

Benzodiazepines: Pharmacology to Co-Prescribing Risks and Concerns

The Role of Benzodiazepines in the Treatment of Anxiety

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This educational program is designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation.

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## Learning Objectives

At the conclusion of this session, attendees should be able to:

- Describe epidemiology of anxiety and panic attacks
- Describe non-pharmacological treatment for anxiety and panic attacks
- Describe role and risks of benzodiazepines in treatment and other pharmaceutical products

### Target Audience

Physicians, physician assistants, advanced practice pharmacists, APRNs, residents, & fellows who prescribe controlled substances.

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## CME Accreditation

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## The Role of Benzodiazepines for the Treatment of Anxiety

Tae Woo Park, MD, MSc  
Brown University

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### Overview

- Overview of anxiety disorders
- Treatments for anxiety disorders
- Benzodiazepines as a treatment for anxiety disorders
- Risks of benzodiazepines
- Benzodiazepine discontinuation

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### Overview of anxiety disorders

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### What is anxiety?

- Fear vs. anxiety
  - Fear is a response to a present or imminent danger
  - Anxiety is a response to a possible, future danger
- Symptoms of fear include:
  - Thoughts of imminent threat
  - Escape
  - Sympathetic arousal
- Symptoms of anxiety include:
  - Worry
  - Avoidance
  - Muscle tension

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### Anxiety Disorders

- Generalized anxiety disorder (GAD)
  - Excessive anxiety or worry that is difficult to control
  - Often about everyday concerns
  - Other symptoms: restlessness, muscle tension, sleep, concentration
- Panic disorder
  - Panic attack: chest pain, shortness of breath, sweating, increased heart rate, derealization, fear of dying
  - Worry about future attacks
  - Might be accompanied by agoraphobia – fear of places that one can't escape

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### Anxiety Disorders

- Posttraumatic stress disorder (PTSD)
  - Exposure to trauma
  - Re-experiencing trauma: intrusive memories, dreams, flashbacks
  - Avoidance
  - Changes in mood/cognition
  - Changes in arousal/reactivity
- Obsessive compulsive disorder (OCD)
  - Intrusive, unwanted thoughts or urges
  - Repetitive behaviors or mental acts performed in response to obsessions to reduce distress
- Social anxiety disorder (SAD)
  - Fear or anxiety in social situations where person is scrutinized
- Specific phobias
  - Fear or anxiety about a specific object or situation

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### Anxiety disorders are highly prevalent

- NESARC (2001-2002)
  - Any anxiety disorder (excluding PTSD, OCD) in past year: 11%
  - GAD: 2%
  - Panic disorder: 2%
  - Social anxiety disorder: 3%
  - Specific phobia: 7%
- NCS-R (2001-2003)
  - Any anxiety disorder in past year: 18%
  - GAD: 3%
  - Panic disorder: 3%
  - Social anxiety disorder: 7%
  - Specific phobia: 9%
  - PTSD: 4%
  - OCD: 1%

Grant et al., 2004  
Kessler et al., 2005

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### Anxiety disorders are costly

- Lower quality of life
- Lower work productivity
- Higher health care costs
- Economic burden in the US: >\$42 billion per year

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### Treatments for anxiety disorders

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### Evidence-based treatments for anxiety

- Pharmacological
  - Selective serotonin reuptake inhibitors (SSRI)
  - Serotonin–norepinephrine reuptake inhibitors (SNRI)
  - Benzodiazepines (BZD)
  - Tricyclic antidepressants (TCA)
  - Anti-seizure medications
  - Other: hydroxyzine, mirtazapine
- Psychosocial
  - Cognitive behavioral therapy
  - Exposure therapy
  - Psychodynamic psychotherapy
  - Acceptance-based therapies
  - Relaxation therapy

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### Approach to GAD treatment

- Step 1: Assessment, diagnosis, education
- Step 2: Low-intensity psychosocial interventions (self-help, groups)
- Step 3: High-intensity psychosocial interventions
  - CBT or relaxation
- OR
- Pharmacological treatment
  - SSRI, SNRI
  - BZD only as short-term measure during crises

NICE, 2011

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### Approach to panic disorder treatment

- First-line treatments:
  - SSRI
  - SNRI
  - TCA
  - BZD (monotherapy only in absence of co-occurring mood disorder)
  - CBT
- If first-line treatment is unsuccessful:
  - Augment
  - Switch

APA, 2009

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### Approach to PTSD

- First-line treatments:
  - SSRI
  - Exposure-based CBT
  - Eye movement desensitization and reprocessing
- BZDs effective for general anxiety and insomnia in PTSD but NOT for core PTSD symptoms (re-experiencing traumatic event, avoidance/numbing)
- Thus, BZDs are NOT recommended for monotherapy

APA, 2004,  
2009

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### Approach to OCD

- CBT (exposure and response prevention)
- SSRI
- Clomipramine (TCA)
- BZDs are NOT recommended

APA, 2007

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### Approach to social anxiety disorder

- SSRI
- SNRI
- CBT
- Psychodynamic psychotherapy
- Self-help
- BZDs are NOT recommended

NICE, 2013

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**Benzodiazepines as a treatment for anxiety disorders**

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**Efficacy of benzodiazepines individually**

- Alprazolam
  - FDA approved for anxiety disorders and panic
  - Multiple small short-term studies show efficacy in GAD
  - 2 large RCTs: efficacious for panic in short-term (8 weeks)
- Diazepam
  - FDA approved for anxiety disorders
  - Multiple small short-term studies show efficacy in GAD and panic

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**Efficacy of benzodiazepines individually**

- Clonazepam
  - Multiple small short-term studies show efficacy for panic
  - Few trials show efficacy for SAD
  - May be effective as augmentation treatment if SSRI fails for SAD
- Lorazepam
  - Few small trials show efficacy for GAD and panic

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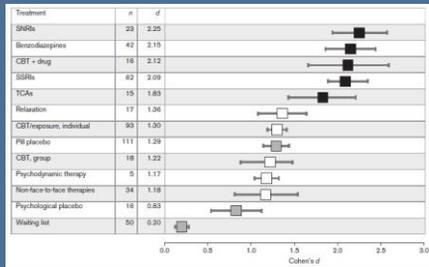
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### Efficacy of benzodiazepines

Meta-analysis for GAD, panic, and SAD



Bandelow, 2015

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### Benzodiazepines vs. antidepressants

- BZDs vs. TCAs
  - Panic meta-analysis:
    - BZDs slightly better than TCAs in response to treatment
    - BZDs much better than TCAs in dropout rates and adverse events
  - GAD: 3 studies – one found TCA better, another found BZD better, the other found similar efficacy
- BZDs vs. SSRI/SNRIs
  - No difference in response rate between diazepam and venlafaxine in one GAD study
  - Lorazepam similar to paroxetine in another GAD study
  - Clonazepam better than paroxetine in one open-label panic study

Offidani, 2013

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### Long-term benzodiazepine use

- Lack of efficacy
  - Most RCTs tested BZDs short-term efficacy (less than 16 weeks)
- Therapeutic tolerance
  - Only a small percentage of patients increase dose above concerning levels (Soumerai, 2003)
  - On average, doses lower over time (Nagy, 1989)
- Cognitive impairment
  - Meta-analysis: long-term BZD users showed impairment in multiple domains (sensory processing, psychomotor speed, non-verbal memory, visuospatial, etc.) (Barker, 2004)

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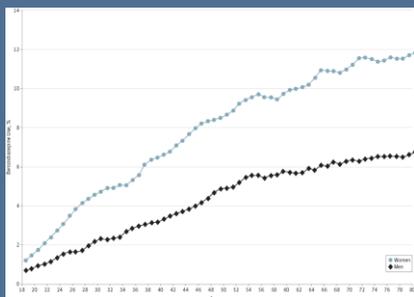
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### Benzodiazepine use in the US in 2008



Olfson, 2015



### Long-term benzodiazepine use in US

**Table 1. Prevalence of Any Benzodiazepine Use, Long-term Benzodiazepine Use, and Use of Long-Acting Benzodiazepines by Sex and Age Group in the United States in 2008\***

Variable	Mean age, y, %			
	18-35	36-50	51-64	65-80
<b>US Population</b>				
With any benzodiazepine use, y	2.6	5.4	7.4	8.7
Among men	1.7	3.7	5.3	6.1
Among women	3.6	7.1	9.2	10.8
<b>Among Persons With Any Benzodiazepine Use</b>				
With long-term benzodiazepine use <sup>b</sup>	14.7	22.4	28.0	31.4
Among men	15.6	22.8	28.4	28.8
Among women	14.2	22.2	27.8	32.6
With any long-acting benzodiazepine use, y	24.1	25.4	25.4	23.8
Among men	25.9	29.5	29.4	27.1
Among women	22.7	23.3	23.4	22.4

\*The data source was 2008 LifeLink Information Assets (LifeLink) Longitudinal/Prevalence Database, 2008 (IMS Health Inc).  
<sup>b</sup>Long-term use defined as 120 days or more supply of benzodiazepines during 2008.



Olfson, 2015



### Top 10 drugs for GAD in 2001

**Table 1. Top 10 Drugs Prescribed for Generalized Anxiety Disorder<sup>1</sup>**

Drug	%
<b>Benzodiazepine</b>	
Alprazolam (Xanax)	15
Lorazepam (Ativan)	10
Clonazepam (Klonopin)	9
Diazepam (Valium)	4
<b>Antidepressant</b>	
Paroxetine (Paxil)	12
Venlafaxine (Effexor/Effexor XR)	6
Sertraline (Zoloft)	5
Citalopram (Celexa)	4
Nefazodone (Serzone)	4
Buspirone (BuSpar)	9
Total Top 10	78
Benzodiazepine use in top 10	38
SSRI use in top 10	21

<sup>1</sup>Data from the National Disease and Therapeutic Index moving annual totals.<sup>2</sup>



**Prevalence of benzodiazepines in PTSD and OCD**

- 30% of US veterans with PTSD had BZD prescription in 2009
  - Majority of those with BZD prescription had co-morbid panic
- In one Brazilian study, 38% of participants with OCD used BZDs
  - Most participants using BZDs also were using other medications, usually an SSRI

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**Risks of benzodiazepines**

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**Mortality**

- Risk of all-cause mortality associated with sedative-hypnotics (Parsaik, 2015)
  - 43% increased risk in recent meta-analysis of 25 studies
  - Risk similar in men and women
  - 60% increased risk in BZD users
  - Risk in Z-drug users not statistically significant

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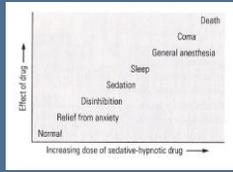
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### Benzodiazepine overdose




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### Benzodiazepine overdose

#### Rapid Recovery From Massive Diazepam Overdose

David J. Greenblatt, MD; Elaine Woo, MD; Marcia Divoll Allen, RN; Paul J. Orsulak, PhD; Richard I. Shader, MD

Two patients were hospitalized in moderately deep coma after ingestion of large doses of diazepam (500 and 2,000 mg) with suicidal intent. Neither patient experienced important complications; both recovered fully and were discharged within 48 hours. Concentrations of diazepam and its three pharmacologically active metabolites (desmethyldiazepam, temazepam, and oxazepam) were determined in multiple samples drawn during and after hospitalization. High concentrations of all four compounds were present in early samples, then declined slowly during the next one to two weeks. Rapid clinical recovery after diazepam overdose is not attributable to rapid elimination of active compounds from the body, but more likely to adaptation or tolerance to their depressant effects. (JAMA 240:1672-1674, 1978)

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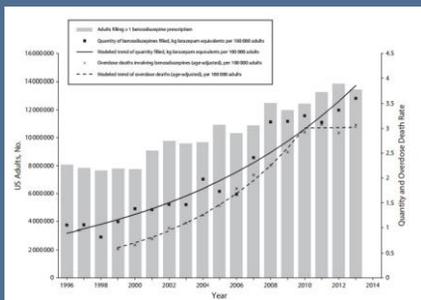
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### Benzodiazepine overdose trends



Bachhuber, 2016

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### Benzodiazepines and opioids

	Hazard ratio	95% CI
<b>BZD exposure status</b>		
None	1.00 (ref)	-
Former	2.33	2.05-2.64
Current	3.72	3.36-4.12
<b>BZD dose prescribed</b>		
>0-10	1.00 (ref)	-
>10-20	1.59	1.34-1.90
>20-30	2.27	1.86-2.79
>30-40	2.47	1.96-3.11
>40	2.93	2.29-3.76

Park, 2015

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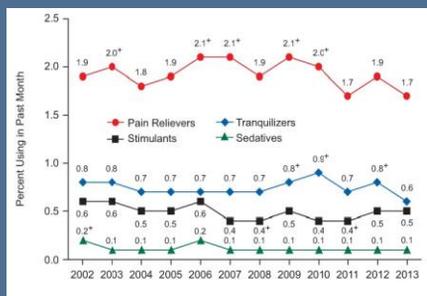
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### Past-month non-medical psychotherapeutic drug use



NSDUH, 2013

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### Risk of benzodiazepine addiction

Figure 2 Table. Percentages of Year-Before-Last Initiates Who Were Dependent on the Initiated Substance in the Past Year, by Substance: 2004-2006

Substance	Percent
Heroin	13.4%
Crack**	9.2%
Marijuana	5.8%
Stimulants*	4.7%
Cocaine (Not including Crack)**	3.7%
Alcohol	3.2%
Pain Relievers*	3.1%
Sedatives*	2.4%
Hallucinogens	1.9%
Tranquilizers*	1.2%
Inhalants	0.9%

Source: SAMHSA, 2004-2006 NSDUHS.

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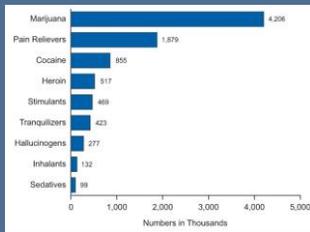
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### Drug use disorders



NSDUH, 2013

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### Benzodiazepines and cognition

- Systematic review: 5 out of 5 studies examining BZD use in Alzheimer's disease found BZDs associated with cognitive deterioration (Defrancesco, 2015)
- Recent case-control study: BZD use associated with 50% increased risk of Alzheimer's Disease (Billioti de Gage, 2015)
  - Dose response relationship found

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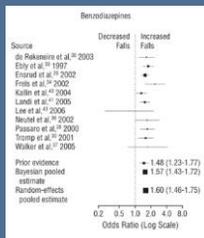
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### Benzodiazepines and falls in older adults



Woolcott, 2009

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### Benzodiazepines and hip fractures

- Systematic review: 6 out of 7 studies found association between BZD use and increased risk of hip fracture (Cumming, 2003)
  - Increased risk was 50-110%
  - Higher doses associated with increased risk
  - Those who recently started BZDs had increased risk

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### Benzodiazepine discontinuation

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### Benzodiazepine withdrawal symptoms

- Commonly observed symptoms:
  - Anxiety
  - Irritability
  - Insomnia
  - Fatigue
  - Headache
  - Muscle twitching or aching
  - Tremor
  - Sweating
  - Dizziness
  - Poor concentration

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**Benzodiazepine withdrawal symptoms**

- Less common symptoms:
  - Perceptual distortions
  - Depersonalization
  - Hallucinations
  - Paresthesias
  - Formication
  - Sensory hypersensitivities
  - Delirium
  - Seizures

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**Benzodiazepine withdrawal characteristics**

- Factors that increase withdrawal severity
  - Longer duration of treatment
  - Abrupt withdrawal
  - Short half-life BZDs
  - Dose?
- Prevalence of BZD withdrawal
  - Need to distinguish from rebound anxiety
  - Likely 50% of long-term users
- Duration of withdrawal symptoms
  - Usually 2-3 weeks
  - Can last up to 10 weeks

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**Benzodiazepine discontinuation setting**

- ASAM placement criteria
  - History of severe withdrawal symptoms
  - Risk of severe withdrawal symptoms, seizures, or other medical complications
  - Current withdrawal symptoms
  - Comorbid psychiatric symptoms
  - Patient supports to assist with outpatient care

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### Discontinuation approach

- Medication options:
  - Taper with same BZD
  - Switch to long half-life BZD, then taper
  - Phenobarbital
- Length of taper:
  - No RCTs comparing different lengths
  - Large range of lengths in BZD discontinuation studies
  - 10-25% reduction per week
  - Smoother at start, more difficult towards end
  - Individualize but set clear goals

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### Adjunctive medications

- Melatonin - sleep
- Trazodone - sleep
- Valproate – GABAergic
- Very little evidence for other medications
- Consider antidepressant or non-BZD hypnotic for underlying disorder

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### Psychosocial interventions

- Several meta-analyses have found that adding a psychosocial intervention improves outcomes
  - CBT best studied
    - Psychoeducation
    - Relaxation training
    - Cognitive restructuring

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**Other interventions**

- Letter from general practitioner and booklet with self-help strategies was effective in 3 studies (Parr, 2008)
- Recent RCT using pharmacy-delivered self-help booklet and 21 week tapering protocol was effective (Tannenbaum, 2014)

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**Outcomes**

- With gradual dose reduction, successful discontinuation in 2/3 of patients
- Predictors of unsuccessful discontinuation (Rickels, 1998)
  - History of substance use problems
  - Panic disorder
  - Higher pre-taper anxiety/depression
  - Personality pathology
- Relapse is common
  - 27-74% in 3 different studies over 2-3 year period

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