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Topiramate impairs cognitive function in methadone-maintained individuals with concurrent cocaine dependence

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Abstract

Topiramate is being investigated as a potential pharmacotherapy for the treatment of addictive disorders. However, its cognitive side effects raise concerns about its use, especially in populations with cognitive impairment, such as persons with chronic substance use disorders. This study investigated the topiramate's cognitive effects in individuals dually dependent on cocaine and opioids as part of a double-blind, randomized, controlled trial of topiramate for the cocaine dependence treatment. Following five weeks of stabilization on daily oral methadone ($M=96$ mg), participants were randomized to topiramate ($n=18$) or placebo ($n=22$). Cognitive testing took place at two time points: study weeks 4-5 to assess baseline performance and 10-13 weeks later to assess performance during stable dosing (300 mg topiramate or placebo). All participants were maintained on methadone at both testing times, and testing occurred two hours after the daily methadone plus topiramate/placebo administration. The topiramate and placebo groups did not differ on sex, level of education, premorbid intelligence, methadone dose, or illicit drug use. Topiramate slowed psychomotor and information processing speed, worsened divided attention, reduced n-back working memory accuracy, and increased the false alarm rate in recognition memory. Topiramate had no effects on visual processing, other measures of psychomotor function, risk-taking, self-control, Sternberg working memory, free recall, and metamemory. These findings indicate that topiramate may cause cognitive impairment in this population. This effect may limit its acceptability and use as a treatment in individuals with chronic opiate and cocaine use disorders, among whom pre-existing cognitive impairments are common.

Keywords

methadone maintenance; cocaine; topiramate; substance dependence; cognition

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Widespread cocaine use by methadone maintenance patients contributes to increased health risks and poor treatment outcomes (Dobler-Mikola et al., 2005). No pharmacological agent

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to date has been approved to treat cocaine dependence. Topiramate, an agonist for gamma-aminobutyric acid A (GABA-A) receptors and antagonist at glutamate α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and glutamate kainate 1 (Glu-K1) receptors, has shown promise as a pharmacotherapy across a range of substance use disorders. In animal models, GABA agonists are associated with reduced responsiveness to cocaine, conditioned cues, and self-administration (Barrett, Negus, Mello, & Caine, 2005; Weerts, Froestl, & Griffiths, 2005), and glutamate antagonists are associated with reduced cocaine reinforcement, reinstatement, and cocaine seeking (Kalivas, 2004), and may help to increase motivation to quit cocaine among non-treatment seekers (Dakwar, Levin, Foltin, Nunes, & Hart, 2013).

Human studies of topiramate support its potential for treating substance use disorders. In clinical trials, topiramate treatment resulted in longer cocaine abstinence (Johnson et al., 2013; Kampman et al., 2004; Kampman et al., 2013) and reduced methamphetamine use and relapse (Elkashef et al., 2012) compared to placebo. Topiramate has shown effectiveness in treating alcohol dependence (Baltieri, Daro, Ribeiro, & de Andrade, 2008; Johnson, Rosenthal, et al., 2007; Shinn & Greenfield, 2010). In male – but not female – tobacco smokers, topiramate was associated with improved quit rates, reduced withdrawal symptoms, and less post-cessation weight gain (Anthenelli, Blom, McElroy, & Keck, 2008). Case and retrospective studies found that topiramate was effective for reducing withdrawal symptoms during opioid detoxification (Zullino, Cottier, & Besson, 2002; Zullino et al., 2004). Topiramate has also shown some success as a treatment for disorders sharing symptoms or comorbid with substance use, including impulsive-compulsive disorders (e.g., binge eating, obsessive-compulsive disorder) and posttraumatic stress disorder (Berlin et al., 2011; Reas & Grilo, 2014; Shinn & Greenfield, 2010; Watts et al., 2013). High adverse event rates and attrition limit its acceptability.

Potential cognitive side effects raise concerns about topiramate use (Loring, Williamson, Meador, Wiegand, & Hulihan, 2011). Topiramate studies have found impairments in learning and memory, psychomotor function, and language in patients with drug dependence (Johnson, Roache, et al., 2007; Johnson, Rosenthal, et al., 2007), epilepsy (Eddy, Rickards, & Cavanna, 2011), and migraine (Romigi et al., 2008) as well as in healthy volunteers (Park & Kwon, 2008). Johnson, Roache, et al. (2007) used a double-blind, placebo-controlled, crossover design to measure acute cognitive effects of topiramate (0mg, 100mg, 200mg) administered prior to intravenous methamphetamine (0mg, 15mg, 30mg) in recently abstinent, non-treatment seeking methamphetamine-dependent participants ($n=10$). They found evidence of both improved and worsened cognitive performance, which could present compliance barriers for individuals that endorse cognitive enhancement as a significant reason for continued methamphetamine use (Brecht et al., 2004; Cretzmeyer et al., 2004; von Mayrhauser, Brecht, & Anglin, 2002). A clinical trial of topiramate (300 mg/day) for alcohol dependence treatment ($n=371$) found a greater rate of cognitive adverse events (i.e., worsening of concentration) in the treatment group compared to those receiving placebo (14.8% vs. 3.2%) (Johnson, Rosenthal, et al., 2007).

The efficacy of topiramate treatment for cocaine dependence in methadone maintenance patients should be evaluated in light of possible cognitive effects. Although healthy adults

have shown some cognitive difficulties following topiramate administration, the single study including persons with methamphetamine dependence (Johnson, Roache, et al. 2007) found mixed results. Individuals with chronic substance use disorders may be sensitive to topiramate's cognitive side effects due to an increased likelihood of low functional reserve and pre-morbid cognitive impairment (Fein & Di Sclafani, 2004; Ivanov, Schulz, London, & Newcorn, 2008; Yucel, Lubman, Solowij, & Brewer, 2007). Abuse of opiates and cocaine has been associated with cognitive impairment and could potentially exacerbate the cognitive side effects of topiramate (Beveridge, Gill, Hanlon, & Porrino, 2008; Lundqvist, 2010; Mintzer et al., 2007; Zacny, 1995). The present study sought to provide an assessment of topiramate's effects on cognitive performance in individuals dually dependent on cocaine and opioids as part of a treatment trial of topiramate for cocaine dependence during methadone maintenance treatment.

Method

Participants

This study of cognitive performance was conducted as part of an outpatient randomized double-blind clinical trial of topiramate for cocaine dependence in participants dually dependent on opioids and cocaine, the results of which are reported elsewhere (Umbricht et al., 2014). The study was approved by the Johns Hopkins School of Medicine institutional review board and was conducted from 2007 to 2011 at an outpatient methadone clinic in Baltimore, Maryland. Participants were recruited through flyers in local drug treatment and clinical care settings, and through advertisements in local print newspapers. Participants were paid \$80 for completing two to four training sessions on the cognitive tasks and \$50 for each cognitive assessment session.

Study eligibility criteria were: 1) cocaine and opioid dependence (based on an evaluation with the Structured Clinical Interview for DSM-IV [SCUD]) and seeking treatment; 2) age between 18 and 55 years; 3) eligible to receive methadone maintenance treatment; 4) no allergy to sulfonamide medications or topiramate; 5) no chronic disorders with risk of acidosis; 6) no history of nephrolithiasis, or unexplained hematuria; 7) not on Highly Active Antiretroviral Therapy; 8) no glaucoma, family history of glaucoma, intra-ocular pressure >20 mm Hg, or one sided-blindness; 9) no seizure disorder or use of antiepileptic medications; 10) no current benzodiazepine dependence; 11) no serious psychiatric illness (psychosis, dementia); 12) no pregnancy, lactation, or refusal to use an effective contraceptive method. Computerized randomization to placebo and topiramate groups was stratified on 1) gender; 2) age (<40 years old, Y/N); 3) cocaine withdrawal severity (Cocaine Selective Severity Assessment [CSSA] 20, Y/N; Kampman et al., 2004); 4) and current alcohol dependence. A detailed description of participant screening and randomization can be found in Umbricht et al. (2014).

Data are reported for the 40 participants who completed cognitive testing sessions at baseline and at stable dosing (see Cognitive Assessment below), of which 22 were randomized to placebo (P) and 18 were randomized to topiramate (TPM) (Figure 1). The 22 P participants include four who completed baseline cognitive assessment after receiving their first placebo dose after the lead-in placebo period, because that would not be expected

to affect performance. Five TPM participants were excluded from the present analyses due to completing the baseline cognitive assessment after receiving their first active topiramate dose, because that could have affected performance. The proportions of enrolled subjects who completed both assessments, and the proportions included in the final analysis did not differ significantly between the placebo and topiramate groups (p 's=.69, .41, respectively). Of these 40 participants, 19 P and 16 TPM participants completed the larger clinical trial. Thirty-two additional participants (whose data are not reported here) completed only the first cognitive testing session: 1) six participants were not randomized, 2) 14 participants were randomized to P, and 3) 12 participants were randomized to TPM. At week 5, t -test and χ^2 analyses comparing characteristics and drug use between participants completing one ($n=32$) vs. two ($n=40$) cognitive testing sessions revealed that the one-session only group had a significantly lower mean methadone dose ($M=86.9$, $SD=23.2$; $t(70)=-2.079$, $p=.041$) and less sedative use (past 30 days: $X^2(1)=5.236$, $p=.022$).

Procedure

Methadone Maintenance Treatment—All 40 participants received methadone maintenance treatment. Methadone (methadose 10 mg/mL, Mallincrodt, Inc., Hobart, N.Y.) was administered daily by nursing staff who used an automated pump system. Participants, clinic, and medical staff were blind to the methadone dose. Doses started at 30 mg/day and increased over three weeks to a maintenance dose of 100 mg/day. Doses for patients transferring from pre-study methadone maintenance treatment were continued at the same dose level. At any time participants could request a dose decrease, and a dose increase could be requested after week seven. Individual and group counseling was provided to all patients. Counseling was based on a manualized staged level of treatment. Participants could be administratively discharged for violating clinic rules or for missing three consecutive visits to the clinic. Participants were tested for drugs on the day of each cognitive testing session with a urine toxicology screen (benzodiazepines, opioids, cocaine) using an EMIT system (Syva Co., Palo Alto, CA).

Study Medication Dosing—Following three weeks of study-related methadone dosing, all participants started a two-week, double blind placebo lead-in period followed by randomization to TPM ($n=18$) or P ($n=22$) groups. Participants and staff were blind to the TPM/P conditions. Study capsules of TPM and P were prepared at an on-site research pharmacy from bulk topiramate (LGM Pharmaceuticals, Inc., Boca Raton, FL) and lactose monohydrate powder, N.F. as diluent (Ruger Chemical Co., Inc., Portland, OR). Lactose was premixed with 5 PPM denatonim benzoate (Bitrex®, Market Actives, LLC, Portland, OR) to give a similar bitter taste to all capsules. Following the methadone dose, participants received topiramate capsule in the morning under supervision and were given one capsule to take home with instructions to ingest it in the evening. TPM participants received ascending doses of topiramate during weeks 6 to 12 and stable doses of 300 mg/day during weeks 13 to 20. Topiramate capsules contained topiramate loose filled and supplemented with lactose powder and placebo capsules consisted lactose powder. Ninety-six percent of topiramate doses were administered as intended in the mornings of the clinic visit for the duration of the study through the second cognitive assessment session. Participants reported compliance with taking evening study medication doses.

Clinical evaluation—Current drug use was obtained by interview using the Addiction Severity Index (McLellan et al., 1992) during study enrollment (week 1). Cocaine withdrawal severity (CSSA) was measured using an 18-item clinician-administered questionnaire during the week of baseline cognitive assessment (Kampman et al., 1998).

Cognitive Assessment—Participants completed training on the cognitive battery prior to the first experimental session to reduce potential practice effects. Tasks included in the cognitive battery were chosen based on relevance for individuals with substance use disorders, specifically opiate and cocaine abuse and dependence (Vandrey & Mintzer, 2009). A broad range of cognitive domains was included in order to provide comparison with studies of topiramate effects on cognition (e.g., Loring et al, 2011; Meador et al., 2005; Sommer, Mitchell, & Wroolie, 2013). Estimated IQ was measured using the Shipley's Institute of Living Scale (Zachary, Paulson, & Gorsuch, 1985). Participants performed cognitive testing two hours after morning drug administration (methadone plus the morning capsules) at two time points during the study. The first session (baseline) was conducted at weeks 4-5, following stabilization on methadone (i.e., Placebo lead-in). The second session (stable dosing) was conducted during weeks 15-18 during stable P or TPM dosing (i.e., after 2-5 weeks of 300 mg/day of TPM).

Sensory Processing: The Flicker Fusion task assessed visual acuity and temporal discrimination (Simonson & Brozek, 1952). Participants viewed a light stimulus across increasing and decreasing frequency curves and used a toggle switch to indicate the points at which flickering of the stimulus appeared to stop (fusion threshold) and start (flicker threshold). The dependent measure was the average of the flicker and fusion thresholds.

Psychomotor Function: 1) A standing balance task measured the ability to stand on one leg with eyes closed; the dependent measure was the number of seconds balanced on each leg (a maximum of 30 sec for each leg). 2) A simple reaction time (RT) task measured the time to respond to a visual stimulus that appeared on the screen at random intervals, with dependent measures being the median RT and RT range (absolute difference between maximum and minimum RT) to assess variability. 3) Circular lights involved rapid hand-eye coordinated movements in which the participant pressed a series of 16 buttons (circularly arranged around a 54-cm diameter) as rapidly as possible in response to the randomly sequenced illumination of their associated lights (Griffiths, Bigelow, & Liebson, 1983); the dependent measure was the number of correct button presses during a 60 second trial. 4) A computerized task analogous to the Trail-Making Test was administered to assess psychomotor speed (Trails A), the ability to shift between sets within working memory (Trails B), and conceptual flexibility, or executive function (Trails B minus Trails A) (Mintzer, Frey, Yingling, & Griffiths, 1997; Reitan & Wolfson, 1993). Dependent measures were completion time in seconds.

Attention: 1) Focused attention was measured using a computerized version of the Digit Symbol Substitution Test (DSST) (McLeod, Bigelow, & Liebson, 1982; Wechsler, 1997). The dependent measures were number attempted (speed) and proportion correct (accuracy). 2) Divided attention was measured using a computer task that included simultaneous visual

tracking of central targets and monitoring of peripheral targets (Kleykamp, Griffiths, & Mintzer, 2010). Dependent measures associated with tracking were tracking moves (number of times the cross hair was moved on the screen), tracking deviation (distance in pixels between the central target and cross hair), and tracking overlap (number of times the cross hair and central target overlapped). Dependent measures associated with monitoring were mean RT (time between peripheral target onset and participant response), and proportion correct (peripheral target response accuracy). Outcomes for this task assessed speed (tracking moves, mean RT) or accuracy (tracking deviation, tracking overlap, and proportion correct).

Risk-Taking: A modified computerized version (Mintzer & Stitzer, 2002) of the Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994) assessed risk-taking. Dependent measures were the total number of cards selected from each of the four decks and the difference in card number selected from the advantageous versus disadvantageous decks, calculated separately for the decks associated with high frequency (i.e. C–A) and low frequency (i.e. D–B) of penalties, total winnings, and losses.

Self-Control: Delay discounting for a hypothetical reward was assessed with a computer decision-making task previously used in many studies (e.g., Baker, Johnson, & Bickel, 2003; Johnson & Bickel, 2002). Participants made a series of choices between receiving a standard larger later reward option (\$1,000) and an adjusting smaller immediate reward option. For each of 7 delays (ranging from 1 day to 25 years), the task adjusted choices in order to hone in the smaller immediate amount judged equal in value to the delayed rewards. The dependent measure was the extent of delay discounting, expressed as area under the curve (AUC) (Myerson, Green, & Warusawitharana, 2001).

Working Memory: Working memory was assessed using 1) the n-back task (Jonides et al., 1997; Mintzer & Griffiths, 2007) and 2) a modified Sternberg task (Mintzer & Griffiths, 2007; Sternberg, 1969). The n-back task required participants to click “yes” or “no” to indicate whether the current letter on the screen matched the target letter ‘n’ positions back for sixty trials in each memory load condition, n (0, 1, 2, and 3). Dependent measures were the proportion of yes responses made to target letters (hit rate), proportion of yes responses made to non-target letters (false alarm rate), signal detection measures of sensitivity in distinguishing between target and non-target letters (d') and response bias (C), and median reaction times to correct trials. The Sternberg task asked participants whether a probe letter had appeared in a specific position of a presented memory set for 12 trials in each condition: non-memory control (i.e., the memory set remained on the screen during probe presentation) and 12-sec delay (between memory set and probe presentation) Dependent measures were accuracy and median RT on correct trials.

Episodic Memory and Metamemory: Episodic memory was assessed using word recall and recognition, which included confidence judgments (Mintzer & Stitzer, 2002). Dependent measures were number of correct responses for recall and proportion of ‘old’ responses made to words that were previously studied (old) (hit rate), proportion of ‘old’ responses to new, unstudied words (false alarm rate), and signal detection measures of

sensitivity in distinguishing between old and new words (d') and response bias (C) for recognition memory (Snodgrass & Corwin, 1988). Metamemory was evaluated by calculating the Goodman-Kruskal gamma correlation between confidence ratings and recognition memory accuracy, collapsed across old and new words for sufficient power (Goodman & Kruskal, 1954).

Data analysis—Participant characteristics of age, years of education, estimated IQ, methadone dose, and cocaine withdrawal severity (independent samples t -test), and sex and race (chi -square test) were evaluated with group (P, TPM) as the factor. Cognitive performance outcomes were evaluated using mixed models with an AR(1) covariance structure with 2 factors: group and session (baseline, stable dosing). Analysis of the n-back working memory task included the additional factor of memory load (1, 2, 3-back), with the 0-back control condition as a covariate. Analysis of the Sternberg working memory task included the non-memory control condition as a covariate. Pairwise comparisons were only conducted for variables with significant F -values (Fisher's LSD; Keppel, 1991). All models were run with Proc Mixed in SAS 9.3 (SAS Institute, Inc., Cary, NC). Statistical significance was set at $p < 0.05$.

Results

Participant characteristics in the two groups are shown in Tables 1 and 2. The groups did not differ on age, education, estimated IQ, sex, methadone dose, or cocaine withdrawal severity. Outcome measures from the cognitive battery are shown in Tables 3 and 4. Groups did not differ in percent positive urine samples for opiates ($F[1,38] = .494, p = .486$), cocaine ($F[1,38] = .212, p = .648$), or benzodiazepines ($F[1,38] = 1.289, p = .263$) from baseline cognitive assessment through stable dosing cognitive assessment. The main trial found no group differences in percent positive urines for opiates and cocaine and for the longest consecutive string of cocaine negative samples (Umbricht et al., 2014). No significant chi -square group differences were found for number of drug-positive urine samples at either session. Screens for benzodiazepines are missing from four participants for the baseline cognitive testing session (3 P, 1 TPM) and one TPM participant for the stable dosing session. No significant chi -square differences were found in proportions of participants self-reporting drug use (heroin/opiates, cocaine, methadone, sedatives, alcohol, cannabis) for the week before baseline or for the week before stable dosing cognitive assessment; participants reporting drug use did not differ in number of uses of each drug category, as measured by t -tests.

Sensory Processing and Psychomotor Function

There was a significant main effect of session on the balance test, indicating that participants performed worse during the stable dosing session ($F[1,38] = 4.46, p = .041$) relative to baseline. There were no significant effects on Flicker-Fusion task performance, Simple Reaction Time, or the Circular Lights task.

The group $\times$ session interaction was significant for Trails A completion time ($F[1,38] = 6.38, p = .016$), however pairwise comparisons did not reach significance. A main effect of session ($F[1,38] = 4.71, p = .036$) showed fewer Trails B errors during the stable dosing session

relative to baseline. A significant main effect of group ($F[1,38]=5.12, p=.029$) showed slower Trails B-A completion time overall for the TPM group relative to P.

Attention

There was a significant group x session interaction for DSST number of trials attempted ($F[1,38]=14.90, p<.001$). Pairwise comparisons showed that the P group attempted significantly more trials during the stable dosing session relative to baseline, whereas the TPM group attempted significantly fewer trials during the stable dosing session relative to baseline. Pairwise comparisons also found that the TPM group attempted fewer trials than P during the stable dosing session. A main effect of group found that the TPM group completed fewer trials overall relative to the P group ($F[1,38]=5.08, p=.030$).

For the Divided Attention Task, there was a significant group x session interaction for tracking deviation ($F[1,30]=4.46, p=.043$). Pairwise comparisons showed that the TPM group had greater tracking deviation than the P group during the stable dosing session. A main effect of group showed that the TPM group had greater tracking deviation ($F[1,38]=4.45, p=.042$) and decreased tracking overlap ($F[1,38]=5.75, p=.022$) than the P group overall.

Risk-Taking

A group x session interaction for deck A selection frequency was at the trend level of significance ($F[1,38]=3.860, p=.057$). No other variables had significant main effects or interactions.

Self-Control

No significant effects were found for the delay discounting task.

Working Memory

Significant group x session interactions for hit rate ($F[1,38]=19.48, p<.001$) and d' ($F[1,38]=28.66, p<.001$) on the n -back task showed that the TPM group had significantly fewer hits and lower d' than the P group during the stable dosing. Moreover, the TPM group had significantly fewer hits and lower d' during the stable dosing session compared to baseline. A main effect of session was found for both hit rate ($F[1,38]=13.91, p=.001$) and d' ($F[1,38]=15.46, p<.001$), showing fewer hits and lower d' during the stable dosing session compared to baseline. A marginal group x session x condition interaction was found for d' ($F[2,75]=3.11, p=.051$) (Figure 2). A group x session interaction for false alarm rate was at the trend level ($F[1,38]=3.95, p=.054$). A main effect of condition was found for all variables ($p's<.05$), revealing more accurate and faster task performance with decreased memory load.

For the Sternberg task, a main effect of session ($F[1,37]=7.38, p=.010$) showed greater accuracy in the stable dosing session relative to baseline.

Episodic Memory

A significant group x session interaction on the recognition memory task showed that the TPM group had more false alarms ($F[1,34]=4.55, p=.040$) during the stable dosing session compared to baseline. The P group had significantly fewer false alarms during stable dosing compared to TPM. Significant main effects of group ($F[1,38]=6.10, p=.018$) and session ($F[1,34]=5.70, p=.023$) showed that the P group had a more conservative response bias than the TPM group (i.e., more likely to respond “new”) and that both groups had a decrease in response bias (i.e., more liberal response bias; more likely to respond “old”) during the stable dosing session relative to baseline. A significant main effect of session revealed more hits ($F[1,34]=7.25, p=.011$) during the stable dosing session relative to baseline. There were no significant effects on the recall task or metamemory.

Discussion

Compared to the baseline assessment conducted while participants were on methadone (but not on TPM), at steady state on a 300 mg topiramate dose, performance was worse on select measures of psychomotor function and information processing speed, working memory (n-back), divided attention, and episodic memory. Notably, the TPM group showed worsened performance relative to baseline on measures that showed improvement over time for the P group (Trails A, DSST, and divided attention), suggesting that the effects of TPM counteracted these effects and further worsened performance. Illegal drug use did not likely account for group performance differences because urine screens showed no differences between groups. While TPM was associated with worse performance on several measures, there were also some measures of cognitive functioning that did not show significant worsening associated with TPM, including visual processing, certain measures of psychomotor function, risk-taking, self-control, Sternberg working memory, free recall, and metamemory.

This study is the first to measure the cognitive effects of topiramate in a group dually dependent on opioids and cocaine. The present findings are consistent with topiramate-related impairment in psychomotor speed and memory found in previous studies with other populations. Johnson, Roache, et al. (2007) found that acute TPM administration with and without methamphetamine infusion produced psychomotor slowing, but improved attention/concentration in a small sample of recently abstinent methamphetamine-dependent individuals. The improved performance was attributed to several potential factors, including reduced anxiety and enhanced mood. Studies of cognitively healthy individuals have found TPM-related effects on cognition, including worsened learning and memory, attention/vigilance, and fluency as well as psychomotor slowing, with the absence of practice effects, when compared to placebo (Loring et al., 2011; Meador et al., 2005; Sommer, Mitchell, & Wroolie, 2013). In epilepsy and migraine patients, cognitive effects account for a high rate of intolerable adverse effects associated with TPM, and include slowed response time and worsened verbal fluency (Bootsma et al., 2009; Sommer et al., 2013). Cognitive effects may persist for the length of time TPM is used in epilepsy patients; however withdrawal from or a reduction in the dose of TPM has been associated with recovery in performance on verbal fluency, working memory, and psychomotor speed (Kockelmann, Elger, & Helmstaedter,

2003; Lee, Jung, Suh, Kwon, & Park, 2006; Sommer et al., 2013; Thompson, Baxendale, Duncan, & Sander, 2000). Importantly, some measures have shown that worsened task performance associated with TPM dosing may reach a sufficient magnitude to affect daily and occupational functioning (Mills et al., 2008; Salinsky et al., 2005).

The eventual acceptability and use of topiramate as a treatment for substance use disorders may be limited due to these effects on cognition, which could potentially exacerbate pre-existing cognitive impairments in individuals with chronic substance use disorders. The cognitive side-effects associated with TPM may be reduced with a slow titration schedule (Kushner, Khan, Lane, & Olson, 2006; Loring et al., 2011; Park & Kwon, 2008); but, the slow titration schedule used in the current study did not eliminate the worsened performance seen on several of the cognitive tasks. Some individuals with low educational attainment, polydrug use, and/or a psychiatric history may be more vulnerable to cognitive worsening, and therefore not ideal candidates for treatment with TPM (Sommer et al., 2013).

There are several limitations to the study. There was a relatively small sample size available in this trial, and this reduces power; concurrent drug use and individual differences among participants introduce additional variability into the data analysis. Furthermore, measuring cognitive performance at a single dose of topiramate reduces generalizability to other doses. The cognitive battery was chosen to be comprehensive but did not always overlap with measures used in past studies of topiramate (e.g., word fluency). Finally, the cognitive measures had limited ecological validity, reducing understanding of implications on real-world function. Future studies of substance-dependent individuals should evaluate cognitive effects with respect to TPM dose as time since last dose.

Despite these limitations, this study provides valuable information about the cognitive effects of topiramate in persons who are undergoing treatment for opioid dependence, and who have comorbid cocaine use. The findings from this study show that persons treated with topiramate had slower processing of information and increased memory errors; effects such as these may make non-pharmacological treatment interventions for these patients particularly challenging to administer. Although some studies have suggested that topiramate can be beneficial for the treatment of substance use disorders, the present findings suggest that any benefits seen with this medication should be carefully weighed against the adverse cognitive effects reported here. A careful assessment of topiramate's cognitive effects suggest that this medication may have an unfavorable profile for use in persons with dependence on cocaine and opiates, and that future medications development should consider risks relative to benefits and other options with a more favorable cognitive profile.

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Figure 1.

Participant flow from baseline cognitive assessment to stable dosing cognitive assessment. Due to scheduling difficulties, several participants completed their baseline cognitive assessment after randomization and during active dosing (week 6). Four of the 22 P participants were included in the analysis despite the late baseline assessment. Five additional TPM participants were excluded from analysis due to completing the baseline assessment after taking one or more topiramate doses, reducing the sample from 23 to 18.

Figure 2.

N-back d' (sensitivity) as a function of group (Placebo, Topiramate) during baseline and stable dosing for the 1-back, 2-back, and 3-back conditions. Data represent adjusted means (for which no standard error is available) with the 0-back non-memory control condition as covariate. Mixed models analysis showed a three-way interaction of group x session x condition (see Table 4 and Results section for details).

Table 1
Participant Characteristics and Drug Use

<u>Participant Characteristics</u>	<u>Placebo (n=22)</u>	<u>Topiramate (n=18)</u>	<u>Range</u>
Age	40.6 (5.9)	43.4 (5.3)	31 – 53
Years of Education	11.6 (1.4)	11.5 (1.7)	6 – 15
Estimated IQ	88.2 (13.8)	87.8 (11.9)	66 – 110
Methadone Dose (mg)	98.9 (12.8)	92.2 (12.6)	45 – 115
Cocaine Withdrawal Severity	11.14 (8.4)	14.35 (11.2)	0 – 43
Sex (Male/Female)	13/9	9/9	
Race (Black/Caucasian)	13/9	13/5	

Note.

Values for age, years of education, IQ, and methadone dose represent *mean (standard deviation)*. Values for sample size, sex, and race represent *n*. Methadone dose (*range* 20-115) and cocaine withdrawal severity (CSSA) (*range* 0-43) were reported for week 5, prior to the first dose with TPM. CSSA was not collected for one P participant. *T*-test and *Chi-Squared* analyses revealed no significant group differences for any participant characteristics.

Table 2

Pre-trial Self-Reported Drug Use

Drug	Placebo (n=22)		Topiramate (n=18)		Days Used Analysis		
	Past 30d Use % (n)	Days Used <i>M(SD)</i>	Past 30d Use % (n)	Days Used <i>M(SD)</i>	<i>df</i>	<i>t</i>	<i>p</i>
Heroin	95.5 (21)	25.9 (8.3)	83.3 (15)	27.9 (7.5)	34	0.75	0.456
Cocaine	100 (22)	17.8 (9.7)	100 (18)	22.6 (8.4)	38	1.65	0.108
Methadone	36.4 (8)	17.5 (11.8)	38.9 (7)	21.3 (10.9)	13	0.64	0.532
Alcohol	54.5 (12)	10.7 (9.8)	50.0 (9)	10.7 (10.9)	19	0.00	1.000
Sedatives	13.6 (3)	1.3 (0.6)	16.7 (3)	1.3 (0.6)	4	0.00	1.000
Cannabis	31.8 (7)	11.3 (11.5)	33.3 (6)	3.0 (2.1)	11	1.72	0.113

Note.

Values for 'days used' were calculated from participants reporting *any use* in the 30 days prior to initiation into the clinical trial. The four participants not reporting recent heroin use were already on methadone maintenance prior to starting the trial.

Table 3
Performance on sensory processing, psychomotor, attention, risk-taking, and self-control tasks at baseline and during stable dosing

Measure	Placebo		Topiramate	
	Baseline	Stable Dosing	Baseline	Stable Dosing
Flicker Fusion				
Threshold Frequency	33.0 (0.9)	33.9 (1.3)	35.7 (1.9)	37.0 (2.4)
Balance (s) ^b	8.3 (1.4)	7.8 (1.0)	10.6 (1.8)	7.4 (1.3)
Simple RT				
Median RT (ms)	409.3 (29.9)	415.1 (24.6)	447.6 (35.4)	454.7 (47.7)
RT Range (ms)	2939.8 (980.8)	1997.3 (483.2)	5996.3 (2975.1)	4401.3 (1069.1)
Circular Lights				
# Correct	48.6 (2.0)	51.9 (1.7)	49.7 (2.3)	46.2 (2.9)
Trail Making Test				
Trails A time (s) ^c	89.1 (14.8)	69.6 (5.6)	73.2 (4.9)	93.5 (9.1)
Trails B time (s)	145.1 (20.4)	116.6 (10.9)	168.8 (19.1)	175.9 (18.9)
Trails B – A time (s) ^a	56.0 (10.3)	47.0 (8.8)	95.5 (19.1)	82.4 (16.7)
Trails A Errors	0.9 (0.5)	1.5 (1.0)	0.7 (0.3)	0.3 (0.1)
Trails B Errors ^b	1.2 (0.6)	0.6 (0.2)	2.2 (0.8)	0.7 (0.3)
DSST				
# Trials Attempted ^{a, c}	23.7 (1.5)	27.9 (1.5)	23.1 (1.7)	19.3 (1.7)
Proportion Correct	91.7 (1.8)	92.3 (1.8)	85.0 (6.0)	89.3 (3.6)
Divided Attention				
# Tracking Moves	8492.0 (254.4)	8728.6 (278.4)	8602.3 (240.9)	8580.2 (307.0)
Tracking Deviation (pixels) ^{a, c}	42.4(4.1)	36.4 (2.7)	47.2(3.1)	51.9(5.6)
Tracking Overlap (accuracy) ^a	56.8 (3.4)	59.5 (2.5)	48.7 (3.1)	48.1 (3.9)
Mean RT (monitoring, ms)	1119.6 (72.9)	1015.0 (60.8)	932.3 (74.3)	951.2 (60.3)
Proportion Correct ^b (monitoring)	0.8 (0.0)	0.9 (0.0)	0.9 (0.0)	0.9 (0.0)
Iowa Gambling Task				
Deck A Frequency	23.7 (1.7)	24.0 (1.5)	19.7 (1.7)	19.6 (2.1)
Deck B Frequency	29.5 (2.0)	29.2 (2.0)	28.9 (2.0)	29.6 (2.1)
Deck C Frequency	25.7 (1.7)	26.4 (1.6)	28.3 (1.8)	27.9 (2.5)
Deck D Frequency	21.1 (1.9)	20.4 (1.9)	23.1 (2.2)	18.8 (1.9)
Total Winnings	-262.5 (175.8)	-326.1 (172.0)	-213.9 (137.7)	-227.8 (138.8)
Loans	1050.0 (99.7)	1063.6 (96.2)	911.1 (81.6)	955.6 (129.9)
Delay Discounting				
AUC	0.34 (0.06)	0.31 (0.06)	0.30 (0.06)	0.40 (0.09)

Note.

Values represent *Mean (Standard Error)*.

^aSuperscript letters indicate significant main effect of group

^b main effect of session

^c or group x session interaction.

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Table 4

Performance on memory tasks at baseline and during stable dosing.

Measure	Placebo		Topiramate	
	Baseline	Stable Dosing	Baseline	Stable Dosing
nBack 1				
Hit rate ^{b, c}	0.8	0.9	0.9	0.8
False Alarm rate	0.10	0.1	0.1	0.2
d' (sensitivity) ^{b, c}	2.6	2.9	2.8	2.3
C (response bias)	0.2	0.2	0.2	0.2
Median RT (ms)	989.5	993.2	1004.9	1020.7
nBack 2				
Hit rate ^{b, c}	0.6	0.6	0.7	0.4
False Alarm rate	0.2	0.2	0.2	0.2
d' (sensitivity) ^{b, c}	1.4	1.6	1.7	0.5
C (response bias)	0.3	0.4	0.4	0.7
Median RT (ms)	1034.3	1067.4	1081.9	1108.2
nBack 3				
Hit rate ^{b, c}	0.5	0.5	0.4	0.3
False Alarm rate	0.2	0.2	0.2	0.2
d' (sensitivity) ^{b, c}	1.0	0.9	1.0	0.5
C (response bias)	0.5	0.5	0.7	0.8
Median RT (ms)	1032.4	1074.2	1070.3	1037.7
Sternberg				
Delay: Accuracy ^b	58.2	67.4	61.9	67.4
Delay: Median RT (ms)	3450.0	3528.3	3863.9	3575.6
Free Recall				
# Correct Responses	3.8 (0.6)	4.1 (0.7)	3.9 (0.8)	3.2 (0.8)
Recognition Memory				
Hit rate ^b	0.6 (0.0)	0.7 (0.0)	0.7 (0.1)	0.7 (0.0)
False Alarm rate ^c	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.5 (0.1)
d' (sensitivity)	0.9 (0.2)	1.2 (0.2)	1.1 (0.2)	0.9 (0.2)
C (response bias) ^{a, b}	0.23(0.1)	0.2 (0.1)	0.1 (0.1)	-0.4 (0.2)
Metamemory				
Gamma	0.2 (0.1)	0.1 (0.1)	0.3 (0.1)	0.2 (0.1)

Note.

Values represent *Mean (Standard Error)*.

^aData for the n-back and Sternberg tasks are adjusted means (for which no standard errors are available) with the non-memory control condition (0-back, no delay) as covariate. Superscript letters indicate significant main effect of group

^bmain effect of session

^c or group x session interaction.

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