Early Change in Depressive Symptom Severity With Naltrexone-Bupropion Combination and Its Association With Reduction in Methamphetamine Use in ADAPT-2 Trial

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Abstract

Objective: This study evaluated whether depressive symptom severity improved early with extended-release naltrexone and bupropion combination (naltrexone-bupropion) compared to a placebo in individuals with moderate/severe methamphetamine use disorder and predicted subsequent use of methamphetamine.

Methods: This secondary analysis from the Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder (ADAPT-2) trial, which was conducted from May 23, 2017–July 25, 2019, included 326 individuals with a 9-item Patient Health Questionnaire (PHQ-9) score ≥5 at baseline. Repeated-measures mixed model analyses evaluated early (baseline-to-week-4) changes in depressive symptom severity with naltrexone-bupropion versus placebo and provided slope estimates for PHQ-9 change. Additional depression outcomes included response (≥50% reduction in PHQ-9 from baseline) and remission (PHQ-9 ≤4). Methamphetamine treatment response was ascribed if 3 out of 4 urine drug screens were negative during weeks 5 and 6. Logistic regression analyses evaluated whether changes in depression predicted methamphetamine treatment response. Covariates included age, sex, race, ethnicity, and baseline PHQ-9.

Results: There was a greater reduction in PHQ-9 scores at week 4 with naltrexone-bupropion versus placebo (estimate = −2.52; standard error = 0.81). At week 4, depression response (odds ratio [OR] = 2.54; 95% confidence limit [CL], 1.42–4.55) and remission (OR = 3.04; 95% CL, 1.57–5.87) were more likely with naltrexone-bupropion versus placebo. Greater baseline-to-week-4 reduction in PHQ-9 was associated with a higher likelihood of methamphetamine treatment response (OR = 3.74, 95% CL, 1.28–10.93) and explained 24.8% (95% CI, 6.7%–60.3%) of the effect of naltrexone-bupropion on methamphetamine treatment response.

Conclusion: Use of naltrexone-bupropion was associated with early reduction in depressive symptom severity compared to a placebo, which was associated with a higher likelihood of reduction in subsequent methamphetamine use.

Trial Registration: ClinicalTrials.gov identifier: NCT03078075

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The urgent need to develop novel treatments for methamphetamine use disorder is underscored by the increase in its prevalence rate in the US[1] which has been accompanied by the exponential increases in overdose deaths involving methamphetamine[2] and the absence of any US Food and Drug Administration (FDA)-approved medication for this indication.[3,4] In previous studies, bupropion[5–7] and naltrexone[8] individually had shown some evidence for efficacy in the treatment of methamphetamine use disorder. Subsequently, an initial pilot study was designed to evaluate the feasibility and preliminary efficacy of combining injectable naltrexone plus oral bupropion.[9] This study informed the design (every-3-week injections)

Clinical Points

- Individuals with methamphetamine use disorder often experience symptoms of depression.
- Use of naltrexone-bupropion may be effective in reducing overall depression.
- Improvement in depression accounted for approximately 25% of the treatment effect of naltrexone-bupropion on methamphetamine treatment response.

and implementation of the Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder (ADAPT-2) trial, which demonstrated the efficacy of extended-release naltrexone and bupropion (naltrexone-bupropion) in reducing methamphetamine use in individuals with moderate/severe methamphetamine use disorder.[10] However, the mechanisms that potentially contributed to the combination's treatment effect remain unclear. Understanding these mechanisms can inform the development of novel therapeutic approaches, given that even with naltrexone-bupropion, fewer than 1 in 6 individuals attained methamphetamine treatment response (defined as 3 negative urine drug screens [UDS] out of 4 possible UDS in the last 2 weeks of the 6-week treatment period).[10] As bupropion is an antidepressant medication,[11] evaluating whether early reduction in depressive symptom severity is associated with reduction in subsequent methamphetamine use may support the evaluation of novel antidepressant treatments for methamphetamine use disorder.

Depression is common in individuals with methamphetamine use disorder. Individuals with methamphetamine use disorder have 2.8 times higher odds of depression as compared to those without this disorder.[12] Studies of individuals entering addiction treatment programs[13,14] or clinical trials[15–17] have found high rates (>40%) of depression in individuals with methamphetamine use disorder. The presence of depression may be associated with adverse longer-term outcomes,[18,19] and continued heavy use of methamphetamine has been linked to persistently elevated levels of depressive symptoms.[20] In studies of behavioral therapies that have evaluated the association between changes in depression severity and methamphetamine use, prior methamphetamine use has been associated with higher severity of depressive symptoms subsequently, whereas prior depressive symptom ratings do not affect subsequent methamphetamine use.[16,21] While several antidepressant medications have been evaluated in individuals with methamphetamine use disorder,[6,7,22–26] evaluation of how changes in depression are associated with subsequent methamphetamine use has been limited by the findings that these medications, including bupropion,[23,24] mirtazapine,[25] and sertraline,[26] did not significantly improve depression as compared to placebo. These findings may have been related to modest sample size and relatively poor adherence to medications. With its large sample size and high rates of documented treatment adherence (75.1% in the naltrexone-bupropion group and 83.5% in the placebo group),[10] the ADAPT-2 trial may be ideally suited to evaluate whether change in depression severity with naltrexone-bupropion is a potential mediator of its effect on methamphetamine use outcomes. Therefore, in this secondary analysis of data from ADAPT-2 trial, we asked the following 2 specific questions:

1. Do individuals with methamphetamine use disorder randomized to naltrexone-bupropion versus placebo report greater reduction in depressive symptom severity?
2. Is reduction in depressive symptom severity associated with subsequent methamphetamine use outcome?

These questions are consistent with the approach outlined by Kraemer and colleagues that describe mediators as changes occurring during the course of treatment that may explain differential effects of one treatment (for example, naltrexone-bupropion) versus another (placebo).[27,28] Answering these questions may help identify processes by which naltrexone-bupropion works in reducing methamphetamine use and could help inform the development of future treatments.[27]

METHOD

Study Design

Detailed methods of the ADAPT-2 trial (NCT03078075), including the study protocol, were published previously by Trivedi et al.[10] Approvals from the institutional review board (IRB) at UT Southwestern as the central IRB and local IRBs at 4 sites were obtained before enrollment of subjects. This study was registered with ClinicalTrials.gov (https://clinicaltrials.gov/) as NCT03078075. At 8 sites in the United States, patients with moderate or severe methamphetamine use disorder based on the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (*DSM-5*) were invited to participate in the trial and enrolled after obtaining written informed consent from each participant. Participants were 18–65 years of age, reported methamphetamine use on at least 18 of the 30 days preceding the date of informed consent, provided 2 or more methamphetamine-positive urine samples

(obtained ≥2 days apart) within 10 days before randomization, and were opioid-free at the time of randomization. Participants were excluded if they were undergoing concurrent treatment for substance use disorder, had an expected need for opioid-containing medications (eg, planned surgery) during the trial, or did not meet additional criteria designed to ensure that participation would be safe (eg, participants would not be eligible if they had conditions that increased the risk of seizure, were receiving ongoing treatment with tricyclic antidepressants, xanthines [theophylline and aminophylline], systemic corticosteroids, nelfinavir, efavirenz, chlorpromazine, central nervous system stimulants [eg, Adderall, Ritalin], monoamine oxidase inhibitors, or any contraindicated medications, or were at imminent risk of suicide or homicide). Participants who had been diagnosed with a specific medical or psychiatric disorder were evaluated on a case-by-case basis to ensure safe participation in the study and were not routinely excluded.

Eligible participants were randomized in a 12-week double-blind randomized controlled trial of naltrexone-bupropion or matching placebo injections and pills that utilized a sequential parallel comparison design[29] of two 6-week-long stages. In the first stage, participants were randomized to naltrexone-bupropion or placebo in a 0.24:0.76 ratio. In the second stage, nonresponders to placebo were rerandomized to naltrexone-bupropion or placebo in a 1:1 ratio.

Study Interventions

The study interventions consisted of 12 weeks of pharmacotherapy with either naltrexone-bupropion or a matching placebo, medical management, and medication adherence procedures. In both stages of ADAPT-2, those randomized to the active medication combination received extended-release naltrexone (380 mg) as an intramuscular injection every 3 weeks and daily extended-release bupropion (target dose of 450 mg/day). Those randomized to placebo received matching injectable and pill placebos. All participants also received weekly medical management sessions where they met individually with a study clinician for approximately 20-minute sessions that focused on (1) setting abstinence from methamphetamine as a goal, (2) ensuring adherence with study medication and procedures, and (3) assessing current functioning. These sessions also included reviews of adverse events and potential medication side effects. Procedures for enhancing oral study medication adherence included discussions about adherence in medical management sessions, observed dosing of oral medication during in-person visits, and dosing videos using a smartphone application (AiCure)[10] to document study medication administration on non-clinic days.

Clinical Assessments and Study Outcomes

9-Item Patient Health Questionnaire. The PHQ-9 is a 9-item self-report scale that measures symptoms that correspond to those of a major depressive episode. Each item is scored from 0 to 3, with 0 indicating the absence of the symptom and 3 indicating the presence of the symptom nearly every day.[30] Total score of PHQ-9 ranged from 0 to 27, with higher scores indicating greater severity of depressive symptoms, and scores of 0–4, 5–9, 10v14, 15–19, and ≥20 corresponding to severity of minimal, mild, moderate, moderately severe, and severe depression, respectively. The PHQ-9 was administered once weekly with a recall period of 1 week, instead of the typically assessed period of 2 weeks.

Urine drug screen. Urine samples were collected unobserved at each twice-weekly clinic visit. For the purpose of the primary outcome of ADAPT-2, any missing samples were imputed as positive.[10] Onsite UDS tests were conducted using an FDA-cleared assay to detect the presence of methamphetamine, amphetamine, benzodiazepine, marijuana, opiates, cocaine, ecstasy (MDMA), oxycodone, methadone, barbiturate, and buprenorphine. Before drug screening, a temperature assessment and a validity assessment were performed on all urine samples to indicate normal ranges for creatinine, pH (at minimum), nitrate, glutaraldehyde, specific gravity, bleach, and pyridinium chlorochromate. Samples that did not pass the temperature or validity assessment were not tested and deemed positive for methamphetamine.

Study outcomes. The primary outcome of the ADAPT-2 trial was treatment response (referred hereafter as methamphetamine treatment response), defined as at least 3 methamphetamine-negative UDS out of a possible 4 during the last 2 weeks of each 6-week stage of the trial.

Analytical Sample for This Report

As this secondary analysis was intended to evaluate early reduction in depressive symptoms (and its association with subsequent methamphetamine use), the analytic sample was restricted to individuals with at least mild severity of self-reported depressive symptoms at baseline (score of 9-item Patient Health Questionnaire [PHQ-9] ≥5). Furthermore, data from only Stage 1 of this study were used as the available sample size, and the occurrence rates of methamphetamine treatment response in Stage 2 were half of those in Stage 1,[10] thereby further restricting the ability to detect treatment-related reductions in depressive symptoms, and the association of these changes with subsequent methamphetamine use outcome.

Statistical Analysis Plan

Descriptive statistics were used to summarize the baseline characteristics. To evaluate if there was a significant change in depression severity from baseline to week 4 with naltrexone-bupropion versus placebo,

repeated measures mixed model analyses with all available visits were used with PHQ-9 as the dependent variable; treatment-group–by-week interaction as the independent variable of interest; and age, sex, race, and ethnicity as covariates. The slope of change in PHQ-9 over this period was obtained from mixed model analysis[31] to estimate average change in PHQ-9 over time from baseline to week 4, and was used as the dependent variable in subsequent logistic regression analyses with methamphetamine treatment response as the outcome. At week 4, response in depressive symptoms, referred to hereafter as PHQ-9 response, was ascribed if there was ≥50% reduction in depression severity at week 4 as compared to baseline. At week 4, remission of depressive symptoms, referred to hereafter as PHQ-9 remission, was ascribed if the week 4 PHQ-9 score was <5, indicating the presence of minimal depression.[30,32] PHQ-9 response or remission was not defined for those with missing PHQ-9 values at each visit (20, 37, 50, and 69 at weeks 1, 2, 3, and 4, respectively). Separate logistic regression analyses for PHQ-9 response and PHQ-9 remission at week 4 were used with treatment group as the independent variable of interest and age, sex, race, ethnicity, and baseline PHQ-9 as covariates to evaluate if there was a greater likelihood of improvement in depression with naltrexone-bupropion versus placebo.

Three separate logistic regression models were used to evaluate if changes in PHQ-9 from baseline to week 4 (using slope estimates from aforementioned mixed model analysis), PHQ-9 response, or PHQ-9 remission were associated with a higher likelihood of methamphetamine treatment response (primary outcome of ADAPT-2 trial) even after controlling for treatment group, age, sex, race, ethnicity, and baseline PHQ-9.

Mediation analyses were used to evaluate whether the slope of change in PHQ-9 (a continuous mediator variable) accounted for the association between the treatment group (binary variable: naltrexone-bupropion and placebo) and methamphetamine treatment response (a binary outcome variable).[33] The mediation analyses were conducted with three separate models. Model 1 was a logistic regression model with methamphetamine treatment response as the outcome variable, treatment group as the independent variable of interest, and included age, sex, race, ethnicity, and baseline PHQ-9 as covariates. Model 2 was a linear regression analysis with slope of change in PHQ-9 as the dependent variable and included age, sex, race, ethnicity, and baseline PHQ-9 as covariates. Model 3 was a logistic regression model that included Model 1 plus the slope of change in PHQ-9 (as the continuous mediator model). A thousand-fold bootstrapping was used to estimate a 95% confidence interval (CI) for the percent of effect mediated by the slope of PHQ-9.

In exploratory analyses, we used a cross-lagged panel model to evaluate whether postbaseline (ie, at weeks 1, 2, and 3) UDS (negative indicated as "0" and positive as "1") predicted depression improvement (response, defined as "0" if improvement <50% as compared to baseline and "1" if improvement is ≥50% as compared to baseline) at the next visit and vice versa.

All analyses were conducted using SAS 9.4 except the cross-lagged panel model, which was conducted using Mplus Version 8.3.

RESULTS

Consistent with the primary report,[10] participants of ADAPT-2 trial included in this report were predominantly male (222/326, 68.1%), non-Hispanic (282/326, 86.5%), and white (248/326, 76.1%) with an average age of 40.1 years (SD of 10.3); see Table 1 for demographic information by treatment groups. Among those included

Table 1.

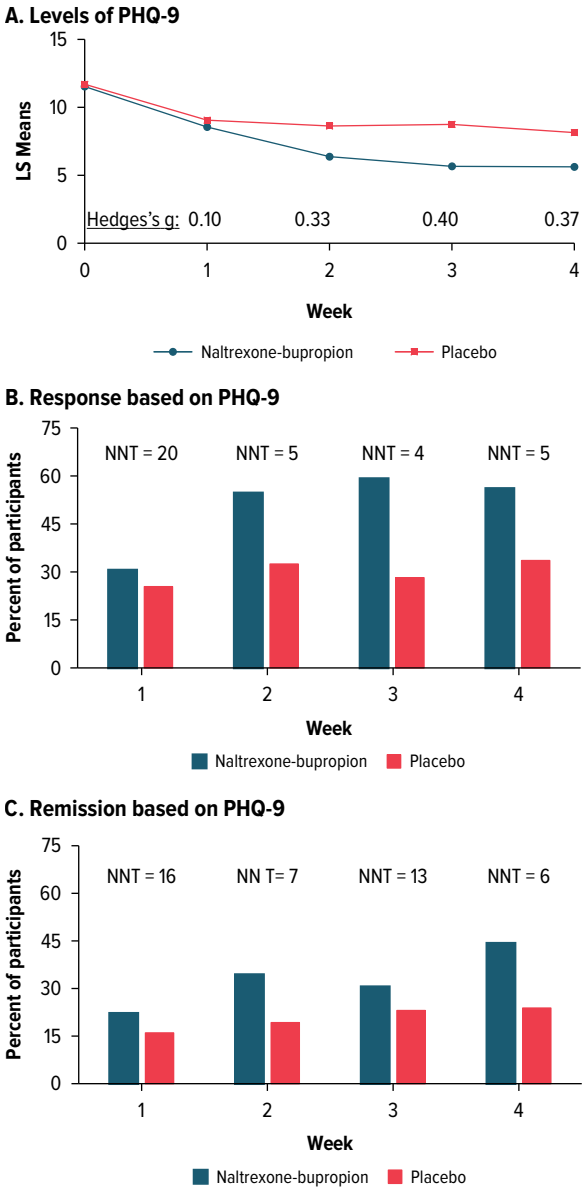
Demographic Characteristics of ADAPT-2 Trial Participants With Mild or Higher Severity of Self-Reported Depressive Symptoms

	Total (N=326)		Naltrexone-Bupropion (n=84)		Placebo (n=242)	
Categorical variables	**N**	**%**	**N**	**%**	**N**	**%**
Male sex	222	68.1	59	70.2	163	67.4
Hispanic ethnicity	44	13.5	10	11.9	34	14.1
White race	248	76.1	66	78.6	182	75.2
Continuous variables	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age in years	40.1	10.3	40.6	10.7	40.0	10.1
Number of days that methamphetamine was used in 30 days before informed consent	26.6	4.1	26.7	4.1	26.6	4.2
Age of first methamphetamine use	24.9	9.9	25.0	10.4	24.9	9.8
PHQ-9 score	12.9	5.5	12.8	5.5	12.9	5.5

Abbreviations: ADAPT = Accelerated Development of Additive Treatment for Methamphetamine Disorder, PHQ-9 = 9-item Patient Health Questionnaire.

Figure 1.

Improvement in Depression Severity With Naltrexone-Bupropion Combination Vs Placebo in the ADAPT-2 Trial Among Participants With Mild or Higher Severity of Self-Reported Depressive Symptoms

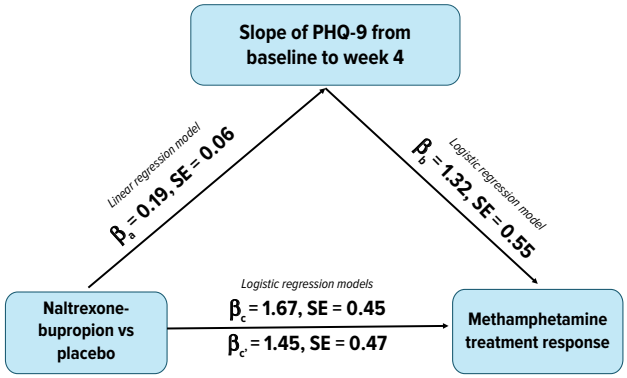


Abbreviations: ADAPT = Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder, LS means = least square means, NNT = number needed to treat, PHQ-9 = 9-Item Patient Health Questionnaire.

in this report (n = 326), 23 attained methamphetamine treatment response in Stage 1 with rates of 16.7% (14/84) and 3.7% (9/242) in naltrexone-bupropion and placebo treatment groups, respectively, with an odds ratio [OR] (95% confidence limit [CL]) of 5.18 (2.15, 12.47) for methamphetamine treatment response in Stage 1 with naltrexone-bupropion vs placebo.

Figure 2.

Mediation of the Effect of Naltrexone-Bupropion Combination on Methamphetamine Treatment Response by Reduction in Depression Severity



Abbreviation: PHQ-9 = 9-Item Patient Health Questionnaire.

Do Individuals With Methamphetamine Use Disorder Randomized to Naltrexone-Bupropion vs Placebo Report Greater Reduction in Depressive Symptom Severity?

Yes. There was significant difference between naltrexone-bupropion and placebo treatment groups in (treatment group-by-visit interaction: $F = 5.92$; $df = 4, 1140$; $P = .0001$) after controlling for age ($F = 3.17$; $df = 1, 316$; $P = .076$), sex ($F = 0.98$; $df = 1, 318$; $P = .32$), race ($F = 1.53$; $df = 2, 307$; $P = .22$), and ethnicity $F = 5.92$; $df = 2, 314$; $P = .95$). As shown in Figure 1, Panel A, there was a greater reduction in PHQ-9 with naltrexone-bupropion as compared to placebo. The estimated difference in least square means of PHQ-9 between naltrexone-bupropion and placebo groups at weeks 1, 2, 3, and 4 were −0.65 (SE [SE] = −0.50; $P = .77$), −2.25 (SE = 0.78; $P = .004$), −3.09 (SE = 0.80; $P = .0001$), and −2.52 (SE = 0.81; $P = .0018$), respectively. See Figure 1, Panel A, for Hedges g at each postbaseline visit until week 4. Furthermore, week 4 PHQ-9 response and remission rates were higher with naltrexone-bupropion (43/79 [54.4%] and 45/83 [54.2%]) than with placebo (86/226 [38.1%] and 84/239 [35.2%]) with unadjusted OR (95% CL) of 2.54 (1.42, 4.55) and 3.04 (1.57, 5.87) of PHQ-9 response and remission, respectively. See Figure 1, Panels B and C, for number needed to treat values for response and remission as outcomes, respectively. After controlling for age, sex, race, ethnicity, and baseline PHQ-9, the OR (95% CL) for higher likelihood of week 4 PHQ-9 response and remission with naltrexone-bupropion versus placebo were 1.89 (1.12, 3.19) and 2.59 (1.40, 4.78), respectively.

Table 2.

Logistic Regression Models Predicting Methamphetamine Treatment Response in Stage 1 of ADAPT-2 Trial[a]

	Treatment response predicted by PHQ-9 slope Odds ratio (95% CL)	Treatment response predicted by PHQ-9 response Odds ratio (95% CL)	Treatment response predicted by PHQ-9 remission Odds ratio (95% CL)
PHQ-9 slope	3.74 (1.28, 10.93)	NA	NA
PHQ-9 response vs nonresponse at week 4	NA	2.19 (0.83, 5.82)	NA
PHQ-9 remission vs nonremission at week 4	NA	NA	1.80 (0.64, 5.09)
Treatment group (naltrexone-bupropion vs Placebo)	4.27 (1.71, 10.64)	6.30 (2.40, 16.50)	6.43 (2.45, 16.89)
Age in years	0.98 (0.94, 1.02)	0.95 (0.91, 1.00)	0.96 (0.91, 0.99)
Sex (male vs female)	0.59 (0.23, 1.50)	0.60 (0.22, 1.63)	0.59 (0.22, 1.61)
Ethnicity (non-Hispanic vs Hispanic)	1.73 (0.33, 9.06)	2.26 (0.44, 11.57)	2.02 (0.40, 10.24)
Race (non-White vs White)	0.82 (0.24, 2.77)	0.79 (0.23, 2.69)	0.74 (0.22, 2.55)
Baseline PHQ-9	0.97 (0.89, 1.06)	1.02 (0.94, 1.11)	1.04 (0.96, 1.14)

[a]For PHQ-9 response and remission models, the number of individuals included was 256 due to missing values for PHQ-9 at week-4.
Abbreviations: ADAPT = Accelerated Development of Additive Treatment for Methamphetamine Disorder, PHQ-9 = 9-item Patient Health Questionnaire.

Is This Reduction in Depressive Symptom Severity Associated With Subsequent Methamphetamine Use Outcome?

Yes. In logistic regression models, there was a significant effect of the slope of PHQ-9 on the likelihood of response. Specifically, for each unit change in PHQ-9 slope, the OR (95% CL) for a higher likelihood of treatment response was 3.74 (1.28, 10.93), see Table 2 for the full model results. ORs (95% CLs) for higher likelihood of treatment response among those with week 4 PHQ-9 response and remission were 2.19 (0.83, 5.82) and 1.80 (0.64, 5.09), respectively; also see Table 2 for full model results.

Results of models included in mediation analyses (adjusted for age, sex, race, ethnicity, and baseline PHQ-9) are presented in Figure 2, including higher slope of PHQ-9 (indicating greater reduction in depression severity) with naltrexone-bupropion ($\beta = .19$, SE = 0.06, $P = .0008$) and higher likelihood of stage 1 treatment response (OR [95% CL] of 5.31 [2.19, 12.90] with naltrexone-bupropion that was reduced in models that included slope of PHQ-9 [OR (95% CL) of 4.27 (1.71, 10.69)]). Therefore, in mediation analyses, the slope of PHQ-9 accounted for 24.8% (95% bootstrapped confidence interval: 6.7%–60.3%) of the effect of naltrexone-bupropion on methamphetamine treatment response.

In a cross-lagged panel model, as shown in Figure 3, positive UDS at 1 visit was significantly associated with a higher likelihood of positive UDS at the next visit. Similarly, attainment of response based on PHQ-9 at 1 visit was associated with a higher likelihood of PHQ-9 response at the next visit, see Figure 3 for details. Attainment of response at week 3 was associated with a lower likelihood of positive UDS at week 4 ($\beta = -0.91$, SE = 0.40, $P = .023$). All other estimates of PHQ-9 response predicting UDS at next visit and vice versa were not statistically significant.

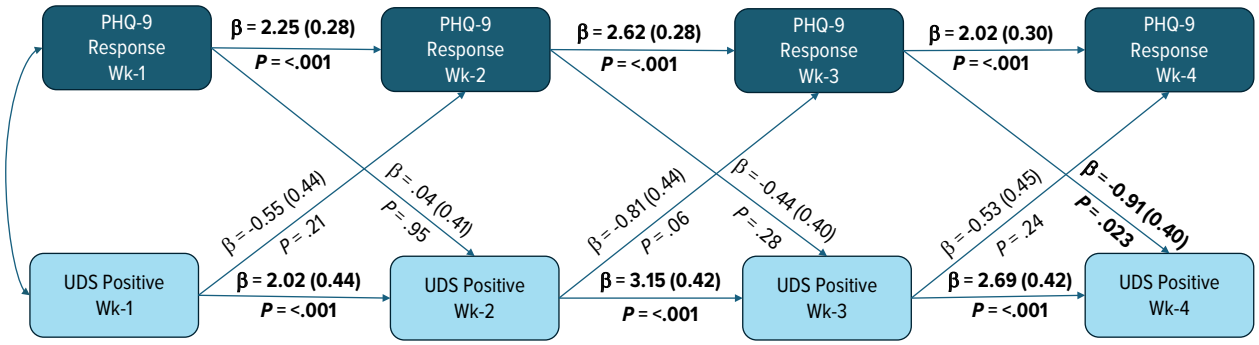
DISCUSSION

In this large study comparing naltrexone-bupropion versus placebo, a significant reduction in overall depressive symptom severity was observed during the first 4 weeks of naltrexone-bupropion treatment, and this reduction was associated with a higher likelihood of methamphetamine treatment response. Furthermore, in mediation analyses, these reductions in depression severity accounted for an estimated 24.8% of the effect of naltrexone-bupropion on methamphetamine treatment response. At week 4, PHQ-9 response and remission rates were higher with naltrexone-bupropion versus placebo. While similar in direction to the reduction in depression severity, attainment of PHQ-9 response or remission at week 4 was not significantly associated with methamphetamine treatment response. In the cross-lagged panel model, UDS and PHQ-9 responses at 1 visit were predictive of the UDS and PHQ-9 responses, respectively, at the subsequent visit. PHQ-9 response at week 3 was associated with a lower likelihood of positive UDS at week 4, further indicating that improvement of depression in this study was associated with a greater likelihood of methamphetamine treatment response.

Findings of this report differ from prior studies of antidepressant medications for stimulant use disorder by finding a greater reduction in depression severity with the active treatment as compared to placebo.[23–26] There are several reasons that may account for this difference. The sample size of the ADAPT-2 trial was much larger than previous trials, thereby improving our ability to detect differences. Unlike prior studies that used bupropion monotherapy,[7,22–24] this study combined bupropion with extended-release injectable naltrexone. Furthermore, the total dose of bupropion used in ADAPT-2 (450 mg/day) was higher than in prior studies. The ADAPT-2 study design included the use of an application

Figure 3.

Cross Lagged Panel Model to Evaluate the Effect of Post-Baseline Urine Drug Test on Subsequent Depression Improvement and Vice Versa[a]



[a]PHQ-9 response indicates improvement in PHQ-9 by ≥50% as compared to baseline. UDS positive indicated urine drug screen positive for methamphetamine at that visit.
Abbreviation: PHQ-9 = 9-Item Patient Health Questionnaire.

to monitor adherence (AiCure)[10] to oral medication (bupropion or oral placebo), which may have resulted in greater compliance with oral medications as compared to prior studies.

These findings have potential clinical and research implications. Measurement-based care approaches[34] that incorporate routine screening for depression in health care settings[35,36] may help identify individuals who have persistently elevated depression and are therefore less likely to improve with naltrexone-bupropion as compared to placebo. Furthermore, identifying difficult-to-treat depression in individuals with methamphetamine use disorder may facilitate the use of novel FDA-approved treatments for depression,[37] such as repetitive transcranial magnetic stimulation and intranasal esketamine, which, by improving symptoms of depression, may result in improved methamphetamine treatment response. Potential research implications include testing of novel treatments, especially rapid-acting antidepressants such as the combination of dextromethorphan and bupropion (approved by the US FDA in 2022[38]) or intravenous ketamine.[39] Notably, there is an ongoing multisite study of ketamine for methamphetamine use disorder (NCT06496750), which could help extend these findings regarding early changes in depression severity mediating the reduction in methamphetamine use.

There are several limitations of this report. The ADAPT-2 trial was not designed to evaluate whether early change in depression severity was associated with methamphetamine treatment response. Thus, these secondary analyses may not have been adequately powered. Missing values regarding week 4 PHQ-9 response and remission may have contributed to the lack of significant association between these measures of improvement in depression and methamphetamine treatment response. The analytical approach in this report is limited by not evaluating whether changes in methamphetamine use were associated with subsequent depression change.[16,21] Changes in depressive symptoms may have been potentially influenced by concomitant medications, such as other antidepressants, which were not systematically assessed nor were prohibited in this study. Generalizability of these findings may be limited because of ADAPT-2 eligibility restrictions, which favored enrollment of individuals with moderate/severe methamphetamine use disorder and heavy use of methamphetamine, and prior studies had suggested a stronger effect of bupropion among the subgroup with less severe methamphetamine use.[10] These findings also may not apply to individuals with methamphetamine use disorder and treatment-resistant depression (as prior responses to antidepressants were not systematically assessed) and to those with acute suicidal ideation or behaviors, who were excluded from this study.

In conclusion, in this secondary analysis of ADAPT-2 trial, there was a greater reduction in depression severity with naltrexone-bupropion versus placebo, and this reduction was associated with a higher likelihood of subsequent reduction in methamphetamine use.

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