Topiramate for Cocaine Dependence: A Systematic Review and Meta-Analysis of Randomized Control Trials.

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Abstract

Aims: To assess the efficacy of topiramate in treating cocaine use disorder (i.e., retention, efficacy, safety, and craving reduction) through a systematic review and meta-analysis.

Methods: We searched six scientific databases from inception to December 23, 2014 with no date limits. Data were systematically reviewed, extracted and analyzed. Studies were included if they were peer-reviewed randomized control trials with participants meeting diagnostic criteria for cocaine dependence or cocaine use disorder, with the treatment arm involving topiramate with or without psychosocial intervention, and the control arm involving no intervention or psychosocial intervention with or without placebo. A random-effects meta-analytic model was computed.

Results: Five studies met inclusion criteria (n = 518). Topiramate was compared with placebo (4 studies), and no medication (1 study). In a meta-analysis, we observed no significant differences between topiramate and placebo in improving treatment retention (risk ratio [RR] = 0.84; 95% Confidence Interval [CI]: 0.67-1.05, p = 0.12). However, compared with a placebo, use of topiramate was associated with increased continuous abstinence in two of five studies (RR = 2.52; 95% CI: 1.35-4.73, p = 0.004). No differences were observed in frequency of adverse effects reported between topiramate and placebo (RR=1.03; 95% CI = 0.87-1.23, p=0.72). Topiramate was significantly associated (p<0.05) with a reduction in craving in only one of five studies.

Conclusions: Evidence does not currently support the use of topiramate to improve treatment retention for cocaine use disorder, though it may extend cocaine abstinence with a similar risk of adverse events compared with placebo.

Word Count: 249
1. Introduction

Cocaine use disorder is reported at high levels globally, and is associated with a range of health and social harms, including stroke, cardiac abnormalities and risk of HIV infection among others (1,2). Worldwide, cocaine is used by over 14 million people (3). It is the illegal substance that is associated with the highest prevalence of visits to American hospital emergency departments (4).

Currently, there are no FDA approved, evidence-based pharmacological treatment options for individuals experiencing cocaine use disorder (5). Due to the limited pharmacological options for treating cocaine use disorder, psychosocial interventions remain the standard of care (7). To that end, while cognitive behavioral therapy (CBT) has demonstrated limited effectiveness in decreasing dropout from treatment and use of cocaine, reported relapse rates remain high with any single psychosocial therapy (8).

There is robust evidence that dopamine increases in the mesocorticolimbic system as a result of cocaine use are responsible for the addictive effects of this substance (9). However, medication directly modulating the dopamine system has not been useful in decreasing cocaine use (10). Other neural pathways may also partially account for cocaine’s addictive potential.

GABA and Glutamate are the main inhibitory and excitatory neurons in the brain and are indirectly involved in modulating the effects of the dopamine release in the reward pathway of the brain (5). Glutamatergic neuronal connections to the nucleus accumbens as well as alterations in glutamate synaptic transmissions are associated with relapse to drug use (6). Thus, medications that increase GABA neuronal activity or regulate glutamate have the potential to be effective in managing cocaine use disorder by mitigating dopamine release, reward and relapse. Indeed, this is the mechanism by which anticonvulsant medications, such as carbamazepine, gabapentin and topiramate are hypothesized to work in the context of
substance use disorder (11,12). Topiramate has demonstrated positive effects in the treatment of alcohol dependence and some promise in methamphetamine use disorder (13,14). Therefore, there has been growing interest in this medication for treatment of stimulant dependence, and in particular for managing crack cocaine and cocaine dependence (15).

In 2011, the Cochrane Collaboration Group presented a review of Anticonvulsants for Cocaine Dependence (12). Overall, the authors did not find evidence to support the use of anticonvulsants as a group compared with placebo. However, there was a positive group-by-time effect observed in one study of topiramate (14). Findings such as this have reinforced interest in the therapeutic effect of this medication for cocaine addiction. Since the publication of this review, additional clinical trials have examined the role of topiramate in cocaine use disorder. However, no recent systematic assessments specifically investigating the efficacy of Topiramate have been undertaken.

This systematic review and meta-analysis therefore identifies, summarizes and analyzes current scientific evidence on the efficacy of topiramate for the treatment of cocaine use disorder. We therefore sought to assess the effect of topiramate therapy on (1) treatment retention (2) efficacy (3) safety and (4) craving reduction in cocaine use disorder through a systematic review and meta-analyses of randomized control trials (RCTs).

2. Methods

We employed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for this study (16).

2.1 Search strategy and inclusion criteria

All English-language, scientifically peer-reviewed studies were eligible for inclusion. Six electronic databases were searched across all available dates to obtain relevant trials: The Cochrane Drugs and Alcohol Group Specialized Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE CINAHL, PsycINFO and PubMed. These databases
were searched by combining selected MeSH terms and free-text terms related to cocaine
dependence and use disorder: cocaine (abuse or dependence or disorder or addiction) AND
topiramate. We also searched the main electronic sources of ongoing trials: The ISRCTN
registry (http://www.isrctn.com/), Clinical Trials.gov (www.clinicaltrials.gov/), International
Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en), and Trialsjournal.com.
References of all relevant papers were reviewed to identify further studies of relevance.
When needed, authors of potentially relevant studies were contacted for further information.

Studies were included if they met the following criteria: 1) studies were scientifically peer-
reviewed; 2) they employed RCT methods (with no requirement for blinding); 3) participants
met diagnostic criteria for cocaine dependence or cocaine use disorder as defined in the
DSM-IV or DSM-V manuals with or without a concurrent disorder; 4) treatment was defined
as topiramate with or without a psychosocial intervention; and 5) control conditions were
defined as placebo medication only, or psychosocial intervention with or without placebo
medication, regardless of other concurrent treatment and 6) outcomes assessed included
treatment retention, efficacy (i.e., any measure of change in cocaine use), adverse events and
craving reduction.

2.2 Outcome Measures

The following outcomes were assessed: 1) treatment retention was measured via
dropout rates; 2) efficacy was defined as continuous abstinence in the final three weeks of the
study period, or the number of weeks of cocaine free urine, or as a percentage of cocaine
negative urine samples per treatment condition, or via self-reported mean cocaine use days in
the previous month; 3) safety was measured by the number of participants reporting adverse
events related to use of topiramate; and 4) craving reduction was assessed through subjective
reduction of cocaine craving rating scale scores, specific to each study. These outcomes were
assessed among the studies during varied time periods ranging from 4-13 weeks depending
on study length. The level of statistical significance to assess differences between treatment and control groups was set *a priori* at $p < 0.05$.

It is noteworthy that with the new terminology changes in the Diagnostic Statistical Manual (DSM-V), cocaine abuse and dependence have been combined into cocaine use disorder, which is measured on a scale from mild to severe. Although imprecise, cocaine dependence equates to moderate to severe cocaine use disorder and cocaine abuse is similar to the mild subtype (18,19).

2.3 Data extraction

All citations identified by search were independently screened based on title and abstract by two reviewers (DK, MS). Each potentially relevant study was reviewed in full text and assessed for all inclusion criteria. Any disagreements were resolved by discussion among reviewers (DK, MS) and additional investigators (JK, DW). Relevant data from eligible articles (sociodemographics, type of interventions, outcomes) were then extracted.

2.4 Quality Assessment

Study quality was assessed according to the criteria indicated in the Cochrane Handbook for Systematic Reviews of Interventions (17). Each study was assessed for risk of bias in random sequence generation and allocation concealment (i.e., selection bias). Blinding of participants and personnel (i.e., performance bias) and of outcome assessment (i.e., detection bias) was measured. Incomplete outcome data (i.e., attrition bias) was recorded for each eligible study. Each category of bias was assigned a rating of low, high or unclear risk using protocols from the Cochrane Handbook.

2.5 Analysis

For the meta-analysis, dichotomous outcome measures (e.g., treatment retention, continuous abstinence, and adverse events) were analyzed by calculating the risk ratio (RR) for each trial, with uncertainty in each result expressed via 95% confidence intervals (CIs).
Continuous outcomes (e.g., percentage of cocaine-positive urine samples, urinary cocaine free weeks, level of cocaine craving) were analyzed by calculating the mean difference (MD) between experimental and control groups. Weighted mean differences and 95% CIs were calculated by comparing and pooling mean score differences from the end of treatment to baseline for each group. If outcomes were reported in less than two studies, a meta-analysis was not computed due to lack of data.

Information on missing data was collected where possible from study authors. If study authors were unable to supply this information, missing data were obtained or calculated from values in the primary studies according to suggested procedures in the Cochrane Handbook for Systematic Reviews of Interventions (17).

Given the expected heterogeneity of results among studies due to differences in populations and in types of interventions, we employed a random-effects meta-analytic model. The I-squared ($I^2$) statistic was employed to test the presence of heterogeneity between trials.

3. Results

We identified 273 potentially eligible studies in the peer-reviewed literature. After removal of duplicates and application of the inclusion criteria (Figure 1), five studies ($n = 518$) were found eligible for review (16,20-22,25). Four studies were excluded either because they were not an RCT (26), treatment was not exclusive to topiramate with or without a psychosocial intervention (27), the study design involved an in-patient laboratory setting (28), or the study publication did not report outcome data (29).

All participants in the included studies met the DSM-IV or V diagnostic criteria for cocaine dependence or use disorder, with cocaine and/or crack cocaine use; 71% were male; mean age 42.9 years. The mean duration of trials was 13 weeks (range 12 to 18 weeks). The mean dose of topiramate provided to participants was 260 mg/day. Four studies assessed
topiramate vs. a placebo, with both groups receiving psychosocial intervention. One study compared topiramate plus psychosocial intervention vs. psychosocial intervention alone. All five studies were conducted in outpatient setting.

Quality assessments for each study are presented in Table 1. All studies were found to carry a low risk for selection bias. There was a mixed risk of bias relating to blinding of participants and outcome assessments, which was particularly pronounced in the only open label randomized study included (25). There is unclear risk for attrition bias in all studies except one in which the risk was high (16). Treatment retention was assessed via the dropout rate in all four studies comparing topiramate vs. placebo (16,20-22) and as attendance of CBT sessions in one study comparing topiramate vs. psychosocial intervention alone (25).

With respect to measures of cocaine use, the number of participants with continuous abstinence was reported in two studies (16,20). Urinary cocaine-free weeks (20), percentage of cocaine-negative urine samples (22), and the average days of self-reported cocaine use in the previous 30 days (25) were each available from one study.

Adverse events, expressed as the proportion of participants experiencing unexpected or dangerous effects in the experimental or control groups, were reported in all studies (15,20-22,25).

Measures of craving using various rating scales were used in all five studies (16,20-22,25).

3.1 Systematic Review Results

Kampman et al., 2004 gradually increased topiramate over an 8-week period (0-200mg/day) in Pennsylvania, USA. This resulted in significantly more cocaine abstinence measured by negative urine toxicology over a 3-week period between weeks 8-13 in favor of topiramate ($p <0.05$). However, treatment retention did not differ between groups ($p = 0.96$). Craving was assessed using the Brief Craving Scale, and decreased in both groups without
significant difference ($p = 0.11$). Adverse events were characterized as mild and equally distributed between groups.

Kampman et al. (21) conducted a 13-week study with cocaine and alcohol dependent participants in Pennsylvania, USA. Patients were abstinent before being randomized and titrated on topiramate, up to 300mg daily. Topiramate was not found to be significantly more efficacious in reducing cocaine use ($p = 0.16$) and craving (Minnesota Cocaine Craving Scale) compared to a placebo. However, the topiramate group was more likely to be retained in treatment ($p = 0.04$) and showed significantly higher levels of abstinence from cocaine use in the final three weeks of the trial ($p = 0.01$) compared with the control group. Adverse events were mild and evenly distributed across groups ($p > 0.05$).

Johnson et al. (20) conducted a 12-week study in which topiramate was titrated up to a maintenance dose of 300mg/day in Virginia, USA. An intent-to-treat analysis demonstrated that topiramate was significantly more effective in increasing cocaine non-use days and urinary cocaine free weeks compared with placebo ($p = 0.02$). Also, the authors observed a decrease in craving as measured via the Brief Substance Craving & Cocaine Selective Severity Assessment Scale ($p < 0.05$), but no improvement in treatment retention among the topiramate group vs. the control group ($p = 0.40$). No difference in frequency of adverse events were observed between groups ($p = 0.66$) and no serious events (i.e., deaths) were reported.

Umbricht et al. (22) studied cocaine dependent methadone maintenance patients in Maryland, USA. Participants were randomly allocated into four groups, in which participants received money vouchers contingent or non-contingent on drug abstinence in addition to either topiramate or placebo. Major outcomes were assessed over a 12-week period with patients on 300mg/day of topiramate. Authors found no significant differences between topiramate and placebo in terms of treatment retention ($p = 0.44$), cocaine abstinence, which
was measured as percentage of cocaine negative urine samples ($p = 0.54$), or craving as measured via the Cocaine Selective Severity Assessment Scale ($p > 0.05$), regardless of contingency method employed. The authors concluded that topiramate is safe but ineffective at managing cocaine dependence.

Nuijten et al. (25) evaluated Topiramate in a 12-week open label trial, titrating up to a dose of 200mg/day in The Hague, Netherlands. The intent to treat analysis did not show improvement in treatment group retention ($p = 0.15$) or reduced cocaine use ($p = 0.23$) or craving as measured via the adapted Obsessive Compulsive Drinking Scale ($p > 0.05$) vs. the control group. Also, in the treatment group, 72% vs. 13% of controls reported adverse effects; however, none were recorded as serious. The majority of adverse events were classified as transient or mild, i.e., paresthesias, non-severe gastro-intestinal complaints and fatigue.

### 3.2 Meta-analysis Results

The meta-analytic results of topiramate vs. placebo are presented below. It was not possible to convert all data reported on outcomes into meta-analysis due to variance in reported data.

Because only one study reported on the efficacy of topiramate vs. a psychosocial intervention alone (25), meta-analytic results for this outcome were not computed.

#### 3.2.1 Treatment retention

Acceptability of treatment was measured via participant dropout. Dropouts were assessed in four studies (16,20-22) with 444 participants (note: for the Umbricht et al. study, only data from participants in the non-contingency management arm were included in the meta-analysis [$n = 92$]). As shown in Figure 2a, the results of the meta-analysis suggest that the mean difference in dropouts was not statistically significant between participants in the topiramate vs. control groups, while moderate heterogeneity between studies was observed.
As shown in Table 1, one study reported a particularly high risk of attrition bias for this outcome (16).

3.2.2 Efficacy of topiramate

As shown in Figure 2b, a two-study meta-analysis (16,20) that included data from 210 participants demonstrated significant positive impacts of topiramate on abstinence from cocaine use for three weeks or longer. Because other measures of topiramate efficacy (i.e., percentage of cocaine negative urine samples per treatment condition, self-reported mean cocaine use days in the previous month) were not reported across all studies or were assessed using different statistical methods, they were not amenable to investigation via meta-analysis.

3.3.3 Adverse effects

Two studies (20,22) pooled data from 234 participants, and meta-analytic results (Figure 2c) demonstrated no significant increase in the frequency of adverse events among those assigned to topiramate vs. a control group.

3.3.4 Craving

Craving reduction was not amenable to meta-analysis as there was substantial variation in cocaine craving rating scales used. Overall, there was an improvement in subjective craving scores with topiramate in one study (n = 142) (20), though we caution that no significant effect or craving reduction was found in four other studies (n = 302) (16,21,22,25).

4. Discussion

The results of the present systematic review and meta-analyses suggest that limited evidence exists suggesting that topiramate is efficacious in the treatment of cocaine use disorder. As such, and given the limited number of RCTs that we identified, there is not at present sufficient evidence supporting the routine clinical use of topiramate to improve patient retention or long-term treatment of cocaine use disorder. Existing scientific data
suggest, however, that topiramate may improve abstinence from cocaine at high dose ranges between 200-300 mg daily. For example, continuous abstinence increased significantly among participants assigned to topiramate vs. a control condition in two studies (16,20) while a third study reported a similar pattern of cocaine abstinence as assessed via an increase in cocaine urinary free weeks (20).

One explanation for negative findings in the literature may be attributable to the study design and population differences in the US (16,20-22) and Dutch (25) studies. Higher levels of baseline cocaine use, a lower maximal dose of topiramate (200mg/day), in addition to a shorter titration period over 3 weeks used by Dutch researchers rather than the minimum 8 weeks used by US studies may contribute to the disparity in results.

Topiramate has been associated with reduced alcohol intake (23) and often cocaine and alcohol use disorders co-occur (24). Co-morbid alcohol and cocaine dependence was analyzed in only one study (20). The authors note that low baseline use of alcohol in their sample may have contributed to the lack of positive results noted. In addition, the study population was not screened for DSM-IV alcohol dependence criteria, limiting application of findings in this study.

Adverse events were no higher in the treatment population enrolled in topiramate compared with placebo treated groups. Slow titration over several weeks may be a possible explanation for this finding. In all studies, no adverse events were characterized as serious, and were often described as mild. Although this suggests that topiramate may be a safe medication for cocaine use disorder, titrating patients up to high doses while mitigating adverse events and treatment retention is challenging and may take several weeks to months given the gradual titration this medication requires (30,31) This places into question the practicality of topiramate as a treatment in marginalized stimulant-using populations (32-34).

It is also noteworthy that the positive effects of topiramate were reported among
participants provided with ongoing CBT. This effect has been observed previously by Kim & Lawrence (5), who propose that the success of topiramate as a medication for stimulant use disorder hinges on cocaine-dependent participants also receiving CBT. It is thought that the inhibitory learning processes of CBT are mediated through γ-aminobutyric acid (GABA) potentiation (35). As topiramate works by increasing GABA levels, it may therefore synergistically enhance the effects of CBT on abstinence (5).

The results presented in the present systematic review and meta-analysis should be considered in context of the following limitations. First, there is a very small scientific literature base regarding the efficacy of topiramate in managing cocaine use disorder. Second, although the methodological quality of the included RCTs was generally high, the sample sizes were quite small. Third, in spite of a comprehensive bibliographic search, all but one of the 5 included studies were conducted in the USA, which may limit the generalizability of the results. Fourth, outcome measures were not uniformly reported across studies and, therefore, were difficult to combine in a meta-analysis. Cocaine abstinence was amenable to meta-analysis as it was reported in a consistent manner by multiple studies (16,20). In these studies, cocaine abstinence is defined as no use across the last 3 weeks of the study. However, as the same authors report (16,20), generalizability is limited and these two studies reported greatly discordant results: 50% vs. 20% abstinence, respectively. In addition, of the three studies that we were unable to include in the meta-analysis as a result of differences in measured outcomes, one reported a finding of efficacy while two did not, suggesting overall that the data on the efficacy of Topiramate is mixed. Given that Topiramate therapy requires a slow titration of up to a month or longer to achieve effective dosage, this outcome may not capture those patients who cannot tolerate the full dose required. In addition, the results do not capture those who may have benefited from a lower dose. Finally, with respect to study quality, we identified a risk of bias related to inconsistent blinding of participants, as well as
an unclear level of risk of attrition bias across studies. Given these multiple potential sources of bias, our findings should be interpreted with caution. These findings also suggest that future studies seeking to identify the effectiveness of Topiramate in treating cocaine use disorder should address a priori these potential sources of bias to ensure a minimum level of quality in this emerging research area.

As such, further research is required to improve our understanding of the efficacy of topiramate in the treatment of cocaine use disorder. Indeed, researchers are encouraged to pursue larger randomized investigations analyzing relevant standardized outcomes following the use of topiramate (e.g., number of total negative urine screens or longest duration of cocaine abstinence) to enable meaningful contributions to clinical practice. In addition, the mental health of patients was measured as a secondary outcome by various different scales, such as the Hamilton Depression Rating Scale. However, the relationship between topiramate use and impact on mental health scores should be explored further (36). In conclusion, the sum of the studies undertaken to date suggest that topiramate is associated with both positive and negative outcomes among patients with cocaine use disorders. In the absence of consistent evidence, clinicians must balance the possible benefits of this treatment against its potential limited efficacy.

Acknowledgements

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References


30. Johnson BA. Recent advances in the development of treatments for alcohol and cocaine dependence: focus on topiramate and other modulators of GABA or glutamate function. CNS Drugs. 2005;19(10):873-96.


Figure 1. Flow diagram of study selection process

Records identified through database searching (n = 273)

Additional records identified through other sources (n = 5)

Records after duplicates removed (n = 214)

Records screened (n = 210)

Records excluded (n = 201)

Full-text articles assessed for eligibility (n = 9)

Full-text articles excluded as did not meet inclusion criteria (n = 4)

Studies included in qualitative synthesis (n = 5)

Studies included in quantitative synthesis (meta-analysis) (n = 5)
Figure 2: Forest Plot: Meta-Analysis

a) Treatment Retention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tr>
<td>Johnson et al. 2013</td>
<td>26</td>
<td>71</td>
<td>97</td>
<td>0.79</td>
<td>[0.52, 1.21]</td>
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<tr>
<td>Kampman et al. 2004</td>
<td>3</td>
<td>20</td>
<td>23</td>
<td>0.63</td>
<td>[0.41, 0.93]</td>
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</tr>
<tr>
<td>Kampman et al. 2013</td>
<td>26</td>
<td>87</td>
<td>113</td>
<td>0.67</td>
<td>[0.47, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Umbach et al. 2014</td>
<td>21</td>
<td>41</td>
<td>62</td>
<td>1.22</td>
<td>[0.88, 1.68]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>225</strong></td>
<td><strong>219</strong></td>
<td><strong>444</strong></td>
<td></td>
<td><strong>0.85 [0.60, 1.22]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 444

Heterogeneity: Test (Q) = 7.52, df = 3 (P = 0.08); I² = 69%
Test for overall effect: Z = 0.88 (P = 0.39)

b) Continuous Abstinence

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td>Kampman et al. 2004</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>2.90</td>
<td>[1.29, 6.01]</td>
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</tr>
<tr>
<td>Kampman et al. 2013</td>
<td>17</td>
<td>83</td>
<td>100</td>
<td>2.97</td>
<td>[1.23, 7.17]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>107</strong></td>
<td><strong>107</strong></td>
<td><strong>214</strong></td>
<td></td>
<td><strong>2.43 [1.31, 4.53]</strong></td>
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</tr>
</tbody>
</table>

Total events: 214

Heterogeneity: Test (Q) = 0.00, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.05)

c) Adverse Effects

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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</thead>
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<tr>
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<td>50</td>
<td>71</td>
<td>121</td>
<td>1.05</td>
<td>[0.90, 1.23]</td>
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<tr>
<td>Umbach et al. 2014</td>
<td>5</td>
<td>45</td>
<td>50</td>
<td>1.31</td>
<td>[0.87, 1.96]</td>
<td></td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>116</strong></td>
<td><strong>118</strong></td>
<td><strong>234</strong></td>
<td></td>
<td><strong>1.06 [0.91, 1.23]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 234

Heterogeneity: Test (Q) = 0.00, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)
### Table 1: Characteristics of included studies

<table>
<thead>
<tr>
<th>Study/County</th>
<th>Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Risk Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kampman 2004 USA</td>
<td>Randomized, placebo controlled, double blind</td>
<td>N=40&lt;br&gt;Mean age 40 years&lt;br&gt;Male 97.5%&lt;br&gt;African American 90%&lt;br&gt;Caucasian 10%&lt;br&gt;Use of cocaine in the previous month: mean 7&lt;br&gt;Route of cocaine ingestion: intranasal 12.5%, smoked 87.5%.&lt;br&gt;Substance abuse and mental health exclusion criteria: Current dependence (DSM IV) on any additional drug except nicotine; psychosis, dementia, use of psychotropic medication</td>
<td>1) Topiramate + Psychosocial&lt;br&gt;Starting dose 25 mg/day increased to 200 mg/day by week 8.&lt;br&gt;(2) Placebo + Psychosocial</td>
<td>Study retention&lt;br&gt;Compliance&lt;br&gt;Adverse effects&lt;br&gt;Use of cocaine</td>
<td><img src="chart.png" alt="Risk Rating" /></td>
</tr>
<tr>
<td>Kampman 2013 USA</td>
<td>Randomized, placebo controlled, double blind</td>
<td>N=170&lt;br&gt;Mean age 44 years&lt;br&gt;Male 79%&lt;br&gt;African American 82.94%&lt;br&gt;Caucasian 17%&lt;br&gt;Use of cocaine in the previous 30d: mean 12.7&lt;br&gt;Route of cocaine ingestion: oral 1%, nasal 21%, smoking 77.4%, injection 0.5%.&lt;br&gt;Substance abuse and mental health exclusion criteria: Current dependence (DSM-IV criteria) on any additional drug except nicotine and cannabis; psychosis, dementia, and the use of other psychotropic medications</td>
<td>1) Topiramate + Psychosocial&lt;br&gt;Starting dose 25 mg/day increased to 300 mg/day by week 8.&lt;br&gt;(2) Placebo + Psychosocial</td>
<td>Study retention&lt;br&gt;Compliance&lt;br&gt;Adverse effects&lt;br&gt;Primary outcome&lt;br&gt;Weekly self-reported by Timeline Follow back, UBT results&lt;br&gt;Secondary outcome&lt;br&gt;Previous 30 day measures of days of cocaine use, other drugs, money spent to obtain etc.&lt;br&gt;Minnesota Cocaine Craving Scale&lt;br&gt;Overall cocaine withdrawal symptoms (CSSA).</td>
<td><img src="chart.png" alt="Risk Rating" /></td>
</tr>
<tr>
<td>Study</td>
<td>Randomization</td>
<td>Placebo controlled</td>
<td>Double blind</td>
<td>Outpatient duration:</td>
<td>Patient characteristics</td>
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<tr>
<td>Johnson</td>
<td>Randomized, placebo controlled, double blind</td>
<td>USA</td>
<td>Outpatient duration: 12 weeks</td>
<td>N=142</td>
<td>Mean age 43.7 years; Male 72.5%; Black 70.4%; White 28.9%; Asian 0.7%</td>
</tr>
<tr>
<td>Nuijten</td>
<td>Randomized, Non-placebo controlled, Open-label</td>
<td>Netherlands</td>
<td>Outpatient duration: 12 weeks</td>
<td>N=74</td>
<td>Mean age 42.3 year Male 81.6% European background 63.5%</td>
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<tr>
<td>Risk Rating Legend:</td>
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<tr>
<td>A: Random sequence generation (selection bias)</td>
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<td>B: Allocation concealment (selection bias)</td>
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<td>C: Blinding of participants and personnel (performance bias)</td>
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<td>D: Blinding of outcome assessment (detection bias)</td>
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<td>E: Incomplete outcome data (attrition bias)</td>
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<tr>
<td>Green Circle: Low Risk</td>
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<td>Red Circle: High Risk</td>
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<tr>
<td>Amber Circle: Insufficient data for analysis – Unclear Risk</td>
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</tbody>
</table>

| Umbricht 2014 USA | N=171  
Mean age (±SD) 42 ± 7 years old  
60% African American  
48% females  
Median CSSA score: 28  
No differences in baseline cocaine craving (CSSA > 20) between groups  
21% in methadone maintenance prior to study  
Substance abuse and mental health exclusion criteria: Current benzodiazepine dependence; serious psychiatric illness | Topiramate induction: 7 weeks  
Stabilized at 300 mg/day: 8 weeks Tapered: final 3 weeks  
Contingency Management (CM): Monetary voucher incentives contingent on drug abstinence  
Voucher incentives supplied for 12 weeks  
Non-CM: Monetary voucher incentives not contingent on drug abstinence | Primary outcome measures: Cocaine abstinence, based on urine sample result  
Treatment retention: Weeks between study admission and discharge or dropout  
Secondary outcome measures: Percentage of participants achieving 3 consecutive weeks of cocaine abstinence  
Adverse events  
Opioid use based on urine toxicology testing  
Weekly self-reports of cocaine, alcohol, cigarette and other drug use (TLFB)  
Cocaine craving (CSSA) |