Drug and Alcohol Dependence xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Topiramate for cocaine dependence during methadone maintenance treatment: A randomized controlled trial

Annie Umbricht*, Anthony DeFulio, Erin L. Winstanley, D. Andrew Tompkins, Jessica Peirce, Miriam Z. Mintzer, Eric C. Strain, George E. Bigelow

Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA

ARTICLE INFO

Article history:
Received 24 April 2013
Received in revised form 18 March 2014
Accepted 30 March 2014
Available online xxx

Keywords:
Cocaine dependence
Antiepileptic
Topiramate
Glutamate
GABA
Contingency Management

ABSTRACT

Background: Dual dependence on opiate and cocaine occurs in about 60% of patients admitted to methadone maintenance and negatively impacts prognosis (Kosten et al. 2003. Drug Alcohol Depend. 70, 315). Topiramate (TOP) is an antiepileptic drug that may have utility in the treatment of cocaine dependence because it enhances the GABAergic system, antagonizes the glutamatergic system, and has been identified by NIDA as one of only a few medications providing a "positive signal" warranting further clinical investigation. (Vocci and Ling, 2005. Pharmacol. Ther. 108, 94).
Method: In this double-blind controlled clinical trial, cocaine dependent methadone maintenance patients ($N = 171$) were randomly assigned to one of four groups. Under a factorial design, participants received either TOP or placebo, and monetary voucher incentives that were either contingent (CM) or non-contingent (Non-CM) on drug abstinence. TOP participants were inducted onto TOP over 7 weeks, stabilized for 8 weeks at 300 mg daily then tapered over 3 weeks. Voucher incentives were supplied for 12 weeks, starting during the fourth week of TOP induction. Primary outcome measures were cocaine abstinence (*Y*/*N*) as measured by thrice weekly urinalysis and analyzed using Generalized Estimating Equations (GEE) and treatment retention. All analyses were intent to treat and included the 12-week evaluation phase of combined TOP/P treatment and voucher intervention period.
Results: There was no significant difference in cocaine abstinence between the TOP vs. P conditions nor between the CM vs. Non-CM conditions. There was no significant TOP/CM interaction. Retention was not significantly different between the groups.
Conclusion: Topiramate is not efficacious for increasing cocaine abstinence in methadone patients.

1. Introduction

Methadone is effective in the treatment of opioid dependence, but does not affect cocaine use, even at high doses (Castells et al., 2009). This is especially problematic in light of the fact that the majority of patients presenting for opioid maintenance treatment have concurrent cocaine dependence, which negatively impacts overall prognosis (Kosten et al., 2003). Nevertheless, effective adjunctive pharmacotherapies for cocaine dependence in this population are lacking. TOP has been identified as a strong candidate for this purpose (Vocci and Ling, 2005). In a key pilot study of relapse prevention in cocaine dependent men, TOP promoted abstinence at twice the rate of that achieved the placebo group (Kampman et al., 2004).

Topiramate [2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate] was FDA approved in 1996 for the treatment of adult seizures. TOP increases GABA central levels and potentiates its action at the $GABA_A$ receptor (Braga et al., 2009). TOP is an AMPA receptor antagonist at the glycine site, a selective GluK1 inhibitor (Braga et al., 2009) and decreases presynaptic glutamate release (Alves et al., 2003).

GABA antagonism and glutamate potentiation have each been identified as having potential value in the treatment of cocaine dependence. GABA agonists reduce the dopamine response to cocaine, response to conditioned cues, and cocaine self-administration (Barrett et al., 2005; Weerts et al., 2005). The presynaptic GABA reuptake inhibitor tiagabine appeared to reduce cocaine use in methadone maintenance (Gonzales et al., 2007) and vigabatrin (an irreversible inhibitor of intrasynaptic GABA

* Corresponding author. Tel.: +1 410 550 1917; fax: +1 410 550 0011/+1 410 550 1924.
E-mail address: annieumbricht@jhu.edu (A. Umbricht).

http://dx.doi.org/10.1016/j.drugalcdep.2014.03.033
0376-8716/

transaminase) increased cocaine abstinence in parolees (Brodie et al., 2009), though a later clinical trial showed no effect (Somoza et al., 2013). Prefrontal glutamatergic neurons innervating the nucleus accumbens play a critical role in cocaine reinforcement (McFarland et al., 2003; Kalivas, 2004). Glutamate inhibition blocks cocaine-induced reinstatement of cocaine seeking (Cornish and Kalivas, 2000; McFarland et al., 2003). Glutamate is involved in memory and neuroplasticity and a disruption of glutamate homeostasis could be at the core of compulsive drug taking (Kalivas et al., 2009). In preclinical studies, antagonists at AMPA-receptors (a glutamate receptor subtype) decreased cue-induced cocaine seeking (Bäcktröm and Hyytiä, 2006). Drugs with potential to restore glutamate homeostasis show promise as potential treatments for cocaine addiction (Moran et al., 2005; Peters et al., 2008; Kalivas, 2009). Given the potential of medications targeting independently the GABA and glutamate systems to help patients abstain from cocaine use, targeting these systems simultaneously with a medication such as TOP is of particular interest.

In addition to its potential for directly reducing cocaine use, TOP may have broad beneficial effects that further enhance its utility in the treatment of cocaine dependent methadone patients by addressing a variety of other symptoms and conditions common among poly-substance users. For example, TOP has produced promising results in treating other substance use disorders, reducing drinking in alcohol dependence (Johnson et al., 2003, 2004; Johnson, 2005; Baltieri et al., 2008), reducing relapse to alcohol use after detoxification (Rubio et al., 2009), and promoting smoking cessation in men (Anthenelli et al., 2008). More broadly, TOP has been evaluated for the treatment of chronic pain (Khoromi et al., 2005), aggression (Nickel et al., 2004, 2005a,b), compulsive disorders (Van Ameringen et al., 2006), and anxiety (Berlant, 2004; Khan and Liberzon, 2004).

The current study was designed to evaluate whether TOP would increase cocaine abstinence in cocaine dependent methadone patients. Participants were randomly assigned to one of four conditions in which they received TOP or placebo (P), and received vouchers contingent on providing cocaine negative urine samples (CM) or independently of their urine sample results (Non-CM). This design was planned as a means of comparing the effects of TOP against positive (CM) and negative (P) controls, as CM has been repeatedly demonstrated as successful in reducing cocaine use in methadone patients (Lussier et al., 2006; Prendergast et al., 2006). In all groups, voucher earnings were dependent on attendance and morning pills were consumed under observation. These procedures were designed to enhance attendance and TOP adherence across all participants. A secondary goal of the study was to evaluate the safety and acceptability of TOP in methadone patients, as there are no prior evaluations of TOP in this population.

2. Methods

2.1. Trial design and study flow

This randomized double-blind clinical trial featured a 2 × 2 factorial design. It was approved by the Johns Hopkins Medicine institutional review board and conducted from 2007 to 2011 at an outpatient methadone clinic on the Johns Hopkins Bayview Medical Campus, Baltimore, Maryland.

Fig. 1 shows the study timeline. Opioid and cocaine dependent adults who passed a telephone screening interview were scheduled for a full interview to determine eligibility. Participants were induced and stabilized on methadone, then, during a placebo lead-in period, they received one capsule ingested with the methadone dose, followed by mouth check; a second capsule dispensed in a blister pack was given for evening ingestion, with request to return the empty blister pack the following day. At the end of week 5, participants were randomly assigned to one of 4 treatment conditions: TOP/CM, P/CM, TOP/Non-CM, and P/Non-CM. Participants and staff were blind to time of randomization and changes in medication doses. Randomization was stratified on gender, age (≤40 years old, *Y*/*N*), cocaine withdrawal severity (Cocaine Selective Severity Assessment [CSSA] ≤20, *Y*/*N*; Kampman et al., 2004), and current alcohol dependence (DSM-IV-R, Structured Clinical Interview for DSM-IV [SCID]). Computerized stratified randomization with a 1:1:1:1 allocation ratio was implemented by staff members with no participant contact.

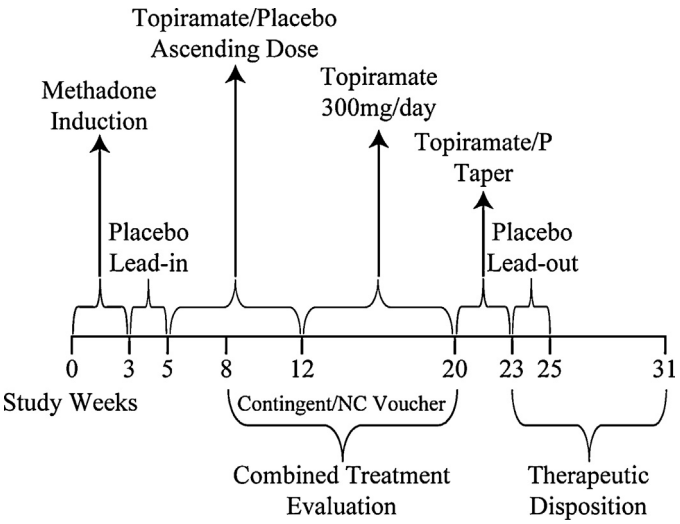

Fig. 1. Study timeline.

Contingency management procedures were implemented during weeks 9 through 20, which constituted the 12-week combined treatment evaluation phase. Capsules were discontinued after the topiramate taper and placebo lead-out phases. During the disposition phase, participants either continued methadone treatment at the clinic or were transferred to other community clinics of their choice.

2.2. Participants and recruitment

Participants were eligible if they were: (1) cocaine and opioid dependent and seeking treatment; (2) between 18 and 55 years old; (3) eligible for methadone maintenance; and (4) able to comply with study requirements. Participants were excluded for (1) sulfonamide or topiramate allergy; (2) diabetes, respiratory insufficiency, or other chronic risk factor for acidosis; (3) prior kidney stones, or unexplained blood in the urine; (4) current participation in Highly Active Antiretroviral Therapy; (5) glaucoma, family history of glaucoma, intraocular hypertension, or one-sided blindness; (6) seizure disorder or use of antiepileptic medications; (7) current benzodiazepine dependence; (8) serious psychiatric illness; (9) pregnancy, lactation, or sexual activity without effective contraception. Participants were recruited through flyers in local drug treatment, clinical care settings, and through advertisements in local print newspapers.

2.3. Intake and safety procedures

At intake, applicants were interviewed with the SCID and the Addiction Severity Index (ASI) to determine eligibility, urine samples were obtained for toxicology and urinalysis testing, and blood samples were tested for CBC, chemistry (liver and kidney function, amylase, lipase) and optional HIV testing. Medical evaluation was conducted, including EKG, visual acuity with corrected vision, and contact tonometry (Reichert Tonopen XL, Depew, NY) to measure intraocular pressure (IOP). Visual acuity and tonometry

Please cite this article in press as: Umbricht, A., et al., Topiramate for cocaine dependence during methadone maintenance treatment: A randomized controlled trial. Drug Alcohol Depend. (2014), http://dx.doi.org/10.1016/j.drugalcdep.2014.03.033