



**What's All the "GABA" 'Bout? Pregabalin and Gabapentin Abuse**

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**Disclosures**

- This presentation was not a part of the presenter's official duties at the VA and does not represent the opinion of the VA
- The presentation will include "off-label" uses of some medications, for example gabapentin and tricyclic antidepressants (TCAs)



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**Learning Objectives**

- Review the proposed mechanisms of action (MOA) for gabapentin and pregabalin.
- Explain the proposed rationale as to why gabapentin and pregabalin have become drugs of abuse.
- Identify signs and symptoms of withdrawal that an addicted or tolerant patient may experience upon abrupt discontinuation of gabapentin or pregabalin.
- Discuss updates on changes in pain management given the increase in gabapentin and pregabalin abuse.



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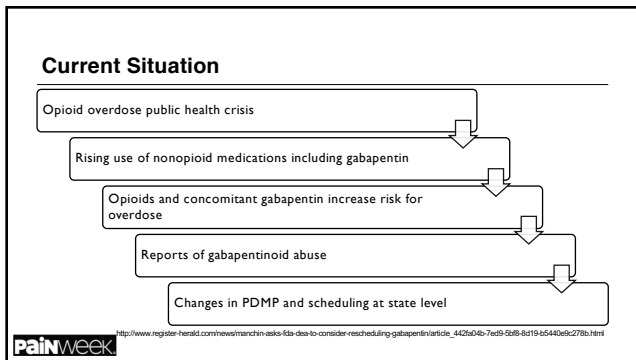
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**Gabapentin and Pregabalin:  
Pharmacology and Pharmacokinetics**

**PainWeek**

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**Fact or Alternate Fact?**

- Gabapentin and pregabalin work on GABA.

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**Mechanism of Action**

Structurally related to GABA and has GABA-mimetic properties

Do not

- Alter uptake or breakdown
- Convert into GABA
- Bind to GABA<sub>A</sub> or GABA<sub>B</sub>

Binds to the  $\alpha 2\text{-}\delta$  subunit of the voltage-gated calcium channel

Reduces the  $\text{Ca}^{2+}$ -dependent release of pro-nociceptive neurotransmitters

Decreases release of glutamate, NE, and substance P

Dworkin RH et al. Pain. 2007;133:227-251.  
Schnitker P. CNS Drugs. 2014;28:491-496.  
Micromedex 2.0 Online. <http://www.micromedexsolutions.com/micromedex2librarian>.  
J Clin Psychiatry. 2007; Mar;68(3):483-4

**PainWeek**

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**FDA-approved Indications**

- Pregabalin
  - Neuropathic pain associated with diabetic peripheral neuropathy (DPN)
  - Post-herpetic neuralgia (PHN)
  - Adjunctive therapy for adult patients with partial onset seizures
  - Fibromyalgia
  - Neuropathic pain associated with spinal cord injury
- Gabapentin
  - PHN
  - Adjunctive therapy in treatment of partial onset seizures, with and without secondary generalization, in adults and pediatrics  $\geq 3$  years

Lyrica package insert. New York: Parke-Davis; Dec 2016.  
Neurontin package insert. New York: Parke-Davis; Sept 2015.

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**FDA-approved Indications**

- Gabapentin enacarbil
  - Moderate-to-severe restless legs syndrome (RLS)
  - PHN
- Gabapentin ER
  - PHN
- Pregabalin CR
  - PHN
  - Neuropathic pain associated with DPN

Horizant package insert. Arbor Pharmaceuticals, Atlanta, GA: LLC: October 2016.  
Lyrica CR package insert. New York, NY; Pfizer: October 2017.  
Gralise package insert. Newark, CA; Depomed, Inc: Dec 2012.

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**Off-label Uses**

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**Pregabalin**

- Bipolar disorder
- Alcohol/narcotic withdrawal
- Anxiety
- ADHD
- Restless legs syndrome
- Trigeminal neuralgia
- Non-neuropathic pain

**Gabapentin**

- Insomnia
- Neuropathic pain
- Drug and alcohol addiction
- Anxiety
- Bipolar disorder
- Migraines

**PainWeek** CNS Drugs. 2014;28:491-496.  
Addiction. 2016;111:1160-1174.

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**Role in Pain**

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- NICE
  - Gabapentin - 1<sup>st</sup> line treatment for neuropathic pain
- ADA Diabetic Peripheral Neuropathy
  - Consider pregabalin or duloxetine as initial approach
- AAN Diabetic Peripheral Neuropathy
  - Offer pregabalin
  - Consider gabapentin
- Neuropathic Pain Special Interest Group of International Association for the Study of Pain
  - Gabapentin, pregabalin first line

**PainWeek** Addiction. 2016;111:1160-1174.  
Neurology. 2011;76(26):1758-1765.  
Diabetes Care. 2017;40(10):156-1564.  
May Clin Proc. 2010;85(3 Suppl):S3-S14.

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**Role in Pain**

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- Multimodal post-operative pain management
  - Pain scores
  - Opioid doses
  - Opioid side effects
  - Controversy around dosing and timing
- Acute or chronic sciatica
  - No benefit for pregabalin
- Nonspecific low back pain
  - Ineffective
  - Contribute to ADE

**PainWeek** Pain. 2007. 132:237-251.  
PLoS Med. 2017;14(8):e1002369.  
Medicine. 2017;96(21):e9982.  
Spine. 2013;38(22):1947-1952.  
NEJM. 2017;376(12):1111-1120.  
Br J Anaesth. 2011;106(4):454-462.  
JAMA Surg. 2017;eop.

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**Dosing**

**Gabapentin**

- Start at gabapentin 300 mg PO QHS
- Increase by 300 mg PO q3days
- Max dose of 3600 mg/day
- Adequate trial considered 6-8 weeks
- Requires renal dose adjustments beginning at CrCl <60ml/min
- Taper over 1 week if discontinuing

Dworkin RH et al. Pain. 2007; 132:237-251. Druggist® System, Micromedex®2.0, Greenwood Village, Colorado Accessed 8 Aug 2013

**PainWeek**

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**Dosing**

**Pregabalin**

- Start at 50 mg PO TID
- Titrate to 100 mg PO TID
- Max dose 600 mg/day
- Adequate trial requires 6-12 weeks
- Requires renal dose adjustments beginning at CrCl<60 mL/min
- Gradually taper off if discontinuing

Dworkin RH et al. Pain. 2007; 132:237-251. Druggist® System, Micromedex®2.0, Greenwood Village, Colorado Accessed 8 Aug 2013

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**Dosing**

 <p><b>Gabapentin enacarbil (PHN)</b> Days 1-3: 600 mg AM Day 4: 600 mg BID No benefit beyond 1200 mg/day</p>	 <p><b>Gabapentin ER</b> Day 1: 300 mg daily Day 2: 600 mg daily Days 3-6: 900 mg daily Days 7-10: 1200 mg daily Days 11-14: 1500 mg daily Day 15: 1800 mg daily</p>	 <p><b>Pregabalin CR</b> 165 mg/day initial Increase to 330 mg/day within 1 week Max 660 mg/day</p>
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Horizant package insert. Arbor Pharmaceuticals, Atlanta, GA: LLC: October 2016. Lyrica CR package insert. New York, NY; Pfizer: October 2017. Gralise package insert. Newark, CA; Depomed, Inc: Dec 2012.

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### Comparing Pharmacokinetics

Gabapentin	Pregabalin
<ul style="list-style-type: none"> <li>F=42-57%</li> <li>Nonlinear pharmacokinetics (PK)</li> <li>Slower onset</li> <li>Lower affinity for receptor</li> </ul>	<ul style="list-style-type: none"> <li>F=83.9-97.7%</li> <li>Linear PK</li> <li>Faster onset</li> <li>Higher affinity for receptor</li> </ul>

Itaku M et al. Pain Med. 2011;12:1112-1116.  
O'Connor AB ET AL. Am J Med. 2008;120(10A):S22-S32.  
Moulin DE et al. Pain Res manage. 2007;12(1):13-21.  
Neurontin® package insert. New York, NY: Pfizer; 2013. June.  
Neurontin® package insert. New York, NY: Pfizer; 2013. June.

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### Converting Case

• BT is a 57 yo male with diabetic peripheral neuropathy on gabapentin 600 mg PO TID. He continues to complain of symptoms and says he heard about pregabalin on TV. How would you convert this patient from gabapentin to pregabalin?

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### Converting

Pregabalin ~ 6 x as potent as gabapentin

Cross-titration method	Stop-start method
Reduce gabapentin dose by 50% and initiate 50% of equivalent pregabalin dose x 4 days	Discontinue gabapentin and increase pregabalin to full equivalent dose
	Stop gabapentin and start equivalent dose of pregabalin

Itaku M et al. Pain Medicine. 2011;12:1112-1116.  
Bockbrader HN et al. American J Therapeutics. 2012; 00(1): 1-10.

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**Converting Case**

- Cross-titration
  - Decrease gabapentin to 300 mg PO TID + initiate pregabalin at 75 mg PO BID x 4 days
  - Discontinue gabapentin + increase pregabalin to 150 mg PO BID
- Stop-Start
  - Discontinue gabapentin
  - Initiate pregabalin 150mg PO BID



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**Tapering**

- Avoid abrupt discontinuation to limit withdrawal symptoms
- Taper over at least 1 week



Lyrica package insert, New York: Parke-Davis, Dec 2016.  
Neurontin package insert, New York: Parke-Davis, Sept 2015.

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**Focus on Suicidal Ideation**

- Pooled analysis of 199 placebo-controlled trials of 11 different antiepileptic drugs (AED)
  - AED treated n=27,863 patients, Placebo n=16,029 patients
  - OVERALL: 0.43% AED treated patients vs. 0.24% of placebo patients
    - Relative risk 1.8, 95% CI: 1.2,2.7
  - Nonpsychiatric/epilepsy indications: 0.18% AED patients vs 0.1% placebo
    - Relative risk 1.9
- Presents as early as 1 week
- Persists for duration of treatment
- Did not vary by age
- Chronic pain associated with suicide
- Counsel patients



Lyrica package insert, New York: Parke-Davis, Dec 2016.  
Neurontin package insert, New York: Parke-Davis, Sept 2015.

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### Gabapentin Increases Overdose Odds

- Population-based nested case-control study
- Cases (1,256 cases) were opioid users who died of an opioid-related cause matched with up to 4 controls (4,619 controls)
- Primary exposure was gabapentin use 120 days preceding index date
- 12.3% of cases and 6.8% of control were prescribed gabapentin
- Odds increased 49% if prescribed gabapentin + opioid
- High dose gabapentin (1800 mg/day) about 60% increased odds compared to moderate dose
- Very high dose (2,200 mg/day) associated with 2-fold increased odds

PLoS Med. 2017;14(10):e1002396.



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### Pregabalin Increases Overdose Odds

- Population-based, nested, case-control study
- Cases (1,417 cases) were opioid users who died of an opioid-related cause matched with up to 4 controls (5097 controls)
- Primary exposure was pregabalin use 120 days preceding index date
- Significantly increased odds of opioid-related death OR 1.68
- High doses was associated with increased odds aOR 2.51
- Low or moderate dose associated with increased odds aOR 1.52

Ann Intern Med. 2018;169(10):732-734.



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### FDA Drug Safety Communication 12-19-2019

- 49 cases from 2012-2017
  - 12 people died with gabapentinoids
- Serious breathing problems with gabapentinoids with respiratory risk factors
  - Concomitant medications
    - Opioids
    - Anti-anxiety medications
    - Antidepressants
    - Antihistamines
  - COPD
  - Elderly
- Less evidence of respiratory issues with gabapentinoids used alone in healthy patients

<https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin>



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### FDA Drug Safety Communication 12-19-2019

- Educate patients and caregivers about potential risks and to seek immediate medical attention
- Start at lowest dose and monitor for respiratory depression and sedation
- Adjust gabapentinoid for renal dysfunction
- Be cognizant of additive effects of sedating or CNS-depressing medications
- Management of respiratory depression
  - Observation
  - Supportive measures
  - Reduction or withdrawal of CNS depressants

<https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin>



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### Role in Addiction Treatment

- Pregabalin
  - Alcohol withdrawal
  - Alcohol relapse prevention (abstinence similar to naltrexone)
  - Benzodiazepine/opioid withdrawal
  - Some evidence to prevent cocaine relapse
- Gabapentin
  - Evidence in opioid, THC, alcohol addictions
  - Gabapentin *suggested* in APA AUD Guidelines
    - Goal of reducing or abstaining from alcohol
    - Prefer topiramate or gabapentin or intolerant or did not respond to naltrexone or acomprostate
    - No contraindications

CNS Drugs, 2014;28:491-496  
Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder. APA.  
<https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9781615371569>



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### Gabapentin and Pregabalin Abuse



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**Patient Case**

- Ms. Smith is a 67 yo woman with PMH significant for mood disorder, alcohol abuse, and polyneuritis
- **Medications:** naproxen 550mg PO daily, amitriptyline 100mg PO daily, and gabapentin titrated up to 4800mg PO daily
- Began to exhibit fraudulent behavior:
  - Requesting medication without a prescription
  - Exaggerated symptoms
  - Physician consulted and then changed when demands not met
- Ran out of medication and could not obtain refill



Pharmacopsychiatry, 2007, Jan;40(1):43-4.

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**Gabapentinoid Use in U.S. 2002-2015**

- 346,177 adults prescribed gabapentin or pregabalin from Medical Expenditure Panel Survey
- 82.6% of patients prescribed gabapentin
- Significant increase in gabapentinoid prescribing during study
  - 2002 1.2% prescribed gabapentin or pregabalin
  - 2015 3.9% prescribed gabapentin or pregabalin
- Changes in 2008
  - No increase in gabapentin until 2008
  - Pregabalin use plateaued and no increase following

JAMA Intern Med. 2018;epub2018/01/04.



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**Abuse Potential in U.S. Commercially Insured**

- Retrospective cohort analysis from Truven Health MarketScan® Commercial Claims and Encounters database
- 11,247,216 unique patients aged 16-64 years with 2 or more claims for commonly abusable medications for ≥ 120 days
- Lorenz-1 curves calculated: percentage of total drug supply consumed by top 1% of users over 12 month period
  - Lorenz-1 curve ≥ 15% = high potential for abuse



Clin Drug Investig. 2017;37:763-773.

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### Abuse Potential in U.S. Commercially Insured

- Lorenz-1 curves
  - Opioid 37%
  - Gabapentin 19%
  - Pregabalin 15%
  - Alprazolam 14%
  - Zolpidem 13%
- Supply per day for top 1%
  - Gabapentin
    - Mean 11,274 mg/day, median 9,534 mg
  - Pregabalin
    - Mean 2,474 mg/day, median 2,219 mg/day



Clin Drug Investig. 2017;37:763-773.

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### FDA Adverse Events Reporting System (FAERS)

- Post-marketing surveillance
- October 2012 – December 2016 total 4,935,048 events for 294,652 unique medications
- \*Coingestants not known

Event	Gabapentin	Pregabalin
Total ADE	10,038	571
Abuse-related	576	58
Abuse-related fatalities*	106	24



Res Soc Adm Pharm. 2019;15:953-958.

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### U.S. Poison Control Center Data

- National Poison Data System 2013-2017, 74,175 gabapentin exposures, increased 72.3%
- Demographics (all exposures)
  - Mean age: 44.6 years
  - Male 40.2%
  - Female 59.2%
- Intentional cases: 51,932 cases
  - 41,948 attempted suicide
  - 3537 abuse exposures
- Isolated exposures: 22,737 (31%), increased 35%
  - 1014 (4.5%) intentional abuse
  - 1709 (7.5%) intentional misuse
  - 9387 (41%) suicide attempts



Clinical Toxicology. 2019.

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### U.S. Poison Control Center Data

- Co-ingested substances
  - Sedative-hypnotic 23%
  - Other 19.3%
  - Antidepressant 13%
  - Antihypertensive 10%
  - **Opioid 9%**
- Geographic findings
  - WV and KY worst
- Outcomes from isolated exposures
  - Admission 16.7%
    - Critical care unit 53.9%
    - Non critical care unit 46.1%



Clinical Toxicology. 2019.

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### Prevalence

- Lifetime prevalence in general population estimated at 1.1% of patients
- Prevalent in opioid abuse populations
  - 15-22% gabapentin misuse
  - 40-65% abuse of gabapentin with prescription
- > 50% of patients with history of substance use disorder
  - Opioid use disorder common



Addiction. 2016;111:1160-1174.

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### Mechanism of Action: Abuse

- Not entirely known
- GABA analogues which may induce addictive behaviors in the same manner as benzodiazepines
- Pregabalin:
  - Schedule V
  - Six-fold higher binding affinity for the  $\alpha_2\text{-}\delta$  subunit
  - Quicker absorption rate and greater bioavailability



Eur J Clin Pharmacol. 2013 Jun;69(6):1335-42.  
Res Soc Admin Pharm. 2019;15:953-958.

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### Pregabalin Package Insert

- In a small patient population (N=15) of recreational users of sedative/hypnotic drugs, pregabalin administered as a 450mg single dose produced the following results:
  - "Good drug effect"
  - "High"
  - "Liking"
- The above effects were similar to that reported with a 30mg single dose of diazepam
- In addition, controlled trials of >5500 patients found that 4% of patients treated with pregabalin reported *euphoria* as an ADR
  - Reported rates range from 1-12%



Lyrica package insert, New York, NY: Pfizer, Inc.; 2013.

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### Gabapentin Package Insert

- Small number of post-marketing reports of misuse and abuse
- Taking higher than recommended doses
- Unapproved uses or to treat withdrawal
- History of polysubstance abuse
- Assess history of drug abuse
- Monitor for s/sx of gabapentin misuse or abuse



Neurontin package insert, Pfizer; New York, NY; October 2017

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### Doses for Abuse

- Abused in a wide variety of doses
  - Therapeutic range - no prescription
  - Supratherapeutic range
- 3-20 times clinically used amounts
- Taken as one large dose
- Tolerance develops leading to dose increase



Addiction 2016;111:1160-1174  
Opioid Drugs 2016;28:491-496  
Drugs 2017;7403-454.

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### Frequency of Abuse

- General population
  - More than once weekly 13.1%
  - Once weekly – once monthly 50%
  - Less frequently 36.8%
- Opioid abuse population
  - 25 of the last 30 days

**PainWeek** Drugs. 2017;77:403-426.

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### Sources

- Healthcare providers (52-63%)
- Family or acquaintances (57.8%)
- Internet (47.3%)
- Drug dealer
- International (7.8%)

**PainWeek** Addiction. 2016;111:1160-1174.  
Drugs. 2017;77:403-426.

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### Cost

- Street value and sold/traded for illicit drugs
- Gabapentin on the street (referred to as "gabbies" or "Budweiser's" in the UK) costs approximately £1/300mg which is equivalent to \$1.65/300mg
- In Appalachian Kentucky, the street cost of gabapentin was reported to be <\$1/pill
- \$1-7 per pill depending on strength

**PainWeek** Addiction. 2016;111:1160-1174.  
CNS Drugs. 2016;34(307):847-54.  
Ann Pharmacother. 2016;Mar 50(3):229-33.  
BMJ. 2013;Nov 5;347:f6747.  
Br J Gen Pract. 2012;Aug;62(601):406-7.  
Am J Psychiatry. 2010;May;167(5):607-8.

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### Coingestants

Gabapentin	<ul style="list-style-type: none"> <li>Alcohol</li> <li>Cannabis</li> <li>Selective serotonin reuptake inhibitors</li> <li>Lysergic acid diethylamide (LSD)</li> <li>Amphetamine</li> <li>Gamma-hydroxybutyrate</li> <li>Opioids</li> <li>Benzodiazepines</li> </ul>
Pregabalin	<ul style="list-style-type: none"> <li>Alcohol/gabapentin/benzodiazepines</li> <li>Cannabinoids</li> <li>LSD</li> <li>Salvia</li> <li>Heroin/opiates</li> <li>Amphetamines/synthetic cathinones</li> </ul>

Psychiatry Psychosom. 2011;80(2):119-22.  
CNS Drugs. 2014;28:491-496.  
Addiction. 2016;111:1160-1174.

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### Factors Leading to Abuse

Wide-spread use
Multiple off-label uses
Gabapentin is relatively cheap
Ease of obtaining a prescription
Not controlled (gabapentin) or low potential for abuse (pregabalin)

Addiction. 2016;111:1160-1174.  
Drugs. 2017;77:403-426.

**PainWeek**

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### Reasons for Abuse

Recreational	Mood/anxiety	Potentiating effects of drug abuse treatment	Intentional self-harm
Reduce pain	Reduce cravings/withdrawal from other substances	Substitution for other drugs	Addiction to gabapentin

Addiction. 2016;111:1160-1174.

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### Common & Novel Methods of Abuse

▪ Parachuting

**Painweek**

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### Common & Novel Methods of Abuse

<p>Gabapentin</p> <ul style="list-style-type: none"> <li>▪ Orally</li> <li>▪ Intravenously (IV)</li> <li>▪ Snorting</li> <li>▪ Intramuscular (IM)</li> <li>▪ "Cutting agent" in street heroin</li> </ul>	<p>Pregabalin</p> <ul style="list-style-type: none"> <li>▪ Orally</li> <li>▪ Intravenously (IV)</li> <li>▪ Snorting</li> <li>▪ Smoking</li> <li>▪ Rectally ("plugging")</li> <li>▪ "Parachuting"</li> </ul>
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Br J Gen Pract. 2012;Aug;62(601):406-7.  
Psychiatr Psychosom. 2011;80(2):118-22.  
The LYRIC (pregabalin) Mega-Trend. Available at: [bluelight.org](http://bluelight.org).  
Schlana F. CNS Drugs. 2014;28:491-496.

**Painweek**

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### Effects of Abuse

<p><b>Gabapentin</b></p> <ul style="list-style-type: none"> <li>Euphoria</li> <li>Improve sociability</li> <li>Marijuana-like "high/relaxation"</li> <li>Zombie-like effects</li> <li>Sedative/opiate "buzz"</li> <li>Psychedelic/3,4-methylenedioxy-N-methylamphetamine-like effects</li> </ul>	<p><b>Pregabalin</b></p> <ul style="list-style-type: none"> <li>Alcohol/GHB/benzodiazepine-like effects</li> <li>Euphoria</li> <li>Entactogenic feelings</li> <li>Dissociation</li> <li>Coping with opioid withdrawal</li> </ul>
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CNS Drugs. 2014;28:491-496.  
Eur J Clin Pharmacol. 2013 Jun;69(6):1335-42.  
Pharmacopsychiatry. 2007;Jan;60(1):43-6.

**Painweek**

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### Effects of Gabapentin & Pregabalin Abuse

- "...the pregabalin erases my benzo, opiate withdrawal and cravings... In my opinion, anything over 900mg is a waste – too sedating"
- "The only downside to gabapentin so far as I can tell, is the onset. These little guys take upwards of an hour to really start to kick in, but luckily they last for 4-8 hours it seems..."
- "I feel as if I'm on a super amphetamine rush and can tackle anything, yet feel so content it's like I'm on a fully sedated opiate buzz."
- "...pregabalin outshines gabapentin. Far less dosage to achieve the same recreational high. Also not as strong of a half life allowing one to use the drug more frequently."

**PainWeek** Psychother Psychosom. 2011;80(2):118-22.

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### Overdose

- Onset: soon after ingestion
- Duration: 10h
- Effects typically mild to moderate
- Fatalities or intubation – rare
- Common effects
  - Hypotension
  - Tachycardia
  - CNS effects
- Symptoms more likely after gabapentin 1200 mg
- Survivals reported with up to 11,500 mg of pregabalin and 91,000 mg of gabapentin

**PainWeek** Drugs. 2017;77:403-426.

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### Overdose

- Severe events more of a concern in renal dysfunction
- Fatalities more common when ingested with other substances
- 90% of fatalities associated with opioids
- German toxicology reports from 2010-2012 with pregabalin
  - General population 2% of cases year 1, 4% of cases in year 2
  - Known substance use disorder 5.5% in year 1, 29.8% in year 2
- Finnish toxicology reports from 2010-2011
  - Pregabalin 2.3%
  - Gabapentin 0.31%

**PainWeek** Drugs. 2017;77:403-426.

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### Withdrawal

- Onset ranges from 12 hours to 7 days after termination of use
  - Majority of cases report onset between 24-48 hours
- At least one reported case of a newborn baby experiencing withdrawal due to mother's gabapentin use while pregnant



Ann Pharmacother. 2016 Mar;50(3):229-33.

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### Withdrawal Signs/Symptoms

Psychomotor agitation	Confusion	Craving	Disorientation
Arterial HTN	Tachycardia	Tremor	Insomnia
Nausea	Headache	Diarrhea	Diaphoresis



J Addict Med. 2013 Mar-Apr;7(2):147-9.  
 Eur J Clin Pharmacol. 2013 Jun;69(6):1335-42.  
 J Clin Psychiatry. 2007 Mar;68(3):483-4.  
 Ann Pharmacother. 2016 Mar;50(3):229-33.

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### Withdrawal Treatment

- Benzodiazepines: ineffective?
- Antipsychotics: ineffective?
- Benzotropine: ineffective?
- Anticonvulsants: effective (in terms of seizure control)
- Pregabalin: effective
- Gabapentin: effective



J Addict Med. 2013 Mar-Apr;7(2):147-9.  
 Eur J Clin Pharmacol. 2013 Jun;69(6):1335-42.  
 J Clin Psychiatry. 2007 Mar;68(3):483-4.  
 Ann Pharmacother. 2016 Mar;50(3):229-33.  
 Drugs. 2017;77:468-626.

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**Patient Case: Revisited**

- Ms. Smith is a 67 yo woman with PMH significant for mood disorder, alcohol abuse, and polyneuritis
- She was actually taking *at least 7200mg of gabapentin daily!*
- Upon running out of gabapentin, she developed typical withdrawal symptoms and was hospitalized
  - Upon discharge, gabapentin discontinued
  - ~3 months later, gabapentin re-prescribed
  - ~5 months after discharge, she had resumed gabapentin abuse in combination with diazepam



Journal of Clinical Psychopharmacology, 2007, Jan;40(1):43-4.

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**Patient Case: Revisited**

- Taper off gabapentin
- Behavioral Health referral
- Taper BZD



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**State Prescription Drug Monitoring Program (PDMP)**

Pregabalin is a Schedule V controlled substance	<ul style="list-style-type: none"> <li>• Already reported to the database in some states</li> <li>• Some states do not require the reporting of schedule V medications</li> </ul>
States have ADDED gabapentin prescriptions to database reports	<ul style="list-style-type: none"> <li>• Minnesota</li> <li>• Ohio</li> <li>• Kentucky</li> <li>• Massachusetts</li> <li>• North Dakota</li> <li>• Virginia</li> <li>• West Virginia</li> <li>• Wyoming</li> </ul>
States have ADDED gabapentin as a schedule V	<ul style="list-style-type: none"> <li>• Tennessee</li> <li>• Kentucky</li> <li>• Michigan</li> <li>• West Virginia</li> </ul>



http://www.painweek.com/.../Pregabalin%20Dose%20Restriction%20in%20Ohio%20ABRS%2012-13-14.pdf  
[http://www.painweek.com/.../State\\_PDP\\_Tracking\\_Document.xls](http://www.painweek.com/.../State_PDP_Tracking_Document.xls)  
[http://www.fda.gov/oc/2009/08/0809.pdf](http://www.fda.gov/oc/2009/08/080809.pdf)

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**Indicators of medication abuse**

- Requesting specific medications
- Requesting higher doses
- Doctor shopping
- Claims of lost/stolen medications
- Using multiple pharmacies
- Early refill requests
- Negative UDM – but not routinely part of testing



Addiction, 2017;77:403-426.

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**Summary**

- Gabapentin and pregabalin abuse can occur
  - Common and novel routes of administration
  - Therapeutic and supratherapeutic doses
- More common in patients with history of substance use disorder
- Coingestants often involved
- Patients can experience withdrawal if gabapentin and pregabalin are stopped abruptly
- Certain state Prescription Drug Monitoring Programs (PDMPs) are adding gabapentin



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**3 Things for Monday**

1. Assess a patient's substance abuse history, psychiatric history, and concurrent medications before prescribing
2. Be aware of higher risk groups
3. Monitor for early refills and/or limiting the quantity supplied



CNS Drugs, 2014;28:491-496.  
Addiction, 2017; 77:403-426.

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**Assessment Q1**

- The proposed MOA for gabapentin and pregabalin include
  - a) Binding to GABA receptors
  - b) Increasing glutamate, norepinephrine, and substance P
  - c) Binding to the  $\alpha 2-\delta$  subunit of the voltage-gated calcium channel
  - d) Inhibiting serotonin reuptake

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**Assessment Q2**

- Factors that have contributed to the abuse of gabapentin include all of the following EXCEPT:
  - a) High cost
  - b) Ease of obtaining a prescription
  - c) Non-controlled substance status
  - d) Multiple uses/indications

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**Assessment Q3**

- JB is a 47 yo female with a history of opioid use disorder, DM, and diabetic neuropathy. She has been taking her prescribed gabapentin as a single 3600 mg dose and ran out 36 hours ago. She has presented with headache, hypertension, insomnia, tremor, and sweating. What do you give the patient to treat her gabapentin withdrawal symptoms?
  - a) Baclofen
  - b) Lorazepam
  - c) Gabapentin
  - d) Benzotropine

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**What's All the "GABA" 'Bout? Pregabalin and Gabapentin Abuse**

Courtney Kominek, PharmD, BCPS, CPE

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