



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

Thomas B. Gregory, PharmD, BCPS, CPE, FASPE

Disclosures

- Nothing to disclose

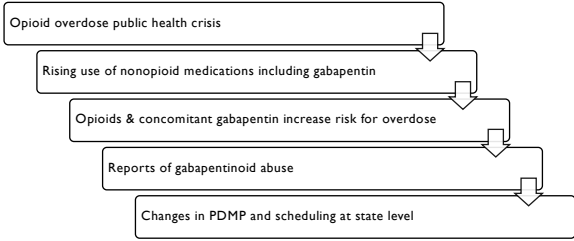


Learning Objectives

- Review the proposed mechanisms of action for gabapentinoids
- Explain the proposed rationale as to why gabapentin and pregabalin have become drugs of abuse
- Identify signs and symptoms of withdrawal that a patient may experience upon abrupt discontinuation of gabapentin or pregabalin



Current Situation



http://www.register-herald.com/news/march-in-asko-fda-dea-to-consider-rescheduling-gabapentin/article_4426d04b-7ed9-56b8-8d19-65440dc27fb.html

Gabapentin and Pregabalin: Pharmacology and Pharmacokinetics



Mechanism of Action

- Structurally related to GABA and has GABA-mimetic properties
- The gabapentinoids do NOT
 - Alter uptake or breakdown
 - Convert into GABA
 - Bind to GABA_A or GABA_B
- Binds to the $\alpha 2-\delta$ 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



Dworkin RH et al. Pain. 2007;133:237-251.
Schiffman F. CNS Drugs. 2014;28:491-496.
Micromedex 2.0 Online. <http://www.micromedexsolutions.com/micromedex2/brain>.
J Clin Psychiatry. 2007 Mar;68(3):483-4

FDA-Approved Indications

- Pregabalin
 - Neuropathic pain associated with diabetic peripheral neuropathy
 - Postherpetic 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

<https://online.lexi.com/lco/action/home> accessed 4.8.2019



FDA-Approved Indications (cont'd)

- Gabapentin enacarbil
 - Moderate-to-severe restless legs syndrome
 - Postherpetic neuralgia (PHN)
- Gabapentin ER
 - PHN
- Pregabalin CR
 - PHN
 - Neuropathic pain associated with diabetic peripheral neuropathy

<https://online.lexi.com/lco/action/home> accessed 4.8.2019



Off-Label Uses

Pregabalin

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

Gabapentin

- Insomnia
- Neuropathic pain other than listed previously
- Drug and alcohol addiction
- Anxiety
- Bipolar disorder
- Migraines

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



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 and pregabalin as first line



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

Role in Pain (cont'd)

- 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 averse events



Pain. 2007. 132:237-251.
 PLoS Med. 2017;14(8):e1002369.
 Medicine. 2017;96(23):e6982.
 Spine. 2013;38(22):1947-1952.
 NEJM. 2017;376(12):1111-1120.
 Br J Anaesth. 2011;106(4):454-462.
 JAMA Surg. 2017;epub.

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 weeks
- Requires renal dose adjustments beginning at CrCl <60ml/min
- Taper over 1 week if discontinuing



https://online.lexi.com/doc.action?docId=docIdpatch_69661 accessed 4.4.2019

Dosing (cont'd)

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



https://online.lexi.com/lco/action/doc/retrieve/docid/patch_0152021 accessed 4.4.2019

Dosing (cont'd)



Gabapentin enacarbil
 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



<https://online.lexi.com/lco/action/home> accessed 4.8.2019

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



Ibuku M et al. Pain Med. 2011;12:1112-1116.
 O'Carroll AB ET AL. Am J Med. 2008;112(10A):S29-S32.
 Moulou DE et al. Pain Res manage. 2007;12(1):13-21.
<https://online.lexi.com/lco/action/home> accessed 4.8.2019

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?



Converting

Pregabalin ~ 6 x as potent as gabapentin

Cross-titration 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-start method

- Stop gabapentin and start equivalent dose of pregabalin



Iliju M et al. Pain Medicine. 2011;12:1112-1116; Bookbinder HW et al. American J Therapeutics. 2012; 0(0): 1-10.

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



Tapering

Avoid abrupt discontinuation to limit withdrawal symptoms

Taper over at least one week



<https://online.lexi.com/loc/action/home> accessed 4.8.2019

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 one week
- Persists for duration of treatment
- Did not vary by age
- Chronic pain associated with suicide
- Counsel patients



<https://online.lexi.com/loc/action/home> accessed 4.8.2019

Gabapentin and Opioid Overdose

- 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 (2200 mg/day) associated with 2-fold increased odds



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

Pregabalin and Opioid Overdose

- 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 (5,097 controls)
- Primary exposure was pregabalin use 120 days preceding the index date

- Significantly increased odds of opioid-related death, OR 1.68
- High doses was associated with increased, adjusted OR 2.51
- Low or moderate dose associated with increased, adjusted OR 1.52



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

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 and alcohol addictions
 - Gabapentin *suggested* in APA AUD Guidelines
 - Prefer topiramate or gabapentin
 - If intolerant to or did not respond to naltrexone or acamprosate

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.9781616371999> accessed 4.8.2019



Gabapentin and Pregabalin Abuse



Patient Case

- Ms. Smith is a 67 yo woman with PMH significant for mood disorder, alcohol abuse, and polyneuritis
- Current medications include 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



Gabapentoid Use in US 2002-2015

- 346,177 adults prescribed gabapentin or pregabalin from Medical Expenditure Panel Survey
- 82.6% of patients prescribed gabapentin
- Significant increase in gabapentoid 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.



Startling Statistics

- The European Medicines Agency (EMA) trended the number of pregabalin ADRs reported from 3/2006 to 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

CNS Drugs. 2016 Jul;30(7):647-54.
Ann Pharmacother. 2018 Mar;52(3):229-33.
Am J Psychiatry. 2015 May;172(5):487-9.



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)

PainWeek 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: 1424 mg
 - Mean age: 36 yo
 - 63.6% of reports were male patients

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

Demographics – 2015/2016

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

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

PainWeek

Prevalence of Substance Use Disorders

- 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
- Greater than 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

- Patients 16-64 years old and had ≥ 2 pharmacy claims for alprazolam, gabapentin, pregabalin, zolpidem, or any opioid medication
- Potential abuse defined as
 - ≥ 3 claims exceeding the daily dose threshold
 - ≥ 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: Abuse

- Reduces the release of neurotransmitters
 - Glutamate
 - Noradrenaline
 - Serotonin
 - Dopamine
- GABA analogues which may induce addictive behaviors in the same manner as benzodiazepines
- Pregabalin
 - 6-fold higher binding affinity for the α₂-δ subunit
 - Quicker absorption rate and greater bioavailability



Eur J Clin Pharmacol. 2013 Jun;69(6):1335-42.

Pregabalin and Abuse

- In a small patient population (N=15) of recreational users of sedative/hypnotic drugs, pregabalin administered as a 450 mg single dose produced the following
 - "Good drug effect"
 - "High"
 - "Liking"
- The above effects were similar to that reported with a 30 mg single dose of diazepam
- In addition, controlled trials of > 5,500 patients found that 4% of patients treated with pregabalin reported *euphoria* as an ADR
 - Reported rates range from 1-12%

<https://online.lexi.com/lco/action/home> accessed 4.8.2019



Doses for Abuse

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

Addison, 2016;111:1160-1174.
CNS Drug, 2014;28:491-494.
Drugs, 2017;77:403-426.



Frequency of Abuse

- General population
 - More than once weekly 13.1%
 - Once weekly to once monthly 50%
 - Less frequently 36.8%
- Opioid abuse population
 - Use 25 out 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%)

Addiction. 2016;111:1160-1174.
 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/ 300 mg which is equivalent to \$1.65 / 300 mg
- In Appalachian Kentucky, the street cost of gabapentin was reported to be < \$1 / pill
- \$1-7 per pill depending on strength

Addiction. 2016;111:1160-1174.
 CNS Drugs. 2016 Jul;30(7):647-54.
 Ann Pharmacother. 2016 Mar;50(3):229-33.
 BMJ. 2013 Nov 8;347:f6747.
 Br J Gen Pract. 2012 Aug;62(661):486-7.
 Am J Psychiatry. 2013 Nov;170(5):487-6.



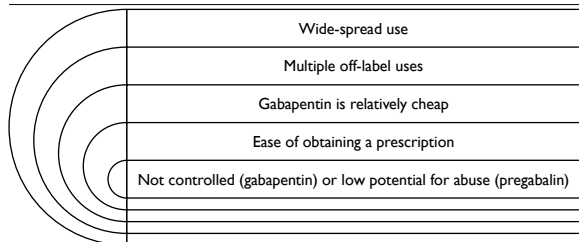
Coingestants

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

Psycholther Psychosom. 2011;80(2):118-22.
 CNS Drugs. 2014;28:491-495.
 Addiction. 2016;111:1160-1174.



Factors Leading to Abuse



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

Common & Novel Methods of Abuse

- Parachuting



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"

Br J Gen Pract. 2012 Aug;62(601):406-7.
 Psychother Psychosom. 2011;80(2):118-22.
 The LYRICA (pregabalin) Mega Thread. Available at: bluesight.org.
 Schiliana 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 effects

Pregabalin

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

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



Overdose

- Onset: soon after ingestion
- Duration: 10 hours
- 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 11.5 grams of pregabalin and 91 grams of gabapentin

Drugs, 2017;77:403-426.



Overdose (cont'd)

- 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%

Drugs, 2017;77:403-426.



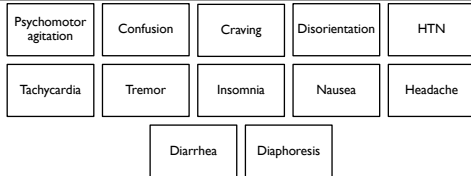
Withdrawal

- 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



J Addict Med. 2013 Mar-Apr;7(2):147-9.
 Eur J Clin Pharmacol. 2013 Jun;89(6):1335-42.
 J Clin Psychiatry. 2007 Mar;68(3):483-4.
 Ann Pharmacother. 2016 Mar;50(3):229-33.



Withdrawal Management

- 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;89(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.



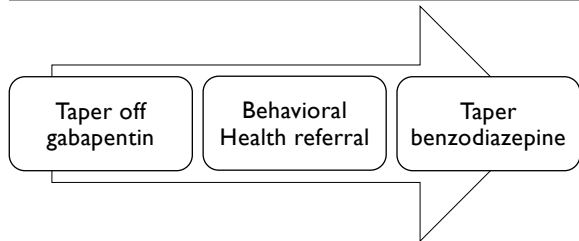
Patient Case: Revisited

- 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
 - Approx. 3 months later, gabapentin re-prescribed
 - Approx. 5 months after discharge, she had resumed gabapentin abuse in combination with diazepam



Journal of Pain and Agitation 2007 Jan;4(1):43-4.

Patient Case: Revisited (cont'd)



State Prescription Drug Monitoring Program (PDMP)



- 14 states have some degree of legislation (or in process) regarding the controlled substance scheduling or PDMP reporting of gabapentin as of 2018
- Pregabalin continues to be a schedule 5 controlled substance per federal DEA regulations

■ US states and jurisdictions where gabapentin is classified as a Schedule V medication with controlled reporting to a PDMP
 ■ US states and jurisdictions with forthcoming legislative and/or regulatory language for gabapentin to be listed as a Schedule V medication
 ■ US states and jurisdictions with mandates reporting to a PDMP
 ■ US states and jurisdictions with forthcoming legislative and/or regulatory requirements for reporting to a PDMP
 ■ US states and jurisdictions in deliberations



State Working Health Policy 2018; 11: 100-116.10.2147330MPP.5165504 accessed 4.5.2019

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.

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