



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

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Disclosures

- Axial Healthcare – Consultant
- The views and opinions expressed in this presentation are those of the author and does not necessarily reflect the official policy or position of any agency of the United States government, including the Department of Veterans Affairs, as well as employers, employee affiliates and/or pharmaceutical companies mentioned or specific drugs discussed. It was not prepared as part of official government duties for Dr. Brooks.

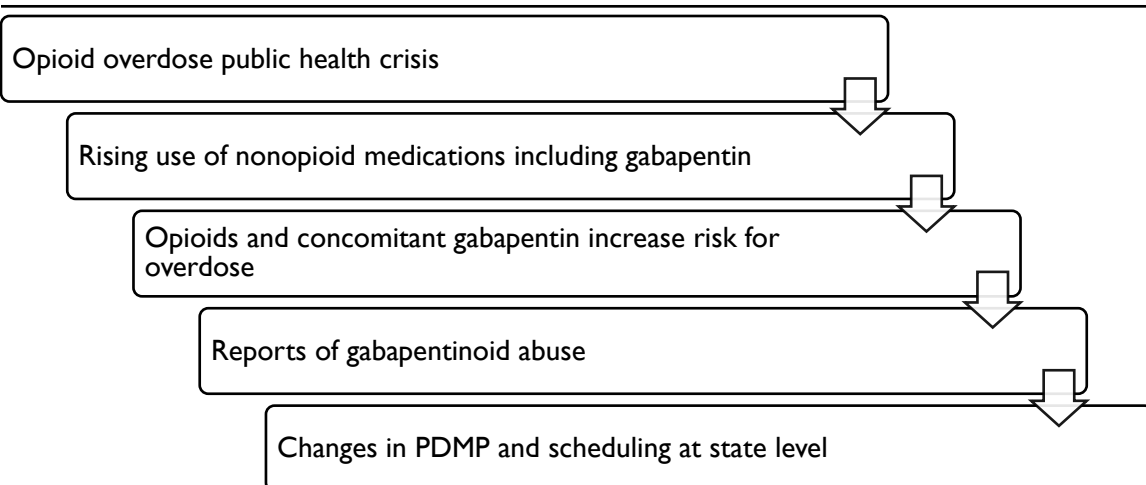


Learning Objectives

- 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.



Current Situation



1. http://www.register-herald.com/news/manchin-asks-fda-dea-to-consider-rescheduling-gabapentin/article_442fa04b-7ed9-5bf8-8d19-b5440e9c278b.html
 2. *N Engl J Med*. 2017 Aug 3;377(5):411-414.

Gabapentin and Pregabalin: Pharmacology and Pharmacokinetics



Fact or Alternate Fact?

- Gabapentin and pregabalin work on GABA.



Mechanism of Action

Structurally related to GABA and has GABA-mimetic properties

Do not

- Alter uptake or breakdown
- Convert into GABA
- Bind to GABA_a or GABA_b

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

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

Decreases release of glutamate, NE, and substance P

- PainWeek**
1. Dworkin RH et al. Pain. 2007;1332:237-251.
 2. Schifano F. CNS Drugs. 2014;28:491-496.
 3. Micromedex 2.0 Online. <http://www.micromedexsolutions.com/micromedex2/librarian>.
 4. J Clin Psychiatry. 2007 Mar;68(3):483-4

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 ≥ 3 years

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

FDA-approved Indications

- Gabapentin encarbil
 - Moderate-to-severe restless legs syndrome
 - PHN
- Gabapentin ER
 - PHN
- Pregabalin CR
 - PHN
 - Neuropathic pain associated with DPN



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

Role in Pain

- NICE
 - Gabapentin - 1st 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



1. Addiction. 2016;111:1160-1174.
2. Neurology. 2011;76(20):1758-1765.
3. Diabetes Care. 2017;40(10):136-1564.
4. May Clin Proc. 2010;85(3 Suppl):S3-S14.

Role in Pain

Multimodal postoperative 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

1. Spine. 2013;38(22):1947-1952.
2. NEJM. 2017;376(12):1111-1120.
3. Br J Anaesth. 2011;106(4):454-462.

4. Pain. 2007. 132;237-251.
5. PLoS Med. 2017;14(8):e1002369.
6. Medicine. 2017;96(21):e6982.
7. JAMA Surg. 2017;epub.

Off-label Uses

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

1. CNS Drugs. 2014;28:491-496.
2. Addiction. 2016;111:1160-1174.

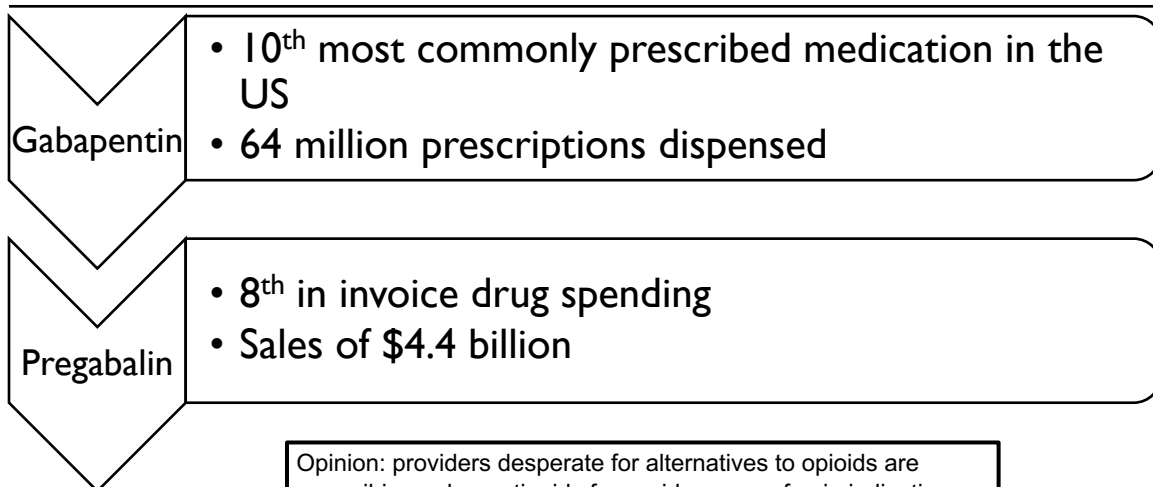
Gabapentinoid Use in U.S. 2002-2015

- 346,177 adults prescribed gabapentin or pregabalin between 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.

Gabapentinoid Prescribing Data - 2016



N Engl J Med. 2017 Aug 3;377(5):411-414.

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.

Pregabalin Increases Overdose Odds

- Population-based nested case-control study
- Study population: Ontario residents eligible for public drug coverage
- Cases (1,417 cases) were opioid users who died of an opioid-related cause matched with up to 4 controls (5,097 controls)
- Recent exposure was pregabalin use 120 days preceding index date
- Odds increased 68% if prescribed pregabalin + opioid
- High dose pregabalin (>300 mg/day) had much greater odds compared to no pregabalin exposure (adj. OR 2.51)
- Low or moderate dose pregabalin (\leq 300 mg/day) had lower but still significant odds of opioid-related death



Ann Intern Med. 2018 Aug 21. doi: 10.7326/M18-1136. [Epub ahead of print].

Gabapentin

Dosing

- Initial dose: 300mg PO at bedtime
- Increase by 300-400mg every 3-7 days, as tolerated, to lowest effective dose
- Maximum total daily dose: 3600mg
- Renal dose adjustment required

Monitoring

- Baseline LFT and SCr and then monitor every 6-12 months thereafter
- Potential for misuse/abuse
- Suicidal thoughts and behavior

Side effects

- Dizziness
- Weight gain/edema
- Sedation



Gabapentin [package insert]. New York, NY: Pfizer, Inc.; 2015.

Gabapentin

Renal Dose Adjustment

CrCL 30-59 mL/min:
400-1400mg/day in
2 divided doses

CrCL 15-29 mL/min:
200-700mg/day once
daily

15 mL/min: 100-
300mg once daily
<15mL/min: reduce
daily dose in
proportion to CrCL



Gabapentin [package insert]. New York, NY: Pfizer, Inc.; 2015.

Pregabalin

Dosing

- Initial dose: 75mg PO BID
- Titrate up to 150mg PO BID or 100mg POTID
- Doses up to 600mg have been evaluated with no significant additional benefit (increase in ADRs)
- Renal dose adjustment required

Monitoring

- Baseline LFT and SCr and then monitor every 6-12 months thereafter
- Potential for misuse/abuse
- Suicidal thoughts and behavior

Side effects

- Dizziness
- Weight gain/edema
- Sedation



Pregabalin [package insert]. New York, NY: Pfizer, Inc.; 2016.

Pregabalin

CrCL (mL/min)	Total Pregabalin Daily Dose (mg/day)				Dose Regimen
≥60	150	300	450	600	BID or TID
30-60	75	150	225	300	BID or TID
15-30	25-50	75	100-150	150	Daily or BID
<15	25	25-50	50-75	75	Daily

- Per package insert: if dosed pre-dialysis, will require supplemental dose following hemodialysis.
- AVOID need for supplemental dose by administering pregabalin consistently in the evening time or post-dialysis!



Pregabalin [package insert]. New York, NY: Pfizer, Inc.; 2016.

Dosing



Gabapentin encarbil (PHN)

Days 1-3: 600 mg AM
Day 4: 600 mg BID
No benefit beyond
1200 mg/day



Gabapentin ER

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



Pregabalin CR

165 mg/day initial
Increase to 330
mg/day within 1 week
Max 660 mg/day



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

Comparing Pharmacokinetics

Gabapentin

- F=42-57%
- Nonlinear pharmacokinetics (PK)
- Slower onset
- Lower affinity for receptor

Pregabalin

- F=83.9-97.7%
- Linear PK
- Faster onset
- Higher affinity for receptor



1. Ifuku M et al. Pain Med. 2011;12:1112-1116.
2. O'Connor AB ET AL. AM J Med. 2009;112(10A):S22-S32.
3. Moulin DE et al. Pain Res manage. 2007;12(1):13-21.
4. Neurontin® package insert. New York, NY; Pfizer; 2013 June.
5. Lyrica® package insert. New York, NY; Pfizer; 2012 July.

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



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

Converting Case

- Background: Mr. Stevens is a 68-year-old male with diabetic peripheral neuropathy. His past medication history is significant for type 2 diabetes, uncontrolled hypertension, chronic kidney disease with CrCl=43 mL/min, and benign prostatic hypertrophy (BPH).
- Current status: ADR with amitriptyline. SNRI not appropriate. Pain has been reduced with some functional benefit with gabapentin 600 mg PO BID. Patient heard about pregabalin on TV and wants to give it a try.
- Question: What would you suggest?



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



1. Ifuku M et al. Pain Medicine. 2011;12:1112-1116.
2. Bockbader HN et al. American J Therapeutics. 2012; 0(0): 1-10.

Converting Case

▪ Answer:

– Two approaches

- Reduce gabapentin to 300 mg PO BID and initiate pregabalin 50 mg PO BID x 1 week, then discontinue gabapentin and increase pregabalin to 100 mg PO BID
- Discontinue gabapentin, initiate pregabalin 100 mg PO BID



Tapering

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



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

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



1. CNS Drugs. 2014;28:491-496.
2. Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder. APA. <https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9781615371969>

Gabapentin and Pregabalin Misuse and Abuse



Definitions

Misuse

- Taking a legal prescription medication for a purpose other than the reason it was prescribed
- Taking a drug not prescribed to you

Abuse*

- Taking a legal prescription medication for a purpose other than the reason it was prescribed
- Taking a drug not prescribed to you **AND**
- End goal of taking a drug or substance is to get a pleasant or euphoric feeling

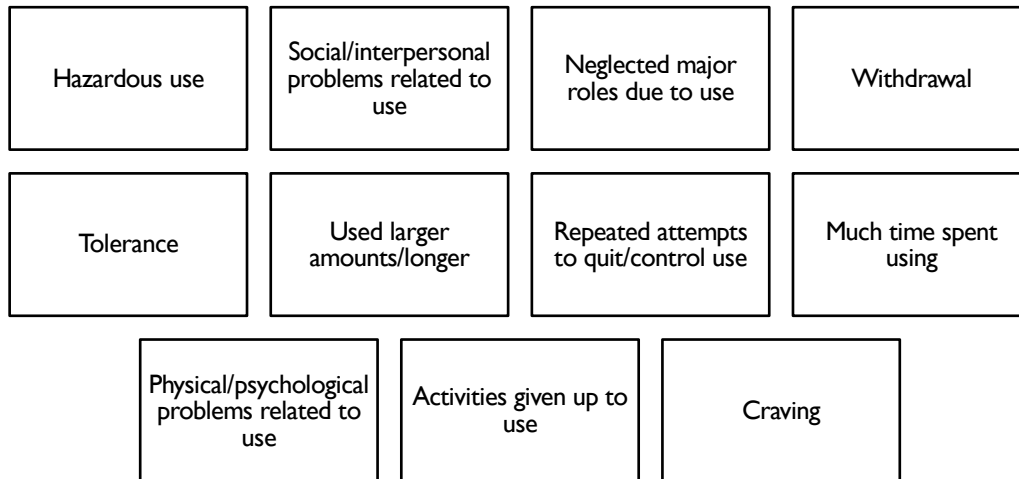
* Applies to illicit or nonprescription medications/substances as well



Combating Misuse and Abuse of Prescription Drugs: Q&A with Michael Klein, Ph.D.. Available at: <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm220112.htm>

DSM-5 Substance Use Disorders

Two or more substance use disorder criteria within a 12-month period.



PainWeek

Am J Psychiatry 170:8, August 2013.

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



PainWeek

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

Startling Statistics

- The European Medicines Agency (EMA) trended the number of pregabalin ADRs reported from 3/2006-7/2015
 - Reports peaked in 2013 (2154 total), decreased in 2014 (1593 total), and totaled 1387 reports as of 7/15/2015
- The EMA received a total of 4301 ADR reports related to gabapentin abuse/dependence issues between 3/2004-7/2015
- Users of gabapentin are more likely to abuse oxycodone, buprenorphine, and benzodiazepines compared with nonusers



1. CNS Drugs. 2016 Jul;30(7):647-54.
2. Ann Pharmacother. 2016 Mar;50(3):229-33.
3. Am J Psychiatry. 2015 May;172(5):487-8.

Demographics

- Females > males or females = males
- Average age
 - Samples 21-43 years
 - Case reports 41 years
- Reports from
 - US (n=22)
 - UK (n=4)
 - Germany (n=1)
 - Poland (n=1)
 - India (n=1)
 - South Africa (n=1)
 - France (n=1)



Addiction. 2016;111:1160-1174.

Demographics – 2013

- A study of random UDS samples (N=124) in patients being treated for opioid dependence with agonist therapy (methadone or buprenorphine) significant for:
 - 12.1% of urine samples positive for pregabalin (n=15)
 - 11/15 patients admitted to buying pregabalin from heroin addicts or drug dealers
- Query of the German Federal Institute for Drugs and Medical Devices regarding pregabalin abuse/dependence significant for:
 - 55 total reports of pregabalin abuse and dependence
 - Mean daily dose: 1424mg
 - Mean age: 36 yo
 - 63.6% of reports were male patients



1. Eur J Clin Pharmacol. 2013 Dec;69(12):2021-5.
2. Eur J Clin Pharmacol. 2013 Jun;69(6):1335-42.

Demographics – 2015/2016

- From 3/2004-7/2015 4301 ADR reports related to gabapentin
 - 1.27:1 female to male ratio
- From 3/2006-7/2015 7639 ADR reports related to pregabalin
 - 1.13:1 female to male ratio
- Common to have history of substance use disorder



1. Annals Pharmacother. 2016;50(3):229-233.
2. CNS Drugs. 2016;30:647-654.

Demographics – Prison System

- Search of inmate lockers revealed only 19/96 inmates in possession of gabapentin were prescribed gabapentin
- Diverting gabapentin for high



Drugs. 2017;77:403-426.

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.

Retrospective Cohort Analysis from Insurance Claims Database

- Inclusion: Patients 16-64 years old and had ≥ 2 pharmacy claims for alprazolam, gabapentin, pregabalin, zolpidem, or any opioid medication (ex. patch formulations or fentanyl products)
- Potential abuse: ≥ 3 claims exceeding the daily dose threshold and ≥ 3 rolling quarters where the dispensed supply exceeded the threshold
- Results:
 - 3.2% and 4.9% of patients were potentially abusing gabapentin or pregabalin alone
 - 24% of gabapentin patients on opioids and 28% of pregabalin patients on opioids meeting criteria for potential abuse



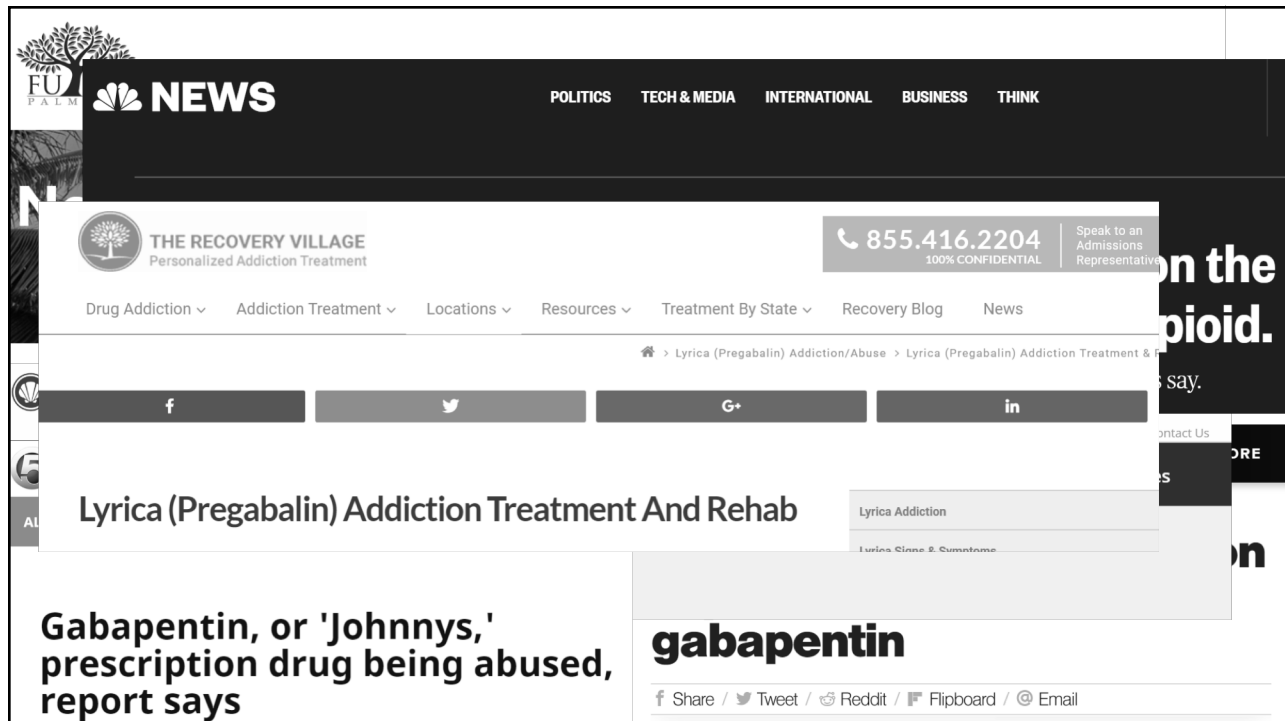
Psychiatr Q. 2016;87(4):763-767.

Mechanism of Action: Misuse and Abuse

- Reduces the release of neurotransmitters, including:
 - Glutamate
 - Noradrenaline
 - Serotonin
 - Dopamine
- 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.



The screenshot shows a news article from NBC News. The top navigation bar includes 'POLITICS', 'TECH & MEDIA', 'INTERNATIONAL', 'BUSINESS', and 'THINK'. The article is titled 'Lyrica (Pregabalin) Addiction Treatment And Rehab'. A sidebar on the right contains a phone number '855.416.2204' and a link to 'Speak to an Admissions Representative'. The main text area features a large headline: 'Gabapentin, or 'Johnnys,' prescription drug being abused, report says'. Below the headline, there is a sub-headline 'gabapentin' and a list of social media sharing options: 'Share / Tweet / Reddit / Flipboard / Email'. The article is attributed to 'Lynne Stone & Sumitomo'.

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%



PainWeek

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

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

Doses for Misuse and Abuse

- Misused and/or 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



1. Addiction. 2016;111:1160-1174.
2. CNS Drugs. 2014;28:491-496.
3. Drugs. 2017;77:403-426.

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



Drugs. 2017;77:403-426.

Sources

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



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

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 (street name in the US: “Johnny’s”)
- \$1-7 per pill depending on strength

PainWeek

1. Addiction. 2016;111:1160-1174.
2. CNS Drugs. 2016 Jul;30(7):647-54.
3. Ann Pharmacother. 2016 Mar;50(3):229-33.
4. BMJ. 2013 Nov 8;347:f6747.
5. Br J Gen Pract. 2012 Aug;62(601):406-7.
6. Am J Psychiatry. 2015 May;172(5):487-8.

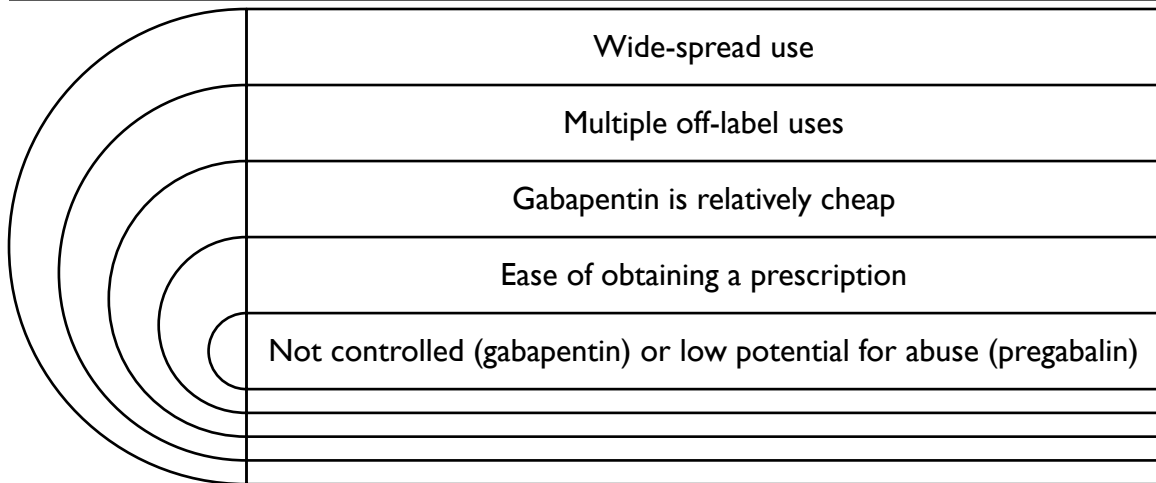
Coingestants

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

1. Psychother Psychosom. 2011;80(2):118-22.
2. CNS Drugs. 2014;28:491-496.
3. Addiction. 2016;111:1160-1174.

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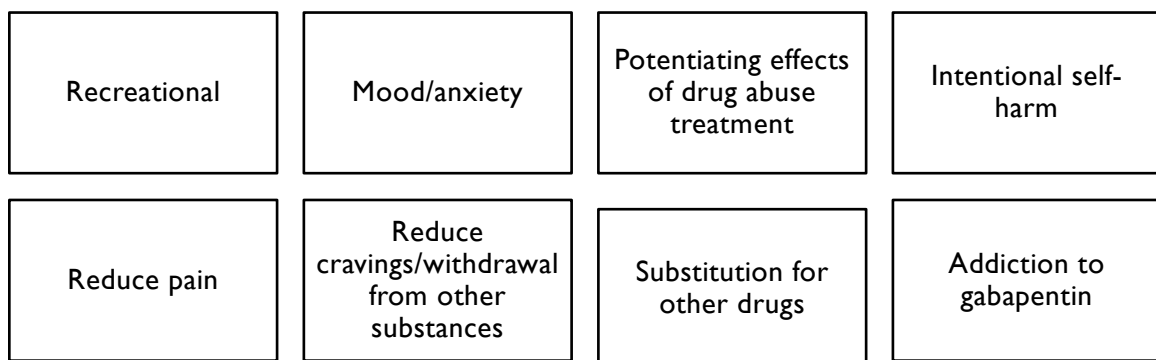
Factors Leading to Misuse and Abuse



PainWeek

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

Reasons for Misuse and Abuse

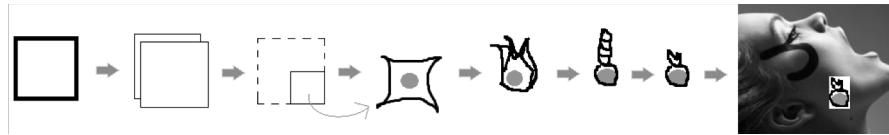


PainWeek

Addiction. 2016;111:1160-1174.

Common & Novel Methods of Abuse

▪ Parachuting



PainWeek

Common & Novel Methods of Abuse

Gabapentin

- Orally
- Intravenously (IV)
- Snorting
- Intramuscular (IM)
- "Cutting agent" in street heroin

Pregabalin

- Orally
- Intravenously (IV)
- Snorting
- Smoking
- Rectally ("plugging")
- "Parachuting"

PainWeek

1. Br J Gen Pract. 2012 Aug;62(601):406-7.
2. Psychother Psychosom. 2011;80(2):118-22.
3. The LYRICA (pregabalin) Mega Thread. Available at: bluelight.org.
4. Schifano F. CNS Drugs. 2014;28:491-496.

Effects of Abuse

Gabapentin

Euphoria
 Improve sociability
 Marijuana-like “high/relaxation”
 Zombie-like effects
 Sedative/opiate “buzz”
 Psychedelic/3,4-methylenedioxy-N-methylamphetamine-like effects

Pregabalin

Alcohol/GHB/benzodiazepine-like effects
 Euphoria
 Entactogenic feelings
 Dissociation
 Coping with opioid withdrawal

PainWeek

1. CNS Drugs. 2014;28:491-496.
2. Eur J Clin Pharmacol. 2013 Jun;69(6):1335-42.
3. Pharmacopsychiatry. 2007 Jan;40(1):43-4.

Effects of Gabapentin & Pregabalin Misuse/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.

Effects of Pregabalin Misuse/Abuse

600mg	<ul style="list-style-type: none"> • Stumbling, disorientation, increased physical and psychological awareness, difficulty driving, slurred and broken speech, hearing and visual alterations/hallucinations, double and blurred vision, increased sexual performance
900mg	<ul style="list-style-type: none"> • Strong feelings of drunkenness, difficulty waking, alteration of color perception, little euphoria
1200mg	<ul style="list-style-type: none"> • Drowsiness, euphoria, empathetic feelings (similar to Ecstasy)
> 1500mg (to 5g)	<ul style="list-style-type: none"> • Uncontrollable drowsiness, frequent hallucinations, great euphoria, frequent dissociative events (similar to dextromethorphan effects), behavioral inhibition, anxiety



Guide to the management of gabapentinoid misuse. Available at:
<https://www.prescriber.co.uk/article/guide-to-the-management-of-gabapentinoid-misuse/>.

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



Drugs. 2017;77:403-426.

Overdose

- Severe events more of a concern in renal dysfunction
- Fatalities more common when ingested with other substances
 - Opioids and other sedatives
- 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%



1. Drugs. 2017;77:403-426.
2. Brain Sci. 2018 Apr 22;8(4).

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.

Withdrawal Signs/Symptoms

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



PainWeek

1. J Addict Med. 2013 Mar-Apr;7(2):147-9.
2. Eur J Clin Pharmacol. 2013 Jun;69(6):1335-42.
3. J Clin Psychiatry. 2007 Mar;68(3):483-4.
4. Ann Pharmacother. 2016 Mar;50(3):229-33.
5. Guide to the management of gabapentinoid misuse. Available at: <https://www.prescriber.co.uk/article/guide-to-the-management-of-gabapentinoid-misuse/>.

Withdrawal Treatment

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

PainWeek

1. J Addict Med. 2013 Mar-Apr;7(2):147-9.
2. Eur J Clin Pharmacol. 2013 Jun;69(6):1335-42.
3. J Clin Psychiatry. 2007 Mar;68(3):483-4.
4. Ann Pharmacother. 2016 Mar;50(3):229-33.
5. Drugs. 2017;77:403-426.

Gabapentinoid Dose Reduction in Misuse and Abuse

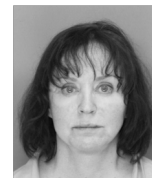
- Public Health England (PHE) recommends a collaborative and conservative approach
- “If the prescriber decides to prescribe above the maximum dose in the summary of product characteristics, this should be for a short period of time with an aim to reduce the patient to below the licensed maximum dose in a short period of time and within the guidance provided by PHE.”
- Maximum reduction rate for pregabalin: 50-100mg/week
- Maximum reduction rate for gabapentin: 300mg every 4 days



Guide to the management of gabapentinoid misuse. Available at:
<https://www.prescriber.co.uk/article/guide-to-the-management-of-gabapentinoid-misuse/>

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



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

Patient Case: Revisited

- Taper off gabapentin
- Behavioral Health (Substance Abuse) referral
- Taper BZD
- Naloxone kit? → if opioid misuse/abuse suspected



State Prescription Drug Monitoring Program (PDMP)

- Pregabalin is a Schedule V controlled substance
 - Already reported to the database in some states
 - Some states do not require the reporting of schedule V medications
- States that have ADDED gabapentin prescriptions to database reports include:
 - Minnesota
 - Ohio
 - Kentucky → now C-V status
 - Massachusetts
 - North Dakota
 - Virginia
 - West Virginia → now C-V status
 - Wyoming
 - New Jersey

1. <http://pmp.pharmacy.state.mn.us/>
2. <http://pharmacy.ohio.gov/Documents/Pubs/Special/QARRS/Reporting%20Gabapentin%20Products%20to%20QARRS%20%E2%80%93%20Effective%2012-1-2016.pdf>
3. <http://www.chfs.ky.gov/os/oig/KASPER.htm>
4. <http://www.njconsumeraffairs.gov/pmp/Pages/regulations.aspx>
5. https://www.wynews.com/theet/news/new-laws-on-opioids-and-gabapentin-go-into-effect/article_b9013859-8871-50e9-a460-2b69f3c4b73a.html



Indicators of medication abuse

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



Addiction. 2017;77:403-426.

Signs of Potential Misuse of Gabapentinoids

Presenting intoxicated, impaired or disheveled (esp. if change from normal presentation)
Loss of interest in alternative hobbies or activities
Early requests for prescriptions
“Lost” prescriptions
Unauthorized dose increases
Concurrent misuse of related illicit drugs
Obtaining the medication from other sources
Withdrawal symptoms reported or reporting unintended psychotropic effects
No interest in the diagnosis for which gabapentinoid is being used, including refusal of additional work-up or testing
Worsening mental health presentation
Aggressive complaining
Prescription forgery



Guide to the management of gabapentinoid misuse. Available at:
<https://www.prescriber.co.uk/article/guide-to-the-management-of-gabapentinoid-misuse/>.

Summary

- Gabapentin and pregabalin misuse and 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



4 Things for Monday

1. Assess a patient's substance abuse history, psychiatric history, and concomitant medications before prescribing
2. Be aware of higher risk groups (take a good social history)
3. Monitor for early refills and/or limiting the quantity supplied
4. Check your state PDMP!



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

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 $\alpha 2$ - δ subunit of the voltage-gated calcium channel
 - d) Inhibiting serotonin reuptake

PainWeek

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

PainWeek

Assessment Q3

- Signs of gabapentin and pregabalin withdrawal include all of the following EXCEPT:
 - a) Cravings
 - b) Hypotension
 - c) Insomnia
 - d) Headache



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

Abigail Brooks, PharmD, BCPS