

Gabapentinoid Abuse: An Alarming Trend

Kirk Evoy, PharmD, BCACP, BC-ADM, CTTS
University of Texas at Austin College of Pharmacy

Disclosures

Employer:

- **University of Texas at Austin College of Pharmacy**
Clinical Assistant Professor
- **University of Texas Health Science Center at San Antonio School of Medicine**
Adjunct Clinical Assistant Professor
- **University Health System**
Clinical Pharmacist

Financial Interests:

- No conflicts of interest to disclose

Learning Objectives

1. Summarize the current literature regarding the epidemiology and prevalence of gabapentinoid abuse
2. Identify risk factors for gabapentinoid abuse and typical patterns of abuse
3. Define the potential harms of gabapentinoid abuse
4. Describe the role of pharmacists and technicians in identifying and reducing gabapentinoid abuse

The Current Issue

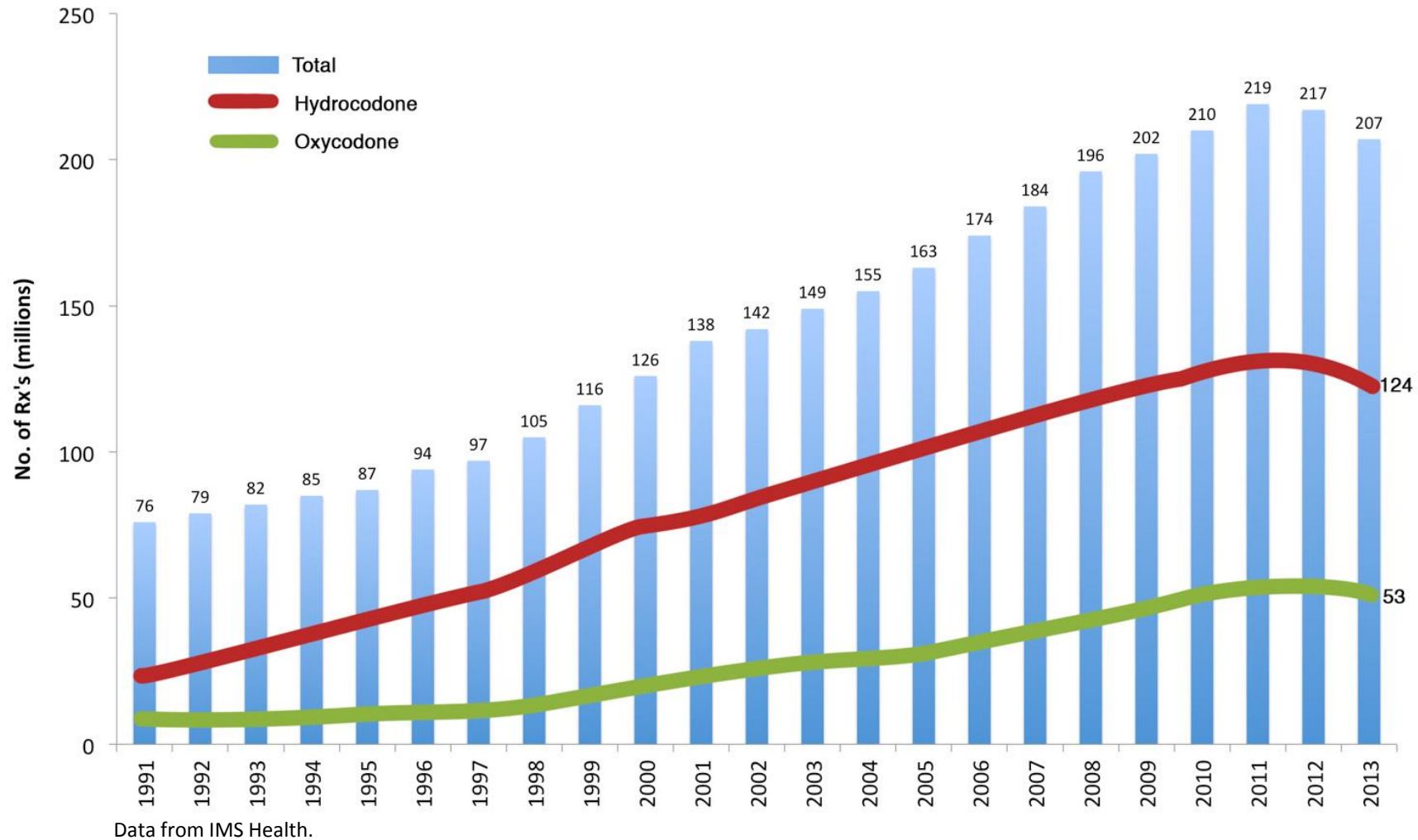
Prescription drug abuse is an emergent epidemic

- 52 million Americans have used Rx med for nonmedical purposes at least once
- Since 2000, Rx overdose deaths up 137%
- 2014: most overdose deaths in US history
- Abuse of opioid analgesics largely implicated



<http://www.post-gazette.com/stories/2014/01/22/1401000756315se-ed98-4892-8166-5ac80823ca.png>

The Current Issue



The Current Issue

Gabapentin(GBP) and pregabalin(PRG) abuse on the rise

- 2010 list of new recreational psychoactive substances in Europe
- Warning added to European PRG labeling
- Growing black market
- Increased reports of related fatalities
- PRG scripts ↑350% and GBP ↑150% in UK from 2007-2012

The Current Issue

Gabapentin (Neurontin®)

- FDA-approved in 1993
- Indicated for herpetic neuralgia and epilepsy
- Up to 95% of prescribing is off-label
- NOT a controlled substance

Pregabalin (Lyrica®)

- FDA-approved in 2004; brand name only
- Indicated for neuropathic pain, post-herpetic neuralgia, seizures, and fibromyalgia
- Schedule V controlled substance
- 3x faster absorption, 2.5x greater potency, non-saturable kinetics

The Current Issue

Gabapentin and pregabalin

- Both act as gamma-aminobutyric acid (GABA) analogues
- Mechanism of action not entirely understood
 - GABA-modulating drugs commonly abused: alcohol, benzodiazepines, Z-hypnotics
 - Effects on dopaminergic system may contribute as well

The Current Issue

Why gabapentinoids?

- Potentiate recreational effects of other drugs
 - Opioids, alcohol, benzos, marijuana, amphetamine, LSD, baclofen, SSRIs, quetiapine
 - Methadone clinic patients report using to potentiate effects of methadone
- Avoid detection on UDS
- Achieve highs when other drugs unavailable
- Attenuate withdrawal of other medications
- Self-medicate (e.g., pain, anxiety)

Schwan S, et al.. Eur J Clin Pharmacol. 2010 Sep;66(9):947-53.
Alblooshi H, et al. Subst Abuse Treat Prev Policy 2016;11:19.
Reeves RR, et al. Am J Psychiatry 2014;171(6):691.
Reeves RR, et al. CNS Disord. 2014 Sep 11;16(5).
Eastwood JA, et al. Forensic Sci Int 2016;266:197-201.

Schifano F, et al. Psychother Psychosom. 2011;80(2):118-22.
McNamara S, et al. Ir Med J. 2015 Nov-Dec;108(10):309-10.
Grosshans M, et al. Am J Psychiatry. 2010 Jul;167(7):869.
Baird CR, et al. Eur Addict Res. 2014;20(3):115-8.
Kruszewski SP, et al. J Psychiatr Pract. 2009 Jul;15(4):314-9.

Systematic Review

59 studies describing GBP and/or PRG abuse/misuse/overdose (July 2016)

- **Study type:**

- 24 epidemiologic (15 PRG, 3 GBP, 6 both)
- 3 clinical abuse liability studies (2 PRG, 1 GBP)
- 16 case reports/series of abuse (7 PRG, 9 GBP)
- 17 case reports/series of acute overdose (5 PRG, 12 GBP)

- **Study location:**

- 26 in Europe
- 25 in USA
- 4 in Asia
- 1 in Africa
- 3 international

Extent of Abuse

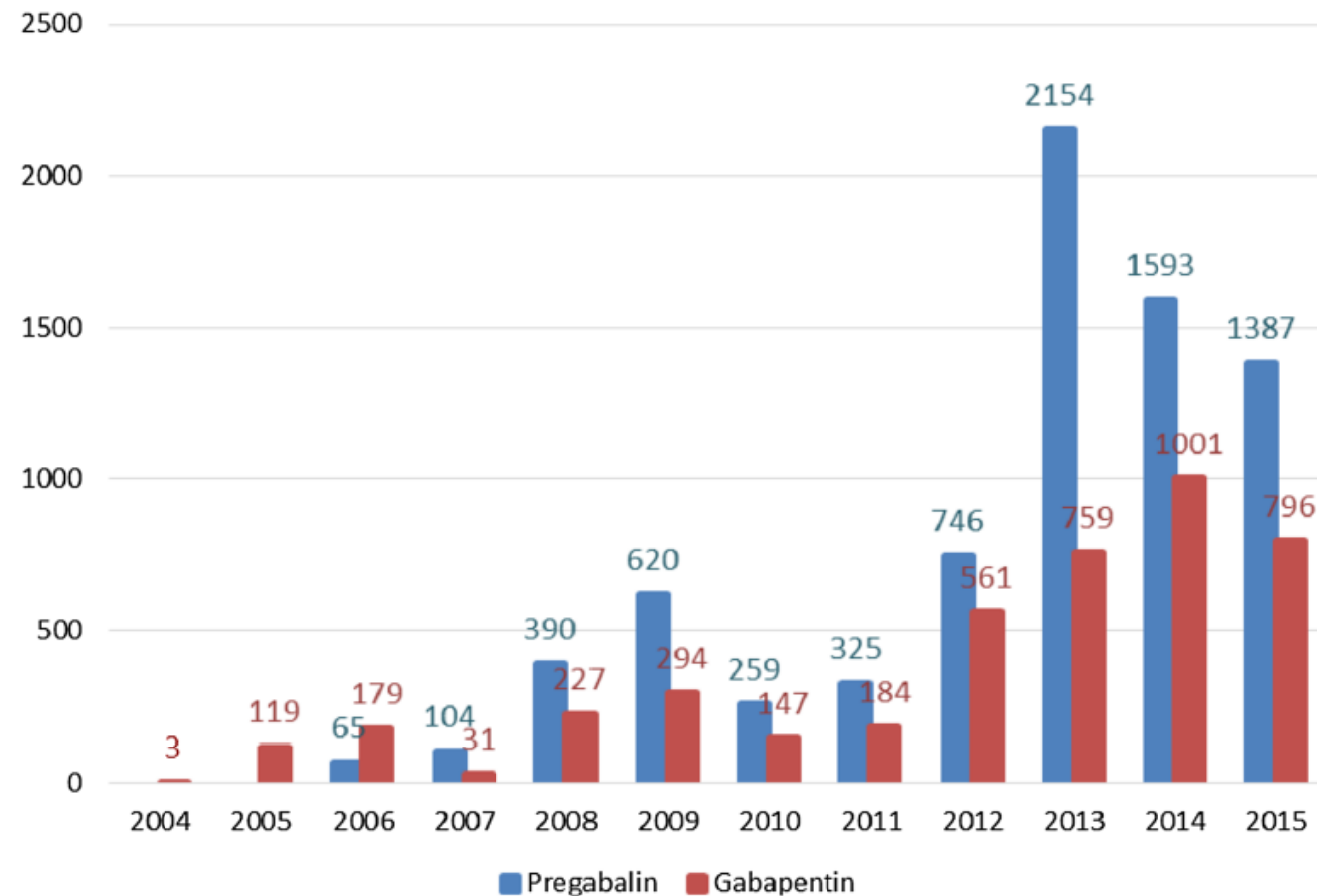
Early Warning Signs

- Schwan et al. (2010)
 - First published study identifying PRG abuse
 - Identified 16 reports of abuse/misuse/dependence to Swedish spontaneous adverse reporting system
 - Large increase in 2008-2009
- Caster et al. (2011)
 - Analysis of World Health Organization Individual Case Safety Reports
 - Identified signals of PRG abuse dating back to 2005

Extent of Abuse

- Chiappini, et al. (2016)
 - Queried EudraVigilance for reports of GBP/PRG abuse/misuse/dependence from 2004-2015
 - 7639 PRG events and 4301 GBP events
 - >75% of reports since 2012
- Swedish and German AE databases also reveal significant increase in recent years

Spontaneous Reports of GBP or PRG abuse, misuse or dependence by year



Data from EudraVigilance adverse event reporting system

Extent of Abuse

- Kapil, et al. (2014)
 - Only study to assess life-time prevalence in general population
 - Surveyed UK cohort aged 16-59 (N=1500)
 - Lifetime prevalence of non-prescribed use:
 - GBP: 1.1%
 - PRG: 0.5%
 - Cannabis: 28.1%
 - Cocaine: 8.1%

Extent of Abuse

Significantly more common in former or current substance abuse patients

- Predominantly linked to opioid abuse; little correlation with alcohol abuse
- Rates of abuse among patients with a substance use disorder:
 - Pregabalin: 3-68%
 - Gabapentin: 15-22%
- Smith, et al. (2015)
 - Study of 503 opioid abusers in Appalachian Kentucky
 - 15% used GBP to get high within last 6 months
 - 165% increase in recreational GBP use from year prior and 2,950% increase since 2008

Effects Experienced

Abuse Potential Studies

- Zacny, et al. (2012)
 - 75 or 150 mg PRG +/- oxycodone in **16 non-drug-abusing volunteers**
 - No abuse liability with or without oxycodone
- Pfizer (pre-marketing)
 - 450 mg PRG dose in **15 recreational drug users**
 - “Good drug effect”, “liking”, “high” \approx 30 mg diazepam
- Lile, et al. (2016)
 - 600 and 1200mg GBP produced similar drug liking to THC in 8 cannabis users
 - Increased THC drug-liking when administered concurrently

Effects Experienced

Euphoria as an adverse effect of pregabalin

- Euphoria in pre-marketing clinical trials:
 - 4% overall vs. 1% overall with placebo
 - Select cohorts, rates as high as 12%
- Zaccara, et al. (2011)
 - Meta-analysis of 38 pregabalin clinical trials
 - Euphoria: second most commonly reported adverse effect

Effects Experienced

High doses may produce both sedative and dissociative/psychedelic properties

- Euphoria
- High/stoned
- Improved sociability/uninhibited behavior
- Marijuana or benzodiazepine-like relaxation
- Amphetamine like trip
- Sedation
- Amnesia
- Empathy
- Dissociation
- Hallucinations
- Numbness
- Contentment

Pattern of Abuse

Schifano, et al. (2011)

- Systematic study of web reports from 108 websites
- Doses >>> recommended max
- Tolerance develops and wears off rapidly
- Multiple routes of administration
- PRG superior to GBP

Pattern of Abuse

Gabapentinoid abuse typically involves supratherapeutic doses

- Max recommended doses:
 - PRG 600 mg/day
 - GBP 3,600 mg/day as divided doses
- Pregabalin abuse doses:
 - Gahr, et al (2013): 55 reports of abuse to German AE database; mean dose of 1424 mg PRG
Case reports: median dose of 2100mg PRG (range 800-7,500mg)
- Gabapentin abuse doses:
 - Case reports: median dose of 3600 mg GBP (range 1,500-12,000mg)

Pattern of Abuse

Frequency of misuse

- Kapil, et al. (2014)
 - Cohort of general UK population
 - Weekly: 13%
 - Between weekly and monthly: 50%
 - Monthly: 37%
- Smith, et al. (2015)
 - 503 nonmedical opioid users surveyed
 - GBP abusers: used GBP 25 of past 30 days on average

Pattern of Abuse

Source of GBP/PRG

- Kapil, et al. (2014)
 - 63.1%: health care providers
 - 57.8%: family or acquaintances
 - 47.3%: internet
 - 13.1%: legitimate prescription
 - 7.8%: abroad
- Smith, et al. (2015)
 - Physicians: 52%
 - Drug dealers: 36%
- Wilens, et al. (2014)
 - Among US opioid dependent patients undergoing substance abuse treatment:
 - 40% GBP and 50% PRG abuse rates among patients prescribed those medications
 - 13% GBP and 6% PRG abuse among those NOT prescribed a gabapentinoid

Pattern of Abuse

Multiple routes of administration have been reported

- Oral
- Injection
- Smoked or inhaled
- Rectal plugging
- Parachuting

Typical Abusers

- Young
- Low income
- H/O recreational drug abuse
- Psychiatric co-morbidities???
- Prisoners???
- **Past or current opioid abuse**

Typical Abusers

Past or current opioid abuse as a risk factor

- Grosshans, et al. (2013)
 - 124 German patients undergoing substance abuse treatment
 - Patients treated for **opioid abuse**: 12.1% abused PRG
 - Patients treated for **non-opioid addiction**: 2.7% abused PRG
- Wilens, et al. (2015)
 - 196 US patients undergoing substance abuse treatment
 - Patients treated for **opioid abuse**: 22% misused GBP and 7% PRG
 - Patients treated for **non-opioid addiction**: 0% misused GBP or PRG
- Bastiaens, et al. (2016)
 - 250 former US prisoners with psychiatric comorbidities undergoing substance abuse treatment
 - Patients treated for **opioid abuse**: 26% misused GBP
 - Patients treated for **non-opioid abuse**: 4% misused GBP

Risks of Abuse

Overdose

- Relatively safe, even in acute overdose
 - Hypotension, tachycardia, sedation, dizziness, mental clouding
 - Reported survival following doses as high as 11.5g PRG and 91g GBP
- Rarely sole cause of death
- Contributor in polysubstance abuse fatalities
 - Additive CNS depressant effects
 - Studies of post-mortem toxicology show increasing detection of GBP and PRG

Baird C, et al. *Eur Addict Res* 2014;20:115-118

Hakkinen M, et al. *Forensic Science International* 2014;241:1-6.

Middleton O. *J Forensic Sci* 2011;56:1373-1375.

Schauer SG, et al. *Military Medicine* 2013;178:119. [Abstract].

Braga AJ, et al. *Anaesthesia*. 2007 May;62(5):524-7.

Fernandez MC, et al. *Clin Toxicol* 1996;34(4):437-39.

Risks of Abuse

Gabapentinoids increasingly being implicated in death on toxicology reports

- Lottner-Nau, et al. (2013)
 - Analysis of German post-mortem toxicology reports from 2010-2012
 - PRG detected in 2% of patients year-1 and 4% year-2
 - Among known drug abusers, PRG detected in 5.5% in year-1 and 29.8% in year-2
- Hakkinen, et al. (2014)
 - Analysis of Finnish post-mortem toxicology reports from 2010-2011
 - PRG detected in 2.3% of cases and GBP (0.31%)
 - PRG main cause of fatal poisoning in 29 cases and GBP in 1 case
 - 90% of gabapentinoid-related fatalities involved opioids
- Chiappini, et al. (2016)
 - Analysis of European Medicine Agency adverse event reporting system from 2004-2015
 - 27 deaths involving PRG and 86 deaths involving GBP identified
 - More than 1/3 of reported deaths occurred in 2014

Risks of Abuse

Dependence and Withdrawal

- Cravings, self-titration, drug-seeking suggest dependence in some cases
- Benzodiazepine or alcohol-like withdrawals reported
 - Alleviated rapidly with resumption of gabapentinoid
 - Not relieved with BZDs
- Multiple reports of relapse shortly after detox

Role of Providers and Pharmacists

Be cognizant of drug-seeking behaviors

- Case reports note various means of pharmacy and physician deception
 - Doctor shopping
 - Fabricating symptoms
 - Requesting early refills
 - Filling at multiple pharmacies in rapid succession
 - Requesting specific drugs or higher doses during appointment
 - Receiving same prescription from multiple providers
 - Claiming medications were lost or stolen
 - Requesting not to bill insurance

Role of Providers and Pharmacists

Adjust prescribing to reduce diversion

- Judiciously escalate doses and prescription quantities
 - National drug utilization database analyses
 - Sweden: 8.5% of patients prescribed PRG at >max dose
 - Denmark: 9.6% of patients prescribed PRG >600 mg/day and 0.65% >1200 mg/day
- Consider risk vs. benefit of off-label uses with little evidence

Role of Providers and Pharmacists

Urine drug screens

- Likely not cost-effective to universally screen
- May consider in:
 - Patients suspected of gabapentinoid abuse
 - Patients suspected of opioid abuse
 - Patients undergoing substance abuse treatment
- Negative urine drug screens may indicate diversion

Role of Providers and Pharmacists

Additional considerations

- Adequately control pain
- Avoid abrupt discontinuation to prevent withdrawal
- Many providers unaware of risk - alert prescribers of abuse potential
- Continued post-marketing surveillance crucial

Conclusion

- Gabapentinoids maintain important role in treating many chronic conditions
- Abuse of pregabalin and gabapentin is a growing concern
- Need for greater emphasis on identifying risk factors for and signals of abuse
- Safe prescribing of gabapentinoids should be emphasized

Review Question

Which of the following is a key risk factor for gabapentinoid abuse?

- A. Age >70
- B. Diabetic neuropathy diagnosis
- C. Female gender
- D. History of opioid abuse

Review Question

Which of the following is true regarding potential risks of gabapentinoid abuse?

- A. Gabapentinoid overdoses are generally fatal
- B. Benzodiazepines are generally effective for treating gabapentinoid withdrawal symptoms
- C. Studies have shown a recent increase in the rates of detection of gabapentin or pregabalin in post-mortem toxicology reports
- D. Withdrawal is not a concern with gabapentinoids so these medications should be immediately discontinued in patients suspected of gabapentinoid abuse

Review Question

Which of the following represents a role pharmacists can play in reducing gabapentinoid abuse?

- A. Discuss with prescribers risk versus benefit of high dose, large quantity or off-label gabapentinoid prescriptions
- B. Educating other providers on gabapentinoid abuse potential
- C. Monitoring for possible signs of diversion
- D. All of the above

Gabapentinoid Abuse: An Alarming Trend

Kirk Evoy, PharmD, BCACP, BC-ADM, CTTS
evoy@uthscsa.edu