Extended-Release Mixed Amphetamine Salts and Topiramate for Cocaine Dependence: A Randomized Controlled Trial

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Background: Cocaine dependence is a substantial public health problem, yet there are no clearly effective medication treatments. Amphetamine and topiramate have both shown promise for the treatment of cocaine dependence in preclinical and early-stage clinical studies.

Methods: Eighty-one cocaine-dependent adults were randomized to receive a combination of extended-release mixed amphetamine salts (MAS-ER) and topiramate or placebo for 12 weeks under double-blind conditions. MAS-ER doses were titrated over 2 weeks to a maximum dose of 60 mg daily, and topiramate doses were titrated over 6 weeks to a maximum dose of 150 mg twice daily. All participants received a supportive behavioral intervention. The primary outcome was the proportion of individuals who achieved 3 consecutive weeks of abstinence as measured by urine toxicology confirmed self-report.

Results: The overall proportion of participants who achieved 3 consecutive weeks of abstinence was larger in the extended-release mixed amphetamine salts and topiramate group (33.3%) than in placebo group (16.7%). There was a significant moderating effect of baseline total number of cocaine use days (Wald $\chi^2 = 3.75$, $df = 1$, $p = .05$) on outcome, suggesting that the combination treatment was most effective for participants with a high baseline frequency of cocaine use.

Conclusions: The results of this study supported our hypothesis that the combination of MAS-ER and topiramate would be superior to placebo in achieving 3 weeks of consecutive abstinence. These findings provide evidence that the combination of MAS-ER and topiramate is efficacious in promoting abstinence in cocaine-dependent individuals.

Key Words: Amphetamines, clinical trial, cocaine dependence, topiramate, treatment, substance dependence

There are approximately 1.6 million current users of cocaine in the United States (1), and the past-year prevalence of cocaine dependence is estimated to be 1.1% (2), yet there are no effective pharmacotherapies for cocaine dependence. Standard psychosocial treatments for cocaine are not effective for many cocaine-dependent patients with an average abstinence rate of approximately 30% (3). Several dozen double-blind, randomized controlled trials for cocaine dependence have been conducted (4–6), and although several agents have shown promise, none has been shown to be clearly effective.

The acute effects of cocaine are due to its central inhibition of catecholamine uptake, particularly dopamine, by binding to the dopamine transporter (7). Substitution pharmacotherapy, which has been proven effective for opioid (8) and nicotine (9) dependence, is a plausible strategy for treating cocaine dependence. Findings with the positron emission tomography raclopride displacement procedure have shown that deficient dopamine transmission is associated with failure to respond to behavioral treatment (10). Stimulant medication may correct this deficit and may improve the salience of competing reinforcers to cocaine by enhancing dopamine release. Psychostimulants, including amphetamine, methylphenidate, bupropion, and modafinil, have been studied as treatments for cocaine dependence, both in patients with (11,12) and without (13–19) co-occurring attention-deficit/hyperactivity disorder. The results of these studies have been mixed with regard to effects on cocaine use outcomes, with promising therapeutic effects reported for dextroamphetamine (20). Amphetamine and cocaine have similar pharmacological and clinical characteristics; they differ mainly in onset of action and half-life. The mechanism of action of amphetamine is to both block dopamine reuptake and promote dopamine release.

Gamma-amino butyric acid (GABA) modulates the dopaminergic system and cocaine effects (21), and anticonvulsant agents that facilitate GABA activity have increasingly become the focus of study as potential pharmacotherapy for cocaine dependence. As a medication class, anticonvulsants have not been shown to be effective for the treatment of cocaine dependence (22), but individual agents, including topiramate (23) and vigabatrin (24), have demonstrated therapeutic benefit in preliminary controlled trials. Topiramate is an anticonvulsant agent that enhances GABA activity (25) and antagonizes glutamate transmission through effects at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptors.(26) In addition to the evidence of promoting abstinence in cocaine-dependent patients (23), topiramate has demonstrated evidence of efficacy in treating alcohol (27,28) and nicotine (29) dependence. The presumed mechanism for the therapeutic action of topiramate across substance dependence classes is by augmenting GABAergic activity and inhibiting glutaminergic excitation, leading to decreased midbrain dopaminergic activity (30,31), and topiramate has also been shown to reduce stimulant-induced dopamine activation as well (32).

For certain disorders, the use of multiple drugs simultaneously, typically with distinct mechanisms of action, is essential to obtain a desired therapeutic outcome (33). Promising separate lines of research of amphetamine and topiramate as single-agent pharmaco-

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therapies for cocaine dependence have suggested that studying the combined effects of these two medications was warranted. We hypothesized that by combining these two agents with distinct mechanisms of action, additive or synergistic effects would emerge and yield a more robust clinical benefit and that a combination of a psychostimulant and topiramate may help normalize striatal dopamine signaling by both increasing baseline levels of dopamine transmission and reducing cocaine-induced dopamine release, in theory both decreasing craving and cocaine-induced reinforcement.

Therefore, we conducted a randomized double-blind placebo-controlled trial of extended-release mixed amphetamine salts (MAS-ER) combined with topiramate for the treatment of cocaine dependence. We selected target doses of MAS-ER and topiramate based on studies of amphetamine for cocaine dependence (14) and topiramate for cocaine and alcohol dependence (23,27,28). We hypothesized that the proportion of participants achieving 3 consecutive weeks of cocaine abstinence during the study would be greater for the combined pharmacotherapies group compared with the placebo group. Three consecutive weeks of abstinence is a clinically meaningful outcome associated with more favorable long-term outcomes (34). We also explored secondary outcomes including treatment retention, abstinent weeks during the study period, and medication adherence, safety, and tolerability.

Methods and Materials

Participants

All participants were seeking outpatient treatment for problems related to cocaine use and were recruited by local advertising or by clinical referrals in the New York City metropolitan area. We enrolled 81 participants who met DSM-IV-TR (35) criteria for cocaine dependence. Participants were 18 to 60 years old, reported using cocaine at least 4 days during the 28 days prior to study entry, and had a body mass index 18 kg/m^2 or less. Participants were excluded if they had a DSM-IV-TR diagnosis of major depressive disorder, bipolar disorder, schizophrenia or any psychotic disorder other than transient psychosis due to substance use; a DSM-IV-TR Axis I psychiatric disorder that was unstable or likely require treatment during the study period; physiological dependence on any substances (other than cocaine, nicotine, or cannabis) that would require medical intervention; were prescribed psychotropic medication other than for insomnia; a current diagnosis of psychostimulant abuse or dependence; were at significant risk for suicide; coronary vascular disease as indicated by clinical history or electrocardiogram; unstable physical condition such as poorly controlled hypertension, acute hepatitis, or poorly controlled diabetes; a history of seizures; history of an allergic reaction to MAS-ER (or other amphetamine analogs) or topiramate; were pregnant or lactating; prescribed carbonic anhydrase inhibitors; had a history of glaucoma or kidney stones; had a history of failure to respond to either study medication for cocaine dependence; or were compelled to receive treatment to avoid imprisonment or other penalties. This study was reviewed and approved by the Institutional Review Board of the New York State Psychiatric Institute, and all participants gave written informed consent.

Treatment

The study was a single-site, randomized, double-blind, parallel-group, 14-week clinical trial comparing the combination of MAS-ER and topiramate to placebo, with a 1-week single-blind placebo lead-in, a 12-week double-blind study period, and a 1-week taper. The clinical trial was conducted at the Substance Treatment and Research Service of Columbia University Medical Center/New York State Psychiatric Institute. After determining study eligibility, participants began a 1-week single-blind placebo lead-in phase to assess their baseline severity of cocaine use and the ability to comply with study procedures. Successful completers of the single-blind placebo lead-in were randomized to the combination of MAS-ER and topiramate or placebo in a 1:1 allocation. The randomization was stratified by a whether one of the 3 placebo lead-in week urine toxicology samples was positive for the cocaine metabolite benzoylecgonine (BE).

Following randomization, study medications were administered under double-blind conditions for 12-weeks. MAS-ER, topiramate, and matching placebo were packaged in matching gelatin capsules with a lactose filler and 12.5 mg of riboflavin. Each week, all participants were provided with two medication bottles under double-blind conditions, one labeled "MAS-ER or placebo" and the other labeled "topiramate or placebo." If a participant could not tolerate at least 10 mg per day of the study medication labeled "MAS-ER or placebo," all study medications were discontinued; no minimum was set for the medication labeled "topiramate or placebo." The MAS-ER doses began at 10 mg daily and were titrated over 2 weeks to a maximum dose of 60 mg daily, and topiramate doses began at 25 mg daily were titrated over 6 weeks to a maximum dose of 150 mg twice daily. Reductions in dosing were made for intolerable adverse effects. Participants in each group received an identical number of capsules. Participants were instructed to take the MAS-ER or placebo capsules in the morning and the topiramate or placebo capsules in the morning and the evening. Each week, participants were asked to return all bottles and unused medication.

All patients had a weekly individual session with a study psychiatrist using a structured compliance enhancement manual designed for pharmacotherapy trials in subjects with substance use disorders (36). The goal of compliance enhancement therapy is to achieve high-quality supportive treatment that reinforces adherence to study procedures and the study medication regimen. Sessions were approximately 30 min in duration and were focused on 1) setting abstinence from cocaine use as a goal, 2) participant compliance with study medications and procedures, and 3) current functioning. Mutual help support group (e.g., Narcotics Anonymous) attendance was encouraged.

Progressive incentive payments were provided for attendance to enhance compliance with study procedures and retention. Participants earned an additional $10 voucher each week that they returned their pill bottles and any remaining medication. Perfect attendance and compliance with returning pill bottles would result in a participant earning $592 in vouchers over the study period. Voucher earnings were redeemable for retail goods or services designated by the participant. Participants were also compensated in cash for transportation costs per visit.

Assessment

During the screening period, a comprehensive psychiatric and medical evaluation, and the Structured Clinical Interview (SCID) for DSM-IV Axis I disorders (37) interview were performed. Self-reported cocaine use for the prior 28 days was measured using the timeline followback method (38).

Participants were scheduled to attend three assessment visits per week. At each study visit, a urine sample for toxicology and ultraviolet detection of riboflavin was obtained, and vital signs and adverse effects were assessed. On a weekly basis, a timeline followback assessment of cocaine use was performed and medication compliance was assessed using a calendar procedure and pill count. Serum for topiramate levels were collected at weeks 6, 10,