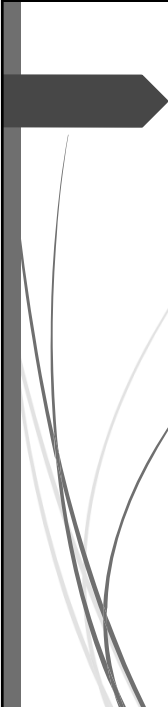


# **Patient Safety: Gabapentin and Trazodone Off-label Use is Out of Control**

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1



## **Disclosure**

- Jeannette Wick has no relationships with ineligible companies.

2

## 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

3



4



## 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

5



## Audience Engagement Question

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

- A. Chronic insomnia
- B. Major depressive disorder
- C. Pruritis

6

# 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<sup>+</sup> currents by high voltage activated channels containing the  $\alpha 2\delta$ -1 subunit

7

# Gabapentin

- ▶ FDA approved
  - ▶ postherpetic neuralgia
  - ▶ adjunctive therapy in partial seizures
- 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).

Lenzer J. *BMJ*. 2004;328(7450):1217.

8

## 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-HT<sub>2A</sub>**, and 5-HT<sub>2C</sub> 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

Jaškowska J, et al. *Molecules*. 2021;26(3):769.

9

## 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

10

## 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

- Sales: \$22.31 millions (2017), \$23.89 million (2018), \$23.93 million (2019), \$26.1million (2020)
- Off-label use for insomnia has surpassed its use as an antidepressant

11

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

12

## 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 arrhythmias possible, serotonin syndrome
- Significant association with QTc > 500 ms
- CYP3A4 and CYP2D6 substrate: alcohol, amphetamines, azelastine and others can ↑ toxic, CNS, and serotonergic effects

Ryan K, et al. *Cardiovasc Toxicol*. 2022;22(9):866-877.

13

## 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
    - Uhhawlyho| #dv| #r #xufk dvh #ohj dco| #lqg #q #dujh# xdqwlvhv
- 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/>

14

## 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/>

15

## 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.

Cochran BN, et al. *Drug Alcohol Depend.* 2014;138:202-208.

16



## 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."

Kurtz SP, et al. *Pharmacoepidemiol Drug Saf.* 2019;28(5):700-706.

17

## Common Problems: Trazodone

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

18

# Gabapentin

Panacea?

19

## 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

20

## 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."

Pande AC, et al. *Bipolar Disord.* 2000;2(3 Pt 2):249-255. Vieta E, et al. *J Clin Psychiatry.* 2006;67(3):473-477.  
 Astaneh AN, Rezaei O. *Int J Psychiatry Med.* 2012;43(3):261-271. Prisciandaro JJ, et al. *Addict Biol.* 2022;27(1):e13085.

21

## 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

Backonja M, et al. *JAMA.* 1998;280:1831-36. 33. Rowbotham M, et al. *JAMA.* 1998;280:1837-42.

22

## 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

Avidan AY, et al. *CNS Drugs*. 2016;30(4):305-316. Inoue Y, et al. *Sleep Med*. 2021;85:138-146. Aurora RN, et al. *Sleep*. 2012;35(8):1037.

23

## 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

Morrison M, et al. *Am J Drug Alcohol Abuse*. 2019;45(4):385-391.

24

## Trazodone

Miracle drug?



25

## Audience Engagement Question

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

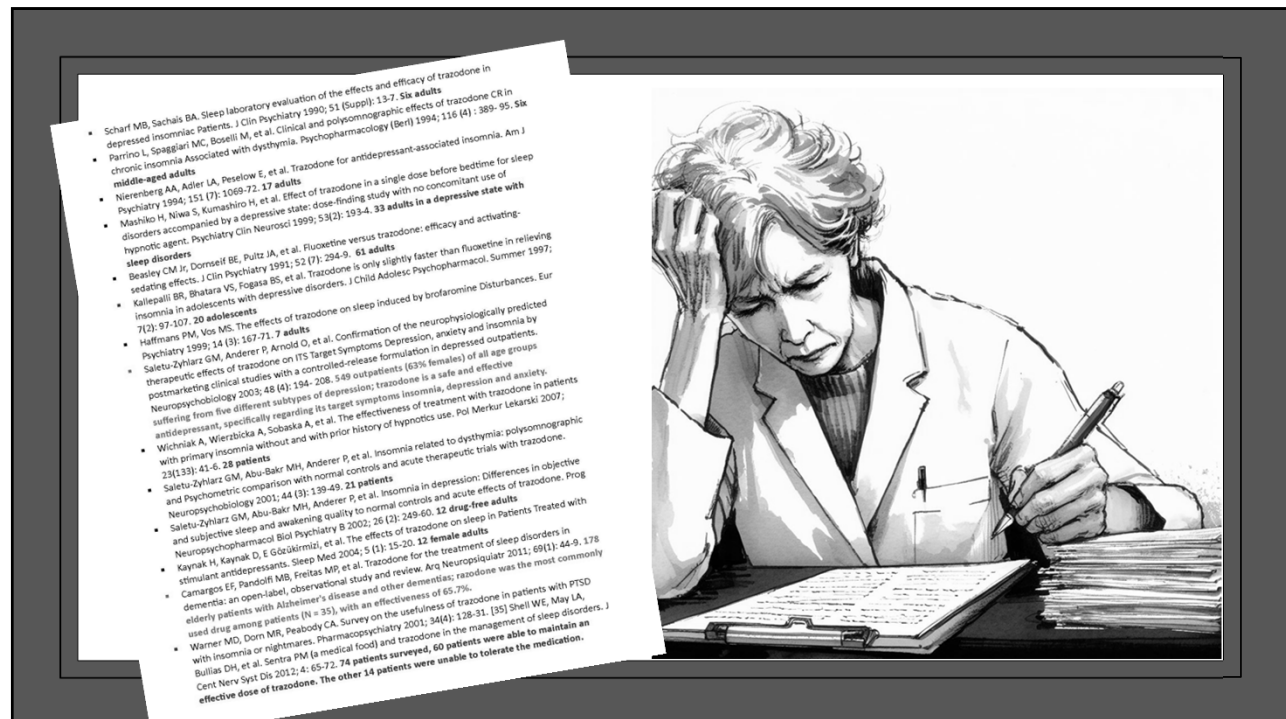
- A. Little evidence is available to support the use of trazodone in any of its purported off-label uses.
- B. The best evidence supports its use in chronic insomnia, with more than 15 RCTs indicating it is effective.
- C. A surprise finding has been that it is effective for behavioral issues in kids who have ADHD; it may help adults, too.

26

## Trazodone in Insomnia

- ▶ Most frequent reason for trazodone prescriptions
- ▶ Previously, researchers assumed that 5HT<sub>2A</sub> antagonism was sufficient to induce sleep
  - ▶ 10 mg of trazodone saturates almost 100% of 5HT<sub>2A</sub> receptor
  - ▶ Hypnotic effect appears only at higher doses when it affects alpha 1 and H1 receptors

27



• Scharf MB, Sachais BA. Sleep laboratory evaluation of the effects and efficacy of trazodone in depressed insomnia: Patients. *J Clin Psychiatry* 1990; 51 (Suppl): 3-7. **Six adults**  
 • Parrino L, Spaggiari MC, Boselli M, et al. Clinical and polypharmacologic effects of trazodone CR in chronic insomnia associated with dysthymia. *Psychopharmacology (Berl)* 1994; 116 (4) : 389-95. **Six middle-aged adults**  
 • Nierenberg AA, Adler LA, Peselow E, et al. Trazodone for antidepressant-associated insomnia. *Am J Psychiatry* 1994; 151 (7) : 1069-72. **17 adults**  
 • Mashiko H, Niwa S, Kumashiro H, et al. Effect of trazodone in a single dose before bedtime for sleep disorders accompanied by a depressive state: dose-finding study with no concomitant use of hypnotic agent. *Psychiatry Clin Neurosci* 1999; 53(2): 193-4. **33 adults in a depressive state with sleep disorders**  
 • Beasley CM Jr, Dorrosel BE, Pultz JA, et al. Fluoxetine versus trazodone: efficacy and activating/sedating effects. *J Clin Psychiatry* 1991; 52 (7) : 294-9. **61 adults**  
 • Kallepalli BR, Bhatara VS, Fogasa BS, et al. Trazodone is only slightly faster than fluoxetine in relieving insomnia in adolescents with depressive disorders. *J Child Adolesc Psychopharmacol*. Summer 1997; 7(2): 97-107. **20 adolescents**  
 • Hattmans PM, Vos MS. The effects of trazodone on sleep induced by brofaromine Disturbances. *Eur Psychiatry* 1999; 14 (3) : 167-71. **7 adults**  
 • Saletu-Zylharz GM, Anderer P, Arnold O, et al. Confirmation of the neurophysiologically predicted therapeutic effects of trazodone on IFS target Symptoms Depression, anxiety and insomnia in postmarketing clinical studies with a controlled-release formulation in depressed outpatients. *Neuropsychobiology* 2003; 48 (4) : 194- 208. **549 outpatients (63% females) of all age groups**  
 • Kaynak H, Kaynak D, E Göçükmüsi, et al. The effects of trazodone on sleep in Patients Treated with antidepressant, specifically regarding its target symptoms Insomnia, depression and anxiety: an antidepressant, specifically regarding its target symptoms Insomnia, depression and anxiety. *Pol Merkur Lekarski* 2007; 23(133): 41-6. **28 patients**  
 • Saletu-Zylharz GM, Abu-Bakr MH, Anderer P, et al. Insomnia related to dysthymia: polysomnographic and Psychometric comparison with normal controls and acute therapeutic trials with trazodone. *Prog Neuropsychobiology* 2001; 44 (3) : 139-49. **21 patients**  
 • Saletu-Zylharz GM, Abu-Bakr MH, Anderer P, et al. Insomnia in depression: Differences in objective and subjective sleep and awakening equality to normal controls and acute effects of trazodone. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26 (2) : 249-60. **12 drug-free adults**  
 • Kaynak H, Kaynak D, E Göçükmüsi, et al. The effects of trazodone on sleep in Patients Treated with stimulant antidepressants. *Sleep Med* 2004; 5 (1) : 15-20. **12 female adults**  
 • Camargos EF, Pandolfi MB, Freitas MP, et al. Trazodone for the treatment of sleep disorders in dementia: an open-label, observational study and review. *Arg Neuropsiquiatr* 2011; 69(1): 44-9. **178 elderly drug among patients (N = 35), with an effectiveness of trazodone in patients with PTSD**  
 • Warner MD, Dorn MR, Peselody CA. Survey on the usefulness of trazodone in the management of sleep disorders with insomnia or nightmares. *Pharmacopsychiatry* 2001; 34(4): 128-31. [35] Shell WE, May LA, Bullian DH, et al. Sentra PM (a medical food) and trazodone in the management of sleep disorders. *J Cent Nerv Syst Dis* 2012; 4: 65-72. **74 patients surveyed, 60 patients were able to maintain an effective dose of trazodone. The other 14 patients were unable to tolerate the medication.**

28

## Trazodone in ADHD

- Researchers identified 16,547 trazodone prescriptions, representing 8.4% (n = 2,705) of 32,134 children with ADHD
  - Most for children  $\geq 10$  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."

Klein TA, et al. *J Pediatr Pharmacol Ther.* 2022;27(2):132-140.

29

## Trazodone in Other Off-label Uses



30

## Trazodone in Other Diagnoses

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

Cuomo A, et al. *Riv Psichiatr.* 2019;54(4):137-149. Chen CY, et al. *J Neurol.* 2021;268(8):2951-2960. Smales ET, et al. *Ann Am Thorac Soc.* 2015;12(5):758-764. Heinzer RC, et al. *Eur Respir J.* 2008;31(6):1308-1312. Warner MD, et al. *Pharmacopsychiatry.* 2001;34(4):128-131. Grippe TC, et al. *Chronobiol Int.* 2015;32(9):1311-1314.

31

## 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

Fink HA, et al. *BJU Int.* 2003;92(4):441-446.

32



## Reddit!

### Gabapentin

- ▶ What to expect for gabapentin high?
- ▶ Im [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 users back pocket.**
  - ▶ If you need to abort a trip in an emergency situation, take a trazodone pill.

33

## Veterinary Prescribing

### Gabapentin

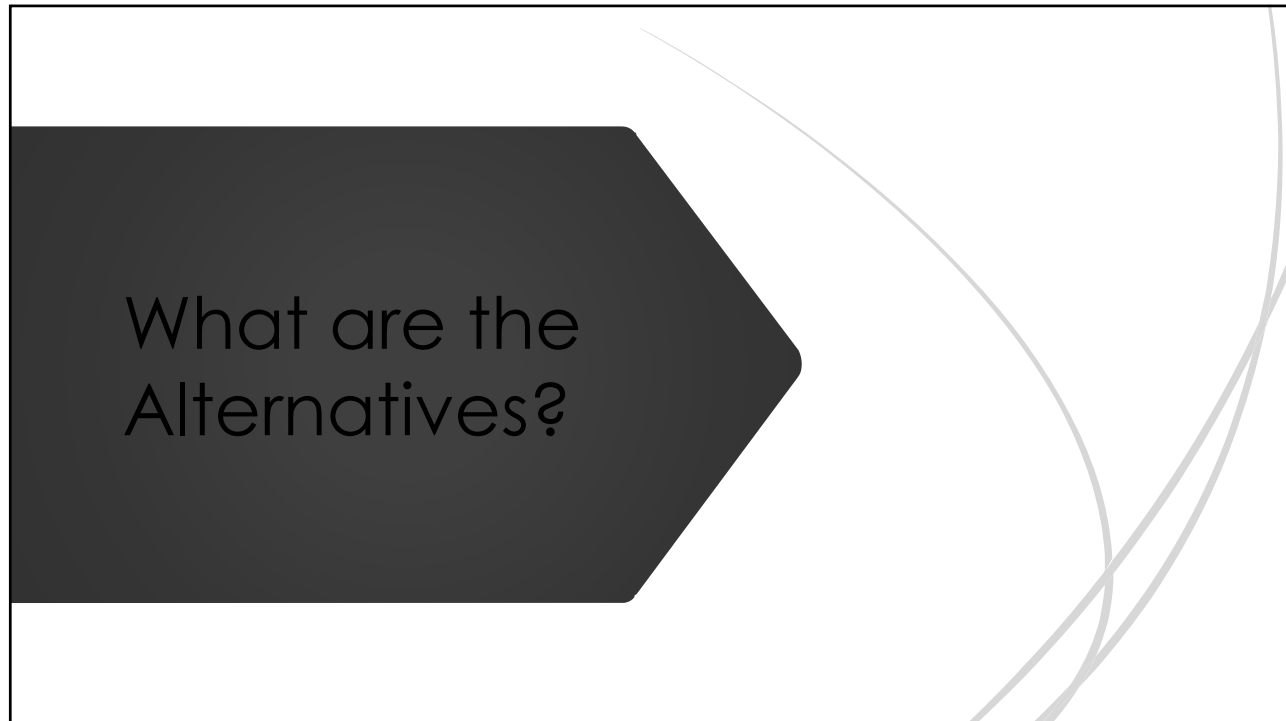
- ▶ Seven RCTs
  - ▶ Dogs, cats, cattle, horses
  - ▶ Transport- and examination-related anxiety
  - ▶ Pain
  - ▶ Seizures
- ▶ **The human oral solution of gabapentin contains XYLITOL, which should be avoided in veterinary patients.**

### Trazodone

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

Hoffman EA, et al. *Vet Anaesth Analg*. 2018;45(6):754-759. Murphy LA, et al. *J Am Vet Med Assoc*. 2017;250(4):408-416. Murphy LA, et al. *J Am Vet Med Assoc*. 2017;250(4):408-416. Stevens BJ, et al. *J Am Vet Med Assoc*. 2016;249(2):202-207. Orlando JM, et al. *J Feline Med Surg*. 2016;18(6):476-482. Gruen ME, et al. *J Am Vet Med Assoc*. 2014;245(3):296-301. Jay AR, et al. *Am J Vet Res*. 2013;74(11):1450-1456. van Haften KA, et al. *J Am Vet Med Assoc*. 2017;251(10):1175-1181. Trbolova A, et al. *BMC Vet Res*. 2017;13(1):288. Plessas IN, et al. *Vet Rec*. 2015;177(11):288. Glynn HD, et al. *J Vet Pharmacol Ther*. 2013;36(6):550-561. Aghighi SA, et al. *Vet Anaesth Analg*. 2012;39(6):636-646. Terry RL, et al. *J Vet Pharmacol Ther*. 2010;33(5):485-494. Wagner AE, et al. *J Am Vet Med Assoc*. 2010;236(7):751-756.

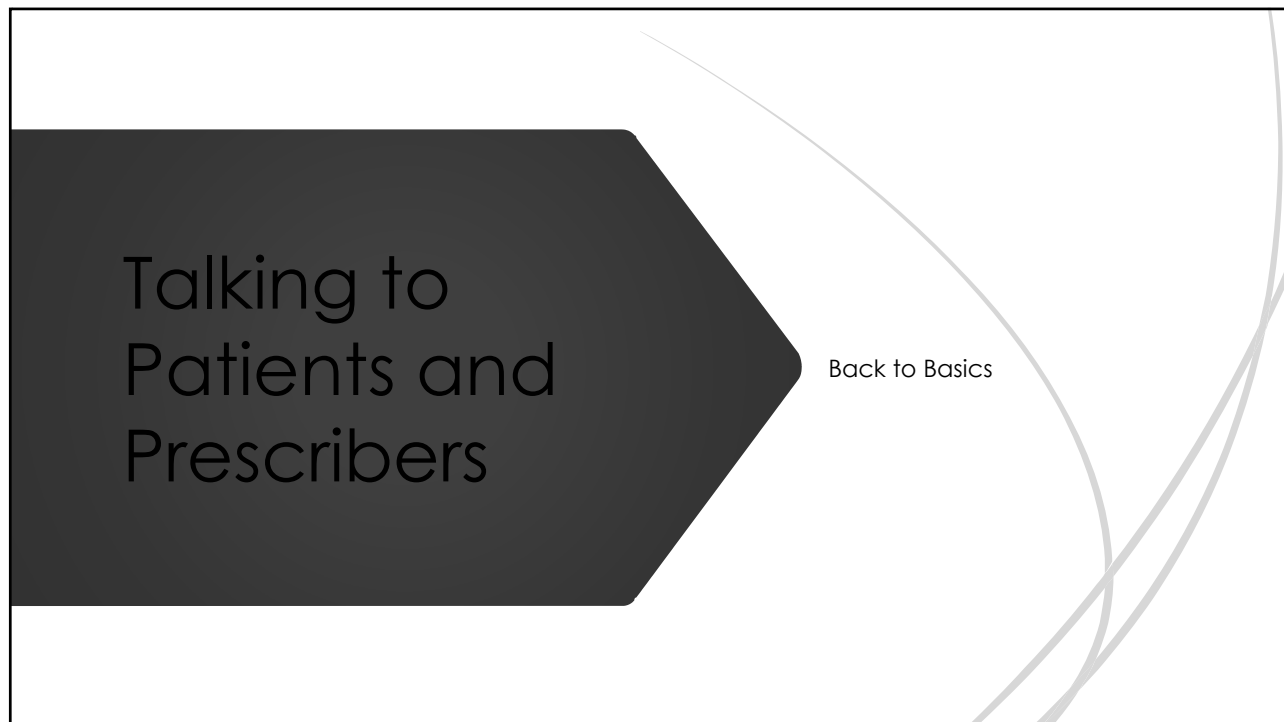
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36



37

A slide with a dark grey arrow-shaped graphic on the left. The main heading is "Audience Engagement Question". Below it is a list of three multiple-choice options (A, B, and C) regarding a clinical scenario. The background features light grey curved lines.

## Audience Engagement Question

- 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.

38



## 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.

39



## 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

40



## 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.

41



## 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

42

## 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

43



44



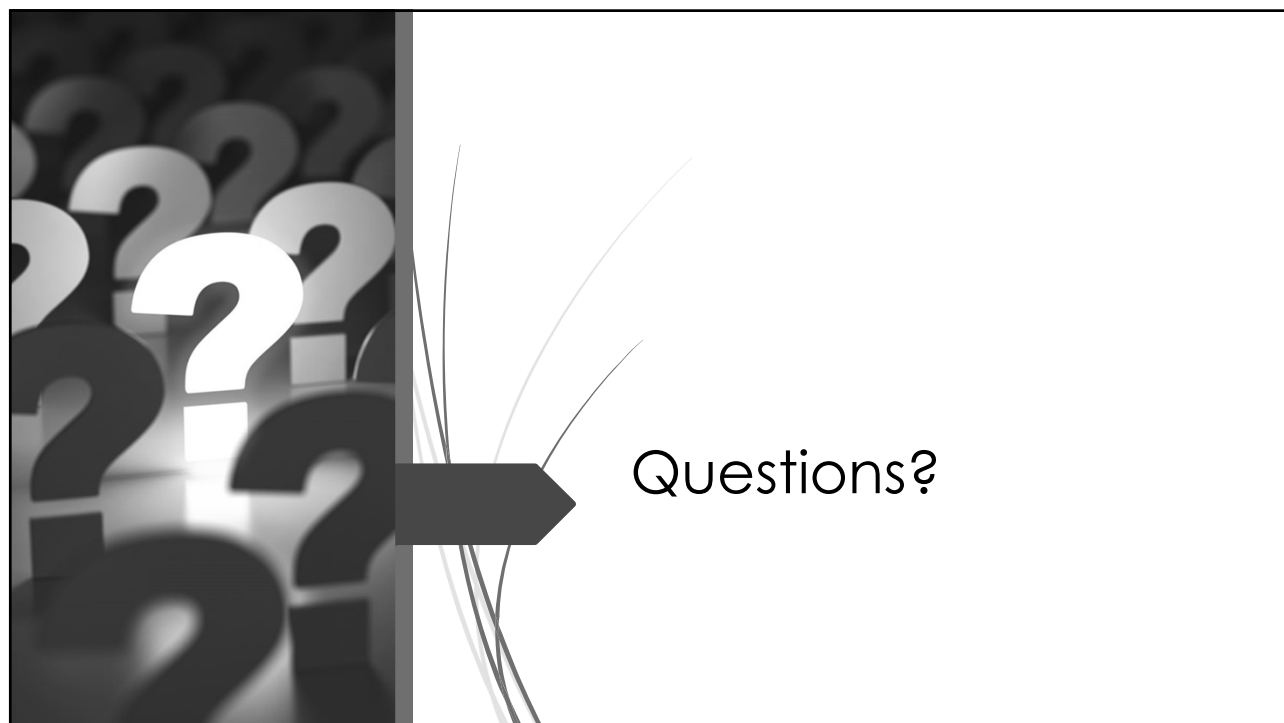
**Conclusion**

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

45



Questions?

46