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Psychiatry and Addictions Case Conference
UW Medicine | Psychiatry and Behavioral Sciences

BENZODIAZEPINES FOR ANXIETY DISORDER TREATMENT

WHEN, IF EVER, WOULD I CONSIDER USING BENZODIAZEPINES FOR LONG-TERM TREATMENT OF ANXIETY DISORDERS?

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GENERAL DISCLOSURES

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GENERAL DISCLOSURES

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SPEAKER DISCLOSURES

- No conflicts of interest relevant to this topic
- Medical Director, PAL for Moms
  - Weekdays 9-5
  - Free
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  - Funded by Washington State Health Care Authority

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PLANNER DISCLOSURES

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CASE

- A 60 yo woman presents with a long history of generalized anxiety disorder. She also has a history of hypertension and sleep apnea (using CPAP). She has taken benzodiazepines for more than 20 years and is currently on alprazolam 1 mg qid. She does not want to change this medication because she says it has been very helpful and “I don’t know what I would do without it.” She knows she needs it because she becomes very anxious before each dose. She has no history of substance use disorders but was recently prescribed oxycodone after knee surgery.

- Would you have prescribed a benzodiazepine for her?
- When, if ever, would you prescribe a benzodiazepine for long-term treatment of an anxiety disorder?

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OBJECTIVES

1

Review the epidemiology of benzodiazepine prescribing/use

2

Describe the evidence for efficacy with long-term treatment of anxiety disorders

3

Discuss indications for and potential approaches to prescribing benzodiazepines

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BENZODIAZEPINES AND ANXIETY DISORDERS

- Benzodiazepines are NOT a first-line treatment for any anxiety disorder, for OCD and related disorders, or for PTSD

Yet they are very commonly prescribed…

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BENZODIAZEPINE USE AND MISUSE

- 2015-2016 National Survey on Drug Use & Health
  - Adults 18 or older
- 30.6 million (12.6%) with past year BZ use
  - 25.3 million (10.4%) prescribed
  - 5.3 million (2.2%) misuse; misuse 17.2% of overall BZ use
- Highest prescription use in 50-64 yo (12.9%), more common in women and non-Hispanic Whites
- Misuse associated with opioid or stimulant misuse
    - Maust et al., Psych Services, 2019
- 2008 study showed long term use (≥ 120 days) ranging from 14.7% (ages 18-35) to 31.4% (ages 65-80)
    - Olfson et al., JAMA Psychiatry, 2015

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ALTERNATIVES

- First-line treatments for anxiety disorders
  - SSRIs (SNRIs)
  - CBT
- Alternative anxiolytics
  - Buspirone
  - Pregabalin
  - Gabapentin
  - Hydroxyzine
  - Beta blockers
  - Atypical antipsychotics
  - Clonidine
  - Prazosin
  - Mindfulness/meditation
  - Other therapies

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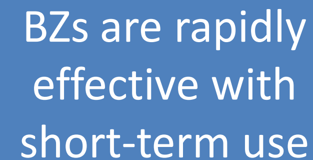
BZS VS ANTIDEPRESSANTS

- Meta-analysis of 56 studies
- 12,655 participants
- Effect sizes:
  - SSRIs: 0.33
  - SNRIs: 0.36
  - BZs: 0.50



– Gomez et al., Expert Opin Pharmacother 2018

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LONG-TERM TREATMENT

- 8 studies of BZs for anxiety disorders for ≥ 13 weeks
- 4 compared BZs (lorazepam vs. diazepam, ketazolam vs. diazepam, alprazolam vs. lorazepam) over 4-6 months
  - BZs equally effective
  - Superior to placebo; sedation/drowsiness more common than with placebo
  - BZ effects greatest in first 4 weeks
    - Shinfuku et al., 2019

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LONG-TERM TREATMENT

- 4 were of maintenance treatment (20 weeks – 36 months after acute trials)
  - Clorazepate vs. buspirone, alprazolam vs. imipramine vs. placebo, clonazepam vs. paroxetine
  - All medications effective; efficacy maintained
  - Lowest rate of dropout, side effects with BZs
  - Taper after 3 years -> lower relapse rate after clonazepam vs paroxetine
    - Shinfuku et al., 2019

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LONG-TERM TREATMENT: TAKE HOME POINTS

- Very few studies
- Little efficacy data to support long-term BZs OR preference for SSRIs
- Effects of BZs greatest in first 4 weeks, antidepressants catch up by 8 weeks
- Greater tolerability with BZs
- No evidence for tolerance (need for dose increases) in patients with anxiety disorders over time (up to 3 years)
    - Shinfuku et al., 2019; Willems et al., 2013; Rickels, 2018

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CLONAZEPAM AUGMENTATION FOR SOCIAL ANXIETY DISORDER

- 181 nonresponders to 10 weeks sertraline
- Sertraline + clonazepam (up to 3 mg/d) vs. sertraline + placebo for 12 weeks:

	Remission	Response
Sertraline + clonazepam	27%	56%
Sertraline + placebo	17%	36%

NNT = 5 for response, 10 for remission

Pollack et al., 2014

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ADVERSE EFFECTS

- Sedation
- Psychomotor impairment (driving), accidents
- Falls, hip fractures
- Anterograde amnesia
- Behavioral disinhibition
- Tolerance, dependence, withdrawal
- Increased risk for dementia?

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BZS AND DEMENTIA

- 235,465 people > 20 yo hospitalized for affective disorder
- 76% used BZs/Z-drugs over average of 6 years follow up
- Compared with same-age controls
- Covariates: gender, age, education, marital status, diabetes, cardiovascular disease, SUD
- No association between dementia and any use/cumulative dose of BZs, Z-drugs, short- vs. long-acting drugs, other anxiolytics (hydroxyzine, buspirone, pregabalin)

    - Osler and Jorgensen, Am J Psychiatry, 2020

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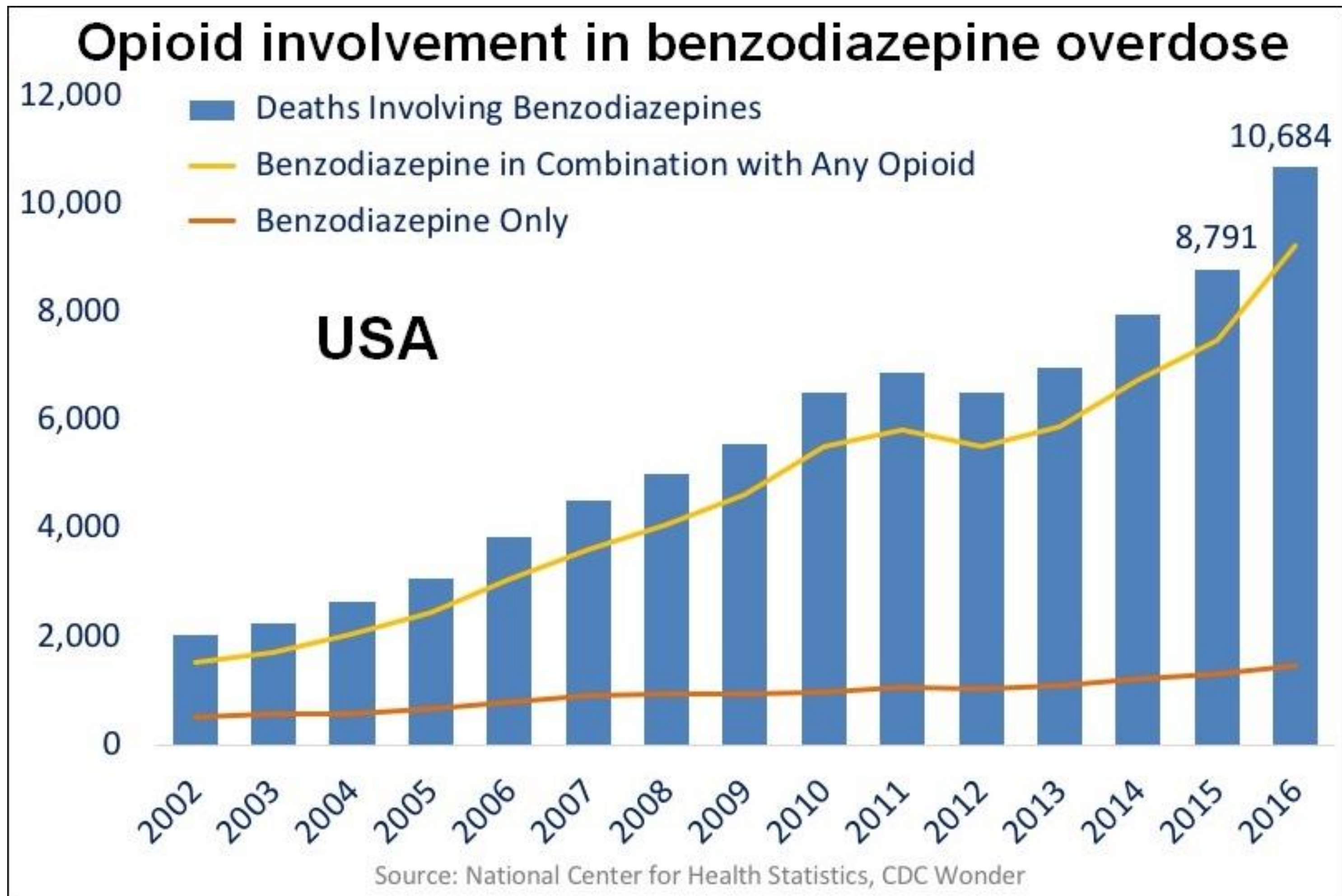
FDA warning (August 31, 2016): Benzodiazepines + opioids: Slowed/difficult breathing, death



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WHEN WOULD YOU USE A BENZODIAZEPINE?

- Need for rapid relief of disabling symptoms, short-term treatment
- Nothing else works (including therapy)
- Patient cannot tolerate side effects of other medications
- Adjunct early in treatment

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INITIAL PRESCRIBING

- What diagnosis/symptom?
- For how long?
- Risk factors
- How will you know if medicine is effective?
- Select medicine with pharmacokinetics that match intended use
- Prescribe realistic amount and refills
- Talk with patient about first dose, abuse potential, warning signs

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MONITORING

- Regular follow up
- Document refills, timing, expected refill date
- Warning signs:
  - Lost prescriptions
  - Need for early refills
  - Need for higher doses
  - Missed appointments

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TREATMENT PARTNERSHIP AGREEMENT

Agreement to:

- Inform provider of any history of substance abuse
- Inform provider of use of any sedatives, other medications, drugs
- No replacement prescriptions
- Take medication as prescribed
- Attend appointments
- Get benzodiazepine(s) from only one provider
- Submit to urine drug screens as needed

Documentation that risks explained to patient

Signed by provider and patient

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TAKE HOME POINTS

- BZs are effective for rapid, short-term relief of anxiety, and limited data suggest effects persist with long-term treatment
- Their utility is limited by potential harms
- Even when prescribing short-term, consider other alternatives
- Is the condition acute or chronic?
- What is the plan for ending BZ treatment? If long-term, what would be indications for stopping?

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QUESTIONS?

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