (Week 6) timepoint. Secondary outcomes related to feasibility will include enrollment, attendance, retention, and overall acceptability, measured at study completion (Week 6) timepoint.
2. To evaluate the safety of using exenatide as an adjunct treatment for CUD. Primary outcomes related to safety will include adverse events monitored at each clinic visit.
3. To evaluate clinical effects of exenatide on cocaine use and addiction-related behaviors. Primary outcome related to clinical effects will be cocaine use as measured by urine drug screens at the end-of-treatment (Week 6) timepoint. Secondary outcomes related to clinical effects will include cocaine use as measured by self-report, craving, drug demand, and depressive and affective symptoms assessed during each visit.

Study Design

The study will employ a case series design with the intervention (extended-release exenatide) run as a single-arm open-label pilot. The framework for this study is exploratory. All participants will receive evidence-based standard of care outpatient treatment for CUD. Primary and secondary outcomes will undergo visual analysis to determine within-subject change as a function of treatment, along with simple descriptive statistics for the group as a whole. At this early planning stage of research on exenatide treatment, a larger scale RCT design was not considered appropriate for feasibility, ethical and methodological reasons.

Study Population

Inclusion criteria:

1. between 18 and 60 years of age
2. meet DSM-5 criteria for current cocaine use disorder as measured by the Structured Clinical Interview for DSM-5 (SCID: First 2015)
3. have at least 1 cocaine-positive urine specimen (≥ 150 ng/mL) during intake
4. be in acceptable health on the basis of interview, medical history and physical exam
5. have hematology and chemistry laboratory tests that are within reference limits (±10%), with the following exception: pancreatic tests (lipase and amylase) must be within normal limits
6. consent to use an acceptable method of birth control during study participation and for one month after discontinuation of the study medication. Non-hormonal methods of contraception are recommended, including barrier contraceptives (e.g., diaphragm, cervical cap, male condom) or intrauterine device (IUD). Steroid contraceptives if used with non-hormonal methods are acceptable
7. be able to understand the consent form and provide written informed consent
8. be able to provide the names of at least 2 persons who can generally locate their whereabouts

Exclusion criteria:

1. current DSM-5 diagnosis for substance use disorder (of at least moderate severity) other than cocaine, marijuana, alcohol, or nicotine
2. current alcohol use that meets for physiological dependence requiring detoxification or makes participation medically unsafe as determined by the medical director
3. have a DSM-5 axis I psychiatric disorder, or anorexia nervosa, or neurological disease or disorder requiring ongoing treatment and/or making study participation unsafe (e.g., psychosis, dementia)
4. significant current suicidal or homicidal ideation
5. Type 1 or type 2 diabetes mellitus (previously diagnosed or indicated by HbA1C level of ≥6.5%)
6. have medical conditions contraindicating exenatide pharmacotherapy (e.g., personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, severe gastrointestinal disease (severe gastroparesis), previous history of pancreatitis or risk of pancreatitis, creatinine clearance <45 or end stage renal disease, previous medically adverse reaction to exenatide or other GLP-1 receptor agonists)
7. taking medications that could adversely interact with exenatide (e.g., oral or injectable blood glucose lowering medications)
8. having conditions of probation or parole requiring reports of drug use to officers of the court
9. impending incarceration
10. pregnant or nursing for female patients

Study Procedures

The study site is the Treatment Research Clinic of the Center for Neurobehavioral Research on Addiction (CNRA), a university-supported center of excellence within the UTHealth Department of Psychiatry and Behavioral Sciences. Established and effective recruitment strategies at the CNRA include newspaper and radio ads, social media posts, referrals from local treatment professionals and former research patients. Those responding to recruitment ads are first screened by phone, then undergo a general intake evaluation protocol (HSC-MS-05-0322) consisting of a drug history and psychiatric evaluation (SCID), physical examination and laboratory testing (chemistry screen, complete blood count, urinalysis, and a 12 lead EKG) prior to signing informed consent to participate in a specific study. For the current study, participants who complete the general intake evaluation protocol and are determined to be eligible will be invited to participate. We expect to screen 10 participants in order to enroll four.

All participants will receive six weeks of treatment as usual (TAU), consisting of standard psychosocial treatment for CUD, delivered by trained masters-level therapists at the CNRA. This treatment will include weekly in-person individual Drug Counseling sessions focusing on providing education and recovery support, according to a standard treatment manual (Crits-Christoph et al. 1999).

The pharmacological intervention (extended-release exenatide) will be given as an add-on to TAU. Exenatide will be purchased commercially as Bydureon® for subcutaneous (SC) injection and administered at a dose of 2 mg once a week for a total of 6 weeks. Per the FDA-approved label, 2 mg of Bydureon is administered SC once a week, at any time of day and with or without meals. Exenatide is supplied as a powder with a solvent for once-weekly injection. Each single-dose, dual-chamber pen contains 0.65 mg of diluent and 2 mg of exenatide, which remains isolated until mixed. Between weekly injection visits, the therapist will conduct a brief (20 minute) phone check-in session with their client to assess functioning, provide support, and encourage ongoing participation. Participants will receive $15 compensation for attending each weekly study visit plus $30 for attending the study completion visit at week 6.

Study medication risks and safety monitoring

Rosenstock and colleagues evaluated extended release exenatide in **non-diabetic** subjects with and without prediabetes. The most common side effect of the treatment was nausea (25%), however, there were no differences in withdrawal rates due to nausea between the treatment and the placebo groups. No serious adverse effects were reported in this study (Rosenstock et al. 2010). A meta-analysis of six randomized controlled trials investigating the use of exenatide in overweight and obese subjects without diabetes reported that there were no serious adverse events in the included studies (Su et al. 2016). There were no episodes of hypoglycemia in the studies that used hypoglycemia as an outcome. The most common adverse events in the exenatide group, included nausea, vomiting, diarrhea, constipation and abdominal distension. Another meta-analysis of the studies investigating GLP-1R agonists in overweight and obese subjects without diabetes reported that GLP-1R agonists did not increase the number of participants who withdrew or dropped out from studies (Zhang et al. 2015). Neither diarrhea nor hypoglycemia appeared more frequently in the GLP-1R agonist group than that in the control group; however, subjects assigned to GLP-1R agonists reported more nausea and vomiting than those in the control group. Collectively, these findings demonstrate that GLP-1R agonist therapy is safe in persons without diabetes, and that the side effect profile of GLP-1R agonists is similar among diabetes and non-DM patients.

Risks associated with study medication will be minimized through careful assessment. During screening, participants will be assessed for contraindications for Bydureon: hypersensitivity to drug/class/components, diabetes mellitus type 1, history of pancreatitis, personal of family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2, creatinine clearance <45 or ESRD. Screening will consist of a detailed medical history and physical exam and blood tests including complete blood count, complete metabolic panel, and pancreatic enzymes levels. Potential participants with diabetes mellitus type 1, creatinine clearance <45 or ESRD, abnormal levels of pancreatic enzymes, those with a history or at risk for pancreatitis, and those with personal and/or family history of thyroid C-cell tumor will be excluded from participation in this study. During the study, participants' vital signs, overall wellbeing, and potential side effects of Bydureon will be assessed at each weekly visit, and finger stick blood glucose levels will be assessed prior to each dose of the medication. Subsequent doses of Bydureon will not be administered if any of the following occur: hypoglycemia (blood glucose <70 mg/dL), severe injection site reaction, hypersensitivity reaction, anaphylaxis, angioedema, cholecystitis, and cholelithiasis or if the Study Physician (CoI, Dr. Michael Weaver) believes that there may be any reason to withhold exenatide.

Assessment schedule

Table 1 provides a summary of the outcome measures to be completed during the study.

	Enrollment	**Treatment (week)**					
Intake	0	1	2	3	4	5	6
Informed consent	X						
Eligibility determination (per HSC-MS-05-0322)	X						
Safety labs (amylase/lipase/HbA1C)	X						
Outcome variables							
Treatment participation		X	X	X	X	X	X
Satisfaction Survey							X
Side effects/AE		X	X	X	X	X	X
Vital signs/weight	X	X	X	X	X	X	X
Finger-stick glucose monitoring		X	X	X	X	X	X

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Carbon monoxide (CO)	X	X	X	X	X	X	X
Breath alcohol concentration (BAC)	X	X	X	X	X	X	X
Urine pregnancy test	X	X		X		X	X
Urine drug screen (UDS)	X	X	X	X	X	X	X
Cocaine Timeline Followback (TLFB)	X	X	X	X	X	X	X
Craving	X	X	X	X	X	X	X
Drug Demand	X						X
Beck Depression Inventory II (BDI-II)	X			X			X
Positive/Negative Affect Schedule (PANAS)	X			X			X
Visual analogue scale (VAS) of drug effects	X	X	X	X	X	X	X
Diet	X						X
Intervention							
Exenatide injection		X	X	X	X	X	X
Drug counseling session		X	X	X	X	X	X
Phone check-in session		X	X	X	X	X	X

Description of Outcome Measures

- **Treatment participation** will be measured according to number of weekly clinic visits attended and completion rates at end-of-treatment (week 6).
- A **Satisfaction Survey** will be used to assess treatment acceptability using a 4-point Likert scale to rate services on various dimensions, such as quality, adequacy, appropriateness, and accessibility. We will adapt this measure to include acceptability ratings related to exenatide pharmacotherapy.
- **Side effects** (i.e., nausea, vomiting, dyspepsia, diarrhea, constipation, headache, injection-site pruritus, injection-site nodule) and **AEs** will be assessed at each clinic visit by Dr. Yammine.
- **Vital signs** will be assessed at each clinic visit and will include systolic and diastolic blood pressure, heart rate, respiratory rate, oral temperature, and weight.
- **Finger-stick blood glucose** levels will be assessed prior to each dose of exenatide (if blood glucose is <70 mg/dL, subsequent doses of exenatide will not be administered).
- **CO** breath testing will follow standard measurement procedures and will be used to evaluate smoking status (Sandberg et al. 2011).
- **BAC** breath testing using a breathalyzer will estimate recent alcohol consumption and be used to judge signs of alcohol-related impairment that may influence study participation.
- **Urine pregnancy test** will be performed prior to the first dose of exenatide, every two weeks thereafter, and at the last day of treatment.
- **UDS** levels of the cocaine metabolite, benzoylecgonine (BE) ≥ 300 ng/mL will be coded as "positive" for cocaine use. Standard UDS collection methods used at the CNRA will be followed.
- **TLFB** will be administered as a self-report measure of substance use frequency and quantity. In addition to cocaine, other substances (e.g., alcohol, marijuana, nicotine) will be assessed using standard TLFB interview methodology (Sobell et al. 1996).
- **Craving** will be assessed using the Brief Substance Craving Scale (BSCS: Somoza et al. 1995), a 16-item, self-report measure of craving for cocaine and other substances over a 24 hour period. Intensity, duration, and frequency of craving are rated on a 0-4 point Likert scale. The sum of the three scores yields a craving composite measure.
- **Drug Demand** will be used as a measure of reward sensitivity. We will administer the computerized cocaine purchasing task in which participants are asked to make repeated choices between hypothetical purchases of cocaine at varying prices (Bruner and Johnson 2014).

- **BDI-II** and **PANAS** will be used to measure depressive symptoms and affective experiences, respectively.
- **VAS** will be used to measure subjective effects of cocaine experienced during the previous week. Participants will be asked to rate on a 100 mm line (0=not at all; 100=extremely) the drug effects they experienced, e.g., euphoria, high, anxious.
- **Diet** will be assessed at baseline and at the end of treatment using the Automated Self-Administered 24-hr Dietary Assessment Tool (ASA24: Kirkpatrick et al. 2014)

Data and Safety Monitoring

The Principal Investigators (Schmitz, Yammine) will be responsible for knowing the policies of the local IRB. In this capacity, they will maintain accurate documentation of CPHS correspondence and reports and oversee the handling of all possible study-related adverse events. The CNRA has longstanding data collection and safety monitoring system in place that will be available for the proposed study. This includes staff training, manual driven processes, weekly audit of data collection/entry, medical screening with results reviewed by on-site nurse and physician, use of standardized assessments, continued medical monitoring during treatment, use of a certified (CLIA) analytical laboratory to perform urine toxicology testing, procedures to monitor medication compliance, collaboration with the statistician who oversees data analysis and system management. The PI will assure that the above systems are in place and functioning properly for the duration of the study.

The CNRA has a Data and Safety Monitoring Board (DSMB) that provides independent oversight of all active protocols involving patient safety data. DSMB members include Drs. Jan Blalock (UT-MDA Cancer Center), Edward Fann (Baylor College of Medicine-Psychiatry), Daryl Ishaq Shorter (Baylor College of Medicine), and Claudia Pedrozo (UTHealth Department of Pediatrics). The current study will be included in the list of protocols reviewed annually (and as needed) by the DSMB.

Adverse events (AE) will be reported to CPHS. Serious AEs will be reported immediately (verbally within 24 hours) to CPHS and the DSMB. A written report will follow as soon as possible but in no more than three days and will contain information regarding the date of the AE, description of the AE, severity rating (Grade 1 to 4), assessment of cause, whether the AE indicates an increased risk for current or future subjects, and whether changes to the informed consent form are necessary.

Statistics

Primary analyses will report results related to feasibility, safety and clinical outcomes. Individual data will be plotted graphically and visual analysis will be used to assess change over time in treatment. Summary descriptive statistics will be reported on the sample as a whole. Given the small sample size used in case studies, quantitative statistical testing is not appropriate. Results will be used to determine if a subsequent larger scale trial is warranted.

Ethics

IRB approval will be sought from CPHS. Participation in this study is completely voluntary. All participants will be informed of the nature of the procedures and associated risks. Participants will be informed that they can withdraw from the study at any time and that this will have no adverse impact on the study or on their own future treatment. Individuals will participate in the study only after they provide verbal and signed consent. Trained research personnel will obtain consent in a private room where participants feel comfortable. Informed consent will be documented in writing via the participants' and investigators' signatures.

Data handling, record keeping, quality assurance

- The study protocol and all data generated will be held in strict confidence by the Investigators and will not be released to any unauthorized third party without prior written consent/approval by the participant.
- The CNRA PIs and Quality Manager, Jessica Vincent, have substantial experience in the design and implementation of data management procedures that provide accurate recording and storage of data, participant confidentiality, and timely analysis.
- The CNRA treatment research clinic has a workstation room with four (4) dedicated computerized systems for research participants to complete digital questionnaires and self-report forms under supervision of authorized personnel.
- CNRA research computers are equipped with the major data management and analysis software programs needed for the proposed project. All data files are automatically backed up daily.
- Information Technology at UTHealth provides onsite computer support staff to ensure timely and reliable services.

Publication Plan

We will publish research results in a peer-reviewed journal and/or present findings at a scientific conference.

References

Bouhlal S et al. (2017) Acute effects of intravenous cocaine administration on serum concentrations of ghrelin, amylin, glucagon-like peptide-1, insulin, leptin and peptide YY and relationships with cardiorespiratory and subjective responses Drug Alcohol Depend 180:68-75 doi:10.1016/j.drugalcdep.2017.07.033

Brunchmann A, Thomsen M, Fink-Jensen A (2019) The effect of glucagon-like peptide-1 (GLP-1) receptor agonists on substance use disorder (SUD)-related behavioural effects of drugs and alcohol: A systematic review Physiol Behav 206:232-242 doi:10.1016/j.physbeh.2019.03.029

Bruner NR, Johnson MW (2014) Demand curves for hypothetical cocaine in cocaine-dependent individuals Psychopharmacology (Berl) 231:889-897 doi:10.1007/s00213-013-3312-5

Crits-Christoph P et al. (1999) Psychosocial treatments for cocaine dependence: National Institute on Drug Abuse Collaborative Cocaine Treatment Study Arch Gen Psychiatry 56:493-502.

Eren-Yazicioglu CY, Yigit A, Dogruoz RE, Yapici-Eser H (2020) 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 14:614884 doi:10.3389/fnbeh.2020.614884

First MB, Williams, J.B.W., Karg, R.S., Spitzer, R.L. (2015) Structured Clinical Interview for DSM-5-Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV). American Psychiatric Association, Arlington, VA

Hernandez NS, Ige KY, Mietlicki-Baase EG, Molina-Castro GC, Turner CA, Hayes MR, Schmidt HD (2018) Glucagon-like peptide-1 receptor activation in the ventral tegmental area attenuates cocaine seeking in rats Neuropsychopharmacol 43:2000-2008 doi:10.1038/s41386-018-0010-3

Hernandez NS, O'Donovan B, Ortinski PI, Schmidt HD (2019) Activation of glucagon-like peptide-1 receptors in the nucleus accumbens attenuates cocaine seeking in rats Addict Biol 24:170-181 doi:10.1111/adb.12583

Kirkpatrick SI et al. (2014) Performance of the Automated Self-Administered 24-hour Recall relative to a measure of true intakes and to an interviewer-administered 24-h recall Am J Clin Nutr 100:233-240 doi:10.3945/ajcn.114.083238

Maxwell JC (2020) Is Cocaine Coming Back? A Commentary Subst Use Misuse 55:345-348 doi:10.1080/10826084.2019.1664592

Rosenstock J, Klaff LJ, Schwartz S, Northrup J, Holcombe JH, Wilhelm K, Trautmann M (2010) Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without pre-diabetes Diabetes Care 33:1173-1175 doi:10.2337/dc09-1203

Sandberg A, Skold CM, Grunewald J, Eklund A, Wheelock AM (2011) Assessing recent smoking status by measuring exhaled carbon monoxide levels PLoS One 6:e28864 doi:10.1371/journal.pone.0028864

Sobell LC, Brown J, Leo GI, Sobell MB (1996) The reliability of the Alcohol Timeline Followback when administered by telephone and by computer Drug Alcohol Depend 42:49-54.

Somoza E, Dyrenforth S, Goldsmith J, Mezinskis J, Cohen M In search of a Universal Drug Craving Scale. In: Annual Meeting of the American Psychiatric Association, Miami, Florida, May 20-25 1995.

Su N et al. (2016) Exenatide in obese or overweight patients without diabetes: A systematic review and meta-analyses of randomized controlled trials Int J Cardiol 219:293-300 doi:10.1016/j.ijcard.2016.06.028

Zhang F, Tong Y, Su N, Li Y, Tang L, Huang L, Tong N (2015) Weight loss effect of glucagon-like peptide-1 mimetics on obese/overweight adults without diabetes: A systematic review and meta-analysis of randomized controlled trials J Diabetes 7:329-339 doi:10.1111/1753-0407.12198