"Author Material" Referenced in "Topiramate for the Treatment of Cocaine Addiction"

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Notes on the Study Design

Health checks at screening included physical examination, 12-lead electrocardiogram, electrolytes, liver enzymes, complete blood count, urinalysis, urine pregnancy test for women, history of medication use, history of drug (including cocaine) use, and a tuberculin (purified protein derivative) skin test or chest X-ray, or both, to exclude a diagnosis of tuberculosis. Exclusion criteria for eligibility based on health checks included serious medical illness (eg, tuberculosis), psychiatric conditions requiring ongoing medicinal treatment, pregnancy or lactation, nephrolithiasis or renal impairment, and court-mandated drug abuse treatment. See below for the full list of inclusion and exclusion criteria from the study protocol.

Commercially available topiramate (Topamax®; Ortho-McNeil Neurologics, Titusville, NJ) was over-encapsulated in opaque gelatin capsules (Shionogi Qualicaps®) filled with lactulose. (Importantly, topiramate has been available generically since April 2009.) Matching placebo capsules were of the same color and consistency and filled with lactulose.

Study participants were compensated $20 following the initial screening visit, $10 at the completion of each study visit, $15 for the completion of each follow-up visit, and a $5 bonus for attending all three study visits in a week.

Criteria for inclusion:

- Males and females who have given written informed consent.
- Ages 18 years and above, and must have a BMI >18 kg/m².
- Good physical health as determined by a complete physical examination, an EKG within normal limits, and laboratory screening tests within acceptable parameters (see exclusion criteria).
- Current DSM-IV diagnosis of cocaine dependence.
- Seeking treatment for cocaine dependence.
- At least one positive urine drug screen for cocaine at screen or baseline prior to randomization.
- The pregnancy test for females at intake must be negative. Additionally, women of childbearing potential must be using an acceptable form of contraception. These include: oral contraceptives, hormonal (levonorgestrel) or surgical implants, or barrier plus spermicide.
- Literacy in English and ability to read, understand, and complete the ratings scales and questionnaires accurately, follow instructions, and make use of the behavioral treatments.
- Answered an advertisement in the newspaper/radio/television, and expressing a wish to stop using cocaine.
- Willingness to participate in behavioral treatments for cocaine dependence.

Criteria for exclusion:

- Current dependence, defined by DSM-IV criteria, on any psychoactive substance other than cocaine, alcohol, nicotine, caffeine, or marijuana or physiological dependence on alcohol requiring medical detoxification. Although heavy alcohol use and "behavioral" dependence may be included, physiological dependence on alcohol showing signs of withdrawal at zero breath alcohol levels and requiring medical detoxification will cause exclusion. (Note: Subjects who tested positive for other drugs with the exception of cocaine and marijuana may be included at the discretion of the principal investigator if deemed not dependent.)
- Neurological or psychiatric disorders, such as:
    - Psychosis;
    - Bipolar illness.
- Any Axis 1 disorder that warrants treatment or would preclude safe participation in the protocol.
- Organic brain disease.
- Dementia.
- Bulimia/anorexia nervosa.
- Seizure disorders or epilepsy.

  - Any disorder which would require ongoing treatment or which would make study agent compliance difficult;
  - History of suicide attempts (30 days prior to screening) assessed by SCID and/or current suicidal ideation/plan as assessed by SCID.
- Serious medical illnesses including, but not limited to:
  - Uncontrolled hypertension;
  - Kidney stones;
  - History of glaucoma;
  - Significant heart disease, including myocardial infarction within one year of enrollment;
  - Angina;
  - Active hepatitis;
  - Clinically significant cardiovascular abnormality (EKG);
  - Disease of the gastrointestinal system, liver, or kidneys that could result in altered metabolism or excretion of the study agent;
  - History of major gastrointestinal tract surgery (e.g., gastrectomy, gastrostomy, bowel resections);
  - Current or historical diagnosis of chronic disease of the gastrointestinal tract (e.g., ulcerative colitis, regional enteritis, or gastrointestinal bleeding);
  - Serious, potentially life-threatening, or progressive medical illness other than addiction that may compromise subject safety or study conduct;
  - Renal impairment (calculated GFR of less than 60 as a lower limit).
- Mandated by the court to obtain treatment for cocaine dependence.
- Anyone who, in the opinion of the investigator, would not be expected to complete the study protocol because of probable incarceration or relocation from the clinic area.
- AIDS.
- HIV with CD4 positive T cell counts < 500 mm^3.
- Any subjects on any pharmacotherapy for the treatment of AIDS or HIV will be excluded.
- Active syphilis that has not been treated, or refused treatment for syphilis.
- Severe or life-threatening adverse reactions to medications (including topiramate) in the past or during this clinical trial.
- Currently on active treatment with topiramate.
- Receipt of a drug with known potential for toxicity to a major organ system within 30 days prior to study entry (e.g., isoniazid, methotrexate).
- Female subjects who are pregnant, lactating, or not adhering to an acceptable form of contraception at any time during the study.
- Concurrent (within two weeks of randomization) regular use of psychotropics including, but not limited to, antidepressants, anxiolytics, anti-psychotics, anticonvulsants, and psychomotor stimulant-type medications, St. John's Wort, yohimbine, ginkgo biloba, horehound, or any other central nervous system active herbal preparations.
- Use of any opiate substitutes (methadone, LAAM, buprenorphine) within 1 month preceding screening.
- Clinically significant hematological or biochemical test results that in the view of the study physician require immediate or urgent treatment.
- Pyrexia of unknown origin or neuroleptic malignant syndrome.
- Serious medical comorbidity requiring medical intervention or close supervision, or any condition which can interfere with the receipt of topiramate.
- Received inpatient or outpatient treatment for cocaine dependence within the last 4 weeks, or previously participated in a clinical trial utilizing topiramate.
- Electroconvulsive therapy within the 3 months preceding screening.
- Members of the same household.
- Urine must be free of opiates, amphetamines, barbiturates, benzodiazepines, prescription and non-prescription drugs with the exception of cocaine and marijuana.

Quantification of Benzoylecgonine (BE) and Creatinine (Cr)

These assays were performed at the Biological Psychiatry Analytical Lab located in the Department of Psychiatry at the University of Texas Health Science Center, San Antonio, Texas.

HPLC grade acetonitrile, methanol, dichloromethane, and isopropanol were purchased from Burdick and Jackson (Muskegon, MI, USA). Water used for preparation of all solutions was Milli-Q Water (Millipore, Bedford, MA, USA). Potassium phosphate was obtained from Fisher Scientific (Fair Lawn, NJ, USA). Benzoylecgonine (BE) standard solution (1 mg/ml) was purchased from Sigma Chemical Company (St. Louis, MO).

Urine was collected according to standard procedures, and pH was adjusted to 5 with diluted acetic acid (0.1 M). Five-milliliter aliquots were placed in properly labeled, capped polypropylene test tubes for storage at –80°C until the day of the assay for BE and creatinine (Cr).

On the day of the assays for Cr and BE, the samples were thawed at room temperature. An aliquot was removed from each tube for the quantification of Cr according to the instructions in the assay kit (Oxford Biomedical Reseach Creatinine kit).

For the quantification of BE, 3 ml of urine for each patient, calibrator, and control sample was placed in polypropylene tubes with 100 µl of a 100 µg/ml solution of nalorphine (internal standard) and 2 ml of 100 mM phosphate buffer (pH 6). The samples were thoroughly mixed by vortexing. If necessary, sample pH was adjusted to 6.0 ± 0.5 with 1.0 M KOH. For the extraction of BE, Bond Elut Certify columns were used. The columns were pretreated with 2 ml of methanol, then 2 ml of 100 mM phosphate buffer (pH 6), which were drawn through the columns on a vacuum manifold. The samples were then loaded onto the Bond Elut columns at a flow rate of about 2 ml/min. Next, the columns were rinsed sequentially with 6 ml of Milli-Q water and 3 ml of 1 M acetic acid and then allowed to dry under vacuum for 5 min. At that time, 6 ml of methanol was applied to the columns as a final rinse. Then, 2 ml of a solution containing dichloromethane:isopropanol (80:20) and 2% ammonium hydroxide was run through the columns to elute BE (this elution solvent was prepared daily). The final eluates were evaporated to dryness under a gentle nitrogen stream. The dried sample was dissolved in 250 µL of mobile phase (see below), and then 100 µl of each sample was injected into the HPLC system for the quantification of BE.

The HPLC system consisted of a Waters model 510 pump, Waters model 717 sample injector, Waters model 2587 UV detector for HPLC, and Alltima C18 column (5 micron, 4.5 ID × 150 mm L). The flow rate of the mobile phase was 1.2 ml/min. BE and nalorphine are detected at a fixed wavelength of 234 nm. The isocratic mobile phase contained 8% acetonitrile, 12% methanol, and 80% of a solution of 9.6 mM KH_2PO_4 (pH 2.5).

For the quantification of BE, the ratio of peak area of BE to nalorphine was compared against the linear regression of ratios of a set of spiked calibrator samples (0.1, 1, 5, and 10 µg/ml) using Waters Empower chromatographic software. The detection limit for BE was 0.1 µg/ml. BE concentration in urine is expressed as µg/ml.

The final results for quantification of BE in urine were expressed as the ratio of BE to Cr concentrations in ng BE/mg Cr.

Validation of BE Assay: Recovery of BE from urine samples was determined to be 63% by comparing a 5-point concentration curve (0.1, 1, 5, and 10 µg/ml) of unextracted samples of BE against that of extracted samples. The recovery was linear across all concentrations tested, and the regression coefficient of the extracted concentration curve was r = 0.999. Precision for within-day and between-day tests was <10%. The accuracy for low- and high-range control samples was <10%. Benzoylecgonine is stable indefinitely when stored at ≤–70°C.

Strict procedures are in place for the documented transfer of samples from the distal locations to UPL. Urine samples have been stored at ≤–80°C in freezers whose temperatures are monitored on a 24-hours/day basis. Also, strict procedures for transfer of patient samples to test tubes for the performance of the assays have been standard in our laboratory for many years. The transfer of data from laboratory worksheets to our EXCEL databases is double-checked, and the data files are backed up immediately after entry and after double-checking of the data. In short, we have established procedures for maintenance of the integrity of the samples that we analyze and the data that we collect.

Guidance Document for Scoring Use and Non-Use Days for Topiramate Trial of Cocaine Dependence[*]

The following are the logical steps in the sequence of scoring cocaine use and non-use days. This guidance document assumes that the study design included a 2-week baseline assessment period and an 8-week treatment period.

1. Use the following modified Preston rules to determine if a urine sample is considered positive or negative for new use (the Preston rules take carryover of BE into account) as follows:

The following rules indicate that a sample is positive for new use:

RULE 1: An increase in cocaine metabolite concentration over concentration of preceding urine specimen to any value over 300 ng/ml.

Note: It does not matter how long before the preceding sample was collected. If the concentration of the current specimen is greater than the preceding specimen, there was new use in the interim.

RULE 2: Both of the following occur: 1) cocaine metabolite concentration is greater than 300 ng/mL and 2) cocaine metabolite concentration is greater than one-half of the concentration measured in the preceding urine specimen.

Note: The concept here is that due to the excretion rate of BE in the urine that concentrations greater than half the concentration of the preceding sample are only possible if there is new use. Although it does not matter how long before the preceding sample was collected as long as samples were collected, at least one-day apart, this rule really applies to samples collected two days apart as RULE 4 applies to cases where samples are greater than two days apart.

RULE 3: Cocaine metabolite is greater than 300 ng/ml in the first urine specimen collected in the study.

Note: Because there is no earlier specimen, this sample, by default, is considered positive because carryover cannot be determined.

RULE 4: If the previous urine specimen was collected more than 2 calendar days before, urine specimen with cocaine metabolite greater than 300 ng/ml.

Note: Because there is no sample within two days, there is no way to establish if a carryover effect has occurred, these sample are *de facto* considered positive.

RULE 5: Creatinine less than 20 mg/dL and cocaine metabolite/creatinine ratio is increased compared to that of previous specimen. (Cocaine metabolite does not have to be above 300 ng/ml).

Note: Creatinine concentrations less than 20 mg/ml suggest that the urine sample is not physiologic and has been diluted in some manner.

[*] **Provided courtesy of Dr. Shou-Hua Li at the National Institute on Drug Abuse.**

EXAMPLE:

Study Day	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
BE ng/mL	800		399		275			325		800		625
BE +/-	+		-		-			+		+		+

Note: Every urine sample collected during the study between the start of the two-week baseline (shown as negative study days) and day 57 is scored as positive or negative for new use based on urine BE.

Study day –7 is positive per rule 3. (in the example above the study starts on day –7, this is not typically the case but is presented this way due to space layout constraints)

Study day –5 is negative per rule 2.

Study day –3 is negative because it is not considered positive by any rule.

Study day 1 is positive due to rule 4.

Study day 3 is positive due to rule 1.

Study day 5 is positive due to rule 2.

2. Use the subject's self-report of use in combination with the urine BE positive/negative scores from above to assign each study day as a use or non-use day without taking into consideration concordance rates as follows:

a. Self report of use are accepted in all cases.

Note: For every day in the study that the subject reports that they have used cocaine, score that day as a use day ignoring the urine BE levels. Remember, use and non-use days are also scored for each baseline measurement day of the study because some of the outcome measures will be compared to baseline use. Urine collected on the first day of the study before medication is given may be used to assess the preceding days as a use or a non-use day during baseline, if self-reports are given for these days.

b. Subject reports no new use since last urine BE or within the preceding 72 hours (whichever is the shorter time frame) but urine BE shows new use, then score the preceding day as a use day.

c. The first day of investigational agent administration (patch application) is scored as missing.

d. Study days after day 56 are not scored; however, urine collected on day 57 may be used to assign a score to day 56.

e. If there is no urine after the last sample to confirm or disprove use, the subject's self report will be used to score that last study day. However, this may be overruled after calculating the concordance rate, if the concordance rate is <70%.

EXAMPLE:

Study Day	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	0	0	0	0	0	0	1	0	0	0	0
BE +/-	+		-		-			+		+		+
Score	0	0	0	0	0	0	1	M	0	0	1	0

0 = No use or no new use; 1 = use or new use, M = missing or unknown; SUI = self report of use; BE = urine BE results (+) = no new use, (-) = new use; Score = assignment of use or non-use day.

Notes:

Day –7 is scored as no new use because the subject reported no use and there is no day –6 urine to overrule this.

Day –1 was scored as new use even though the subject reported no new use because the day 1 urine specimen was positive.

Day 1 was scored as missing because this is the first day of investigational agent administration and by default is not scored.

Day 2 was scored as no new use even though the day 3 urine specimen was positive because the subject did report use on day 1 which could account for the positive urine on day 3.

3. ***How to handle missing data.*** The examples above show complete data sets. However, participants in substance abuse studies frequently miss visits. The following rules apply to missing data.

a. If there is no self report for a day, the day will be scored as missing, unless there is a urine specimen the following day that is positive. In this case, the day will be scored as a use day unless the subject reported use since the last urine specimen or within the preceding 72 hours.

b. Self report days of non-use will be considered as missing if not followed by a urine BE assessment within 7 days.

Note: This rule does not apply to the last day of the study (day 56 or earlier if the subject terminated the study earlier). If the subject reports new use, then this last day is scored as new use (standard rule from above). However, if the subject reported no new use on this day and a urine specimen is available for the next day, this urine sample will be used to score the last day of treatment. Alternatively, if the subject reports no new use and no urine specimen is available for the next day, the day will be scored as no new use unless the concordance rate is < 70%, in which case it will be scored as missing.

EXAMPLE:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	1	0	0	0	0
BE +/-	-		+									+
Score	0	1	1	M	0	0	0	1	0	0	1	0

0 = No use or no new use; 1 = use or new use, M = missing or unknown; SUI = self report of use; BE = urine BE results (+) = no new use, (-) = new use; Score = assignment of use or non-use day.

Note: In this example, the self report of use/non-use on study day 6, is not followed by a urine sample until 8 days later on study day 14. Self-report of use/non-use is on study day 7 through 13 are followed by a urine result on day 14 and are thus not considered missing.

4. Determine concordance rate for each subject.

Once a complete data set has been collected for a subject (this could be for an interim or final analysis) and the use and non-use days determined, the concordance rates can be calculated for the subject as follows (note that data for the interim analysis will be from a frozen locked dataset; however, it is not expected that the data is fully cleaned, thus, these data may change at the final analysis):

Percentage non-concordance between self-report of use and urine BE data will be calculated for each study subject as the percentage of the number of days that were scored as use days based on urine BE data overruling self-report divided by the total number of urine samples that were used to evaluate concordance, as follows:

% non-concordant = # non-concordant use days/total urine samples used to evaluate concordance * 100%, thus

% concordant = 100 - % non-concordant.

Notes:

Baseline scores will be used in the calculations of concordance regardless of whether the baseline period is two weeks-long or less. Baseline may not be followed immediately by treatment. If treatment does not immediately follow baseline, the first consecutive 14 day period used to establish baseline requirements for urine specimens (six total specimens over a consecutive two week period, three of which must be positive for BE and no more than 4 specimens collected in one week) will be considered the baseline period. If the number of baseline days is less than 14 for a participant, this will need to be considered in the statistical analysis.

Day 57 urine will be used to evaluate the last treatment day (Day 56) as use or non-use day and will be included in the denominator of % non-concordance calculation. Day 57 is the cut-off day and urines after Day 57 will not be used.

On-site cocaine test cups are used for screening but only the results if quantitative assay will be used for scoring purposes.

There may be a delay between the date of randomization and the date of treatment. The date of randomization is considered study day 1. These gaps between the start of treatment will need to be considered in the statistical analysis.

If the patient dropped out, the last clinic visit is considered to be the last study day.

EXAMPLE:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	1	0	0	0	0
BE +/-	-		+									+
Score	0	1	1	M	0	0	0	1	0	0	1	0

0 = No use or no new use; 1 = use or new use, M = missing or unknown; SUI = self report of use; BE = urine BE results (+) = no new use, (-) = new use; Score = assignment of use or non-use day.

Notes: Although this is not a complete data set, it serves the purpose of providing an example of the concordance rate calculation. In the above example, there is 1 discordant result on day 13. Thus, 1 is the numerator of the discordant rate calculation. There are 2 urine specimens used to establish concordance, the specimens on study days 5 and 14. Thus, 2 is the denominator of the discordant rate calculation. Therefore:

% non-concordant = 1 non-concordant use days/2 total urine samples used to evaluate concordance * 100% = 50%

% concordant = 100 – 50 % non-concordant = 50 % concordant

5. For subjects whose concordance rates are < 70%, the non-use days must be re-evaluated.

Rule: When the concordance rate between self report and urine BE for the individual is < 70 %, non-use day scores will be considered as missing, if not followed by a urine specimen in 3 days.

EXAMPLE 1:

Original Scores:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	0	0	0	0	0
BE +/-	-		+									+
Score	0	1	1	M	0	0	0	0	0	0	1	0

0 = No use or no new use; 1 = use or new use, M = missing or unknown; SUI = self report of use; BE = urine BE results (+) = no new use, (-) = new use; Score = assignment of use or non-use day.

Notes: The concordance rate for this dataset is 50% and there is a longer than 3 day gap between urine specimens, thus the dataset will be re-scored as follows:

Re-scored:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	0	0	0	0	0
BE +/-	-		+									+
Score	0	1	1	M	M	M	M	M	0	0	1	0

0 = No use or no new use; 1 = use or new use, M = missing or unknown; SUI = self report of use; BE = urine BE results (+) = no new use, (-) = new use; Score = assignment of use or non-use day.

Notes:

Day 6 stays as missing because it was not followed by a urine result within 7-days.

Days 7, 8, 9, and 10 are re-scored as missing because there is no urine result in the next 3 days.

Days 11, 12, and 13 scores do not change because there is a urine result within the next 3 days (day 14).

EXAMPLE 2:

Original Scores:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	0	0	0	0	0
BE +/-	-		+					+				+
Score	0	1	1	0	0	0	1	0	0	0	1	0

0 = No use or no new use; 1 = use or new use, M = missing or unknown; SUI = self report of use; BE = urine BE results (+) = no new use, (-) = new use; Score = assignment of use or non-use day.

Notes: The concordance rate for this dataset is 33.3% and there is a longer than 3 day gap between urine specimens, thus the dataset will be re-scored as follows:

Re-scored:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	0	0	0	0	0
BE +/-	-		+					+				+
Score	0	1	1	M	0	0	1	0	0	0	1	0

0 = No use or no new use; 1 = use or new use, M = missing or unknown; SUI = self report of use; BE = urine BE results (+) = no new use, (-) = new use; Score = assignment of use or non-use day.

Notes:

Day 6 is re-scored as missing because there is no urine specimen in the next 3 days.

The following is an example of the scoring of a complete dataset for an individual:

Study Day	SUI	BE +/-	Score	Study Day	SUI	BE +/-	Score
-14	1	+	1	22	0	+	0
-13	0	+	0	23	0		1
-12	0		0	24	1	+	1
-11	1	-	1	25	0		0
-10	0		M	26	0		0
-9	0		0	27	0	+	M
-8	0		0	28	0		0
-7	0		1	29	0		0
-6	1	+	1	30	0		1
-5	1	+	1	31	1	+	1
-4	1	+	1	32	0		0
-3	0		0	33	0		0
-2	0		0	34	1	+	1
-1	1		1	35	0		0
1	0	+	M	36	1	+	1
2	0		0	37	0		0
3	1	-	1	38	1	+	1
4	0		0	39	0		0
5	0		0	40	0		0
6	0	+	M	41	0	+	0
7	0		M	42	0		1
8	0		M	43	0	+	0
9	1		1	44	0		1
10	0		M	45	0	+	M
11	0		M	46	0		0
12	0		0	47	1		1
13	0		0	48	0		0
14	0		1	49	1	+	1
15	1	+	1	50	0	+	0
16	1		1	51	0		0
17	0		0	52	0	-	0
18	0		0	53	0		0
19	0		1	54	0		1
20	0	+	0	55	0	+	M
21	1		1	56	0		M

Concordance rate = 66.7 %; no urine specimen is available on day 57; day 1 is the first day of investigational agent administration.

Notes on Data Quality

Data quality (including double-data entry) was supervised by a master's-level database coordinator and statistician. Individual plots were checked for unusual values and completeness. Efficacy values were validated as correct against case records.

Notes on the Statistical Analysis

In the analysis for the primary outcome variable, we assumed that data were missing at random (MAR). We, therefore, did a sensitivity analysis to examine that premise. Under MAR principles, mixed-effects models would yield consistent estimates, which are preferred over other approaches to handling dropout—eg, last observation carried forward.[1] Since MAR cannot be tested,[2] we investigated the relationship between dropout and longitudinal outcomes by a joint random effects model.[3] In this model, the repeated measures of weekly proportion of cocaine non-use days were modeled by the mixed-effects model above, while the random effects were plugged into the Cox model for time to dropout to link the two models. In both sub-models, we adjusted for the following risk factors: treatment, age of onset, gender, race (white vs nonwhite), weekly mean proportion of cocaine non-use days before randomization, and the frequency of self-reported cocaine use in the 30 days before informed consent. The estimation was implemented in SAS Proc NLMIXED.[4, 5] Such a method was adopted in our previous study.[6] We found that after adjusting for risk factors, the time to dropout did not depend on the random effects from the longitudinal model of proportion of cocaine non-use days (P=.10), indicating that dropout was not informative. We also did multiple testing on the proportionality assumption in the Cox model by including an interaction of log(time) and each risk factor in an individual model, and found that proportionality was not violated for any risk factors. The parameter estimates for the longitudinal outcomes from this joint model were similar to those in the model assuming MAR. This sensitivity analysis provided evidence of the validity of the MAR assumption.

The secondary outcome variable, urinary cocaine-free weeks, was either negative for benzoylecgonine on all three urine specimens collected per week or not (ie, positive)—a binary variable.

For the exploratory outcome variables: a) The Cocaine Selective Severity Assessment subscales were each defined on 3 binary responses. For the subscale measuring the highest intensity of craving in the last 24 hours, subjects rated with "no desire at all" (score=0) were considered to have no craving for cocaine, while subjects with higher scores were considered to have craving. For the subscale measuring the frequency of the urge to use cocaine in the last 24 hours, subjects rated with "never" (score=0) were considered to have no urge for cocaine, while subjects with higher scores were considered to have an urge. Also, subjects rated with both "no desire at all" in the highest intensity subscale and "never" in the frequency subscale were considered not to have severity, while subjects with the other combinations were considered to have severity. b) The Brief Substance Craving Scale for cocaine was defined on 2 binary responses. Subjects were considered to have no craving if subjects were rated with "none at all/never" in all three subscales of intensity, frequency, and duration of craving, while subjects with the other combinations were considered to have craving. For the subscale measuring the intensity of craving on the worst day, subjects rated with "none at all" (score=1) were considered to have no craving, while subjects with higher scores were considered to have craving. c) The Clinical Global Impression-Observer (CGI-O) and Clinical Global Impression-Self (CGI-S) subscales were each defined on 4 binary responses. For the cocaine global severity subscale, subjects rated with "no symptoms" (score=1) or "borderline symptoms" (score=2) were considered not to have clinically significant severity of cocaine dependence, while subjects rated with higher scores were considered to have clinically significant severity. Similarly, for the cocaine global improvement subscales, subjects were considered to have clinically significant improvement if they were rated "very much improved" (score=2) or "much improved" (score=3), while subjects who were rated with higher scores or "not assessed" (score=1) were considered not to have experienced clinically significant improvement. All binary outcome variables were analyzed using a generalized linear mixed-effects model, and the total score of eight specific problems associated with cocaine dependence in the CGI-O scale was analyzed using a linear mixed-effects model. All these models were used to assess the treatment effect, the time effect, and the interaction effect between them, and were adjusted for the same set of covariates described in the primary analysis and the baseline measure of the different outcome variables. A Kaplan-Meier survival analysis was used to determine whether there was any difference in the time to dropout between treatment groups.

All statistical tests done for other variables were specified along with the results.

Significance level was specified using two-tailed tests at .05. All statistical analyses were performed with SAS 9.2 software (SAS Institute, Cary, NC).

Power Analysis

Since the weekly proportion of cocaine non-use days is a quasi-continuous variable, and assuming that it is distributed normally, the treatment effect can be tested with F-tests on means in the analysis of variance and covariance in a repeated-measures model. To be conservative, we have adopted power analysis methods as described in Cohen[7] (see details in Chapter 8). Since there was no prior published study on topiramate treatment of cocaine dependence at the inception of planning for this study, we have estimated the effect size based on Carroll and colleagues'[8] study on the effectiveness of disulfiram for the treatment of individuals dependent on both alcohol and cocaine at increasing the maximum number of weeks abstinent from cocaine (effect size=0.77 for cognitive behavioral treatment and disulfiram versus cognitive behavioral treatment alone; F=7.67, *P*=.007; see Table 2, p. 721). Assuming conservatively an effect size of 0.5 for topiramate versus placebo in the proportion of cocaine non-use days, with a sample size of 140 subjects (70—ie, 50%—in each treatment arm), we have >80% power to detect a significant treatment effect at a two-sided significance level of .05. The effect size index here (f) for the F-test was defined by Cohen[7] as one-half of the effect size for a special case of k=2 populations (f=d/2).

Comparative Table of Retention Rates Across Representative Pharmacotherapy Trials of Medications to Treat Cocaine Dependence over the Last 10 Years

Study	Retention rate at study end
Present study of topiramate for cocaine dependence	60% for topiramate group, 52% for placebo group, 56% overall
Atomoxetine for cocaine dependence (Walsh et al., 2013)[9]	48% for atomoxetine group, 64% for placebo group, 56% overall
Modafanil for cocaine dependence (Dackis et al., 2012)[10]	61% for modafanil group, 49% for placebo group, 57% overall
Vigabatrin for cocaine dependence (Brodie et al., 2009)[11]	62% for vigabatrin group, 42% for placebo group, 51% overall
Baclofen for cocaine dependence (Kahn et al., 2009)[12]	67% overall
Tiagabine for cocaine dependence (Winhusen et al., 2007)[13]	54% for tiagabine group, 58% for placebo group, 56% overall
Ondansetron for cocaine dependence (Johnson et al., 2006)[14]	47% for ondansetron 4 mg group, <35% for ondansetron 1 mg + ondansetron 0.25 mg + placebo groups
Gabapentin for cocaine dependence (Bisaga et al., 2006)[15]	52% overall
Selegiline for cocaine dependence (Elkashef et al., 2006)[16]	65% for selegiline group, 73% for placebo group, 69% overall
Disulfiram for cocaine dependence (Carroll et al., 2004)[17]	47% overall
Baclofen for cocaine dependence (Shoptaw et al., 2003)[18]	26% for baclofen group, 23% for placebo group, 24% overall

Comments Pertaining to Future Trials

We speculated about two possible modalities whereby topiramate's therapeutic effects in treating cocaine dependence could be augmented in future clinical trials. First, we have hypothesized that the addition of another medication such as ondansetron, a 5-HT_3 receptor antagonist that has shown promise in treating cocaine dependence,[14] might result in an added or synergistic therapeutic effect. Second, we have proposed that a personalized approach whereby those with a notable amount of adverse events could be excluded from participation, or specific genotypes associated with an enhanced therapeutic response could be identified, or both, could help to identify "high responders" to treatment. We are pursuing both possibilities actively.

Because topiramate has been shown to be efficacious treatment for alcohol dependence,[19, 20] and now in cocaine-dependent individuals, some of whom were comorbid for alcohol abuse or dependence, it would be important to determine formally whether it has utility in treating comorbid alcohol and cocaine dependence. Furthermore, it would be of interest to determine whether topiramate has a wider potential to treat other substance-use disorders besides those already proposed, which also include treating smoking in individuals with comorbid alcohol dependence[21] and preventing relapse in methamphetamine addicts.[22]

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