

# Extended observation of reduced methamphetamine use with combined naltrexone plus bupropion in the ADAPT-2 trial

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## Funding information

National Institute on Drug Abuse of the United States (US) National Institutes of Health, Grant/Awards Numbers: UG1DA020024, K01DA051329, UG1DA013035, UG1DA040316, UG1DA013727 and UG1DA015815; US Department of Health and Human Services, Contract Numbers: HHSN271201500065C (Clinical Coordinating Center, the Emmes Company) and HHSN271201400028C (Data and Statistics Center, the Emmes Company); Career Development Award from the US National Institute of Mental Health, Grant/Award Number: K23MH126202 (to M.K.J.); O'Donnell Clinical Neuroscience Scholar Award from the University of Texas, Southwestern Medical Center.

## Abstract

**Background and aims:** A 12-week placebo-controlled, sequential parallel Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder (ADAPT-2) trial evaluated the effects of extended-release injectable naltrexone plus extended-release oral bupropion (NTX + BUPN) on methamphetamine (MA) use over two stages. This study reports on the previously unpublished stage 2 MA use in participants randomized at stage 1 to receive NTX + BUPN through both stages compared with those assigned to placebo.

**Design:** This is a secondary analysis of the US National Institute on Drug Abuse (NIDA) ADAPT-2 network trial.

**Setting:** The parent ADAPT-2 trial was carried out across multiple NIDA Clinical Trials Network (CTN) sites in the United States.

**Participants:** This analysis includes 403 people with MA use disorder who participated in the ADAPT-2 CTN trial.

**Intervention and comparator:** NTX + BUPN was compared with placebo over the course of the trial.

**Measurement:** MA use was measured by urine drug screens conducted twice weekly for 12 weeks, then once in week 13 and once in week 16 post-treatment follow-up.

**Findings:** Participants on NTX + BUPN in stage 1 showed an additional 9.2% increase [95% confidence interval (CI), 0.09%–17.9%,  $P = 0.038$ ] during stage 2 in their probability of testing negative for MA, with a total increase of 27.1% (95% CI, 13.2%–41.1%,  $P < 0.001$ ) over the full 12 weeks of treatment. In contrast, participants on placebo in both stages increased in probability of testing MA-negative by a total of 11.4% (95% CI, 4.1%–18.6%,  $P = 0.002$ ) over all 12 weeks. The 12-week increase among participants on NTX + BUPN was significantly greater—by 15.8% (95% CI, 4.5%–27.0%,  $P = 0.006$ )—than the increase among those on placebo.

**Conclusion:** For people with methamphetamine (MA) use disorder receiving treatment with extended-release injectable naltrexone plus extended-release oral bupropion (NTX + BUPN), continued treatment with NTX + BUPN after 6 weeks is associated with additional reductions in MA use up to 12 weeks.

## KEYWORDS

abstinence, bupropion, clinical trial, methamphetamine, naltrexone, reduction

## INTRODUCTION

Methamphetamine (MA) and other amphetamine-type stimulants account for the second largest class of substances used by people globally, with the number of people using MA increasing from 33 million in 2010 to 34 million in 2020 [1]. Over the past decade, overdose deaths because of MA have increased most heavily in the United States (US)—about fivefold—followed by Canada and Australia [1]. Still, there is currently no approved medication to treat of MA use disorder.

The first open-label pilot for combined extended-release injectable naltrexone plus extended-release oral bupropion (NTX + BUPN) showed efficacy for treating severe MA use disorder [2]. Separately, NTX [3, 4] and BUPN [5–7] have shown some efficacy for treating MA use disorder. A systematic review and meta-analysis showed modest reductions in amphetamine-type stimulant (ATS) use and cravings with BUPN treatment [8]. This and the uses of BUPN to treat nicotine dependence and depression and NTX (an opioid antagonist) to treat opioid use disorder and alcohol use disorder further supported development of trials combining these agents for the indication of MA use disorder [9].

Main findings from the multi-site randomized placebo-controlled trial by the US National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) coined ADAPT-2 (protocol CTN-0068) showed efficacy of NTX + BUPN for reducing MA use [9]. Although participants originally randomized to NTX + BUPN treatment improved in the first 6 weeks of the trial, further changes in MA use in this group from weeks 7 to 12 is unknown because of the sequential parallel comparison design used. Therefore, this analysis aims to estimate change in MA use during weeks 7 to 12 in participants receiving NTX + BUPN for the full 12 weeks of the study compared to placebo.

## METHODS

### Study design

This study is a secondary analysis of the ADAPT-2 trial. The primary outcome for this analysis is estimated change in MA use based on MA urine screens conducted during stage 2 (weeks 7–12) and posttreatment (weeks 13–16) among participants who started receiving NTX + BUPN in stage 1 (weeks 1–6) compared to those on placebo. This secondary analysis was not pre-registered and the results should be considered exploratory, but the main trial has been registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03078075). Full detail of the methods and main outcome findings are published elsewhere [9].

### Participants

All 403 participants in the parent ADAPT-2 trial [9] are included. Participants in the parent trial had to (1) meet the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria for moderate or severe MA use disorder; (2) report using MA on at least 18 of the

30 days before consent; (3) have two or more MA-positive urine screens within the 10 days before randomization; and (4) be opioid-negative at the time of randomization. People were excluded from the trial if they were already undergoing treatment for a substance use disorder, intended to use opioids for medical reasons during the trial or were deemed to have safety risks.

### Intervention

Extended-release NTX (380 mg) or placebo was administered using standard single-use intramuscular injection kits on weeks 1, 4, 7 and 10 [9]. Extended-release BUPN or placebo was provided weekly in matching blister cards of 150-mg tablets [9]. Doses started at 150 mg on the day of stage 1 randomization (and stage 2 re-randomization) and increased to 450 mg by the third day. At the end of the trial (week 13), participants received a tapering dose for 4 days before discontinuing.

### Description of the parent trial

The parent trial, ADAPT-2, used a randomized placebo-control sequential parallel design that was carried out across eight NIDA CTN clinical sites throughout the United States from 23 May 2017 to 25 July 2019 [9]. The trial defined a treatment response as screening MA-negative on at least three of four possible urine drugs screens in weeks 5 to 6 and 11 to 12.

The CTN Data and Statistics Center centrally conducted randomization and rerandomization. Randomization was stratified by site using an urn scheme [10] and blinded to staff and participants. In stage 1 (weeks 1–6), 109 participants were assigned to NTX + BUPN and 294 were assigned to placebo based on an a priori ratio of 0.26:0.74. There were 225 participants on placebo who did not show a response in stage 1, and by design, were re-randomized ~1:1 such that 114 switched to receive NTX + BUPN and 111 remained on placebo in stage 2 (weeks 7–12). Those originally assigned to NTX + BUPN in stage 1 stayed on NTX + BUPN in stage 2. Those assigned to placebo that had a treatment response stayed on placebo. Appendix S1 diagrams this participant flow throughout the trial.

The sample size calculation for the parent trial determined that 370 participants randomized at a ratio of 0.26:0.74 were needed for 90% power to detect a weighted difference between trial groups in stage 1 where 24% on NTX + BUPN would have a treatment response and 15% on placebo would have a response [9].

### Measurement

The outcome for this secondary analysis was repeated measures of MA screening results from urine samples obtained twice weekly over 12 weeks of treatment, then once on week 13 and once on week 16 during posttreatment follow-up.

## Analysis

Statistical analyses were conducted using R using the software package *GLMMadaptive* for model fitting [11]. Piecewise mixed effects logistic regression was used to estimate changes in odds of providing a negative urine test at each study visit, comparing NTX + BUPN versus placebo over the 16-week study period. The mixed effects logistic regression model included a random intercept and random slope for each participant. Change points (i.e. breaks in slope) were modeled at each visit with a NTX (or placebo) injection—administered at the first weekly visit of weeks 1, 4, 7 and 10—and at week 13 posttreatment follow-up.

The rerandomization of 114 participants on placebo showing no improvement in stage 1 to NTX + BUPN in stage 2 poses a potential bias when comparing the NTX + BUPN group to placebo during stage 2: the placebo group may have decreased (whereas the NTX + BUPN group may have increased) in the number of participants less likely to respond to treatment. To reduce this potential bias, multiple imputation (1000 imputations) was used to simulate twice weekly urine results from these 114 participants as if they had stayed in placebo in stage 2. Specifically, a mixed effects logistic sub-model was fitted using only the 225 participants re-randomized in Stage 2. Next, fixed effects were computed from the maximum likelihood estimates of the imputation sub-model, and subject-specific random effects were sampled conditional on the fixed effects and variance component estimates. The parameter estimates were then used to create pseudo-responses for the 114 participants re-randomized to NTX + BUPN in stage 2, as if they had remained in placebo. As a result, all 294 participants assigned to placebo in stage 1 were modeled as being on placebo across both stages. The 109 participants assigned to NTX + BUPN in stage 1 simply stayed on NTX + BUPN in stage 2 of the trial and comprised the group of interest in this analysis. Missingness

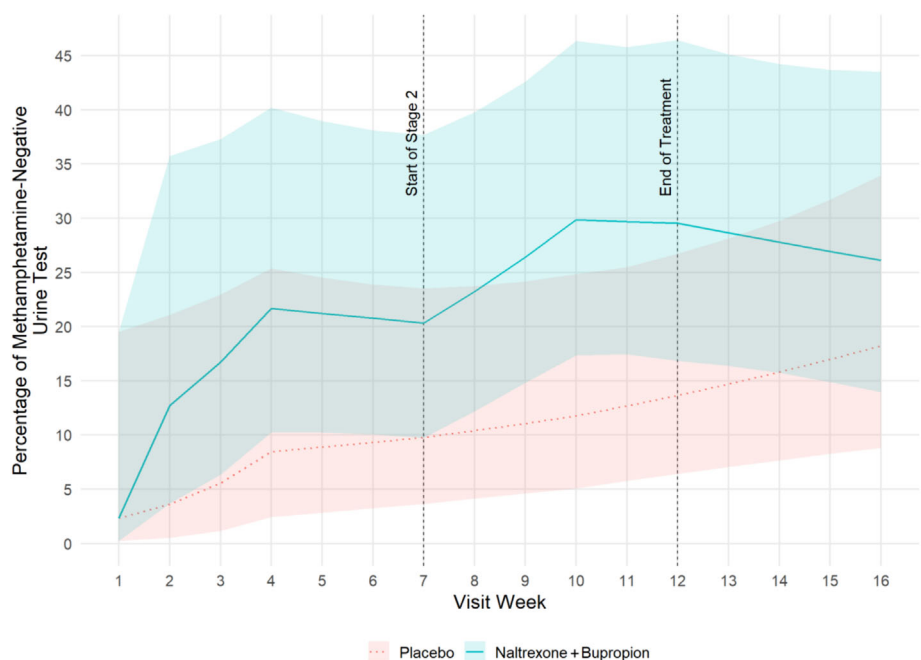
in urine results either because of dropout or intermittent missingness was analyzed and did not have a significant association with participant assignment to NTX + BUPN or placebo.

Parameter estimates were obtained by fitting a mixed effects logistic regression sub-model on each imputed dataset and pooled via Rubin's rules. Study site was included as a covariate to adjust for confounding. Sensitivity analyses using likelihood ratio tests supported the exclusion of demographic variables—age, sex assigned at birth and race/ethnicity—that showed no significant statistical effect on the model fit.

Missed study visits were assumed to be missing at random (MAR) and accommodated for by the logistic mixed effects model. A sensitivity analysis for the MAR assumption was obtained by imputing missing responses using both last observation carried forward and an extreme scenario assuming missing responses were always MA-positive results. In both situations, we recovered a statistically significant result indicating greater MA use reductions in the NTX + BUPN arm compared to placebo, suggesting that our results are robust to even severe departures from the MAR assumption. Predicted probabilities of testing MA-negative over time were obtained from the pooled regression models by marginalizing over the random effect distribution [12] and empirical distribution of participants by site [12].

## RESULTS

Figure 1 plots the marginal expected percentage of MA-negative urine screens with pointwise 95% confidence bands in both the NTX + BUPN and placebo groups over 12 weeks of treatment and weeks 13 and 16 posttreatment follow-up visits. Table 1 displays the changes in the expected percentage of MA-negative urine tests from weeks 1 to 6, from weeks 7 to 12, over the full 12 weeks of treatment



**FIGURE 1** Marginal expected mean percentage (with pointwise 95% confidence bands) of methamphetamine-negative urine tests over 12 weeks while on naltrexone plus bupropion versus placebo, and during posttreatment follow-up from week 13 to week 16.

**TABLE 1** Change in percentage of methamphetamine-negative urine tests over time by treatment group, estimated as marginal predicted probabilities.

Treatment group	Timeframe	Change	95% CI		P
			Lower	Upper	
NTX + BUPN	Stage 1 (week 1–6)	18.4%	7.9%	28.8%	0.001
NTX + BUPN	Stage 2 (week 7–12)	9.2%	0.5%	17.9%	0.038
NTX + BUPN	Both stages (week 1–12)	27.1%	13.2%	41.1%	<0.001
NTX + BUPN	Post-treatment (week 13–16)	–2.5%	–8.8%	3.7%	0.427
Placebo	Stage 1 (week 1–6)	7.0%	1.8%	12.2%	0.008
Placebo	Stage 2 (week 7–12)	3.9%	–0.3%	8.1%	0.072
Placebo	Both stages (week 1–12)	11.4%	4.1%	18.6%	0.002
Placebo	Post-treatment (week 13–16)	3.5%	–1.2%	8.2%	0.140

Abbreviation: NTX + BUPN, extended-release injectable naltrexone plus extended-release oral bupropion.

and from week 13 to 16 of post-treatment follow-up, separately for participants on NTX + BUPN and for those on placebo.

Participants treated with NTX + BUPN continued to increase in the expected percentage of MA-negative urine tests provided during stage 2, from 20.3% (95% CI, 9.9%–37.1%) at week 7 to 29.5% (95% CI, 16.9%–46.3%) at week 12. This 9.2% increase was significant (95% CI, 0.5%–17.9%,  $P = 0.038$ ) (see Table 1). Among those on placebo, the expected percentage of MA-negative urine tests during stage 2 was 9.8% (95% CI, 3.6%–24.0%) at week 7 and 13.7% (95% CI, 6.4%–27.0%) at week 12, but this 3.9% difference was not significant (95% CI, –0.3% to 8.1%,  $P = 0.072$ ).

Over the full 12 weeks of treatment, the total increase in the expected percentage of MA-negative urine tests among those on NTX + BUPN was 27.1% (95% CI, 13.2%–41.1%,  $P < 0.001$ ) (see Table 1). Among those on placebo, the 12-week total increase in the expected percentage of MA-negative urine tests was 11.4% (95% CI, 4.1%–18.6%,  $P = 0.002$ ). The increase in MA-negative urine tests during the 12 weeks of treatment was significantly greater in participants on NTX + BUPN than in those on placebo (difference-in-difference = 15.8%, 95% CI, 4.5%–27.0%,  $P = 0.006$ ).

During post-treatment follow-up (weeks 13–16), neither the NTX + BUPN group nor placebo group showed significant change.

## DISCUSSION

Our findings suggest that ongoing NTX + BUPN treatment yields statistically significant reductions in MA-use that continue from weeks 7 to 12. The lack of change in MA use from weeks 13 to 16 follow-up corresponds to treatment concluding in week 12. Whether or not the lack of change in MA use during posttreatment is because of treatment completion is uncertain, but future research with crossover designs may help to replicate and explore this possibility. Modeling change points using piecewise linear regression allowed us to capture shifts in MA use over time, and in turn, a more granular description of treatment response over the full trial. This approach aligns with growing scientific support for assessing treatment response on a spectrum

of substance use reduction [13,14]. Reductions in use during treatment tend to be gradual [13], and less use is in turn associated with lower risk of comorbidities [14]. In these ways, our stage 2 findings expound on previously published stage 1 findings on the efficacy of NTX + BUPN for reducing MA use, and allude to the possibility of additional benefit with longer treatment duration.

This analysis may be limited because of the change in composition of the placebo condition following re-randomization of the subset of non-responsive placebo participants to NTX + BUPN at week 7. However, multiple imputation approaches were used to mitigate additional bias from this re-randomization, simulating outcomes for these participants as if they had remained on placebo. Additionally, missed visits during the trial were assumed to be MAR, which is accommodated for by the logistic mixed effects regression model.

Given that MA use appeared to decrease for an additional 6 weeks (12 weeks total), it remains to be determined whether continued NTX + BUPN treatment past 12 weeks would yield further reductions in use. Prior stimulant use disorder treatment trials suggest that change in use is gradual (consistent with our findings), unlikely to result in sustained abstinence in a typical 12-week trial, and dependent on treatment duration [15]. This warrants future clinical trials to quantify changes in MA use beyond 12 weeks and to identify the optimal duration of treatment with this medication.

## AUTHOR CONTRIBUTIONS

**Michael J. Li:** Conceptualization (equal); formal analysis (supporting); investigation (equal); supervision (equal); writing—original draft (lead); writing—review and editin (lead). **Brendon Chau:** Formal analysis (lead); methodology (equal); software (lead); validation (lead); writing—review and editing (equal). **Thomas Belin:** Formal analysis (equal); methodology (equal); supervision (equal). **Thomas Carmody:** Data curation (lead); formal analysis (supporting); investigation (equal); methodology (equal); supervision (equal); writing—review and editing (equal). **Manish K. Jha:** Investigation (supporting); validation (supporting); writing—review and editing (equal). **Elise N. Marino:** Investigation (supporting); validation (supporting); writing—review and editing

(equal). **Madhukar Trivedi:** Conceptualization (equal); funding acquisition (lead); investigation (equal); methodology (equal); supervision (lead); writing—review and editing (equal). **Steven J. Shoptaw:** Conceptualization (lead); funding acquisition (lead); investigation (lead); methodology (equal); supervision (lead); writing—original draft (equal); writing—review and editing (equal).

## ACKNOWLEDGEMENTS

This research was supported by awards (UG1DA020024, K01DA051329, UG1DA013035, UG1DA040316, UG1DA013727 and UG1DA015815) from the National Institute on Drug Abuse (NIDA) of the National Institutes of Health; and by the Department of Health and Human Services under contract numbers HHSN271201500065C (Clinical Coordinating Center, the Emmes Company) and HHSN271201400028C (Data and Statistics Center, the Emmes Company). M.K.J. is supported by Career Development Award from the NIMH (K23MH126202) and the O'Donnell Clinical Neuroscience Scholar Award from the University of Texas, Southwestern Medical Center.

## DECLARATION OF INTERESTS

Alkermes provided Vivitrol (naltrexone for extended-release injectable suspension) and matched placebo free of charge for use in this trial under a written agreement with the US National Institute on Drug Abuse. T.C. has been a consultant for Alkermes and Holmusk Technologies. S.J.S. has received clinical supplies for his research from Indivior, Alkermes and Gilead Sciences. M.K.J. has received contract research grants from Acadia Pharmaceuticals, Neurocrine Bioscience, Navitor/Supernus and Janssen Research and Development; has received honorarium to serve as Section Editor of the Psychiatry and Behavioral Health Learning Network and as Guest Editor for Psychiatric Clinics of North America from Elsevier; has received consultant fees from Eleusis Therapeutics US, Janssen Global Services, Janssen Scientific Affairs, Boehringer Ingelheim and Guidepoint Global; has received fees to serve on Data Safety and Monitoring Board for Worldwide Clinical Trials (Eliem and Inversargo), Vicore Pharma and IQVIA (Click); and honoraria for educational presentations from North American Center for Continuing Medical Education, Medscape/WebMD, Clinical Care Options, H.C. Wainwright and Company and Global Medical Education. M.T. has provided consulting services to Acadia Pharmaceuticals, Alkermes, Alto Neuroscience, Axsome Therapeutics, Biogen MA, Cerebral, Circular Genomics, Compass Pathfinder Limited, GH Research, GreenLight VitalSign6, Heading Health, Janssen Pharmaceutical, Legion Health, Merck Sharp and Dohme Corp., Mind Medicine, Myriad Neuroscience, Naki Health, Navitor, Neurocrine Biosciences, Noema Pharma AG, Orexo US, Otsuka America Pharmaceutical, Perception Neuroscience Holdings, Pharmerit International, Policy Analysis, Praxis Precision Medicines, PureTech LYT, Relmada Therapeutics, Rexahn Pharmaceuticals, SAGE Therapeutics, Signant Health, Sparian Biosciences, Titan Pharmaceuticals, Takeda Pharmaceuticals, WebMD. He has received grant/research funding from NIMH, NIDA, NCATS, American Foundation for Suicide Prevention, Patient-Centered Outcomes Research Institute and Blue Cross

Blue Shield of Texas. Additionally, he has received editorial compensation from Engage Health Media, and Oxford University Press. M.J.L., B.C., T.B. and E.N.M. have no disclosures to report.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the U.S. National Institute on Drug Abuse Clinical Trials Network Big South/West Node upon request.

## CLINICAL TRIAL REGISTRATION

The parent trial, ADAPT-2, was registered at [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT03078075.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Li MJ, Chau B, Belin T, Carmody T, Jha MK, Marino EN, et al. Extended observation of reduced methamphetamine use with combined naltrexone plus bupropion in the ADAPT-2 trial. *Addiction*. 2024. <https://doi.org/10.1111/add.16529>