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Cocaine self-administration disrupted by the *N*-methyl-D-aspartate receptor antagonist ketamine: a randomized, crossover trial

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Abstract

Repeated drug consumption may progress to problematic use by triggering neuroplastic adaptations that attenuate sensitivity to natural rewards while increasing reactivity to craving and drug cues. Using an established laboratory model aimed at evaluating behavioral shifts in the salience of cocaine now vs. money later, we evaluated the effect on cocaine use of a single sub-anesthetic dose of the *N*-methyl-D-aspartate receptor antagonist ketamine, which converging evidence suggests may work to correct problematic neuroadaptations and restore motivation for non-drug rewards. We found that ketamine, as compared to the control, significantly decreased cocaine self-administration by 67% relative to baseline at greater than 24 hours post-infusion, the most robust reduction observed to date in human cocaine users and the first to involve mechanisms other than stimulant or dopamine agonist effects. These findings signal new directions in medication development for substance use disorders.

Introduction

Substance use disorders are characterized by progressively uncontrollable drug use despite negative consequences. It is now recognized that repeated drug consumption may evolve into problematic use by precipitating sustained neural adaptations.[1,2] These adaptations are thought to originate in neuroplastic alterations in striatal and prefrontal glutamate neurotransmission,[1] and have been hypothesized to be implicated in several functional alterations in individuals with substance use disorders, such as abnormal glutamate homeostasis in the anterior cingulate cortex (ACC), impaired prefrontal modulation of mesolimbic structures (e.g., amygdala and nucleus accumbens: NAcc), and disruptions in dopamine signaling in the NAcc.[1-3] Vulnerabilities associated with these alterations, and that may contribute to problematic use, include reduced sensitivity to non-drug rewards, heightened motivation for drug use (craving), compulsive drug-seeking to override

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diminished subjective drug effects, poor impulse control, delay discounting (diminishing the value of a reward if delayed), and heightened reactivity to cravings, drug cues, and stress.[1-4]

Though these adaptations have been studied extensively with cocaine in laboratory animals, they have been resistant to pharmacotherapy in human research. Further, despite decades of research, there remain no consistently effective medications for cocaine use disorders. Modulation of the *N*-methyl-D-aspartate receptor (NMDAR), the main glutamate receptor involved in neural plasticity, disrupts the reinforcing effects of cocaine in rodents,[5] but comparable modulators have proven ineffective in humans.[6-8] In addition, preliminary data indicate that infusing brain-derived neurotrophic factor (BDNF) into the medial prefrontal cortex of mice disrupts cocaine use, perhaps by promoting neuroplasticity to reverse drug-related adaptations.[9] In preclinical human research, however, the only agents found to reduce cocaine self-administration, albeit modestly, are stimulants such as modafinil and amphetamine,[10,11] consistent with existing data (e.g., for opioids) concerning the effect of agonists on self-administration.[12]

Recent clinical research with the NMDAR antagonist ketamine, a widely used dissociative anesthetic, indicates that a single sub-anesthetic intravenous (i.v.) infusion produces rapid relief for depressive and anxiety disorders, with the therapeutic response continuing to grow in magnitude after all metabolites have cleared and generally peaking at 24-72 hours.[13] This unique effect has been attributed to the promotion of prefrontal neural plasticity via downstream mechanisms involving BDNF and other factors,[13-15] as well as sustained modulatory benefits such as improvement of ACC glutamate homeostasis and attenuation of functional network hyperconnectivity.[13,16,17] Preliminary data indicate that these mechanisms may also extend to addressing the adaptations associated with drug dependence, with a single sub-anesthetic ketamine infusion found to rapidly improve two dependence-related vulnerabilities by self-assessment: low motivation for non-drug rewards and high cue-induced craving.[4] In the absence of behavioral data, however, it is not possible to conclude whether these effects on motivation and craving represent new evidence that ketamine targets dependence-related deficits, or whether they constitute an extension of its recognized impact on comparable subjective states, such as anxiety or dysphoria.[13]

To expand on these data, we modified an established laboratory model of drug self-administration to assess the effect of ketamine on cocaine use. The paradigm was designed to detect behavioral shifts in the relative salience of cocaine now vs. money later at greater than 24 hours post-infusion, and therefore allowed for evaluating whether the hypothesized effects of ketamine on craving, motivation for non-drug reward, and delay discounting impact on cocaine use. We predicted that ketamine, compared to an active control, would significantly decrease the number of cocaine choices, ranging from 0 to 5, ascertained at around 28 hours post-infusion, a time-point at which its psychiatric efficacy generally peaks and long after active metabolites and psychoactive effects have cleared.[13] Other aims pertained to the persistent effects of ketamine on reactivity, and on craving and drug use in the natural ecology.

Methods

Overview

20 non-depressed, cocaine dependent individuals disinterested in treatment or abstinence completed this crossover trial approved by the New York State Psychiatric Institutional Review Board (NCT02596022). After understanding research risks and providing informed consent, participants were hospitalized up to 3 times in a controlled research unit for 6 days at a time, and each hospitalization was separated by two weeks to account for carry-over effects and to assess cocaine use in the natural ecology. Each 6-day hospitalization involved 1) an initial 2-day washout period; 2) a 28-minute "sample session" on Day 3 when 2 obligatory free-base cocaine doses (25 mg) were smoked to allow for assignment of value to the research cocaine and to intensify craving; 3) a 52-minute i.v. infusion on Day 4; 4) a 70-minute "choice session" of 5 choices (25 mg cocaine vs. $11) on Day 5; and 5) discharge on Day 6. During the first hospitalization, participants received an infusion of normal saline so as to identify, and exclude from research, individuals who do not robustly choose cocaine prior to the active infusions (≤2 choices). In the second and third hospitalizations, participants were randomized (1:1) to counter-balanced orderings of 52-minute sub-anesthetic infusions of ketamine (0.71 mg/kg) or of the active control midazolam (0.025 mg/kg) under double-blind conditions. The study was powered to detect a difference of at least 1 cocaine choice between active conditions by paired *t*-test. No psychotherapy or behavioral treatment was provided.

Participants

We recruited participants by word of mouth, advertising, and referral. At the first contact, a standardized telephone interview was conducted. Individuals who preliminarily met entry criteria were scheduled for a first screening visit, during which the they gave informed consent to provide a urine sample for toxicology and urinalysis, to meet with research staff for a standardized diagnostic evaluation (SCID)[18] and with a psychiatrist for a medical and psychiatric evaluation, and for completion of the Hamilton Depression Scale (HAM-D)[19] and Dissociative Experiences Scale (DES).[20] If still eligible, they underwent serum collection (comprehensive blood cell assessment with differential: CBC; electrolyte panel including liver function tests; pseudocholinesterase levels to assess for appropriate metabolism of cocaine; pregnancy tests for females) and other diagnostic tests (electrocardiogram: ECG). Applicants were considered eligible if they were medically healthy, non-treatment seeking cocaine dependent individuals who met minimum use criteria (at least two occasions of free-base cocaine use a week, at greater than $40 each time), who were between the ages of 21 and 55, and who did not have a history of abuse of or adverse reaction to ketamine or benzodiazepines. Individuals with physiological dependence on certain other substances (opioids, alcohol, benzodiazepines), with a history of psychotic or dissociative symptoms, with current depressive or anxiety symptoms indicative of a DSM-IV disorder[18], with a first-degree family history of psychosis, with obesity (BMI > 35), or with cardiovascular or pulmonary disease were excluded. Eligible patients were scheduled for another visit during which they provided informed consent and were admitted into the protocol.

Cocaine self-administration

The cocaine administration procedures in this study were identical to those previously used at our Institution and elsewhere, and the laboratory paradigm of self-administration was adapted from established models evaluating medication effects on abstinence initiation.[10-12,21]

Various protections were in place to reduce the risks associated with cocaine administration. Participants were provided with continuous ECG monitoring, automated blood pressure assessments, and medical coverage during cocaine administration and up to 2 hours afterwards.

The dose of free-base cocaine used in this study (25 mg) has been safely administered in prior studies with minimal adverse effects, and has been consistently associated with moderate-to-high subjective effects.[10,11,22] Cocaine was produced and packaged by the New York State Psychiatric Institute (NYSPI) pharmacy, prepared by experienced staff, and administered to participants over the course of one minute. A Pyrex tube fitted with a mesh filter served as the smoking implement, or "stem." Stems were constructed to function as uniformly as possible, with only negligible differences in the density and tightness of the mesh. Self-administration procedures occurred in the same room and at around the same time of day. Efforts were taken to control other variables (e.g., amount of sleep; receipt of auxiliary medications; interactions with staff; food, cigarette, and caffeine consumption) that might impact on cocaine use and choice behavior.

Two cocaine doses (25mg) were administered starting at 1 pm on Day 3 of each hospitalization, following a 2-day washout period. This session was intended to allow participants to sample and assign value to the research cocaine, to prepare participants for the choice session, and to heighten cocaine craving. On Day 5, participants underwent a session of five choices (25 mg of free-base cocaine or $11), starting at about 2 pm (around 28 hours post-infusion). $11 at discharge has been determined in previous trials to be of comparable value to the 25 mg dose of cocaine[10-12]; earned money was provided at discharge from the inpatient laboratory on Day 6.

All cocaine administrations occurred fourteen minutes apart, and strict precautions were in place to ensure that participants were safe to receive initial and subsequent doses. The choice to use cocaine or receive money was ascertained at the beginning of the session and at seven minutes into the 14-minute interval between cocaine administrations. The design of the study made it unlikely that there were any drug-drug interactions between cocaine and ketamine or midazolam, the active metabolites of which have short half-lives (1, 3, and 6 hours, respectively) and short-lived effects. Various ratings occurred after each dose was administered. Levels of craving and arousal were also assessed using the visual analogue scale (VAS) every four minutes between choices or drug administrations.

Infusion Procedures

In addition to the sham infusion in Inpatient Phase 1 (saline over 52 minutes), two counter-balanced active infusions were administered, each on Day 4 of Inpatient Phases 2 and 3. The sham infusion was provided initially so as to identify, and exclude from continuing in the

study, participants who do not choose cocaine at least 3 times in the absence of the two study conditions. Choice behavior following the sham infusion also served as the baseline for determining the percent reduction in cocaine self-administration for the active conditions. So as to minimize risk, all infusions were given in a highly controlled inpatient setting. Blinded staff was involved with infusion administration and intravenous placement.

Patients were not exposed to cocaine in the 24 hours prior to the infusion and did not eat from the midnight before so as to reduce the risk of nausea, adverse interactions, and aspiration. Participants were informed throughout the study that they may possibly receive any of various substances at each infusion, including amantadine, buspirone, d-cycloserine, ketamine, lorazepam, memantine, methamphetamine, saline, or any combination of these. This blinding procedure is intended to disguise what drug is specifically given so as to minimize expectancy effects.[4] Similarly, it aimed to minimize the risk that participants would clearly identify the medications that were administered.

Active control (2-min saline bolus followed by midazolam 0.025 mg/kg in saline infused over 50 minutes) or ketamine hydrochloride (0.11 mg/kg 2-min bolus followed by 0.60 mg/kg in saline over 50 minutes) were prepared and packaged for slow-drip infusion by the NYSPI pharmacy, and administered at around 11 am on day 4. The dose of ketamine was selected on the basis of published reports suggesting that it was well tolerated.[22] It was also the highest dose tolerated by participants in our preliminary studies.[4,23] Midazolam was chosen as the active control because it produces a mild change in consciousness, further obscuring the distinction between conditions so as to ensure blinding, and because of its short half-life, without any known persistent (> 8 hours) effect on cue reactivity or cocaine dependence.[24] Blood pressure, heart rate, and blood oxygen saturation were continuously monitored. Medical coverage was provided during and up to two hours after the infusion; a psychiatrist provided a brief safety and psychiatric evaluation at the end of the monitoring period.

Prior experience with sub-anesthetic ketamine administration in research and clinical settings suggest that psychological preparation and relaxation exercises reduce or prevent the anxiety that might develop during administration.[25] In our preliminary study,[4] we found relaxation and breathing exercises to be helpful when administered before, and in some cases during, the infusion, and these were also employed here. A Clinician Administered Dissociative States Scale (CADSS) was administered at the conclusion of the infusion by a research assistant.[26] Participants also completed various assessments pertaining to subjective effects.

Follow-up

Participants met thrice weekly with research staff for 2 weeks following each hospitalization. They provided urine at each visit for toxicology testing; provided information on drug use; and completed various assessments and questionnaires pertaining to cocaine craving, reactivity, and side effects from the study medications.

Compensation

Participants were given $5 for each screening visit to defray the costs of travel, as well as $20 for screening itself. Non-completers earned $30 a day for the inpatient phase, while completers earned $60 a day. There was also a final completion bonus of $60. The bulk of compensation for the inpatient stays was provided in installments during the final week.

Money earned during choice days was provided at discharge from each hospitalization, along with $100; the maximum participants might receive on Day 6 was therefore $155. The $100 provided at discharge from each hospitalization was ultimately deducted from the final amount at the end of study. Participants were also provided $25 for each follow-up visit. Total compensation for each participant was a maximum of $1590.

Statistical Analyses

The distribution of values in dependent variables was found to be normal using Shapiro-Wilk tests for all conditions. SAS[27] was used to perform all tests. For the primary outcome (cocaine choices post-ketamine vs. post-midazolam) and for non-reactivity scores, a paired *t*-test was conducted comparing post-infusion values during the 2nd and 3rd hospitalizations, with 2-tailed $\alpha = 0.05$. Order effects were assessed by comparing outcomes for each condition by order received (i.e., 2nd or 3rd hospitalization). For secondary analyses of subjective drug effects, drug use, and craving, we conducted analyses of variance (ANOVA) and paired *t* tests, with 2-tailed $\alpha = 0.05$ and corrected accordingly for each repeated-measures analysis.

Findings

Participants

To obtain our final sample size of 20, we enrolled 26 participants. Four participants were removed due to not choosing cocaine sufficiently at baseline after the saline infusion, one removed for inability to comply with study procedures and one removed for seeking treatment. The final sample was predominantly African American and unemployed, with high baseline cocaine use (Table 1).

All participants tolerated study procedures without notable adverse effects. As expected,[22,23] ketamine led to acute dissociation that resolved within 30 minutes post-infusion (Fig 1a). There were no persistent dissociative (1b) or other adverse effects. Participants did not report significant changes in their pre-infusion responses to cocaine administration over the course of study participation, with the potency and quality of sample doses rated consistently (1c) and thus unlikely to impact on post-infusion choice behavior. Post-infusion cocaine effects could not be analyzed because a number of participants did not choose cocaine at all following ketamine.

Two participants maintained abstinence in follow-up after receiving ketamine during the 2nd hospitalization. This finding is consistent with prior data suggesting ketamine promotes abstinence in previously disinterested individuals.[4] Though ineligible for a 3rd hospitalization to prevent obligatory cocaine administration, they were included in the final

sample so as to compare abstinence rates following the first active infusion (2/10 post-ketamine vs. 0/10 post-midazolam). The remaining 18 were included in the primary analysis pertaining to cocaine self-administration, as well as in secondary analyses.

Cocaine self-administration

Ketamine led to an average 1.61 cocaine choices 28 h post-infusion (vs. 4.33 choices with midazolam) (t_{17df}=5.43, $p < 0.0001$), a 67% reduction from (post-saline) baseline (Fig 2a). There were no order effects, suggesting 2 weeks was sufficient to allow ketamine effects on self-administration to subside.

Cocaine use in the natural ecology

Use reduction relative to baseline was calculated for each time-point during the 2-week follow-up period after each active condition. Ketamine led to significant reductions in cocaine use initially, but ceased to separate from midazolam after several days (Fig 2c).

Cocaine craving

We evaluated cocaine craving, assessed with a 100-mm Visual Analogue Scale (VAS) at each time-point, starting with 24 hours post-infusion. As with use, ketamine significantly reduced craving initially but not throughout the monitoring period (Fig 2d).

Non-reactivity

We evaluated the effect of ketamine on the non-reactivity subscale of the Five Facet Mindfulness Questionnaire, which measures the extent to which participants endorse tolerating distress without engaging in problematic behavior.[28] Reactivity is thought to represent a key deficit contributing to such vulnerabilities as stress sensitivity and impulsivity.[29] Ketamine led to a significantly higher non-reactivity score of 3.46 (vs. 2.92 with midazolam, out of a maximum score of 5, t_{17df}=-2.39, $p < 0.05$) lasting at least 48 hours post-infusion.

Discussion

This investigation of the NMDAR antagonist ketamine is the first to indicate that a medication beyond stimulants or dopamine agonists may exert promising effects on cocaine use under controlled laboratory conditions. The disruption in cocaine self-administration is the most robust observed to date in human cocaine users,[10,11] and the persistent effects on drug use in the natural ecology after a single ketamine dose (with some participants sustaining abstinence for at least 2 weeks) suggest clinical utility. While generalizability might be limited by the highly controlled methodology and homogenous sample, these findings provide new evidence that ketamine may have enduring effects on problematic behavior and decision-making, alongside the previously reported effects on subjective states, such as dysphoria.[13]

Although this trial is not designed to identify underlying neuronal mechanisms, it demonstrates that cocaine self-administration is reduced by a pharmacotherapy hypothesized to provide benefit by rapidly correcting neuroplastic adaptations. Indeed, the data argue that

ketamine disrupts drug use by targeting two important adaptations: drug craving and the disproportionate valuation of immediate drug over delayed non-drug rewards.[4] The effects on reactivity provide further insight into possible mechanisms.[29] These findings may be interpreted as expanding on preclinical research identifying but unsuccessfully targeting dependence-related neuroplastic changes[1] and signal new directions in medication development for cocaine use disorders, with important implications for substance use disorders more generally given the broad overlap in the pathophysiology of neuroadaptations to different drugs.[1-3]

There are some key differences between the methodology of this trial and of previous investigations assessing medication effects on cocaine self-administration. First, our participants were not simply cocaine users exceeding minimum use criteria; they also met DSM-IV criteria for cocaine dependence. Prior laboratory-based research has focused almost entirely on cocaine users who met minimum use criteria without necessarily meeting diagnostic criteria for dependence.[10-12,21] Alongside leading to a diagnostically heterogeneous population, these selection criteria might compromise the evaluation of medication effects because non-dependent participants may not exhibit the vulnerabilities that are being targeted. Second, unlike the majority of prior research, we introduced at the beginning of the trial a single-blind sham condition (distinct from the active control provided subsequently) to ascertain baseline cocaine self-administration, and to exclude from further participation individuals who do not robustly choose cocaine. This design decision, like the first, was intended to ensure that the study population demonstrated impairment.

Given the robustness of the disruption in cocaine use at 28 hours post-ketamine, it is possible that this effect would have been apparent more acutely, as has been observed with the anti-depressant response,[13] though this was not tested in favor of assessing relatively persistent benefits. These sustained reductions in drug use, observed after all ketamine metabolites were expected to be excreted, resembles the persistence of its effects on mood and anxiety,[13] and suggests involvement of similar down-stream pro-plasticity and modulatory mechanisms.[4] These similarities may be interpreted to support the emerging hypothesis that certain neural adaptations are shared by affective, stress-related and substance use disorders,[4,30] despite variability in their development and expression, and that pharmacotherapy aimed at addressing these common deficits, such as ketamine, may be effective for different disorders. Preclinical research with rodents provides preliminary evidence that the anti-depressant and anti-addiction effects of ketamine involve similar mechanisms; ketamine has been shown to mitigate distress related to amphetamine withdrawal by normalizing NAcc dopamine neurotransmission through down-stream activity,[30] and to disrupt alcohol consumption via a neuroplastic mechanism involving mammalian target of rapamycin,[31] which has also been identified as a critical pathway for the effect of ketamine on depression.[32] Research is needed to elucidate the differences in pathophysiology of drug- and stress-related adaptations so as to more effectively target their diverse psychiatric and behavioral manifestations, and to further clarify the mechanisms by which ketamine disrupts problematic drug use.

Though its rapid and apparently persistent effects suggest a role in initiating abstinence, it remains to be determined how ketamine might be feasibly integrated into the treatment of

substance use disorders. Decades ago, intramuscular ketamine showed promise for alcohol and opioid problems in the context of a “psychedelic psychotherapy” aimed at utilizing its psychoactive effects therapeutically.[33] Ketamine has since demonstrated abuse liability given these hallucinogenic effects,[34] but this risk is substantially minimized by the slow-drip i.v. route and administration in medical contexts.[13,22,23,35,36] Safety may be further optimized by embedding the infusion into a framework aimed at managing its psychoactive properties,[23,35,37] or by developing comparable compounds associated with diminished abuse liability.[13,38]

Sustaining efficacy represents another challenge. Serial infusions or maintenance medications extending the neurobiological activity of ketamine might be helpful.[12,38] A behavioral treatment platform may also be important for further targeting dependence-related deficits and facilitating behavioral modification. Relapse prevention treatment, for example, emphasizes developing non-reactivity to drug cravings and impulses,[39] and may serve to leverage ketamine effects into persistent behavioral changes. Therefore, alongside proposing a novel medication strategy with unprecedented benefits for cocaine use disorders, these findings suggest new approaches for integrated medication-behavioral treatments, and provide promise for better addressing a disabling group of disorders often refractory to available interventions. Research is needed to replicate these findings, extend them to clinical settings, and elucidate the mechanisms by which ketamine ameliorates dependence-related vulnerabilities.

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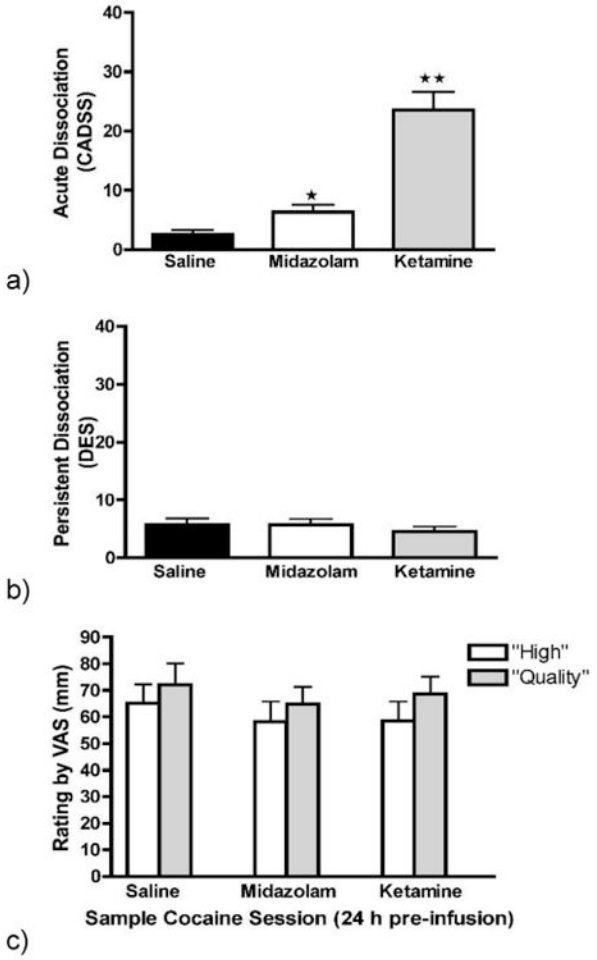

Figure 1. Subjective Effects of Infusions and Cocaine Administration

a) Ketamine led to significantly greater acute dissociation during the infusion, ascertained through a scale focused on acute effects (Clinician Administered Dissociative Symptoms Scale: CADSS), than did both midazolam and saline, ** $p < 0.001$, while midazolam led to greater acute dissociation than did saline, * $p < 0.01$. b) There were no significant differences between infusions on persistent dissociative effects, ascertained at least 24 hours post-infusion using a scale intended for persistent effects (Dissociative Experiences Scale: DES). c) There were no significant differences in the subjective effects or value of the sample cocaine sessions under each condition.

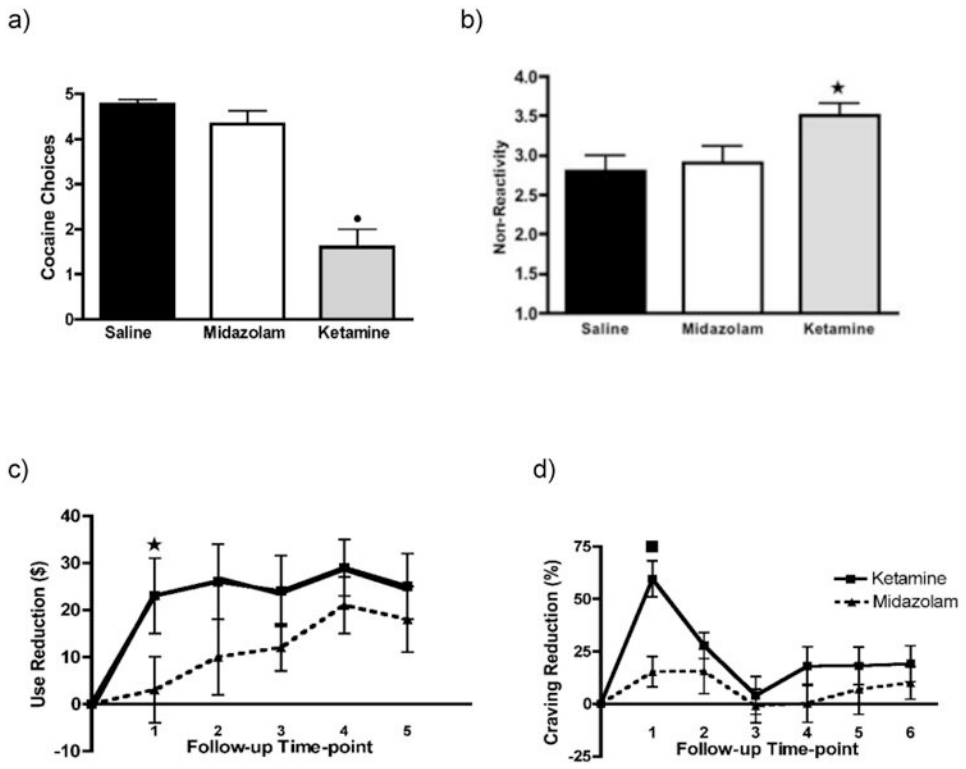

Figure 2. The effects of ketamine on cocaine self-administration and related outcomes

a) Shown are choices of cocaine at 28 h post-infusion for each condition, with ketamine leading to. significantly less use than midazolam: 4.33 vs. 1.61 choices t_{17df}=5.48, • $p <$ 0.0001. Error bars signify. standard error of the mean (s.e.m.). b) Ketamine significantly promoted non-reactivity at 48 hours postinfusion. compared to midazolam. Shown are non-reactivity scores of the Five Facet Mindfulness. Questionnaire (FFMQ), from a maximum possible score of 5: 3.46 vs. 2.92, t_{17df}=-2.39, ★ $p < 0.05$. c). Ketamine (vs. midazolam) led to reduction in cocaine use, calculated in $, in the natural ecology,. with each time point corresponding to mean use over the preceding 3-day period. Initial reduction in use. ($22.45 vs. $3.20, t_{17df} =2.97, ★ $p < 0.05$) lost significance subsequently. d) Ketamine (vs. midazolam). significantly reduced desire/craving for cocaine by visual analogue scale ratings, calculated as percent. change from the corresponding time-point following the saline infusion. Ketamine led to significant craving. reduction prior to discharge (59.6% vs. 15.3%, t_{17df}=3.44, ■ $p < 0.01$) but not at subsequent time-points

Table 1
Participant Demographic and Morbidity Information (n=20)

Age, Years (SD)	**48.6 (6.1)**
African-American	n=15, 75%
Hispanic	n=4, 20%
White	n=1, 5%
Male	n=11, 55%
Unemployed	n=16, 80%
Education (>12 Yrs H.S. equivalent)	n=15, 75%
Baseline Cocaine Choices (SD)	4.78 (0.43)
Cocaine Use Days/Past Month (SD)	9.8 (7.2)
Cocaine Amount/Day, $(SD)	46.88 (30.74)