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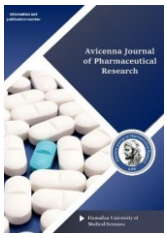

Review Article

Gabapentin: Current and Emerging Applications in Pharmacology

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Abstract

Gabapentin, originally developed as an antiepileptic drug, has demonstrated diverse mechanisms of action and therapeutic effects across various medical conditions, including neuropathic pain, epilepsy, substance use disorders, and tremor management. Gabapentin primarily acts by binding to the alpha2delta-1 subunit of voltage-gated calcium channels, inhibiting the synaptic trafficking of alpha2delta-1-NMDA receptor complexes, and modulating glutamate transmission. This mechanism contributes to its effects on neuropathic pain, epilepsy, and tremor. Additionally, gabapentin reduces P/Q-type calcium channel activity, inhibits AMPA receptor-mediated neural responses, and modulates adenosine receptor signaling, which underlies its anticonvulsant and analgesic properties. Gabapentin also suppresses protein kinase C (PKC) activity, affecting pain pathways and NMDA receptor interactions. Its effects on TRPV1 translocation and A2A receptor signaling further extend its utility to managing sleep disturbances, chronic pain, and involuntary movements. Despite its favorable safety profile, careful monitoring of dose-dependent adverse effects and potential drug interactions is essential. This comprehensive review underscores gabapentin's versatile pharmacological profile, highlighting the need for further research to optimize its clinical applications across diverse medical disciplines.

Keywords: Analgesics, Anti-Anxiety Agents, Anticonvulsants, Gabapentin, Gamma-Aminobutyric Acid

Introduction

Gabapentin, a widely used gabapentinoid drug, is primarily indicated for the treatment of neuropathic pain and epilepsy. As a synthetic analogue of the neurotransmitter gamma-aminobutyric acid (GABA), gabapentin exerts its inhibitory effects on neuronal activity, primarily through binding to the α2δ-1 subunit of voltage-gated calcium channels [1]. Initially approved by the U.S. Food and Drug

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Administration (FDA) in 1993, gabapentin has been available in generic form in the United States since 2004. It was first introduced as an anti-spasmodic agent and later gained widespread use as an adjunct therapy alongside conventional anticonvulsant medications [2, 3]. Chemically, gabapentin is classified as 1-(aminomethyl) cyclohexaneacetic acid [4].

Key pharmacokinetic properties of gabapentin are summarized in Table 1. Briefly, oral bioavailability ranges from 30–60%, absorption is mediated by the saturable L-amino transporter 1 (LAT1) system — which also facilitates drug transport across the blood–brain barrier — and peak plasma concentrations are reached within 2–3 hours. Gabapentin undergoes minimal hepatic metabolism and is excreted renally as unchanged parent drug. Its elimination half-life of 5–7 hours may extend to up to 50 hours in patients with severe renal impairment (creatinine clearance <30 mL/min) [5, 6].

Table 1. Pharmacokinetic Parameters of Gabapentin

Pharmacokinetic Parameter	Value / Details
Route of administration	Oral
Bioavailability	30-60% (dose-dependent reduction due to saturable LAT1 absorption)
Absorption mechanism	L-Amino Transporter 1 (LAT1): a saturable transporter; also mediates blood-brain barrier (BBB) penetration
Dose-bioavailability relationship	Inverse: as oral dose increases, fractional bioavailability decreases due to LAT1 saturation
Time to peak plasma concentration (Tmax)	2-3 hours after oral administration
Plasma protein binding	Negligible (drug is not significantly protein-bound)
Volume of distribution	High
Elimination half-life (normal renal function)	5-7 hours; may be prolonged with repeated dosing due to saturation of elimination pathways
Elimination half-life (CrCl <30 mL/min)	Up to 50 hours
Hepatic metabolism	Minimal; gabapentin is not significantly metabolized by the liver
Excretion	Renal, primarily as unchanged parent drug
Pregnancy/lactation	Insufficient safety data; excreted into breast milk; effects on breastfed infants unknown [103]

The FDA-approved indications for gabapentin include the management of postherpetic neuralgia and focal (partial) onset seizures. Off-label applications encompass a broad range of conditions, such as moderate to severe alcohol use disorder, alcohol withdrawal, refractory chronic cough, fibromyalgia, generalized anxiety disorder, neuropathic pain unrelated to postherpetic neuralgia, panic disorder, chronic pruritus (including malignancy-related and uremic pruritus), restless legs syndrome, and vasomotor symptoms associated with menopause. Gabapentin is also used as an adjunct to antidepressants or as monotherapy for social anxiety disorder [1, 7, 8].

Additional conditions for which gabapentin has been explored in clinical studies include bipolar disorder, essential tremors, mood disorders, postoperative analgesia, nausea and vomiting, migraine prophylaxis, headaches, painful diabetic neuropathy, insomnia, and bruxism [7, 8]. In this review, we aim to provide a comprehensive overview of the mechanisms of action and clinical applications of gabapentin.

Gabapentin Mechanism of Action

Voltage-Gated Calcium Channels

Gabapentin primarily exerts its therapeutic effects in neuropathic pain and epilepsy by binding to the alpha2delta-1 protein, which serves as the subunit of voltage-gated Ca^{2+} channels [9]. This protein plays a crucial role in neuropathic pain, and neuronal injury can result in its upregulation [10]. Although alpha2delta-1 is targeted in epilepsy treatment, it does not directly mediate its therapeutic effects but

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rather influences the N-methyl-D-aspartate (NMDA) receptor, a key glutamate receptor, which plays a significant role in epileptogenesis [1]. NMDA receptor activity is characterized by prolonged channel opening and enhanced excitatory postsynaptic transmission, factors that may contribute to increased seizure susceptibility [11]. Neuronal damage can amplify NMDA receptor function both pre- and postsynaptically [12, 13]. Research has shown that alpha2delta-1 serves as a potent modulator of NMDA receptors, forming alpha2delta-1-NMDA receptor complexes that increase synaptic NMDA receptor expression, thereby exacerbating neuropathic pain. Gabapentin alleviates neuropathic pain by preventing the trafficking of these complexes to the neuronal surface [1]. The response to gabapentin is influenced by variations in the binding properties of the alpha2delta subunit [14], which result in differing affinities and functional outcomes in voltage-gated Ca^{2+} channels [15, 16]. Besides its role in neuropathic pain and epilepsy, this receptor is also implicated in sleep regulation [17, 18]. Additionally, alpha2delta receptors play a role in tremor pathophysiology. Although the precise mechanism of tremor remains unclear, alterations in glutamate and GABA levels are considered contributing factors. Studies indicate that alpha2delta agonists, such as gabapentin, can effectively ameliorate tremor by modulating glutamate transmission within the thalamus. Gabapentin achieves this by reducing the surface expression of NMDA receptors via the formation of alpha2delta complexes, thereby alleviating involuntary movements [9, 12].

Protein Kinase C (PKC)

Protein kinase C (PKC) is a family of serine/threonine kinases involved in various cell signaling pathways within the nervous system. PKC acts as a key regulator of NMDA receptor activity, and its activation or inhibition significantly impacts NMDA receptor function. Specifically, phosphorylation by PKC regulates the physical interaction between the alpha2delta-1 subunit and NMDA receptors. PKC activation enhances alpha2delta-1-NMDA receptor association, whereas its inhibition reduces the expression of this protein complex. The PKC gamma subunit, which is calcium- and diacylglycerol-dependent, plays an important role in nociceptive processing [19]. Experimental studies have demonstrated that gabapentin significantly suppresses spinal PKC expression, resulting in pain relief [20]. PKCε, another isoform, is particularly involved in both inflammatory and neuropathic pain states [18, 19]. The localization of PKCε to neuronal membranes is essential for the phosphorylation of target proteins that mediate pain responses [20, 21]. Gabapentin also affects Transient Receptor Potential Vanilloid 1 (TRPV1), a non-selective cation channel found in primary afferent neurons that respond to noxious stimuli. Gabapentin inhibits TRPV1 translocation within peripheral nerve fibers, preventing phosphorylation-induced activation and exerting analgesic effects [22-24].

Adenosine

Adenosine is a purine compound that functions as an extracellular signaling molecule in both the central and peripheral nervous systems [25]. It is released locally in response to trauma and ischemia [26, 27]. Four subtypes of adenosine receptors—A1, A2A, A2B, and A3—have been identified [25, 28]. The anti-allodynic effects of gabapentin are primarily mediated through the activation of spinal A1 adenosine receptors, whereas motor dysfunction effects are attributed to A2 receptor activation. The role of A2A receptors in sleep regulation is well established, with studies indicating that patients with insomnia exhibit reduced adenosine levels. Gabapentin enhances A2A receptor signaling, thereby promoting slow-wave sleep [29-31]. A1 receptors predominantly mediate inhibitory neurotransmitter release, while A2 receptors facilitate excitatory neurotransmission and motor control. A2A receptors are highly concentrated in the neostriatum, and their dysregulation contributes to involuntary movements observed in conditions such as Parkinson's disease. Antagonism of A2A receptors helps reduce these involuntary movements by inhibiting excitatory neurotransmitter release [32]. Gabapentin's ability to influence adenosine receptor function contributes to its efficacy in managing tremor [32-34].

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P/Q-Type Calcium Channels

P/Q-type calcium channels are high-voltage-activated presynaptic channels predominantly expressed in central nervous system neurons [35, 36]. The "P" and "Q" designations originate from their discovery in Purkinje cells and cerebellar granule cells, respectively, where they are highly expressed. These channels play diverse biological roles, with the regulation of neurotransmitter release being one of their most critical functions [37]. Gabapentin exerts its effects by inhibiting Ca^{2+} influx through P/Q-type voltage-gated calcium channels, which are predominant in glutamatergic synapses. This inhibition significantly reduces the release of excitatory amino acids, such as glutamate, thereby decreasing postsynaptic excitability and contributing to gabapentin's anticonvulsant properties [38].

AMPA Receptors

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor is one of the primary receptors for glutamate and plays a key role in tremor pathophysiology [9]. AMPA receptors mediate fast synaptic transmission in the central nervous system and are crucial in the development and propagation of epileptic activity [39]. Under normal conditions, the brain predominantly expresses Ca^{2+}-impermeable AMPA receptors; however, in pathological states such as epilepsy, the upregulation of Ca^{2+}-permeable AMPA receptors occurs [40, 41]. Animal studies have demonstrated that gabapentin can inhibit AMPA receptor-mediated neural responses, further supporting its role in seizure control [38].

Clinical Aspects of Gabapentin in Adult Patients

Gabapentin has well-established roles in the management of PHN, focal seizures, and RLS, offering effective symptom relief when appropriately titrated. Its flexible dosing schedule allows customization based on patient needs and tolerability. However, optimization requires monitoring for side effects such as somnolence, dizziness, and weight gain.

Additionally, its off-label use in adults and pediatric populations has been explored in various studies. Continued research into off-label uses will further clarify its therapeutic potential in diverse populations [42-46].

Gabapentin for Pain Management

Gabapentin was evaluated in a non-randomized stepped-care protocol for persistent facial pain in patients unresponsive to TCAs (n=19; mean dose 973.7 mg/day), achieving a ≥50% pain reduction in 36.8% of participants; outcomes were influenced by patient age, comorbidities, and extent of pain distribution [42]. In a 12-week double-blind RCT (n=150), gabapentin 1,200–2,400 mg/day significantly improved BPI pain severity and interference scores in fibromyalgia versus placebo, with dizziness, sedation, and weight gain as the principal adverse effects [43]. Across three trials in painful diabetic neuropathy and treatment-resistant neuropathic pain, gabapentin was comparable in efficacy to duloxetine, with a faster onset of pain relief observed in one study; combination regimens were generally safe and well tolerated, with pregabalin being associated with greater edema and weight gain [44–46]. Gabapentin 300 mg TID also significantly reduced the incidence of moderate-to-severe chemotherapy-induced neuropathy in paclitaxel-treated breast cancer patients (n=40) [47]. In a crossover trial in hemodialysis patients with neuropathic pruritus (n=29), gabapentin 300 mg post-HD produced approximately 50% symptom reduction, comparable to pregabalin 75 mg/day [48]. Complete trial characteristics and outcomes are summarized in Table 2.

Table 2. Summary of Clinical Trials Evaluating Gabapentin Across Therapeutic Areas

Therapeutic Area / Indication	Study Design	N	Dose & Duration	Key Outcomes	Ref
Pain Disorders					
Facial/myofascial pain (TCA non-responders)	Non-randomized	19a	Mean 973.7 mg/day; NR	>=50% pain reduction in 36.8% of patients; response influenced by age, comorbidities, and pain extent	[42]
Fibromyalgia	DB, PC,	150	1,200-2,400	Significant improvement in BPI pain severity	[43]

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	RCT		mg/day; 12 weeks	and interference vs placebo; dizziness, sedation, weight gain more prevalent	
Painful diabetic neuropathy (PDN) vs duloxetine	Randomized, open-label	86	300 mg/day; 12 weeks	Both gabapentin and duloxetine improved VAS, DNS, DNE, NDS; no significant between-group difference	[44]
Painful diabetic peripheral polyneuropathy (PDPP) vs duloxetine	DB, RCT	104	300 mg/day, titrated to 900 mg; 8 weeks	Both drugs improved VAS, Sleep Interference Score, CGIC; gabapentin showed faster improvement at week 1	[45]
Treatment-resistant neuropathic pain (duloxetine + gabapentin)	Open-label	407	>=900 mg/day gabapentin; 12 weeks	All regimens (duloxetine, pregabalin, combination) safe and tolerable; nausea with duloxetine; edema/weight gain with pregabalin	[46]
Chemotherapy-induced neuropathy (paclitaxel)	DB, PC, RCT	40	300 mg TID per 2-week chemo cycle	Significantly reduced moderate-to-severe neuropathy incidence vs placebo (nerve conduction velocity and patient-reported outcomes)	[47]
Neuropathic pruritus and pain in hemodialysis	Prospective crossover	50 (29 with pruritus)	300 mg after each HD session; 6 weeks	~50% symptom reduction; gabapentin 49.9% vs pregabalin 47.7%; comparable safety profiles	[48]
Perioperative Management					
Post-op pain: transurethral prostate resection	RCT	181	600 mg, single dose 2h preop	Reduced VAS, tramadol consumption, and nausea; increased patient satisfaction vs placebo	[49]
Post-op pain: uterine aspiration (first-trimester)	RCT	111	600 mg preop, single dose	Reduced pain at 10 and 30 min post-op; no effect on intraoperative pain or nausea	[50]
Post-op pain: craniotomy (suboccipital/subtemporal)	RCT	122	600 mg preop + 2h before anesthesia	Reduced acute pain at 24 h; decreased propofol and remifentanil use; increased sedation at 2 h	[51]
Post-op pain cessation (mixed surgical cohort)	RCT	410	1,200 mg preop + 600 mg TID x 72h; follow-up at 6 and 12 months	Did not accelerate pain cessation; modestly increased opioid cessation rate at 6 and 12 months vs lorazepam	[52]
Post-op pain: inguinal herniorrhaphy	RCT	120 males	400 / 800 / 1,200 mg preop	Reduced VAS and fentanyl consumption vs placebo; higher doses associated with somnolence	[53]
Post-op pain: laparoscopic sleeve gastrectomy	RCT	50	1,200 mg preop, single dose	Reduced morphine over 24 h; improved preoperative anxiety scores vs placebo	[54]
Perioperative anxiety - general anesthesia	Prospective, DB, PC	63	1,200 mg preop, single dose	Significant anxiolysis without sedation or memory impairment	[55]
Perioperative anxiety - major surgery (highly anxious)	DB, RCT	44 females	1,200 mg, 2- 3 h preop	Reduced anxiety and pain catastrophizing; higher NRS and RASS sedation scores vs placebo	[56]
Post-spinal anesthesia headache and pain	DB, PC	120	300 mg preop + q12h for 24h	Reduced headache incidence/severity, postoperative pain, and morphine consumption	[57]
Post-dural puncture headache (PDPH)	RCT	42	NR; 4-day course vs caffeine/ergotamine	Reduced VAS headache severity and vomiting frequency vs caffeine/ergotamine	[58]
Sedation in mechanically ventilated ICU patients	DB, RCT	43	300 mg TID, add-on to fentanyl + midazolam	Reduced midazolam/fentanyl requirements; lower delirium incidence; target sedation (RSS 2-3) achieved in both groups	[59]
Etomidate-induced myoclonus (general anesthesia)	DB, PC, RCT	100	400 / 800 / 1,200 mg, 2h preop	800 and 1,200 mg reduced myoclonic movement incidence/severity; higher doses increased preoperative sedation	[60]
Eye Disorders					
Acquired pendular nystagmus (APN) - MS/OPT	Crossover	16 (29 eyes)	300 mg QID; NR	Improved visual acuity, oscillopsia, and eye movement recordings; comparable efficacy to memantine	[61, 62]
Dry eye disease / neuropathic ocular pain	Comparative RCT	72	600 mg/day, titrated to 1,800-2,400 mg; 6 weeks	Superior improvement in OSDI, Schirmer's test, and tear breakup time vs standard therapy alone	[63]
Post-photorefractive keratotomy (PRK) pain	RCT	150	300 mg TID, from 2 h post-surgery; 3 days	Lower VAS pain scores vs placebo; comparable to pregabalin 75 mg TID	[64]
Neurological Conditions (Tremor & Headache)					
Multiple tremor disorders (essential, Parkinson's,	Open-label	67	NR; 16 months	Greatest absolute reduction in MS tremor; greatest relative improvement in orthostatic	[65]

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MS, writing, orthostatic)				tremor; male sex and shorter disease duration predicted better response	
Headache: aneurysmal subarachnoid hemorrhage	DB, PC, RCT	16	100 mg titrated to 900 mg TID; 7 days	No significant reduction in NPS or opioid use vs placebo	[66]
Migraine prophylaxis vs topiramate	Randomized, open-label	40	300-1,200 mg/day; 90 days	Similar reduction in headache severity, frequency, and duration vs topiramate 50-200 mg; dizziness and weight gain with gabapentin	[65, 66]
Migraine: dose-response study	DB, RCT	523	1,200 / 1,800 / 2,400 / 3,000 mg/day; 20 weeks	No significant overall difference vs placebo; best response at 1,200-1,800 mg (67-68% vs 54% placebo); strong placebo effect at all doses	[65, 66]
Vasomotor Symptoms (Hot Flashes)					
Hot flashes - postmenopausal women	DB, PC, RCT	59	900 mg/day (->2,700 mg open-label extension); 12 weeks	45% reduction in flash frequency; 54% composite score reduction vs 29%/31% with placebo	[67]
Hot flashes - breast cancer patients on tamoxifen	DB, PC, RCT	420	900 mg/day; 8 weeks	46% decrease in hot flash severity score vs placebo	[68]
Hot flashes - breast cancer, antidepressant-refractory (Phase III)	RCT	118	NR; NR	49-60% reduction in hot flash frequency and severity	[69]
Hot flashes - gastroretentive gabapentin (G-GR) in menopause	DB, PC, Phase 3 RCT	600	600 mg AM + 1,200 mg PM; 24 weeks	Significant reduction in moderate-to-severe hot flash frequency/severity at weeks 4, 12, 24; improved sleep quality	[70]
Hot flashes vs fluoxetine - postmenopausal crossover	Crossover RCT	79	300 mg/day vs fluoxetine 20 mg/day; 4 weeks/arm	Significant improvement in vasomotor symptoms (Greene Climacteric Scale) vs fluoxetine	[71]
Sleep Disorders					
Transient insomnia (sleep phase advance model)	DB, PC, Multicenter RCT	254	250 mg, 30 min before bedtime; 28 days	Reduced WASO and increased TST on days 1 and 28 (PSG and self-report); no next-day functional impairment	[72]
Sleep bruxism vs stabilization splint	Single-blind RCT	20	300 mg nightly; 2 months	Reduced SB episodes/hour and masseter EMG intensity; superior slow-wave sleep and sleep efficiency vs splint	[73]
Psychiatric & Substance Use Disorders					
AUD - gabapentin + naltrexone	RCT	150	Titrated to 1,200 mg/day + naltrexone 50 mg; 16 weeks	Longer heavy-drinking-free periods and lower craving in weeks 1-6; benefits not sustained beyond week 6; improved sleep quality	[74]
AUD - monotherapy dose-response	RCT	150	900 or 1,800 mg/day; 12 weeks	Both doses improved abstinence and reduced heavy drinking; 1,800 mg more effective; improved insomnia, dysphoria, craving	[75]
AUD - high-dose monotherapy	DB, PC, RCT	40	3,600 mg/day; 8 weeks	Significantly reduced heavy drinking days and increased abstinent days vs placebo	[76]
AUD with alcohol withdrawal	DB, PC, RCT	96	1,200 mg/day; 2014-2018	Higher rates of no-heavy-drinking days and complete abstinence vs placebo	[77]
OUD - gabapentin + methadone	DB, PC, RCT	60	300 mg + methadone 40-120 mg; 3 weeks	Lower cumulative methadone doses, particularly in opium-dependent patients	[78]
OUD - gabapentin during buprenorphine detoxification	DB, PC, RCT	24	Titrated to 1,600 mg/day; 5 weeks	Significantly reduced opioid-positive urine in weeks 3-4; withdrawal symptom severity similar between groups	[79]
Bipolar disorder - acute mania (+ lithium)	RCT	60	900 mg/day + lithium; 6 weeks	Significant improvement on YMRS vs lithium alone	[80]
Bipolar disorder + comorbid cannabis use disorder	DB, PC, Crossover RCT	22	Up to 1,200 mg/day; 1 week/arm + washout	Increased glutamate in dACC/rBG; reduced cannabis use and mood symptoms in more severe cases	[81]
Respiratory Conditions					
Chronic refractory cough	DB, PC, RCT	62	Up to 1,800 mg/day; 10 weeks	Significant improvement in Leicester Cough Questionnaire quality-of-life score vs placebo; nausea and fatigue noted	[83]
GERD-related refractory cough vs baclofen	Open-label RCT	234	Up to 900 mg/day (add-on after failed	~55% cough resolution, comparable to baclofen; fewer adverse effects than baclofen	[84]

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			omeprazole); 8 weeks		
COVID-19-related cough (+/- montelukast)	RCT	180	NR; NR	Significant reductions in BCSS and VAS; greatest BCSS improvement with gabapentin + montelukast combination	[85]
Pediatric Applications					
Neurogenic bladder after spina bifida surgery	RCT	44 (mean age 6.1 y)	20 mg/kg/day; 1 year	Improvement in all groups; gabapentin + oxybutynin superior; gabapentin monotherapy best tolerated	[87]
Emergence agitation after desflurane - strabismus surgery	DB, PC, RCT	70 (ages 2-6 y)	5 mg/kg preop	Significantly lower EA severity; longer extubation/emergence times vs placebo	[88]
Emergence agitation after sevoflurane - tonsillectomy	RCT	NR (ages 6-12 y)	NR	Lower EA incidence and reduced postoperative analgesic requirements vs placebo	[89]
Phantom limb pain prevention - pediatric bone tumor amputation	DB, PC, RCT	45	300-900 mg/day, from 4 days preop; 30 days	Lower pain intensity and incidence at final follow-up vs placebo	[90]
Post-op pain: spinal fusion for scoliosis (adolescents)	DB, RCT	50	15 mg/kg preop + 10 mg/kg q8h; 3 days post-op	Reduced pain in first 2 postoperative days; no significant overall difference across 5 days	[91]

Abbreviations: APN, acquired pendular nystagmus; AUD, alcohol use disorder; BPI, Brief Pain Inventory; BCSS, Breathlessness Cough and Sputum Scale; CGIC, Clinical Global Impression of Change; dACC, dorsal anterior cingulate cortex; DB, double-blind; DNE, Diabetic Neuropathy Examination; DNS, Diabetic Neuropathy Symptoms; EA, emergence agitation; GERD, gastroesophageal reflux disease; HD, hemodialysis; MS, multiple sclerosis; NPS, Numeric Pain Scores; NR, not reported; NRS, Numeric Rating Scale; OSDI, Ocular Surface Disease Index; OPT, oculopalatal tremor; OUD, opioid use disorder; PC, placebo-controlled; PDN, painful diabetic neuropathy; PDPP, painful diabetic peripheral polyneuropathy; PRK, photorefractive keratotomy; PSG, polysomnography; RASS, Richmond Agitation-Sedation Scale; RCT, randomized controlled trial; rBG, right basal ganglia; RSS, Ramsay Sedation Score; SB, sleep bruxism; TCA, tricyclic antidepressant; VAS, Visual Analogue Scale; WASO, wake after sleep onset; YMRS, Young's Mania Rating Scale.

Gabapentin in Post-Operative Pain, Headache, Nausea, Vomiting, and Sedation

Gabapentin has been evaluated as a perioperative adjunct across multiple surgical settings [49–60]. Single preoperative doses of 600–1,200 mg consistently reduced postoperative VAS pain scores, opioid or tramadol consumption, and nausea in procedures ranging from transurethral prostate resection and uterine aspiration to craniotomy, inguinal herniorrhaphy, and laparoscopic sleeve gastrectomy; higher doses were associated with dose-dependent somnolence [49–54]. Gabapentin 1,200 mg preoperatively produced significant anxiolytic effects without impairing memory in two RCTs [55, 56], reduced post-spinal anesthesia headache severity and morphine consumption [57], and outperformed caffeine/ergotamine in post-dural puncture headache over a four-day course [58]. In mechanically ventilated ICU patients, gabapentin 300 mg TID as add-on therapy significantly reduced midazolam and fentanyl requirements and lowered delirium incidence versus placebo [59], while gabapentin 800–1,200 mg attenuated etomidate-induced myoclonic movements during anesthesia induction [60]. Full trial details are presented in Table 2.

Gabapentin in Eye Disorders

Gabapentin has demonstrated therapeutic potential across three distinct ocular conditions [61–64]. In a single-center crossover trial (n=16; 29 eyes), gabapentin 300 mg four times daily improved visual acuity, oscillopsia amplitude, and eye movement recordings in acquired pendular nystagmus, with efficacy comparable to memantine [61, 62]. In patients with severe dry eye disease and neuropathic ocular pain (n=72), adding gabapentin (titrated to 1,800–2,400 mg/day) to standard therapy significantly improved OSDI scores, Schirmer's test results, and tear breakup time versus standard therapy alone [63]. In a three-arm RCT for post-photorefractive keratotomy pain (n=150), gabapentin 300 mg TID produced VAS pain scores significantly lower than placebo and comparable to pregabalin 75 mg TID [64]. Details are presented in Table 2.

Gabapentin for Tremor Management

In a 16-month open-label study of 67 patients with various tremor disorders, gabapentin as adjunct

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therapy produced the greatest absolute reduction in MS tremor and the greatest relative improvement in orthostatic tremor; male sex and shorter disease duration were predictors of a more favorable response [65]. Study details are presented in Table 2.

Headache and Migraine Management

Gabapentin showed no significant benefit over placebo in aneurysmal subarachnoid hemorrhage-related headache (n=16, titrated to 900 mg TID over seven days). As migraine prophylaxis in an open-label trial (n=40, 300–1,200 mg/day, 90 days), gabapentin was comparable to topiramate in reducing headache severity, frequency, and duration. In a larger dose-response RCT (n=523, 20 weeks), no overall superiority over placebo was demonstrated; the 50% responder rates were 67–68% at 1,200–1,800 mg/day versus 54% with placebo, with diminishing returns at higher doses and a strong placebo effect throughout [65, 66]. Full data are in Table 2.

Gabapentin in the Management of Hot Flashes

Five RCTs have demonstrated gabapentin's efficacy in managing vasomotor symptoms [67–71]. Gabapentin 900 mg/day reduced hot flash frequency by 45% and the composite severity–frequency score by 54% versus placebo in postmenopausal women [67], and produced a 46% decrease in hot flash severity score in tamoxifen-treated breast cancer patients [68]. In antidepressant-refractory patients, gabapentin alone or combined reduced hot flash frequency and severity by 49–60% [69]. The gastroretentive formulation (600 mg AM + 1,200 mg PM) sustained significant reductions through 24 weeks with improved sleep quality [70], and gabapentin 300 mg/day outperformed fluoxetine 20 mg/day on the Greene Climacteric Scale in a crossover study. Dizziness and somnolence were the most commonly reported adverse effects and generally diminished over time [71]. Full data are in Table 2.

Gabapentin for Insomnia Management

In a 28-day multicenter double-blind RCT (n=254), gabapentin 250 mg taken 30 minutes before bedtime significantly reduced wake after sleep onset (WASO) and increased total sleep time (TST) on days 1 and 28, with no next-day functional impairment; headache and mild transient somnolence were the only notable adverse effects [72].

Gabapentin in the Management of Sleep Bruxism

In a two-month single-blind RCT (n=20), gabapentin 300 mg nightly significantly reduced sleep bruxism episodes per hour, bruxism time index, and masseter EMG intensity versus baseline, with superior improvements in slow-wave sleep and overall sleep efficiency compared to stabilization splint therapy [73].

Gabapentin in Alcohol Use Disorder Treatment: Four RCTs support gabapentin's utility in alcohol use disorder [74–77]. When added to naltrexone (n=150), gabapentin produced longer periods free of heavy drinking, lower craving scores, and improved sleep quality during the first six weeks, though these benefits were not sustained beyond this period [74]. As monotherapy, 1,800 mg/day was superior to 900 mg/day in achieving abstinence and reducing heavy drinking [75]; high-dose monotherapy at 3,600 mg/day over eight weeks also significantly reduced heavy drinking days [76]. In a withdrawal-focused trial (n=96, 1,200 mg/day), gabapentin significantly increased rates of complete abstinence versus placebo [77]. Full data are in Table 2.

Gabapentin in Opioid Use Disorder Management

In two controlled trials, gabapentin 300 mg combined with methadone (n=60) significantly lowered cumulative methadone dose requirements over three weeks, particularly in opium-dependent patients [78]. During buprenorphine detoxification (n=24), gabapentin titrated to 1,600 mg/day significantly reduced opioid-positive urine samples in weeks 3–4, with withdrawal symptom severity similar between groups [79].

Gabapentin for Bipolar Disorder

Adding gabapentin 900 mg/day to lithium (n=60) significantly improved YMRS scores after six weeks compared to lithium alone [80]. In a crossover trial in patients with bipolar disorder and comorbid cannabis use disorder (n=22), gabapentin up to 1,200 mg/day increased glutamate levels in the dorsal anterior cingulate cortex (dACC) and right

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basal ganglia (rBG), with reduced cannabis use in those with more severe baseline presentations [81]. A meta-analysis of 55 double-blind RCTs found inconclusive evidence for gabapentin in bipolar disorder overall, with moderate support for its anxiolytic properties [82].

Gabapentin for Chronic Cough Management

In a 10-week double-blind RCT (n=62), gabapentin up to 1,800 mg/day significantly improved Leicester Cough Questionnaire scores versus placebo, with nausea and fatigue as the main adverse effects [83]. In refractory GERD-related cough (n=234), add-on gabapentin up to 900 mg/day and baclofen 60 mg/day both achieved approximately 55% cough resolution over eight weeks, with gabapentin having a more favorable adverse effect profile [84]. Among hospitalized COVID-19 patients with cough (n=180), gabapentin alone and combined with montelukast significantly reduced BCSS and VAS scores, with the greatest BCSS improvement in the combination group [85]. Details are in Table 2.

Gabapentin in Pediatric Patients

Gabapentin is an established treatment for pediatric partial-onset seizures and neuropathic pain, with dosing adapted by age and weight and a favorable efficacy profile comparable to amitriptyline [86]. Neurogenic bladder (spina bifida): In a one-year RCT (n=44, mean age 6.1 years), all groups improved, with gabapentin + oxybutynin combination achieving the greatest detrusor pressure reduction; gabapentin monotherapy was best tolerated [87]. Emergence agitation: Preoperative gabapentin 5 mg/kg reduced EA severity after desflurane anesthesia in children aged 2–6 undergoing strabismus surgery (n=70), and lowered EA incidence and analgesic requirements in children aged 6–12 undergoing tonsillectomy under sevoflurane [88, 89]. Phantom limb pain: In 45 pediatric patients undergoing amputation for bone tumors, gabapentin 300–900 mg/day starting four days preoperatively and continued for 30 days significantly reduced phantom limb pain intensity and incidence at final follow-up versus placebo [90]. Post-operative pain (scoliosis): In 50 adolescents undergoing spinal fusion, gabapentin (15 mg/kg preop + 10 mg/kg q8h × 3 days) reduced pain in the first two postoperative days without a significant overall difference across five days [91].

Current Guidelines on Gabapentin Use

Gabapentin has established its place across multiple clinical guidelines for various conditions, including essential tremor, epilepsy, diabetic neuropathy, hot flashes, alcohol withdrawal, and ALS. Its effectiveness in symptom management, favorable tolerability, and versatility in combination therapies make it a valuable pharmacologic option across different patient populations [92-101].

Adverse Effects of Gabapentin

Although gabapentin offers significant therapeutic benefits, its potential adverse effects should be considered. The most frequently reported side effects include somnolence, dizziness, and ataxia, with occasional occurrences of nystagmus, fatigue, myalgia, and dry mouth, varying in frequency across patients [11, 12]. While these effects are generally not life-threatening, they may pose risks in certain conditions, such as hypotension, which can increase the likelihood of falls and related complications.

Rare but serious adverse reactions, including Stevens-Johnson syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, have been documented in case reports. These hypersensitivity reactions, although less common with gabapentin compared to other antiepileptic drugs, warrant caution, particularly in patients with a history of severe drug allergies [102]. Given gabapentin's primary renal excretion, dose adjustments are required based on creatinine clearance; recommended dose ranges are presented in Table 3 [103].

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Table 3. Gabapentin Dose Adjustment Based on Renal Function (Immediate-Release Formulation)

CrCl (mL/min)	Total Daily Dose	Dosing Frequency	Notes
>60	900-3,600 mg/day	Three times daily (TID)	Standard dosing range for most adult indications
30-59	400-1,400 mg/day	Twice or three times daily (BID/TID)	Moderate dose reduction required
15-29	200-700 mg/day	Once or twice daily (QD/BID)	Significant dose reduction required
<15	100-300 mg/day*	Once daily (QD)	Maximum 300 mg/day as cited in this review
Hemodialysis (supplement)	125-350 mg post each HD session	Per hemodialysis session	Loading dose 300-400 mg after first session; supplemental dose after each subsequent 4-hour session

Gabapentin Interactions

In terms of drug interactions, gabapentin generally has a low potential for significant interactions, except metoclopramide, particularly its intranasal form, which may exacerbate dizziness, confusion, and drowsiness in elderly patients. Gabapentin also exhibits pharmacodynamic synergy with central nervous system (CNS) depressants such as sedative-hypnotics, opioids, antidepressants, and H1 antihistamines, potentially leading to respiratory depression, especially in older adults and patients with comorbidities. Although these interactions are not absolute contraindications, close monitoring is advisable [104].

Currently, there are insufficient data on the safety of gabapentin during pregnancy, and while it is excreted into breast milk, its effects on breastfed infants remain unknown [105].

Despite its favorable safety profile, gabapentin requires careful consideration regarding dose adjustments in renal impairment, potential CNS depressant interactions, and the possibility of rare but serious allergic reactions. Appropriate patient selection and monitoring can help maximize its therapeutic benefits while minimizing risks [106].

Discussion

This comprehensive review highlights gabapentin's remarkable pharmacological versatility, extending far beyond its original indication as an antiepileptic agent. The evidence presented demonstrates that gabapentin's therapeutic breadth stems from its multifaceted mechanistic profile, primarily centered on α2δ-1 subunit modulation but extending to NMDA receptor trafficking, PKC signaling, adenosine receptor engagement, and P/Q-type calcium channel inhibition [1, 9, 14, 38]. These molecular targets collectively explain gabapentin's efficacy across pain, seizure, movement, sleep, and substance use disorders. The α2δ-1–NMDA receptor complex represents a particularly important mechanistic insight. By preventing synaptic trafficking of this complex, gabapentin reduces excitatory neurotransmission in a manner distinct from conventional GABAergic agents [1]. This mechanism not only underlies its anticonvulsant and analgesic properties but also positions gabapentin as a modulator of glutamatergic tone relevant to tremor pathophysiology and potentially to mood and substance use disorders [9, 12]. The observation that PKC-mediated phosphorylation regulates α2δ-1–NMDA association further suggests that patient-specific differences in PKC activity may contribute to response variability [15, 19, 20]. In the pain domain, gabapentin has established efficacy in postherpetic neuralgia and painful diabetic neuropathy, with comparable outcomes to duloxetine in head-to-head trials [44, 45]. However, the finding that gabapentin may provide faster initial pain relief in certain patients warrants further investigation, as does the potential for combination therapy with duloxetine or pregabalin in treatment-resistant cases [46]. The preventive efficacy against chemotherapy-induced neuropathy represents a particularly promising prophylactic application, though larger confirmatory trials are needed [47].

The perioperative literature reveals consistent benefits in reducing postoperative pain, opioid consumption, and associated symptoms such as nausea and anxiety [49–54]. These effects appear dose-dependent, with higher doses conferring

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greater analgesic benefit at the cost of increased sedation. The anxiolytic properties observed in preoperative settings, combined with reductions in post-dural puncture headache severity, suggest gabapentin's utility extends beyond pure analgesia to modulation of the stress and nociceptive response cascade [55–58]. In critical care, gabapentin's ability to reduce midazolam and fentanyl requirements while lowering delirium incidence positions it as a valuable adjunct in mechanically ventilated patients [59]. The mitigation of etomidate-induced myoclonus further demonstrates its potential role in anesthesia protocols, though sedation trade-offs require careful titration [60]. The emerging applications in substance use disorders represent some of the most clinically significant off-label findings. In AUD, gabapentin demonstrates dose-dependent improvements in abstinence rates and withdrawal symptom alleviation, with particular benefit when combined with naltrexone in early treatment phases [76, 77]. However, the observation that these benefits may diminish over time suggests gabapentin may be most appropriately positioned as an adjunctive bridge therapy rather than standalone maintenance treatment. In OUD, the reduction in methadone requirements and opioid-positive urine samples during buprenorphine tapering supports gabapentin's role in detoxification protocols, though its effects on acute withdrawal symptoms appear modest [80, 81]. The sleep-modulating properties of gabapentin, mediated through A2A receptor enhancement and slow-wave sleep promotion, have implications beyond insomnia management. Improved sleep architecture may contribute to its efficacy in alcohol withdrawal, where sleep disruption is a major relapse trigger [29–31, 74]. Similarly, the superiority over stabilization splints in sleep bruxism management, particularly regarding slow-wave sleep enhancement, suggests a mechanistic benefit beyond
simple muscle relaxation [75]. In movement disorders, gabapentin's tremor-reducing effects, most pronounced in orthostatic and MS-related tremors, align with its thalamic glutamate-modulating properties [9, 12, 65]. However, the predictive value of male gender and shorter disease duration for treatment response indicates that patient selection criteria require refinement. Several limitations temper these promising findings. The off-label evidence base is predominantly composed of small, single-center trials with short follow-up periods, limiting generalizability. Heterogeneous dosing regimens and outcome measures across studies preclude meta-analytic synthesis for many indications. The substantial placebo effects observed in migraine prophylaxis and other conditions highlight the need for adequately powered, well-controlled trials [68]. Additionally, the relationship between plasma gabapentin concentrations and clinical response remains poorly characterized, complicating dose optimization. Pharmacokinetic constraints also warrant consideration. The saturable LAT1-mediated absorption produces nonlinear bioavailability, meaning dose increments yield diminishing returns in plasma exposure [5, 6]. This characteristic, combined with primarily renal elimination, necessitates careful dose adjustment in elderly patients and those with renal impairment—populations in whom gabapentin is frequently prescribed. The paucity of pregnancy safety data and unknown effects on breastfed infants further limit prescribing confidence in reproductive-age women [105]. From a mechanistic perspective, while α2δ-1 binding is well established, the precise relationship between receptor occupancy and downstream functional effects remains incompletely understood. The interindividual variability in clinical response may reflect genetic polymorphisms in CACNA2D1, differences in NMDA receptor subunit composition, or compensatory changes in alternative calcium channel subtypes. Biomarker-driven studies investigating these factors could enable personalized dosing and patient selection strategies. Future research priorities should include: (i) large-scale, multicenter RCTs with extended follow-up for off-label indications; (ii) head-to-head comparative effectiveness trials against standard-of-care therapies; (iii) pharmacogenomic studies to identify response predictors; (iv) development of novel formulations with improved pharmacokinetic profiles; and (v) real-world evidence studies to capture long-term safety and effectiveness in diverse clinical populations. Addressing these gaps will be essential to optimize gabapentin's clinical utility and define its precise positioning within evolving

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treatment algorithms across multiple medical disciplines.

Conclusion

Gabapentin represents a highly versatile therapeutic agent, leveraging its multifaceted mechanisms of action to address complex medical conditions, including neuropathic pain, epilepsy, and tremor. By modulating calcium channels, NMDA and AMPA receptors, PKC pathways, and adenosine receptor signaling, gabapentin effectively manages symptoms across neurological, psychiatric, and pain-related disorders. A generally favorable safety profile complements its broad therapeutic scope, although dose adjustments and monitoring are required in specific populations. The diverse molecular targets of gabapentin provide a foundation for exploring novel indications and optimizing its clinical utility. Future research should focus on large-scale trials to establish long-term safety, refine dosing strategies, and further elucidate its mechanisms, paving the way for expanded applications in modern pharmacotherapy. Gabapentin's growing role across disciplines highlights its significance as a cornerstone in evidence-based medical practice.

List of Abbreviations

AMPA: α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BPI: Brief Pain Inventory
dACC: Dorsal anterior cingulate cortex
EMG: Electromyography
FDA: U.S. Food and Drug Administration
GABA: Gamma-aminobutyric acid
HD: Hemodialysis
NMDA: N-Methyl-D-aspartate
OSDI: Ocular Surface Disease Index
PHN: Postherpetic neuralgia
PKC: Protein kinase C
RBG: Right basal ganglia
RCT: Randomized controlled trial
RLS: Restless legs syndrome
TCA: Tricyclic antidepressant
TID: Three times daily
TRPV1: Transient receptor potential vanilloid 1
TST: Total sleep time
VAS: Visual analog scale
WASO: Wake after sleep onset
YMRS: Young Mania Rating Scale

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Conflict of interest

The authors declare that there is no conflict of interest.

Ethical issue

Not applicable

Contribution statement

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