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Topiramate-phentermine combinations reduce cocaine self-administration in humans

Craig R. Rush [a,*], William W. Stoops [a,d], Joshua A. Lile [a,b,c], Joseph L. Alcorn III [a], B. Levi Bolin [a], Anna R. Reynolds [a], Lon R. Hays [b], Abner O. Rayapati [b]

[a] Department of Behavioral Science, University of Kentucky College of Medicine, 1100 Veterans Drive, Medical Behavioral Science Building, Lexington, KY, 40536-0086, USA
[b] Department of Psychiatry, University of Kentucky College of Medicine, 245 Fountain Court, Lexington, KY, 40509-1810, USA
[c] Department of Psychology, University of Kentucky College of Arts and Sciences, 171 Funkhouser Drive, Lexington, KY, 40506-0044, USA
[d] Center on Drug and Alcohol Research, University of Kentucky College of Medicine, 845 Angliana Ave, Lexington, KY, 40508, USA

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ABSTRACT

Rationale: Cocaine use disorder is an unrelenting public health concern. Despite nearly four decades of research, an FDA approved medication is not yet available.
Objectives: The objective of this human laboratory study was to demonstrate the initial efficacy, safety and tolerability of topiramate-phentermine combinations for cocaine use disorder.
Methods: Thirty-one (31) participants with cocaine use disorder completed this mixed-model inpatient laboratory study. Participants were maintained on topiramate (0 [N = 11], 50 [N = 9] or 100 [N = 11] mg/day). Each topiramate group was concurrently maintained on phentermine (0, 15, 30 mg). Drug self-administration, subjective responses and cardiovascular effects following acute doses of intranasal cocaine (0, 40, 80 mg) were determined during separate experimental sessions after at least seven (7) days of maintenance on each condition.
Results: The three groups of participants were well matched demographically and generally did not differ significantly in their responses to a range of doses of intranasal cocaine (0, 10, 20, 40, 80 mg) during a medical safety session. Maintenance on topiramate and phentermine alone significantly decreased cocaine self-administration although these effects were modest in magnitude. Combining topiramate and phentermine robustly decreased cocaine self-administration. Topiramate and phentermine were well tolerated alone and combined, as well as in conjunction with cocaine.
Conclusions: The results of the present study support advancing topiramate-phentermine combinations as a putative pharmacotherapeutic for cocaine use disorder.

1. Introduction

Cocaine use disorder is an unrelenting public health problem. Approximately two million Americans were current (i.e., past month) cocaine users in 2019 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2020). Cocaine use produces multiple health problems and is associated with other negative health consequences including comorbid psychological disorders, cigarette smoking and greater likelihood of acquiring sexually transmitted infections (Chen et al., 2001; Coller and Hutchinson, 2012; Rounsaville et al., 1991; Substance Abuse and Mental Health Services Administration (SAMHSA, 2014; Van Tieu and Koblin, 2009). Recognition that cocaine overdose rates are increasing (Kariisa et al., 2019), as well as health disparities in cocaine overdose (i.e., increased overdose rates in Black Americans; Cano et al., 2020; Shiels et al., 2018), make the dangers posed by cocaine use even more evident.

Identifying an effective pharmacotherapeutic for cocaine use disorder has been a priority with the National Institute on Drug Abuse for nearly four decades. The Food and Drug Administration has yet to approve a medication for cocaine use disorder despite having tested at least 64 medications in more than 100 trials (Chan et al., 2019; Czoty et al., 2016). These findings along with the epidemiological data

* Corresponding author at: Department of Behavioral Science, University of Kentucky Chandler Medical Center, 1100 Veterans Drive, Medical Behavioral Science Building, Room 140, Lexington, KY, 40536-0086, USA.
E-mail address: crush2@email.uky.edu (C.R. Rush).

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described above underscore the need for novel strategies to identify an effective pharmacotherapeutic for cocaine use disorder. One novel strategy is to combine medications.

Herein, we report the results of a study that determined the behavioral (i.e., drug self-administration and subjective responses) and cardiovascular (i.e., heart rate and blood pressure) effects of intranasal cocaine (0, 40, 80 mg) in separate groups of non-treatment-seeking participants meeting criteria for cocaine use disorder during maintenance on topiramate (0, 50 or 100 mg/day). Participants in each topiramate group were concurrently maintained on phentermine (0, 15 and 30 mg/day). This study was designed based on recommendations for testing medication combinations for substance use disorders including: 1) targeting multiple neurotransmitter systems; 2) combining drugs with some efficacy when tested alone; and 3) testing low doses of the constituent drugs to minimize side effects (Lee and Leggio, 2014; Stoops and Rush, 2014).

We chose topiramate because it is a glutamate antagonist and γ-Aminobutyric-Acid (GABA) agonist. Glutamate and GABA are the most abundant excitatory and inhibitory neurotransmitters in the brain, respectively. Chronic cocaine exposure lowers basal glutamate levels in central corticostriatal regions (e.g., Kalivas, 2009). A recent study with human participants found significant reductions in glutamate concentrations in cocaine abusers relative to healthy controls (Engeli et al., 2020). Chronic cocaine use may also disrupt central GABA systems (Volkow et al., 1998). There is also a complex interplay between these systems such that glutamate activity in the nucleus accumbens affects the action of GABA neurons which, in turn, regulate dopamine activity (Kalivas, 2007; Torregrossa and Kalivas, 2008). Topiramate has shown some efficacy for cocaine use disorder (e.g., Chan et al., 2019; Baldacara et al., 2016; Kampman et al., 2004, 2013; Johnson et al., 2013a).

We chose phentermine because it is a dopamine agonist (Baumann et al., 2000; Balcioglu and Wurtman, 1998a, 1998b; Shoaib et al., 1997). Abused stimulants, including cocaine, produce their behavioral and physiological effects *via* interaction with monoamine transporters (i.e., dopamine, serotonin, and norepinephrine) (Fleckenstein et al., 2000, 2007; Rothman and Glowa, 1995). Dopamine, however, plays an especially prominent role in mediating the abuse-related effects of stimulants including cocaine (Lile, 2006; Pierce and Kumaresan, 2006). Phentermine attenuates cocaine-induced increases in mesolimbic dopamine levels (Rothman et al., 1996). Phentermine also decreases responding for cocaine in non-human primates (Glowa et al., 1997; Stafford et al., 1999). We are unaware of any published reports that tested phentermine as a putative pharmacotherapy for cocaine use disorder in humans.

We hypothesized: 1) cocaine would maintain self-administration and produce prototypical stimulant-like subjective and cardiovascular effects; 2) maintenance on topiramate or phentermine alone would attenuate the behavioral effects of cocaine; 3) combining topiramate and phentermine would more robustly attenuate the behavioral effects of cocaine; and 4) topiramate-phentermine combinations would be safe and well tolerated in conjunction with cocaine.

2. Method

The Medical Institutional Review Board of the University of Kentucky approved this study. This study was conducted in accordance with all relevant guidelines, including the 1964 Declaration of Helsinki.

2.1. Participants

Thirty-one (31) non-treatment-seeking participants provided sober, written informed consent to participate and completed this mixed-model, placebo-controlled, inpatient study. In order to be eligible for the study, participants had to be healthy and without contraindications to cocaine, topiramate or phentermine. Participants had to report recent use of cocaine, meet diagnostic criteria for a cocaine use disorder (i.e., abuse or dependence) according to a computerized Structured Clinical Interview for DSM-IV (SCID) that was reviewed by a psychiatrist or psychologist and provide a benzoylecgonine positive urine sample during screening to verify recent cocaine use status. Screening procedures for all participants included a medical history questionnaire, laboratory chemistries (e.g., blood chemistry screen, complete blood count and urinalysis), electrocardiogram and a brief psychiatric examination. Participants were excluded from participation if a study physician deemed the screening results to be abnormal (e.g., electrocardiogram was outside normal limits). Participants with histories of serious physical disease, current physical disease or current or past histories of serious psychiatric disorder, including current or past histories of other substance abuse or dependence, that in the opinion of a study physician would have interfered with study participation (e.g., physiologic dependence on opioids, alcohol or benzodiazepines; schizophrenia; major depression; bipolar disorder) were also excluded. Decisions to exclude participants on these grounds were based on review of screening materials and/or history and physical examination conducted by a study physician. Female participants had to be using an effective form of birth control (e.g., birth control pills, IUD, condoms or abstinence) in order to participate.

2.2. General procedures

Participants were enrolled as inpatients at the University of Kentucky Center for Clinical and Translational Science (CCTS) Clinical Services Core (CSC) for up to 33 days and completed a drug-free practice, medical-safety and nine (9) experimental sessions. During inpatient admission, participants received standard caffeine-free hospital meals. Urine samples were collected daily and expired breath samples were collected prior to each session to confirm drug and alcohol abstinence, respectively. Pregnancy tests were conducted daily on urine samples from the female participants. All pregnancy tests were negative throughout their participation. When not in session, participants could smoke cigarettes periodically as long as CSC staff was available to escort them to the designated smoking area.

2.3. Practice Session

Participants completed a single practice session to familiarize them with the study procedures.

2.4. Medical safety session

Participants completed one, single-blind medical safety session to ensure they could tolerate intranasal cocaine. Intranasal cocaine doses (i.e., 0 [placebo], 10, 20, 40 and 80 mg) were administered in ascending order. Placebo (i.e., 0 mg) was administered at 0900. The subjective-effect questionnaires and cardiovascular measures described below were completed 30 min before placebo administration (i.e., 0830), immediately following and at 15-minute intervals for 45 min. Subsequent cocaine administrations were separated by 45 min.

2.5. Topiramate and phentermine maintenance

All drugs were administered in a double-blind fashion. Only study investigators and the Investigational Drug Service staff had access to dose orders in order to maintain the blind. These individuals did not interact with participants during experimental sessions, nor did they collect experimental data.

Drug maintenance began on the day immediately following the Medical Safety Session and continued throughout the protocol. Topiramate (0, 50, 100 mg/day) and phentermine (0, 15, 30 mg/day) were prepared by over-encapsulating commercially available doses in a size 0 capsule. All capsules were then filled with cornstarch. Placebo capsules were identical but contained only cornstarch.

The maintenance period for each condition was at least seven (7)

days. Participants randomized to 50 or 100 mg/day topiramate initially received 12.5 and 25 mg immediate release topiramate, respectively, twice daily (0700 and 1900 h) for three (3) days. Participants then received their target dose (i.e., 25 and 50 mg BID, respectively) for four (4) days prior to completing the first block of experimental sessions. This dosing regimen allowed participants to acclimate to a lower topiramate dose before receiving their target dose and was the rationale for topiramate being a between-subject variable. Participants randomized to placebo were also maintained for seven (7) days to maintain the study blind, but their capsules contained only cornstarch.

Phentermine (0, 15, 30 mg) was administered once daily at 0700 h. Within each topiramate cohort, the phentermine doses were tested in ascending order such that the lower dose (15 mg/day) was tested prior to the higher dose (30 mg/day). Placebo phentermine (0 mg) was interspersed randomly (e.g., 0-15-30; 15-0-30; or 15-30-0). This dosing sequence was violated twice due to oversight (i.e., one subject in the 0 mg/day topiramate group and the other in the 50 mg/day topiramate group). Both of these participants were initially maintained on 30 mg/day phentermine. Visual inspection of the behavioral and cardiovascular data suggests these individuals responded similarly to the other participants in their respective groups.

After at least seven (7) days of maintenance on the first topiramate-phentermine condition, participants completed a block of three experimental sessions described below. Maintenance on the assigned condition continued during each block of experimental sessions. Upon completion of the first block of experimental sessions, participants continued maintenance on the assigned topiramate condition, while the phentermine dose was changed to the next condition. Maintenance on the second topiramate-phentermine condition also lasted at least seven (7) days before the next block of experimental sessions was completed. Upon completion of the second block of experimental sessions, participants continued maintenance on the assigned topiramate condition, while the phentermine dose was changed to the final condition. Maintenance on the final topiramate-phentermine condition also lasted at least seven (7) days before the third block of three experimental sessions was completed. Participants were discharged from the study the day after completing the third block of experimental sessions.

2.6. Experimental sessions

Participants received the appropriate maintenance doses at 0700 h on the morning of all experimental sessions. Participants were allowed to smoke a cigarette prior to experimental sessions that started at 0900 h and were not allowed to smoke again until the session ended approximately 7.5 h later. Sessions consisted of a Sampling Phase and a Self-Administration Phase. These phases were separated by approximately three-hours during which time lunch was available.

2.6.1. Sampling phase

Participants completed a sampling phase in each experimental session to acquaint them with the effects of the cocaine dose available during that session. Baseline subjective and physiological measures were completed at approximately 0900 h. At approximately 0930 h, the intranasal cocaine dose (0, 40 or 80 mg) available during that session was administered. Cocaine sampling doses (0, 40, 80 mg) were prepared by combining the appropriate amount of cocaine HCl (Medisca Inc., Plattsburgh, NY, NDC:38779-0723-03) with lactose to equal a total of 120 mg powder. During all cocaine administrations, a nurse presented the subject with the powder, a mirror and a standard razor blade. The participant was instructed to divide the powder into two even "lines" and insufflate one line of powder through each nostril using a 65-mm plastic straw within 2 min. Doses were not administered if heart rate was ≥100 bpm, systolic blood pressure was ≥150 mmHg or diastolic blood pressure was ≥100 mmHg or if clinically significant and/or prolonged ECG abnormalities were detected. These dosing thresholds (i.e., heart rate, systolic, and diastolic) were lowered to heart rate ≥90 bpm, systolic blood pressure ≥140 mmHg, and diastolic blood pressure ≥90 mmHg at the behest of the Food and Drug Administration in the final year of the study. Cocaine dosing order was randomized for each subject. Immediately after dosing and at 15-minute intervals for the next hour, subjective, performance and physiological measures were completed. The sampling phase ended at approximately 1030 h.

2.6.2. Self-administration phase

The self-administration phase began at approximately 1330 h. During this phase, participants completed 10 trials in which they were required to choose between 1/10th of the cocaine dose insufflated during the sampling session or USD $0.25 on a progressive-ratio task (i.e., the sum of cocaine and money choices in each session was always 10).

Cocaine self-administration during maintenance on the topiramate-phentermine combinations were assessed using a progressive-ratio task. Participants were able to earn drug or money by responding on a computer mouse. Cocaine and money were available on concurrent, independent progressive-ratio schedules as described previously (Stoops et al., 2012, 2019). The initial ratio to obtain a reinforcer was 400 clicks. The response requirement for each subsequent choice of that specific reinforcer increased by 100 (i.e., 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300 responses if a subject responded exclusively for cocaine or money). The dependent measure for this task was number of doses earned, out of a maximum of 10 (i.e., 100 % of the sampling dose). Each potential cocaine amount participants could earn (e.g., 4, 8, 12, 16, 20, 24, 28, 32, 36 and 40 mg for the 40 mg dose) was admixed with lactose to equal a total of 120 mg powder. Following completion of the task, the research assistant communicated the appropriate blinded dose code to the nursing staff (e.g., 4 mg in the 40 mg dose condition was labeled Dose 1), who then presented the dose to the subject for self-administration. Participants then insufflated the chosen dose, at approximately 1415 h, and completed subjective and physiological measures at 15-minute intervals for 60 min. Sessions ended at approximately 1515 h.

2.7. Subjective effects questionnaire

Subjective measures included a locally developed Drug-Effect Questionnaire (Rush et al., 2003) and the Adjective Rating Scale (Oliveto et al., 1992) These measures have previously been shown to be sensitive to the effects of stimulants (Rush et al., 2009).

2.8. Cardiovascular measures

Heart rate, blood pressure, and heart rhythmicity (*via* ECG) were recorded using a Dinamap digital monitor (Critikon, Pro 1000, Tampa, FL). Telemetry-certified nurses interpreted the results of the ECG with instructions to contact a study physician regarding abnormalities.

2.9. Discontinuation of topiramate

Upon discharge, participants were tapered off topiramate. Each participant received fourteen (14) envelopes (i.e., doses for 0700 and 1900 for seven days). The first eight envelopes contained half of their target dose (i.e., 12.5 or 25 mg BID). The remaining six envelopes contained placebo. Participants maintained on placebo were given envelopes that contained placebo capsules only.

2.10. Subject payment

Participants were paid $40 for each day they resided on the CSC and received a $40 completion allowance for these days if they completed the entire experiment. The amount earned by the subject was disbursed to them upon completion of the study and during follow up visits. Payments were disbursed once per week following discharge in amounts up to $500 dollars until the subject was paid in full. When participants

returned on a weekly basis to receive their payments, we surveyed them regarding their drug use since being discharged from the study. Participants could also earn up to a total of $22.50 on the progressive-ratio task across all sessions, depending on their choices between drug and money. A maximum of $2842.50 could be earned for participating in the study.

2.11. Data analysis

Data were analyzed using analysis of variance (ANOVA; Statview, Cary, NC) as described below. Effects with $p \leq 0.05$ were considered significant for all statistical analyses.

Demographics data were analyzed using a one-way ANOVA with Topiramate Group (0, 50, 100 mg/day) as a between-subject factor. Categorical data (i.e., sex and race) were analyzed using Chi Square (χ^2). Subjective and cardiovascular data from the Medical Safety Session were analyzed as peak effect (i.e., the maximum score observed following an administration of a cocaine dose (0, 10, 20, 40, 80 mg) using mixed-model ANOVA with Topiramate Group (0, 50, 100 mg/day; between-subject factor) and Cocaine (0, 10, 20 40, 80 mg, within-subject factor) as the variables. Differences were inferred if the main effect of Topiramate Group or the interaction of Topiramate Group and Cocaine attained significance. Progressive-ratio data from the Experimental Sessions were analyzed as number of doses earned using a three-factor mixed-model ANOVA with Topiramate Group (0, 50, 100 mg/day; between-subject factor), Phentermine (0, 15, 30 mg/day; within-subject factor) and Cocaine (0, 40, 80 mg; within-subject factor) as the variables. Planned comparisons were then conducted using appropriate two-way ANOVA (i.e., repeated measure or mixed model) to discern main effects of Phentermine or Topiramate as well as interactions, alone or together, with cocaine. These analyses compared the dose effect of cocaine alone (i.e., during maintenance on 0 mg Topiramate and 0 mg Phentermine, henceforth referred to as placebo maintenance) with the cocaine dose effects curves during maintenance on each of the eight topiramate-phentermine maintenance conditions. Differences were inferred from these analyses if the main effect of Maintenance Condition or the interaction of Maintenance Condition and Cocaine attained significance. Subjective and cardiovascular measure data from the sampling phase, when participants received the same doses of cocaine, were analyzed as peak effect (i.e., the maximum score observed in the 60 min following administration of the cocaine sampling dose) in the same fashion as data from the progressive-ratio task.

3. Results

3.1. Demographics

Table 1shows the demographics of the participants for each topiramate group. There were no significant differences between these groups ($F_{2,28}$ values = 0.08–2.96 or χ^2 values 0.0–0.81; p values > 0.05).

3.2. Medical safety session

3.2.1. Subjective-effects questionnaires

A main effect of Cocaine was detected on 17 items from the Drug Effect Questionnaire (Active, Alert, Energetic; Any Effect, Bad Effects; Good Effects; High; Irregular, Racing Heartbeat; Like Drug; Nauseous, Queasy, Sick to Stomach; Nervous, Anxious; Performance Impaired; Performance Improved; Rush; Shaky, Jittery; Stimulated; Talkative, Friendly; Willing to Pay For; and Willing to Take Again) as well as the Stimulant Subscale of the Adjective Rating Scale ($F_{2,28}$ values = 3.03–20.1, p values < 0.05). Neither the main effect of Topiramate Group ($F_{2,28}$ values = 0.09–1.85, p values < 0.05) nor the interaction of Topiramate Group and Cocaine ($F_{8,118}$ = values 0.35–1.88, p values > 0.05) attained significance in these analyses.

A significant interaction of Topiramate Group and Cocaine was observed on a single measure, Sluggish, Fatigued, Lazy ($F_{8,118}$ values = 2.52, p = 0.0149). This interaction was attributable to cocaine dose dependently increasing these ratings in the 100 mg Topiramate Group but not in the 0 or 50 mg Topiramate Groups (data not shown).

Table 1
Demographic and Substance Use Variables by Group. Data are Means (Standard Deviation).

	TOP (0 mg) (N = 11)	TOP (50 mg) (N = 9)	TOP (100 mg) (N = 11)
Demographics			
Age	44.8 (5.42)	42.2 (11.9)	44.5 (2.5)
Female	3	1	3
Race			
Caucasian	2	3	3
African American	9	6	8
Education (Years)	12.6 (1.1)	12.3 (0.9)	12 (1.5)
Alcohol and Cigarette Use			
DAST	8.0 (54.9)	6.6 (3.5)	11 (5.2)
MAST	8.2 (7.7)	3.1 (4.1)	11 (10.5)
AUDIT	7.4 (7.6)	3.8 (2.6)	7.5 (6.3)
Drinks/Week	10.8 (13.5)	6.2 (7.8)	15.5 (17.4)
Tobacco Cigarettes/ Day	9.8 (7.2)	8.0 (5.6)	9.3 (7.0)
Cocaine Use			
Years Used	23.3 (6.7)	16.3 (10.3)	21.6 (4.7)
Days Used Past Week	3.0 (1.3)	3.3 (1.5)	2.9 (1.8)
Days Used Past Month	13.5 (8.7)	12.3 (6.5)	12.3 (7.6)
Money Spent Past Week ($)	84.1 (78.4)	114.4 (139.3)	116.4 (127.8)
Money Spent Past Month ($)	367.7 (219.0)	430.0 (457.9)	470.9 (701.0)
Past Month Drug Use			
Days Used Opioids	0.1 (0.3)	0.8 (2.3)	0.3 (0.7)
Days Used Cannabis	13.2 (13.2)	8.1 (10.6)	10.0 (12.6)

Note. All values presented as mean (standard deviation) or counts/percentages. TOP = Topiramate; MAST = Michigan Alcohol Screening Test; DAST = Drug Abuse Screening Test.

3.2.2. Cardiovascular measures

A main effect of Cocaine was detected on heart rate, as well as systolic and diastolic blood pressure ($F_{2,28}$ values = 8.4–16.22, p values < 0.0001). Neither the main effect of Topiramate Group ($F_{2,28}$ values = 0.38–2.86, p values > 0.05) nor the interaction of Topiramate Group and Cocaine ($F_{8,118}$ values = 0.84–1.7, p values > 0.05) attained significance in these analyses.

3.3. Experimental sessions

3.3.1. Cocaine self-administration

Fig. 1 shows the self-administration results. Three-way ANOVA revealed a significant main effect of Cocaine ($F_{2,4} = 33.91$, $p < 0.0001$) and Phentermine ($F_{2,4} = 4.85$, $p = 0.011$) as well as a near-significant effect of Topiramate ($F_{2,28} = 3.02$, $p = 0.065$). Cocaine significantly increased the number of doses earned regardless of the maintenance condition. Planned comparisons of the cocaine dose effect during maintenance on placebo versus phentermine alone (15 or 30 mg/day; left panel of Fig. 1, circles versus diamonds or triangles) revealed main effects of Cocaine ($F_{2,20}$ = 22.9 and 24.62, respectively, p values < 0.0001) and Maintenance Condition ($F_{1,10} = 6.98$ and 8.6, respectively $p < 0.03$).

Planned comparisons of the cocaine dose effect during maintenance on placebo versus 50 mg/day topiramate plus phentermine (0, 15 or 30 mg/day; circles in left panel of Fig. 1 versus circles, diamonds or triangles in the middle panel) revealed a main effect of Cocaine ($F_{2,2}$ = 21.83, 14.95 and 16.46, respectively, $p < 0.0001$). Planned comparisons of the cocaine dose effect during maintenance on placebo versus 50 mg/day topiramate plus 15 mg/day phentermine revealed a main effect of Maintenance Condition ($F_{1,18} = 6.93$, $p = 0.017$; circles in left panel of

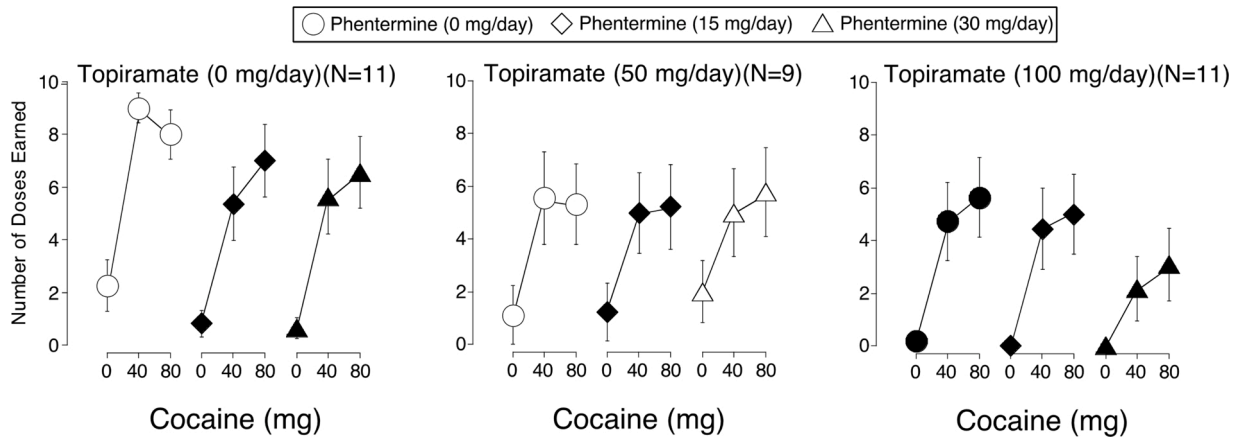

Fig. 1. Mean (± SEM) Number of Doses Earned (maximum = 10) on the Progressive-Ratio Procedure for cocaine (0, 40, 80 mg) during maintenance on topiramate (0 mg/day) and phentermine (0, 15, 30 mg/day) (Left Panel); topiramate (50 mg/day) and phentermine (0, 15, 30 mg/day) (Center Panel); and topiramate (100 mg/day) and phentermine (0, 15, 30 mg/day) (Right Panel). Filled symbols indicate the cocaine dose effect under the indicated maintenance condition differed significantly from the cocaine dose effect observed with maintenance on 0 mg/day topiramate plus 0 mg/day phentermine (i.e., circles in the left panel).

Fig. 1 versus diamonds in the middle panel).

Planned comparisons of the cocaine dose effect during maintenance on placebo versus 100 mg/day topiramate plus phentermine (0, 15 or 30 mg/day; circles in left panel of Fig. 1 versus circles, diamonds or triangles in the right panel) revealed a main effect of Cocaine ($F_{2,2} = 24.97$, 25.77 and 17.5, respectively, $p < 0.0001$). Planned comparisons of the cocaine dose effect during maintenance on placebo versus 100 mg/day topiramate plus 0 mg/day revealed a main effect of Maintenance Condition ($F_{1,20} = 7.67$, $p = 0.02$; circles in left panel of Fig. 1 versus circles in right panel). Planned comparisons of the cocaine dose effect during maintenance on placebo versus 100 mg/day topiramate plus 0 or 15 mg/day phentermine revealed a main effect of Maintenance Condition ($F_{1,18} = 7.67$ and 8.77, respectively, $p = 0.02$; circles in left panel of Fig. 1 versus circles or diamonds or in right panel). Comparison of the cocaine dose effect during placebo maintenance versus 100 mg/day topiramate plus 30 mg/day phentermine (i.e., circles in left panel of Fig. 1 versus triangles in the right panel) revealed a main effect Maintenance Condition ($F_{1,20} = 25.9$, $p < 0.0001$) and an interaction of Cocaine and Maintenance Condition ($F_{2,40} = 3.48$, $p = 0.04$).

3.3.2. *Subjective-effects questionnaires*

Three-way ANOVA revealed a main effect of Cocaine on 16 items

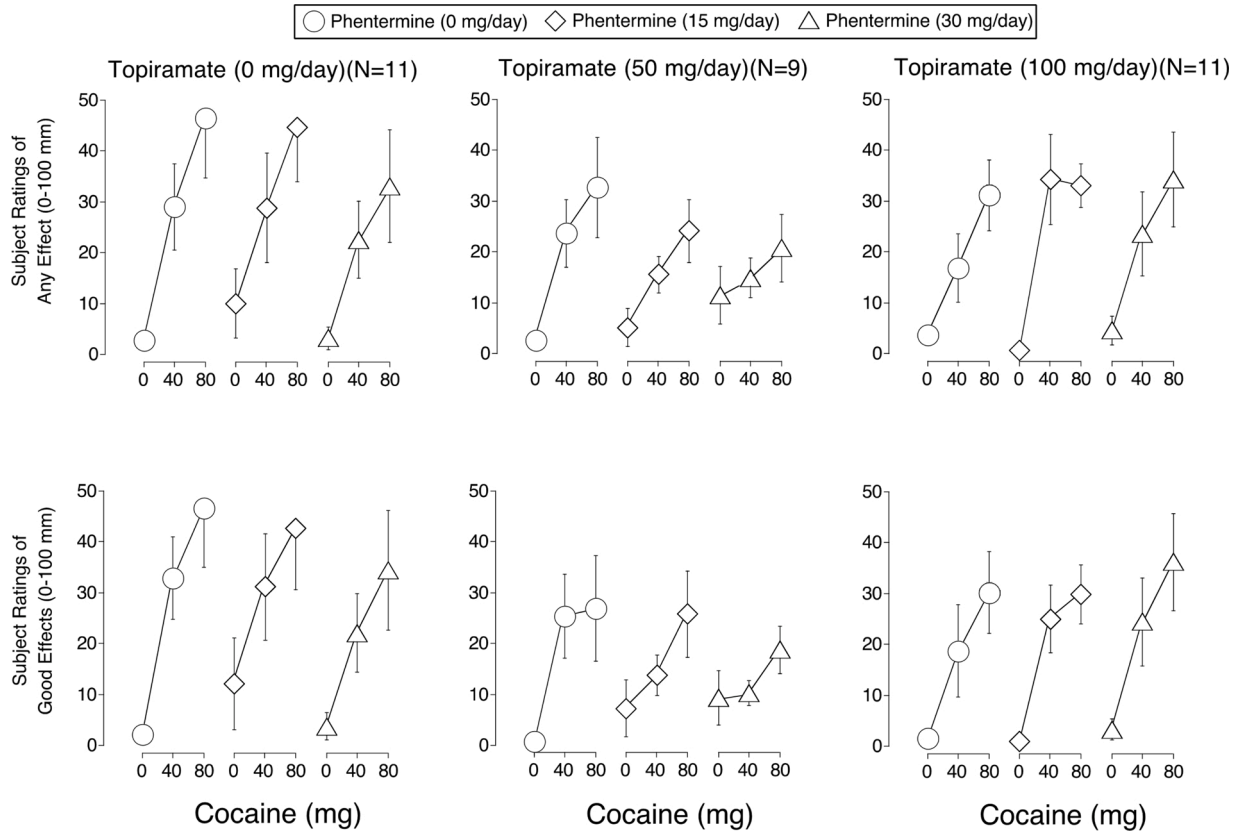

Fig. 2. Mean (±SEM) peak subject ratings of Any Effect (top panels) and Good Effects (bottom panels) from the Drug Effect Questionnaire. Details are the same as Fig. 1.

from the Drug Effect Questionnaire (Active, Alert, Energetic; Any Effect; Euphoric; Good Effects; High; Like Drug; Nervous, Anxious; Performance Impaired; Performance Improved; Rush; Shaky, Jittery; Sluggish, Fatigued, Lazy; Stimulated; Talkative, Friendly; Willing to Pay For; and Willing to Take Again) as well as the Stimulant and Sedative Subscales of the Adjective Rating Scale ($F_{2,4}$ values = 3.51–40.3, p values <0.036). No other effects were detected. Fig. 2 shows the cocaine dose effects for two items from the Drug Effect Questionnaire: Any Effect and Good Effects.

Three-way ANOVA revealed a main effect of Cocaine ($F_{2,4} = 10.08$, p = 0.0002) and an interaction of Cocaine and Topiramate ($F_{4,56} = 2.75$, p = 0.037) on ratings of Irregular Heartbeat ($F_{2,4}$ values = 3.82–40.3, p values < 0.028) on the Drug Effect Questionnaire. Three-way ANOVA revealed a significant main effect of Cocaine ($F_{2,4} = 7.31$, $p < 0.002$) and an interaction of Topiramate and Phentermine ($F_{4,56} = 2.85$, $p = 0.032$) on ratings of Nauseous, Queasy or Sick to Stomach on the Drug Effect Questionnaire. However, planned comparisons failed to reveal differences between the cocaine dose effect during placebo maintenance and any of the topiramate-phentermine combinations for both of these measures (data not shown).

3.3.3. Cardiovascular measures

Fig. 3 shows the cocaine dose effects for heart rate and diastolic pressure results. Three-way ANOVA for heart rate revealed a significant main effect of Cocaine ($F_{2,4} = 21.77$, $p < 0.0001$) and Phentermine ($F_{2,4} = 4.45$, $p = 0.016$). Planned comparisons for the cocaine dose effect during placebo maintenance versus 30 mg/day phentermine (i.e., circles versus triangles in left panel of Fig. 1) revealed a main effect of Maintenance Condition ($F_{1,10} = 11.7$, $p = 0.007$). There were no other significant differences between the cocaine dose effect curves.

Three-way ANOVA for diastolic pressure revealed a significant main effect of Cocaine ($F_{2,4} = 19.7$, $p < 0.0001$) as well as an interaction of Cocaine and Phentermine ($F_{2,8} = 3.05$, $p = 0.02$). However, planned comparisons failed to reveal differences between the cocaine dose effect during placebo maintenance and any of the topiramate-phentermine conditions. Three-way ANOVA for systolic pressure revealed only a significant main effect of Cocaine ($F_{2,4} = 32.67$, $p < 0.0001$; data not shown).

4. Discussion

The present experiment determined the behavioral (i.e., self-administration and subjective responses) and cardiovascular (i.e., heart rate and blood pressure) effects of intranasal cocaine (0, 40, 80 mg) during maintenance on topiramate (0, 50, 100 mg/day) in separate groups of non-treatment seeking participants with cocaine use disorder concurrently maintained on phentermine (0, 15, 30 mg/day). Below we discuss the findings in the context of the extant literature regarding the effects of cocaine in participants treated with topiramate and phentermine, alone and combined.

4.1. Cocaine alone

Cocaine alone maintained self-administration and produced prototypical subjective and cardiovascular effects. The constellation and magnitude of effects observed here were qualitatively and quantitatively similar to those observed previously with intranasal cocaine in our laboratory and others (e.g., Foltin and Haney, 2004; Greenwald et al., 2010; Bolin et al., 2017; Stoops et al., 2019).

4.2. Topiramate alone

Topiramate alone (100 mg/day) significantly reduced cocaine self-administration in the present study, although the magnitude of this

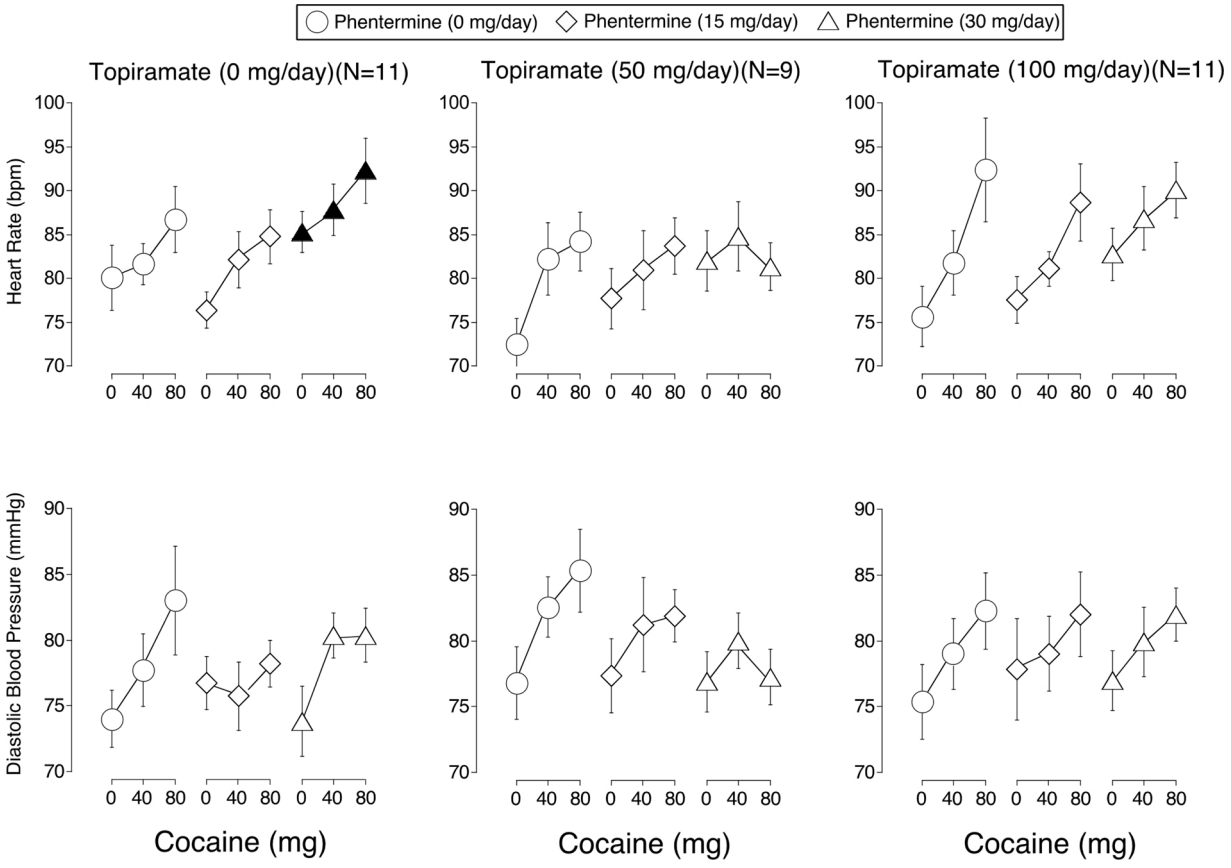

Fig. 3. Mean (±SEM) peak Heart Rate (top panels) and Diastolic Blood Pressure (bottom panels) blood pressure. Details are the same as Fig. 1.

effect was moderate (i.e., 30–47 %). Topiramate maintenance did not alter the subjective or cardiovascular effects of cocaine to a statistically significant degree.

The results of the present study are generally concordant with those from a previous experiment that determined the reinforcing and subjective effects of intravenous cocaine (0.325 and 0.65 mg/kg) in cocaine-dependent participants (N = 24) maintained on topiramate (0 or 200 mg/day) (Johnson et al., 2013a). In that study, topiramate maintenance significantly attenuated the reinforcing effects of the higher cocaine dose (i.e., 0.65 mg/kg) as measured by the crossover point on a monetary multiple-choice procedure relative to placebo maintenance. Interestingly, topiramate maintenance significantly enhanced the reinforcing effects of the lower cocaine dose (i.e., 0.325 mg/kg). Topiramate maintenance significantly attenuated ratings of craving engendered by the higher cocaine dose (i.e., 0.65 mg/kg) but significantly increased ratings of euphoria and stimulated induced by the lower cocaine dose (i.e., 0.325 mg/kg).

Consistent with the results of human laboratory studies, topiramate reduced cocaine use in clinical trials (Baldacara et al., 2016; Johnson et al., 2013b; Kampman et al., 2004, 2013). In the seminal clinical trial, patients dependent on cocaine were randomly assigned to receive 200 mg/day topiramate or placebo (N = 20/group) for eight weeks (Kampman et al., 2004). A significantly greater percentage of topiramate-maintained patients were abstinent from cocaine relative to their placebo-treated counterparts by the end of the trial (i.e., approximately 45 and 10 %, respectively). These results have been systematically replicated and a meta-analysis also suggests that topiramate is effective for cocaine use disorder (Baldacara et al., 2016; Johnson et al., 2013b; Singh et al., 2016).

4.3. Phentermine alone

Phentermine maintenance significantly reduced cocaine self-administration although this effect was moderate in magnitude (i.e., 13–40 %). We are unaware of any published reports that determined the effects of cocaine in humans maintained on phentermine. The present findings are concordant with those from preclinical experiments (Glowa et al., 1997; Stafford et al., 1999). In both of these studies, phentermine decreased responding for cocaine in non-human primates. Phentermine (0.1–5.6 mg/kg) decreased responding for cocaine by approximately 50–90 % in these studies. Greater reductions in cocaine self-administration might have been observed in the present study had higher phentermine doses been tested (e.g., 45–60 mg/day).

The reductions in cocaine self-administration during phentermine maintenance are concordant with previous human laboratory studies and clinical trials that tested d-amphetamine as a putative pharmacotherapeutic for cocaine use disorder (Greenwald et al., 2010; Lile et al., 2020; Rush et al., 2010). A recent study from our laboratory, for example, determined the effects of oral d-amphetamine SR (0, 30, 60 mg/day) maintenance on intravenous cocaine (0, 3, 10, 30 mg/70 kg) self-administration (Lile et al., 2020). Participants (N = 16) responded on a progressive-ratio schedule to receive the sampled cocaine dose or money ($6). Under placebo d-amphetamine maintenance, cocaine dose-dependently increased self-administration. The active doses of d-amphetamine produced similar reductions in the self-administration of each of the cocaine doses (i.e., 40, 70 and 17 %, respectively). The results of human laboratory studies are concordant with those from clinical trials showing amphetamine maintenance reduces cocaine use in the natural ecology (e.g., Grabowski et al., 2001, 2004; Mooney et al., 2009; Nuijten et al., 2016).

Phentermine (30 mg/day) maintenance augmented the effects of cocaine on heart rate. While statistically significant, this effect was not clinically meaningful. On average, the combined effects of cocaine and phentermine did not result in tachycardia.

4.4. Topiramate-phentermine combinations

Topiramate-phentermine combinations significantly reduced cocaine self-administration in the present study. Combining topiramate (100 mg/day) and phentermine (30 mg/day) decreased cocaine (40 and 80 mg) self-administration by 76 % and 61 %, respectively. Together, these are among the largest reductions in cocaine self-administration observed in a human laboratory study.

We are unaware of any published clinical trials that determined the efficacy of topiramate-phentermine combinations for cocaine use disorder. Two clinical trials are germane, however, because they determined the efficacy of a topiramate-amphetamine combination for cocaine use disorder (Levin et al., 2020; Mariani et al., 2012). In the earlier double-blind trial, patients (N = 81) with cocaine use disorder were randomly assigned to placebo or a topiramate (150 mg/day) plus extended release amphetamine salt combination (60 mg/day) for 12 weeks (Mariani et al., 2012). The proportion of patients who achieved three consecutive weeks of abstinence was approximately double in the topiramate-amphetamine group (33.3 %) versus the placebo group (16.7 %). In the more recent trial, patients (N = 127) with cocaine use disorder from two sites were randomly assigned to placebo or topiramate (200 mg/day) plus extended release mixed amphetamine salt (60 mg/day) for 12 weeks (Levin et al., 2020). The proportion of participants able to achieve three weeks of abstinence at the end to trial was significantly higher in the topiramate-amphetamine patients (i.e., 14.1 %) relative to their placebo-treated counterparts (i.e., 0%). The effects of the topiramate-amphetamine combination were a bit more robust when the data were analyzed as percent of patients who achieved three weeks of continuous abstinence at any point in the trial (i.e., 21.9 and 6.3 %, respectively).

One of the clinical trials described above acknowledged the possibility the topiramate-amphetamine combination may not be more effective than the constituent drugs alone (Levin et al., 2020). Determining the relative contribution of the constituent drugs alone relative to a combination may not be feasible in a clinical trial because at least four conditions would be necessary (i.e., Placebo + Placebo, Drug A + Placebo; Placebo + Drug B, and Drug A + Drug B) (Stoops and Rush, 2014). Such a design obviously increases the number of participants needed as well as other resources. The human laboratory is an ideal environment to determine the relative contribution of the constituent drugs alone relative to a combination because these studies are more efficient and less resource intense. The results of the present human laboratory study suggest the effects of the topiramate-phentermine combinations are larger than those observed with the constituent drugs alone. Both topiramate (100 mg/day) and phentermine (30 mg/day) alone, for example, decreased self-administration of 40 mg cocaine (47 and 40 %, respectively). In contrast, combining these doses produced robust decreases in cocaine self-administration relative to placebo maintenance (i.e., 76 %). Topiramate (100 mg/day) and phentermine (30 mg/day) alone also decreased self-administration of 80 mg cocaine (30 and 18 %, respectively), but the combination produced larger reductions (i.e., 61 %). These results suggest the effects of topiramate and phentermine on cocaine self-administration are approximately additive.

4.5. Limitations

A few limitations of the present study should be noted. The present study tested relatively low doses of all three drugs, cocaine, topiramate and phentermine. Whether higher doses of topiramate and phentermine would further decrease cocaine self-administration is unknown. As noted above, the doses topiramate and phentermine used in present study were chosen based on the recommendation to test low doses of the constituent drugs to minimize side effects (Lee and Leggio, 2014; Stoops and Rush, 2014). Similarly, the doses of intranasal cocaine tested were relatively low. Whether topiramate-phentermine combinations would

decrease self-administration of higher cocaine doses using a different route (i.e., smoked or intravenous) is unknown.

5. Conclusions

Cocaine use disorder is an unrelenting public health concern. Despite nearly four decades of research, an effective medication is not yet approved for cocaine use disorder. The results of the present human laboratory study support advancing topiramate-phentermine combinations as a putative pharmacotherapeutic for cocaine use disorder.

Contributors

Dr. Rush contributed to the study design, statistical analyses, daily operations, conducted the statistical analyses, and wrote the manuscript. Drs. Stoops and Lile contributed to the study design and assisted in the preparation of the manuscript. Drs. Alcorn, Bolin and Reynolds contributed to the daily operations. Drs. Hays and Rayapati contributed to the study design and supervised all medical aspects of the study. All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

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