Trends
in Psychiatry and Psychotherapy

JOURNAL ARTICLE PRE-PROOF
(as accepted)

Review Article

Topiramate Therapy in Cocaine Use Disorder: A Systematic Review and meta-analysis of Randomized Controlled Trials

Sridevi Shanmugam, Saravana Arunkumar, Vishal Agrawal, Praveen Kumar

http://doi.org/10.47626/2237-6089-2025-1117

Original submitted Date: 05-Jun-2025

Accepted Date: 22-Sep-2025

Topiramate Therapy in Cocaine Use Disorder: A Systematic Review and meta-analysis of Randomized Controlled Trials

Short Title: Topiramate Therapy in Cocaine Use Disorder

Sridevi Shanmugam[1], Saravana Arunkumar[2], Vishal Agrawal[1], Praveen Kumar[3]

[1]Department of Psychiatry, Essex Partnership University NHS Foundation trust, Essex, United Kingdom.
[2]Department of Emergency Medicine, Mid and South Essex NHS Partnership Trust, East of England, United Kingdom.
[3]Department of Psychiatry City Hospital, Aberdeen, United Kingdom.

Corresponding Author:
Dr Sridevi Shanmugam
General Adult Psychiatry Registrar, Department of Psychiatry
Essex Partnership University NHS Foundation trust, Essex, United Kingdom
Email ID: sridevi.shanmugam@nhs.net
Contact Number 044 7459115472

Abstract

Background: Despite the global burden of cocaine use, no pharmacological agent has received regulatory approval for the treatment of cocaine use disorder (CUD). This study aims to systematically evaluate efficacy and safety of topiramate, with a focus on its impact on treatment retention, cocaine use and abstinence, craving reduction, and safety in individuals diagnosed with CUD.

Methods: To identify all relevant studies, a comprehensive search strategy was employed across several electronic databases. The search strategy focused on terms related to CUD and topiramate from January 1, 2000, to December 31, 2024. Eligible studies included randomized controlled trials comparing topiramate with placebo, standard treatments, or non-pharmacological interventions.

Results: Ten studies were included in the current review. Meta-analysis revealed a statistically significant benefit of topiramate compared to control in promoting cocaine abstinence (Risk Ratio [95% Confidence Interval] = 2.83 [1.68–4.76]; $p<0.05$). However,

no statistically significant difference was observed between topiramate and control groups regarding craving reduction (standardized mean difference = -0.28 [-1.92-1.36]). Overall, treatment retention outcomes across the included studies were mixed favoring topiramate with no statistical difference between two cohorts in dropout rates (RR = 0.94 [0.69 - 1.28]). The risk of adverse events was comparable between the topiramate and control groups (RR = 1.06 [0.91–1.23]; p = 0.44).

Conclusion: Topiramate may aid early abstinence and reduce cocaine use in individuals with CUD, with generally favorable treatment retention and tolerability. However, its effect on craving reduction appears limited, and further robust studies are needed to confirm its long-term efficacy and safety.

Registration Number: PROSPERO 2025, CRD420251021915

Keywords: Topiramate, cocaine use disorder, cocaine abuse, abstinence, treatment retention.

Introduction

Cocaine use disorder (CUD) defined as the compulsive use of cocaine despite significant medical, psychological, and behavioral consequences, is a chronic and relapsing condition with substantial public health implications.[1]Globally, cocaine remains one of the most widely abused illicit substances. Several US-based epidemiological analyses have reported increasing prevalence of both cocaine consumption and CUD across adult and adolescent populations[2–4], with drug overdose-related mortalities increasing from 8.2 fatalities per 100,000 individuals in 2002 to 32.6 in 2022.[5]Approximately 2.1% of the UK population aged 16-59 years used cocaine between March 2023 and 2024. The consumption was higher among adolescents, with 3.8% using cocaine in the 16-24 age group.[6] In 2020, The United Nation had reported a 36% increase in the incidence of CUD-related deaths, coinciding with the COVID-19 pandemic.[7] Chronic cocaine use poses physiological harm resulting in malnutrition, bowel necrosis, increased susceptibility to blood-borne infections (HIV and hepatitis C), and Parkinson's disease.[8] Cocaine overdose may also lead to life-threatening events such as seizures, heart attacks, and

cardiovascular accidents.[8] Given the medical and societal burden associated with CUD, the development of effective interventions for treatment and mitigating adverse outcomes of CUD remains an urgent public health priority.

Efforts to identify a viable pharmacotherapy for CUD are a longstanding priority for the National Institute on Drug Abuse, for the last 40 years.[9] Even after the evaluation of over 64 pharmaceutical agents across more than 100 clinical trials, the Food and Drug Administration has not sanctioned a medication targeting this condition.[10,11] However, among these trials, topiramate has demonstrated potential therapeutic benefits, with clinical studies reporting increased abstinence rates in CUD patients, irrespective of baseline cocaine use status.[12] Such findings have intensified the interest of researchers in the efficacy of topiramate for CUD management, and whether it is a suitable candidate for pharmacotherapy.

There remains a significant gap in access to evidence-based psychosocial programs, such as cognitive-behavioral therapy, contingency management and other structured behavioral interventions. There are several barriers to the limited reach of psychosocial programs, such as insufficient infrastructure, the lack of standard treatment protocols, prolonged waiting times, and a lack of or restricted access to specialized addiction services for patients with co-occurring mental health disorders.[13] The high cost, and shortage of trained clinicians further constrain service provision.[13] Furthermore, a substantial proportion of individuals, even after undergoing psychosocial therapy, continue to engage in cocaine consumption.[14] In this context, topiramate represents a feasible pharmacological option with potential use in CUD treatment.[15] However, topiramate should be viewed primarily as an adjunct that may facilitate abstinence and craving reduction.

Topiramate is FDA-approved for treating seizures, preventing migraine, and managing chronic weight (as combination therapy with phentermine). It is also prescribed for managing epilepsy and migraine in the UK.[16] However, topiramate is not approved for use in patients CUD. Topiramate has been shown to reduce extracellular dopamine release in the brain, a process critical to the reinforcement and reward mechanisms

associated with cocaine use.[17,18] This dopaminergic attenuation is a downstream consequence of its primary mechanism of action i.e. enhancement of Gamma-Aminobutyric Acid (GABA)ergic inhibition and antagonism of AMPA/kainate glutamate receptors.[17-19] Additionally, the anxiolytic properties of topiramate contribute to its therapeutic efficacy. Johnson et al. (2013) reported that topiramate reduces the reinforcing effects of high-dose cocaine, promoting sustained abstinence.[20] Clinical trials have reported favorable efficacy and safety of topiramate in treating cocaine dependence in patients.[21,22] While preliminary evidences suggest that topiramate may offer clinical benefit in the treatment of CUD, the current body of evidence is of moderate quality. Further high-quality clinical studies will be important to clarify its place in stimulant addiction care.

To further evaluate the efficacy and safety of topiramate in the management of CUD, a systematic review and meta-analysis were previously conducted. However, the limited number of studies and small sample sizes restricted the generalizability of the findings.[18]A more recent review by Nourredine et al. (2021) assessed the role of topiramate across multiple substance use and eating disorders, with partial consideration of its effects on CUD.[19] To address these limitations, the present systematic review and meta-analysis provides an updated evaluation of the available evidence on topiramate in patients with CUD. This study focuses on key clinical outcomes reported in randomized controlled trials (RCTs), including treatment retention, reduction in cocaine use, adverse effects, and craving reduction. By offering a comprehensive assessment of topiramate's therapeutic impact, the review aims to inform and support clinical decision-making in the management of CUD.

Methodology

This systematic review and meta-analysis was conducted in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[23] The review protocol was prospectively registered in the International

Prospective Register of Systematic Reviews (PROSPERO) under the registration number ID CRD420251021915.

Study objectives:

This study aims to evaluate key clinical outcomes from RCTs on the use of topiramate in the treatment of CUD, including treatment retention, reduction in cocaine use, adverse effects, and craving reduction. The goal is to provide evidence that supports informed clinical decision-making in the management of CUD.

Search Strategy

To identify all relevant studies, a comprehensive search strategy was employed across several key electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE (via Ovid), and PubMed. In addition to the electronic database search, we manually screened the reference lists of previously published original research articles, systematic reviews, and meta-analyses relevant to the topic. Furthermore, a manual search of the reference lists of all included studies was performed to ensure comprehensive coverage and to identify any additional eligible studies that may have been missed during the initial search.

The search strategy focused on terms related to CUD and topiramate from January 1, 2000, to December 31, 2024, to capture the most recent evidence. The primary search string incorporated a combination of controlled vocabulary (e.g., MeSH terms in MEDLINE) and free-text keywords to maximize sensitivity. The core search terms were Cocaine Use Disorder (cocaine OR "cocaine abuse" OR "cocaine dependence" OR "cocaine disorder" OR "cocaine addiction") and Topiramate (topiramate OR epitomax®).

Eligibility Criteria

Studies were included in this systematic review and meta-analysis if they met the following criteria: randomized controlled trials (RCTs) evaluating the efficacy and safety of topiramate as the primary intervention for CUD; studies that investigated the use of topiramate in the treatment of CUD, including treatment retention, reduction in cocaine use, adverse effects, and craving reduction; studies with a control or comparison group receiving a placebo, standard pharmacological treatment (e.g. antidepressants, other medications for substance use disorders), or non-pharmacological interventions (e.g. cognitive behavioral therapy, motivational interviewing) alone or in combination with placebo; studies including adult participants (≥18 years old) diagnosed with CUD according to recognized diagnostic criteria (e.g., DSM-IV, DSM-5, ICD-10); studies where cocaine was the primary substance of concern. Studies including participants with polysubstance use were included if the primary focus of the intervention and outcome assessment was on cocaine use.

Studies were excluded if they are non-randomized studies (e.g. observational studies, case reports, case series); studies not specifically focused on the treatment of CUD; studies where topiramate is not the primary intervention being evaluated for CUD (e.g. studies primarily investigating the use of topiramate for comorbid conditions); animal studies; reviews, editorials, commentaries, and conference abstracts; studies not published in English (initially).

Outcome Measures

The outcomes assessed in this review included treatment retention, efficacy, safety, and craving reduction. Treatment retention was measured by dropout rates reported in each study. Efficacy was assessed by determining the continuous abstinence during the final three weeks of the study. The safety profile of topiramate was evaluated by the incidence of treatment-emergent adverse events. This was determined by the number of participants within the topiramate treatment groups reporting any adverse event

considered by the study investigators to be potentially related to the study medication. Craving reduction was assessed using subjective cocaine craving rating scales, specific to each study. Participant and intervention characteristics including location, study design, number of participants, inclusion criteria, demographics, duration and dosage of intervention, and control, were collected.

Heterogeneity in the reporting of these outcome measures across individual trials was anticipated, and strategies for data synthesis, including standardized mean differences or risk ratios where appropriate, were planned to account for this variability in the meta-analysis. Where feasible, sensitivity analyses were intended to explore the impact of different outcome definitions on the overall findings.

Data Extraction

All studies identified through the search were independently screened by two reviewers based on titles and abstracts. Full-text articles of potentially relevant studies were retrieved and assessed for eligibility according to the predefined inclusion criteria. Any disagreements were resolved through discussion between the reviewers and, when necessary, in consultation with additional investigators. Relevant data, including socio-demographic characteristics, type of intervention, and reported outcomes, were extracted from the eligible studies.

Quality Assessment

The quality of included studies was evaluated using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. The risk of bias (ROB) was independently evaluated by two reviewers using the Cochrane RoB 2: a revised tool for assessing the risk of bias in RCT.[24] Any disagreements that occurred throughout the course were resolved via discussion.Each study was assessed for potential risk of bias across five key domains: bias arising from the randomization process; bias due to

deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. For each domain, the risk of bias was categorized as low risk of bias, high risk of bias, or some concerns, following the standard Cochrane Handbook methodology.

Analysis

A meta-analysis was conducted to synthesize evidence regarding the efficacy of topiramate for cocaine abstinence, its effect on treatment retention, and the risk of adverse effects compared to placebo or ‘standard of care with or without placeboin participants with CUD.

Statistics

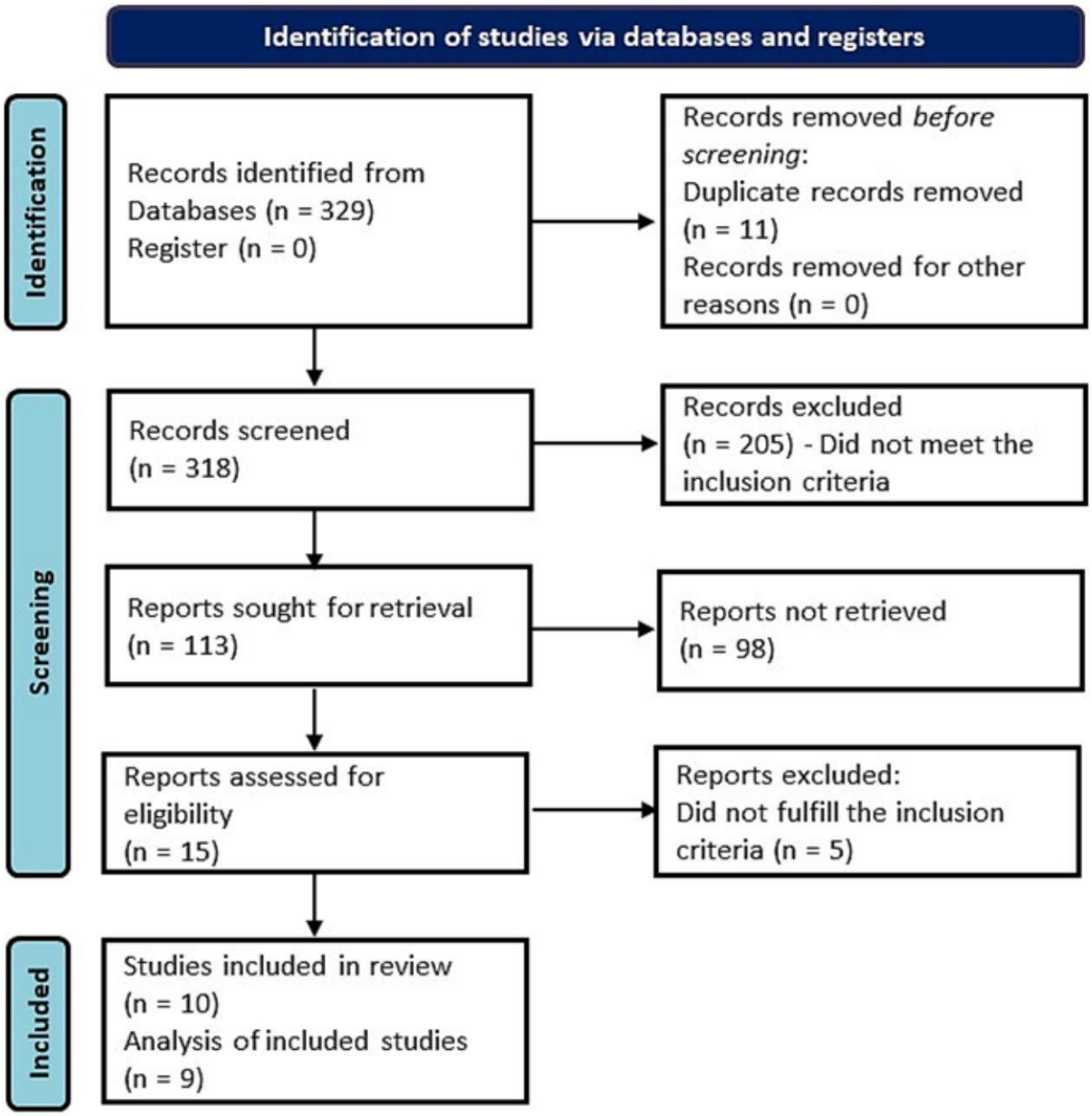
Meta-analyses were conducted using RevMan software, employing two distinct random effects models to synthesize the evidence. Firstly, the Mantel-Haenszel method was utilized to estimate the pooled Risk Ratio (RR), providing a summary measure of the relative risk across included studies. Secondly, the inverse variance method was applied to calculate the pooled Standardized Mean Difference (SMD), allowing for the synthesis of continuous outcomes reported on different scales. The results of both analyses were presented visually in forest plots, which display the study-specific estimates along with their corresponding confidence intervals, as well as the overall pooled effect size and its associated uncertainty.

Results

Search Results

A total of 329 records were initially identified through electronic database searches, as illustrated in Figure 1. Following the removal of 11 duplicate records, 318 unique articles were screened based on titles and abstracts. Of these, 205 records were excluded that did not meet the eligibility criteria. Subsequently, 15 articles underwent full-text assessment, and 5 studies were excluded for not fulfilling the inclusion criteria. Finally,

10 studies that met the inclusion criteria were included for systematic review, out of which 9 were analyzed for meta-analysis.



Study characteristics

A total of ten studies were included in the systematic review (Table 1).[20–22,25–31] Among these studies, all were randomized, double-blinded clinical trials, except for three studies that were randomized non-blinded trials,[26,30] and a post-hoc analysis.[29] Most of the study participants were from United States of America (USA),[20,22,25,28,29,31] followed byIran,[26,27] Brazil[21] and the Netherlands.[30]

Table 1: Characteristics of the included study

Author (Year)	Country	Study Design	Number of Participants (Intervention and Control)	Inclusion criteria	Age (years)	Gender Distribution	Ethnicity	Duration
Kampman et al. (2004)[22]	USA	RCT, PCB, DB, pilot trial	Intervention: 20 Control: 20	a) DSM-IV cocaine-dependent b) treatment-seeking c) low cocaine withdrawal symptom severity d) ≥3 days of abstinence before study initiation	40	Male: 97.5% Female: 2.5%	African American: 90%, Caucasian: 10%	13 weeks
Johnson et al. (2013)[25]	USA	RCT, PCB, DB	Intervention: 71 Control: 71	a) DSM-IV cocaine-dependent	43.7	Male: 72.5% Female: 27.5%	African: 70.4% Caucasian: 28.9%	12 weeks

							Asian: 0.7%	
Johnson et al. (2013b)[20]	USA	RCT, PCB, DB, crossover trial	24	a) DSM-IV cocaine-dependent b) non-treatment-seeking	34	Male: 79.17% Female: 20.83%	N/A	9 days
Kampman et al. (2013)[28]	USA	RCT, PCB, DB	Intervention: 83 Control: 87	a) DSM-IV cocaine-dependent b) Alcohol dependent	44	Male: 79% Female: 21	African American: 83% Caucasian: 17%	13 weeks
Nuijten et al. (2014)[30]	Netherlands	RCT, OL, feasibility trial	Intervention: 36 Control: 38	a) DSM-IV cocaine-dependent b) ≥8 days of cocaine use in the last month c) predominant administration by basing	Intervention: 43.3 Control: 41.3	Male: 81.6%, Female: 18.4%	European: ~64%	12 weeks
Umbricht et al. (2014)[31]	USA	RCT, PCB, DB	Intervention: 53 Control: 60	a) DSM-IV cocaine-dependent opioid users b) treatment-seeking c) Methadone maintenance	42	Male: 42% Female: 58%	African American: 60%	12 weeks

Baldaçara et al. (2016)[21]	Brazil	RCT, PCB, DB	Intervention: 29 Control: 29	a) DSM-IV cocaine-dependent b) exclusive use of crack cocaine	N/A	Male: 100% Female: 0%	N/A	12 weeks
Pirnia et al. (2017)[26]	Iran	Single centre RCT	Intervention: 25 Control: 25	a) Cocaine-dependent b) males c) abstinence period of 1 month	18-31	Male: 100% Female: 0%	N/A	12 weeks
Pirnia et al. (2018)[27]	Iran	Single center PCB, RCT	Intervention: 25 Control: 25	a) Cocaine-dependent b) methadone maintained	18-55	Male: 100% Female: 0%	N/A	12 weeks
Blevins (2019)[29]	USA	Post-hoc analysis of a DB, PCB, RCT	-	a) DSM-IV cocaine-dependent	N/A	N/A	N/A	12 weeks

**DB: double-blinded, DSM: diagnostic and statistical manual of mental disorders, N/A: not available, OL: open-label, PCB: placebo-controlled, RCT: randomized controlled trial, USA: United States of America.*

Across all studies, a total of 342 participants were allocated to the intervention group receiving topiramate treatment, while 355 in the control group received placebo and behavioral therapies, either alone or in combination. Additionally, 24 participants were administered both, placebo and topiramate, in a crossover trial design.[20] Participants' age ranged from 18 to 55 years. The mean age of the participants was 41 years (mean age not reported in few studies).[21,26,27,29] The proportion of male participants was higher, accounting for approximately 77.2% of the total study population (gender distribution not reported in few studies.[21,29] DSM-IV diagnostic criteria were used for the assessment of CUD in the majority of the studies[20–22,25,28–31] except two.[26,27] Topiramate dosing exhibited

limited heterogeneity across the included studies, with all trials administering either 200 mg or 300 mg per day. The mean final dose, based on the maximum dose following titration was 255.5 mg/day, while the median dose was 300 mg/day. The duration of the studies varied between 9 days and 13 weeks, with a median duration of 12 weeks.

Efficacy of Topiramate in cocaine abstinence and use

The therapeutic effects of topiramate in patients with CUD are outlined in Table 2. Across six studies,[21,22,26–28,31] urine benzoylecgonine tests (UBT) were the primary measure of cocaine abstinence. Two investigations indicated a greater likelihood of achieving cocaine abstinence in participants receiving topiramate, particularly during the initial four weeks of treatment, suggesting a potential early therapeutic benefit.[21,22] Additionally, continuous abstinence for three weeks was significantly higher in the topiramate participants compared to controls in two studies.[22,28] A post-hoc analysis reported a statistically significant improvement in impulsivity scores, as measured by the Barratt Impulsiveness Scale-11, following topiramate intervention.[29] However, three studies observed no statistically significant difference in overall abstinence rates between topiramate and placebo groups.[27,28,31] Umbricht et al. (2014) found no significant difference in the longest duration of cocaine abstinence between the two treatment arms.[31]

Table 2: Clinical outcomes of topiramate in CUD patients as described in included studies

Author (Year)	Intervention	Control	Primary Outcome	Secondary Outcome	Results for Outcomes Compared to Placebo	Summary
Kampman et al. (2004)[22]	Topiramate (200	Placebo + CBT	Cocaine abstinence (UBT)		GEE analysis of UBT: p=0.01	GEE analysis of UBT reported a

	mg/day) + CBT			Abstinence	Abstinence continuous 3 weeks: $\chi 2 = 3.9$, d.f. = 1, p=0.05	significant difference after week 8, favoring topiramate. The Topiramate group was more likely to be abstinent and treatment adhered to. Topiramate reduced the severity of addiction. No significant difference was observed in treatment retention and cocaine craving. It demonstrated a comparable safety profile.
				Treatment retention	t = −0.052 d.f. = 38 p=0.96	
				Addiction severity index	F(1/34) = 4.12 p=0.05	
				Cocaine craving	F(1/34) = 2.70 p=0.11	
				Treatment adherence	t = −2.7 d.f. = 34 p=0.01	
				Safety	No significant difference	
Johnson et al. (2013)[25]	Topiramate (300 mg/day) + CBT	Placebo + CBT	Weekly proportion of cocaine nonuse days		Effect size, 0.48; F = 5.66; p=0.02	Topiramate is more efficacious than placebo in increasing cocaine nonuse days, and are more likely to have urinary cocaine-free weeks. It significantly improves craving and
				Urinary cocaine-free weeks	OR=3.21; 95% CI, 1.24-8.32; p=0.02	
				Craving	p<0.05	
				Safety	p=0.66	
				Global functioning	p<0.05	

						global functioning.
Johnson et al. (2013b)[20]	Topiramate (100mg twice daily)	Placebo	VAS-Euphoria		F=7.03, p=0.004	Topiramate reduces craving and preference for cocaine over money induced by high cocaine doses, while has negative effects on low-dose cocaine. Its impact on mood is ambiguous. Topiramate demonstrated a good safety profile
			VAS-Stimulated		F=7.53, p=0.0042	
			VAS-Craving		F=7.55, p=0.0026	
			MCQ-Price		F=32.80, p<0.0001	
				POMS	Pretreated with topiramate compared with placebo: mean difference=−3.79, 95% CI: −6.73 to −0.86, p=0.015)	
				Safety	p>0.05	
Kampman et al. (2013)[28]	Topiramate (300 mg daily)	Placebo	Cocaine abstinence (UBT)		Weekly cocaine abstinence: Kruskal-Wallis χ2(1)=2.01, p=0.16	The topiramate group was more likely to be abstinent at 3 weeks. Topiramate had statistically significant higher treatment retention and lower alcohol craving. Topiramate was not
					Abstinence continuous for 3 weeks: χ2(1)=6.7 p=0.01	
			Alcohol Use		GEE Z=−0.76, p=0.45	
				Treatment retention	Kruskal-Wallis χ2(1)=4.24, p=0.04	
				Alcohol craving	Z=1.99, p<0.05	

				Cocaine craving	No significant difference compared to the control	better than placebo in reducing overall cocaine and alcohol use. Subjects with severe cocaine withdrawal symptoms responded better to topiramate. No significant difference was observed in cocaine craving, addiction severity, illness severity, and cocaine withdrawal symptoms.
				Addiction severity index	p>0.19	
				Illness severity and improvement	Z= 1.31, p=0.19	
				cocaine withdrawal symptoms	Z=0.99, p=0.32	
Nuijten et al. (2014)[30]	Topiramate (200 mg/day) + CBT	CBT only	Treatment retention		HR=0.67; 95% CI=0.4-1.2; p=0.15	Topiramate was safe and well-tolerated but did not improve treatment retention or reduce cocaine use compared to CBT alone. It reported no significant difference in other
			Crack cocaine use		F=1.6 df=1 p=0.23	
				Safety	No serious adverse events Adverse events: Intervention: 72.2%; Control: 13.2%	
				Cocaine use	Crack-cocaine use days: F=1.6; p=0.23	

				Other substance use	p>0.05	substance use, health, and social functioning.
				Cocaine craving	F=0.3 p=0.60	
				Mental health	F=1.5 p=0.23	
				Physical health	F=0.7 p=0.44	
				Patient Satisfaction	t=0.71; df=64; p=0.48	
Umbricht et al. (2014)[31]	Topiramate (300mg/day) + Voucher Incentives (CM or Non-CM)	Placebo + Voucher Incentives (CM or Non-CM)	Cocaine abstinence (UBT)		p=0.86, OR: 1.051, 95%CI: 0.6 – 1.84	Topiramate is not efficacious for increasing cocaine abstinence in methadone patients. Contingency management also did not improve outcomes.
			Longest duration of cocaine abstinence		No significant difference	
			Treatment retention		p=0.44	
				Opiate use	p=0.013	
				Cocaine craving	No significant difference	
				Psychiatric symptoms	No significant difference	
Baldaçara et al. (2016)[21]	Topiramate (50-200mg daily)	Placebo	Treatment retention		OR = 1.072 p=0.908	Topiramate had no significant impact on treatment retention. It positively improved cocaine abstinence with higher negative UBT, reduced cocaine
			Cocaine abstinence (UBT)		OR = 8.687 p<0.001	
				Reduction in cocaine use	-3.108 g p<0.001	
				Reduction in frequency of use	-0.784 times per week p=0.005	

						quantity, and reduced cocaine frequency. The effect was more pronounced in the initial 4 weeks than at 12 weeks.
Pirnia et al. (2017)[26]	Topiramate (25-300mg/day), CM, Combined	Placebo	Cocaine abstinence (UBT)		NA	Topiramate, CM, and combined treatment were effective in reducing cravings. Combined treatment had the highest effect on craving reduction.
				Cocaine craving	Craving scores (95% CI) Topiramate: 12.04 (p=0.05) CM: 13.89 (p=0.05) Combined: 10.92 (p=0.01) Control: 16.89 (p>0.05).	
Pirnia et al. (2018)[27]	Topiramate (25-300mg/day) + BBCET	Placebo + BBCET	Cocaine abstinence (UBT)		p>0.05	Topiramate was not better than placebo in reducing positive UBT results. Topiramate was better in reducing cocaine cravings. It was not associated with increased depressive symptoms.
				Cocaine craving	p<0.01	
				depression increase	P>0.05	

Blevins (2019)[29]	Topiramate (300 mg/day) + CBT	Placebo + CBT	Barratt Impulsiveness Scale		F=5.76 p=0.017	The main effect of topiramate on the Barratt Impulsiveness Scale-11 as a measure of treatment response was significant.

BBCET: brief behavioral compliance enhancement treatment, CBT: cognitive behavioral therapy, CI: confidence interval, CM: contingency management, df: degree of freedom, GEE: generalized estimating equations, HR: hazards ratio, MCQ: multiple choice questions, OR: odds ratio, POMS: profile of mood states, UBT: urine benzoylecgonine test, VAS: visual analog scale.

Boldface signifies statistical significance at p<0.05

The effect of topiramate on reducing cocaine consumption was evaluated in three studies.[21,25,30] Two studies reported significantly higher cocaine-free days and lower quantity and frequency of cocaine intake following topiramate treatment.[21,25] Baldaçara et al. (2016) quantified a mean decrease of 3.16 grams in weekly cocaine quantity and a reduction of 0.78 in weekly cocaine use frequency.[21] One study found no significant reduction in overall cocaine consumption.[30] While topiramate may provide early abstinence and reduce cocaine use in specific populations, the overall findings regarding its efficacy on cocaine abstinence and use remain heterogeneous across studies.

Treatment retention

Treatment retention was assessed in fivestudies.[21,22,28,30,31] Only one study, by Kampman et al. (2013), demonstrated a statistically significant improvement in treatment retention rates in the topiramate group compared to placebo (p = 0.04).[28] However, in four out of five studies; Kampman et al. (2004), Nuijten et al. (2014), Umbricht et al. (2014), and Baldaçara et al. (2016), the treatment retention rate between control and topiramate cohort were comparable (p = 0.96, p = 0.15, p = 0.44, and p = 0.908, respectively).[21,22,30,31]

Kampman et al. (2004) reported a significant improvement in treatment adherence in the topiramate group in comparison with placebo.[22] Overall, treatment retention outcomes across the included studies were mixed, favouring topiramate.

Safety

Across the included studies, topiramate generally demonstrated a favorable safety profile. No serious adverse events were reported in any studies. The majority of studies found no statistically significant differences in the incidence of adverse events with topiramate treatment compared to placebo, suggesting good tolerability.[20,22,25,30] Study by Nuijten et al. (2014) indicated a higher incidence of adverse events in the cohort administered with topiramate (72.2%) than the control group (13.2%), though no serious adverse effects were reported.[30] Additionally, studies assessing psychiatric symptoms[31] and mood changes[27] did not identify any statistically significant elevation in psychiatric adverse effects or depressive symptoms associated with topiramate use. Therefore, the available data suggests a lack of severe psychiatric or physiological side effects that would preclude its clinical application.

Cocaine craving

The majority of studies reporting on the efficacy of topiramate in cocaine craving reduction found no significant effect. Kampman et al. (2004, 2013), Nuijten et al. (2014), and Umbricht et al. (2014) all observed that the craving reduction with topiramate was comparable to the placebo, indicating no significant improvement in craving measures with topiramate.[22,28,30,31] Conversely, some studies suggested a beneficial effect. Johnson et al. (2013) and Pirnia et al. (2018) reported statistically significant reductions in craving ($p < 0.05$) in the topiramate groups compared to placebo.[25,27] Similarly, Johnson et al. (2013b) found that topiramate significantly reduced craving, as measured by visual

analog scales.[20] Therefore, topiramate may exert anti-craving effects that require validation with further studies.

Risk of Bias

An evaluation of the risk of bias within the included studies is detailed in Figure S1 (Supplementary material). The risk of bias due to non-random sequence generation was consistently low across all the studies, indicating that participant allocation to treatment arms was well-randomized. For allocation concealment, most of the studies reported a minimal risk of bias,[22,25–31] while allocation concealment remained unclear in two studies.[20,21] Blinding of both participants and investigators, was well-implemented in most studies,[20,21,25–29,31] with two studies having unclear and high risk.[22,30] Detection bias, concerning the blinding of outcome assessment, exhibited greater variability, with some studies adequately blinding assessors,[26,30] while others had unclear or high risk.[20–22,25,27–29,31] Incomplete outcome data posed a risk in several studies due to high attrition rates.[21,22,25–31] Selective reporting bias was low across most cases,[20–22,25,28–31] but two studies had a high risk.[26,27] Overall, selection and reporting bias was low, with some concerns about performance, detection, and attrition bias.

Meta-analysis

A meta-analysis was conducted to synthesize evidence regarding the efficacy of topiramate for cocaine abstinence, its effect on treatment retention, and the risk of adverse effects compared to placebo in participants with CUD.

Efficacy of Topiramate

A total of three studies underwent analysis.[21,22,28] The assessment included 137 patients in the topiramate intervention group and 133 in the control group. We used a random-

effects model with the Mantel-Haenszel method, that provided a pooled risk ratio (RR) of 2.83 (95% confidence interval [CI]: 1.68–4.76, p< 0.05). This indicates a significantly higher likelihood of achieving abstinence from cocaine use in individuals receiving topiramate compared to placebo. (Figure2). The absence of significant heterogeneity suggests consistency in effect size across studies.

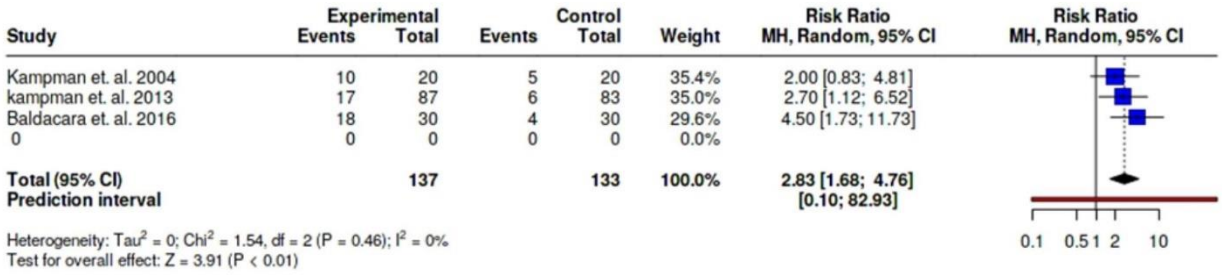


Figure 2 -

Treatment Retention

A total of five studies underwent analysis.[21,22,25,28,31] The assessment included 255 patients in the topiramate intervention group and 249 in the control group. The random-effects model with the Mantel-Haenszel method yielded a RR of 0.86 (95% CI: 0.62–1.19, p= 0.36) (Figure 3), indicating that topiramate did not demonstrate a statistically significant effect on treatment retention compared to placebo. The test for overall effect was not significant, and no substantial heterogeneity was detected, indicating uniform effect sizes across studies.

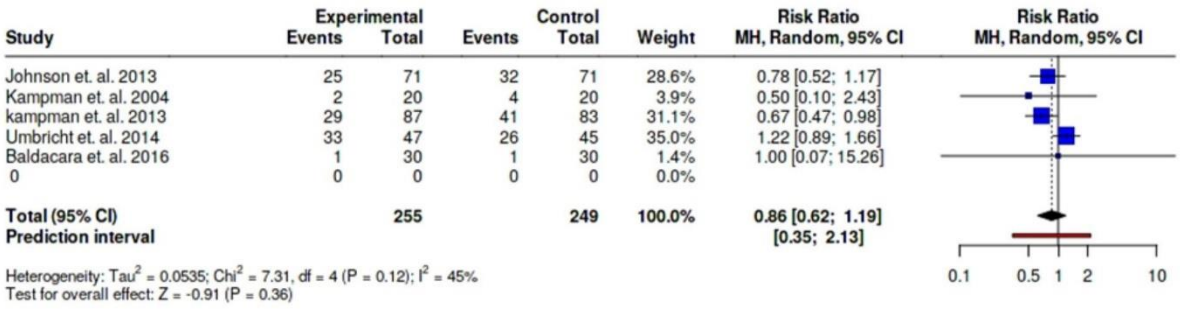


Figure 3 -

Dropout Rates

Overall, 6 studies were analyzed with a total of 281 subjects in the experimental cohort and 291 subjects in the control cohort.[22,25,27,28,30,31] Based on the analysis performed using random effects model with Mantel-Haenszel method, there was no statistical difference between the two cohorts. The overall RR was 0.94 (0.69 - 1.28) (Figure S2). Notable variability was not detected, suggesting that the effect sizes across cohorts remained uniform in both scale and direction.

Craving Reduction

Three studies were analyzed, including a total of 94 participants in the experimental group and 88 in the control group.[26,27,30] A random effects model using the inverse variance method was applied to assess the standardized mean difference (SMD) between the groups. The pooled SMD was -0.28, with a 95% confidence interval ranging from -1.92 to 1.36, indicating no statistically significant difference between the two cohorts (Figure S3). Additionally, the overall effect test was not significant. However, substantial heterogeneity was observed ($p<0.01$), suggesting considerable variability in effect size across studies. The I^2 statistic was 95%, indicating that most of the variability is due to true differences among studies rather than chance. Potential sources for significant heterogeneity are differences in participant demographics, such as country of origin and gender distribution;

intervention protocols with different behavioral therapies provided in addition to topiramate; and outcome measures using different tools for assessing craving including the cocaine craving questionnaire and the modified Obsessive Compulsive Drinking Scale (OCDS).

Adverse effects

To evaluate the risk of adverse effects, a meta-analysis of four studies was conducted, involving 436 participants (219 in the topiramate group and 217 in the control group).[21,25,29,31] The adverse effects were analyzed employing the random effects model with the Mantel-Haenszel method. A comparative account of the rate of adverse effects between the control and topiramate yielded no statistical difference between the two groups (p=044). The overall RR was 1.06 with a 95% CI of 0.91 - 1.23 (Figure 4). The test for overall effect was not statistically significant, and no substantial heterogeneity was detected, suggesting a consistent effect size across studies.

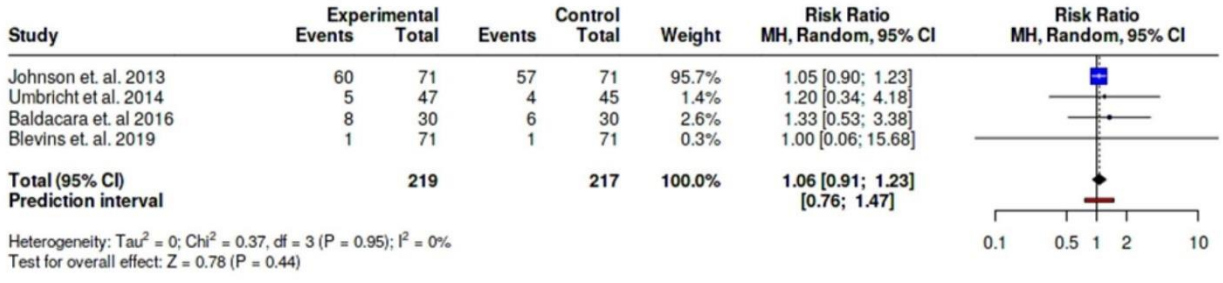


Figure 4 -

Discussion

This updated systematic review and meta-analysis assessed the efficacy and safety of topiramate in treating CUD from 10 studies. Topiramate demonstrated statistically

significant efficacy in promoting cocaine abstinence, as indicated by both individual trials and pooled analyses.[21,22,28] Specifically, using topiramate resulted in a statistically significant increase in cocaine-free days and a reduction of frequency and amount of cocaine use in some studies.[21,22,25,28] However, not all trials observed significant benefits, highlighting inconsistencies in the evidence.[27,30,31] While some studies suggested a positive effect on craving reduction,[20,25,27] majority of the studies found no statistically significant difference between topiramate and placebo suggesting that its potential anti-craving properties require further validation.[22,28,30,31] Evidence from multiple studies indicates that topiramate demonstrates either superior or equivalent treatment retention rates when compared to control groups.[21,22,28,30,31] This suggests that topiramate is well-tolerated and not associated with increased rates of discontinuation or dropouts. Collectively, these results indicate that topiramate may have a role in the management of CUD, though additional high-quality trials are warranted to confirm its clinical use.

These findings align with previous meta-analyses.[10,18] A prior study reported a 2.4 times higher chance of cocaine abstinence at 3 weeks with topiramate administration compared to control (RR, 2.43; 95% CI, 1.31–4.53;p = 0.005).[18] Similarly, Chan et al. (2019) observed an increased abstinence with topiramate treatment with an RR of 2.56.[10] Topiramate improves cocaine dependence by facilitating GABA transmission and decreasing dopamine release in the cortico-mesolimbic system. Additionally, it inhibits glutamatergic transmission, particularly at alpha-amino-3-hydroxy-5-methylisoxazole-4-propionicacid (AMPA)/kainate receptors, which may diminish the euphoric effects of cocaine and reduce its craving.[20,32]

The meta-analysis of adverse events showed no statistically significant difference in the incidence of adverse events between the topiramate-treated and placebo groups, suggesting a favorable safety and tolerability profile.[20,22,25] A probable explanation for this observation may be the slow titration protocols implemented over several weeks. These results suggest that topiramate may be a relatively safe pharmacotherapeutic option for CUD. However, achieving therapeutic doses while minimizing adverse effects remains a significant challenge. The necessary slow titration process can extend over several weeks

to months,[33,34] which may impact treatment retention, particularly when subtherapeutic doses administered during the initial titration phases do not adequately address ongoing substance use. Furthermore, the prolonged titration period raises concerns about whether topiramate can be a feasible and viable therapeutic option, particularly in marginalized populations with high rates of stimulant use.[35]

It is noteworthy that the observed benefits of topiramate were evident even in CUD patients receiving concurrent CBT. CBT reduces drug craving through targeted interventions. Specifically, CBT helps patients recognize situational and internal cues that elicit drug-seeking behaviors and avoid such situations whenever feasible.[13] Patients acquire several cognitive and behavioral coping mechanisms to manage emergent craving episodes. These strategies include diverting attention, recalling negative effects, and substituting them with positive thoughts.[36] The inhibitory learning processes underlying CBT are hypothesized to mediate via the potentiation of GABA signaling.[37] Based on the fact that topiramate increases GABA concentrations, the concurrent administration of topiramate with CBT may synergistically enhance abstinence outcomes through complementary effects on the GABAergic pathway.[17]

Study Limitations

The findings must be interpreted with caution given certain limitations of the included studies. The relatively small number of studies and sample sizes, may influence the robustness of conclusions. Additionally, more than half of the included evidence originates from the USA, which restricts the generalizability of the findings to the global population. The maximum duration of treatment was limited to 13 weeks, precluding assessment of long-term efficacy and outcomes. While this review represents an update to a previous systematic review,[18] only five new studies have been incorporated over six years. This suggests slow research in this domain. Lastly, the outcome reporting across studies was heterogeneous, with substantial variations in clinical outcomes and measures. Therefore, several relevant outcomes, such as cocaine craving, could not be

pooled for analysis. Despite these limitations, this study presents an updated systematic review and meta-analysis, offering a comprehensive assessment of the therapeutic efficacy of topiramate in patients with CUD.

From a clinical perspective, topiramate may offer a modest but clinically relevant benefit as an adjunctive pharmacotherapy for promoting early abstinence in CUD patients. Its efficacy is particularly promising during the initial weeks of treatment, indicating a possible role in facilitating short-term abstinence or in bridging patients into more sustained behavioral or psychosocial interventions. However, routine clinical adoption of topiramate for CUD cannot yet be broadly endorsed. Future research should address several gaps in knowledge, including dosage and titration schedules, treatment duration, safety profile, and identifying the target patient population.

Conclusion

Topiramate was associated with an increase in cocaine-free days and a reduction in the frequency and amount of cocaine use in most of the included studies. This meta-analysis suggests that topiramate may be effective in promoting early cocaine abstinence. Its impact on craving reduction was generally limited, suggesting that its potential anti-craving properties require further validation. It demonstrated favorable treatment retention rates comparable to placebo, suggesting good overall tolerability. These findings indicate that topiramate may offer therapeutic benefits for individuals with CUD; however, further high-quality research is warranted to confirm its clinical efficacy and long-term safety in optimizing patient outcomes.

The date of the last literature review: 31st December 2024

Acknowledgement: Authors would like to acknowledge Dr Shahu Ingole from ‘Science Plus’ for support in data analysis and manuscript editing.

Conflict of Interest: Authors have no conflict of interest to declare.

Author contributions: CRediT TaxonomySridevi ShanmugamConceptualization-Lead, Data curation-Lead, Formal analysis-Equal, Methodology-Equal, Project administration-Equal, Validation-Equal, Writing - original draft-Lead, Writing - review & editing-EqualSaravana Arunkumar Conceptualization-Supporting, Data curation-Supporting, Formal analysis-Equal, Methodology-Equal, Project administration-Equal, Supervision-Equal, Validation-Equal, Writing - original draft-Equal, Writing - review & editing-SupportingVishal AgrawalData curation-Supporting, Formal analysis-Supporting, Methodology-Equal, Project administration-Equal, Validation-Supporting, Writing - original draft-Supporting, Writing - review & editing-SupportingPraveen KumarConceptualization-Supporting, Formal analysis-Equal, Methodology-Equal, Project administration-Supporting, Validation-Supporting, Writing - original draft-Supporting, Writing - review & editing-Equal

Handling Editor: Dr. Thiago Roza

References

1. Schwartz EKC, Wolkowicz NR, De Aquino JP, MacLean RR, Sofuoglu M. Cocaine Use Disorder (CUD): Current Clinical Perspectives. Subst Abuse Rehabil 2022;13:25–46. 10.2147/SAR.S337338

2. Simpson KJ, Moran MT, McCall KL, Herbert J, Foster ML, Simoyan OM, et al. Increasing heroin, cocaine, and buprenorphine arrests reported to the Maine Diversion Alert Program. Forensic Sci Int 2019;303:109924. 10.1016/j.forsciint.2019.109924

3. Schneider KE, Krawczyk N, Xuan Z, Johnson RM. Past 15-year trends in lifetime cocaine use among US high school students. Drug Alcohol Depend 2018;183:69–72. 10.1016/j.drugalcdep.2017.10.028

4. John WS, Wu LT. Trends and correlates of cocaine use and cocaine use disorder in the United States from 2011 to 2015. Drug Alcohol Depend 2017;180:376–84. 10.1016/j.drugalcdep.2017.08.031

5. NCHS. Drug Overdose Deaths in the United States, 2002–2022. National Center for Health Statistics; 2024.

6. Office for National Statistics. Drug misuse in England and Wales: year ending March 2024 [Internet]. 2024;Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/crimeandjustice/articles/drugmisuseinenglandandwales/yearendingmarch2024

7. UNODC. Global Report on Cocaine 2023 Local dynamics, global challenges. United Nations Publication; 2023.

8. Prince V, Bowling KC. Topiramate in the treatment of cocaine use disorder. Am J Health Syst Pharm 2018;75(1):e13–22. 10.2146/ajhp160542

9. Rush CR, Stoops WW, Lile JA, Alcorn JL, Bolin BL, Reynolds AR, et al. Topiramate-phentermine combinations reduce cocaine self-administration in humans. Drug Alcohol Depend 2021;218:108413. 10.2146/ajhp160542

10. Chan B, Kondo K, Freeman M, Ayers C, Montgomery J, Kansagara D. Pharmacotherapy for Cocaine Use Disorder—a Systematic Review and Meta-analysis. J Gen Intern Med 2019;34(12):2858–73. 10.1007/s11606-019-05074-8

11. Czoty PW, Stoops WW, Rush CR. Evaluation of the “Pipeline” for Development of Medications for Cocaine Use Disorder: A Review of Translational Preclinical, Human Laboratory, and Clinical Trial Research. Pharmacol Rev 2016;68(3):533–62. 10.1124/pr.115.011668

12. Brandt L, Chao T, Comer SD, Levin FR. Pharmacotherapeutic strategies for treating cocaine use disorder—what do we have to offer? Addiction 2021;116(4):694–710. 10.1111/add.15242

13. Farhoudian A, Razaghi E, Hooshyari Z, Noroozi A, Pilevari A, Mokri A, et al. Barriers and Facilitators to Substance Use Disorder Treatment: An Overview of Systematic Reviews. Subst Abuse Res Treat 2022;16:11782218221118462.

14. Medicines and Healthcare products Regulatory Agency (MHRA). Safety review to begin on topiramate [Internet]. 2022;Available from: https://www.gov.uk/government/news/safety-review-to-begin-on-topiramate

17. Kim JH, Lawrence AJ. Drugs currently in Phase II clinical trials for cocaine addiction. Expert Opin Investig Drugs 2014;23(8):1105–22. 10.1517/13543784.2014.915312

18. Singh M, Keer D, Klimas J, Wood E, Werb D. Topiramate for cocaine dependence: a systematic review and meta-analysis of randomized controlled trials. Addiction 2016;111(8):1337–46. 10.1111/add.13328

17. Kim DS, Kwak SE, Kim JE, Won MH, Choi HC, Song HK, et al. The effect of topiramate on GABAB receptor, vesicular GABA transporter and paired-pulse inhibition in the gerbil hippocampus. Neurosci Res 2005;53(4):413–20.

18. Gensel JC, Tovar CA, Bresnahan JC, Beattie MS. Topiramate Treatment Is Neuroprotective and Reduces Oligodendrocyte Loss after Cervical Spinal Cord Injury. PLoS ONE 2012;7(3):e33519.

20. Johnson BA, Roache JD, Ait-Daoud N, Gunderson EW, Haughey HM, Wang X, et al. Topiramate's effects on cocaine-induced subjective mood, craving and preference for money over drug taking. Addict Biol 2013;18(3):405–16. 10.1111/j.1369-1600.2012.00499.x

21. Baldaçara L, Cogo-Moreira H, Parreira BL, Diniz TA, Milhomem JJ, Fernandes CC, et al. Efficacy of topiramate in the treatment of crack cocaine dependence: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry 2016;77(3):398–406. 10.4088/JCP.14m09377

22. Kampman KM, Pettinati H, Lynch KG, Dackis C, Sparkman T, Weigley C, et al. A pilot trial of topiramate for the treatment of cocaine dependence. Drug Alcohol Depend 2004;75(3):233–40. 10.1016/j.drugalcdep.2004.03.008

19. Nourredine M, Jurek L, Angerville B, Longuet Y, De Ternay J, Derveaux A, et al. Use of Topiramate in the Spectrum of Addictive and Eating Disorders: A Systematic Review Comparing Treatment Schemes, Efficacy, and Safety Features. CNS Drugs 2021;35(2):177–213. 10.1007/s40263-020-00780-y

23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;n71. 10.1136/bmj.n71

24. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;l4898. 10.1136/bmj.l4898

25. Johnson BA, Ait-Daoud N, Wang XQ, Penberthy JK, Javors MA, Seneviratne C, et al. Topiramate for the Treatment of Cocaine Addiction: A Randomized Clinical Trial. JAMA Psychiatry 2013;70(12):1338. 10.1001/jamapsychiatry.2013.2295

26. Pirnia B, Moradi AR, Pirnia K, Kolahi P, Roshan R. A Novel Therapy for cocaine dependence during abstinence: A randomized clinical trial. Electron Physician 2017;9(7):4862–71. 10.19082/4862

27. Pirnia B, Soleimani A, Malekanmehr P, Pirnia K, Zahiroddin A. Topiramate for the Treatment of Dually Dependent on Opiates and Cocaine: A Single-center Placebo-controlled Trial. Iran J Public Health 2018;47.

28. Kampman KM, Pettinati HM, Lynch KG, Spratt K, Wierzbicki MR, O'Brien CP. A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. Drug Alcohol Depend 2013;133(1):94–9. 10.1016/j.drugalcdep.2013.05.026

29. Blevins D, Wang X, Sharma S, Ait-Daoud N. Impulsiveness as a predictor of topiramate response for cocaine use disorder. Am J Addict 2019;28(2):71–6. 10.1111/ajad.12858

30. Nuijten M, Blanken P, Van Den Brink W, Hendriks V. Treatment of crack-cocaine dependence with topiramate: A randomized controlled feasibility trial in The Netherlands. Drug Alcohol Depend 2014;138:177–84. 10.1016/j.drugalcdep.2014.02.024

31. Umbricht A, DeFulio A, Winstanley EL, Tompkins DA, Peirce J, Mintzer MZ, et al. Topiramate for cocaine dependence during methadone maintenance treatment: A randomized controlled trial. Drug Alcohol Depend 2014;140:92–100. 10.1016/j.drugalcdep.2014.03.033

32. Siniscalchi A, Bonci A, Biagio Mercuri N, Pirritano D, Squillace A, De Sarro G, et al. The Role of Topiramate in the Management of Cocaine Addiction: a Possible Therapeutic Option. Curr Neuropharmacol 2015;13(6):815–8. 10.2174/1570159x13666150729222643

33. Biton V, Edwards KR, Montouris GD, Sackellares JC, Harden CL, Kamin M, et al. Topiramate titration and tolerability. Ann Pharmacother 2001;35(2):173–9. 10.1345/aph.10093

34. 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. 10.2165/00023210-200519100-00005

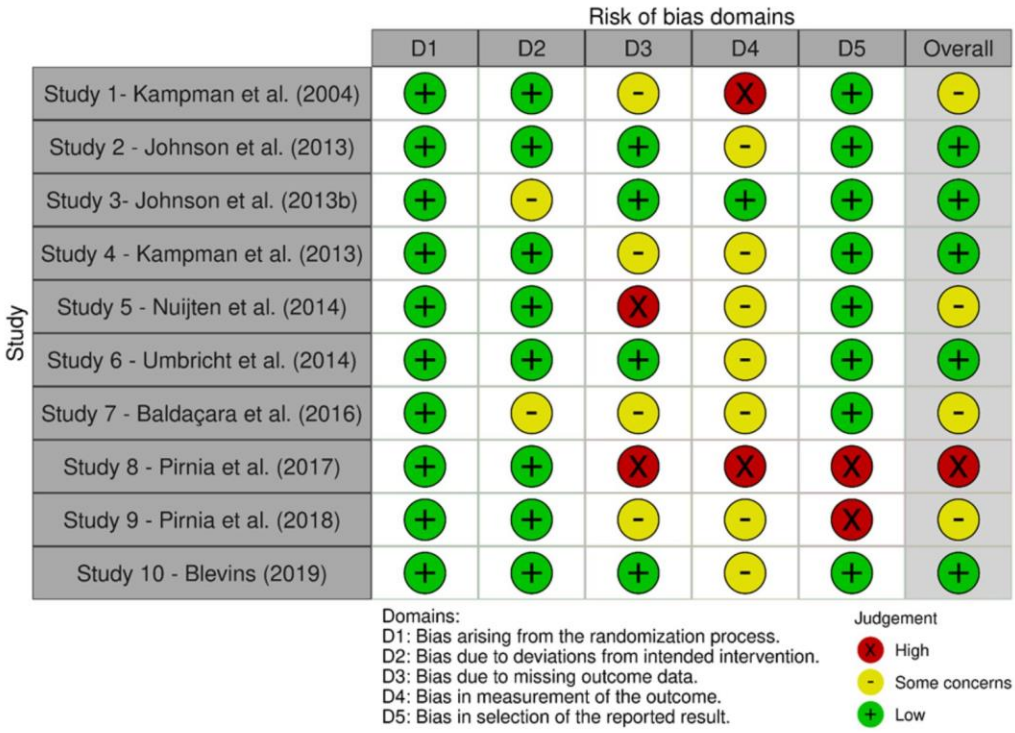
35. Sánchez-Hervás E, Secades-Villa R, Gómez FJS, Romaguera FZ, García-Rodríguez O, Yanez EM, et al. Treatment dropout in cocaine addicts. Adicciones 2010;22(1):59–64.

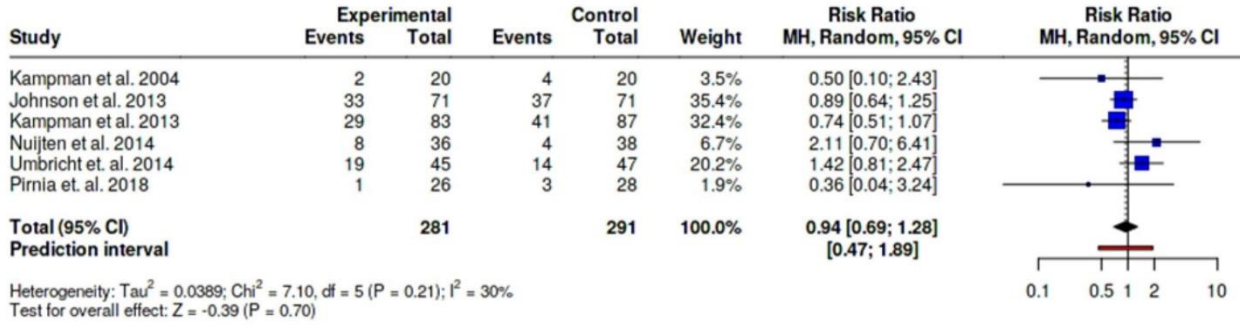
13. Kampman KM. The treatment of cocaine use disorder. Sci Adv 2019;5(10):eaax1532. 10.1126/sciadv.aax1532

36. Carroll KM, Onken LS. Behavioral therapies for drug abuse. Am J Psychiatry 2005;162(8):1452–60. 10.1176/appi.ajp.162.8.1452

37. Radhu N, Daskalakis ZJ, Guglietti CL, Farzan F, Barr MS, Arpin-Cribbie CA, et al. Cognitive behavioral therapy-related increases in cortical inhibition in problematic perfectionists. Brain Stimulat 2012;5(1):44–54. 10.1016/j.brs.2011.01.006

Supplementary material





Study	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nuijten et al. 2014	5.20	3.8000	44	6.30	4.4000	38	33.9%	-0.27 [-0.70; 0.17]
Pirnia et. al. 2017	12.04	2.2900	25	16.89	3.0900	25	32.9%	-1.76 [-2.42; -1.10]
Pirnia et. al. 2018	24.31	2.2100	25	21.84	1.9300	25	33.2%	1.17 [0.57; 1.78]
Total (95% CI)			**94**			**88**	**100.0%**	**-0.28 [-1.92; 1.36]**
Prediction interval								**[-21.24; 20.68]**

Heterogeneity: $Tau^2 = 2.0195$; $Chi^2 = 41.27$, df = 2 ($P < 0.01$); $I^2 = 95\%$
Test for overall effect: Z = -0.33 (P = 0.74)