Sedative-Hypnotic Use Disorder

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Objectives

1. Review the epidemiology of sedative-hypnotic use disorder including escalating prescribing practices
2. Outline when and why the use of sedative-hypnotics may be of concern and problematic
3. Review the management and treatment approach to individuals with physiological dependence on sedative-hypnotics

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Benzodiazepines (BZD): mechanism of action

Enhance GABA activity

- GABA is the major inhibitory neurotransmitter of the CNS, it decreases neuronal excitation
- $GABA_A$: depressant effect
- Benzodiazepine (Bz) receptors:
  - Bz_1: Sleep-inducing effect
    - Site of action of zolpidem
  - Bz_2 and Bz_3 : antiseizure, antianxiety and muscle relaxation effects

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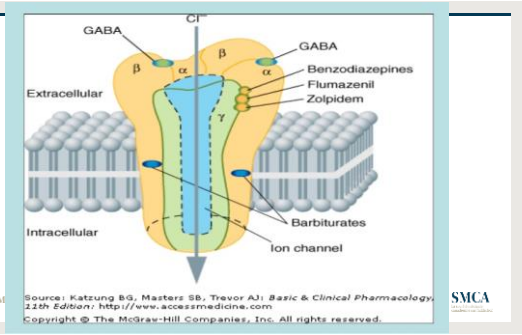

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

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BZD - Therapeutic uses

- Anticonvulsant
- Muscle Relaxant
  - Cerebral palsy, dystonia
- Amnesia with Sedation
  - Peri-operative or medical procedures
- Alcohol withdrawal
- Insomnia
- Acute agitation

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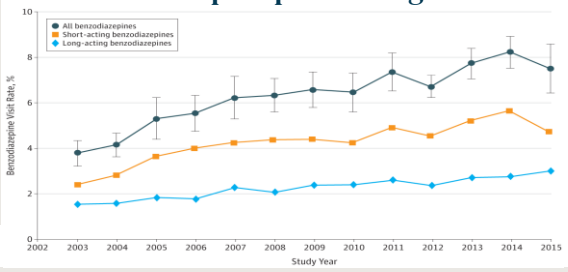
Benzodiazepine prescribing Rates



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Sedative-,hypnotic-, or anxiolytic- related disorders

Drug Class	Generic name	Trade name	Street names
Benzodiazepines	Alprazolam	Xanax®	Z-bars, bars
	Clonazepam	Rivotril®	K-pins
	Diazepam	Valium®	Vs, tranks, downers
	Flurazepam	Dalmane®	tranks, downers, nerve pills
	Lorazepam	Ativan®	nerve pills, tranks, downers
	Temazepam	Restoril®	rugby balls, tems, jellies
	Triazolam	Halcion®	Up Johns, tranks, downers
Non-benzodiazepine sleep medication	Zopiclone	Imovane®	Z-drug
Barbiturates	Pentobarbital	Nembutal®	barbs, M&Ms, nembies
	Amobarbital	Amytal®	angels, blue heavens

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Epidemiology

Past-Year Use of Sedatives and Tranquilizers in Canada:

- General population (age 15+): 9.1%
- Youth (age 15–24): 4.0% for 2011
- Adults (age 25+):10.1%
- Seniors (age 65+): 14.4% in 2011
- Gender: females (12%) males (5.9%)

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Sedative-,hypnotic-, or anxiolytic- related Use Disorder

- Prevalence:
  - 12-17 year olds: 0.3%
  - 18+: 0.2%

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BZD - Therapeutic uses - Psychiatric

- Severe acute anxiety

*** Not first line treatment for any chronic anxiety disorder**

- Severe generalized anxiety disorder unresponsive to other treatments
- Panic disorder, social phobia
- Adjunctive treatment of depression, bipolar affective disorder and schizophrenia

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Benzodiazepines: Why taper?

- Usually not because patient "addicted"
- **Possible benefits of tapering**:
  - more alert, energetic
  - better able to make positive life changes
  - not need drug anymore
  - avoid future adverse effects
- High risk if concomitant use of other depressants
- Need to be aware of comorbid medical conditions and consider physiological stress to patients of tapering, patients with chronic medical conditions experience withdrawal more severely

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BENZODIAZEPINES: ADVERSE EFFECTS

ACUTE

- Sedation (depressant)
- Decreased respiratory drive
- Overdose (with other drugs - esp. alcohol and opioids)
- Disinhibition

CHRONIC

- Decreased Neurocognition
- Physiologic Dependency: Tolerance, Withdrawal
- Addiction (Intoxication Syndromes)

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WHEN IS BZD USE PROBLEMATIC?

Risk Factors for BZD abuse

1. **Comorbid substance use disorders**
   a. 80% of BZD abuse part of polydrug abuse
   b. 40% of alcohol abuse
2. **Psychiatric comorbidities:**
   (Personality Disorder, chemical coping)
3. **Genetic vulnerability** (tolerance)
4. **Environmental factors**
5. **Pharmacodynamics of BZD** (most reinforcing BZD)

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RISK EVALUATION & MANAGEMENT STRATEGIES

1. Assessment of Risk Factors
2. Treatment Goals
3. Treatment Agreement
4. Care Plan
5. Medical Monitoring:
   - Reassess comorbidites & Diagnoses
   - How is Functional Status Progressing?
   - Progress in Behavioural Therapies ?
6. Management: Have a Plan to manage Complications

Benzodiazepines—Side Effects, Abuse Risk and Alternatives Longo et al. Am Fam Physician. 2000 Apr 1;61(7):2121-2128.

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ADDRESSING PROBLEMATIC BDZ USE:

- Other sedating drugs
- COPD, sleep disorders
- Elderly (esp long acting)
- Liver dysfunction
- Comorbidities are the rule, not the exception
- If prescribing: careful assessment, care plan, Rx goals

medical monitoring management:

- Have a plan to reassess ++ & manage complications
- Should clearly state intended short term nature and dependence potential

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Benzodiazepine withdrawal

- The clinical picture looks like a rebound hyperexcitability with:
  - body changes in a direction opposite to that seen with the first administration of the drug
- **Time course**:
  - ***Acute syndrome***:
    - For Short-acting BZDs (lorazepam, oxazepam), 3 to 7 days
    - Longer for longer acting drugs (e.g. diazepam)
  - ***Protracted withdrawal***:
    - less intense symptoms for 3-6 months

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Benzodiazepine withdrawal

- ***Symptoms are likely to include***:
  - Headaches and anxiety (80%)
  - Insomnia (70%)
  - Tremors (60%)
  - Fatigue (60%)
  - Perceptual changes
  - Tinnitus
  - Sweating
  - Decrease concentration
- ***Abrupt abstinence after higher doses could cause delirium and seizures***

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BZD withdrawal

- **Factors influencing severity**:
  - Duration of drug use
  - Doses used
  - Drug half-life
  - Individual personality style
  - Expections from patient and physician

Khong E, Sim MG, Hulse G.Benzodiazepine Dependence. *Aust Fam Physician.* 2004 Nov;33(11):923-6

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Treatment of BZD withdrawal

- Good physical exam / screening investigations
- Consider inpatient detoxification (hospital setting)
  - If using diazepam ≥ 60 mg / day OR unknown dosage
- If outpatient, taper BZDs over 1 to 6 month-duration
  - On average, taper over 8 to 12 weeks
  - If too long, withdrawal becomes 'the morbid focus of the patient's existence'
- Either use the same BZD for taper **or** convert to long-acting (e.g. diazepam)

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BDZ (Duration Action)	Onset of effect	Equivalence to 5 mg diazepam	Elimination $t_{1/2}$	Active Metabolites
Short <12h				
Alprazolam (Xanax)	fast	0.25-0.5	6-14	Yes
Triazolam (Halcion)	fast	0.125-0.25	1.5-5.5h	No
Oxazepam (Serax)	slow	8-12	6-12h	No
Medium (10-15h)				
Lorazepam (Ativan)	fast	0.5-1	10-20h	No
Temazepam (Restoril	intermediate	5-17	6-24	Yes
Long >24h				
Flurazepam (Dalmane)	fast	7.5-15	50-100h	Yes
Diazepam (Lorazepam)	fast	5 mg	20-100h	Yes
Clonazepam (Rivotril)	intermediate	0.5-1	17-50h	No
Chlordiazepoxide (Librium)	intermediate	10-25	7-25h	Yes

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Treatment of BZD withdrawal

- **Converting to diazepam**

Table II. Some equivalents to diazepam 10 mg for subsequent tapered withdrawal[a]

Benzodiazepine	Equivalent dose (mg)
Chlordiazepoxide	30
Loprazolam	2
Lorazepam	1
Lormetazepam	2
Nitrazepam	10
Oxazepam	30
Temazepam	20

a Diazepam is usually taken in three or four fractions during the day – morning, afternoon, evening and before going to bed.

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Treatment of BZD withdrawal

- **Treatment agreement on schedule and process**
  - « we agree that the goal is zero BZD »
  - Weekly dispensing of medication if necessary
  - No BZD PRN during the taper
- **Close monitoring of the patient during the taper**
  - Monitor increase alcohol consumtion / other drug use
- **Non-pharmacological intervention for anxiety**
  - Patient to keep a diary of symptoms and triggers
  - CBT (targeting underlying condition)
  - Physical exercise
  - Relaxation techniques
  - Sleep hygiene

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Treatment of BZD withdrawal

- **Potential pharmacological agents to consider**:
  - Carbamazepine: some evidence, but not enough to systematically recommend
    - 200 to 800 mg / day
  - Valproic acid (250 mg TID) / Gabapentin / Trazodone
  - SSRIs: if there is an underlying untreated anxiety / mood disorder
    - *Was the patient depressed or anxious before the dependence?*
  - ***Remember***:
    - There is no medication approved for chronic insomnia

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Basic principles in primary care

- Psychoeducation
- Techniques to deal with anxiety and insomnia
- Letter from the GP suggesting ↓ in the use of BZD
- Acknowledge that withdrawal could be stressful
- Advise changes in lifestyle such as physical activity
- Avoid stimulants and alcohol
- Refer to support group
- Refer to specialized program / agency

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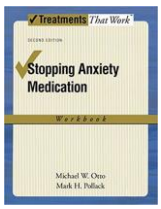
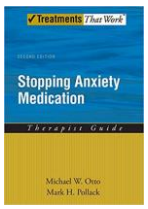
Treatments That Work!





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DISCONTINUATION

Symptom Recurence/Relapse	Common Anxiety or Insomnia Can present rapidly or slowly Consider alternative treatment
Rebound	• Occurs within hours-days • Qualitatively more intense • Transiently worse than before benzo initiation • Short duration and self limited
Pseudowithdrawal	• Overinterpretation of symptoms • Expectation of withdrawal leads to experiencing abstinence symptoms • Expectation created by physicians and media
True Withdrawal	• Symptoms and signs related to physiological dependence • Results from a reversal of neuroadaptive changes in the CNS that were induced by chronic Benzo use

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Resources

- **benzo.org.uk** by Professor Heather Ashton
  - information about the effects that BZDs have on the brain and body and how these actions are exerted
  - Detailed suggestions on how to withdraw after long-term use and individual tapering schedules for different BZDs are provided
- http://www.open-pharmacy-research.ca/
  - Deprescribing algorithm
- Deprescribing.org

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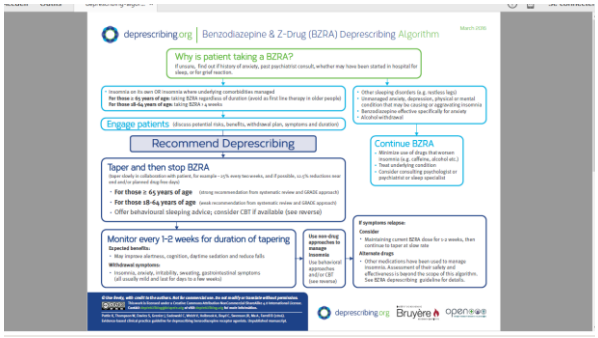

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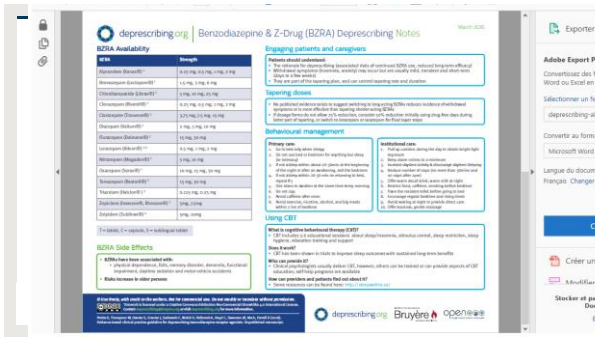

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