Title: **Does childhood adversity alter opioid drug reward? A conceptual replication in outpatients before surgery**

Short title: opioid drug reward after childhood adversity

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Abstract

Introduction: Opioid analgesic treatment after surgery entails some risk of persistent use. Experiences of childhood adversity has been shown to increase opioid reward in preclinical models, ~~and was~~a finding recently extended to healthy humans. We tested whether childhood adversity similarly increased opioid reward, operationalised as drug-induced mood boost~~,~~ and subjective ~~high and~~ drug liking, in outpatients receiving opioids on the operating table.

Methods: This observational study recruited patients entering a Norwegian hospital for an outpatient surgical procedure. An opioid analgesic was administered intravenously (remifentanil; Minto model, effect site concentration: 5ng/ml, or oxycodone 5mg) in the minutes before general anaesthesia. Verbal numerical ratings of feeling good and anxious were collected 1 minute before and 1-3 minutes after opioid infusion. Ratings of drug liking, disliking, and feeling high were also collected. Patients (n = 155) completed measures of childhood aversity (childhood trauma and socio-economic status) at a later date.

Results:

Discussion:

Keywords: Childhood trauma; childhood adversity, opioids; pleasure; subjective effects; reward; analgesics

1. Introduction

Experiences of childhood adversity (such as abuse, neglect, and household dysfunction) are prevalent among people with opioid use disorders (OUD) (1, 2). Several mechanisms may underlie this link, including the use of opioids to cope with dysregulated emotion processing (3), heightened pain sensitivity (4), increased stress vulnerability (5), and greater impulsivity (6) after childhood adversity. Another important mechanism contributing to this link may be an increased sensitivity to opioid reward. In the context of childhood adversity, neurodevelopmental changes to reward and motivation networks may contribute to heightened reward responses to drugs such as opioids, leading to a greater risk of abuse and addiction (7).

Preclinical research supports neurobiological changes in reward networks in animals exposed to early adversity, paired with altered drug responses (8-10). Rodents exposed to maternal separation or limited bedding and nesting as infants (both models of early adversity in animals) demonstrate greater self-administration of opioids, conditioned place-preference for opioid-paired areas (8), resistance to extinction of opioid-seeking behaviours, and faster reinstatement of opioid seeking-behaviours when exposed to cues (9). This effect ~~was~~ has been shown to be stronger for opioids over other drugs such as stimulants or alcohol, indicating an opioid-specific preference after experiences of early adversity (10). ~~Heightened reward responses among animals with early adversity were also associated to reductions in mu-opioid receptor density, and a reduced analgesic response to the drug~~ (8, 10)~~. Reduced mu-opioid receptor expression after early life stress has also been reported for mice~~ (11)~~, and preliminary positron emission tomography (PET) evidence also linked reductions in resting mu-opioid receptor availability to insecure childhood attachment styles. T~~There are several potential mechanisms to help explain this heightened reward response after early adversity~~.~~ Panksepp (11) proposed that opioid drugs ~~may~~ mimic the pleasure experienced from caring social bonds by binding to the mu-opioid attachment circuitry, and that exposure to adverse social factors (such as isolation) may increase the desirability of opioids. Accordingly, this may be one explanation for an ~~and that this~~enhanced pleasure response to opioids ~~will~~ may be greater ~~among for~~those with limited early experiences of ~~stable~~ caring social bonds in childhood. However, support for this theory has scarcely been translated from preclinical findings to humans.

A recent translational study measured reward responses to morphine in people with and without experiences of childhood adversity (12). Using a placebo-controlled, double-blind opioid administration design, this study examined subjective and behavioural responses to an intramuscular dose of morphine (0.15 mg/kg) in healthy participants with either severe or no history of childhood abuse and neglect. Individuals with severe childhood

adversity rated the effects of morphine as more likeable, ~~felt more~~ euphoric, and reported greater wanting for more drug from 15 minutes after the morphine administration. The childhood adversity group also rated less disliking, nausea and dizziness from 90 minutes after the dose compared with the non-~~trauma~~ adversity group. However, behavioural indices of reward from a progressive ratio paradigm where participants could work for hypothetical rewards (money or more morphine) did not significantly differ between the two groups. ~~Furthermore, morphine increased physical pain threshold and tolerance to a comparable degree in the two groups.~~ These results represent important initial evidence that childhood adversity could enhance risk of opioid misuse via increased drug reward in humans.

Opioid analgesics such as morphine are critical medicines that are administered to millions of people every year. Rates of persistent use after surgical treatment in the USA are 5-10% (13, 14). Known risk factors of persistent opioid use after surgery include conditions such as depression, anxiety and chronic pain (15), which are also more frequent in people who experienced childhood adversity. Here, we examined whether childhood adversity increases ~~risk of opioid misuse via~~ positive ~~drug~~ effects of opioids given in a medical context. Positive drug effects are considered a sign of higher abuse liability (5)~~. , and these results could~~ may help ensure at-risk patients ~~receive~~ the best practice treatment, and informing more individualised approaches to the prescribing of opioid analgesics. Furthermore, ~~a~~As replication and generalisation are critical components of the scientific method, it is essential to understand whether the previous findings are generalisable to naturalistic contexts where opioids are frequently administered.

We aimed to conceptually replicate the findings from the previous study (12) in generally healthy patients undergoing outpatient surgery. In this observational study, patients were given an intravenous dose of either remifentanil or oxycodone ~~-~~as part of routine care prior to being anaesthetised. Both drugs are opioid agonists that are fast-acting and primarily stimulate the μ-opioid receptor subtype, and are frequently used both pre- and post-operatively to provide quick and effective pain relief. Patients~~, and~~ were asked to give verbal numerical ratings of ~~mood~~ how good and how anxious they felt immediately before and one minute after ~~drug~~ opioid infusion, as well as to rate their liking of the effects, disliking of the effects, and feeling high between one and three minutes after ~~the drug administration. Several months after their surgery, p~~Patients later completed additional state and trait measures. ~~In line with the prior findings, w~~We ~~firstly~~ Our primary ~~hypothesei~~sed ~~wase~~re that patients with greater childhood adversity (higher trauma) ~~and lower socio-economic status scores)~~ would 1) exhibit a larger mood boost (*feeling good*), and 2) ~~paired with~~ express greater *liking* of the drug effects ~~and feeling high~~ after the opioid administration, conceptually replicating the previous findings. The ~~We did not expect any effect on opioid~~

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~~disliking or feeling high~~ in the minutes after infusion. *~~For ff~~eeling high*~~,~~ translation ~~the translation used was~~is~~was~~ not deemed as a positive drug effect in a Norwegian population (16)~~.~~, and we did not expect any effect of childhood adversity on *disliking* or *feeling high.* ~~Anxiety was not measured in the prior study, however W~~we ~~A secondly secondary~~ expected ~~hypothesised was~~ that childhood adversity would be associated with greater anxiety relief after opioid administration. ~~Although~~ Since anxiety is typically higher in people with childhood trauma and opioid use disorder (17), and relief has been cited as a motivator for continued opioid use (18), we also explored the links between childhood trauma and anxiety pre- and post-drug. Identifying relationships between childhood adversity and opioid drug effects ~~Support for these hypotheses~~ in this pre-operative surgery population has ~~large~~ implications for pain management in patients at higher risk due to childhood adversity.

2.0 Methods

2.1 Participants and procedure

This observational study of subjective opioid drug effects in day surgery patients receiving pre-operative opioid analgesics as part of routine care was part of a broader research project (see Figure 1 for an overall timeline). We recruited 269 generally healthy patients (~~n = 269~~defined in line with the American Society of Anesthesiologists' Physical Status Classification System, ASA I-II (19)) admitted for outpatient surgery at Kongsberg Hospital in Norway between April 2018 to June 2021. Outpatient surgeries were typically minor abdominal, minor gynecological, minor orthopaedic, otorhinolaryngological, or colorectal~~, or skin~~ surgeries. For recruitment, patients were sent a letter ~two weeks prior to the procedure with information about their upcoming surgery, in addition to the study information sheet, consent form, and some routine clinical questions. All patients provided informed written consent on the morning before the surgery. The study protocol was approved by the internal review board (data protection officer) at Kongsberg Hospital.

Of the initial sample, 220 (82%) were then successfully recontacted by phone and/or email between August 2021 and February 2022 (between 4-40 months after the surgery) and agreed to complete the relevant outcomes for this study. A total of 155 (71%) patients completed these additional questionnaires, and are the final sample size for this study. Patients were asked to provide additional consent, and subsequently received the questionnaires either electronically by email, or hardcopy by post (depending on the patient's preference). The email contained a link to the electronic questionnaire form using the University of Oslo's online data collection software (*Nettskjema)*, and responses were automatically stored in on the University of Oslo's secure data storage server TSD. Hardcopy questionnaires were received and completed by post and registered manually by

one of the hospital research personnel. If patients had not completed the questionnaires within one week, they were sent reminders by email. In the case of repeated responses, the earliest complete response was used for the analyses. Cases where the patients responded with the same answer for all questions were considered invalid and excluded from analyses. The follow-up data collection was approved by the Regional Ethics Committee (Rek Sør-Øst D: 198224).
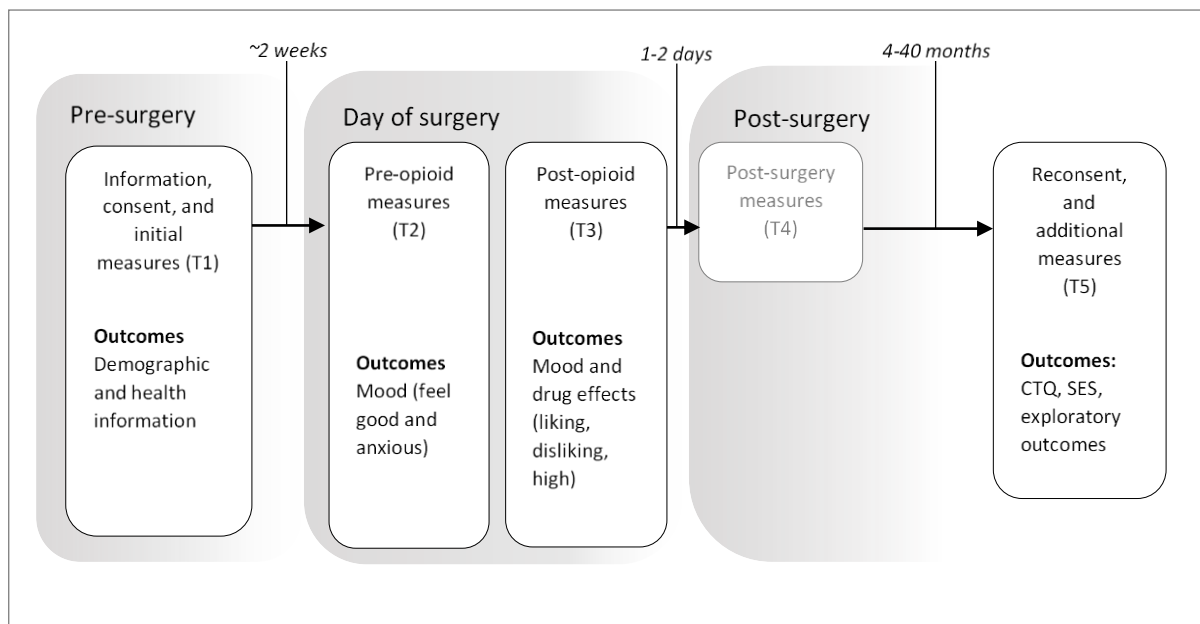

Figure 1. Study procedure in the context of the broader research project. T – timepoint for data collection. T4 is in grayscale to indicate that outcomes that were collected but are not included within the current study. CTQ – childhood trauma questionnaire, SES – socio-economic status.

2.2 Opioid administration and subjective effects

As part of routine care for the surgical procedure, patients were given an intravenous opioid analgesic three to five minutes before being administered the general anesthetic. Patients were informed by the medical personnel that they would be given medication for pain and for sleep while on the operating table. For the patients consented into the study, tTheis opioid analgesic was either remifentanil (n=157, 59%; Minto model, effect site concentration; 5 ng/ml; surgeries conducted Jan 2018-May 2019), or oxycodone (n=112, 41%; 5 mg; surgeries conducted Nov 2019-June 2021). The type of opioid administered was selected at the discretion of the medical professional delivering the medication. Both opioids led to comparable subjective intoxication, as reported in the broader research trial (16).
Immediately prior to opioid administration, patients were asked by the medical personnel to verbally rate their mood for: (i) how good they felt; and (ii) how anxious they felt, on a scale

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from ~~0-10~~ (0 ~~–~~ (not at all) ~~-~~, 10 ~~–~~ (very much) (pre-drug scores). At precisely one minute following the opioid dose, patients were asked to rate their mood again (i-ii), in addition to ~~rating~~ the subjective opioid effects on a scale from 0-10 for: (iii) how high they felt; (iv) how much they liked any of the effects of the drug; (v) how much they disliked the effects. These took between one and three minutes to complete. The drug effect items are from the Drug Effect Questionnaire (DEQ; 20), a measure frequently used for psychopharmacological research exploring acute drug effects. All patient responses were recorded by pen and paper by the medical personnel.

2.3 Other measures

The primary predictor ~~of interest~~ for childhood adversity ~~in this study~~ was a history of childhood ~~adversity~~abuse and neglect, which was measured by the Childhood Trauma Questionnaire (CTQ; 21) ~~and MacArthur Scale of Subjective Social Status in childhood~~ (MSSS; 22). The CTQ is a 28-item measure of experiences of abuse and/or neglect in childhood across five subcategories: emotional and physical abuse, emotional and physical neglect, and sexual abuse. Responses are made on a 5-point Likert-scale (1 - never true, 5 - very often true), where the total severity score across all subscales is calculated. Another exploratory measure of childhood adversity was the MacArthur Scale of Subjective Social Status in childhood (MSSS; 22), a measure of childhood ~~The MSSS is a measure of~~ socioeconomic status (SES)~~,~~ where patients were asked to rate their family's SES compared to the rest of the Norwegian society when they were young, on a one item scale (0 – low, 10 - high). ~~The scale was presented as a ladder, and they were asked to imagine the ladder as representing the structure of the Norwegian population.~~ The families with the highest income, education and most respected jobs were located at the top of the ~~ladder~~scale, and the families with either no or the lowest ranged education, jobs, and money at the bottom of the ~~ladder~~scale.

Choice of other exploratory measures were guided by previous research linking adversity with substance use and mental health. This included an assessment of problematic substance use by the both the Alcohol Use Disorders Identification Test (AUDIT; 23) and the Drug Use Disorders Identification Test (DUDIT; 24), which comprise of 10-11 items answered by either 5-point (0 – never, 4 – almost daily) or 3-point (0 – no, 4 – yes, this year) Likert scales. Mental health was measured by the 14-item Hospital Anxiety and Depression scale (HADS; 25) (4-point Likert response scale: 0 – not at all, 3 – all the time), and loneliness was measured with the Three Item Loneliness Scale (T-ILS; 26) (3-point Likert scale; 1 - hardly ever, 3 - often). Mindfulness was measured by the 15-item Five Facet Mindfulness Questionnaire (FFMQ; 27) (5-point Likert scale, 1 – never, 5 – very often). Pain

catastrophising was measured the 13-item Pain Catastrophizing Scale (PCS; 28), (5-point Likert scale, 0 – not at all, 4 – all the time). Total scores were computed for all exploratory outcomes. Demographic data such as *age* (years), *sex* (male, female), and *weight* (kg), were collected, in addition to *opioid type* (oxycodone, remifentanil), and *surgery type* (categorical and dummy coded).

2.4 Analyses

Data was analysed using R v4.1.1 (29). ~~Prior to analyses, data were checked for n~~Normality of residuals using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Bootstrapping using random sampling with replacement (5000 iterations) was used if any of the two tests were significant ($p > .01$ for the Shapiro-Wilk and $p > .05$ for the Kolmogorov-Smirnov). ~~were deemed acceptable if p>.01 and p>.05, respectively.~~ The threshold for the ~~standard~~ Shapiro-Wilk test was adjusted due to overestimates of non-normality in samples when n>50 (30). ~~, and Tests were also followed by visually inspection of residuals~~ using histograms and Q-Q plots ~~to determine the nature of non-normality. , in addition to assessing for o~~Outliers ~~were~~ for the CTQ scores were assessed using boxplots. ~~and missing data and were~~ Some extreme values were expected as there is typically a reduction in variation in CTQ scores for the moderate-severe range, however these ~~will~~ were ~~be~~ retained and reported. Extreme values were not expected for drug effect outcomes as these were bounded between 0 and 10 (11-point integers). ~~Only p~~Patients ~~who have~~ with a ~~both pre and~~ post-drug rating~~s~~ for a given outcome and a CTQ score ~~will~~ were ~~be~~ included in that analysis. ~~Patients with more >50% missing data for the one of the primary outcomes were~~ was excluded from ~~that~~ analyses, ~~M~~issing values were treated as missing. The alpha criterion for significance was p<.05 and p-values were corrected for multiple testing using the Holm-Bonferroni correction.

2.4.1 Primary analyses

Multiple linear regressions were conducted ~~for the conceptual replication component of the analysis.~~ to assess whether the primary predictor ~~The predictor~~ variable~~s~~ for childhood adversity ~~were childhood trauma~~ (CTQ score) ~~, childhood SES (MSSS score), and a combined childhood adversity score that was calculated by standardising and computing the product of both CTQ and MSSS scores (where higher scores indicated higher trauma and lower SES).~~ was significantly positively associated with *feeling good* (H1), and *drug liking* (H2). ~~, disliking, and feeling high. Separate A~~analyses ~~were conducted for the predictor variables to assess both the independent (CTQ and SES) and combined effect on the outcomes.~~ adjusted for demographic variables (*age*, ~~gender~~*sex*), *weight*, *opioid type*, and *surgery type* ~~were included in all analyses~~. The analyses ~~for~~of feeling good ~~and anxious~~

~~were~~ adjusted for the ~~baseline~~ pre-drug ratings by entering pre-drug responses as predictors in the regression, as th~~is~~ese~~y~~ ~~were~~ was also measured before as well as after opioid administration. The regression equation for these analyses were:

$$\hat{Y}(\text{post-drug score}) = \beta^0 + \beta^1(CTQ) + \beta^2(age) + \beta^3(sex) + \beta^4(opioid) + \beta^5(weight) +$$
$$\beta^6(surgery) + \beta^7(\text{pre-drug score}\cancel{s}) + \epsilon$$

Surgery type was categorical and dummy coded, where a regression coefficient was obtained for each level of the variable. Pre-drug scores in the regression equation were only relevant for *feeling good*.

The findings were interpreted as a full conceptual replication if both H1 and H2 were confirmed by a significant positive association between CTQ score with post-drug *feeling good* and *drug liking*, or a partial conceptual replication if one of the two were significant. Regression coefficients (betas) were interpreted for effect size. For non-significant findings or significant associations in the opposite direction than hypothesised, we concluded that the conceptual replication was unsuccessful, and this was interpreted in the context of the methodological differences including: CTQ as a continuous measure instead of pre-stratified groups, with fewer people in the moderate-severe range, and differences in drug type, dose, administration route, and the context of use (open-label surgery setting compared to placebo-controlled research study).

Bayesian posterior probabilities were calculated to assess the robustness of the findings, using the 'rstan' (31) and 'rethinking' packages (32). Quadratic approximation was used to calculate the posterior probabilities [outcome$_i$ ~ Normal(μ_i, σ)] for the centered linear relationships with CTQ score [$\mu_i = \alpha + \beta(CTQ_i - \bar{x})$]. Priors were constructed using the means, standard deviations and slopes from the previous study (12) and were tested using prior predictive simulations, with *drug liking*: α ~ Normal(30,15), σ ~ Uniform(0,20) and β ~ Normal(0,1); and *feeling good* (measured as *euphoria* in the previous study): α ~ Normal(20,10), σ ~ Uniform(0,10) and β ~ Normal(0,1). The posterior mean, 89% credible interval, and 89% highest posterior density intervals (HPDI; the narrowest interval containing 89% of the probability mass) for betas were reported alongside each regression. Posterior predictive checks were also conducted to assess the reliability of the Bayesian models. Such that the results from the Bayesian analysis did not concur with the frequentist analysis, potential reasons for the lack of robustness were discussed.

2.4.2 Exploratory analyses

In separate exploratory analysis, we ~~also~~ assessed opioid-induced *disliking, feeling high* and *anxiety relief* as outcomes. We also explored~~, in addition to~~ childhood SES (MSSS score) as a predictor variable to examine SES as a possible early life stressor. ~~In a complementary analysis, changes in mood ratings following opioid administration were categorised into three ordinal outcomes: feeling better, same, or worse. This allowed us to calculate the probability of an opioid-induced mood boost in people with higher compared with lower childhood adversity scores. The change scores were analysed using a multinomial logistic regression with the same predictors, where 'no change' was entered as the reference category and 'increased' and 'decreased' were the outcomes.~~

~~For~~ Other exploratory analyses included ~~,~~ Pearson's correlations ~~were used~~ to assess associations between the predictors and outcomes with: alcohol and other drug use, mental health, and loneliness. ~~While~~ Overall, based on the literature we expected that greater childhood ~~stress (measured by score on CTQ and MSSS)~~ adversity to be ~~are~~ associated with more adverse long-term outcomes, ~~these analyses are were exploratory~~ including higher AUDIT and DUDIT scores, more mental ill health and higher loneliness ~~and corrected for multiple comparisons~~. Spearman's Rho correlations were used for non-parametric data, or Stuart-Kendall Tau-c if rank ties are high. The alpha level for exploratory analyses was~~ere~~ not corrected for multiple testing as they were considered hypothesis-generating (33).

2.5 Level of bias and control

As a registered prospective analysis, we have designated a Level 2 bias control because the wider dataset (n = 269) has been acquired and partially observed as part of the broader research project (16). However, the main predictor, CTQ scores, and the exploratory variables, have not been accessed or observed, nor do any of the authors know which individuals make up the subset of participants (n = 155, 71%) that provided data for the current analysis. Steps to reduce bias include: (i) The submission of the pre-specified analysis script to provide transparency on the analytical plan and contingencies before this data has been observed; (ii) calculating the posterior probabilities using a Bayesian framework to assess the robustness of the results; (iii) using the Holm-Bonferroni alpha correction on the confirmatory tests; (iv) ensuring the lead authors of the manuscript responsible for analysis have had limited exposure to the data that has already been accessed as part of the broader research project

3.0 Results

3.1 Sample descriptives

3.2 Childhood adversity and post-drug feeling good and liking (hypothesis 1-2)

3.3 Exploratory analyses

4.0 Discussion

Discussion points of the manuscript will include:

- Whether the results from this study may help inform best practice treatment, and individualised approaches to the prescribing of opioid analgesics.

- The level of variation of childhood trauma will be different to the previous study. If the hypotheses are supported, this could imply a graded effect of childhood adversity on subjective drug effects. If the hypotheses are not supported, this may be due to limited numbers in the severe range of childhood trauma.

- The current sample will also vary on other potentially important characteristics e.g., mental health and substance use that were exclusion criteria in the prior study. The exploratory analyses will shed light on the association of these with the variables of interest.

- Contextual differences in opioid use and populations of people between this and the previous study. This will be particularly important if the hypothesis is fully rejected.

- Exploratory analyses are not corrected for multiple testing because they are hypothesis-generating rather than confirmatory, and thus any significant effects of these outcomes should be highlighted as preliminary.

- Unlike the previous study, anxiety relief has not been tested before using a placebo-controlled design and thus we will not be able to rule out regression to the mean for any findings related to post-opioid effects. As with all exploratory findings, the findings will need to be replicated in future research.

PCI-RR study design:

Question	Hypothesis	Sampling plan	Analysis Plan	Rationale for deciding the test sensitivity	Interpretation given different outcomes	Theory that could be shown wrong
Can we conceptually replicate the findings that childhood adversity results in altered subjective effects of opioids naturalistically in generally healthy patients undergoing day surgery?	After the administration of an opioid analgesic, patients with greater childhood adversity will report: Primary hypotheses: H1: A greater mood boost (feeling good), and H2: greater liking of the effects (conceptually replicating the previous study)., and feeling high We do not expect to find effects of adversity on disliking the opioid effects or feeling high. Anxiety relief will be examined in exploratory analyses., as previous research has	The study is using existing data collected as part of a larger observational research project. This study recontacted patients to complete additional measures, including for childhood adversity. The sample size was therefore constrained to as many respondents for the additional measures of the original sample size, which was n = 155. To ensure adequate power, aA post-hoc power analysis with a sample size of 155 and a small – medium effect size (f² = .05) indicated a power of 0.78, which is sufficient to explore the research question.	A series of Two separate linear regressions will be conducted with to examine the effects of childhood trauma questionnaire (CTQ) total score as the predictor, and childhood adversity on each of the outcome variables: drug liking and feeling good as outcomes. The p-values for feeling good and liking will be corrected for multiple tests using the Holm-Bonferroni method.A multinomial regression will be conducted to examine change scores	The effect size and hypotheses were based on a recent study that compared responses to a dose of morphine in people with either severe or no childhood adversity. On a 100-pt scale, this study reported a mean difference of 17.99 (95% CI: 6.69, 29.30) for subjective euphoria, and a medium effect size d = 0.65 for euphoria. fFor liking, and a mean difference of 14.67 (95% CI = 0.48, 28.87) and small-medium effect size d = 0.39 for liking. The current naturalistic study uses continuous variables and an alternative design, however a post-hoc power calculation using existing estimates of effect size indicates sufficient power for a small- medium effect.	H1 will be accepted if CTQ is significantly positively associated with post-drug feeling good, and we will conclude that people with childhood adversity are more sensitive to the mood-enhancing effects of the drug in a medical pre-operative context. H2 will be accepted if CTQ is significantly positively associated with post-drug liking. We will conclude that people with childhood adversity are more sensitive to the subjectively pleasurable drug effects in a medical pre-operative context. The robustness of the association will be supported by a Bayesian posterior to assess the most plausible beta coefficients and the degree of uncertainty. We will consider the study as a full conceptual replication of the previous study if both H1 and H2 are significant, or a partial conceptual replication if only one is significant in the predicted direction. H1 and H2 will be rejected if we find no effect, or significant effects in the opposite direction. ThisAny null or opposite effect would will be interpreted as down to differences in: (i) the context of opioid use (e.g., surgery compared with a research study or recreational use), (ii) motivations for use (e.g., people who would take part in acute drug study vs surgery sample). We will also interpret the findings in line with the different opioid drugs, doses, and route of administration, in addition to the amount of variation with CTQ scores. Lack of support for these hypotheses may indicate: (1) how differences in the context of opioid use (e.g., surgery compared with a research study or recreational	Existing theory indicates a heightened risk of opioid addiction after adversity via a sensitivity to subjectively pleasurable effects. The addition of post-drug anxiety could also indicate the role of greater anxiety relief as a concurrent risk factor. The current study aims to test this theory in naturalistic settings. If the current outcomes do not support this theory, it is possible that this may indicate childhood adversity may not be considered a risk factor for persistent use of medically prescribed opioids in medically prescribed populations. It may highlight the importance of methodological differences and potential challenges in generalising laboratory-based research to naturalistic settings, which is important when considering these studies for policy.

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	~~indicated that effects of adversity on disliking emerges later.~~		~~for feeling good and feeling anxious.~~ ~~Childhood adversity will be measured by childhood history of trauma, and childhood socio-economic status. Separate analyses will assess the independent contributions for trauma and SES, followed by a final linear analyses on the combined effect by standardising the scores and computing a product score (greater childhood adversity indicated by higher trauma and lower SES).~~		~~use) is important when considering altered subjective effects. Effects may be interpreted differently between these contexts due to different motivations for use.~~ ~~(2) differences in drug, dose, and route of administration are also important to consider and may help to explain inconsistent findings with the previous research.~~ ~~'severe'.~~ ~~We will not over-interpret a null effect for these reasons, but rather discuss the methodological differences.~~	However, given the methodological differences and limitations in power we would ~~not over~~ only cautiously interpret ~~than~~ is null effect. ~~It may also highlight the importance of methodological differences and potential issues~~ challenges in ~~generalising laboratory-based research to naturalistic settings, which is important when considering these studies for policy.~~

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