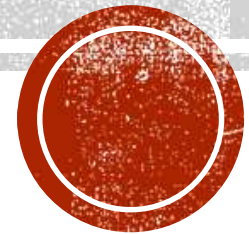


GABAPENTINOLIDS IN PAIN MEDICINE: FROM PHARMACOLOGY TO PRACTICAL PRESCRIBING



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A CONCISE HISTORY OF GABAPENTINOIDS : FROM SERENDIPITY TO SCRUTINY

- The gabapentinoid story begins not with pain, but with epilepsy.
- In 1970s, scientists sought to create a centrally-acting GABA-mimetic that could cross BBB.
- By adding a cyclohexyl ring to the GABA backbone, they synthesized Gabapentin (patented in 1977), expecting a potent anticonvulsant.



- The hypothesis was wrong.
- Researchers soon discovered that gabapentin does not bind to GABA-A or GABA-B receptors, nor does it alter GABA metabolism.
- Despite this mechanistic failure, serendipity intervened:
preclinical neuropathic pain models in the 1980s revealed **unexpected analgesic properties**. No one yet understood why.
- In 1990, Gabapentin's target was identified :
 $\alpha 2\text{-}\delta$ subunit of presynaptic voltage-gated Ca channels → reduces Ca influx
→ ↓ release of excitatory neurotransmitters including glutamate, substance P, CGRP.

This explained both anticonvulsant and analgesic effects.



- In 1993, FDA approves gabapentin (Neurontin) for partial-onset seizures.
- In 2002, FDA approves gabapentin for Postherpetic Neuralgia (PHN) [**its first pain indication**]

- Learning from gabapentin's pharmacokinetic limitations (saturable absorption, zero-order kinetics at therapeutic doses), Pfizer developed Pregabalin (Lyrica) (2004–2007)

- Pregabalin offered linear, dose-proportional absorption, enabling faster titration and predictable dosing, received approvals for:
 1. Neuropathic pain and epilepsy (EU 2004, US 2005)
 2. Fibromyalgia (FDA, 2007) — **the first drug ever approved for this condition**
 3. Spinal cord injury pain



- **Mirogabalin:**

A third-generation ligand, emerged in Asia (Japan, 2019), **greater $\alpha 2$ - δ selectivity and a potentially wider therapeutic window.**

- **By the 2010s, gabapentinoids were cemented as first-line agents in international neuropathic pain guidelines (IASP, NICE, NeuPSIG), alongside TCAs and SNRIs.**
- **They were embraced as opioid-sparing alternatives in chronic pain management.**
- However, a darker narrative emerged.



- Reports of euphoria, misuse, dependence, and withdrawal syndromes accumulated, particularly in patients co-prescribed opioids or with substance use disorders.
- In 2019, the United Kingdom reclassified gabapentin and pregabalin as Class C controlled substances.
- Multiple US states added them to Prescription Drug Monitoring Programs (PDMPs).
- Today's approach is one of informed caution:
Gabapentinoids remain necessary tools, but prescribing demands risk stratification, monitoring, and awareness of their abuse potential.



GABAPENTIN: AN OVERVIEW



GABAPENTIN: INTRODUCTION & CHEMICAL PROFILE

- Drug Class:

Gabapentinoid anticonvulsant; structurally a GABA analogue.

- Chemical Structure:

Designed as a lipophilic cyclohexane derivative of γ -aminobutyric acid (GABA) to cross the BBB.

- Key Point:

Despite its structural similarity to GABA, gabapentin has no direct GABA-mimetic activity.

It does not bind to GABA-A or GABA-B receptors, nor does it influence GABA reuptake or metabolism.



GABAPENTIN: PRIMARY MECHANISM OF ACTION

- binds to the $\alpha 2\delta$ -1 subunit of voltage-gated Ca channels (VGCCs) located presynaptically throughout CNS

- **Trafficking Disruption:**

disrupts the Ca-dependent trafficking from the endoplasmic reticulum to the plasma membrane.

- **Reduced Channel Density:**

reduction in the number of functional presynaptic VGCCs.

- **Decreased Neurotransmitter Release:**

Fewer channels $\rightarrow$ decrease Ca influx $\rightarrow$ reduces release of several excitatory neurotransmitters.



GABAPENTIN : MODULATION OF NEUROTRANSMITTER RELEASE

- Attenuated release of :

1. Glutamate: The major excitatory neurotransmitter.
2. Substance P: A neuropeptide central to pain transmission.
3. Calcitonin Gene-Related Peptide (CGRP): A potent vasodilator and pain mediator.
4. Noradrenaline: Modulation of noradrenergic descending inhibitory pathways

- Key Consequence:

Gabapentin reduces synaptic hyperexcitability without directly affecting normal synaptic transmission. (It forms the basis of its therapeutic effect in neuropathic pain and seizure)



GABAPENTIN : PHARMACOKINETICS

Absorption:

- Occurs in the small intestine via the L-type amino acid transport system (LAT) .
- This is a saturable, dose-dependent process. Bioavailability decreases with increasing dose:

~60% at 300 mg / ~35% at 1600 mg

- This non-linear kinetics has major clinical implications; **doubling the dose does not double the plasma concentration.**

Metabolism:

- Not metabolized by the liver.
- Does not induce or inhibit cytochrome P450 enzymes → zero drug-drug interactions at the metabolic level.



GABAPENTIN : PHARMACOKINETICS - CON

Excretion:

- Eliminated entirely by renal excretion as unchanged drug.
- Elimination half-life is 5-7 hours and is directly correlated with creatinine clearance.
- Dosage adjustment is mandatory in renal impairment.



GABAPENTIN USE IN RENAL FAILURE

- Unlike most drugs, **gabapentin undergoes absolutely no hepatic metabolism.** It is eliminated from the body entirely by the kidneys as unchanged drug.
- There is a direct, linear correlation between creatinine clearance (CrCl) and both the elimination rate constant and total body clearance of gabapentin.
- **In an ESRD patient with altered mental status and myoclonus, always rule out gabapentin toxicity** before assuming it's simply uremia.
- The treatment is specifically to remove gabapentin via hemodialysis or wait for it to clear.



GABAPENTIN USE IN RENAL FAILURE

Renal Function (CrCl)	Recommended Total Daily Dose	Regimen Details
≥ 60 mL/min	900 – 3600 mg	Standard TID dosing.
30 – 59 mL/min	400 – 1400 mg	BID dosing is recommended.
15 – 29 mL/min	200 – 700 mg	Start at 200 mg once daily.
< 15 mL/min (Pre-Dialysis)	100 – 300 mg	Start at 100 mg once daily.
Hemodialysis (HD)	Loading Dose + Maintenance	



IS GABAPENTIN SAFE AND EFFECTIVE IN PATIENTS WITH HEPATIC IMPAIRMENT?

- Gabapentin is not metabolized by the liver.
- It is renally eliminated unchanged.
- This unique pharmacokinetic profile makes gabapentin a theoretically attractive analgesic option for patients with liver disease, as its clearance is not directly dependent on hepatic function.
- Patients with liver failure are often more susceptible to the drug's nervous CNS side effects (e.g., sedation, dizziness, confusion).



GABAPENTIN USE IN LIVER FAILURE: SPECIAL CONSIDERATIONS & MONITORING

- Patients with liver failure frequently have concurrent renal dysfunction (Hepatorenal syndrome).

- **Risk of Hepatic Encephalopathy:**
 1. Gabapentin has sedative properties.
 2. it can precipitate or worsen hepatic encephalopathy. Monitor patients for signs of confusion, altered mental status, or excessive somnolence.

- Although gabapentin does not interact with cytochrome P450 enzymes, it can have additive CNS depressant effects when used with other sedating medications (e.g., opioids, benzodiazepines).



GABAPENTIN: ADVERSE EFFECTS & SAFETY PROFILE

Common (Dose-Related):

- Somnolence, dizziness, ataxia, fatigue, peripheral edema
- These CNS effects are the primary reason for slow dose titration.

Misuse Potential:

- While traditionally considered to have no abuse liability, **recent data show a potential for misuse, particularly in patients with a history of substance use disorder.** It can produce euphoria, relaxation, and disinhibition.
- This is an evolving safety concern.



GABAPENTIN: ADVERSE EFFECTS & SAFETY PROFILE - CON

Respiratory Depression:

- An FDA warning highlights a risk of serious, **life-threatening respiratory depression when gabapentinoids are used with opioids or other CNS depressants**, particularly in patients with underlying respiratory conditions (e.g. COPD) or the elderly.

Serious (Rare):

- Suicidal ideation or behavior (a class warning for antiepileptics).



GANAPENTIN: FDA-APPROVED INDICATIONS FOR PAIN

- **Postherpetic Neuralgia (PHN):** The only FDA-approved pain indication for gabapentin.

- **Other Pain Indications (Off-Label):**

- 1) Neuropathic Pain:**

- Diabetic peripheral neuropathy, spinal cord injury, HIV neuropathy, phantom limb pain, complex regional pain syndrome (CRPS), cancer-related neuropathic pain

- 2) Acute/Postoperative Pain:** As part of multimodal analgesia for Enhanced Recovery After Surgery (ERAS) protocols.

- 3) Fibromyalgia.**



GABAPENTIN: SUMMARY FOR CLINICAL PRACTICE

- **Start Low, Titrate Slowly:** Begin with a low dose (e.g., 100–300 mg/day) and increase gradually every 1–3 days.
- **Target Effective Dose:** Aim for 1,200–1,800 mg/day in divided doses.
- **Maximum Studied:** 3,600 mg/day
- **Doses >1,800 mg/day offer limited additional benefit.**
- **Taper on Discontinuation:** Do not stop abruptly; taper over at least one week to avoid withdrawal symptoms.
- **Monitor for CNS Effects:** Be vigilant for sedation, dizziness, and confusion, especially in elderly patients or those on other CNS depressants.



WHAT IS GABAPENTIN EFFECTIVE DOSE?

- Doses up to 3600 mg/day are within the studied range and may be necessary for some patients, but the evidence does not support superior efficacy over 1800 mg/day.
- Higher doses primarily increase the risk of adverse events (somnolence, dizziness, peripheral edema) without proportional analgesic benefit.
- Therefore, **1800 mg/day should be considered the optimal target dose, and escalation beyond this should be undertaken with caution, only after weighing risks versus benefits, and with close monitoring for tolerability.**



PREGABALIN : AN OVERVIEW



WHAT IS PREGABALIN?

- A synthetic structural analogue of GABA (γ -aminobutyric acid)
- However – it has zero activity at GABA receptors
- Belongs to the gabapentinoid class
- Developed as **a successor to gabapentin** with improved pharmacokinetics
- Primarily used in neuropathic pain (central & peripheral)

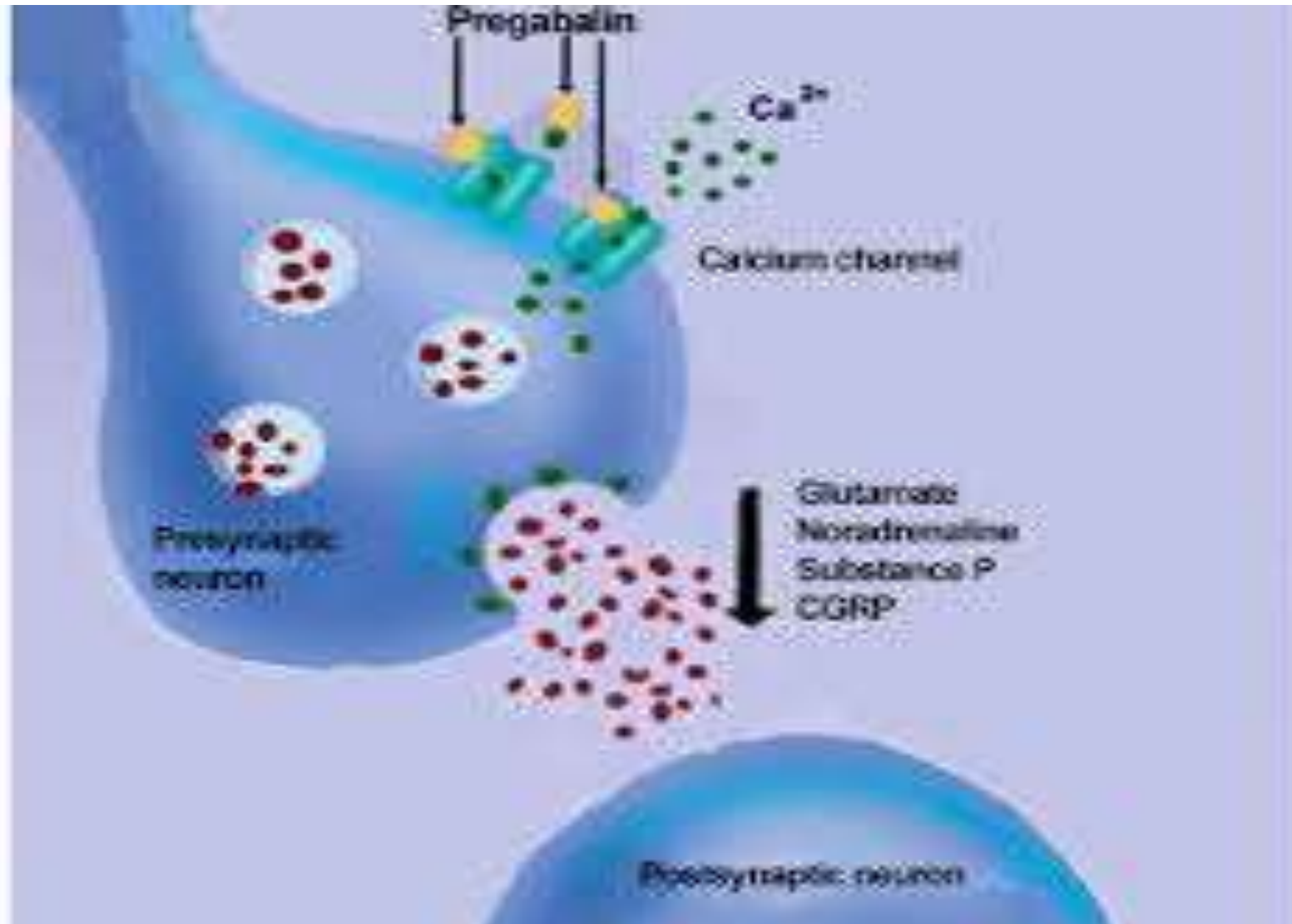


HOW PREGABALIN WORKS – THE TARGET

- Binds with high affinity to the $\alpha_2\text{-}\delta$ subunit of voltage gated Ca channels
- Does not block the channel pore; it's a **modulatory binding**
- Reduces Ca influx into presynaptic nerve terminals
- Decreases the release of several excitatory neurotransmitters:
Glutamate, Substance P, Noradrenaline, CGRP
- The $\alpha_2\delta$ subunit is overexpressed in neuropathic pain states.
- Pregabalin's binding to this target directly **dampens the spinal and supraspinal hyperexcitability** that maintains pain.
- This is why it's effective in **central sensitisation** conditions.



HOW PREGABALIN WORKS - SCHEMATIC



THE STRUCTURAL ADVANTAGE OVER GABAPENTIN

Feature	Gabapentin	Pregabalin
Side chain	Cyclohexane ring (bulky)	Isobutyl group (smaller, flexible)
Absorption	Saturable, non-linear	Linear, predictable
Bioavailability	Decreases with dose (high dose = less %)	~90% at all therapeutic doses
Dosing schedule	3-4 × daily	2-3 × daily
Onset of titration to analgesia	Slower	Faster



PREGABALIN - KEY PHYSICOCHEMICAL PROPERTIES & CLINICAL CORRELATES

- Requires active transport to cross gut and BBB.
- **Pregabalin is essentially an amino acid.**
- It behaves like one: carried by transporters, not metabolised by the liver, no drug-drug interaction through CYPs.
- In our elderly pain patients on multiple drugs, that's a massive advantage.
- No hepatic metabolism (<2%) — excreted unchanged in urine
- No CYP450 interactions — safe with most polypharmacy
- Dose must be adjusted for renal function (CrCl <60 mL/min)



PHARMACOKINETIC SNAPSHOT

- Bioavailability: $\geq 90\%$ (dose independent)
- T_{max}: ~1.5 hours (fast onset of absorption)
- Protein binding: Negligible (0%) → no displacement interactions
- Half-life: ~6.3 hours (unaffected by dose or repeated dosing)
- Elimination: 98% unchanged in urine
- Time to steady state: 24–48 hours

- **Negligible protein binding is an underrated feature.**
- It won't compete with warfarin, NSAIDs, or other highly bound drugs .
- A short half-life means steady state is reached quickly, so you can assess efficacy within a few days of a dose change.”



PREGABALIN SAFETY OVERVIEW

- **Pregabalin is generally well tolerated**, but the safety profile is dose dependent and CNS driven.
- Most side effects are mild to moderate, appear early in titration, and often attenuate over time.
- **In your pain patients, common effects are predictable; serious risks are rare but must be actively managed**



PREGABALIN MOST COMMON ADVERSE EFFECTS (≥5% INCIDENCE)

Adverse Effect	Approx. Incidence
Dizziness	30–45%
Somnolence (Sleepiness)	20–30%
Peripheral Edema	10–15%
Weight Gain	10–12%
Dry Mouth	8–15%
Blurred Vision	7–10%
Ataxia (Incoordination)	6–15%
Cognitive Clouding (“Brain Fog”)	4–8%



PREGABALIN CNS EFFECTS – DIZZINESS & SOMNOLENCE

- Onset: Usually in the first few days, peaking during titration.
- Increases with dose (e.g., dizziness ~24% at 150 mg/day → ~37% at 600 mg/day).
- Tolerance: Develops partially in 1–2 weeks for many patients.

Clinical approach:

- Start low (75 mg BID or 50 mg TID), titrate slowly.
- Advise patient: “Do not drive until you know how it affects you.”
- Older patients and those on other CNS depressants are at higher risk.
- Serious outcome: Falls, fractures, and motor vehicle accidents have been reported .



PREGABALIN WEIGHT GAIN & PERIPHERAL EDEMA

Weight gain:

- ~8% gain $\geq$ 7% of baseline body weight (dose and duration dependent) .
- Mechanism: increased appetite, fluid retention, possibly reduced metabolic rate.
- **Can complicate diabetes, heart failure, osteoarthritis.**

Peripheral edema: (peripheral vasodilation and fluid retention).

- Typically pitting, lower extremity.
- **Not associated with cardiac dysfunction.** Exacerbated by co-administration of thiazolidinediones (pioglitazone, rosiglitazone).
- Action: Monitor weight and edema at each visit. **Consider dose reduction or discontinuation if excessive.**



PREGABALIN SERIOUS ADVERSE EVENTS:

- **Hypersensitivity reactions:** Rare – angioedema (face, tongue, throat), rash, hives. Contraindicated in known hypersensitivity.
- **Suicidal ideation & behaviour:** As with other antiepileptics, a small increased risk; monitor for depression, mood changes. (Incidence ~0.4%)
- **PRES (Posterior Reversible Encephalopathy Syndrome):** Very rare case reports, presents with headache, visual disturbance, hypertension, seizures.
- **Rhabdomyolysis / elevated CK:** Isolated reports, especially in combination with statins(?)



PREGABALIN RESPIRATORY DEPRESSION – A CRITICAL WARNING

- Pregabalin alone has little respiratory effect at therapeutic doses.
- Combination with opioids ,benzodiazepines, alcohol, other CNS depressants significantly increases risk of respiratory depression, coma, and death. (FDA 2019 Warning)

Who is at highest risk?

1. Elderly, COPD, sleep apnea, reduced renal function.
2. Any patient on ≥ 50 morphine milligram equivalents (MME)/day.



PREGABALIN ABUSE, DEPENDENCE & WITHDRAWAL

- **Abuse potential:** Higher than gabapentin; euphoria, dissociation, sedation.
Risk factors: current/past substance use disorder, psychiatric comorbidity.
- **Physical dependence:** Occurs with therapeutic doses over weeks to months.
- **Withdrawal symptoms:**
if abrupt discontinuation: insomnia, headache, nausea, anxiety, diarrhea, hyperhidrosis, palpitations, confusion, agitation, seizures (rare).
- Taper gradually: ≥ 1 week; many experts recommend 2–4 weeks if on high dose or long duration.



PREGABALIN IN SPECIAL POPULATIONS

Renal impairment:

Dose adjustment mandatory

Elderly:

- Clearance declines with age → start at 75 mg/day, titrate slowly; greater sensitivity to dizziness and falls.

Pregnancy:

- Human data limited. In animals, pregabalin caused fetal structural abnormalities at high doses. Avoid unless clearly necessary; use effective contraception.

Lactation:

- Excreted in breast milk in small amounts May cause sedation and poor feeding. Use with caution



PREGABALIN SAFE PRESCRIBING – PRACTICAL CHECKLIST

- Check eGFR before starting and at least annually.
- **Start low, go slow**: 75 mg BID or 50 mg TID, titrate by 75–150 mg/day per week.
- Assess pain response and tolerability at 2–4 weeks; **do not exceed 600 mg/day**.
- **Warn patient**: Do not stop abruptly; do not combine with opioids/alcohol unless discussed.
- **Monitor weight, edema, mood, and signs of misuse at each visit.**
- Taper when discontinuing: reduce by 75–150 mg/day per week.



PREGABALIN FDA APPROVED PAIN INDICATIONS

Indication	Details	Typical Dose Range
Diabetic Peripheral Neuropathy (DPN)	Neuropathic pain due to diabetic polyneuropathy.	150–300 mg/day (starting 50 mg TID or 75 mg BID; max 300 mg/day is generally sufficient)
Postherpetic Neuralgia (PHN)	Persistent neuropathic pain following herpes zoster.	150–300 mg/day (some require 600 mg/day)
Fibromyalgia	Chronic widespread pain with central sensitisation features.	300–450 mg/day (starting 75 mg BID; max 450 mg/day approved for FM)
Neuropathic Pain associated with Spinal Cord Injury (SCI)	Central neuropathic pain after traumatic SCI.	



PREGABALIN APPROVED PAIN INDICATIONS (EUROPE & INTERNATIONAL)

Peripheral neuropathic pain

Includes DPN, PHN, painful polyneuropathy of other origins.

Central neuropathic pain

Specifically includes spinal cord injury pain; off-label but widely used in post-stroke pain, multiple sclerosis pain.

Generalised Anxiety Disorder (GAD)

Not a pain indication, but often comorbid; anxiolytic effect may improve pain coping.



PREGABALIN OFFLABEL PAIN INDICATIONS (EVIDENCE-BASED)

1. Failed Back Surgery Syndrome (FBSS)
2. Cancer related neuropathic pain / Chemotherapy induced peripheral neuropathy (CIPN)
3. Trigeminal neuralgia
4. Complex Regional Pain Syndrome (CRPS)
5. Post operative pain prevention
6. Visceral pain with central sensitisation: e.g., chronic pancreatitis, irritable bowel syndrome



DOSING IN PAIN – THE PRACTICAL “START-LOW, GO-SLOW” APPROACH

Step	Action
Initiation	75 mg BID (or 50 mg TID)
Titration	Increase by 75–150 mg/day at weekly intervals based on response and tolerability
Effective pain range	150–300 mg/day for most peripheral neuropathies; 300–450 mg/day for fibromyalgia; up to 600 mg/day for central pain
Maximum dose	600 mg/day (FDA); 600 mg/day (EMA) – little additional benefit in pain beyond 450 mg/day for many



OCULAR SIDE EFFECTS OF GABAPENTINOIDS

- Visual disturbances are commonly reported but often underestimated.
- They directly impact:
 1. Adherence – patients stop treatment silently.
 2. Function & safety – driving, reading, fall risk.
 3. Differential diagnosis – elderly patients may have coexisting eye disease.
- Rare but serious events (acute glaucoma, retinopathy) require urgent recognition.
- **Pain specialists are the first line in monitoring and deciding to continue, modify, or stop therapy.**



OVERVIEW OF GABAPENTINOID OCULAR ADVERSE EFFECTS

Category	Examples	Frequency	Clinical Relevance
Common & dose-related	Blurred vision, diplopia	6–12% pregabalin; slightly lower gabapentin	Major cause of early discontinuation; often transient
Less common	Nystagmus, visual field defects, photophobia, oscillopsia	1–2%	May indicate CNS toxicity, especially at high doses/renal impairment
Rare but serious	Acute angle-closure glaucoma, retinal pigmentary changes (preclinical), toxic retinopathy	Very rare / case reports	Medical emergency; possible irreversible vision loss
Functional	Amblyopia, abnormal accommodation	~1–5%	



COMMON OCULAR COMPLAINTS – BLURRED VISION & DIPLOPIA

Blurred Vision:

1. Incidence: 6–8% pregabalin, 3–4% gabapentin .
2. Onset: Early in treatment or after dose increase.
3. Mechanism: Unknown; may involve **altered ocular muscle tone or central processing**.
4. Bilateral, symmetrical, not associated with refractive change.
5. Tends to attenuate over 1–2 weeks in many patients.



COMMON OCULAR COMPLAINTS – BLURRED VISION & DIPLOPIA - CON

■ Diplopia (Double Vision):

1. Incidence: 2–4% pregabalin, ~1–2% gabapentin.
2. Typically binocular, horizontal, at near or distance.
3. Often dose dependent ; resolves with dose reduction.
4. Risk factors:

Older age, higher doses, rapid titration, concomitant CNS depressants, renal impairment.



LESS COMMON OCULAR EFFECTS

- **Nystagmus**: indicates cerebellar/vestibular CNS effect. Sign of gabapentinoid toxicity – check renal function, dose.
- **Oscillopsia**: Illusion of environmental movement, highly disabling.
- **Visual field defects**: Rare; usually reversible
- **Photophobia**: Increased light sensitivity, may exacerbate migraine.
- **Oculogyric crisis**:
 - an acute, dramatic neurological condition
 - sustained, involuntary, conjugate (both eyes moving together) upward deviation of the eyeballs.
 - Isolated case reports.



CLINICAL RULE:

- Any new onset involuntary eye movements or oscillopsia should trigger dose reduction or cessation and neurological review.
- (Oscillopsia is the subjective visual perception that the stationary visual world is continuously oscillating, bouncing, swaying, or jumping)



ACUTE ANGLE-CLOSURE GLAUCOMA – A MEDICAL EMERGENCY

- Sudden increase in intraocular pressure due to blockage of aqueous humour drainage.
- Presents with:
severe ocular pain, headache, nausea/vomiting, red eye, cloudy cornea, mid dilated fixed pupil, Halos around lights, sudden vision loss
- Rare case reports (both gabapentin and pregabalin).
- Mechanism:
 - ❑ Possibly uveal effusion or ciliary body edema shifting the lens-iris diaphragm forward (in anatomically predisposed eyes)
 - ❑ Onset: Within hours to days of starting or increasing dose.



ACUTE ANGLE-CLOSURE GLAUCOMA – A MEDICAL EMERGENCY - CON

What you must do:

- Stop the drug immediately.
- Refer for emergency ophthalmological assessment.
- Do not rechallenge.



RETINAL TOXICITY OF GABAPENTINOIDS:

Pregabalin

- Studies in mice and rats: retinal pigmentation, atrophy, retinal thinning
- Mechanism: Unknown; pregabalin binds to melanin containing tissues.
- Human data: **Long term clinical trials did not detect a clear ophthalmoscopic signal.**
- A 2022 case series described 3 patients on long term pregabalin (>3 years) with bilateral pigmentary maculopathy; improvement in visual function upon cessation in some.

■ Gabapentin

- **No strong retinopathy signal, but isolated reports of maculopathy exist**



RETINAL TOXICITY - GABAPENTINOIDS - CON

- Ophthalmology recommendations:

No routine screening mandated, but consider baseline and periodic ophthalmological exam (including fundoscopy) for patients on long term, high dose therapy, especially with visual complaints.



INDICATIONS FOR DISCONTINUATION OF GABAPENTINOIDS – ABSOLUTE “STOP” CRITERIA

Condition	Clinical Red Flag	⚡ Action
Suspected acute angle-closure glaucoma	Eye pain, headache, halos around lights, nausea, fixed mid-dilated pupil	🔥 EMERGENCY STOP — Vision-threatening; refer immediately
Confirmed toxic retinopathy / pigmentary maculopathy	Progressive central vision loss, color desaturation, or abnormal fundoscopy	STOP — Irreversible vision loss is possible
Severe, disabling oscillopsia or nystagmus	Sensation that stationary objects are bouncing/jumping; nystagmus not resolving with dose reduction	STOP — Risk of falls and reduced quality of life
Unexplained significant visual acuity loss	Sudden drop in Snellen chart vision, confirmed by ophthalmological assessment	STOP — Prevent further retinal/optic nerve deterioration
Oculogyric crisis / acute dystonic reaction	Sustained upward eye deviation, forced head tilt, tongue/jaw spasms	STOP — Potential neurological injury; treat acutely with anticholinergics
Severe hypersensitivity with ocular involvement	Rash with eye lesions, conjunctival erosions, or mucosal involvement (e.g., SJS/TEN)	🔥 EMERGENCY STOP — Life-threatening; urgent dermatology/ophthalmology consult



PATIENT ON GABAPENTINOID REPORTS VISUAL COMPLAINT - ALGORITHM

- Is it acute eye pain, red eye, cloudy cornea, halos?
 - | └── Yes → SUSPECT ACUTE ANGLE-CLOSURE GLAUCOMA
 - | |── Stop drug immediately
 - | |── Send to Emergency / Ophthalmology urgently
 - | └── Do not rechallenge. Document reaction.



PATIENT ON GABAPENTINOID REPORTS VISUAL COMPLAINT - ALGORITHM - CON

- Is it new onset oscillopsia, severe nystagmus, or diplopia with objective findings?
 - | └── Yes → STOP drug (with taper if possible) + Neuro - ophthalmology referral
- | └── Is it simple blurred vision / diplopia?
 - | | └── Assess dose, titration speed, renal function, concomitant drugs
 - | | └── Reduce dose or slow titration
 - | | └── **If persistent and disabling after 2–4 weeks at minimum effective dose → Taper and switch agent**
 - | └── **If tolerable, reassurance; warn about driving**



PATIENT ON GABAPENTINOID REPORTS VISUAL COMPLAINT - ALGORITHM - CON

- Are there unexplained visual acuity loss or retinal findings?
 - | └─ Refer to ophthalmology (include drug history)
 - | | └─ If retinal toxicity confirmed → Taper and discontinue permanently
 - | └─ If unrelated, continue with monitoring
 - |
- └─ Continue to monitor at each refill: "Any vision changes?"



MYALGIA DUE TO GABAPENTINOIDS

- Gabapentinoid Myalgia – The Pain Paradox
- Not neuropathic pain. A dull, proximal, symmetrical muscle ache.
- Can occur at any dose, often within weeks of initiation or uptitration.
- May present with mild CPK elevation; severe rhabdomyolysis is rare but reported.



MYOPATHY & THE STATIN OVERLAP

- **Muscle Pain may Becomes a Cardiac Confounder**
- The Problem: Your cardiac patient is almost always on a high-intensity statin.
- Gabapentinoid Effect: Both drugs are independently associated with myalgia and, rarely, myopathy with elevated creatine kinase (CPK).
- New proximal muscle pain. Is it a statin myopathy? A gabapentinoid adverse effect? Or worsening peripheral arterial disease (PAD) due to atherosclerosis?
- The Solution: Document a baseline CPK level and symptom diary before adding the gabapentinoid. This anchors future diagnostic workups.
- You don't want to stop a lifesaving statin for a gabapentinoid side effect misdiagnosed as statin myalgia.



THE STATIN TRAP (CRITICAL FOR CARDIAC PATIENTS)

- **Blame the Gabapentinoid Before the Statin**
- Your patient is likely on a high-intensity statin. New myalgia gets mislabeled "statin myalgia."

- Differentiation Key:

Was the patient stable on their statin for months/years, and myalgia started only after introducing the gabapentinoid? That's the gabapentinoid, not the statin.

- **Stopping a life-saving statin unnecessarily is a preventable mistake.**
- Think drug-drug interaction temporally.



PAIN SPECIALIST'S 3-STEP FOR MYALGIA: DIAGNOSE & MANAGE IN ONE VISIT

1. Baseline:

Before starting, document any muscle symptoms $\pm$ CPK (mandatory in statin users).

2. Suspect:

New proximal aching $\rightarrow$ Check CPK. If $<5\times$ ULN, it's consistent with gabapentinoid myopathy.

3. Confirm & Fix:

- Reduce dose by 30-50% or switch pregabalin $\rightarrow$ gabapentin.
- Resolution of myalgia = diagnosis confirmed.
- **Do not stop the statin. For the neuropathic pain, pivot to duloxetine, nortriptyline, or topical agents.**



THE CARDIAC SAFETY PROFILE OF GABAPENTINOIDS

Where Gabapentinoids Stress the Heart:

1. Volume Overload & Decompensation
2. Cardiac Conduction Delays
3. Respiratory-Mediated Cardiac Arrest
4. Myopathy in the Statin Era



RESPIRATORY DEPRESSION & CARDIAC ARREST OF GABAPENTINOIDS

- Gabapentinoids alone are mild respiratory depressants. Combined with opioids and/or benzodiazepines, create synergistic central apnea.
- The Cardiac Consequence Sequence:
 1. Apnea / Hypopnea
 2. Severe Hypoxia + Hypercapnia
 3. Pulmonary Vasoconstriction (acute right heart strain)
 4. Malignant Arrhythmia (Bradycardia-to-asystole or pulseless electrical activity)
- Many cardiac patients already have central or obstructive sleep apnea. Gabapentinoids worsen the apnea-hypopnea index, creating nocturnal ischemic stress.



VOLUME OVERLOAD – THE PRIMARY CARDIAC THREAT OF GABAPENTINOIDS

- Peripheral Edema is a Failing Heart's Enemy
- Pregabalin (high, dose-dependent) > Gabapentin (moderate).
- Mechanism: Calcium channel modulation in arteriolar smooth muscle causes vasodilation and sodium/water retention.
- In HF, a 2-3 liter fluid shift increases ventricular filling pressures, triggering acute decompensation.
- Studies report increased odds of heart failure hospitalization, particularly with pregabalin.



VOLUME OVERLOAD OF GABAPENTINOIDS: PREVENTION & DETECTION

- Pre-Prescribing:

Check Weight, presence of pre-existing edema, JVP (if exam is possible).

- **Avoid pregabalin entirely in NYHA Class III/IV or known EF $\leq$ 40%.**
- Gabapentin has lesser risk.
- Monitor patient daily weights.
- **Teach this phrase to patient: "Gain 2-3 pounds in a day or 5 pounds in a week? Stop the drug and call your cardiologist today."**



EFFECT ON CARDIAC CONDUCTION OF GABAPENTINOIDS – THE PR INTERVAL

- **Pregabalin can prolong the PR interval (first-degree AV block).**
- Clinical Significance: Generally benign in isolation, but dangerous as part of polytherapy.
- The Dangerous Overlap (Synergistic Blockade) with:
Beta-blockers (e.g., carvedilol, bisoprolol), Non-dihydropyridine calcium channel blockers (verapamil, diltiazem), Digoxin, Amiodarone
- Risk of progression to higher-degree heart block or profound bradycardia.
- Check an ECG before starting pregabalin.
- **A pre-existing PR >200ms combined with an AV nodal blocker is a strong relative contraindication.**



THE WITHDRAWAL-INDUCED CARDIAC STORM

- Abrupt gabapentinoid discontinuation causes a physical withdrawal syndrome characterized by a catecholamine surge.

- Cardiac Manifestations:

Severe sinus tachycardia, Hypertensive urgency, Diaphoresis and tremor mimicking unstable angina

- In a patient with vulnerable coronary plaques or fixed stenosis, this surge in myocardial oxygen demand can precipitate demand ischemia (type 2 MI).
- The Rule: Taper slowly—no faster than 10-25% of the dose per week—and warn the patient that stopping suddenly can feel like a heart event.



SUMMARY OF CARDIAC RISK MANAGEMENT OF GABAPENTINOIDS:

- **Edema:** Treat pregabalin-related edema as a potential heart failure exacerbation, not a benign side effect.
- **Conduction:** Pregabalin + AV nodal blockers = ECG monitoring for heart block.
- **Breathing:** Gabapentinoid + Opioid + Benzodiazepine = The “Triple Threat” for fatal cardiac hypoxia.
- **Muscle:** New pain in a statin user = Check CPK, don't guess.

Managing neuropathic pain cannot come at the cost of decompensating a fragile heart.



GABAPENTINOIDS AND NEURODEGENERATIVE RISK

Alzheimer's Disease & Dementia:

- A definitive, dose-dependent association exists.
- **The higher the cumulative lifetime exposure, the higher the risk.**
- This risk is not confined to the elderly.
- It is disproportionately **elevated in working-age adults (35–64 years)**.

Parkinson's Disease & Parkinsonism:

- Significant association with new-onset parkinsonism.
- Can unmask or worsen underlying motor symptoms (tremor, gait instability) in susceptible patients.



THE PAIN SPECIALIST'S ACTION PLAN – RISK MITIGATION

The "8-Week Rule":

- If no meaningful functional improvement occurs within 8 weeks, deprescribe.
- Do not default to long-term maintenance.

Active Surveillance Protocol:

- Baseline: Screen for subtle cognitive (attention/executive) and motor (gait/tremor) issues.
- Every 3 Months: Reassess. Explicitly ask patients and families about confusion, memory lapses, and unsteadiness.



FINAL SHARP PEARL ABOUT GABAPENTINOIDS NEUROLOGIC RISK

- Gabapentinoids are effective, but they carry a cumulative neurological cost.
- As pain clinicians, we must move from 'prescribe-and-forget' to 'trial, re-evaluate, and taper.'
- Protect the brain while treating the nerve.



THE LAST WORD:

CAN ANYONE IMAGINE PAIN MANAGEMENT WITHOUT GABAPENTINOIDS TODAY?!

- The opioid crisis catapulted gabapentinoids into a "safe" default.
- Robust evidence only for: postherpetic neuralgia, diabetic neuropathy, fibromyalgia (pregabalin).
- Off-label creep into radiculopathy, back pain, migraine—often with weak or no evidence.
- Result: Top 10 global drugs; automatic add-on in many pain clinics.



OUR TOOLKIT WITHOUT GABAPENTINOIDS

- **Oral alternatives with solid evidence:** SNRIs (duloxetine), TCAs (nortriptyline, amitriptyline).
- **Topicals first:** Lidocaine 5% patch, capsaicin 8% patch ; effective, zero systemic risk.
- **Interventional options:** Nerve blocks, radiofrequency ablation, spinal cord stimulation.
- **Non-pharmacological:** Pain neuroscience education, graded exercise, CBT (Cognitive Behavioral Therapy) , acceptance and commitment therapy.



FINAL PROVOCATION:

- "If we had to stop using gabapentinoids tomorrow, would our patients really get worse? Or would we just finally start using other treatments we've been ignoring?"





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