Stage 1 PCI Registered Report - Revision round 2

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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Words: 2664

Figures and tables: 1

Abstract

Introduction: Opioid analgesic treatment after surgery entails some risk of persistent use. Experiences of childhood adversity haves been shown to increase opioid reward in preclinical models, a finding recently extended to healthy humans. We tested whether childhood adversity similarly increased opioid reward, operationalised as drug-induced mood boost and subjective 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 adversity (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) demonstrated: 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 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). There are several potential mechanisms to help explain this heightened reward response after early adversity. Panksepp (11) proposed that opioid drugs 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 enhanced pleasure response to opioids among those with limited early experiences of 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-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.

These results represent important initial evidence that childhood adversity could enhance the 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. In this study~~Here,~~ we examined whether childhood adversity increases positive effects of opioids given in a medical context. Positive drug effects are considered a sign of higher abuse liability (5). 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~~subtype and are frequently used both pre- and post-operatively to provide quick and effective pain relief. Patients were asked to give verbal numerical ratings of how good and how anxious they felt immediately before and one minute after 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. Patients later completed additional state and trait measures. Our primary hypotheses were that patients with greater childhood adversity (higher trauma) would 1) exhibit a larger mood boost (*feeling good*), and 2) express greater *liking* of the drug effects after the opioid administration, conceptually replicating the previous findings. The *feeling high* translation 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*. Since anxiety is typically higher in people with childhood trauma and opioid use disorder (17), and anxiety 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 in this pre-operative surgery population has implications for pain management in patients at higher risk of persistent use due to childhood adversity.

2.0 Methods

2.1 Participants and procedure

This was an observational study of subjective opioid drug effects in day surgery patients who receiveding a pre-operative opioid analgesics, as part of routine care. The study was part of a broader research project (16) (see Figure 1 for an overall timeline). We that recruited 269 generally healthy patients (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 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 which was 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).

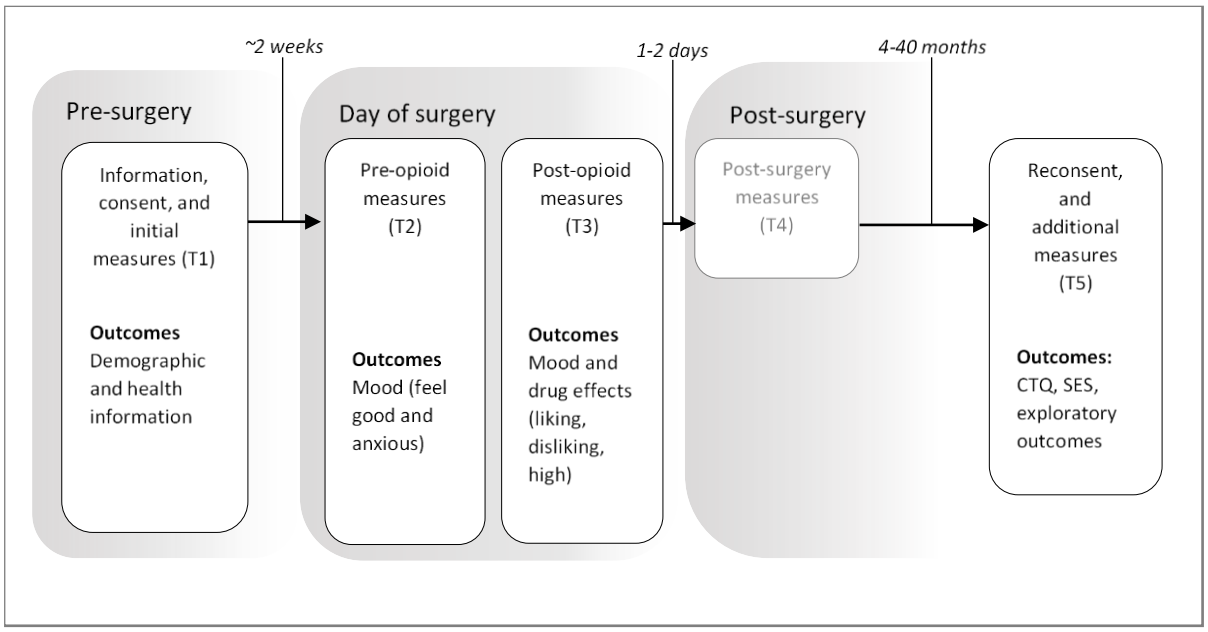

Figure 1. Study procedure in the context of the broader research project. T – timepoint for data collection. T4 is in grayscale to indicate that outcomes ~~that~~ were collected but are not included within the current study. CTQ – childhood trauma questionnaire, SES – socio-economic status.

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. The 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). 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 from 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 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 ratings 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 for childhood adversity was a history of childhood abuse and neglect, which was measured by the Childhood Trauma Questionnaire (CTQ; 21). 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 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 families with the highest income, education and most respected jobs were located at the top of the scale, and the families with either no or the lowest ranged education, jobs, and ~~money~~ income at the bottom of the 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 by 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). Normality of residuals were assessed 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). The threshold for the Shapiro-Wilk test was adjusted due to overestimates of non-normality in samples when n>50 (30).

Outliers (defined as responses >3 standard deviations from the mean) for the CTQ scores were assessed using boxplots. Some extreme values were expected as there is typically a reduction in variation in CTQ scores for the moderate-severe range, however these were retained and reported. Extreme values were not expected for drug effect outcomes as these were bounded between 0 and 10 (11-point integers). Patients with a post-drug rating for a given outcome and a CTQ score were included in that analysis. Missing 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 to assess whether the primary predictor variable for childhood adversity (CTQ score) was significantly positively associated with *feeling good* (H1), and *drug liking* (H2). Analyses adjusted for demographic variables (*age*, *sex*), *weight*, *opioid type*, and *surgery type*. The analyses for feeling good were adjusted for the pre-drug ratings by entering pre-drug responses as predictors in the regression, as this was also measured before as well as after opioid administration. The regression equation for these analyses were:

$$\hat{Y}(post\text{-}drug\ score) = \beta^0 + \beta^1(CTQ) + \beta^2(age) + \beta^3(sex) + \beta^4(opioid) + \beta^5(weight) + \beta^6(surgery) + \beta^7(pre\text{-}drug\ score) + \epsilon \hat{Y}_i = \beta_0 + \beta_1 CTQ_i + \beta_2 Age_i + \beta_3 Sex_i + \beta_4 Opioid_i + \beta_5 Weight_i + \beta_6 Surgery_i + \beta_7 Pre\text{-}drug\ score_i + \epsilon_i \quad ,$$

where Ŷ is post-drug score. *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 and 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 Because the study was only powered to detect small-medium effect sizes, this any null effect was was not interpreted as support for no effect. 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~~ for non-significant ~~findings~~results, using the 'rstan' (31) and 'rethinking' packages (32). Quadratic approximation was used to calculate the posterior probabilities [$outcome_i \sim Normal(\mu_i, \sigma)$] 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*: $\alpha \sim Normal(30,15)$, $\sigma \sim Uniform(0,20)$ and $\beta \sim Normal(0,1)$; and *feeling good* (measured as *euphoria* in the previous study): $\alpha \sim Normal(20,10)$, $\sigma \sim Uniform(0,10)$ and $\beta \sim Normal(0,1)$. The posterior mean ~~, 89% credible interval,~~ and ~~89~~95% highest posterior density intervals (HPDI; the narrowest interval containing ~~89~~95% 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 t~~The Bayesian ~~analysis~~ estimates ~~did not concur with the frequentist analysis, potential reasons for the lack of robustness were discussed~~were interpreted as supporting a potential effect to be examined in a higher-powered study if the 95% HPDI for beta did not overlap with 0, and the most plausible beta given by the posterior mean.

~~*2.4.2 Exploratory analyses*~~

~~In separate exploratory analysis, we assessed opioid-induced *disliking*, *feeling high* and *anxiety relief* as outcomes. We also explored childhood SES (MSSS score) as a predictor variable to examine SES as a possible early life stressor. Other exploratory analyses included Pearson's correlations to assess associations between the predictors and outcomes with: alcohol and other drug use, mental health, and loneliness. Overall, based on the literature we expected that greater childhood adversity to be associated with more adverse long-term outcomes, including higher AUDIT and DUDIT scores, more mental ill health and higher loneliness. 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 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.
- Describing the role of effect sizes in the findings (particularly in the case of non-significant findings), and that we are not powered to detect all plausible effect sizes. For this reason, we could not provide support for the null hypothesis (that there is no effect). We will discuss reasons for why the effect may be smaller than expected, for example that there may be proportionally less people in the severe range of childhood adversity. ~~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 positive 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). 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.	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. A post-hoc power analysis with a sample size of 155 and a small – medium effect size (f^2 = .05) indicated a power of 0.78, which is sufficient to explore the research question.	Two separate linear regressions will be conducted with childhood trauma questionnaire (CTQ) total score as the predictor, and 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.	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) and a medium effect size d = 0.65 for euphoria, 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. However, ~~Any null or opposite effect~~ because the study sample size is limited and we are only~~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)~~ powered to detect medium-large effects, we will not conclude this as support for- the null effect, but rather that we are not powered to reliably detect smaller effects (f^2<.05). The Bayesian intervals will inform on non-significant findings. If the 95% HDPIs do not overlap 0, this may indicate we were not powered to detect the effect, and a higher-powered study should confirm this. If the intervals do overlap with 0, this may provide more support for the null.	Existing theory indicates a heightened risk of opioid addiction after adversity via a sensitivity to subjectively pleasurable effects. We are not powered to support the null hypothesis (that ~~If the current outcomes do not support this theory, it is possible that this may indicate~~ childhood adversity ~~may~~ is not ~~be considered~~ a risk factor for persistent use of medically prescribed opioids). In the case of null findings, we can only tentatively discuss ~~. It may highlight~~ the potential ~~importance~~ role of methodological differences, limited statistical power, or a non-linear effect of adversity We will also broadly explore potential challenges in generalising laboratory-based research to naturalistic settings, which is important

					We will also interpret any findings in line with the different opioid drugs, doses, and route of administration, in addition to the amount of variation with CTQ scores, and study context (hospital vs research study).	when considering these studies for policy. ~~However, given the methodological differences and limitations in power we would only cautiously interpret any null effect.~~

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