# Participant Treatment Assignment Perceptions in the NIDA CTN Cocaine Use Reduction with Buprenorphine (CURB) Study

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## Abstract

**Aims:** The use of blinding in trials is an established element of study design, intended to minimize bias and expectation effects and strengthen the internal validity of the results. The goal of the current analysis was to assess participants' perceptions of their blinded treatment assignment and examine whether these perceptions were associated with the primary outcome results of the trial.

**Methods:** Perceived treatment assignment was evaluated in the National Drug Abuse Treatment Clinical Trials Network (CTN) trial Cocaine Use Reduction with Buprenorphine (CURB) at the end of active medication. Participants were randomly assigned to 1 of 3 conditions: 16mg buprenorphine + naloxone (BUP16), 4mg (BUP4), placebo (PLB), plus cognitive behavioral therapy and XR-NTX.

**Results:** Data was available for 281/302 participants (93%). 57% of participants had an opinion regarding their assignment and 43% were unsure. Of those who had an opinion, 46% guessed correctly. There was no association with actual treatment group (p=0.25). In the BUP16 arm, 55% guessed correctly, 44%in the BUP4 arm and 39% the PLB arm. Perceived treatment assignment was not related to the primary outcome (self-reported cocaine use combined with urine drug screens during last 30 days of medication) or the number of cocaine-negative UDS collected during that period. The fewest average number of days of cocaine use was 6.4 for participants who believed they got BUP16, and greatest for PLB 8.0 days. These differences were not significant (p=0.33). There was no difference in the number of cocaine-negative UDS across perceived treatment (p=0.24).

**Conclusions:** This secondary analysis showed that the blind was maintained in CURB. Participants who speculated about their arm were no more likely to be correct than by chance. The finding increases the confidence in the validity of trial results. Further examination revealed no association with cocaine abstinence.

## Introduction

The aim of the CURB study was to evaluate the safety and effectiveness of buprenorphine with naloxone in the presence of extended-release naltrexone (XR-NTX) for the treatment of cocaine dependence in participants with a history of opioid use. This multi-centered double-blind, placebo-controlled study randomly assigned 302 participants to one of three medication conditions provided on a platform of XR-NTX: daily 4mg buprenorphine + naloxone, 16mg buprenorphine + naloxone, or placebo, for 8 weeks. Clinic visits occurred thrice weekly for observed medication dosing, provision of take-home medication, performing urine drug screens (UDS), safety and other assessments, and once-weekly cognitive behavioral therapy. The active treatment phase was eight weeks and follow-up assessments occurred at 1 month and 3 months post-treatment. Participants were asked about their perceived treatment assignment during weeks 5 and 8. The primary endpoint is the number of cocaine use days during the final 30-day evaluation period for participants who provided at least one day of self-report data during the evaluation period (N=292). Cocaine use on each day during the evaluation period was determined by combining UDS cocaine results and self-reported cocaine use from Timeline Follow-back via the ELCON algorithm (Oden et al. 2013). Based on the primary outcome, there was no statistically significant evidence that either of the buprenorphine arms differed from the placebo in terms of cocaine use, however there was evidence of increased abstinence in the 16mg buprenorphine arm when only considering objective UDS results (Ling et al. 2016).

## Objectives

- To evaluate whether treatment blind was maintained as measured by participant perception of treatment assignment.
- Secondary objectives addressed:
  - Was perceived treatment assignment associated with cocaine abstinence?
  - Was correctly guessing one's treatment assignment associated with cocaine abstinence?

## Methods

- The last blind assessment completed was considered whether at week 8 or 5
- Only participants who provided an opinion on treatment assignment were included in analyses
- Perceived treatment assignment was also split into a guess regarding active (BUP) vs placebo
- Pearson's $\chi^2$ test of association was used for comparisons of perceived and actual assignment
- Quantile regression for the median was used to evaluate the relationship between perceived treatment assignment and both the primary outcome measure and the number of cocaine-negative UDS during evaluation period
- Wilcoxon rank-sum test was used to evaluate association between primary outcome measure and correctly guessing assignment

## Results

✓ 281 participants completed an assessment of their perceived treatment assignment

✓ Of these, 161 (57%) had an opinion on their treatment assignment
- Placebo arm: 55%
- BUP4 arm: 59%
- BUP16 arm: 58%

✓ Table 1 cross-tabulates perceived assignment and actual treatment arm.
- Rate differences statistically significant (p=0.001)
- Placebo participants more likely to believe they were in the BUP4 arm

**Table 1. Perceived vs. Actual Treatment Assignment**

| Perceived Treatment Assignment | Actual Treatment Assignment | | |
|---|---|---|---|
| | Placebo (N=54) | BUP4 (N=52) | BUP16 (N=55) |
| Placebo | 21 (39%) | 13 (25%) | 7 (13%) |
| BUP4 | 22 (41%) | 23 (44%) | 18 (33%) |
| BUP16 | 11 (20%) | 16 (31%) | 30 (55%) |

✓ Table 2 summarizes whether a participant correctly guessed their assignment
- More likely to be incorrect (54%)
- Differences for perceived dose not statistically significant (p=0.249)
- Trend for active v. placebo significant (p<0.001)

**Table 2. Correct Perception vs. Actual Treatment Assignment**

| Perception of Treatment Assignment | Actual Treatment Assignment | | |
|---|---|---|---|
| | Placebo (N=54) | BUP4 (N=52) | BUP16 (N=55) |
| Correct - *three arms* | 21 (39%) | 23 (44%) | 30 (55%) |
| Correct – *active v .plb* | 21 (39%) | 39 (75%) | 48 (87%) |

✓ Table 3 summarizes the comparison of the primary outcome measure and perceived treatment assignment
- Median number of days of cocaine use does not differ significantly across perceived treatment assignments

**Table 3. Primary Outcome Measure and Perceived Assignment**

| Perceived Treatment Assignment | Number of Days of Cocaine Use during Evaluation Period | | |
|---|---|---|---|
| | Median | Range | p-value |
| Placebo | 6 | 0 – 28 | |
| BUP4 | 7 | 0 – 27 | 0.385 |
| BUP16 | 5 | 0 – 28 | |
| Active | 6 | 0 – 27 | 0.366 |
| Placebo | 6 | 0 – 28 | |

✓ Table 4 summarizes the relationship between the primary outcome and a correct perception of assignment
- No statistically significant difference

**Table 4. Primary Outcome Measure and Correct Perception**

| Perception of Treatment Assignment | Number of Days of Cocaine Use during Evaluation Period | | |
|---|---|---|---|
| | Median | Range | p-value |
| Correct - *three arms* | 7 | 0 – 28 | 0.462 |
| Incorrect – *three arms* | 6 | 0 – 22 | |
| Correct – *active v .plb* | 7 | 0 – 28 | 0.997 |
| *Incorrect – active v. plb* | 6 | 0 – 22 | |

✓ Table 5 summarizes the relationship between the number of cocaine-negative UDS and perceived treatment assignment
- No statistically significant difference

**Table 5. Number of Cocaine-negative UDS and Perceived Assignment**

| Perceived Treatment Assignment | Number of Cocaine-negative UDS during Evaluation Period | | |
|---|---|---|---|
| | Median | Interquartile Range | p-value |
| Placebo | 6 | 0 – 13 | |
| BUP4 | 4 | 0 – 14 | 0.242 |
| BUP16 | 7 | 0 – 14 | |
| Active | 5 | 0 – 14 | 0.619 |
| Placebo | 6 | 0 – 13 | |

## Discussion

- The blinding of participants to their dose level was maintained in the CURB study
- However, participants were more likely to guess active (BUP4/BUP16) v. placebo correctly when they were in active arm
- Abstinence from cocaine was not related to their perceived treatment assignment
- Limitations:
  - Only half of participants expressed an opinion on their treatment assignment → limited sample size per arm
  - The final assessment of blind was considered, but some individuals completed the assessment twice → expand to include all available data
- Future exploratory analyses:
  - Experiencing adverse events associated with perception of being in active arm?
  - Association between perceived treatment assignment and compliance?

## Conclusions

- The blind was properly maintained for dose level but not for BUP versus placebo
- Participants were more likely to guess their assignment incorrectly when they had an opinion
- Cocaine abstinence was not associated with perceived treatment assignment

## References

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