Misuse, Addiction and Reclassification of Gabapentin

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Disclosures

• No conflicts of interest to disclose
Objectives

1. Comprehend the relevant pathophysiology and role of gabapentin.
2. Understand statistics of prescription drug misuse and abuse.
3. Evaluate the available literature that discusses current misuse, abuse and overdose of gabapentin.
4. Discuss options and implement a plan to prevent abuse.
Should gabapentin be rescheduled to a CV?

- Yes
- No
- Maybe
Pathophysiology and Role of Gabapentin
Pathophysiology (Seizures and Pain)

• Excess excitatory neurotransmitters:
  • NE, ACh, H, CRF, Glu

• Deficiency in inhibitory neurotransmitters:
  • GABA

• AEDs → decrease abnormal electrical activity by:
  • Increasing GABA
  • Decreasing Glu
  • Blocking Na⁺ channels
  • Blocking or altering Ca²⁺ channels

Gabapentin: Structure

Chemical structure of gabapentin:
• Derived by addition of a cyclohexal group to the backbone of GABA

Other antiepileptic drugs:
• Pregabalin → Same class, similar indications
• Phenibut → Not legal in US

Gabapentin: Indication

• Antiepileptic drug
  • Drugs that prevent rapid, repetitive, excitatory stimulation in the brain

• Labeled:
  • Partial seizures (Neurontin®)
  • Postherpetic neuralgia (Gralise® & Horizant®)
  • Restless leg syndrome (Horizant®)

• Off-label:
  • Diabetic neuropathy (Neurontin®)
  • Fibromyalgia (Neurontin®)
  • Hot flashes (Neurontin®)
Gabapentin: Mechanism of Action

• Not fully understood
• Does not bind at GABA A or B subunits in the brain
  • Still exert GABA-mimetic properties

• Various hypotheses
  • Alpha-2 delta subunit of voltage gated Ca^{2+} channels → main target
  • Possible dopamine release
  • Produces actions responsible for attenuation of pain
Gabapentin Pharmacokinetics

- Given orally
- Plasma concentrations > 2 mcg considered therapeutic
- Protein binding < 3%
- Highly lipid soluble, readily distributed into CNS
- Bioavailability declines with increasing doses
  - Saturable absorption
  - Different with ER dosing
- Eliminated from the systemic circulation via renal excretion as unchanged drug.
  - Half-life of 5-7 hours.
Gabapentin (Neurontin®) Pharmacokinetics
Gabapentin enacarbil: Horizant

- **Prodrug of gabapentin:**
  - Specifically designed to enhance absorption via the GI tract.
  - Improves circulating levels of gabapentin

- **Favorable safety and pharmacokinetics:**
  - Restless leg syndrome
  - Better bioavailability → reaches systemic circulation at a more rapid rate

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Gabapentin ER (Horizant®) Pharmacokinetics
Gabapentin Pharmacokinetics

Approximate equimolar doses in the same healthy adults

- HORIZANT
- Conventional gabapentin

GABAPENTIN CONCENTRATION (µg/mL) vs TIME AFTER DOSING (hr)
Gabapentin: How supplied

• **Capsules:**
  - Gabapentin oral capsule – 100 mg, 300 mg, 400 mg
  - Neurontin® oral capsule – 100 mg, 300 mg, 400 mg

• **Tablets:**
  - Gabapentin oral tablet – 600 mg, 800 mg
  - Neurontin® oral tablet – 600 mg, 800 mg
  - Gralise ER® oral tablet – 300 mg, 600 mg
  - Gralise ER® oral tablet – 30 day starter pack
Gabapentin: How supplied

• **Oral solution:**
  - Gabapentin 250 mg/5 mL solution
  - Neurontin® 250 mg/5 mL solution

• **Tablets ➔ Gabapentin enacarbil ER (Horizant®):**
  - Horizant® ER tablet – 300 mg, 600 mg

• **Max doses:**
  - Gabapentin (Neurontin®) - 3600 mg/day
  - Gabapentin ER (Gralise®) – 1800 mg/day
  - Gabapentin enacarbil ER (Horizant®) – 1200 mg/day
# Gabapentin: Dosing (labeled)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Seizures (IR only)</td>
<td><strong>Adults</strong>: 300 mg PO TID → titrate to 800 mg PO TID</td>
</tr>
<tr>
<td></td>
<td><strong>Children (3-12 years)</strong>: 10-15 mg/kg/day PO in 3 divided doses → titrate upward over 3 days</td>
</tr>
<tr>
<td>Postherpatic neuralgia (PHN) (IR &amp; ER)</td>
<td><strong>IR</strong>: 300 mg PO on day 1 → 600 mg/day on day 2 → 900 mg/day on day 3 → titrate to 1800 mg/day if needed</td>
</tr>
<tr>
<td></td>
<td><strong>ER</strong>: <strong>Gralise®ONLY</strong> → Same as above for first 3-6 days, on 7th day 1200 mg/day, 1500 mg/day on days 11-14 and 1800 mg/day on day 15 and after</td>
</tr>
<tr>
<td></td>
<td><strong>Horizant® ONLY</strong> → 600 mg in the morning for 3 days → day 4, 600 mg BID</td>
</tr>
<tr>
<td>Restless leg syndrome (RLS) (ER only)</td>
<td><strong>Horizant® ONLY</strong> → 600 mg QD with food at 5pm</td>
</tr>
</tbody>
</table>
# Gabapentin: Dosing (off-label)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic neuropathy (IR only)</td>
<td>300 mg PO TID $\rightarrow$ titrate up to max of 3600 mg/day if needed</td>
</tr>
<tr>
<td>Fibromyalgia (IR only)</td>
<td>300 mg PO HS over 1 week $\rightarrow$ titrate to total dose 2400 mg/day with 300 mg PO BID x 1 week, 300 mg PO BID with 600 mg HS x 2 weeks, 600 mg PO TID x 2 weeks, 600 mg PO BID with 1200 mg HS.</td>
</tr>
<tr>
<td>Hot flashes (IR only)</td>
<td>300 mg PO QD, may titrate to 300 mg PO TID if needed</td>
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</tbody>
</table>

- Includes common off-label indications; more available in appendix.
- To discontinue, taper down daily dose by 300 mg/day.
Gabapentin (Neurontin®)

Addictive potential:
- Many GABA-modulating drugs possess abuse potential
  - Alcohol
  - Benzodiazepines
  - Z-hypnotics
- Dopamine
  - Reward system
  - May contribute to abuse potential
  - Dissociative properties
Prescription Drug Misuse Statistics
Prescription Drug Misuse and Abuse

Definition:
- Taking a prescription drug other than prescribed
- Taking someone else’s prescription
- Any non-medical reason \(\rightarrow\) abuse
  - Estimated 54 million people used a prescription medication non-medically at least once in their lifetime

Misused or abused drug classes:
- Opioids
- CNS depressants
  - Sedatives, hypnotics, tranquilizers
- Stimulants

Prescription Drug Misuse and Abuse

CNS depressants:

- Act on the brain by increasing GABA signaling → enhance inhibitory activity on the brain → drowsy or calming effect

  - Benzodiazepines
  - Non-benzodiazepines
    - GABA type A receptor, similar to benzodiazepines
      - Zolpidem (Ambien®)
      - Eszopiclalone (Lunesta®)
      - Zaleplon (Sonata®)
  - Barbituates
Prescription Drug Misuse and Abuse

**CNS depressants: Consequences**

- Slurred speech
- Poor concentration
- Confusion
- Headache
- Light-headedness, dizziness
- Memory and movement impairment
- Hypotension
- Bradypnea
- Substance abuse disorder and addiction
Prescription Drug Misuse and Abuse

ABUSE IS INCREASING

2011-2015 Neurontin prescriptions increased by: 41%

1.1% of the population misuses this medication

22% among patients in addiction treatment

Prescription Drug Misuse and Abuse

2016 Study of Pain & Addiction Patients

70

Of 323

Patients were using Neurontin without a prescription

56% used Neurontin + an opioid

27% used Neurontin + an opioid + muscle relaxant/ anxiety meds

8.6% used Neurontin + other substances
Literature – Article 1
<table>
<thead>
<tr>
<th>Journal</th>
<th>Title</th>
<th>Objective</th>
<th>Study Type</th>
<th>Intervention</th>
</tr>
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<tbody>
<tr>
<td>Drugs, 2017.</td>
<td>“Abuse and Misuse of Pregabalin and Gabapentin.”</td>
<td>Attempt to bring attention to providers about the extent of actual gabapentinoid abuse, characteristics of abusers and potential harms from these trends.</td>
<td>Systemic review/meta-analysis</td>
<td>Searches were conducted via MEDLINE, Chochrane library, ClinicalTrials.gov, US FDA data were indexed through July 28, 2016. Divided searches/results into 4 different categories.</td>
</tr>
</tbody>
</table>
Evoy et al.

**Inclusion**
- Clinical or epidemiological studies
- Meta-analyses
- Case reports/series

**Exclusion**
- Studies that report toxicity, withdrawal or dependence **without** misuse/abuse.

**Fig. 1 Summary of evidence search and selection**

- Electronically-identified articles from PubMed, Cochrane Library, ClinicalTrials.gov, and FDA website
  - Total = 664

  Excluded
  - Not in English = 15
  - Not relevant = 260
  - Duplicates = 302
  - Total = 577

  Full text articles screened
  - n = 87

  Excluded
  - Review articles or not relevant to study = 42

  Articles included from hand search of citations
  - n = 14

  Articles included in review
  - n = 59
Evoy et. al

Results:

- 24 epidemiological studies:
  - 3 → gabapentin alone
  - 6 → gabapentin + pregabalin

- Review of American poison center database → 116 and 23 cases of gabapentin and pregabalin overdose

- Internet based questionnaire → gabapentin (1.1%) and pregabalin (0.5%) misused between 16-59 year-olds in UK

- In Finnish autopsies, 2.61% had gabapentinoids discovered
  - 18.6% gabapentin
  - 48.1% pregabalin
Evoy et. al

Results:

• 24 epidemiological studies:

• Substance abuse disorder
  • Much higher rates of gabapentinoid abuse than general population
  • Scottish methadone clinic
    • 22% used non-prescription gabapentinoids → 19% gabapentin and 3% pregabalin
    • Used to become intoxicated (78%) or potentiate the effects of methadone (38%)
  • United States methadone + psychotropics
    • 40-50% using higher doses of gabapentinoids
    • Former inmates → 16% misused gabapentin, 15% admitted to abuse
Results:

• 3 abuse liability studies:

• Likelihood that drug will be abused for non-medical purposes
  • Conflicting results

• 1200 mg & 600 mg doses of gabapentin
  • Similar effects to THC (in 8 cannabis users)
  • Increased THC drug-liking when co-administered
Evoy et. al

Results:

- **Case Report/Series $$\rightarrow$$ Abuse:**
- 9 case reports/series of gabapentin abuse
  - 14 patients
  - Median age was 37 years
  - 11/16 $$\rightarrow$$ male
  - 10/16 $$\rightarrow$$ psychiatric comorbidities
  - 15/16 $$\rightarrow$$ historically abused another drug
  - Median dose $$\rightarrow$$ 3600 mg (range: 1500 – 12,000 mg)
Results:

• Case Report/Series → Overdose:
  • 12 case reports/series describing 31 acute gabapentin overdoses
    • 91,000 mg highest ingestion
    • Co-administered with valproic acid and alcohol
  • 21 year-old woman ingested 16,000 mg gabapentin + other medications
    • Gabapentin plasma concentration of 126.8 mg/L
    • Serious toxicity
    • Full recovery with oxygenation and plasmapheresis
  • 2 of 3 reports of fatal gabapentin overdoses → gabapentin sole cause
Evoy et. al

Conclusion:

• Current literature suggests growing evidence of abuse with gabapentinoids
• Further study of abuse potential liability and associated risk factors useful

Limitations:

• Inherent risk of bias
• Few studies before 2010
  • Abuse has dramatically increased with published reports
• Assumes class side effects
Case Studies – Article(s) 2
Middleton, Owen, MD.

<table>
<thead>
<tr>
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<th>Study Type</th>
<th>Findings</th>
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</thead>
</table>
| Journal of Forensic Sciences. 2011. | “Suicide by Gabapentin Overdose” | Report the findings of a 62 year old woman with a history of depression, who’s death was caused by an intentional ingestion of excess gabapentin. | Case Report | • 62 year old woman found unresponsive in locked hotel room  
• Various capsules found → included gabapentin, fluoxetine and simvastatin.  
• 150 capsules of 300 mg gabapentin  
• Very clearly a suicide  
• Medical history of depression and several previous episodes of suicide.  
• Other medical history included diabetes, HLD and obesity.  
• **No mention of renal impairment.**  
• Autopsy 22 hrs after death found gabapentin level of 88 ug/mL and clonazepam level 7.6 ng/mL  
• Death was certified as gabapentin toxicity. |
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| International Journal of Legal Medicine. 2015. | “An acute gabapentin fatality: a case report with postmortem concentrations.” | Report the findings of a 47 year old woman, who’s death was caused by accidental gabapentin overdose.                                       | Case Report    | * 47 year old obese women, a hospice worker found dead after attending to her shift  
  * PMH included AVR, chronic pain secondary to MVA → addiction to Rx pain meds  
  * Medication: hydrocodone/APAP but, gabapentin 600 mg found in purse → 26 missing tablets  
    * Postmortem conc. → peripheral blood: 37 mg/L, central blood: 32 mg/L, liver: 26 mg/kg, vitreous 32 mg/L and gastric contents 6 mg.  
    * Central blood negative for other drugs.  
    * Reported as a death related to apparent isolated gabapentin exposure → limitations

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<tbody>
<tr>
<td>Military Medicine. 2013.</td>
<td>“Gabapentin Overdose in a Military Beneficiary.”</td>
<td>Report case of 59 year old military beneficiary that presented to ER after ingestion of 90 g of gabapentin.</td>
<td>Case Report</td>
<td>• 59 year old woman presents to ER after argument with spouse and suicide attempt</td>
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<td>• Presented with mild sedation and nausea</td>
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<td>• 300 capsules of 300 mg IR gabapentin and 4 hydrocodone/APAP tablets ingested 1 hour before arrival</td>
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<td></td>
<td></td>
<td>• <strong>PMH:</strong> diabetes, HTN, HLD, depression</td>
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<td></td>
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<td></td>
<td></td>
<td>• <strong>Medications:</strong> venlafaxine, telmisartan, glipizide, metformin, simvastatin and gemfibrozil.</td>
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<td></td>
<td></td>
<td>• Normal renal function</td>
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<td></td>
<td>• Drug test negative</td>
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<td>• Serum gabapentin drawn 6 hours after ingestion, level was 72.8 ug/mL.</td>
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<td>• Largest reported acute gabapentin ingestion and highest serum level in an overdose patient who survived.</td>
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</table>
Literature – Article 3
### Peckham et al.

<table>
<thead>
<tr>
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<tr>
<td></td>
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<td>• Searches via world wide web with specific language</td>
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<td>• Telephone and email inquiries to state BOP and PDMPs.</td>
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</tbody>
</table>
1) US states and jurisdictions where gabapentin is classified as a CV medication with mandated reporting to PDMP

- State of Kentucky and Tennessee reclassify gabapentin as CV.
- Mid level practitioners (PAs) are not allowed to prescribe
- ARNPs may prescribe if they obtain a DEA license.
- Rxs are now limited to a max of 5 refills or 6 months supply
- Must be reported to a PDMP
2) US states and jurisdictions with forthcoming legislative and/or regulatory language for gabapentin to be labeled a CV medication

• Tennessee ➔ now reclassified to a CV as of July 1st 2018.

3) US states and jurisdictions with mandated reporting to PDMP

• Minnesota, Ohio, Virginia, Wyoming, West Virginia, Mass, North Dakota, Nebraska
Peckham et al.

4) US states and jurisdictions with forthcoming legislative and/or regulatory requirements for reporting to a PDMP

• Kansas and NJ → “Drug of concern” and PDMP proposal → May 7th for NJ and Kansas on July 25\(^{\text{th}}\), 2018

5) US states and jurisdictions in deliberations

• Washington and Hawaii → interprofessional review underway and monitoring national trends
Peckham et al.

Conclusion:

• The opioid epidemic has overshadowed the growing concomitant abuse of other prescription medications used to potentiate an “opioid-like high.”

• Small number of US states have implemented regulatory approaches to mitigate misuse due to absence of federal regulation.

• Article calls for more regulation however, more research is needed to identify to what degree of regulatory oversight is needed to combat gabapentin misuse.
Discussion
Should gabapentin be rescheduled to a CV?

- Yes
- No
- Maybe
## Options and Considerations

<table>
<thead>
<tr>
<th>Gabapentin – Schedule V</th>
<th>Gabapentin - Dangerous Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult for patients to get the medication for legitimate purposes.</td>
<td>• Abuse and potential diversion continues</td>
</tr>
<tr>
<td>Excess steps for providers</td>
<td>• Increase in overdoses (although hard to do)</td>
</tr>
<tr>
<td>What can we replace gabapentin with for neuropathic pain?</td>
<td>• Addicted patients effect society as a whole</td>
</tr>
<tr>
<td>▪ Duloxetine (Cymbalta®)</td>
<td></td>
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<tr>
<td>▪ Venlafaxine (Effexor®)</td>
<td></td>
</tr>
<tr>
<td>▪ Capsaicin cream</td>
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</table>

Pharmacist Involvement

- **Prevention:**

  - Reduce misuse, abuse and diversion.
  - Increase awareness
  - Always use best practices.
Pharmacist Involvement

- **Red flags:**
  - Pattern prescribing
  - Antagonistic drugs
  - Drug cocktails
  - Large quantities
  - Doctor patterns
  - Beyond specialty

- Geographic flags
  - Unlikely coincidences
  - False caregivers
  - Cash payments
  - Early refills
  - Suspicious behavior

Pharmacist Involvement

- Signs of prescription forgery:
  - False contact information
  - Misspellings
  - Photocopies
  - Alterations to prescriptions
  - Different inks or handwritings
  - Quantity, directions, or dosages differing from usual medical usage
  - No abbreviations used or non-standard abbreviations
Conclusion

- Deaths:
  - Limited
  - Bioavailability is saturable, so *not* necessarily concerned with lethal overdose but, *abuse is a problem.*

- Biggest risk factor appears to be those with SUD

- Reports of abuse rapidly rising

- Many states already taking action:
  - Kentucky
  - Tennessee

- Appears **likely** to become a CV drug
Acknowledgements

• Nathan D. Pope, Pharm.D., BCACP, FACA
• James Weems, Pharm.D.
• Natalia Malesa, Pharm D.
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Appendices

Appendix A: Abbreviations

Appendix B: Figure 1. Summary of Evidence Search and Selection from Evoy. et al.

Appendix C: Off-label dosing for gabapentin

Appendix D: Figure 1. Gabapentin regulation, legislation, and monitoring requirements within each US state as of March 1st, 2018 from Peckham et al.
Appendix A: Abbreviations

NE = norepinephrine
ACh = acetylcholine
H = histamine
CRF = corticotropin releasing factor
Glu = glutamate
GABA = gamma-amino butyric acid
Na+ = sodium
Ca2+ = calcium
mL = milliliter
mg = milligram
IR = instant release
ER = extended release
PHN = postherpatic neuralgia
CNS = central nervous system
FDA = Food and Drug Administration
MEDLINE = Medical Literature Analysis and Retrieval System Online
THC = tetrahydrocannabinol
PMH = past medical history
HLD = hyperlipidemia
AVR = aortic valve replacement
MVA = motor vehicle accident
BOP = Board of Pharmacy
PDMP = Prescription Drug Monitoring Program
CV = controlled substance V
PA = Physician Assistant
ARNP = Advanced Registered Nurse Practitioner
Appendix A (continued): Abbreviations

DEA = Drug Enforcement Agency
SUD = substance use disorder
HS = at bedtime
QD = daily
BID = twice daily
TID = three times daily

⇒ Titrate to/following
Appendix B: Summary of Evidence Search and Selection

Fig. 1 Summary of evidence search and selection

Electronically-identified articles from PubMed, Cochrane Library, ClinicalTrials.gov, and FDA website
Total= 664

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Duplicates= 302
Total= 577

Full text articles screened
n= 87

Articles included from hand search of citations
n= 14

Excluded
Review articles or not relevant to study= 42

Articles included in review
n= 59
Appendix C: Off-label dosing for gabapentin

1. Diabetic neuropathy (IR only):
   a. 300 mg PO TID → titrate up to max of 3600 mg/day if needed

2. Fibromyalgia (IR only):
   a. 300 mg PO HS over 1 week → titrate to total dose 2400 mg/day with 300 mg PO BID x 1 week, 300 mg PO BID with 600 mg HS x 2 weeks, 600 mg PO TID x 2 weeks, 600 mg PO BID with 1200 mg HS.

3. Hot flashes (IR only):
   a. 300 mg PO QD, may titrate to 300 mg PO TID if needed

4. Alcohol dependence:
   a. 300 mg PO at bedtime on day 1 → 300 mg PO BID on day 2 → 300 mg PO TID on day 3 → titrate upward over days 4-7 to reach final dosing regimen of 600 mg/day – 1800 mg/day

5. Amyotrophic lateral sclerosis (ALS):
   a. 1000 mg/day PO given in divided doses for 6 months slowed decline of muscle strength and trend of increases survival. Designated as an orphan drug for this indication.

6. Dysautonomia following severe traumatic brain injury (TBI):
   a. 300 mg PO BID. Dosages of up to 600 mg PO TID have been used.

7. Spasticity in multiple sclerosis (MS):
   a. 600-1200 mg/day in divided doses reported improvement in trigeminal neuralgia, paresthesia, spasticity and ocular ataxia.

8. Nystagmus:
   a. 300 mg PO QD → 300 mg PO TID or QID may be effective.

9. Pruritus in hemodialysis patients:
   a. 300 mg PO 3 times weekly after hemodialysis may be effective.

10. Short lasting unilateral neuralgiform headache with conjunctival infection and tearing (SCUNT):
    a. 300 mg PO BID → 300 mg – 1200 mg PO TID may be effective

11. Singultus (hiccups):
    a. 300 mg PO TID → 1200 mg/day OR 400 mg PO TID x 3 days, followed by 400 mg PO OD x 3 days

12. Tremor:
    a. 100 mg PO TID initially → 2400 mg/day in divided doses
Appendix D: Figure 1. Gabapentin regulation, legislation, and monitoring requirements within each US state as of March 1st, 2018.

Figure 1: Gabapentin regulation, legislation, and monitoring requirements within each US state as of March 1, 2018.

Abbreviation: PDMP, Prescription Drug Monitoring Program.