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Extended Release Mixed Amphetamine Salts and Topiramate for Cocaine Dependence: A Randomized Clinical Replication Trial with Frequent Users

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Abstract

Background—Cocaine use disorder (CUD) remains a substantial public health problem with no clearly effective pharmacotherapy available. In a prior trial, combined amphetamine and topiramate treatment significantly reduced cocaine use among individuals demonstrating the most frequent use at baseline. This trial targeted such frequent users.

Methods—A double-blind, randomized placebo-controlled trial, testing the combination of mixed amphetamine salts extended-release (MAS-ER) and topiramate or placebo over a 12-week medication phase was conducted. The two-site outpatient trial included 127 adults (96 males) with

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Contributors

Authors Levin and Kampman designed the study, wrote the protocol, obtained funding and served as PIs of the study at Columbia University and University of Pennsylvania respectively and were responsible for implementation and responsible conduct of the research projects. Authors Choi and Pavlicova undertook the statistical analysis, and authors Levin, Choi, Pavlicova, Mariani and Nunes the interpretation of the data. Author Mahony was responsible for many aspects of study implementation, data collection, supervision and organization, IRB coordination and other study features. Author Brooks offered administrative, technical and material support. Authors Levin, Choi and Pavlicova wrote the first draft of the manuscript. Authors Naqvi, Bisaga, Carpenter and Dakwar provided clinical support. All authors contributed to, edited and have approved the final manuscript.

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CUD using at least 9 days in the prior month. MAS-ER was titrated to a maximum dose of 60 mg/day and topiramate to a maximum dose of 100 mg twice/day. The primary outcome was the proportion of individuals who achieved three consecutive abstinent weeks at the end of the study (EOS) as measured by urine toxicology and self-report.

Results—The proportion of participants achieving three abstinent weeks at the EOS was significantly ($P=.03$) larger in the treatment (14.1%) compared to the placebo group (0.0%), while controlling for baseline cocaine use, sex, current alcohol use disorder, and site. Of note, due to conservative cardiac safety-parameters a considerable number of individuals in the treatment group were discontinued from study medication (20.3%).

Conclusions—While these findings provide further evidence that the combination of MAS-ER and topiramate is efficacious in promoting abstinence in CUD adults with frequent use it remains possible that the combination treatment is no more effective than either treatment alone. Despite this, the study provides a valuable “proof of concept.”

Trial Registration—[Clinicaltrials.gov](https://clinicaltrials.gov) Identifier:

URL: <https://clinicaltrials.gov/ct2/show/NCT01811940>

Keywords

cocaine dependence; amphetamines; topiramate; treatment; clinical trial; substance dependence

1. Introduction

There are approximately 2.2 million current users of cocaine in the US, and 966,000 individuals with a past year cocaine use disorder (SAMHSA, 2018), yet there are no FDA-approved pharmacotherapies for cocaine use disorder (CUD). Standard psychosocial treatments for CUD yield small-to-medium effect sizes and have limited impact for most patients with cocaine use disorder (Dutra et al., 2008; Knapp et al., 2007). Numerous double-blind, placebo-controlled pharmacotherapy clinical trials for CUD have been conducted (Alvarez et al., 2013; Pani et al., 2011; Minozzi et al., 2015a; 2015b), testing agents drawn from a wide variety of medication classes, with no one approach demonstrating clear efficacy in promoting abstinence from cocaine.

Two such promising agents to treat CUD are amphetamine and topiramate. Amphetamine increases dopamine transmission via numerous molecular mechanisms (Faraone, 2018) and may reduce the reinforcing properties of cocaine (Rush et al., 2009; 2010). Amphetamine formulations have shown the most consistent positive therapeutic effects on cocaine use outcomes (Castells et al., 2010; Herin et al., 2010; Negus and Henningfield, 2015; Rush and Stoops, 2012). Extended release mixed amphetamine salts (MAS-ER) was found to be more effective than placebo in promoting abstinence in cocaine-dependent adults with ADHD (Levin et al., 2015). Topiramate, an anticonvulsant agent that enhances gamma amino butyric acid (GABA) activity, antagonizes glutamate transmission through effects at AMPA/kainate receptors (Gibbs et al., 2000; Johnson et al., 2013; Skradski and White, 2000), and in turn may reduce midbrain dopaminergic activity (Johnson, 2004; Johnson et al., 2005a) and nicotine-induced dopamine release (Schiffer et al., 2001). Supporting this approach, other

GABA-ergic agents have been found to reduce cocaine-induced dopamine release (Dewey et al., 1997). Thus, topiramate may modulate the reinforcing effects of co-administered amphetamines so that there are therapeutic gains in dopamine release, with dampened abuse liability. Topiramate has also shown promise as a treatment for CUD (Johnson et al., 2013; Kampman et al., 2004; Kampman et al., 2013; Singh et al., 2016), although one large study conducted in cocaine dependent methadone-maintained patients was negative (Umbricht et al., 2014).

In an earlier paper we hypothesized that the combination of amphetamine and topiramate would normalize dopamine signaling by both increasing dopamine signaling and reducing stimulant-induced dopamine release. This in turn might lead to reduced cocaine craving and decreased cocaine-induced reinforcement (Mariani et al., 2012). This approach is also consistent with a common principle in medical therapeutics of combining agents with different pharmacologic mechanisms to achieve additive or synergistic effects and an overall more potent clinical response. Consistent with this hypothesis, a randomized controlled pilot study among patients with CUD showed that the combination of MAS-ER plus topiramate (Mariani et al., 2012), significantly increased the odds of abstinence, compared to placebo among those participants with more frequent use of cocaine at baseline (>8 use days per month).

Building on the results of the pilot study and the reasons provided above, a confirmatory two-site, double-blind, placebo-controlled randomized trial of MAS-ER combined with topiramate for adults with CUD (using cocaine at least 9 days per month at study entry) was designed to study the effects of combined treatment on more frequent users of cocaine, a particularly difficult to treat population.

2. Materials and methods

2.1. Participants

The study was approved by the Institutional Review Boards of the New York State Psychiatric Institute and the University of Pennsylvania. Participants were seeking treatment for cocaine use and were recruited by local advertising or clinical referrals in the New York City and Philadelphia metropolitan areas. All participants gave informed written consent. We randomized 127 participants who met Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) (APA, 2000) criteria for cocaine dependence. Throughout the paper, we will use cocaine use disorder (CUD) to use current DSM 5 terminology. Participants were 18–60 years old; reported using cocaine at least 9 days during the 28 days (with at least weekly use) prior to study entry; and had a body mass index (BMI) ≥ 18 kg/m². Individuals who were currently stable on a psychotropic medication for at least 3 months were included (this criterion was added post study commencement). Participants were excluded if they: had a current DSM-IV-TR diagnosis of bipolar disorder, schizophrenia or any psychotic disorder other than transient psychosis due to drug abuse (based on a structured clinical interview and a comprehensive psychiatric evaluation done at screening); had an unstable DSM-IV-TR Axis I psychiatric disorder; were prescribed any psychostimulants; had a history of seizures or unexplained loss of consciousness; significant current suicidal risk (based on psychiatric evaluation and

completion of the Columbia-Suicide Severity Rating Scale (Posner et al., 2008)); were opioid dependent; were physiologically dependent on any other drugs (excluding nicotine or cannabis) which may require a medical detoxification (based on clinical judgment during psychiatric evaluation; individuals with Alcohol Use Disorder were included provided that they did not require a medical detoxification); were women who were pregnant, nursing, or unwilling to use adequate contraceptive methods; had unstable physical disorders which made participation hazardous such as uncontrolled hypertension (SBP>140; DBP>90, or HR>100), acute hepatitis (transaminases > 3× upper limit of normal) or uncontrolled diabetes; had evidence of coronary vascular disease as indicated by abnormal ECG, cardiac symptoms, fainting, open-heart surgery and/or arrhythmia, and/or family history of ventricular tachycardia/sudden death; were prescribed carbonic anhydrase inhibitors; had a history of glaucoma, kidney stones, or took any medications that were additive to the bicarbonate lowering effects of topiramate; had a history of failure to respond to a previous adequate trial of either of the candidate medications for CUD; were legally mandated to receive substance use disorder treatment; had a recent history (past 6 months) of a non-cocaine stimulant use disorder.

2.2. Treatment

A randomized, double-blind, parallel-group, 14-week clinical trial compared the combination of MAS-ER and topiramate to placebo, with a one-week single-blind placebo lead-in, a 12-week double blind study period, and a one-week taper was conducted at two sites: The Substance Treatment and Research Service of Columbia University Irving Medical Center/ New York State Psychiatric Institute and the Center for Studies of Addiction of the University of Pennsylvania. Those who were unable to comply with study procedures during the lead-in week were not randomized. Additionally, because we were interested in evaluating the combined intervention as an abstinence initiation strategy, only those using cocaine during the lead-in week (1 day self-reported use) were included and randomized. Randomized participants received either the combination of MAS-ER and topiramate or placebo in a 1:1 allocation for 12-weeks followed by a 1-week taper.

MAS-ER and topiramate were packaged in separate gelatin capsules. Participants in the placebo arm received matching placebo gelatin capsules. MAS-ER, topiramate, and matching placebo gelatin capsules all contained lactose filler and 12.5 mg of riboflavin. MAS-ER doses began at 10 mg daily and were titrated over two weeks to a maximum dose of 60 mg each morning and topiramate doses began at 25 mg daily were titrated over six weeks to a maximum dose of 100 mg twice daily. In the placebo arm, both matching placebo capsules for “MAS-ER” and “topiramate” allowed for blinded physicians to raise and lower “doses” based on clinical judgment. Reductions in dosing were made for participants experiencing clinically significant adverse effects. Participants were given \$10 each week if all bottles and unused medication were returned.

In addition to the study medication, all participants received Medical Management used for Project COMBINE (Anton et al., 2006), and stimulant trials (Johnson et al., 2003), a weekly manual-guided supportive behavioral treatment provided by the research psychiatrist. Sessions were focused on setting abstinence from cocaine use as a goal, reviewing

participant compliance with study medications and procedures, and assessing their current functioning. Progressive incentive payments were provided for attendance to enhance compliance with study procedures and retention. Starting at \$0.50, the payment for each subsequent visit increased by \$0.50. Failure to attend study appointments, complete study assessments, and provide a urine sample reset the payment back to their initial \$0.50 from which the cash would then escalate again according to the same schedule. Attending three consecutive clinic visits following non-attendance would return the payment to the level achieved prior to the missed visit. Incentive payments were not based on providing cocaine negative urines or on medication compliance. Perfect attendance and compliance with returning pill bottles would result in a participant earning \$592 over the study period. Participants were also compensated in cash for transportation costs per visit.

2.3. Assessment

The MINI-International Neuropsychiatric Interview (Sheehan et al., 1998) and Columbia-Suicide Severity Rating Scale (Posner et al., 2008) were performed as part of a comprehensive psychiatric and medical evaluation. Self-reported cocaine use for the prior 28 days was measured using the timeline followback (TLFB) method (Litten and Allen, 1992).

Three assessment visits per week were scheduled with each participant. At each study visit, a urine sample for toxicology and fluorometric detection of urinary riboflavin concentration (Herron et al., 2013) was obtained, along with vital signs. The urine toxicology analyses for cocaine was done using a confirmatory gas chromatography-mass spectrometry (GC-MS) method (detection cutoff was ≥ 150 ng/ml). Adverse events were assessed weekly by the research psychiatrist using the SAFTEE (Johnson et al., 2005b). Each week, a timeline followback assessment of cocaine use was performed and medication compliance was assessed using a calendar procedure and pill count. Serum topiramate levels were collected at weeks 5, 9, and 13. Urine testing for amphetamine was done at each study visit using an immunoassay test (detection cutoff was ≥ 1000 ng/ml). Female participants had urine pregnancy tests performed monthly. Electrocardiograms were performed at weeks 4 and 14.

Self-reported cocaine use was confirmed with a modified Winhusen method (Winhusen et al., 2007). A self-report of use was accepted as a “use day.” Urine samples with benzoylecgonine (BE, a metabolite of cocaine) levels greater than 300 ng/ml were considered positive (this was consistent with the previous trial conducted by Mariani et al. (2012)). A urine sample was considered negative for new use if it was preceded within two days by a sample with twice or more its BE level. If none of the three days preceding a positive urine sample had been self-reported as a use day, the day immediately preceding the sample was labeled a use day. Days with insufficient data to determine use for any individual were designated as cocaine-positive for that particular day.

The Brief Substance Craving Scale (BSCS) (weekly), a 16-item self-rated questionnaire was used to assess the frequency, intensity and amount of time spent craving cocaine and other substances (Somoza et al., 1999).

2.4. Data Analysis

All participants were block randomized with randomly selected blocks of size two, four, and six with stratification by site and by presence of alcohol use disorder (Efrid, 2011). The randomized sequence was designed by an independent statistician and utilized by the research pharmacist. Participants and all other study staff were blind to treatment assignment.

The primary outcome was defined as three consecutive weeks of abstinence at the end of the 12-week medication phase of the trial. Secondary outcomes were: (a) at least 3 consecutive weeks of abstinence during the study, (b) weekly status of cocaine use (determined by urine toxicology samples per participant, positive status occurs if at least one urine sample was positive for benzoylecgonine), (c) cocaine craving and (d) time to dropout.

The primary and secondary outcome (at least 3 consecutive weeks of abstinence) were analyzed in SAS® using logistic regression with predictors: treatment (MAS-ER and topiramate vs. placebo), site (UPENN vs. CUMC), sex (male vs. female), baseline severity of cocaine use (total number of cocaine use days in the 28 days prior to randomization), and presence of alcohol use disorder (AUD). Differential site effects were examined by testing site*treatment or site*treatment*time interactions for each outcome. None of these interaction effects were significant, therefore site was included as a fixed main effect.

Additionally, baseline severity of cocaine use was examined as a moderator of the effect of treatment on abstinence outcomes, to explore whether participants who are using more frequently experience differential treatment effects. Baseline severity of cocaine use in the interaction term was treated in three ways: as a continuous variable, binarized using a median split (9–15 days vs. 16–28 days during 28 days prior randomization) and categorized using tertile splits (9–12 days, 13–18 days, 19–28 days).

Because the primary outcome, three consecutive weeks of abstinence was not observed at all in the placebo group, logistic regression cannot produce a parameter estimate (odds ratio, OR) and corresponding standard error for the treatment variable if there are no observed events in one treatment group. There are several methods (Haldane correction, Firth's penalized approach) that can be utilized in such situation, both giving an approximation of the parameter estimates and corresponding 95% confidence interval. In this manuscript we provide both. The Haldane correction (Fleiss et al., 2013; Haldane, 1956; Lawson, 2004) estimates unadjusted OR for association between primary outcome (with no observed events in placebo group) and treatment. Specifically, a constant of 0.5 is added to each cell of the 2×2 contingency table to enable the computation of an unadjusted odds ratio and confidence interval. Firth's penalized approach (Firth, 1993) produces adjusted OR for association between primary outcome (with no observed events in placebo group) and treatment, adjusted for above mentioned covariates. Using maximization of penalized likelihood function that guarantees that the parameter estimates are finite, Firth's penalized approach produced adjusted Firth's odds ratios and confidence intervals.

Secondary outcome (weekly status of cocaine use) was analyzed using longitudinal mixed effect models with logit link function and a random intercept for participant. Two analyses

were conducted treating participants who dropped out as 1) relapsed or using, and 2) as missing. Secondary outcome (time to drop out) was compared using Kaplan-Meier curves and Cox proportional hazard models.

All analyses described in the preceding sections were conducted on the intent-to-treat sample of all randomized participants with 2-tailed tests and a significance level of 5%. The original sample size of 176 participants was chosen to ensure sufficient power (at least 80%) of a two-sided test with level of significance .05 for detecting difference between the two experimental treatments with respect to the percentage of subjects who achieve continuous 3 weeks of abstinence during the study, when the difference is of clinically meaningful and realistic magnitude. With 88 subjects per group, there is 80% power to detect a difference in the proportions of 10% versus 25.6%. Although the study randomized 127 participants, a significant finding in the primary outcome has been found. This means that we have observed a large enough effect size to be considered significant with 127 participants.

A Data and Safety Monitoring Board met four times during the trial to review study enrollment, overall medication tolerability, adverse and serious adverse events. The DSMB made no recommendations to alter the protocol or cease study enrollment.

3. Results

3.1. Participant Progress in Study and Demographics

Eight-hundred and forty participants were screened, 169 participants entered the trial, and a total of 127 participants (see CONSORT diagram, Figure 1) were randomized to either combined treatment with MAS-ER and topiramate (n=64; 50.4%) or placebo (n=63; 49.6%). Recruitment began in July 2013 and all follow-up was completed in May 2017. Individuals who initiated screening were assessed for potential eligibility in any one of several ongoing cocaine dependence clinical trials. The most common reason for screen failure for this trial was not meeting eligibility criteria. Characteristics of the randomized participants are shown in Table 1.

3.2. Primary outcome

The proportion of participants who achieved three consecutive weeks of abstinence at trial end was 14.1% (9/64) for those receiving treatment and 0% (0/63) for those receiving placebo (see Figure 2). Of the 9 participants who achieved three consecutive weeks of abstinence in the treatment group, 5 were from the CUMC site and 4 were from the UPENN site. The estimated Firth's odds ratio was 19.9 suggesting that those receiving treatment had 19.9 times the odds of achieving three consecutive weeks of abstinence at trial end (95% confidence interval (CI)= 1.5–260.8; $P=.023$) compared to those in the placebo group when adjusted by baseline cocaine using days, sex and site. Baseline cocaine using days (Firth's odds ratio (F-OR)=1.1, 95%CI=0.9–1.2; $P=.38$), sex (F-OR=0.7, 95%CI=0.2–2.8; $P=.58$), AUD (F-OR=1.6, 95%CI=0.4–6.3; $P=.47$) and site (F-OR=1.5, 95%CI=0.3–6.3; $P=.60$) were not significantly associated with the primary outcome. Using the Haldane correction, the unadjusted odds ratio was 21.7 suggesting that the odds of three consecutive weeks of

abstinence at trial end in the treatment group was 21.7 times (95%CI = 1.2–382.1) the odds in the placebo group.

3.3. Secondary outcomes

3.3.1. Continuous Cocaine Abstinence, Use, Craving and Retention—The proportion of participants who achieved any three consecutive weeks of abstinence during the study was larger for those receiving MAS-ER and topiramate (14/64, 21.9%), compared to placebo (4/63, 6.3%; see Figure 2). When comparing this outcome to the primary outcome, 4 patients in placebo group and 5 patients in treatment group achieved any 3-weeks abstinence but not end-of-study abstinence. The odds of any three consecutive weeks of abstinence during the study in the treatment group was 4.6 times (95%CI=1.4–15.2; $P=.01$) that of the placebo group. Baseline cocaine using days ($P=.83$), sex ($P=.86$), AUD ($P=.07$) and site ($P=.42$) were not significantly associated with the secondary outcome.

For both primary and secondary outcomes, there was no significant interaction between treatment group and baseline severity of use, regardless of whether baseline frequency of use was treated as a continuous variable, binarized using a median split or categorized using tertile splits.

The proportion of participants with positive weekly urine toxicology over time was significantly different between treatment arms (time*treatment interaction, $P=.004$; see Figure 3), while adjusting for site ($P=.01$), sex ($P=.49$), and AUD ($P=.23$). In the treatment group, the effect of time was significant; with each week, the proportion of participants with positive urine toxicology significantly decreased (OR=0.92, 95%CI=0.87–0.99; $P=.02$). In the placebo group, the effect of time was not significant, the proportion of participants with positive urine toxicology did not change (OR=1.1, 95%CI=0.99–1.2; $P=.07$). Similar results were obtained when participants who dropped out were treated as missing.

Cocaine craving, measured by the scores for “Want Cocaine”, significantly differed over time between treatment and placebo groups (time*treatment interaction, $P<.001$; see Figure 4) while adjusting for baseline “Want Cocaine” craving scores ($P<.001$), sex ($P=.33$), AUD ($P=.14$) and site ($P=.05$). Even though cocaine craving decreased over time in both groups, the rate of decrease for each group was significantly different (time*treatment interaction, $P<.001$; see Figure 4): with each additional week in the study, craving scores in the treatment group significantly decreased by 0.27 points (95%CI=0.24–0.31; $P<.001$), while in the placebo group, with each additional week in the study craving scores significantly decreased by 0.15 points (95%CI=0.11–0.19; $P<.001$).

The proportion of dropouts in the treatment group was 34% (22/64) and 41% (26/63) in the placebo group. Time to dropout throughout the 12-week trial was not significantly different between the treatment and placebo groups (Hazard Ratio (treatment compared to placebo) = 0.84; 95%CI=0.47–1.48; $P=.54$; see Figure 5), while controlling for sex ($P=.28$), AUD ($P=.31$), and site ($P=.04$).

3.3.2. Safety, Tolerability and Medication Adherence—Adverse events reported by at least 5% of participants are described in Table 2. Dry mouth was the only adverse event

that was reported significantly more in the active medication group (16%, 10/64) versus the placebo group (5%, 3/63; $P=.04$). Four participants had serious adverse events (two in each treatment arm); however, none were deemed to be study-related.

Medication adherence during the medication phase (days 8–91) is described in Table 3. Treatment groups did not significantly differ by the proportion of topiramate or MAS-ER pills taken, or samples that fluoresced for riboflavin. In the treatment group, the median (IQR) of the within-participant proportion of samples positive for MAS-ER was 73% (47%–91%), and positive for topiramate was 100% (33%–100%). For both medications, samples were only included in the prior analyses if study staff had prescribed the medications to be taken the day immediately prior to the collection date, samples were excluded if medication had been held or discontinued by staff for any reason.

The within-participant maximum maintenance dose (mg/day) of MAS-ER was significantly higher in the placebo group's "dose" compared to the treatment group's actual dose ($P=.004$). The proportion of participants who had their MAS-ER doses reduced was significantly higher in the treatment group (31%) compared to the placebo group (14%; $P=.02$). There were no significant group differences in the within-participant maximum maintenance dose (mg/day) of topiramate, or the proportion of participants with dose reductions in either topiramate alone or in both medications. MAS-ER ($P=.046$) and topiramate ($P=.004$) discontinuations were greater in the treatment group (see Table 3). In the treatment group, 13 participants were discontinued from both medications, most commonly for elevated blood pressure or heart rate ($n=6$). Additionally, 3 participants were discontinued from topiramate alone (2 for cognitive side effects and one for changes in carbon dioxide levels).

4. Discussion

The findings of this study show that among cocaine-dependent individuals who use cocaine nine days a month or more, those that received combination therapy (MAS-ER and topiramate) were more likely to become abstinent than those receiving placebo. These results were significant regardless of whether outcome was measured as 3 weeks of abstinence at the end of the study (the primary outcome), any 21 consecutive days during the study, or the weekly proportion of participants with positive cocaine use based on urine toxicology.

This two-site study built on the results of a prior preliminary trial conducted at a single site which found that only for participants using at least 9 days a month, there was significant interaction between treatment arm and baseline frequency of use, with a greater difference in abstinence rates in the more frequently using group (Mariani et al., 2012). Similarly, Ling et al. (2014) found that among methamphetamine-dependent individuals, long acting methylphenidate (OROS-MPH) was not more effective than placebo in reducing methamphetamine use during the last 30 days of active treatment for the sample as a whole, but for those who used 10 days/month, the OROS-MPH arm outperformed the placebo arm.

Within our sample of frequent users, there was no significant effect of baseline frequency of use on either primary or secondary outcomes. It seems that those who used cocaine more than 8 days had the same response to treatment regardless of their actual number of days of use at baseline. One might posit that daily or near daily users would have a greater response to the therapeutic intervention than those using less frequently. However, the study was not adequately powered to investigate such fine-grained associations. Our current and prior study both suggest that those using at least 9 days a month at treatment entry and have stable cardiovascular parameters might be most likely to benefit from the combined intervention.

A minority of individuals had to be discontinued off their medication, primarily due to increases in blood pressure and heart rate. Notably, this rate of discontinuation from all medication was higher in this larger study than our earlier one (20% vs. 5%). This may have been due, in part, to enrolling more frequent users of cocaine. This study had strict medication discontinuation criteria to protect against cardiovascular adverse events, which is prudent when giving amphetamine to individuals with cocaine use disorder. In retrospect, a slower titration rate may have produced less elevated cardiovascular parameters, requiring medication discontinuation. However, based on the current titration schedule and the findings from this study (in contrast to our earlier pilot study), the elevations in blood pressure may require closer monitoring than what is provided in routine clinical settings and limit the generalizability of this approach. With the exception of dry mouth, there were no significant differences between the 2 arms. Taken together, our current and prior study both suggest that those using at least 9 days a month at treatment entry and have stable cardiovascular parameters might be most likely to benefit from the combined intervention.

Diversion is always a concern when prescribing a controlled substance with abuse potential to patients with a use disorder. For example, this has been an ongoing concern with methadone and buprenorphine for treatment of opioid use disorder, although these treatments are clearly effective. Notably, MAS-ER products are less likely to be misused or diverted than immediate release products (Cassidy et al., 2015; Kollins, 2008). Supporting this, a prior trial evaluating long-acting methylphenidate for adolescents with attention-deficit hyperactivity disorder and substance use disorders, loss of pills (and possible diversion) was no different in the methylphenidate or placebo arms (Winhusen et al. 2011). Accordingly, in this trial, the adherence (i.e., the proportion of pills taken of pills prescribed) to both topiramate and MAS-ER were not significantly different between arms suggesting that MAS-ER was not overtly diverted or abused. However, like most trials, adherence is always a concern. Technologies that provide direct observation of pill ingestion (deWorsop et al. 2016) might be preferable for future clinical trials to ensure adequate evaluation of promising medications.

There are several limitations associated with this study. First, the sample size was less than planned and the study concluded before full enrollment could be achieved. Second, drop-out, while similar to other studies (Dackis et al., 2012; Schmitz et al., 2012) conducted in cocaine use disordered individuals, was greater than preferred. This may have been mitigated by a more intensive psychotherapy or a motivational enhancement therapy. Some studies have suggested that contingency management approaches enhance the medications that target monoamines and may also improve retention (Kosten et al. 2003; Moeller et al.

2007; Poling et al. 2008; Schmitz et al. 2008). Future studies might consider these alternative behavioral platforms. Third, because of the relatively short study length, we do not know how participants fared 6 or 12 months after study completion. Notably, Carroll et al. (2014) conducted a secondary analysis on 5 large clinical trials that targeted those with CUD. They found that continuous abstinence, particularly at the end of the clinical trials, was highly correlated with abstinence at follow-up. This suggests that our outcome measures have clinical relevance and are predictive of future outcome. Fourth, the medication discontinuation rate was substantially higher than our earlier trial and this may have hampered our ability to detect even more robust findings. Also, nearly all side effects were experienced more commonly in the active treatment arm, suggesting that adoption of this approach may be challenging, albeit possible, in community settings. However, this approach provides a “proof-of-concept” worth further investigation. Finally, because we administered a combined medication intervention, it remains to be determined whether MAS-ER and topiramate would outperform MAS-ER or topiramate alone. Some of these limitations in a future trial might be overcome by providing greater inducements for retention and including more sites to bolster recruitment.

One might argue that the benefit of the combined pharmacotherapy might be explained by the amphetamine alone. Amphetamine is the class of medications that has shown the most consistent promise as a potential treatment for cocaine use disorder across animal models, human laboratory models, and clinical trials (Czoty et al., 2016). While there are data suggesting that dexamphetamine alone produces end of study abstinence rates greater than placebo (Czoty et al., 2016; Grabowski et al., 2001), our study focused on frequent users, perhaps a group that is more recalcitrant in achieving abstinence and may benefit from combined pharmacotherapy. A meta-analysis conducted by Minozzi et al. (2015a) concluded anticonvulsants are not helpful but there were only a handful of topiramate studies included; the results of these trials were mixed with three positive trials, one clearly negative study conducted in a methadone maintenance population (Umbricht et al., 2014), a population that is often nonresponsive to cocaine treatment interventions and another negative trial that used a fast titration (Nuitjen et al., 2014) leading to high dropouts. Klimas et al. (2017) concluded that this heterogeneity impedes drawing any conclusions regarding topiramate’s efficacy or the utility in using a meta-analytic approach. Given the limitations of the 2 negative trials, topiramate may have therapeutic utility for cocaine use disorder. Thus, until a large trial is conducted using a 4-arm design, (placebo, topiramate alone, amphetamine alone, and the combined medications), it remains unclear what is “driving” the improvement noted in the treatment group.

4.1. Conclusions

The proportion of patients meeting the primary outcome criterion of sustained abstinence at end of study on MAS-ER and topiramate treatment was 14%, compared to 0% for those receiving placebo, corresponding to a number needed to treat (NNT) of approximately 7. This type of outcome measure, a binary indicator of sustained urine-confirmed abstinence, has been criticized as setting “too high a bar”, with the conjecture that less stringent outcomes such as reduced levels of drug use short of abstinence, or improved functioning, would lead to fewer negative trials and discovery of more medications for drug use

disorders. However, the present trial shows that this combined pharmacologic approach can meet the high bar of abstinence, as has been the case with effective medications for opioid (Ayanga et al., 2016) and nicotine use disorders (Cahill et al., 2011), and suggests that this strategy is worthy of further research in the quest to find effective medication treatments for stimulant use disorders.

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Conflict of Interest

Drs. Mariani, Pavlicova, Naqvi, Dakwar, and Carpenter reported no biomedical financial interests or potential conflicts of interest. Also, Ms. Choi, Mr. Brooks and Ms. Mahony reported no biomedical financial interests or potential conflicts of interest. Dr. Levin has acted as an unpaid consultant for Alkermes and US WorldMeds. Dr. Bisaga has received research support from Alkermes, Dr. Nunes has received research support from Alkermes and Braeburn-Camurus and has acted as an unpaid consultant for Alkermes and Braeburn-Camurus. Dr. Kampman has received research support from Opiant Pharmaceuticals, Alkermes, Indivior and Braeburn Pharmaceuticals.

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Highlights

- Participants met criteria for current cocaine use disorder.
- Participants required to report using cocaine more than 8 days in the prior month.
- Randomized to receive mixed amphetamine salts-ER and topiramate or placebo.
- The treatment group achieved higher rates of abstinence at the end of the study.
- Trial shows that this combined pharmacologic approach shows promise.

Figure 1.
CONSORT Diagram

Figure 2.
Proportion of patients achieving 3 weeks of abstinence at end-of-study (primary outcome) and throughout the trial (secondary outcome).

Figure 3. Model-estimated (adjusted by sex, alcohol use disorder, and site) probabilities (in percentages) and 1 standard error of positive urine toxicology, weeks 2–13. Observed proportions are displayed as separate markers.

Figure 4. Model-estimated (adjusted by baseline craving, sex, alcohol use disorder, and site) means and 1 standard error of Craving (“Want Cocaine”), during weeks 2–14 are displayed. Observed means are displayed as separate markers. Baseline (week 0) observed means are connected by dashed lines to estimated means at week 2.

Figure 5.
Kaplan-Meier survival curves of time to dropout by treatment group.

Table 1.Demographic and Clinical Characteristics of Randomized Sample ($N = 127$)^a

Characteristics	Placebo ^b ($n = 63$)	Treatment ^b ($n = 64$)
Age (years)	46.4 (8.4)	46.0 (8.4)
Male	49 (77.8)	47 (73.4)
Race/Ethnicity		
Hispanic/Latino	11 (17.5)	12 (18.8)
White	10 (16.4)	11 (17.7)
Black	42 (68.9)	39 (62.9)
More than 1 race	5 (8.2)	8 (12.9)
Other	4 (6.6)	4 (6.5)
Education		
High School or less	41 (65.1)	38 (59.4)
Some college	13 (20.6)	14 (21.9)
College or Graduate School	9 (14.3)	12 (18.8)
Employment status		
Full-Time	16 (26.2)	15 (27.8)
Part-Time	6 (9.8)	7 (13.0)
Unemployed/Other	39 (63.9)	32 (59.3)
Currently Married	13 (21.3)	7 (12.1)
Site		
CUMC	34 (54.0)	34 (53.1)
UPENN	29 (46.0)	30 (46.9)
Total baseline use days (out of 28 days), median (interquartile range)	15 (11–21)	14.0 (12.0–20.5)
Total dollars of use (in 28 day s), median (interquartile range)	842 (560–1190)	692.5 (412.5–1200)
Current Alcohol Use Disorder	32 (50.8)	30 (46.9)
Current Cannabis Use Disorder	9 (14.3)	7 (10.9)
Current Nicotine Use Disorder	20 (31.8)	21 (32.8)

^aFrequencies may not sum to 127 because of missing values. Four patients did not report their race, twelve patients did not report their employment status, and eight patients did not report their marital status. P values were not computed because they are not meaningful between two randomized treatment arms and not recommended by CONSORT statement (<http://www.consort-statement.org/checklists/view/32--consort-2010/510-baseline-data>.)

^bMean(SD) or n (%) unless noted.

Table 2.

Adverse Events reported by at least 5% of Participants (N=127)

Adverse Event, n (%)	Placebo (n=63)	Treatment (n=64)	<i>p</i> -value (χ^2 test)
Headache	10 (15.9)	9 (14.1)	.78
Insomnia	6 (9.5)	12 (18.8)	.14
Upper Respiratory Infection	9 (14.3)	8 (12.5)	.77
Increased blood pressure	5 (7.9)	10 (15.6)	.18
Anorexia	5 (7.9)	9 (14.1)	.27
Dry mouth	3 (4.8)	10 (15.6)	.04
Fatigue	6 (9.5)	7 (10.9)	.79
Gastrointestinal upset	3 (4.8)	9 (14.1)	.07
Muscle aches	7 (11.1)	5 (7.8)	.53
Paresthesia	5 (7.9)	6 (9.4)	.77
Anxiety	4 (6.3)	6 (9.4)	.74 ^a
Dizziness	3 (4.8)	7 (10.9)	.32 ^a
Drowsiness	7 (11.1)	3 (4.7)	.21 ^a
Diarrhea	4 (6.3)	5 (7.8)	>.99 ^a
Vomiting	2 (3.2)	5 (7.8)	.44 ^a
Increased heart rate	3 (4.8)	4 (6.3)	>.99 ^a

^aFisher's exact test

Table 3.

Medication Adherence (N = 127)

	Placebo (n=63)	Treatment (n=64)	
Medication Adherence	Median (IQR) Mean (SD)	Median (IQR) Mean (SD)	<i>p</i> -value (X^2 test)
Pills Taken (%) ^a			
Topiramate	NA	97.3 (90.2–100.0) 90.9 (14.4)	.44
Mock Topiramate	95.9 (78.5–100.0) 86.6 (20.3)	NA	
MAS-ER	NA	98.2 (89.1–100.0) 93.8 (19.0)	.32
Mock MAS-ER	97.1 (83.3–99.6) 90.3 (16.8)	NA	
Samples Positive (%) ^a			
Fluoresced for riboflavin	81.7 (60.4–98.6) 70.2 (34.4)	78.4 (42.9–93.8) 64.6 (33.8)	.24
Topiramate	NA	100.0 (33.3–100.0) 69.4 (41.7)	NA
MAS-ER	NA	73.3 (46.9–91.4) 63.4 (0.35)	NA
Maximum Maintenance dose (mg/day)			
Topiramate	NA	175.0 (50.0–200.0) 134.0 (73.5)	.38
Mock Topiramate	200.0 (75.0–200.0) 142.5 (74.6)	NA	
MAS-ER	NA	60.0 (30.0–60.0) 46.3 (18.1)	.004
Mock MAS-ER	60.0 (60.0–60.0) 54.1 (14.1)	NA	
Patients with Dose Reduction ^b			
Topiramate	NA	12 (18.8%)	.67
Mock Topiramate	10 (15.9%)	NA	
MAS-ER	NA	20 (31.3%)	.02
Mock MAS-ER	9 (14.3%)	NA	
Both Topiramate and MAS-ER dose reduced ^{b, c}	6 (9.5%)	6 (9.4%)	.98
Patients with Dose Discontinued			
Topiramate	NA	16 (25.0%)	.004
Mock Topiramate	4 (6.4%)	NA	
MAS-ER	NA	13 (20.3%)	.046
Mock MAS-ER	5 (7.9%)	NA	
Both Topiramate and MAS-ER discontinued ^{b, d}	4 (6.4%)	13 (20.3%)	.02

^aProportions are computed as within-participant proportions out of the number of days with available compliance data.

^b Number of participants and percentages (%) are displayed.

^c Tabulations not mutually exclusive to those reductions reported for the medications individually.

^d Tabulations not mutually exclusive to those discontinuations reported for the medications individually.

IQR= interquartile range, NA – not applicable, SD= standard deviation

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