What’s All the “GABA” About? Pregabalin and Gabapentin Abuse

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Faculty

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Disclosures

- Courtney Kominek, PharmD, BCPS, CPE
  – Axial Healthcare – Consultant

- The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of any agency of the United States government, including the Department of Veterans Affairs.

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.
Pharmacology and Pharmacokinetics

Gabapentin and Pregabalin

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$_3$ or GABA$_4$

Binds to the $\alpha_2\delta$ subunit of the voltage-gated calcium channel

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

Decreases release of glutamate, NE, and substance P

J Clin Psychiatry. 2007 Mar;68(3):483-4

FDA-approved Indications

- **Pregabalin**
  - Neuropathic pain associated with diabetic peripheral neuropathy
  - Postherpetic neuralgia
  - Adjunctive therapy for adult patients with partial onset seizures
  - Fibromyalgia
  - Neuropathic pain associated with spinal cord injury

- **Gabapentin**
  - Postherpetic neuralgia
  - Adjunctive therapy in treatment of partial onset seizures, with and without secondary generalization, in adults and pediatrics $\geq 3$ years

### 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

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### Role in Chronic 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

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

**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
### Pharmacokinetics

<table>
<thead>
<tr>
<th>Gabapentin</th>
<th>Pregabalin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td></td>
</tr>
<tr>
<td>F=27-60%</td>
<td></td>
</tr>
<tr>
<td>Tmax=8h</td>
<td></td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
</tr>
<tr>
<td>Low protein binding</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
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<tr>
<td>Renal: 76-81%</td>
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<tr>
<td>$t\frac{1}{2}=5-7h$</td>
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</tr>
<tr>
<td><strong>Absorption</strong></td>
<td></td>
</tr>
<tr>
<td>F=90%</td>
<td></td>
</tr>
<tr>
<td>Tmax=1.5h</td>
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</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
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<tr>
<td>No protein binding</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
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<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td></td>
</tr>
<tr>
<td>Renal: 90%</td>
<td></td>
</tr>
<tr>
<td>$t\frac{1}{2}=6.3h$</td>
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</tr>
</tbody>
</table>

### 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

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


Converting Case

- BT is a 57 yo male with diabetic peripheral neuropathy on gabapentin 1200 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 initiate equivalent dose of pregabalin


Converting Case

- Cross-titration
  - Decrease gabapentin to 600 mg PO TID + initiate pregabalin at 150 mg PO BID x 4 days
  - Discontinue gabapentin + increase pregabalin to 300 mg PO BID

- Stop-Start
  - Discontinue gabapentin
  - Initiate pregabalin 300 mg PO BID
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 and Pregabalin Abuse

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

- 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

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


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

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

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Doses for Abuse

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

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

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
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)

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

Drugs. 2017;77:403-426.
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”

The LYRICA (pregabalin) Mega Thread. Available at: bluelight.org.
**Effects of Abuse**

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

**Pregabalin**
- Alcohol/GHB/benzodiazepine-like effects
- Euphoria
- Enactogenic feelings
- Dissociation
- Coping with opioid withdrawal

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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 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.”

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

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


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.

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Overdose

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

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

Withdrawal Signs/Symptoms

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

Withdrawal Treatment

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

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
Why now?

- Pregabalin available since 2005
- Concerns with abuse more recent (2010)
- Flaws in study
  - Excluding patients with substance use disorders

State Prescription Drug Monitoring Program (PDMP) Website Changes

- Pregabalin is a controlled substance, so these prescriptions are already reported to the database in some states
  - Pregabalin is schedule V medication; some states do not require the reporting of schedule V medications to the database
- States that have ADDED gabapentin prescriptions to database reports include:
  - Minnesota
  - Ohio
  - Kentucky
  - Massachusetts – various supporters pushing to add gabapentin to the list of prescriptions reported

http://pmp.pharmacy.state.mn.us/
http://pharmacy.ohio.gov/Documents/Pubsc/Special/OARRS/Reporting%20Gabapentin%20Products%20to%20OARRS%20Effective%2012-1-2016.pdf
http://ncpdp.org/NCPDP/media/pdf/State_PMP_Tracking_Document.xls
http://www.chfs.ky.gov/os/oig/KASPER.htm
Where do we go from here?

- 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


Where do we go from here?

- Assess a patient’s substance abuse history, psychiatric history, and concurrent medications before prescribing
- Be aware of higher risk groups
- Monitor for early refills and/or limiting the quantity supplied
- Consider establishing a protocol for overdose and withdrawal treatment/prevention

CNS Drugs. 2014;28:491-496.
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