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Sexual Orientation Differences among Men in a Randomized Clinical Trial of Extended-Release Naltrexone and Bupropion for Methamphetamine Use Disorder

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Abstract

Background: Methamphetamine use disorder (MethUD) disproportionately affects men who have sex exclusively with men or with men and women (collectively MSM/W), compared to men who have sex with women (MSW). This study is the first MethUD medication trial to compare treatment effect for these groups, hypothesizing that extended-release injectable naltrexone 380mg every 3 weeks plus oral extended-release bupropion 450mg daily would be less effective for MSM/W than MSW.

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Contributors

All authors worked collaboratively to develop the aims and design for this analysis. Jeremy Kidd, as corresponding author, oversaw the analyses and was responsible for preparing the final manuscript. He had access to all data from the study, both what is reported and what is unreported, and had complete freedom to direct its analysis and its reporting, without influence from the sponsors. There was no editorial direction or censorship from the sponsors. Sabrina Smiley, Phillip Coffin, Frances Levin, and Edward Nunes participated substantially in interpretation of findings and presentation of data. Thomas Carmody performed statistical analyses and reviewed the presentation of data in this manuscript. Madhukar Trivedi was the principal investigator of the parent trial (ADAPT-2) and participated substantially in these analyses and manuscript. All of the authors have revised and approved the final manuscript.

Methods: Data come from men (N=246) in a multi-site, double-blind, randomized, placebo-controlled trial with sequential parallel comparison design. In Stage 1 (6-weeks), participants were randomized to active treatment or placebo. In Stage 2 (6-weeks), Stage 1 placebo non-responders were rerandomized. Treatment response was ≥3 methamphetamine-negative urine samples, out of four obtained at the end of Stages 1 and 2. Treatment effect was the active-versus-placebo between-group difference in the weighted average Stages 1 and 2 responses.

Results: MSM/W (n=151) were more likely than MSW (n=95) to be Hispanic, college-educated, and living with HIV. Adjusting for demographics, among MSM/W, response rates were 13.95% (active treatment) and 2.78% (placebo) in Stage 1; 23.26% (active treatment) and 4.26% (placebo) in Stage 2. Among MSW, response rates were 7.69% (active treatment) and 5.80% (placebo) in Stage 1; 3.57% (active treatment) and 0% (placebo) in Stage 2. Treatment effect was significantly larger for MSM/W (h=0.1479) than MSW (h=0.0227) (p=0.04).

Conclusions: Findings suggest efficacy of extended-release naltrexone plus bupropion for MSM/W, a population heavily burdened by MethUD. While a secondary outcome, this intriguing finding merits testing in prospective trials.

Keywords

gay; bisexual; stimulants; methamphetamine; addiction; psychopharmacology

1. INTRODUCTION

While methamphetamine use has recently increased overall in the United States adult population (Palamar et al., 2020), men who have sex with men (MSM) and men who have sex with men and women (MSMW) constitute two population groups with long-standing, disproportionately high rates for methamphetamine use (Halkitis et al., 2001; Rivera et al., 2021; Substance Abuse and Mental Health Services Administration, 2023). In response to this and elevated rates of other negative health outcomes (e.g., depressive disorders, HIV infection), the U.S. National Institutes of Health designated sexual and gender minorities (including MSM and MSMW) a health-disparities population for research (National Institute on Minority Health and Health Disparities, 2016). There are also differences between methamphetamine use among MSM and MSMW (collectively abbreviated MSM/W) and men who have sex exclusively with women (MSW). For example, high rates of methamphetamine use among MSM/W (Halkitis et al., 2001; Rivera et al., 2021) can be explained in-part by Minority Stress Theory (Meyer, 2003). In this public health framework, individuals from marginalized groups experience distinct and chronic stress (i.e., minority stress) in their daily lives that is derived from discrimination, stigma, and societal prejudice (Meyer, 2003). Minority stressors such as homophobic violence, employment discrimination, housing discrimination and related housing instability, everyday discrimination (e.g., microaggressions), and societal stigma are associated with increased risk for methamphetamine use among MSM/W (Li et al., 2018). Other notable differences between MSM/W and MSW involve combining methamphetamine and sexual behavior (i.e., “chemsex”). Chemsex among MSM/W is highly associated with increased risk for HIV infection (Ostrow, 2009) and likely to involve condomless sex, transactional sex, multiple sexual partners, and longer episodes of sexual activity (Frankis et al., 2018; Nerlander et

al., 2018). There is also a higher prevalence of compulsive sexual behavior among MSM/W with methamphetamine use disorder (MethUD), compared to MSW with MethUD (Jennings et al., 2022; Kelly et al., 2009). Among MSM/W, sexual compulsivity is associated with higher odds of concurrent methamphetamine use (Carrico et al., 2012; Grov et al., 2010; Kelly et al., 2009) and greater HIV risk (Grov et al., 2010). For some MSM/W, sexual compulsivity may be an attempt to cope with negative affect (Carrico et al., 2012), including minority-stress-related emotional dysregulation (Pachankis et al., 2015).

Differences between MSM/W and MSW who use methamphetamine may impact MethUD treatment. Prior studies have signaled that treatment outcomes for MethUD may differ for MSM/W, compared to MSW. For example, two studies (Shoptaw et al., 2006; Shoptaw et al., 2005) delivered parallel high-value contingency management (CM), contingent on drug-negative urines and with the same behavioral reinforcement procedures. The first trial was exclusively for MSM/W (Shoptaw et al., 2005). The second trial included a placebo-controlled evaluation of sertraline plus CM for primarily MSW and women who have sex with men (Shoptaw et al., 2006). Participants in the MSM/W-focused study (Shoptaw et al., 2005) earned three times higher CM rewards for methamphetamine-negative urine samples than men in the MSW trial (Shoptaw et al., 2006) ($662 versus $200), suggesting that MSM/W may have a greater treatment response to CM than MSW. Participants in both trials were diagnosed with DSM-IV methamphetamine dependence by the Structured Clinical Interview, yet differences in their response to CM were striking and provided a motivation for this secondary analysis. There are no randomized, placebo-controlled medications trials for MethUD that have directly compared efficacy for MSM/W and MSW (Kidd et al., 2021).

Naltrexone and bupropion are two medications that have shown evidence of efficacy in treating MethUD (Chan et al., 2019; Siefried et al., 2020). Given elevates rates of methamphetamine use among MSM/W and the previously described differences between MSM/W and MSW with MethUD that could impact treatment outcomes, we conducted a secondary analysis of adult men enrolled in a randomized, placebo-controlled trial of extended-release naltrexone (XR-naltrexone) plus high-dose bupropion for MethUD to determine if there was a differential response rate for MSM/W and MSW. In primary analyses of this trial, there was a statistically significant 11.1% difference in the response rate between participants randomized to active medication treatment versus placebo (Trivedi et al., 2021). Given the relationship of minority stress (Li et al., 2018) and sexual compulsivity (Jennings et al., 2022; Kelly et al., 2009) to MethUD among MSM/W, we predicted that the effect of a medication-only treatment would be lower among MSM/W than MSW. As an exploratory analysis, given prior research on the differences in chemsex behaviors between MSM/W and MSW (Frankis et al., 2018; Nerlander et al., 2018; Ostrow, 2009), we also compared baseline sexual behavior characteristics of MSM/W and MSW to generate hypotheses about factors that might account for any difference observed.

2. METHODS

Data for this secondary analysis come from the Accelerated Development of Addictive Treatment for Methamphetamine Disorder (ADAPT-2) trial (Trivedi et al., 2021). This 12-week randomized, double-blind, placebo-controlled trial was conducted between May

2017 and June 2019 across eight sites in the Northeastern, Southeastern, Southwestern, and Western United States to evaluate the efficacy of combination injectable XR-naltrexone and oral extended-release bupropion for MethUD.

2.1. Participants

Adults ages 18–65 who wanted to quit using methamphetamine were recruited via print, Web, radio, and television advertising and via direct referral from other participants or medical clinics. ADAPT-2 eligibility criteria were Diagnostic and Statistical Manual, 5th edition moderate or severe stimulant use disorder (methamphetamine type); ≥18 days of methamphetamine use in the 30 days prior to consent; ≥2 methamphetamine-positive urine samples in the 10 days prior to randomization; and opioid-negative urine at randomization. Exclusion criteria were current MethUD treatment, an expected need for an opioid medication during the trial, or medical conditions that would make study participation unsafe (e.g., elevated seizure-risk). Participants with co-morbid psychiatric diagnoses were not routinely excluded; these were evaluated on a case-by-case basis to determine if participation was safe. All participants provided written informed consent after receiving a complete description of the study. This secondary analysis was restricted to men enrolled in the ADAPT-2 trial.

2.2. Trial Design

The ADAPT-2 trial utilized a sequential parallel comparison design (Chen et al., 2011) and was conducted in two 6-week stages. In Stage 1, participants were randomized in a 0.26:0.74 ratio to XR-naltrexone 380mg every 3 weeks and oral extended-release bupropion 450mg daily or placebo. After 6 weeks, those who received placebo and did not respond were re-randomized in a 1:1 ratio. Rerandomization was intended to enrich the Stage 2 sample with participants who were unlikely to respond to placebo. Randomization ratios were derived from established protocols for sequential parallel design trials [additional details are available in the ADAPT-2 protocol (Trivedi et al., 2021)]. Results for both stages were combined as detailed in Section 2.4 (Data Analysis).

Injectable XR-naltrexone was administered by study clinicians at randomization and every three weeks thereafter. Oral bupropion was provided weekly in blister packs. Adherence was tracked via self-report at study visits and daily via a smartphone app. Participants were compensated $5 for each dosing video submitted. Study clinicians were blinded to treatment group assignment. The full ADAPT-2 protocol, including adverse events and primary outcome results, are published elsewhere (Trivedi et al., 2021). This trial was conducted with oversight from a data safety monitoring board of the National Institute on Drug Abuse Clinical Trials Network and by a centralized institutional review board (IRB) and the IRBs at four sites.

2.3. Measures

2.3.1. Behavioral sexual orientation—At baseline, 6-week, and 12-week follow-up, participants were asked about past 30-day frequency of male sexual partners (“During the past 30 days, how many sex partners did you have who were male?”) and female sexual partners (“During the past 30 days, how many sex partners did you have who were

female?"). Men who reported male sexual partners at any time-point were classified as MSM (only male partners) and MSMW (male and female sexual partners). Because there were only 14 MSMW and because of the risk of misclassifying some MSMW as MSM if they had female sexual partners outside of the assessment windows, MSM and MSMW were combined (MSM/W). Individuals with only female partners were classified as MSW. We excluded individuals with missing sexual partner data at all time-points.

2.3.2. Additional sexual behavior measures—At baseline, participants were asked to report the past 30-day frequency of oral, anal, or vaginal sex with HIV-positive and HIV-negative partners. These numbers were combined to create a "frequency of sexual activity" measure. Participants were also asked about past 30-day frequency of sex while using methamphetamine (i.e., chemsex) as well as condomless sex. We created an additional variable for percentage of past 30-day sexual encounters that were condomless.

2.3.3. Methamphetamine use and treatment outcome measures—At baseline, participants reported the number of days in the past month they had used methamphetamine. We used this information and past 30-day frequency of chemsex to calculate the percentage of past 30-day methamphetamine use days that involved chemsex (assuming no more than one episode of chemsex per methamphetamine-use day).

For this secondary analysis, we used the same primary outcome as the parent trial (Trivedi et al., 2021): "treatment response" was defined as ≥3 methamphetamine-negative urine tests out of a possible four obtained at the end of Stage 1 (study weeks 5–6) and Stage 2 (study weeks 11–12). Participants with ≥2 missing urine drug screen results or who discontinued the trial were considered non-responders. To combine results across the two trial stages, the weighted average of responses across the stages was calculated for each treatment group (XR-naltrexone plus bupropion and placebo). Overall "treatment effect" (calculated separately for MSM/W and MSW) was defined as the difference in weighted responses between the active medication and placebo groups. Section 2.4 (Data Analysis) contains additional details about the calculation of treatment effect.

2.4. Data Analysis

The intention-to-treat population was used for all analyses. Baseline characteristics, including methamphetamine use and sexual behavior variables, were compared between MSM/W and MSW using t-tests, Wilcoxon 2-sample tests, or chi-square tests as appropriate. Separately for MSM/W and MSW participants, rates of "treatment response" (i.e., dichotomous variable; ≥3 methamphetamine-negative urine tests out of a possible four obtained at the end of Stages 1 and 2) were compared between treatment groups (active medication vs placebo) using the method of Tamura and Huang (Tamura and Huang, 2007) for a two-stage sequential parallel comparison design trial. This method involves using a randomization fraction and a weight, both of which are chosen to maximize the power of the test. Additional information about calculations for randomization ratios and weights can be found in the ADAPT-2 protocol (Trivedi et al., 2021). The "treatment effect" (h) for a sequential parallel comparison design trial is the weighted average proportion of responders on active medication in Stage 1 and Stage 2 minus the weighted average proportion of

responders on placebo in Stage 1 and Stage 2, using the pre-specified weight (0.43 for stage 1, 0.57 for stage 2). Treatment effect was calculated separately for MSM/W and MSW participants. Next, to test the difference in treatment effect between MSM/W and MSW participants, we used a generalized linear mixed-effects model. This model, which was constructed to implement the method of Tamura and Huang, was appropriate for a binary outcome with binomial distribution and logit link function, contained a fixed effect of behavioral sexual orientation subgroup by study stage by treatment group interaction and random person-level intercepts. The difference in treatment effect (*h)* between MSM/W and MSW was tested by an f-test for the contrast of treatment effects between subgroups. Unadjusted models were fit as well as models adjusted for site, age, race, ethnicity, education, employment, HIV serostatus, and baseline days of methamphetamine use. Number needed to treat (NNT), defined as 1/*h*, was also reported. All tests were two-sided and computed using SAS Version 9.4.

3. RESULTS

Of 403 participants enrolled in the ADAPT-2 trial, 277 (68.7%) were cisgender men (there were no transgender men in the trial). After excluding 31 men with missing information about past 30-day sexual partners, the analytic sample for this secondary analysis was 246: 151 MSM/W (61.4%) and 95 MSW (38.6%).

Table 1 presents baseline characteristics for the study sample, stratified by behavioral sexual orientation. MSM/W and MSW were similar in age (40.69 versus 40.36 years, t=0.25, df=244, p=0.806). MSM/W were more likely than MSW to be of Hispanic ethnicity (21.2% versus 9.5%, chi-square=5.8, df=1, p=0.016), to have some college education (81.5% versus 48.4%, chi-square=29.6, df=1, p<0.001), and to be living with HIV (56.3% versus 0%, chi-square=95.3, df=2, p<0.001). There was no significant difference between MSM/W and MSW in the prevalence of moderate-to-severe depression (55.6% versus 48.4%, p=0.270). There were also no significant differences between MSM/W and MSW in treatment condition assignment (i.e., placebo or active medication) or medication adherence.

Table 2 compares baseline past 30-day sexual behavior characteristics of MSM/W and MSW. Nearly all participants (*n*=231, 93.9%) reported oral, anal, or vaginal sex within the past 30-days; over half (*n*=128; 52.0%) reported sex within the past two days. Among MSM/W, the median number of past 30-day sexual partners was 4 (25^{th} percentile, 75^{th} percentile: 2, 12), compared to a median of 1 (25^{th} percentile, 75^{th} percentile: 1, 2) among MSW. The two groups were similar in terms of past 30-day frequency of sex with methamphetamine (MSM/W: median 10, IQR 4–20; MSW: median 10, IQR 3–15, Z=−1.4, p=0.165). MSM/W and MSW reported similar distributions in the percentage of methamphetamine-use days that involved chemsex..

Table 3 compares the adjusted treatment effect of XR-naltrexone plus bupropion versus placebo for MSM/W and MSW. In unadjusted analyses, the treatment effect (weighted average difference in response rates between treatment groups) was significantly larger for MSM/W than MSW (*h* = 0.1564 and NNT= 6.4 versus h=0.0285 and NNT=35.1; f=4.6, numerator df=1, denominator df=378, *p* = 0.03). This difference persisted in analyses that

adjusted for study site and demographics (i.e., age, race, ethnicity, education, employment, HIV serostatus, and baseline days of methamphetamine use), with MSM/W experiencing a significantly larger treatment effect and smaller number-needed-to-treat (NNT) ($h = 0.1479$ and NNT=6.7) than MSW ($h = 0.0227$ and NNT=41.3) (f=4.3, numerator df=1, denominator df=361, $p = 0.04$). There was almost no treatment effect for MSW. In these models, none of the covariates was significantly associated with treatment effect.

4. DISCUSSION

This study is one of the first to present data from a randomized, placebo-controlled trial of a medication intervention for methamphetamine use disorder (MethUD) that compared treatment effect for MSM/W and MSW. Our findings revealed that combination XR-naltrexone and bupropion was efficacious for promoting methamphetamine abstinence among men who have sex with men or with both men and women (MSM/W), a marginalized population that is disproportionately impacted by methamphetamine. Additionally, and surprisingly, there was little effect for men who have sex exclusively with women (MSW). Results from these analyses provide preliminary support for clinical practice change and highlight the need for additional trials prospectively designed to investigate the behavioral, psychological, and neurophysiological factors that may explain differential treatment efficacy of this medication combination for MSM/W and MSW.

4.1. Expanding on previous medication trials for MethUD among MSM/W

There are very few medication trials for MethUD among MSM/W (Kidd et al., 2021). This study expands on earlier trials that individually studied bupropion and naltrexone among MSM with MethUD. For example, Das and colleagues (2010) conducted a pilot feasibility trial of 30 MSM with DSM-IV methamphetamine dependence who were randomized to either extended-release bupropion 300mg daily or placebo. They reported positive tolerability findings. Santos and colleagues (Santos et al., 2016) conducted a feasibility study of oral naltrexone for MSM with co-morbid alcohol use disorder and MethUD. This study was not designed to assess efficacy. In a 10-week placebo-controlled trial of monthly XR-naltrexone for MSM with MethUD, Coffin and colleagues (Coffin et al., 2018) found no difference between placebo and active treatment in the percentage of methamphetamine-positive urines. Notably, participants in the ADAPT-2 trial received XR-naltrexone every three weeks, which may have enhanced the treatment effect (Dunbar et al., 2006). ADAPT-2 also combined naltrexone with high-dose bupropion, a medication with stimulant-like effects; used a higher bupropion dose than previous MethUD trials (Siefried et al., 2020); and incentivized adherence.

4.2. Theorizing potential meditators of differential treatment response for MSM/W and MSW

Differences in baseline sexual behavior between MSM/W and MSW can help generate hypotheses for future studies to investigate the mechanisms of treatment effect for MSM/W. At baseline, nearly all participants in this study reported approximately the same frequency of sexual behavior in general and in combination with methamphetamine. Among both MSM/W and MSW, virtually all sexual encounters were condomless. However, MSM/W

had more sexual partners than MSW; potentially further increasing the HIV/STI risk associated with condomless sex. These findings are in-line with previous research that suggests chemsex may be a qualitatively different phenomenon among MSM/W and MSW. First, while not measured in the ADAPT-2 trial, previous research reveals that sexual compulsivity is more common among MSM/W who use methamphetamine than MSW who use methamphetamine and that compulsivity is associated with higher levels of methamphetamine use (Carrico et al., 2012; Grov et al., 2010; Kelly et al., 2009). Compulsive sexual behavior, recognized as a mental condition in ICD-11 (Grant and Chamberlain, 2016) and as a subcategory of other disorders in DSM-5 (Grant and Chamberlain, 2016), has distinct neuropsychological processes (Derbyshire and Grant, 2015; Pachankis et al., 2014) (e.g., impairments in delayed discounting, reduced behavioral self-efficacy, greater attentional bias for sex-related cues) and neurophysiologic correlates (Klucken et al., 2016; Liberg et al., 2022) (e.g., increased sexual-cue-associated anticipatory responses in the ventral striatum and orbitofrontal cortex). Naltrexone has been studied as a treatment (Derbyshire and Grant, 2015). Furthermore, a recent trial among MSM with co-morbid alcohol use disorder and MethUD found that participants who received oral naltrexone reported significantly greater reductions in condomless anal sex, compared to MSM who received placebo (Santos et al., 2016). Naltrexone also has demonstrated efficacy for treating alcohol (Murphy et al., 2022) and opioid (Sullivan et al., 2019) use disorders and preliminary efficacy for gambling disorder (Mouaffak et al., 2017), conditions that involve compulsive behaviors, by blunting the rewarding effects of alcohol/opioids/gambling and reducing cue-induced craving. Second, previous research with MSM/W has shown that higher levels of impulsivity are associated with more frequent condomless sex (Hahn et al., 2019). Bupropion is FDA-approved for tobacco use disorder (Rigotti et al., 2022) and commonly used off-label to treat attention-deficit hyperactivity disorder (Verbeeck et al., 2017); two conditions that, like MethUD, share impaired impulse control as a key feature (Lee et al., 2019; Verbeeck et al., 2017). Therefore, combination XR-naltrexone and high-dose bupropion may be particularly well-suited to the context of methamphetamine use among MSM/W with MethUD. Because the ADAPT-2 trial did not directly assess compulsivity and impulsivity, future studies are needed to understand their potential role in mediating treatment efficacy for MSM/W.

4.3. Overall effect size and potential for psychotherapy augmentation

Not only did XR-naltrexone plus bupropion demonstrate efficacy for treating MethUD among MSM/W, the treatment effect for MSM/W in this study (h = 0.15; NNT=6.7) was larger than that reported for the overall ADAPT-2 sample (h=0.11; NNT=9.0) (Trivedi et al., 2021). While this finding alone is clinically relevant, the overall effect size is modest. This is not surprising considering how psychologically driven methamphetamine use and chemsex are for many MSM/W. It is possible that medication treatment for MSM/W with MethUD would have even greater signal if combined with behavioral interventions focused on the interpersonal aspects of methamphetamine use, the impact of minority stress on emotional reactivity and self-esteem regulation, and the role that desire for sexual enhancement and concerns about sexual performance play in methamphetamine use among MSM/W (Rajasingham et al., 2012). Candidate behavioral interventions include Cognitive-Behavioral Therapy tailored for MSM/W with MethUD (Reback and Shoptaw, 2014) and Community

Reinforcement Approach to repair social networks (De Crescenzo et al., 2018). Contingency Management also shows strong signal in reducing methamphetamine use among MSM/W (Shoptaw et al., 2005), presumably by promoting prosocial, non-methamphetamine use behaviors.

4.4. Strengths and Limitations

Strengths include that this is the first known randomized, placebo-controlled trial to investigate the differential efficacy of a medication treatment for MethUD among MSM/W and MSW, with those subgroups adequately characterized and sufficient sample size to detect an interaction with treatment. There are limitations. First, as a secondary analysis, we were limited to the measures collected in the ADAPT-2 trial, the primary aim of which had been to evaluate the impact of the medication combination on methamphetamine use. Therefore, the measures of sexual behavior in this study were limited and lacked detailed assessments of sexual identity, chemsex, and other features of sexual behavior (e.g., compulsivity, impulsivity) that could be important in understanding treatment response. In light of this, findings are intended to generate hypotheses for future trials of medical and behavioral therapies for MethUD. Second, due to the small number of men who have sex with men and women (MSMW) in the study, we were not able look at treatment efficacy separately for this group. Third, all participants in this secondary analysis were cisgender men, prohibiting any conclusions about the efficacy of XR-naltrexone plus bupropion for transgender and nonbinary individuals with MethUD. Similarly, most participants were non-Hispanic White, which could limit the generalizability of our findings to non-White populations.

5. CONCLUSIONS

Combination XR-naltrexone and bupropion was efficacious in treating MethUD among MSM/W, but there was no evidence of efficacy among MSW. Additional studies are needed to explore differential responses for these two group to interventions addressing MethUD, in order to better guide future therapeutic research and development efforts.

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Conflict of Interest

Jeremy Kidd and Sabrina Smiley report no financial relationships with commercial interests. Phillip Coffin directs an NIH-funded trial that receives donated tenofovir-emtricitabine from Gilead Sciences. Thomas Carmody has been a consultant for Alkermes. Frances Levin receives grant support from the NIDA, SAMHSA, US World Meds and research support from Aelis Pharmaceuticals. She also receives medication from Indivior for research. In addition, Dr. Levin served as a nonpaid member of a Scientific Advisory Board for Alkermes, Indivior, Novartis, Teva, and US WorldMeds; receives royalties from APA Publishing; and is a consultant to Major League Baseball. Edward Nunes has served as an uncompensated consultant to Alkermes, Indivior, and Camurus, and as an investigator on NIH-funded studies that received in-kind medication from Alkermes, Indivior, and Braeburn/Camurus, and in-kind digital therapeutics from Pear Therapeutics and Chess Health. Steven Shoptaw receives support for research from Gilead Sciences, Alkermes and Indivior. He consults with Aelis Pharmaceuticals.

Declaration of interests:

Drs. Kidd and Smiley reports no financial relationships with commercial interests. Dr. Coffin directs an NIH-funded trial that receives donated tenofovir-emtricitabine from Gilead Sciences. Dr. Carmody has been a consultant for Alkermes. Dr. Levin receives grant support from the NIDA, SAMHSA, US World Meds and research support from Aelis Pharmaceuticals. She also receives medication from Indivior for research. In addition, Dr. Levin served as a nonpaid member of a Scientific Advisory Board for Alkermes, Indivior, Novartis, Teva, and US WorldMeds; receives royalties from APA Publishing; and is a consultant to Major League Baseball. Dr. Nunes has served as an uncompensated consultant to Alkermes, Indivior, and Camurus, and as an investigator on NIH-funded studies that received in-kind medication from Alkermes, Indivior, and Braeburn/Camurus, and in-kind digital therapeutics from Pear Therapeutics and Chess Health. Dr. Shoptaw receives clinical support for his research from Gilead Sciences, Alkermes and Indivior. He also consults with Aelis Pharmaceuticals.

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Table 1.

Baseline characteristics of cisgender men in the ADAPT-2 trial (*N* = 246 participants).

Characteristic	**MSM/W (n = 151) Mean ± SD or n (%)**	**MSW (n = 95) Mean ± SD or n (%)**	**p-value**
Age (years)	40.69 ± 10.31	40.36 ± 10.22	0.806
Race			0.079
White	92 (60.9%)	71 (74.7%)	
Black/African American	27 (17.9%)	12 (12.6%)	
Other	32 (21.2%)	12 (12.6%)	
Ethnicity			**0.016**
Hispanic	32 (21.2%)	9 (9.5%)	
Non-Hispanic	119 (78.8%)	86 (90.5%)	
Education			**<0.001**
High school or less	28 (18.5%)	49 (51.6%)	
Some College or higher	123 (81.5%)	46 (48.4%)	
Employment status			0.363
Unemployed	83 (55.0%)	48 (50.5%)	
Employed	63 (41.7%)	46 (48.4%)	
Retired/Student	5 (3.3%)	1 (1.0%)	
HIV serostatus			**<0.001**
Positive	85 (56.3%)	0 (0.0%)	
Negative	64 (42.4%)	72 (75.8%)	
Unknown, never tested	2 (1.3%)	23 (24.2%)	
Treatment Condition (Phase 1/Phase 2)			0.273
Placebo (not rerandomized)	18 (11.9%)	19 (20.0%)	
XR-NTX + BUP	43 (28.5%)	26 (27.4%)	
Placebo/XR-NTX + BUP	43 (28.5%)	28 (29.5%)	
Placebo/Placebo	47 (31.1%)	22 (23.3%)	

Bold = statistically significant at p < .05.

MSM/W: men who have sex with men only or with both men and women.

MSW: men who have sex exclusively with women

XR-NTX + BUP: combination injectable extended-release naltrexone and oral high-dose bupropion

Table 2.

Baseline past 30-day characteristics of methamphetamine use and sexual behavior, stratified by behavioral sexual orientation.

	MSM/W (N=151) Median (IQR)	**MSW (N=95) Median (IQR)**	**p-value (Wilcoxon 2-sample test)**
Frequency of sexual activity	5.5 (2.0, 15.0)	5.0 (1.0, 15.0)	0.444
Number of male sexual partners	4 (2, 12)	NA	NA
Number of female sexual partners	0 (0, 0)	1 (1, 2)	**<0.001**
Methamphetamine use (days)	28.0 (22.0, 30.0)	29.0 (25.0,30.0)	0.061
Sex with meth (chemsex episodes)	10 (4, 20)	10 (3, 15)	0.165
% meth use days that involved chemsex *	34.5 (16.7, 83.3)	33.3 (10.0, 66.7)	0.073
% of sexual encounters that were condomless	100.0 (94.6, 100.0)	100.0 (100.0, 100.0)	**0.015**

Bold = statistically significant at $p < .05$.

MSM/W: men who have sex with men only or with both men and women.

MSW: men who have sex exclusively with women

*Because participants reported methamphetamine use and chemsex differently (days and episodes, respectively), we calculated percentages of chemsex using the conservative assumption of 1 chemsex episode per methamphetamine-use day.

Table 3.

Comparison of the adjusted treatment effect for extended-release naltrexone plus bupropion (XR-NTX + BUP) versus placebo for MSM/W and MSW participants.

	Stage 1			Stage 2			NTX-BUP vs Placebo Treatment Effect*			
Subgroup	**# Randomized**	**Placebo Responder Rate**	**XR-NTX + BUP Responder Rate**	**# Rerandomized**	**Placebo Responder Rate**	**XR-NTX + BUP Responder Rate**	**Treatment Effect (*h*)**	**Standard Error of *h***	**Number Needed to Treat**	**p-value**
MSM/W	151	(3/108) 0.0278	(6/43) 0.1395	90	(2/47) 0.0426	(10/43) 0.2326	0.1479	0.0357	6.7	0.04
MSW	95	(4/69) 0.0580	(2/26) 0.0769	50	(0/22) 0.0000	(1/28) 0.0357	0.0227	0.0484	41.3	

MSM/W: men who have sex with men only or with both men and women.

MSW: men who have sex exclusively with women

Treatment Effect (*h*): between-group difference (active medication vs placebo) in the weighted average of Stage 1 and Stage 2 respond rates.

*All models were adjusted for study site, age, race, ethnicity, education, employment, HIV serostatus, and baseline methamphetamine use.