Patient Safety: Gabapentin and Trazodone
Off-label Use is Out of Control

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Disclosure

- Jeannette Wick has no relationships with ineligible companies.
Learning Objectives

- At the end of this continuing education activity, pharmacists will be able to
  - LIST the numerous off label uses of gabapentin and trazodone
  - DESCRIBE which of those uses are supported by actual evidence
  - INDICATE the potential adverse effects and medication related problems that patients who take these drugs may experience
  - ARTICULATE ways to approach prescribers with alternative suggestions
Audience Engagement Question

- Which of the following is an off-label use for gabapentin?

A. Postherpetic neuralgia

B. Adjunctive therapy in partial seizures

C. Migraine prophylaxis

Audience Engagement Question

- Which of the following is an off-label use for trazodone?

A. Chronic insomnia

B. Major depressive disorder

C. Pruritis
 Gabapentin

- Gabapentanoid discovered in 1970s → FDA approval in 1993 → generically available since 2004

- Related to
  - mirogabalin, drug manufactured in Japan
  - Gabapentin enacarbil, a prodrug
  - pregabalin related structure and predominant MOA similar → inhibition of Ca+ currents by high voltage activated channels containing the a2d-1subun

Off-label use:
- alcohol withdrawal
- anxiety
- bipolar disorder
- essential tremors
- fibromyalgia
- generalized tonic-clonic seizures
- headache
- insomnia
- interstitial cystitis
- irritable bowel syndrome (IBS)
- migraine prophylaxis
- nausea and vomiting
- neuropathic pain
- painful diabetic neuropathy
- postmenopausal hot flashes
- postoperative analgesia
- post-traumatic stress disorder
- pruritus
- refractory chronic cough
- resistant depressant and mood disorders
- social phobia

Pfizer pleaded guilty on in 2004 to numerous civil and criminal charges for illegally promoting the off-label use of gabapentin (Neurontin).

Trazodone

- Discovered in Italy in the 1960s
- Indicated for depression alone or in combination with other antidepressants
- Introduced a new generation of antidepressants as a non-tricyclic molecule
- Simultaneously inhibits SERT, 5-HT2A, and 5-HT2C receptors
- ↓ likelihood of sexual dysfunction, insomnia, and anxiety common with SSRIs and SNRIs


- Triazolopyridine derivative from the serotonin receptor antagonists and reuptake inhibitors (SARIs) class of antidepressants
- No direct molecular relatives
- Nefazodone, mirtazapine, tryptophan have similar MOA
- Therapeutic dose = 75–100 mg daily in a single dose, can be ↑ to 300 mg daily in divided doses. Rarely, may be ↑ to 600 mg per day

Trazodone

- FDA approved in 1981 for major depressive disorder
- Because of a lack of sufficient clinical data for justifying its use as a sleep aid, trazodone is not FDA-approved for sleep disorders
- Off label
  - Anxiety and insomnia
  - Alzheimer’s disease
  - Apnea and hypopnea episodes in patients with obstructive sleep apnea
  - Bulimia
  - ADHD in children
  - Fibromyalgia
  - PTSD resistant to SSRIs
  - Substance abuse
Follow the Money

**Gabapentin**
- Sales: $45.59 million (2018), $47.15 million (2019), $49.96 million (2020)
- Market valuation of $2.11 billion in 2023
- Predicted to reach a value of $3.54 billion by 2030
- Market growing rapidly
  - Increasing prevalence of neuropathic pain
  - Increase in off-label use
  - Growing availability and awareness
  - Low cost
  - Development of new formulations

**Trazodone**
- Off-label use for insomnia has surpassed its use as an antidepressant

Pharmaceutical marketing practices and prescriber dissatisfaction with currently available pharmacological treatment options may be key factors that contribute to this prescribing trend.
Common Problems: ADRs

Gabapentin
- Most common ADRs include dose-dependent CNS and respiratory depression, dizziness, somnolence, peripheral edema, hypersensitivity reactions, neuropsychiatric effects, and suicidal ideation and tendencies
- ↑CNS depressant effect of other
  - Avoid opioid agonists, BZD

Trazodone
- Most common ADRs include nausea/vomiting, xerostomia, dizziness, drowsiness, fatigue, headache, nervousness, blurred vision
- Bleeding risk if used with antiplatelets or anticoagulants
- Cardiac arrythmias possible, serotonin syndrome
- Significant association with QTc > 500 ms
- CYP3A4 and CYP2D6 substrate: alcohol, amphetamines, azelastine and others can ↑ toxic, CNS, and serotonergic effects


Common Problems: Gabapentin
- ED visits involving nonmedical use of gabapentin increased by 90% between 2008 and 2019
- Concurrent gabapentinoid was present in up to 26% of opioid abusers
  - ~ 24% of individuals had ≥3 instances in which they ingested more than 3,600 mg in a 12-month follow-up period
    - Induces gabapentin's psychoactive effects
    - Potentiates euphoria associated with opioids, fentanyl, marijuana, cocaine, and heroin
    - Physical addiction → users may need 2000 to 3000 mg to create desired effects
    - Ubitxlyho|lizbr|bxuxk|dvlh|bji|daj|bgg|qtdw|jih|xqved
- DILEMMA: Gabapentin was previously viewed as a nonaddictive alternative to opioids for pain treatment

https://www.aspenridgerecoverycenters.com/street-value-of-gabapentin
https://www.addictionresource.net/cost-of-drugs/prescription/gabapentin/
### Common Problems: Gabapentin

- Alabama, Kentucky, Michigan, North Dakota, Tennessee, Virginia, West Virginia = gabapentin is a **controlled substance**
- Connecticut, Indiana, Kansas, Massachusetts, Minnesota, Nebraska, New Jersey, Ohio, Oregon, Utah, Washington D.C., Wisconsin, Wyoming = require **PDMP system reporting**

https://www.drugs.com/medical-answers/gabapentin-narcotic-controlled-substance-3555993/

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### Common Problems: Trazodone

- Examined a large commercial insurance claims database (N > 2.8 million) to identify demographic and healthcare service utilization variables that differentiate patients with OUD diagnoses within 2 years of filling an opioid prescription from those without
  - Male and younger
  - Use multiple pharmacies
  - Less likely to be the primary insured individual
  - More likely to be a dependent or spouse/partner of the primary insured
- Patients who progressed to OUD were ~5 times more likely to use/misuse antidepressants, principally trazodone.

Common Problems: Trazodone

- Systematic review of nonscheduled psychoactive prescription with > 400 reported cases during the period.
  - Cyclobenzaprine, quetiapine, and trazodone met criteria for analysis
  - All used for treatment and/or self-treatment of opioid withdrawal symptoms
- Found a significant, steady ↑ in the diversion of each drug over the period
  - More than five times higher in 2017 than the 2002
- Diversion rates for opioids have ↓ in recent years, rates for cyclobenzaprine, quetiapine, and trazodone have continued to ↑
- “Prescribers need to be aware of illicit markets for these medications and prescribe to their patients with appropriate caution.”


Common Problems: Trazodone

- ADRs occur in >10% of users
- Trazodone overdose can precipitate
  - Arrhythmias
  - Respiratory arrest
  - Coma
- Rare but serious
  - Priapism
Gabapentin

Panacea?

Audience Engagement Question

- Which of gabapentin’s off-label uses has the strongest evidence to support it?

A. Bipolar disorder
B. Alcohol withdrawal syndrome
C. Pain syndromes
Gabapentin in Bipolar Disorder

- Four RCTs, most small or extremely small
- One (N = 60) had positive findings in acute mania as adjunctive treatment
- “The few randomized controlled trials designed to investigate the efficacy of gabapentin in treating bipolar disorder have concluded that there is no significant difference in the effects of the drug compared with placebo.”


Gabapentin in Pain Syndromes, Peripheral Neuropathy, and Diabetic Neuropathy

- Literature in support is more favorable than that concerning its use in various other disease states
- Some issues remain:
  - Variable doses
  - Few direct comparisons to other medications
  - Open-label studies with the potential for bias
- Proven efficacy for treatment of diabetic neuropathy and postherpetic neuralgia

Gabapentin in Restless Leg Syndrome

- An RCT (N = 541) assessed mood and QoL, comparing doses of 600 mg, 1200 mg, and placebo
  - Once daily gabapentin significantly improved QoL in adults with moderate-to-severe primary RLS at all time points examined
  - Affect on mood varied
- Trying to determine how responders differ from nonresponders
  - Patients with typical idiopathic RLS characteristics (positive family history, and no low ferritin level) may derive greatest benefits
  - AASM indicates clinicians can use gabapentin, but evidence is low and the harm/burden assessment = unclear harm/benefit balance


Gabapentin in Alcohol Withdrawal

- One retrospective cohort study (n = 50 patients treated with BZDs, 50 treated with high dosages of gabapentin)
  - Mean LOS and lorazepam dosages were both significantly lower in the gabapentin group
  - BZDs remain the gold standard for management of alcohol withdrawal

Trazodone

 Miracle drug?

Audience Engagement Question

- Which of trazodone’s off-label uses has the strongest evidence to support it?

A. Little evidence is available to support the use of trazodone in any of its purported off-label uses.

B. The best evidence supports its use in chronic insomnia, with more than 15 RCTs indicating it is effective.

C. A surprise finding has been that it is effective for behavioral issues in kids who have ADHD; it may help adults, too.
Trazodone in Insomnia

- Most frequent reason for trazodone prescriptions
- Previously, researchers assumed that 5HT2A antagonism was sufficient to induce sleep
- 10 mg of trazodone saturates almost 100% of 5HT2A receptor
- Hypnotic effect appears only at higher doses when it affects alpha 1 and H1 receptors
Trazodone in ADHD

- Researchers identified 16,547 trazodone prescriptions, representing 8.4% (n = 2,705) of 32,134 children with ADHD
  - Most for children ≥ 10 years
  - Predominantly male (70.7%) but more female children had a filled trazodone prescription than males (10.1% vs 7.7%)
  - Those with trazodone prescriptions were 3 times more likely to have a sleep-related diagnosis as their most common comorbidity (excluding ADHD), compared with those of the same age and sex without a trazodone prescription
  - “Children with ADHD are prescribed trazodone off label and for conditions with no national guidelines or clinical evidence of efficacy. Female children on Medicaid may be prescribed trazodone for concurrent mental health conditions, and further research is warranted regarding potential correlates.”


Trazodone in Other Off-label Uses
Trazodone in Other Diagnoses

<table>
<thead>
<tr>
<th>Off Label Use</th>
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<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>OMG. A miasma of studies! A study (N = 30) over 2 weeks found trazodone appeared to stabilize circadian rhythm</td>
</tr>
<tr>
<td>Apnea/hypopnea episodes in obstructive sleep apnea</td>
<td>Three studies (N = 9 to 15)</td>
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<tr>
<td>Bulimia</td>
<td>One RCT (N = 42): Trazodone superior to placebo to ↓ frequency of binge eating and vomiting</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Zero RCT</td>
</tr>
<tr>
<td>PTSD resistant to SSRIs</td>
<td>One RCT (N = 60) found trazodone ↓ nightmares, helped with sleep onset, and improved with sleep maintenance.</td>
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<tr>
<td>Substance abuse</td>
<td>One study (N = 51) indicates its usefulness in patients taking buprenorphine</td>
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Trazodone and Priapism

As an ADR
- Patients at high risk
  - Sickle cell anemia or sickle trait
  - Leukemia
  - Autonomic nervous system dysfunction
  - Hypercoagulable states

As a treatment
- Controversial topic
  - Meta-analysis of six trials (N = 386), all small, many methodologically weak
  - Appears more helpful in men with psychogenic ED

Reddit!

Gabapentin
- What to expect for gabapentin high?
- I'm [sic] about to take 1500mg and have a red bull [sic] then I will be bulletproof!
- One thing everyone has in common when taking gabapentin is that they become talkative.
- Doctors still hand it out like candy for everything.

Trazodone
- Withdrawal syndrome is #1 comment
- Trazodone withdrawal is brutal
- Trazodone should be in every psychedelic user's back pocket.
  - If you need to abort a trip in an emergency situation, take a trazodone pill.

Veterinary Prescribing

Gabapentin
- Seven RCTs
  - Dogs, cats, cattle, horses
  - Transport- and examination-related anxiety
  - Pain
  - Seizures
  - The human oral solution of gabapentin contains XYLITOL, which should be avoided in veterinary patients.

Trazodone
- Seven RCTs
  - Sedation in dogs and cats
  - Anesthesia adjunct
  - Transport- and examination related anxiety
  - Post-surgical confinement

What are the Alternatives?

- Guideline-directed care
- FDA-approved medications that have undergone well designed, large RCT
A prescriber writes a gabapentin prescription for a patient who has chronic insomnia. The patient is a 27-year-old unemployed male who depends on his wife for support; her job provides insurance. He has been on numerous medications in the last two years. His current medications include oxycodone/acetaminophen, fluoxetine, docusate, and trazodone. Why might you call the prescriber?

A. He is high-risk for opioid use disorder and gabapentin is often abused.

B. He should be on a stimulant laxative since he is taking opioids.

C. This medication has very few side effects. It’s kind of a wonder drug.
Audience Engagement Question

- A prescriber calls about a patient who has erectile dysfunction. He asks you to discuss the likelihood that trazodone will help and reveals that sildenafil did not help. Which of the following is the BEST answer?

A. Trazodone is FDA-approved for this indication, so the likelihood that it will work is pretty good. The patient must stay positive about the possibility.

B. It could work, but the patient runs the risk of developing priapism which is a medical emergency. Are you sure you’ve tried everything?

C. It depends on the cause of the erectile dysfunction. If anxiety, depression, guilt, or relationship concern are factors, it is most likely to help.

Talking to Patients

- Ask patients to tell you why the physician prescribed the medication
- Ask what they have tried before and why they discontinued it
- Review the patient’s medication history
  - Look for red flags
- Emphasize SAFETY
Talking to Prescribers

- Obtaining good quality information about off-label uses is more difficult than for approved indications
- Prescribers often learn about off-label uses from colleagues and pharmaceutical representatives, conferences, and literature searches
- Prescribers may have little time to locate, retrieve, and analyze data.

Talking to Prescribers

- REMEMBER: Off-label use is not necessarily "incorrect or wrong," but that it may require additional scrutiny to ensure patients are receiving safe, effective therapy
- Often, off-label uses emanate from the medication's mechanism of action
- Ask questions of prescribers if they are concerned about the rationale for an off-label prescription
- Consider preparing a handout with the pros and cons of using these drugs off-label
Talking to Prescribers

- Consult guidelines if they are available before calling the prescriber
- List reasonable and FDA-approved alternatives so you can discuss them with authority
- Ask open-ended questions
  - If the prescriber indicates it’s trial and error, ask who will reassess the patient and when? (Volunteer to do some monitoring)
- Don’t be afraid to quote Reddit
Sometimes medications take on a life of their own after FDA approval

We need to disseminate evidence for off-label indications among prescribers, particularly when clinical practice guidelines exist

No medication is a panacea, and if prescribing patterns start to suggest it is, we need to go back and look at the evidence

Questions?