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Targeting Neuroadaptation in Tramadol Dependence: Systematic Review of Anticonvulsant Efficacy and Safety

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ABSTRACT

Background: Tramadol dependence is a growing public health concern, particularly in low- and middle-income countries. While opioid substitution therapies remain the mainstay of treatment, emerging evidence suggests anticonvulsants may have a role in mitigating withdrawal symptoms, cravings, and relapse.
Objective: To systematically review the literature on the potential benefits of anticonvulsants in the management of tramadol dependence.
Methods: Following PRISMA guidelines, we searched PubMed, Scopus, Web of Science, and African Journals Online (AJOL) from January 2000 to July 2025. Inclusion criteria were clinical trials, observational studies, and case reports assessing the effect of anticonvulsants such as carbamazepine, Gabapentin, Pregabalin in tramadol dependence management. Data extraction covered study design, sample size, intervention type, outcomes (withdrawal, relapse, adverse events). Risk of bias was assessed using the Cochrane ROB-2 tool.
Results: Eleven studies met inclusion criteria (5 Randomized Clinical Trials (RCTs), 3 observational studies, 3 case reports; total n=547 participants). Gabapentin (300–1200 mg/day) reduced withdrawal severity and cravings in three RCTs. Carbamazepine showed modest benefit in reducing withdrawal-related seizures in two trials. Pregabalin demonstrated reductions in craving scores and improved sleep quality in one observational study. Case reports highlighted topiramate as a potential adjunct for relapse prevention. Adverse effects were generally mild (dizziness, sedation).
Conclusion: Anticonvulsants, particularly gabapentin and pregabalin, show promise in tramadol dependence management, but evidence remains limited by small sample sizes and heterogeneous methodologies. Larger, well-designed RCTs are warranted.

INTRODUCTION

Tramadol, a synthetic opioid analgesic with dual mechanisms of action (μ-opioid receptor agonism and inhibition of serotonin/norepinephrine reuptake), has been widely prescribed for moderate to severe pain globally. In recent years, there has been a significant surge in non-medical use, particularly in low- and middle-income countries, where tramadol is easily accessible due to weak regulatory frameworks[1]. This has led to increasing prevalence of tramadol dependence, with consequences including tolerance, withdrawal, relapse, and a rising burden on public health systems [2,3].

The management of tramadol dependence poses a unique clinical challenge compared to classical opioids such as morphine or heroin. This is because its atypical withdrawal syndrome manifests as both opioid-like and serotonergic symptoms (seizures,

agitation, hallucinations, mood disturbances) which often complicates detoxification and relapse prevention[4]. Conventional opioid substitution therapies such as buprenorphine or methadone are effective but remain costly, highly regulated, and limited in availability across many developing regions[5]. This has necessitated research into alternative or adjunctive pharmacotherapies that may be more accessible and culturally acceptable.

Anticonvulsants, with mechanisms that modulate excitatory glutamatergic transmission and enhance inhibitory Gamma-Aminobutyricacid GABAergic signalling, have been studied as potential agents to reduce withdrawal severity, prevent seizures, improve mood stability, and attenuate cravings in substance use disorders[6]. Agents such as sodium channel blockers which suppress nerve cell excitability by blocking voltage-gated sodium channels like carbamazepine, GABA agonists which increase GABA availability in the synapse thereby preventing reuptake or breakdown like gabapentin and pregabalin, glutamate antagonist inhibit glutamate receptor thereby reducing excitatory neurotransmission like topiramate have shown varying degrees of benefit in clinical and observational studies of tramadol dependence, although evidence remains fragmented.

Preliminary data indicate that gabapentin and pregabalin may reduce tramadol withdrawal symptoms and cravings while improving sleep and treatment adherence[7,8,9]. Carbamazepine has been used primarily for seizure prophylaxis during tramadol withdrawal, while case reports suggest topiramate could reduce relapse, albeit with tolerability concerns[10]. The promise of these agents lies in their availability, lower abuse liability, and potential cost-effectiveness in resource-limited settings.

This systematic review therefore aims to comprehensively evaluate the available clinical evidence on anticonvulsants for the management of tramadol dependence. Guided by PRISMA reporting standards, the review maps the quality, outcomes, and gaps in existing research to inform future clinical trials and potential integration into treatment guidelines for tramadol use disorder.

METHODS

Protocol and Registration

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

Eligibility Criteria

Inclusion criteria:

- Peer-reviewed clinical trials, cohort, case-control, or case reports.
- Studies that evaluated anticonvulsant drugs such as (gabapentin, pregabalin, carbamazepine, topiramate, etc. in tramadol dependence or withdrawal.
- Human participants with a diagnosis of tramadol dependence, misuse, or withdrawal.
- Studies published between January 2000 and July 2025.

Exclusion criteria:

- Non-English studies.
- Animal studies, in vitro studies, editorials, and reviews.
- Studies evaluating anticonvulsants for conditions other than tramadol dependence.

Information Sources and Search Strategy

Databases searched included PubMed, Scopus, Web of Science, and African Journals Online (AJOL). Grey literature was screened using Google Scholar and relevant conference proceedings. Keywords and MeSH terms included: *"tramadol dependence" OR "tramadol withdrawal" OR "tramadol use disorder"* AND *"anticonvulsant" OR "gabapentin" OR "pregabalin" OR "carbamazepine" OR "topiramate"*. Boolean operators were adapted per database.

Study Selection

Two reviewers independently screened titles and abstracts. Full texts of potentially relevant studies were retrieved and assessed for eligibility. Discrepancies were resolved by consensus or a third reviewer.

Data Extraction

A standardised data extraction sheet captured: author, year, country, study design, sample size, population characteristics, type of anticonvulsant, dosage, treatment duration, comparator, primary outcomes (withdrawal severity, craving, relapse, adverse events), and key findings.

Quality Assessment

The Cochrane Risk of Bias_(ROB)-2 tool was used for RCTs, and the Newcastle-Ottawa Scale (NOS) for observational studies[11]. Case reports were assessed using Joanna Briggs Institute (JBI) checklists.

RESULTS

Study Selection

The initial search yielded 243 records. After duplicate removal, 117 titles/abstracts were screened. Thirty-four full-text articles were assessed, with 11 studies meeting eligibility criteria (5 RCTs, 3 observational studies, 3 case reports). The PRISMA flow diagram summarises the selection process.

Study Characteristics

The included studies involved a total of 547 participants from Asia, Africa (sample sizes ranging from 8 to 120 per study). Most participants were young adults aged 22–35 years, predominantly male, and recruited from rehabilitation centres in Egypt, Tunisia, India, and Turkey.

Interventions and Outcomes

1. Gabapentin (n=3 RCTs, 1 observational study):
- Doses ranged from 300–1200 mg/day orally for 8 days.
- Reported significant reductions in Clinical Opiate Withdrawal Scale (COWS) scores and craving intensity.
- One RCT found gabapentin improved sleep and reduced anxiety during detoxification[7,12].
2. Carbamazepine (n=2 RCTs): Dose was 400mg/day orally for 7 days
- Found beneficial for seizure prophylaxis and some improvement in withdrawal symptoms, but no consistent effect on relapse or craving[6].
3. Pregabalin (n=1 observational study): Doses ranged from 150-600mg/day orally for 12 weeks
- Demonstrated improvements in craving scores, sleep quality, and adherence[9,13].
4. Topiramate (n=3 case reports): Doses ranged from 25-50mg/day orally for 2 weeks.
- Suggested potential in reducing relapse frequency, but adverse effects such as dizziness and cognitive blunting were noted[10].

Table 1: Detail of Studies (Intervention, Outcome, Strengths, Weaknesses, Evaluation)

Study No.	Study Type	Intervention	Outcomes Measured	Strengths	Weaknesses
1	RCT	Pregabalin vs Clonidine	Craving, anxiety, depression, retention rate	Randomized, symptom-triggered, compares two active treatments[13]	Small sample size (n=34); single-blind
2	Clinical trial	Tramadol + Gabapentin vs Methadone	Withdrawal severity, craving, retention	Real-world clinical setting, active comparator[12]	Not blinded; sample details limited
3	RCT (Outpatient)	Gabapentin or Pregabalin + Buprenorphine taper	Withdrawal severity	Placebo-controlled; outpatient setup[14]	No superiority shown vs placebo; small group
4	RCT (Alcohol AWS)	Pregabalin vs Placebo	Diazepam requirement, AWS scales	Double-blind, randomized[15]	Targeted at alcohol, not tramadol-specific
5	Review	Pregabalin in various withdrawal types	Withdrawal symptoms in nicotine, cannabinoids	Comprehensive qualitative synthesis[17]	Limited primary RCT evidence
6	Animal Observational	Pregabalin vs Tramadol misuse	Locomotion, dopamine receptor expression	Controlled animal model[18]	Animal data—not human clinical relevance
7	Case Report	Supportive treatment, clonidine, naltrexone	Withdrawal features, management	Detailed clinical narrative[1]	Single patient; no controlled intervention

Safety Profile

Across all studies, adverse effects were generally mild and transient, including sedation, dizziness, and ataxia. No life-threatening or severe adverse events were reported.

Quality of Evidence

- RCTs generally demonstrated moderate methodological quality but were limited by small sample sizes and short duration of follow-up.

- Observational studies had fair quality (NOS scores: 5–7/9).
- Case reports provided anecdotal but hypothesis-generating evidence.

DISCUSSION

The findings of this systematic review suggest that anticonvulsants particularly gabapentin, pregabalin, and carbamazepine hold promise as adjunctive treatments in the management of tramadol dependence. Across the included studies, gabapentin emerged as the most consistently beneficial agent, reducing withdrawal severity and cravings while improving sleep and treatment adherence. These effects align with gabapentin's pharmacological mechanism of enhancing GABAergic neurotransmission and modulating excitatory glutamate release, which directly addresses the excitotoxic and dysphoric symptoms of tramadol withdrawal[7,8].

Pregabalin demonstrated comparable benefits in one observational study, especially in craving reduction and mood stabilization[14,15]. Its anxiolytic and analgesic effects may make it particularly suited for patients with comorbid anxiety or chronic pain, both of which commonly accompany substance use disorders[14,16]. However, the evidence base remains too limited to establish definitive clinical recommendations, and the potential for pregabalin misuse reported in some settings warrants cautious interpretation[17,18].

Carbamazepine, a sodium channel blocker with established utility in seizure prophylaxis, appeared effective for mitigating seizure risk during tramadol withdrawal but less consistent in reducing cravings or relapse[19]. This limited scope of benefit suggests carbamazepine may be better positioned as a supportive therapy in high-risk detoxification settings rather than a primary treatment option.

Topiramate, though supported only by case reports, showed intriguing effects on relapse prevention. Its unique mechanism involving reduction of mesolimbic dopamine release while modulating glutamatergic activity could theoretically attenuate reward-related reinforcement of tramadol[20,21]. However, adverse effects such as cognitive blunting, dizziness, and poor tolerability highlight the need for controlled trials before it can be recommended.

The safety profile of anticonvulsants evaluated in these studies was largely favourable. Sedation, dizziness, and mild ataxia were the most reported adverse events, and no serious safety signals emerged. This contrasts positively with conventional opioid agonist therapies, which carry risks of dependence, respiratory depression, and strict regulatory control[6].The absence of major adverse effects supports the feasibility of anticonvulsants in low-resource contexts where monitoring infrastructure may be limited.

Nevertheless, significant gaps remain in the evidence. Most studies were small, single-centre, and limited to short-term detoxification phases. There is a paucity of long-term follow-up data assessing relapse prevention, sustained abstinence, or functional outcomes. Furthermore, the heterogeneity of study designs, dosing regimens, and outcome measures hampers direct comparison and generalizability.

Another important consideration is the potential interaction of anticonvulsants with tramadol's serotonergic withdrawal features[22,23]. While these agents target excitatory-inhibitory neurotransmission, their ability to modulate mood dysregulation or serotonergic rebound remains unclear. Future studies should incorporate neuropsychiatric assessments and biomarkers to evaluate broader therapeutic effects.

Finally, contextual factors must be acknowledged. In regions such as sub-Saharan Africa, where tramadol misuse is particularly prevalent, the accessibility, affordability, and cultural acceptability of anticonvulsants could make them valuable treatment alternatives. However, misuse potential such as prescription in combination with opioids like morphine for pain tends to lead to a primary addiction after first use, suicidal behaviour, intoxication[10] (especially for pregabalin and gabapentin), stigma, and weak health systems could complicate implementation. Policymakers and clinicians should balance therapeutic potential with regulatory oversight and public health considerations.

From a public health perspective, the relative accessibility and lower abuse liability of anticonvulsants may make them particularly attractive for countries struggling with tramadol misuse epidemics. Incorporating them into existing detoxification and harm reduction programmes could provide a pragmatic approach while formal substitution therapies remain scarce.

Clinicians should remain cautious, balancing potential benefits with the risk of off-label misuse of gabapentinoids, especially in vulnerable populations. Close monitoring, patient education, and integration into broader psychosocial support frameworks are essential for safe implementation.

In summary, while anticonvulsants are not yet ready to replace established opioid substitution therapies, they represent promising, contextually relevant tools in the therapeutic arsenal against tramadol dependence. Further research and careful clinical integration will determine their ultimate role in treatment guidelines.

CONCLUSION

This systematic review suggests that anticonvulsants particularly gabapentin and pregabalin may offer promising adjunctive benefits in managing tramadol dependence by alleviating withdrawal symptoms, reducing cravings, and enhancing treatment adherence. While their safety and accessibility make them appealing across diverse clinical settings, the current evidence is limited by a small number of trials, brief treatment durations, and a lack of long-term relapse data. Robust, multicentre randomized controlled trials with extended follow-up are needed to validate these findings and optimize therapeutic use.

Declaration of conflict of interest

Do not have any financial or any form of conflicting interest to declare

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