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Topiramate-Associated Cognitive Effects: A Neuropharmacologic Review

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Abstract

Topiramate is a widely used anticonvulsant with a multimodal neuropharmacologic profile and a well-recognized potential to produce cognitive adverse effects. Reported impairments include disturbances in attention, processing speed, memory, verbal fluency, and language, with greater effects observed in some studies at higher doses. Language-related dysfunction, particularly word-finding difficulty and reduced verbal fluency, appears to be among the most consistently described cognitive manifestations. The mechanisms underlying these effects remain incompletely defined. Topiramate modulates several pathways involved in neuronal excitability, including voltage-gated sodium channels, gamma-aminobutyric acid (GABA)-mediated neurotransmission, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate glutamate receptors, carbonic anhydrase, and possibly voltage-gated calcium channels. Experimental studies support effects on both inhibitory and excitatory neurotransmission, while functional imaging and exposure-response studies provide preliminary evidence linking topiramate treatment with altered cognitive processing and language-related network activity. Cognitive effects appear to be influenced by dose and individual susceptibility and may improve following dose reduction or discontinuation. This focused Mini Review summarizes the neuropharmacology of topiramate, examines its principal cognitive effects, and evaluates current evidence regarding possible mechanisms, reversibility, and clinical implications. Overall, the cognitive phenotype appears multifactorial, exposure related, and at least partly reversible, although direct links between individual molecular targets and specific cognitive deficits have not been established.

Keywords: ***Topiramate; Cognition; Neuropharmacology; Verbal fluency; GABA; Glutamate.***

1. Introduction

Topiramate is a second-generation anticonvulsant used in the treatment of epilepsy and prevention of migraine. Its pharmacologic effects involve multiple molecular pathways, including inhibition of voltage-gated sodium channels, enhancement of gamma-aminobutyric acid (GABA)-mediated neurotransmission, antagonism of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate glutamate receptors, and inhibition of carbonic anhydrase [1]. This multimodal pharmacology contributes to its effects on neuronal excitability but also complicates efforts to link individual adverse effects to specific molecular actions.

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Cognitive adverse effects are clinically relevant because they may influence treatment tolerability and daily functioning. Contemporary evidence continues to identify topiramate among anticonvulsants with a comparatively unfavorable cognitive profile [2,3]. Reported effects involve attention, processing speed, memory, executive function, and language. In a 24-week randomized, double-blind, placebo-controlled dose-ranging study of 188 cognitively normal adults, target doses were 64, 96, 192, and 384 mg/day; neuropsychological decline became more frequent at higher doses, with the clearest reliable-change signal at 192 and 384 mg/day [4]. Within the selected literature, language and verbal fluency are recurrently reported as vulnerable domains. Word-finding difficulties were identified in 31 of 431 (7.2%) consecutively and prospectively collected patients with epilepsy taking topiramate [5]. A separate retrospective cross-sectional study of 421 topiramate-treated patients found poorer verbal fluency than matched epilepsy patients receiving other anticonvulsants, untreated epilepsy patients, and healthy controls [6]. Reversibility has been reported after withdrawal or dose reduction, although the available evidence is based largely on small or uncontrolled reassessments and may be affected by concomitant treatment changes [7].

Although the cognitive phenotype associated with topiramate is well recognized, its neuropharmacologic basis remains incompletely defined. Topiramate influences excitatory and inhibitory neurotransmission, ion channel activity, and carbonic anhydrase function, suggesting that its cognitive effects may reflect interactions among several pharmacologic actions rather than a single established mechanism. This focused review examines the principal neuropharmacologic actions of topiramate, summarizes the cognitive domains most consistently affected, and evaluates plausible links between its pharmacology and cognitive effects.

2. Review

2.1 Literature Search Strategy

A focused literature search was conducted using PubMed and Google Scholar to identify English-language, peer-reviewed studies relevant to the neuropharmacology and cognitive effects of topiramate. The initial search was conducted on October 6–7, 2026, and was updated on November 4, 2026. No lower publication-date limit was applied. Search terms included combinations of “topiramate” with “cognition,” “cognitive impairment,” “verbal fluency,” “word finding,” “memory,” “attention,” “GABA,” “glutamate,” “AMPA,” “neuropharmacology,” “functional magnetic resonance imaging,” “dose,” “plasma concentration,” “withdrawal,” “discontinuation,” and “reversibility.” Studies were selected when they directly evaluated cognitive outcomes associated with topiramate, examined its molecular or neurophysiologic actions, assessed dose or concentration relationships, evaluated cognitive change after dose reduction or discontinuation, or provided functional imaging or electrophysiologic evidence relevant to cognitive effects. Priority was given to primary human studies and experimental pharmacology studies, supplemented by recent reviews for mechanistic and clinical context. Reference lists of selected publications were also reviewed to identify additional pertinent studies. More recent primary studies identified during the updated search were considered and incorporated when directly relevant. Because this was a focused narrative Mini Review rather than a systematic review, formal systematic-review methodology, risk-of-bias assessment, and quantitative evidence synthesis were not performed.

2.2 Neuropharmacology of Topiramate

Topiramate has a multimodal pharmacologic profile involving several mechanisms that reduce neuronal excitability. Its well-described actions include inhibition of voltage-gated sodium channels, enhancement of gamma-aminobutyric acid (GABA)-mediated neurotransmission, antagonism of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate glutamate receptors, and inhibition of carbonic anhydrase [1,8]. Effects on voltage-gated calcium channels have also been described, although their contribution to the therapeutic and cognitive effects of topiramate remains uncertain [8].

Experimental studies provide direct support for modulation of both inhibitory and excitatory neurotransmission. Topiramate has been shown to enhance GABA-stimulated chloride influx and GABA-evoked chloride currents in cultured neurons, supporting positive modulation of GABA-mediated inhibitory signaling [9]. In cultured hippocampal neurons, topiramate inhibited kainate-evoked currents without affecting N-methyl-D-aspartate (NMDA)-evoked currents, providing evidence for selective modulation of AMPA/kainate-mediated excitatory neurotransmission [10]. Together with inhibition of voltage-gated sodium channels, these actions provide complementary mechanisms through which topiramate can suppress neuronal excitability [8-10]. Carbonic anhydrase inhibition represents an additional pharmacologic action, although its contribution to the principal neurologic effects of topiramate remains less clearly defined [8].

These pharmacologic actions provide a plausible framework for considering topiramate-associated cognitive effects. Alteration of excitatory and inhibitory neurotransmission may influence cognitive processing, but current evidence does not establish a direct relationship between any individual molecular target and a specific cognitive deficit. The neuropharmacologic basis of topiramate-associated cognitive dysfunction therefore remains biologically plausible but incompletely established [3,8].

2.3 Cognitive Effects

Topiramate-associated cognitive dysfunction is heterogeneous and has been reported across several cognitive domains. Documented effects include reduced attention and concentration, slower processing speed, impaired memory, language disturbance, and reduced verbal fluency [2,3]. Neuropsychological studies have demonstrated deficits in verbal fluency, sustained attention, processing speed, language, and working memory during topiramate treatment [11]. Dose-response findings should be interpreted in the context of the study population. In the 24-week randomized study of 188 cognitively normal adults, target doses were 64, 96, 192, and 384 mg/day; reliable neuropsychological decline occurred in 12%, 8%, 15%, and 35% of participants, respectively, compared with 5% receiving placebo, with the dose-related effect emerging primarily at the higher doses [4]. By contrast, a prospective open study enrolled 47 patients with epilepsy receiving topiramate monotherapy at target doses of 50, 75, or 100 mg/day. Thirty-six completed the 1-year neuropsychological follow-up, and dose-related worsening was reported on digit span and verbal fluency measures [7].

Within the selected literature, language and verbal fluency are among the most consistently reported affected cognitive domains. Mula et al. evaluated 431 consecutively and prospectively collected patients with epilepsy taking topiramate and identified word-finding difficulties in 31 patients (7.2%) [5]. In a retrospective cross-sectional study, Witt et al.

compared 421 topiramate-treated patients with 351 matched epilepsy patients receiving anticonvulsants other than topiramate, 108 untreated epilepsy patients, and 100 healthy controls [6]. Across corresponding treatment conditions, verbal fluency performance under topiramate was 21% to 28% poorer than in the respective condition without topiramate, allowing the authors to distinguish an additional topiramate-associated decrement from the effects of epilepsy and overall medication burden [6]. Unimpaired performance during topiramate treatment was associated with lower dose, higher educational attainment, and later epilepsy onset [6]. Similar language disturbances have also been reported in patients receiving topiramate for migraine prevention [12], indicating that the phenotype has been observed outside epilepsy populations.

Evidence for reversibility is suggestive but methodologically limited. In the 1-year monotherapy study, cognitive performance reportedly improved after topiramate withdrawal with substitution of older anticonvulsants; because withdrawal and medication substitution occurred together, improvement cannot be attributed exclusively to topiramate discontinuation [7]. In a separate study of patients with intractable epilepsy receiving polytherapy, 22 patients underwent within-subject assessment while taking and subsequently after stopping topiramate, and four of these patients also had assessments before treatment, during treatment, and again after treatment; performance improved off topiramate on multiple neuropsychological measures [11]. Thompson et al. compared 18 topiramate-treated patients with 18 matched patients undergoing repeat neuropsychological assessment. Eight topiramate-treated patients then underwent an additional brief, uncontrolled reassessment after withdrawal or substantial dose reduction; seven had discontinued topiramate and one had reduced the dose from 600 to 175 mg/day, with improvement in verbal fluency, verbal learning, and digit span [13]. These findings support at least partial reversibility, but the samples were small, treatment changes were not uniformly controlled, and only subsets of participants underwent repeated withdrawal or dose-reduction assessments.

More recent primary data also emphasize that cognitive effects are not uniform across populations or treatment contexts. In a 2026 double-blind, placebo-controlled trial of 100 veterans with posttraumatic stress disorder and alcohol use disorder receiving prolonged exposure therapy with either topiramate or placebo, no statistically significant between-group differences were observed in verbal learning and memory or processing speed at the assessed time points, and scores remained within normal clinical ranges [14]. This finding does not negate earlier evidence of cognitive adverse effects but reinforces the importance of population, exposure, cognitive domain, and treatment context when interpreting risk.

2.4 Possible Mechanisms and Clinical Implications

The cognitive effects of topiramate may reflect the combined influence of its multiple pharmacologic actions rather than a single established mechanism. Inhibition of glutamatergic neurotransmission, enhancement of GABA-mediated signaling, and modulation of voltage-gated ion channels provide biologically plausible pathways through which topiramate could alter cognitive processing [1,8-10]. However, available evidence does not establish a direct relationship between any individual molecular action and a specific cognitive deficit [3,8].

Functional imaging provides preliminary evidence of altered neural activity during language processing. In an early verbal fluency functional magnetic resonance imaging (fMRI) study of patients with frontal lobe epilepsy, the cross-sectional topiramate subgroup included eight patients and showed reduced task-related deactivation of the default mode network (DMN) compared with patients receiving other anticonvulsants and healthy controls [15]. A subsequent study enrolled 12 patients with epilepsy who developed language disfluency after add-on topiramate and 30 matched healthy controls; six patients achieved complete topiramate withdrawal without seizure relapse and underwent repeat neuropsychological testing and fMRI, with partial improvement in language performance and task-related activation and deactivation after withdrawal [16]. In a larger retrospective cross-sectional fMRI study, 32 patients receiving topiramate, 51 receiving zonisamide, and 62 matched patients receiving levetiracetam were compared; the topiramate group showed poorer cognitive performance and altered frontal and parietal network activity, with impaired task-related deactivation observed specifically with topiramate [17]. These findings support a possible network-level correlate of topiramate-associated cognitive dysfunction, although they remain observational or based on small longitudinal samples and do not identify the underlying molecular mechanism.

Evidence also supports a relationship between topiramate exposure and cognitive impairment. In the 24-week randomized dose-ranging study of cognitively normal adults, neuropsychological decline became more frequent at higher target doses [4]. Marino et al. evaluated 20 healthy volunteers who completed two double-blind, randomized, placebo-controlled crossover studies after a single 100 mg oral dose of topiramate; higher plasma concentrations were associated with greater speech disfluency, poorer verbal recall, and slower reaction time during a working memory task [18]. Because this was an acute single-dose study in healthy volunteers, its concentration-response findings should not be extrapolated directly to chronic treatment in clinical populations. Longer-term evidence derives from the 24-week healthy-adult dose-ranging study and the 1-year epilepsy monotherapy study [4,7]. Improvement after withdrawal or dose reduction has also been reported in smaller longitudinal and repeated-assessment studies [7,11,13,16], but these findings remain vulnerable to confounding from concomitant treatment changes and limited sample sizes. When cognitive symptoms emerge, dose and exposure, patient characteristics, therapeutic benefit, and overall treatment tolerability should be considered together.

2.5 Limitations

Several limitations should be considered when interpreting the literature on topiramate-associated cognitive effects. Many studies involve relatively small samples, epilepsy populations, or concomitant anticonvulsant therapy, creating potential confounding from underlying neurologic disease and polytherapy [5,6,11,13,16]. Randomized studies in cognitively normal adults or healthy volunteers reduce some of these concerns but do not directly reproduce chronic treatment in patients with epilepsy or other clinical indications [4,18]. Conversely, a recent randomized trial in veterans with posttraumatic stress disorder and alcohol use disorder did not identify significant between-group impairment in the cognitive domains assessed [14], illustrating the heterogeneity of findings across populations and treatment contexts. Differences in dose, duration of exposure, study population, neuropsychological instruments, and definitions of impairment further limit direct comparison across studies.

The mechanistic evidence has additional limitations. Although the principal molecular actions of topiramate are well characterized, much of the supporting evidence derives from experimental models, and direct links between individual pharmacologic targets and specific human cognitive deficits have not been established [8-10]. Functional imaging studies provide convergent but still preliminary evidence and include small longitudinal samples or retrospective cross-sectional designs [15-17]. Evidence for reversibility is likewise based mainly on small, partly uncontrolled reassessments, sometimes accompanied by medication substitution or other treatment changes [7,11,13,16]. In addition, this review used a focused narrative search limited to PubMed and Google Scholar and English-language peer-reviewed publications rather than systematic-review methodology; relevant studies may therefore have been missed, and no formal risk-of-bias assessment was performed. Larger prospective studies integrating standardized neuropsychological assessment, measures of topiramate exposure, and functional or electrophysiologic biomarkers may help clarify the mechanisms, predictors, and reversibility of topiramate-associated cognitive dysfunction.

3. Conclusion

Topiramate is associated with a heterogeneous cognitive adverse effect profile involving language, verbal fluency, attention, memory, and processing speed. Dose- and exposure-related effects have been demonstrated in healthy adults and patients with epilepsy, although the magnitude and clinical expression of impairment vary across populations and treatment contexts. Small longitudinal studies suggest that at least some cognitive changes may improve after dose reduction or discontinuation, but interpretation is limited by sample size, concomitant medication changes, and incomplete control conditions. Although topiramate alters multiple neuropharmacologic pathways, including glutamatergic and GABA-mediated neurotransmission and voltage-gated ion channel activity, current evidence does not establish a direct relationship between any single molecular action and a specific cognitive deficit. Functional imaging studies provide preliminary evidence of altered language and cognitive network activity. Overall, cognitive tolerability should be considered alongside therapeutic benefit, with particular attention to dose, exposure, and individual susceptibility.

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5. Conflicts of Interest

The author declares no conflicts of interest.

6. Funding

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7. Ethics Approval

Not applicable.

8. Patient Consent

Not applicable.

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