



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

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Disclosures

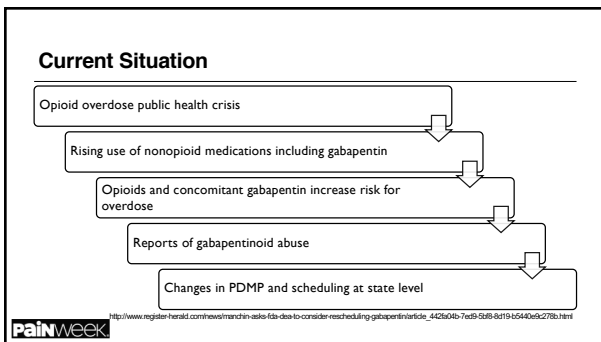
- Honoraria: Daiichi Sankyo
- This presentation was not a part of the presenter's official duties at the VA and does not represent the opinion of the VA
- The presentation will include "off-label" uses of some medications, for example gabapentin and tricyclic antidepressants (TCAs)



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





**Gabapentin and Pregabalin:
Pharmacology and Pharmacokinetics**

PainWeek

Fact or Alternate Fact?

- Gabapentin and pregabalin work on GABA.

PainWeek

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 α2-δ subunit of the voltage-gated calcium channel

Reduces the Ca²⁺-dependent release of pro-nociceptive neurotransmitters

Decreases release of glutamate, NE, and substance P

Ducloux R et al. Pain. 2007;132(2):237-251.
Schnitzler P. CNS Drugs. 2014;28:691-698.
Miconmedex 2.0 Online. <http://www.miconmedex.com/miconmedex2/librarian>.
J Clin Psychiatry. 2007; 168(3):403-4

PainWeek

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

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

PainWeek

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

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.

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

PainWeek Addiction. 2016;111:1160-1174.
Neurology. 2011;76(25):1758-1765.
Diabetes Care. 2017;40(10):156-156A.
May Clin Proc. 2016;91(3 Suppl):S3-S14.

Role in Pain

- 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):e69952.
Spine. 2013;38(22):1947-1952.
NEJM. 2017;376(12):1111-1120.
Br J Anaesth. 2011;106(6):454-462.
JAMA Surg. 2017;e9946.

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. Drugdex® System. Micromedex®/C.O. Greenwood Village, Colorado Accessed 8 Aug 2013

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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. Drugdex® System. Micromedex®/C.O. Greenwood Village, Colorado Accessed 8 Aug 2013

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Dosing

| | | |
|--|---|--|
|  <p>Gabapentin enacarbil (PHN) Days 1-3: 600 mg AM Day 4: 600 mg BID No benefit beyond 1200 mg/day</p> |  <p>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</p> |  <p>Pregabalin CR 165 mg/day initial Increase to 330 mg/day within 1 week Max 660 mg/day</p> |
|--|---|--|

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

Buku M et al. Pain Med. 2011;12:1112-1116.
O'Connor AB ET AL. Am J Med. 2008;112:10A1S22-S32.
Mason DC et al. Pain Res manage. 2007;11:13-21.
Neurocrin® package insert. New York, NY. Pfizer 2013 June.
Lyrica® package insert. New York, NY. Pfizer 2012 July.

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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 |

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

PainWeek

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 1 week



Lyrica package insert, New York, Parke-Davis, Dec 2010.
Neurontin package insert, New York, Parke-Davis, Sept 2015.

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 2010.
Neurontin package insert, New York, Parke-Davis, Sept 2015.

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
- 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.



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 acamprosate
 - No contraindications

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



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

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

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

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

Startling Statistics

- As of 2013 over a 5 year period in the UK
 - Pregabalin prescribing had increased by 350% to 2.7 million
 - Gabapentin prescribing had increased by 150% to 3.5 million prescriptions
- Approximately 1% prevalence rate in general population in UK

PainWeek BMJ. 2013 Nov 6;347:f6747.
Br J Gen Pract. 2012 Aug;62(651):406-7.
Annals Pharmacother. 2016;50(3):229-233.

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

PainWeek CNS Drugs. 2016 Jul;30(7):647-54.
Ann Pharmacother. 2016 Mar;50(3):229-33.
Ann J Psychiatry. 2015 May;172(5):467-8.

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)

PainWeek 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

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 3/2004-7/2015 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

PainWeek Annals Pharmacother. 2016;50(3):229-233.
ONS 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

PainWeek 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

PainWeek 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

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


Mechanism of Action: 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

PainWeek Eur J Clin Pharmacol. 2013 Jun;99(6):1335-42.

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

PainWeek Neurontin package insert. Pfizer; New York, NY: October 2017

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

PainWeek Addiction, 2016;11(1):162-174
 CNS Drugs, 2014;28(4):491-496
 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

PainWeek Drugs. 2017;77:403-426.

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.

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 Jul;30(7):547-54.
Ann Pharmacother. 2016 Mar;50(3):229-33.
BMJ. 2013 Nov 8;347:f6747.
Br J Gen Pract. 2012 Aug;62(930):406-7.
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 |

Psychiatry Psychosom. 2011;80(2):118-22.
 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.

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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

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Common & Novel Methods of Abuse

| | |
|---|--|
| <p>Gabapentin</p> <ul style="list-style-type: none"> ▪ Orally ▪ Intravenously (IV) ▪ Snorting ▪ Intramuscular (IM) ▪ "Cutting agent" in street heroin | <p>Pregabalin</p> <ul style="list-style-type: none"> ▪ Orally ▪ Intravenously (IV) ▪ Snorting ▪ Smoking ▪ Rectally ("plugging") ▪ "Parachuting" |
|---|--|

Br. J Gen Pract. 2012 Aug;62(651):436-7.
 Psychother Psychosom. 2011;80(2):118-22.
 The LYRICA (pregabalin) Mega Thread. Available at: bluesight.org.
 Schizena F. CNS Drugs. 2014;28:491-498.

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Effects of Abuse

| | |
|--|--|
| <p>Gabapentin</p> <ul style="list-style-type: none"> Euphoria Improve sociability Marijuana-like "high/relaxation" Zombie-like effects Sedative/opiate "buzz" Psychedelic/3,4-methylenedioxy-N-methylamphetamine-like effects | <p>Pregabalin</p> <ul style="list-style-type: none"> Alcohol/GHB/benzodiazepine-like effects Euphoria Entactogenic feelings Dissociation Coping with opioid withdrawal |
|--|--|

CNS Drugs. 2014;28:491-498.
 Eur J Clin Pharmacol. 2013;Jun;75(6):1335-42.
 Pharmacopsychiatry. 2007;Jan;40(1):43-4.

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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 Psycholiter Psychosom. 2011;80(2):118-22.

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.

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.

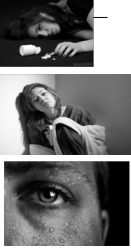
Withdrawal

- 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

PainWeek 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 |



PainWeek J Addict Med. 2013 Mar-Apr;7(2):147-9.
 Eur J Clin Pharmacol. 2013 Jun;85(6):1335-42.
 J Clin Psychiatry. 2007 Mar;68(3):452-4.
 Ann Pharmacother. 2016 Mar;50(3):229-33.

Withdrawal Treatment

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

PainWeek J Addict Med. 2013 Mar-Apr;7(2):147-9.
 Eur J Clin Pharmacol. 2013 Jun;85(6):1335-42.
 J Clin Psychiatry. 2007 Mar;68(3):452-4.
 Ann Pharmacother. 2016 Mar;50(3):229-33.
 Drugs. 2017;77:403-426.

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.

Patient Case: Revisited

- Taper off gabapentin
- Behavioral Health referral
- Taper BZD



State Prescription Drug Monitoring Program (PDMP)

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



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

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

PainWeek 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

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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

PainWeek CNS Drugs, 2014;28:491-496.
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 $\alpha 2-\delta$ 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

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

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

Courtney Korminek, PharmD, BCPS, CPE
