# Rethinking Gabapentinoids for Pain

## Things We Do for No Reason™


Things We Do for No Reason™: Prescribing gabapentinoids for pain
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# A familiar admission on the medical ward

**Patient Profile:** 61-year-old man

- Comorbidities: Asthma, Chronic Kidney Disease (CKD)
- **Presentation:** Admitted with acute-on-chronic lower back pain radiating to the left leg. MRI confirms disc herniation and S1 nerve root compression.

**Current Meds:** Pain is uncontrolled despite ibuprofen and hydrocodone.

**Action Taken:** The hospitalist prescribes gabapentin 300mg every 8 hours.

## Is this the right call?

# A quiet prescribing epidemic

**70 Million**

Gabapentin prescriptions in the US (2021), keeping it consistently in the top 10 prescribed medications.

**6.5 Million**

Pregabalin prescriptions (2021), driving $5.5 billion in sales.

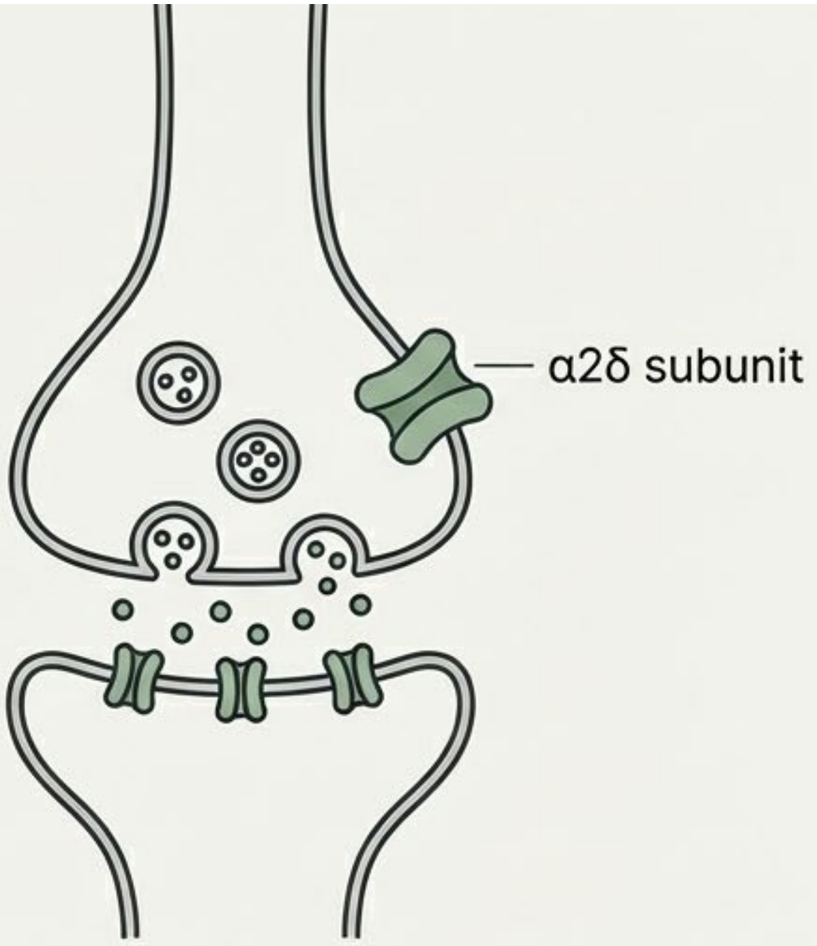
**83%**

The estimated proportion of gabapentinoid prescriptions written for entirely off-label pain management.

# The desperate search for non-opioid alternatives

## The Context

20% of inpatients experience chronic pain.
Driven by efforts to limit opioid prescribing—formalized in the 2016 CDC guidelines—clinicians urgently needed alternatives, leading to the assumption that gabapentinoids offered superior safety and efficacy.



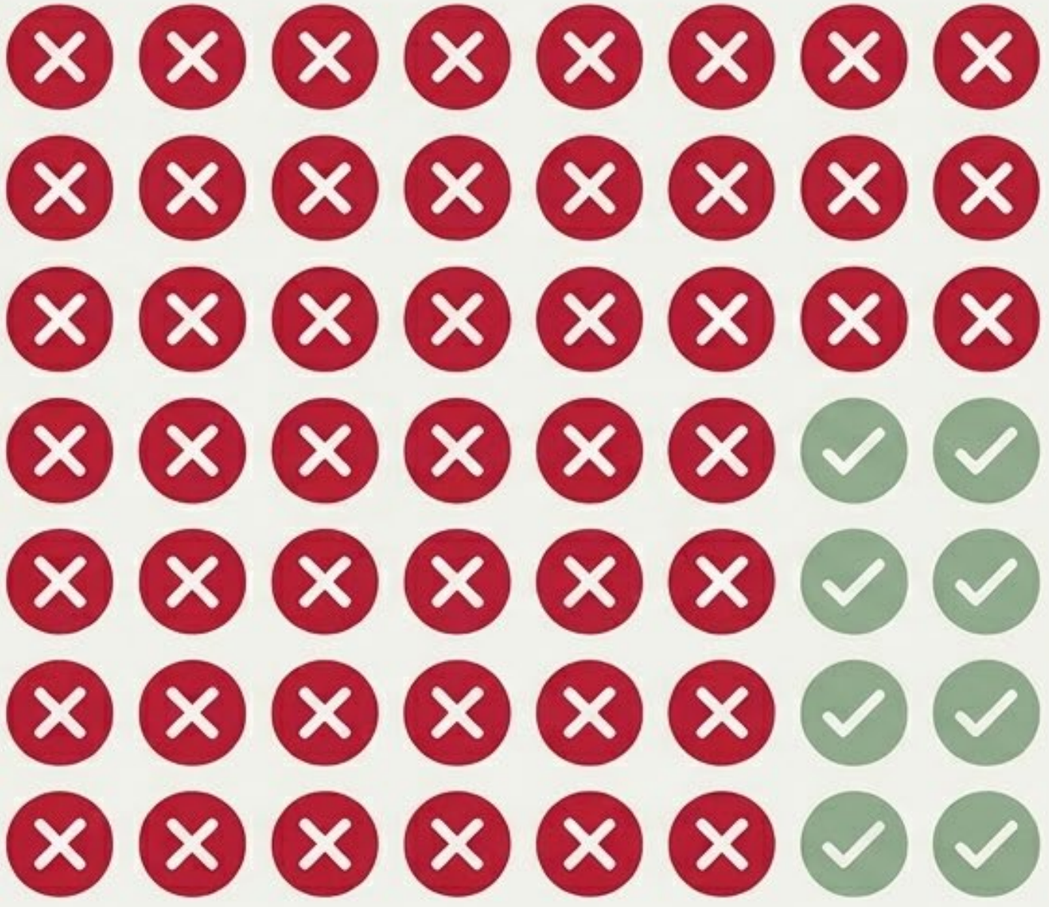

## The Mechanism

Both gabapentin and pregabalin bind to the $\alpha_2\delta$ subunit of calcium channels, theoretically inhibiting the tonic phase of nociception.

# Randomized trials show minimal or no benefit for off-label pain

## The Reality of the Data

- Well-conducted RCTs for off-label indications demonstrate minimal to zero benefit over placebo.
- The largest placebo-controlled trial for acute and chronic sciatica found pregabalin ineffective while increasing adverse events.
- In the few trials showing nominal statistical improvement, pain scores dropped by ≤ 1 point on a 10-point scale—a clinically insignificant difference.



# A literature distorted by off-label promotion

How did perception diverge so sharply from clinical reality?


**Internal documents later revealed the suppression of unfavorable clinical trials and systematic distortion of peer-reviewed articles.**

# Gabapentinoids actively drive routine hospital harms

These medications carry a Number Needed to Harm (NNH) of 3 to 11.

## Neurologic

Up to 33% of patients experience dizziness or somnolence. Post-operative use significantly increases the risk of delirium and new antipsychotic use.

## Respiratory

Increased risk of pneumonia in post-operative settings.

## Musculoskeletal

Significant increase in fall risk, particularly when combined with opioids.

*Note: Gabapentin-induced peripheral edema also affects 2%–8% of users.*

# Synergistic toxicity with central nervous system depressants


## 2019 FDA Warning

Gabapentin and pregabalin can cause fatal respiratory depression, particularly in the setting of respiratory impairment or when combined with other CNS depressants.

## The Opioid Multiplier

Concomitant use of gabapentinoids and opioids increases the risk of opioid overdose by 7-fold (HR: 6.10).

# Standard dosing threatens vulnerable populations

**COPD Patients:** Gabapentinoid initiation is linked to a significantly higher risk of severe COPD exacerbations (HR: 1.39).

**Chronic Kidney Disease (CKD):** Gabapentinoids are eliminated entirely by the kidneys. Dose adjustment is missed in ~50% of hospitalized patients, leading to marked neurotoxicity.

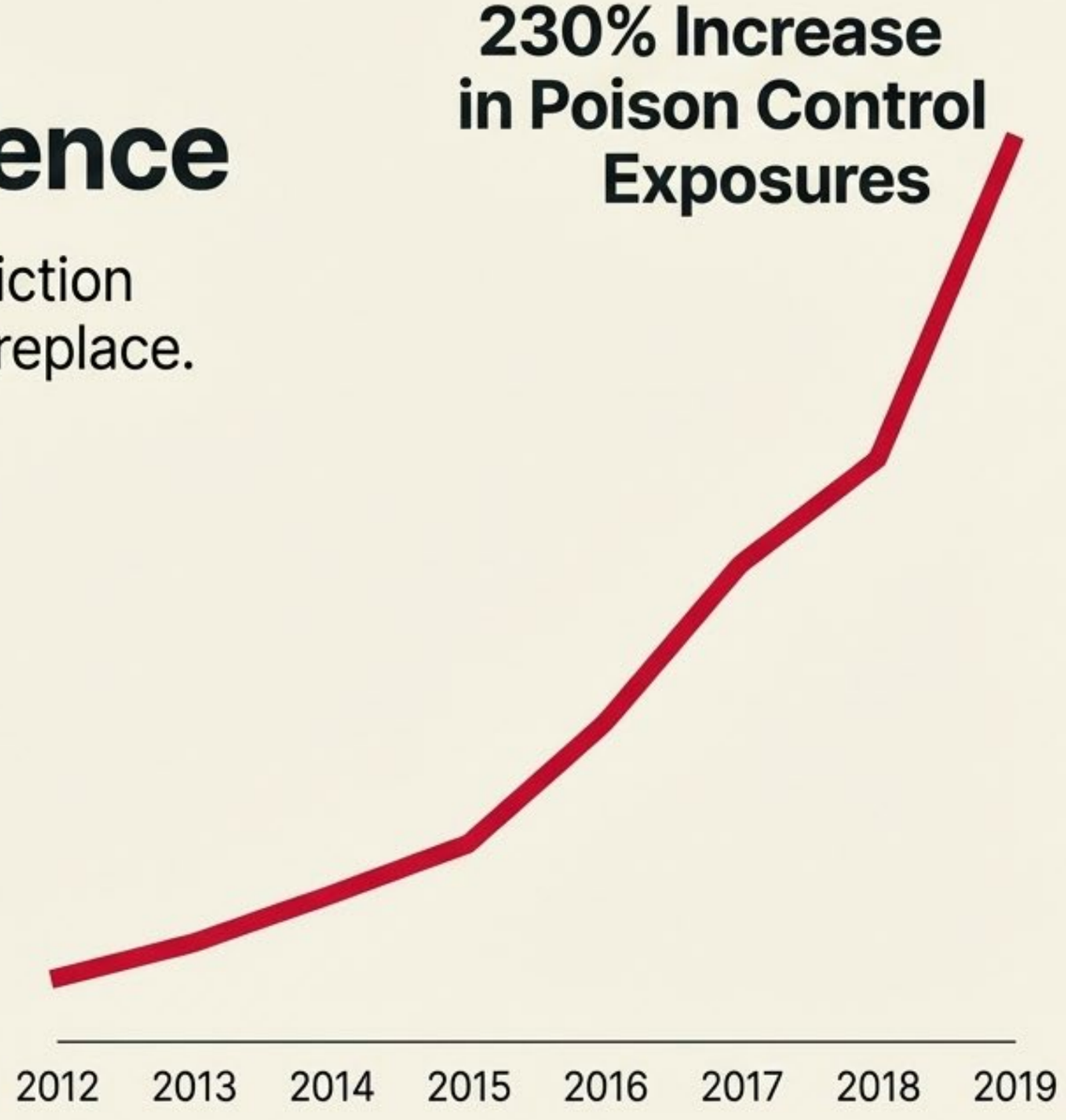
**Frail Individuals:** Observational cohorts link gabapentinoids to a higher risk of bone fractures.

*Additional risk: Fibromyalgia patients face elevated cardiovascular risks (MI, heart failure, DVT/PE).*

# The growing crisis of diversion and dependence

Gabapentinoids are not immune to the addiction pathways of the drugs they were meant to replace.

- **Misuse Rates**: Among patients with substance use disorders, misuse rates approach 15%.
- **Oversight**: 20% of prescriptions exceed FDA-approved dosing limits.
- **Outcomes**: Poison control reports of gabapentinoid-related exposures increased >230% between 2012–2019, with 22% resulting in serious harm or death.
- Tolerance, dependence, and withdrawal are heavily documented even at standard therapeutic doses.



# When are gabapentinoids actually appropriate?

## FDA-Approved Indications

- Postherpetic neuralgia (Gabapentin & Pregabalin)
- Painful diabetic peripheral neuropathy (Pregabalin)
- Fibromyalgia & spinal cord injury pain (Pregabalin)
- Adjunctive treatment for partial-onset seizures

# When are gabapentinoids actually appropriate? (Continued)

## Acute Neuropathic Pain Exception

While trial data is modest, some patients report significant relief. Clinicians may consider a strictly monitored “N-of-1” trial with:

1. A clear plan for therapy duration.
2. Defined criteria for effectiveness.
3. Pre-planned conditions for discontinuation.

**TABLE 1** Randomized clinical trials of gabapentin versus placebo for off-label treatment of pain.

| Study | Condition | No. of participants | Duration (weeks) | Significant difference in pain compared to placebo | Gabapentin dose |
|---|---|---|---|---|---|
| Rauck R, et al. *Pain Pract.* 2013. | DPN | 421 | 12 | No | 1200 mg/day |
| | | | | No | 2400 mg/day |
| | | | | No | 3600 mg/day |
| Gorson KC, et al. *J Neurol Neurosurg Psychiatry.* 1999. | DPN | 40 | 6 | No | 900 mg/Day |
| Atkinson JH, et al. *Pain.* 2016. | Low back pain/radiculoapathy | 108 | 12 | No | Titration up to 3600 mg/day |
| McCleane GJ. *Pain Clin.* 2001. | Low back pain/radiculopathy | 65 | 8 | No | Titration up to 1200 mg/day |
| Baos S, et al. *Anesthesiology.* 2025. | Major cardiac, thoracic and abdominal surgery postoperative pain | 1196 | 16 | No | 600 mg given 2 h preoperatively and 300 mg taken 2 times a day postoperatively |
| Punjani N, et al. *J Urol.* 2024. | Perioperative scrotal surgery pain | 70 | 1 | No | 600 mg given 2 h preoperatively and 300 mg taken 3 times a day postoperatively |
| Lerner DK, et al. *Am J Otolaryngol.* 2024. | Perioperative endoscopic sinus surgery pain | 35 | 1 | No | Titration up to 900 mg/day |
| Horne AW, et al. *Lancet.* 2020. | Chronic pelvic pain | 306 | 16 | No | Titration up to 2700 mg/day |
| Lewis SC, et al. *PLoS One.* 2016. | Chronic pelvic pain | 47 | 26 | No | Titration up to 2700 mg/day |
| Smith DG, et al. *J Rehabil Res Dev.* 2005. | Phantom limb pain | 24 | 6 | No | Titration up to 3600 mg/day |
| Tsui JI, et al. *PLoS One.* 2024. | Chronic pain among people with HIV with alcohol use | 30 | 8 | No | Titration up to 1800 mg/day |
| Hahn K, et al. *J Neurol.* 2004. | HIV neuropathy | 26 | 4 | No | 1200 mg to 2400 mg/day |
| Fowler C, et al. *Anesth Analg.* 2023. | Severe acute pain after cesarean delivery | 70 | 12 | No | Titration up to 1800 mg/day |
| Anghelescu DL, et al. *Pediatr Blood Cancer.* 2020 | Vincristine-related neuropathic pain | 49 | 3 | No | 20 mg/kg/day |
| Hui AC, et al. *Eur J Neurol.* 2011. | Carpal tunnel syndrome | 140 | 8 | No | Titration up to 900 mg/day |
| van de Vusse AC, et al. *BMC Neurol.* 2004. | Complex regional pain syndrome | 58 | 3 | No | Titration up to 1800 mg/day |
| Moskowitz EE, et al. *Injury.* 2018. | Acute pain management in critically ill patients with rib fractures | 40 | 4 | No | Titration up to 900 mg/day |
| Dworkin RH et al. *Pain.* 2009. | Acute zoster | 87 | 4 | No | Maximum dosage of 1800 mg/day |

(Continued)

**TABLE 1** (Continued)

| Study | Condition | No. of participants | Duration (weeks) | Significant difference in pain compared to placebo | Gabapentin dose |
|---|---|---|---|---|---|
| Gordh TE, et al. *Pain*. 2008. | Traumatic nerve injury | 120 | 5 | No | Maximum dosage of 2400 mg/day |
| Backonja M, et al. *JAMA*. 1998. | DPN | 165 | 8 | Yes 1.1 on 0-10 scale, $p < .001$ | Titrated from 900 mg to 3600 mg/day or maximum tolerated dosage |
| Sandercock D, et al. *Diabetes Res Clin Pract*. 2012. | DPN | 147 | 4 | Yes 1.2 on 0-10 scale, $p = .002$ | 3000 mg PM<br>1200 mg AM/1800 mg PM |
| Simpson DA. *Neuromuscul Dis*. 2001. | DPN | 60 | 8 | Yes 1.9 on 0-10 scale, $p < .01$ | 3600 mg/day |
| Costa GB, et al. *J Perianesth Nurs*. 2024. | Perioperative inguinal hernioplasty pain | 77 | 4 | Yes 2.0 on 0-10 scale, $p < .001$ | 900 mg/day |
| AbdelHafeez MA, et al. *Arch Gynecol Obstet*. 2019. | Chronic pelvic pain | 60 | 24 | Yes 1.8 on 0-10 scale, $p < .001$ | Titration up to 2700 mg/day |
| AbdelHafeez MA, et al. *Arch Gynecol Obstet*. 2019. | Chronic pelvic pain | 60 | 24 | Yes 1.8 on 0-10 scale, $p < .001$ | Titration up to 2700 mg/day |
| Bone M, et al. *Reg Anesth Pain Med*. 2002. | Phantom limb pain | 19 | 6 | Yes 1.6 on 0-10 scale, $p = .03$ | Titration up to 2400 mg/day or maximum tolerated dose |
| Serpell MG et al. *Pain*. 2002. | Unspecified neuropathy | 305 | 8 | Yes 0.5 on 0-10 scale, $p = .048$ | Titration up to 2400 mg/day |
| Levendoglu F, et al. *Spine (Phila Pa 1976)*. 2004. | Spinal cord injury | 20 | 8 | Yes 4.3 on 0-10 scale, $p < .001$ | Titration up to 3600 mg/day |
| Arnold LM et al. *Arthritis Rheum*. 2007. | Fibromyalgia | 150 | 12 | Yes 0.9 on 0-10 scale, $p = .01$ | 1,200 mg to 2,400 mg/day |

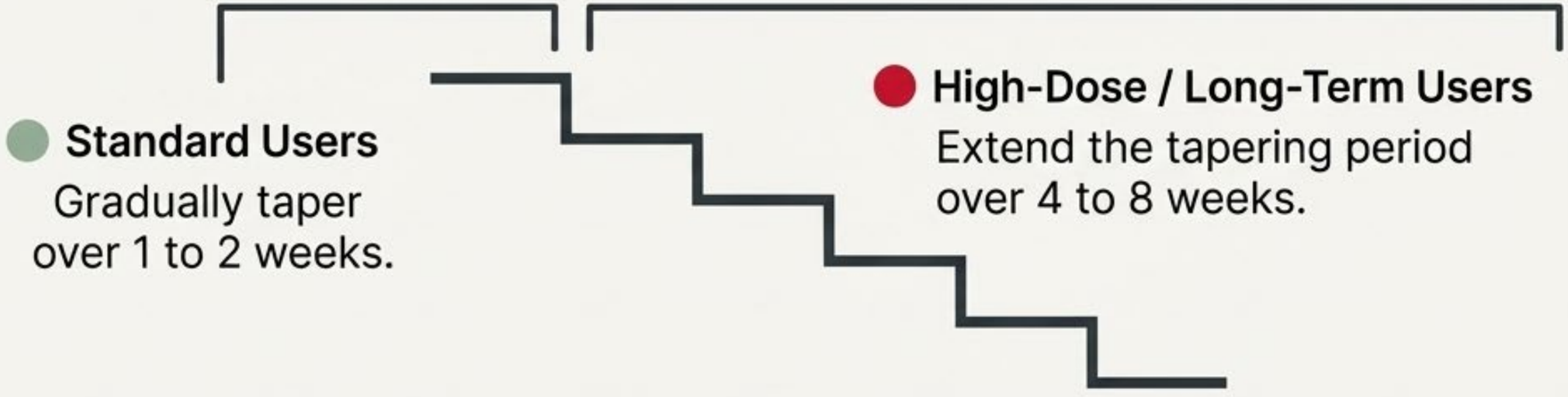
Abbreviation: DPN, diabetic peripheral neuropathy.

**TABLE 2** Randomized clinical trials of pregabalin versus placebo for off-label treatment of pain.

| Study | Clinical condition | No. of participants | Duration (weeks) | Difference in pain compared to placebo | Pregabalin dose |
|---|---|---|---|---|---|
| Kim JS, et al. *Pain.* 2011. | Central post-stroke neuropathic pain | 219 | 13 | No | 150 mg to 600 mg/day |
| Simpson DM, et al. *Neurology.* 2010. | HIV neuropathy | 302 | 14 | No | 150 mg to 600 mg/day |
| Simpson DM, et al. *Pain.* 2014. | HIV neuropathy | 377 | 17 | No | 150 mg to 600 mg/day |
| Mir A, et al. *Breast J.* 2020 | Postoperative pain in breast cancer patients | 150 | 24 | No | 150 mg/day |
| Hincker A, et al. *Pain.* 2019 | Chemotherapy-induced peripheral neuropathy | 23 | 10 | No | 150 mg to 600 mg/day |
| Mathieson S, et al. *N Engl J Med.* 2017. | Acute and chronic sciatica | 209 | 8 | No | 150 mg to 600 mg/day |
| Schlaeger JM, et al. *Pain Manag Nurs.* 2017. | Chronic sickle cell disease related pain | 22 | 12 | No | 75 mg to 600 mg/day |
| Holbech JV, et al. *Pain.* 2015. | Various neuropathic pain syndromes | 73 | 5 | No | 300 mg/day |
| Markman J, et al. *J Neurol.* 2018 | Post-traumatic peripheral neuropathic pain | 539 | 15 | No | 150-600 mg/day |
| Krcevski Skvarc N, et al. *Wien Klin Wochenschr.* 2010. | Acute zoster herpetic neuralgia | 29 | 3 | No | 300 mg/day |
| Pontari MA, et al. *Arch Intern Med.* 2010. | Chronic prostatitis/chronic pelvic pain syndrome | 324 | 6 | No | 150 mg escalated to 600 mg/day |
| van Seventer R, et al. *Eur J Neurol.* 2010. | Post-traumatic peripheral neuropathic pain | 367 | 8 | Yes 0.62 on 0-10 scale, $p = .01$ | 150 mg to 600 mg/day |
| Olesen SS, et al. *Gastroenterology.* 2011. | Chronic pancreatitis | 64 | 3 | Yes 0.58 on 0-10 scale, $p = .02$ | 150 mg escalated to 600 mg/day |
| Vranken JH, et al. *Pain.* 2008. | Central neuropathic pain | 40 | 4 | Yes 2.18 on 0-10 scale, $p = .01$ | 300 mg to 600 mg/day |
| Bismaya K, et al. *Clin J Pain.* 2023. | Carpal tunnel syndrome | 131 | 6 | Yes 1.63 improvement on 1-55 point scale. $p = .025$ | 50 mg escalated to 150 mg/day |

# Safely deprescribing through gradual tapering

When off-label use proves ineffective or toxic, discontinuation is required. Do not stop gabapentinoids abruptly due to well-documented withdrawal syndromes.




Hospitalists should initiate the deprescribing plan prior to discharge and ensure direct handoff to primary care.

# Prioritizing non-pharmacological modalities

Effective pain management requires shifting the focus toward the actual mechanisms of pain perception rather than routine chemical suppression.

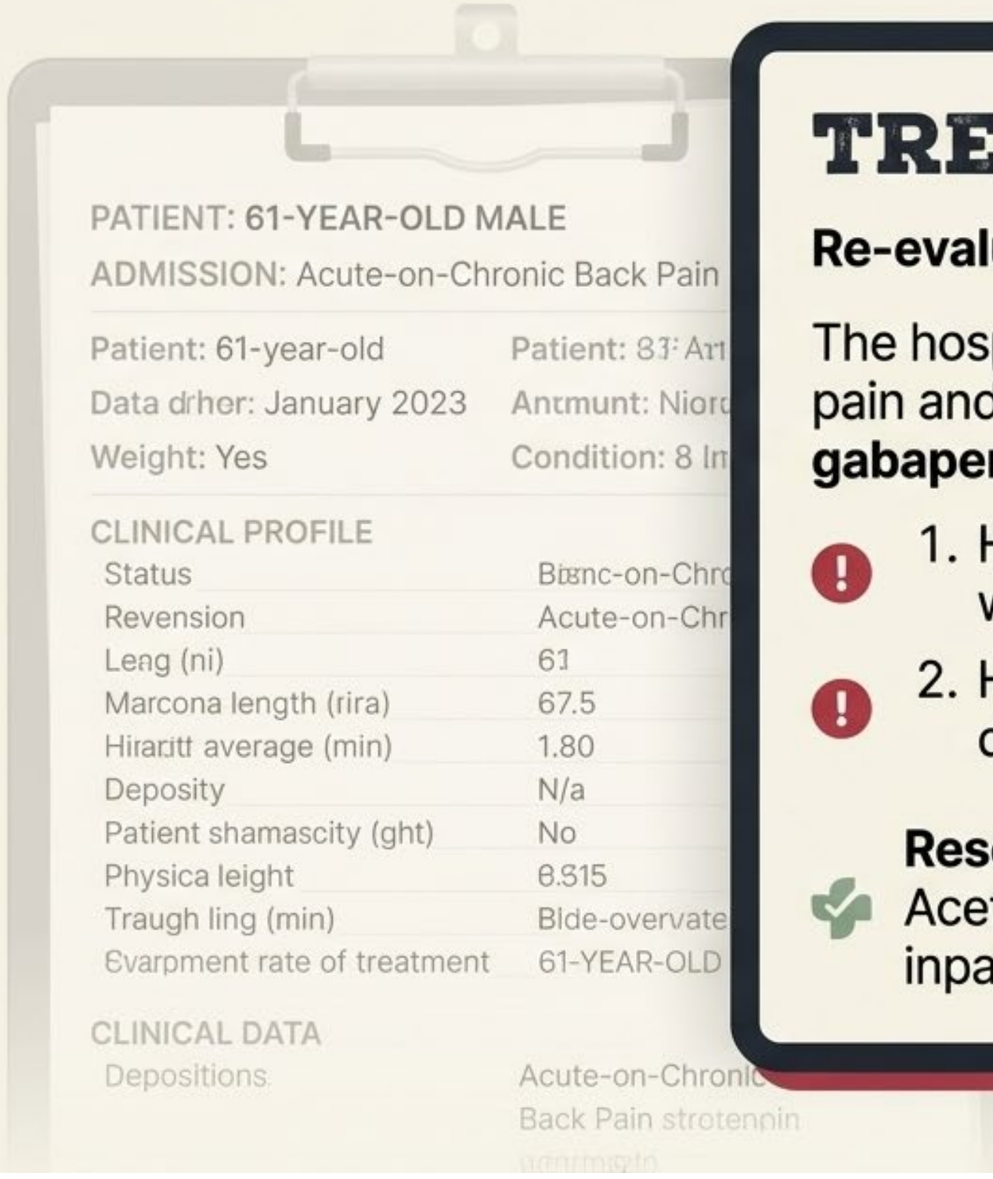
## Physical Approaches

- Targeted Physical Therapy to improve strength and mobility.
- Massage and structured exercise for musculoskeletal pain.

## Cognitive Approaches

- Cognitive-Behavioral Therapy (CBT) and Mindlulness practices.
- Directly modifies the brain’s pain perception and the patient’s emotional response to chronic pain.

# Closing the loop on our admission




## TREATMENT PLAN UPDATE

**Re-evaluating the 61-year-old man:**

The hospitalist reviews the trial data for acute-on-chronic back pain and notes the lack of efficacy. Furthermore, prescribing **gabapentin poses a severe threat** to this specific patient:

1. His CKD guarantees poor clearance and neurotoxicity without strict dose adjustment.
2. His Asthma places him at high risk for fatal respiratory depression, especially while taking hydrocodone.

**Resolution:** The gabapentin is weaned and discontinued. Acetaminophen is optimized, and the patient receives an inpatient physical therapy consult.

# Clinical Takeaways


## 1. Stop routine off-label prescribing

Gabapentinoids are not standard opioid substitutes. Avoid routine use for acute-on-chronic pain, low back pain, or general musculoskeletal pain.


## 2. Assess and Deprescribe

If a patient is admitted on a gabapentinoid, aggressively reassess its efficacy. If ineffective or causing harm, initiate a gradual tapering plan before discharge.


## 3. Adjust for renal function

If prescribing for an approved indication, dosage must be strictly adjusted for creatinine clearance to avoid severe **neurotoxicity**.

# References


- Patel NG, Goese D, Belknap SM, Madeira CL, Barsuk JH. Things We Do for No Reason™: Prescribing gabapentinoids for pain. *J Hosp Med*. 2026; 1-7. **doi:10.1002/jhm.70286**