Feasibility of Exenatide, a GLP-1R Agonist, for Treating Cocaine Use Disorder: A Case Series Study

Luba Yammine, PhD, Jessica C. Balderas, PhD, Michael F. Weaver, MD, and Joy M. Schmitz, PhD

Cocaine use remains a serious public health problem associated with a marked increase in overdose deaths in the past decade. No medications have yet been proven to be effective for the treatment of cocaine use disorder (CUD). Among the highly promising medications have been glucagon-like peptide 1 receptor agonists (GLP-1RA) that are currently used for the treatment of type 2 diabetes mellitus and weight management. Preclinically, GLP-1RAs have been shown to attenuate cocaine self-administration, however, this has not yet been demonstrated in a human laboratory study. The GLP-1RA extended-release exenatide is given as a once-weekly injection, which may be clinically advantageous for addressing medication nonadherence among individuals with CUD. Here, we assess feasibility and safety by reporting on 3 cases of patients with CUD who received 6 weeks of exenatide 2 mg subcutaneously once-weekly in an open-label fashion, along with standard individual drug counseling. We observed excellent attendance and compliance, along with positive end-of-study satisfaction ratings. The medication was well tolerated and without unexpected or severe adverse events. Results for cocaine use and related clinical effects were more mixed, yet encouraging. Future empirical testing of exenatide for treating CUD should utilize a randomized controlled trial design and longer treatment duration.

Key Words: cocaine use disorder, exenatide, glucagon-like peptide 1, feasibility study, case series study

(*J Addict Med* 2023;00: 00–00)

The United States is facing a reemergence of cocaine as an epidemic drug. Despite significant strides in medication development for cocaine use disorder (CUD) treatment, no Food and Drug Administration–approved pharmacotherapies exist. Among novel molecular targets considered for CUD treatment is the glucagon-like peptide 1 (GLP-1) receptor.

GLP-1 is an incretin hormone secreted from the intestinal L-cells and hindbrain nucleus tractus solitarius.[1] Centrally, GLP-1 receptors are expressed in areas associated with drug-induced reinforcement.[2] Preclinical studies have shown that administration of a GLP-1 receptor agonist (GLP-1RA) attenuated cocaine self-administration,[3] cocaine-induced locomotor stimulation,[4] and conditioned place preference.[5] In a human study, cocaine reduced concentrations of GLP-1.[6] The effects of GLP-1 agonism have only been studied preliminarily, without clear evidence of reduction in cocaine taking or subjective effects of cocaine.[7]

In preparation for a larger project examining GLP-1RAs for CUD treatment, we conducted a case-series study involving chronic administration of the GLP-1RA extended-release exenatide. Our primary objective was to evaluate the feasibility and safety of exenatide treatment, as measured by clinic visit attendance, compliance with once-weekly exenatide injection, treatment acceptability, and adverse events. Our secondary objective was to describe potential clinical effects of exenatide on cocaine use, craving, and affective symptoms.

METHODS

Recruitment

Participants were patients previously treated for CUD at an outpatient treatment research clinic who met the following inclusion criteria: (1) age 18 to 60 years, (2) current CUD diagnosis based on the Structured Clinical Interview for DSM-5,[8] (3) acceptable health based on interview, medical history and physical examination, (4) and consenting to an acceptable birth control method during study participation. Individuals were excluded if they (1) met criteria for substance use disorders other than cocaine, marijuana, alcohol or nicotine, (2) had a severe comorbid psychiatric disorder likely to make study participation unsafe, (3) had type 1 or type 2 diabetes mellitus, or (4) reported medical conditions contraindicating exenatide pharmacotherapy or were taking medications that could adversely interact with exenatide.

Procedure

The study was approved by the UTHealth Committee for the Protection of Human Subjects, in accordance with the Helsinki Declaration, and registered at ClinicalTrials.gov [NCT04941521]. Following informed consent, participants received weekly in-person individual drug counseling sessions according to a standard treatment manual.[9] Participants also received open-label exenatide (Bydureon®) 2 mg subcutaneously once-weekly. Between weekly injection visits, therapists conducted 20-minute phone check-ins to assess clients' functioning, provide support, and encourage participation. Participants received $15 compensation for attending weekly clinic visits plus $30 for attending the study completion visit.

From the University of Texas Health Science Center at Houston, Houston, TX.
Received for publication June 20, 2022; accepted January 1, 2023.
The authors report no conflicts of interest.
Supported in part by the Louis A. Faillace, M.D. Professorship to J.M.S.
Send correspondence to Jessica Balderas, PhD, Center for Neurobehavioral Research on Addiction (CNRA), Faillace Department of Psychiatry and Behavioral Sciences, Behavioral and Biomedical Sciences Building (BBSB), 1941 East Road, Houston, TX 77054. E-mail: Jessica.C.Balderas@uth.tmc.edu (alternative: Balderas.jessica@gmail.com).

ISSN: 1932-0620/23/0000-0000
DOI: 10.1097/ADM.0000000000001147

Measures

Feasibility and Safety

Attendance at each weekly clinic visit and compliance with once-weekly exenatide injections was tracked. Vital signs, finger-stick blood glucose levels were assessed, and the National Institute of Mental Health Adverse Events (AE) log was completed before exenatide doses. Treatment acceptability was assessed with an end-of-study satisfaction survey wherein participants rated treatment helpfulness and usefulness, and their desire to change, continue, and recommend the treatment on a 1 (strongly disagree) to 9 (strongly agree) Likert scale.

Clinical Effects

Cocaine use was measured at weekly clinic visits via urine drug screens (UDS) and self-report (timeline follow-back[10]). The Brief Substance Craving Scale[11] measured cocaine craving intensity; higher scores indicated greater intensity. The Beck Depression Inventory-II[12] (BDI-II) and the Positive and Negative Affect Schedule[13] (PANAS) measured depressive and affective experiences, respectively, at weeks 3 and 6.

Data Analysis

Consistent with case-series design, participants' data were visually inspected to assess change over time.

RESULTS

Demographics and Baseline Drug Use

Three individuals (2 males and 1 female), hereafter labeled cases A, B, and C, participated. Lifetime cocaine use ranged from 4 to 31 years, and past 30-day cocaine use ranged from 10 to 23 days (see Table 1).

Attendance

All participants attended 6 clinic visits and received 6 exenatide injections.

Safety

Two participants (cases A and C) reported adverse events (AEs) that were treatment-related but mild in severity. All AEs resolved without treatment. Specifically, case A reported nausea, dyspepsia, diarrhea, headache, and an injection site pruritis; case A and case C experienced injection site nodules that were <5 mm in diameter without accompanying skin discoloration or infection. One serious AE (SAE, case B) involved an episode of chest pain that led the participant to seek care at the emergency department (ED). While at the ED, his chest pain resolved and was deemed likely due to excessive cocaine use; he was discharged to home without treatment. The SAE was deemed unrelated to the study medication. He did not experience subsequent episodes of chest pain. There were no AE-related discontinuations.

Acceptability

Regarding study satisfaction, case B and case C highly rated treatment helpfulness (9, 8) and usefulness (9, 6), indicating that they would strongly recommend (9, 9) and not change (1, 1) the treatment. Case A provided lower ratings for treatment helpfulness (6), exenatide usefulness (3), and likelihood of treatment recommendation (4). All participants rated the desire to continue treatment at or above average (5, 9, 8, respectively).

Cocaine Use

For case A and case C, weekly UDS results were cocaine-positive. Case A reported using cocaine approximately 50% of the days of the week and spending on average $9 to $14 weekly on cocaine. Case C reported using cocaine more than 50% of the days of the week and spending on average $32 to $63 weekly on cocaine. For case B, UDS results were cocaine-positive at weeks 1 to 3, and cocaine-negative at weeks 4 to 6, with $0 spent on cocaine during these weeks. See Figure 1 for details.

Cocaine Craving

Case A rated craving moderate to extremely intense across weeks 1 to 5, before declining to slightly at week 6. Case B reported moderate craving intensity at baseline, which decreased to none across weeks 3 to 6. Case C reported slight craving intensity

TABLE 1. Participants' Sociodemographic and Substance Use Characteristics

Variables	Case A	Case B	Case C
Gender	Female	Male	Male
Age (years)	55	41	55
Race	African American/Black	African American/Black	White
Ethnicity	Non-Hispanic	Non-Hispanic	Hispanic
Education (years)	16	9	14
Tobacco dependency*	High	Moderate	Very low
Use in past 30 days†			
Cocaine	10	21	23
Alcohol	10	12	2
Marijuana	20	1	4
Lifetime use (years)[2]			
Cocaine	31	4	16
Alcohol	19	4	5
Marijuana	10	0	0

*Tobacco dependency as measured by the Fagerstrom Test for nicotine dependence (Heatherton et al., 1991).

†Past 30 days and lifetime years of regular use as measured by the Addiction Severity Index (McLellan et al., 1992).

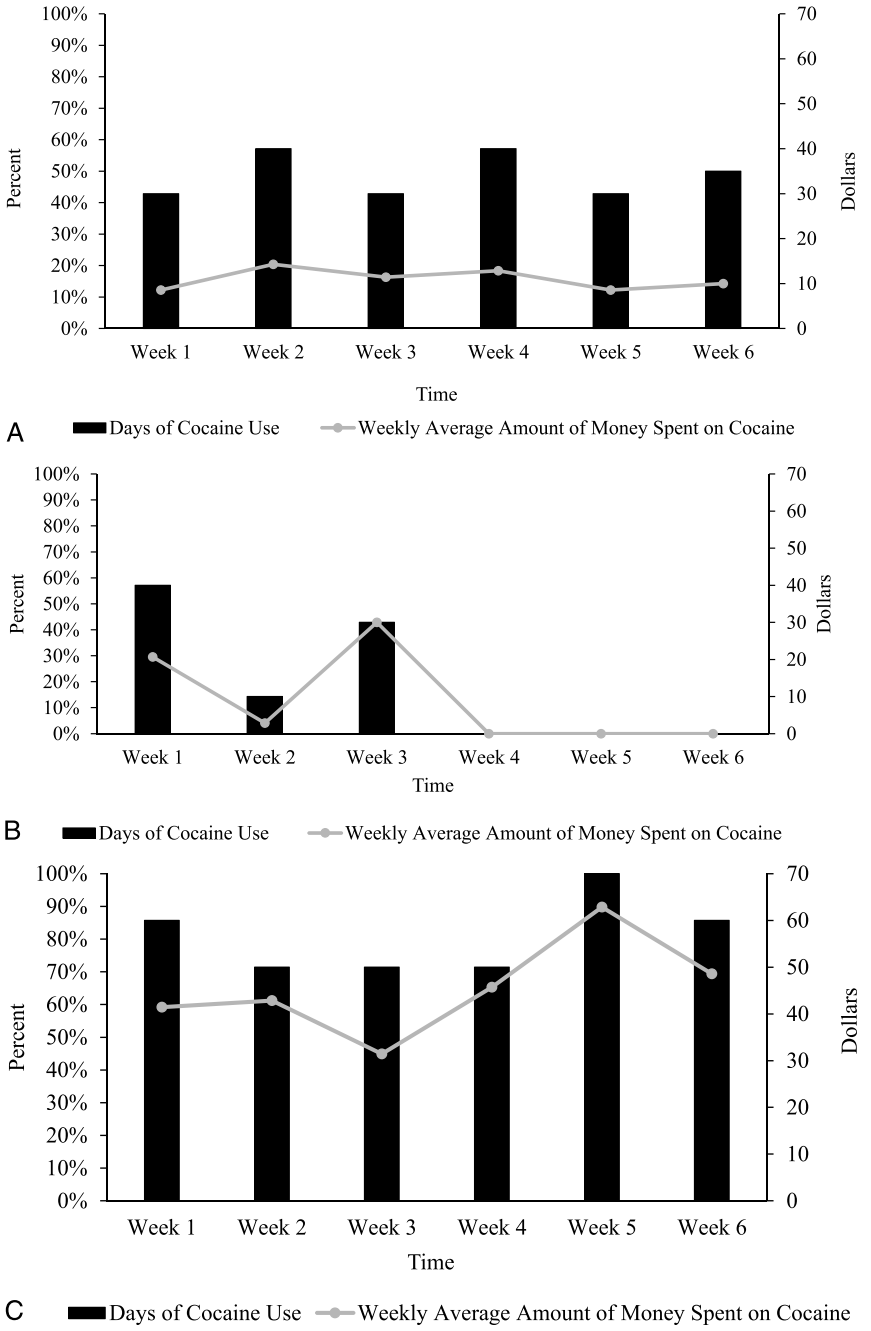

FIGURE 1. Self-reported days of cocaine use and amount of money spent on cocaine averaged across weeks of treatment.

at baseline, which fluctuated between moderate and none across weeks 1 to 6.

Mood

Case A BDI-II baseline score was in the moderate clinical range but decreased to the minimal by week 6. Case B and case C BDI-II scores remained below the clinical range from baseline to week 6. Case A PANAS scores for positive affect remained stable, while negative affect scores declined from baseline to week 6. Case B PANAS-positive affect increased, with no change in negative affect. Case C PANAS positive and negative affect scores were stable.

DISCUSSION

This case series study demonstrates the feasibility and safety of exenatide for CUD treatment. We observed 100% attendance and compliance with once-weekly exenatide injection visits. End-of-study satisfaction ratings were generally positive, with all cases indicating preference for treatment continuation. The medication was well-tolerated without unexpected or severe adverse events. Collection of clinical data on the effects

of exenatide revealed a mixed picture. In 2 cases, cocaine use persisted throughout treatment, alongside fluctuating ratings of craving intensity. Case B was an exception in showing achievement of cocaine abstinence by week 4, which was sustained through week 6. Admittedly, it is difficult to determine whether case B's SAE influenced his substance use, given the plausibility that the SAE contributed to a reduction in cocaine craving irrespective of, or in combination with, exenatide. Nonetheless, case B's achievement of abstinence was associated with decreased cocaine craving, increased positive affect, and high rates of treatment acceptability, suggesting that treatment response was not entirely driven by the SAE. This treatment response is noteworthy, given the selected cases were former patients with a significant history of cocaine use and poor response to previous treatments. It is tempting to consider the potential clinical impact of a 1 in 3 response rate, should the current findings replicate in a larger randomized placebo-controlled trial. These findings add to preclinical data that support a strong scientific premise for targeting GLP-1Rs as an intervention for CUD.[3,14]

Most candidate agents tested for CUD treatment were oral medications requiring daily dosing schedules that are prone to problems with adherence. Indeed, negative findings reported in several CUD trials have been attributed to high rates of medication nonadherence.[15] Long-acting reduced dosing regimens are generally associated with greater patient satisfaction and adherence.[16] Thus, once-weekly injectable exenatide represents a novel and potentially advantageous formulation for achieving optimal adherence in the clinical study and treatment of patients with CUD.

Results from this preliminary case series should be considered cautiously in light of potential biases inherent to non-randomized small sample size studies, lack of control subjects and risk of selection bias. Limitations include the inability to generalize to a larger patient population with varied CUD severity. Whether exenatide "works better" for individuals with less severe CUD, which may have been a factor in the abstinence response of case B, needs to be further examined. Participants' knowledge of receiving exenatide may have affected reports of treatment effects. For our primary aim of assessing feasibility and acceptability, 6 weeks was sufficient to capture the early phase of treatment when dropout rates are highest[17]; however, longer durations with more frequent drug use monitoring are recommended for determining the therapeutic efficacy of a medication for CUD treatment.[18] In particular, steady state plasma exenatide levels are reached within 6 to 7 weeks,[19] beyond the duration of drug exposure in the current study. While the current study monitored patient safety (e.g., assessing for hypoglycemia, SAEs), future studies of longer duration will benefit from additional monitoring of the safety of exenatide among individuals with CUD (e.g., continuous glucose monitoring). Future research should also assess the acceptability of an injectable medication among a larger population of patients with CUD. While exenatide showed good acceptability in the current study, conceivably, anxiety and fear about using an injectable medication could be a barrier to therapy initiation among some patients with CUD. Lastly, the possibility of extraneous factors affecting outcomes cannot be ruled out.

CONCLUSIONS

Despite limitations, the present data from 3 completed cases without missing data strengthens the evidence that treatment consisting of 6-weekly exenatide injections is feasible, acceptable, and safe. Case series like this one allow for screening putative medications for CUD, a field in which numerous drugs have undergone clinical trial evaluation without yielding a Food and Drug Administration–approved medication. The pharmacological actions of GLP-1RAs make them attractive candidate agents for treating CUD.

ACKNOWLEDGMENTS

The authors thank Jessica Vincent and staff at the Center for Neurobehavioral Research on Addiction for their assistance in conducting this study.

REFERENCES

1. Larsen PJ, Tang-Christensen M, Holst JJ, et al. Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem. *Neuroscience* 1997;77:257–270.
2. Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. *J Comp Neurol* 1999;403:261–280.
3. Sorensen G, Reddy IA, Weikop P, et al. The glucagon-like peptide 1 (GLP-1) receptor agonist exendin-4 reduces cocaine self-administration in mice. *Physiol Behav* 2015;149:262–268.
4. Egecioglu E, Engel JA, Jerlhag E. The glucagon-like peptide 1 analogue, exendin-4, attenuates the rewarding properties of psychostimulant drugs in mice. *PLoS One* 2013;8:e69010.
5. Graham DL, Erreger K, Galli A, et al. GLP-1 analog attenuates cocaine reward. *Mol Psychiatry* 2013;18:961–962.
6. Bouhlal S, Ellefsen KN, Sheskier MB, et al. 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* 2017;180:68–75.
7. Angarita GA, Matuskey D, Pittman B, et al. Testing the effects of the GLP-1 receptor agonist exenatide on cocaine self-administration and subjective responses in humans with cocaine use disorder. *Drug Alcohol Depend* 2021;221:108614.
8. First MB. Structured Clinical Interview for the DSM (SCID). In: The Encyclopedia of Clinical Psychology vol. 1–6.
9. Crits-Christoph P, Siqueland L, Blaine J, et al. Psychosocial treatments for cocaine dependence: National Institute on Drug Abuse collaborative cocaine treatment study. *Arch Gen Psychiatry* 1999;56:493–502.
10. Robinson SM, Sobell LC, Sobell MB, et al. Reliability of the timeline Followback for cocaine, cannabis, and cigarette use. *Psychol Addict Behav* 2014;28:154–162.
11. Mezinskis J, Dyrenforth S, Goldsmith JR, et al. Craving and withdrawal symptoms for various drugs of abuse. *Psychiatr Ann* 1998;28:577–583.
12. Beck AT, Steer RA, Ball R, et al. Comparison of Beck depression inventories -IA and -II in psychiatric outpatients. *J Pers Assess* 1996;67:588–597.
13. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. *J Pers Soc Psychol* 1988;54:1063–1070.
14. Fortin SM, Roitman MF. Central GLP-1 receptor activation modulates cocaine-evoked phasic dopamine signaling in the nucleus accumbens core. *Physiol Behav* 2017;176:17–25.
15. Somoza EC, Winship D, Gorodetzky CW, et al. A multisite, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of vigabatrin for treating cocaine dependence. *JAMA Psychiat* 2013;70:630–637.
16. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: A review of literature. *J Behav Med* 2008;31:213–224.
17. López-Goñi JJ, Fernández-Montalvo J, Arteaga A. Addiction treatment dropout: Exploring patients' characteristics. *Am J Addict* 2012;21:78–85.
18. Montoya ID, Hess JM, Preston KL, et al. A model for pharmacological research-treatment of cocaine dependence. *J Subst Abus Treat* 1995;12:415–421.
19. Fineman M, Flanagan S, Taylor K, et al. Pharmacokinetics and pharmacodynamics of exenatide extended-release after single and multiple dosing. *Clin Pharmacokinet* 2011;50:65–74.

