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

Opioid overdose public health crisis

Rising use of nonopioid medications including gabapentin

Opioids and concomitant gabapentin increase risk for overdose

Reports of gabapentinoid abuse

Changes in PDMP and scheduling at state level

- [link to article](http://www.register-herald.com/news/manchin-asks-fda-dea-to-consider-rescheduling-gabapentin/article_442fa04b-7e9b-5bf8-8419-a55440e6c279.html)
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<sub>δ</sub> or GABA<sub>β</sub>

- Binds to the α2-δ subunit of the voltage-gated calcium channel

- Reduces the Ca<sup>2+</sup>-dependent release of pro-nociceptive neurotransmitters

- Decreases release of glutamate, NE, and substance P


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

FDA-approved Indications

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


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

**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

**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

1. CNS Drugs. 2014;28:491-496.
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

Gabapentinoid Prescribing Data - 2016

**Gabapentin**
- 10th most commonly prescribed medication in the US
- 64 million prescriptions dispensed

**Pregabalin**
- 8th in invoice drug spending
- Sales of $4.4 billion

Opinion: providers desperate for alternatives to opioids are prescribing gabapentinoids for a wide-range of pain indications.

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

**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 (≤300 mg/day) had lower but still significant odds of opioid-related death

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

Renal Dose Adjustment

<table>
<thead>
<tr>
<th>CrCL 30-59 ml/min: 400-1400mg/day in 2 divided doses</th>
<th>CrCL 15-29 mL/min: 200-700mg/day once daily</th>
<th>15 mL/min: 100-300mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15mL/min: reduce daily dose in proportion to CrCL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pregabalin

Dosing
• Initial dose: 75mg PO BID
• Titrate up to 150mg PO BID or 100mg PO TID
• 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

<table>
<thead>
<tr>
<th>CrCL (mL/min)</th>
<th>Total Pregabalin Daily Dose (mg/day)</th>
<th>Dose Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>150 300 450 600</td>
<td>BID or TID</td>
</tr>
<tr>
<td>30-60</td>
<td>75 150 225 300</td>
<td>BID or TID</td>
</tr>
<tr>
<td>15-30</td>
<td>25-50 75 100-150 150</td>
<td>Daily or BID</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25 25-50 50-75 75</td>
<td>Daily</td>
</tr>
</tbody>
</table>

• 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!
**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

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**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

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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


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**

- Reduce gabapentin dose by 50% and initiate 50% of equivalent pregabalin dose x 4 days

**Stop-start method**

- Discontinue gabapentin and increase pregabalin to full equivalent dose

- Stop gabapentin and start equivalent dose of pregabalin

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**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

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Tapering

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

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 acomprosate
    - No contraindications

References:
4. Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder. APA.
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/For Consumers/Consumer Updates/ucm220112.htm
### DSM-5 Substance Use Disorders

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

- Hazardous use
- Social/interpersonal problems related to use
- Neglected major roles due to use
- Withdrawal
- Tolerance
- Used larger amounts/longer
- Repeated attempts to quit/control use
- Much time spent using
- Physical/psychological problems related to use
- Activities given up to use
- Craving

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

**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


**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)

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


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

Demographics – Prison System

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

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
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

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 α2-δ subunit
  - Quicker absorption rate and greater bioavailability
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%.
**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

**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

2. CNS Drugs. 2014;28:491-496.
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

Sources

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

Cost

- Street value and sold/traded for illicit drugs
- Gabapentin on the street (referred to as “gobbies” 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

Coingestants

- Gabapentin
  - Alcohol
  - Cannabis
  - Selective serotonin reuptake inhibitors
  - Lysergic acid diethylamide (LSD)
  - Amphetamine
  - Gamma-hydroxybutyrate
  - Opioids
  - Benzodiazepines

- Pregabalin
  - Alcohol/gabapentin/benzodiazepines
  - Cannabinoids
  - LSD
  - Salvia
  - Heroin/opiates
  - Amphetamines/synthetic cathinones

2. CNS Drugs. 2014;28:491-496.
### Factors Leading to Misuse and Abuse

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide-spread use</td>
</tr>
<tr>
<td>Multiple off-label uses</td>
</tr>
<tr>
<td>Gabapentin is relatively cheap</td>
</tr>
<tr>
<td>Ease of obtaining a prescription</td>
</tr>
<tr>
<td>Not controlled (gabapentin) or low potential for abuse (pregabalin)</td>
</tr>
</tbody>
</table>


### Reasons for Misuse and Abuse

<table>
<thead>
<tr>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recreational</td>
</tr>
<tr>
<td>Mood/anxiety</td>
</tr>
<tr>
<td>Potentiating effects of drug abuse treatment</td>
</tr>
<tr>
<td>Intentional self-harm</td>
</tr>
<tr>
<td>Reduce pain</td>
</tr>
<tr>
<td>Reduce cravings/withdrawal from other substances</td>
</tr>
<tr>
<td>Substitution for other drugs</td>
</tr>
<tr>
<td>Addiction to gabapentin</td>
</tr>
</tbody>
</table>

Common & Novel Methods of Abuse

- **Parachuting**

Gabapentin
- Orally
- Intravenously (IV)
- Snorting
- Intramuscular (IM)
- “Cutting agent” in street heroin

Pregabalin
- Orally
- Intravenously (IV)
- Snorting
- Smoking
- Rectally (“plugging”)
- “Parachuting”

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

1. CNS Drugs. 2014;28:491-496.

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.”

Effects of Pregabalin Misuse/Abuse

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>600mg</td>
<td>• 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</td>
</tr>
<tr>
<td>900mg</td>
<td>• Strong feelings of drunkenness, difficulty waking, alteration of color perception, little euphoria</td>
</tr>
<tr>
<td>1200mg</td>
<td>• Drowsiness, euphoria, empathetic feelings (similar to Ecstasy)</td>
</tr>
<tr>
<td>&gt;1500mg</td>
<td>• Uncontrollable drowsiness, frequent hallucinations, great euphoria, frequent dissociative events (similar to dextromethorphan effects), behavioral inhibition, anxiety</td>
</tr>
</tbody>
</table>


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%

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
Withdrawal Signs/Symptoms

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

Withdrawal Treatment

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

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


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

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/
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


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

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.
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 α2-δ subunit of the voltage-gated calcium channel
  d) Inhibiting serotonin reuptake

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
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