# Benzodiazepines: Uses and Risks

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# Overview benzodiazepines

- Examples of benzos and benzo like drugs
- Indications for benzos
- Pharmacology of benzos
- Side effects and contraindications
- Benzo withdrawal
- Benzo tapers

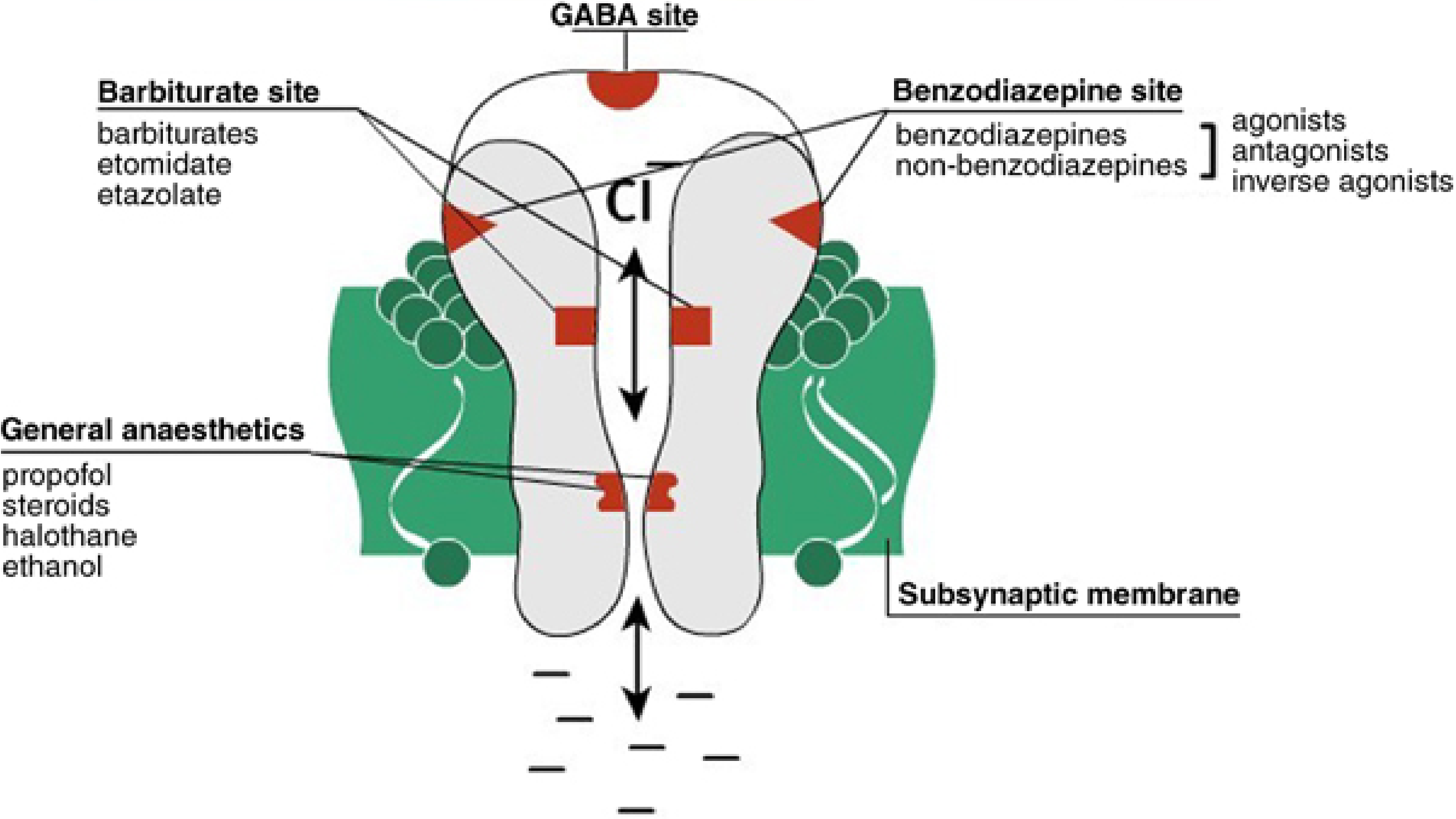
# Sedative/Hypnotics

- Benzodiazepines
- Alcohol
- Z-drugs (Benzo-like sleeping aids)
- Barbiturates
- GHB
- Propofol
- Some inhalants
- Gabapentin? Pregabalin?

# Examples of benzodiazepines

- Midazolam (Versed)
- Triazolam (Halcion)
- Alprazolam (Xanax)
- Lorazepam (Ativan)
- Temazepam (Restoril)
- Oxazepam (Serax)
- Clonazepam (Klonopin)
- Diazepam (Valium)
- Chlordiazepoxide (Librium)

# Sedatives: gaba stimulating drugs have incomplete "cross tolerance"



# Effects from sedative (Benzo) use

- Euphoria/bliss
- Suppresses seizures
- Amnesia
- Muscle relaxation
- Clumsiness, visio-spatial impairment
- Sleep inducing
- Respiratory suppression
- Anxiolysis/disinhibition

# Tolerance to benzo effects?

- **Effects quickly diminish with repeated use (weeks)**
  - Euphoria/bliss
  - Suppresses seizures
- **Effects incompletely diminish with repeated use**
  - Amnesia
  - Muscle relaxation
  - Clumsiness, visio-spatial impairment
  - Seep inducing
- **Durable effects with repeated use**
  - Respiratory suppression
  - Anxiolysis/disinhibition

# If you understand this **pharmacology** you can figure out the rest...

- ***Potency***
  - 1 mg diazepam <<< 1 mg alprazolam
- ***Duration*** of action
  - Half life differences
- ***Onset*** of action
  - Euphoria, clinical utility in acute situations
- Active ***metabolites***
  - Liver safety, self tapering properties

BENZODIAZEPINE (BZ) COMPARISON CHART www.RxFiles.ca Brent Jensen BSP Jul

| Name Generic -TRADE | Equivalent Dose/Class | Peak Level/ ABSORPTION RATE | Average Half-life (hr) | Active Metabolites | Comments (√ = therapeutic use) | INITIAL & MAX DOSE | USUAL DOSE RANGE | $ /Month |
|---|---|---|---|---|---|---|---|---|
| **SHORT ACTING:** more rebound anxiety effect & withdrawal reactions, **better sedative/hypnotic**; preferred over long acting in **elderly** (**less accumulation**) & in patients with **liver disorders** (easier metabolized) | | | | | | | | |
| **Alprazolam** -XANAX (0.25,0.5); (1mg tab, TS 2mg) | D 0.5mg Pregnancy category Triazolo | 1-2 hr *Medium* | 12 (9-20) | Minor Oxidation # | √Anxiety, **Panic attacks** Severe **withdrawal** & some ? antidepressant effect DIs: **Level ↑ by:** diltiazem, Luvox, ketoconazole, grapefruit juice, nefazodone, Prozac, ritonavir; **↓ by:** theophylline. | 0.25mg 4-10mg | 0.25mg po tid 0.5mg po tid | 1 1 |
| **Bromazepam** -LECTOPAM (1.5, 3, 6mg tab) | D 3mg 2-Keto | 1-4 hr *Medium* | 20 (8-30) | Minor Oxidation | √Anxiety ? May exacerbate depression | 3mg 30-60mg | 3mg po hs 6mg po hs | 1 1 |
| **Lorazepam** -ATIVAN (0.5,1,2mg po tab; 0.5,1,2mg sl tab; 4mg/ml amp) | D 1mg 3-Hydroxy | PO 1-4 hr SL/IM 1 hr IV 5-10 min *Medium* | 15 (8-24) | **None** Conjugation # | √ **Anxiety**, Preanesthetic; Other: **sedative**, muscle relaxant, alcohol withdrawal; acute **mania**; **Fewer DI's**, √Status epilepticus - slower onset but longer duration vs diazepam; IM well absorbed | 0.5mg 10mg | 0.5mg po tid 1mg po tid 2mg po tid | 1 1 1 |
| **Oxazepam** -SERAX (10,15,30mg tab) | D 15mg 3-Hydroxy | 1-4 hr *Medium* | 8 (3-25) | **None** Conjugation | √ Anxiety, **alcohol withdrawal** Other: **sedative** Less affected by liver dysfunction; **Fewer DI's** | 10mg 120mg | 15mg po hs 30mg po hs 30mg po tid | 1 1 1 |
| **Temazepam** -RESTORIL (15,30mg cap) | X 10mg 3-Hydroxy | 2-3 hr *Medium* | 11 (3-25) | **None** Conjugation | √ **Sedative/hypnotic**; Other: anxiolytic May delay but not suppress REM sleep **Fewer DI's** | 15mg 60mg | 15mg po hs 30mg po hs | 1 1 |
| **Triazolam** -HALCION (0.125,0.25mg tab) | X 0.25mg Triazolo | 1-2 hr *Rapid* | 2 (1.5-5) | **None** Oxidation | √ Sedative/**hypnotic**; DI's as per alprazolam **Behavioral disturbances in elderly** **Prone to withdrawal / rebound effects** | 0.125mg 0.5mg | 0.125mg po hs 0.25mg po hs | 1 |
| **LONG ACTING:** less rebound symptoms; better choice **when tapering off of BZs** (e.g. clonazepam/diazepam); **withdrawal may be delayed 1-2 wk for 2-Keto group; bedtime dose option for hypnotic & anxiolytic effect** | | | | | | | | |
| **Chlordiazepoxide** (5,10,25mg cap) -LIBRIUM | D 25mg 2-Keto | 1-4 hr *Medium* | 100 | Yes Oxidation | √ Anxiety, preanesthetic, **alcohol withdrawal** Other: sedation; Slower onset vs diazepam | 5mg 200-400mg | 25mg po tid 50mg po tid | 2 3 |
| **Clonazepam** -RIVOTRIL (0.5,1,2mg tab) | D 0.25mg Nitro | 1-4 hr *Rapid* | 34 (19-60) | **None** Oxidation & Nitro reduction | √ Anticonvulsant, **Panic** attack Other: **sedative**, social phobia, akathisia, **acute mania**, restless leg syndrome & neuralgic pain. Used for BZ withdrawal | 0.25mg 10-20mg | 0.5mg po tid 1mg po bid 2mg po tid | 1 2 2 |
| **Clorazepate** -TRANXENE (3.75,7.5,15mg cap) | D 10mg 2-Keto | 0.5-2 hr *Rapid* | 100 Inactive until Metabolized | Yes Oxidation | Hydrolyzed in GI → ↓ clorazepate level by **antacids** √ Anxiety, panic, alcohol withdrawal, seizures | 3.75mg 60-90mg | 3.75mg po bid 7.5mg po bid 15mg po bid | 1 1 2 |
| **Diazepam** -VALIUM (2,5,10mg tab; 10mg/2ml amp; 5mg/ml rectal gel; 10mg/2ml emulsion inj DIAZEMULS) | D 5mg 2-Keto | PO 1-2 hr IM 1hr IV 8 min *Rapid* | 100 | Yes Oxidation | √Anxiety, **muscle relaxant**, seizures, **alcohol withdrawal** & preanesthetic; Other: sedative Quicker onset & **↓ duration** of action vs lorazepam, IM causes pain; **Diazemuls®** IV better tolerated. Used for BZ withdrawal | 2mg 40mg | 2mg po tid 5mg po tid 10mg po tid | 1 1 1 |
| **Flurazepam** -DALMANE (15,30mg cap) | X 15mg 2-Keto | 0.5-1 hr *Rapid* | 100 (40-250) | Yes Oxidation | √ Sedative/**hypnotic**; Quick onset but **accumulates** →**hangover** →confusion, etc. | 15mg 60mg | 15mg po hs 30mg po hs | 1 1 |
| **Nitrazepam** -MOGADON (5,10mg tab) | D 2.5mg Nitro | 0.5-2 hr *Medium* | 30 (15-48) | None Nitro reduction | √ Sedative/**hypnotic**, myoclonic seizures | 5mg 10mg | 5mg po hs 10mg po hs | 1 1 |

**Side effects:** drowsiness, dizziness, ataxia, **dependence**, CNS depression, disorientation, **psychomotor impairment**, confusion, aggression, excitement, **↑ falls & vehicle accidents in elderly** & anterograde amnesia.
Tolerance to sedative/hypnotic, muscle relaxant & anticonvulsant, but less **tolerance** for the anxiolytic & antipanic effects. No **cross-tolerance** with buspirone & SSRI'S; as well often lacks cross-tolerance with alprazolam

# Duration

- High variability half life between benzos

  Midazolam… <1 hour, good for anesthesia

  Lorazepam… ~8 hours, good for panic attacks specific phobias and agitation

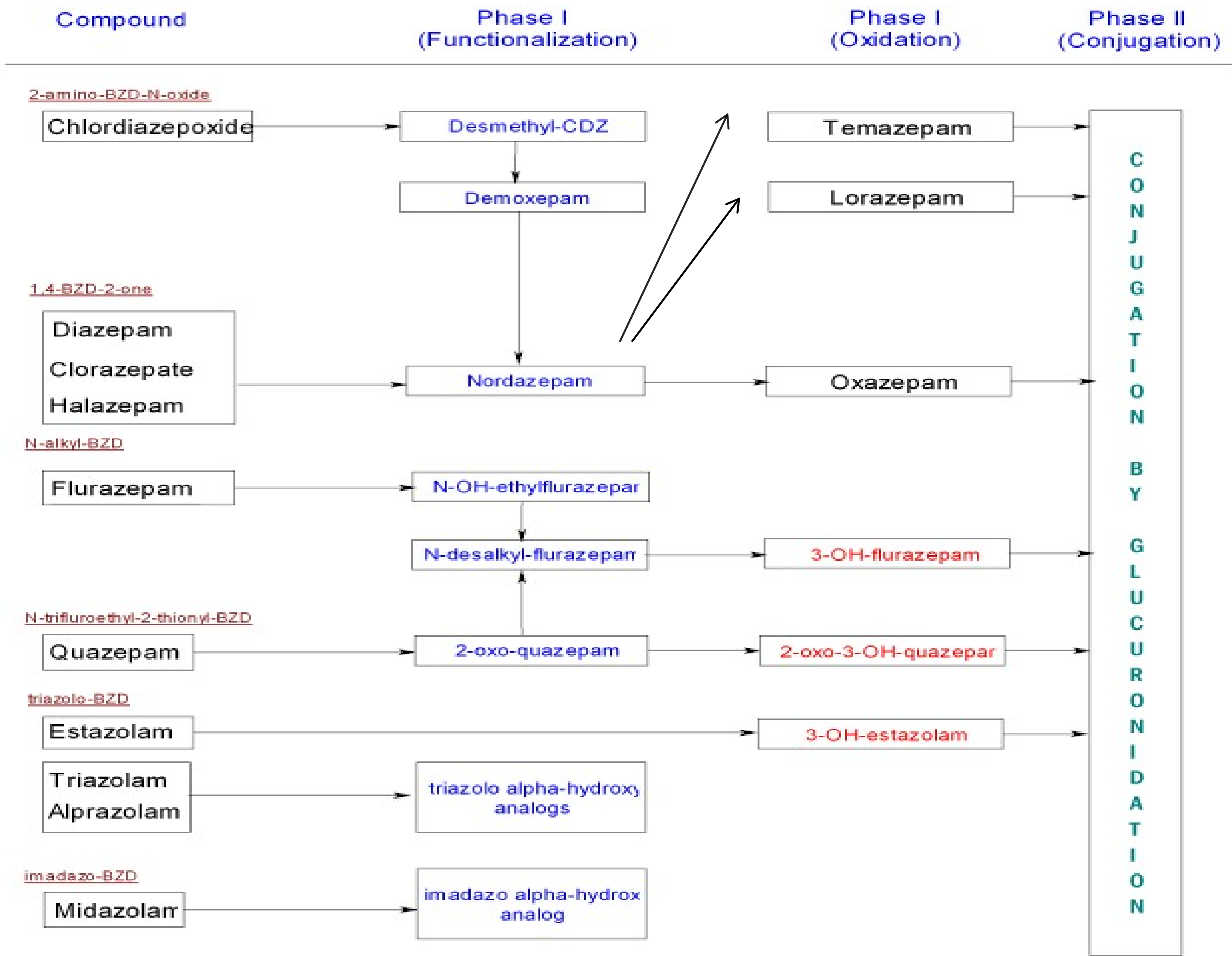
  Diazepam… >1 day, good for alcohol detox and preventing alcohol wd seizures

# Active metabolites

- Certain benzos (Valium, Librium) are metabolized to active compounds.
- These “active metabolites” then also need to be broken down by the liver
- Active metabolites make the drug long acting and “self tapering,” a good thing for detox
- People with liver disease and elderly do not effectively clear the active metabolites and can be sedated for days/weeks

    Diazepam (valium) and chlordiazepoxide (Librium) have active metabolites

# Active Metabolites



# Onset of action

- Onset is different from duration or half life!
  - Diazepam acts more quickly than lorazepam, but also has a longer duration
- Lorazepam (Ativan) kicks in fast if given IV but slow if taken orally
- Rapid onset is good for….
  - Breaking a seizure
  - Panic disorder
  - Getting high

# Benzo variables

- Potency differences
- Time of onset
- Duration
- Active metabolites

# Commonly used benzos and why

- Clonazepam for **General/social anxiety, adjustment**
  - Longer action, less euphoria
- Lorazepam for **panic/phobias (PO), agitation (IV)**
  - Medium onset, shorter half life, less euphoria
- Diazepam for alcohol **detoxification**
  - Self tapering, rapid onset, long half life– but off limits in patients with cirrhosis!
- Midazolam for **anesthesia**
  - Very short half life, easy to titrate, IV
- Temazepam for **sleep**
  - Half life appropriate for 8 hour sleep, less euphoria

# Jennifer’s Case

Table 2. Benzodiazepine Visit Rate by Indication

| Indication[a] | Unweighted No. of Benzodiazepine Visits, 1 Million | | Unadjusted Estimated Benzodiazepine Visit Rate, % (95% CI) | | | |
|---|---|---|---|---|---|---|
| | 2003 (n = 919) | 2015 (n = 1672) | 2003 | 2015 | *P* Value[b] | Adjusted OR (95% CI)[c] |
| Anxiety and depression | 12.8 | 23.7 | 26.6 (22.6-31.0) | 33.5 (28.8-38.6) | .003 | 1.43 (1.05-1.95) |
| Back and chronic pain | 4.9 | 15.1 | 3.6 (2.6-4.9) | 8.5 (6.0-11.9) | <.001 | 2.65 (1.65-4.26) |
| Insomnia | 2.1 | 3.4 | 26.9 (19.3-36.0) | 25.6 (15.3-39.6) | .72 | 0.94 (0.46-1.92) |
| Neurologic[d] | 3.3 | 5.0 | 6.8 (4.8-9.5) | 8.7 (6.2-12.1) | <.001 | 1.37 (0.85-2.22) |
| Other | 9.1 | 24.5 | 1.8 (1.4-2.2) | 4.4 (3.7-5.2) | <.001 | 2.50 (1.90-3.29) |

Abbreviation: OR, odds ratio.

[a] A visit can be ascribed to multiple diagnoses.

[b] Calculated using $\chi^2$ trend test.

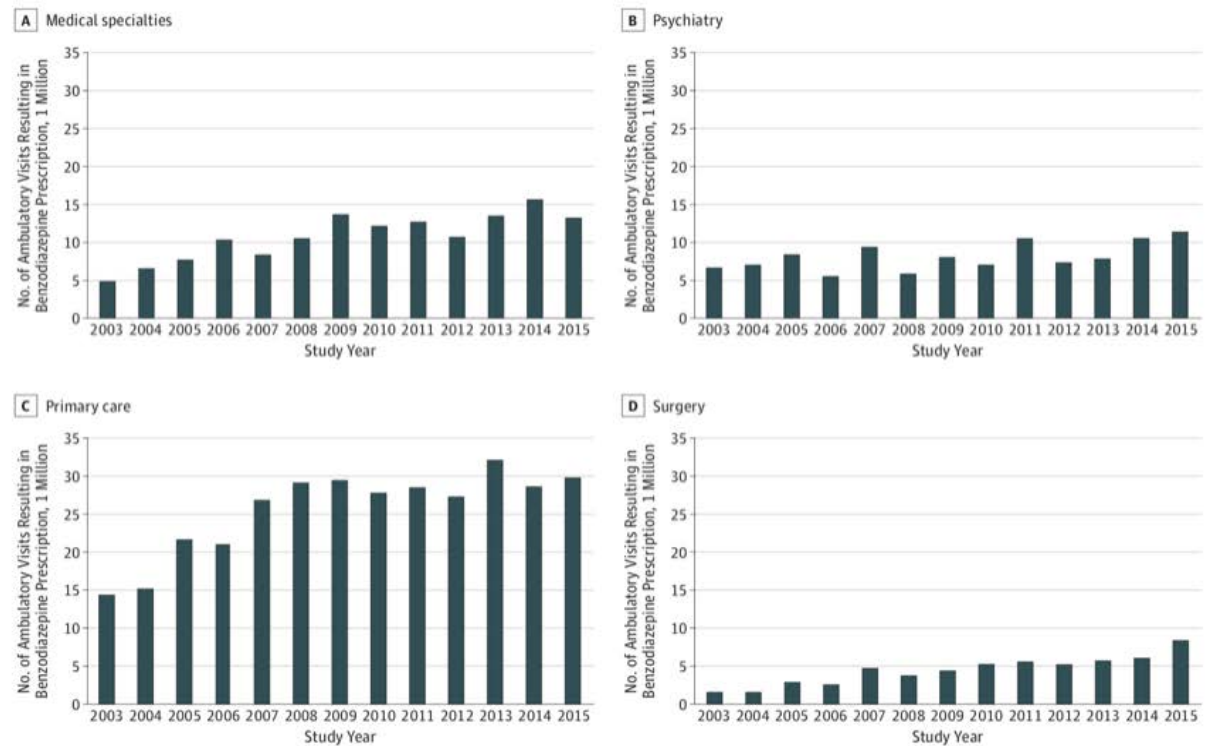
[c] Adjusted for age, sex, race, insurance, region, and location.

[d] Includes headache, seizures, vertigo, and movement disorders.



BZD increase driven by primary care for back pain, anxiety and "other"

Figure 2. Benzodiazepine Visits by Specialty



# Benzos are falling out of favor….

- Don't use benzos long term for anxiety
- Don't use benzos long term for sleep
- Don't use benzos for alcohol detox outside of a controlled setting
- Don't use benzos chronically for seizures
- Don't use benzos for back pain

- Some never use benzos as an outpatient medicine
- Some use only rare doses (five/year), or daily doses over short periods

# Why are benzos are falling out of favor?

- Benzos prevent learning coping skills, making you rely on a pill instead
  - You don’t learn how to fall asleep on your own
  - You don’t learn to manage your anxiety on your own
  - You get “stuck” in your pill use and don’t progress

# Commonly used benzos and why

- Clonazepam for **General and social anxiety**
  - Longer action, less euphoria
- Lorazepam for **panic/specific phobia**
  - Medium onset, shorter half life, less euphoria
- Diazepam for alcohol **detoxification**
  - Self tapering, rapid onset, long half life– but off limits in patients with cirrhosis!
- Midazolam for **anesthesia**
  - Very short half life, easy to titrate, IV
- Temazepam for **sleep**
  - Half life appropriate for 8 hour sleep, less euphoria

# The most important contraindication to benzodiazepine use?

POLL!

# Contraindications

- **Elderly**
- Opioid use
- Respiratory insufficiency
- Pediatric
- Cognitively impaired
- Boarderline personality disorder
- Addiction (use with caution)
- Learning or therapy
- Driving, using machinery
- Use with alcohol

# Use of benzos in elderly associated with falls, hip fractures and death!

# Cary’s Case

# Benzos and Addiction

- Most addicts who use benzos are not addicted to them
  - Benzos useful for mitigating other drugs' toxicity
    - Coming down from methamphetamine
    - Boosting opioids
    - Bridging WD between opioid intoxications
- Benzos are not that addictive
- A true benzo addict is incredibly complex and challenging: risk to themselves and others

Pts with benzo addiction are notoriously poor historians, and unreliable pill takers

They are not lying!
They just don’t remember

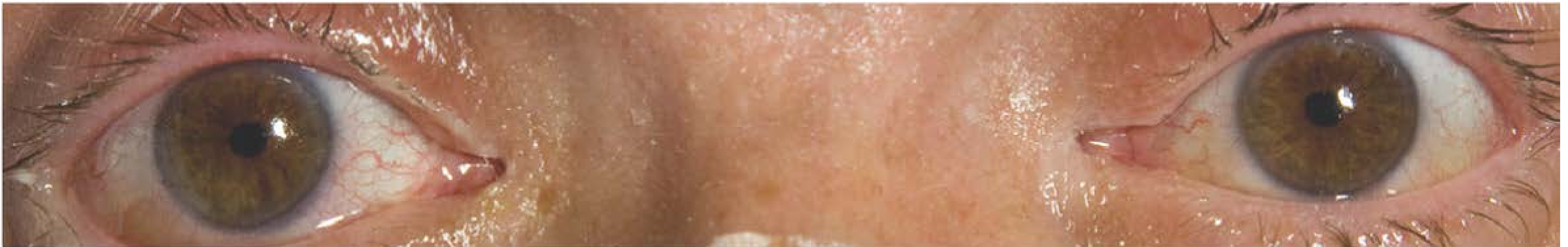
# Organ toxicity from benzos?

POLL!

# Organ toxicity from benzos?

- **Almost NO organ toxicity**
- Contrast that to many of the “safer” alternatives (quetiapine olanzapine)

# Which person is more likely on benzos?



# What else dilates pupils?

- Anticholinergics
- Opioid withdrawal
- Stimulants
- Dissociatives
- Darkness

- …And some people just have large pupils

# Melanie’s Case

# Mental status benzo *intoxication*

- Emotional lability
- Rambling tangential
- Overly disclosing
- Ataxia, clumsiness
- Slowed slurred speech
- Dilated pupils

# Facial bruises from falls are a sign of benzo intoxication

When you determine a patient to be intoxicated on benzos, you have one responsibility, what is it?

POLL!

Assure safe transit home

Not just car keys!

Will they be vulnerable on a bus?

Car accidents, falls, victims of thefts or assaults, getting lost or losing something

Interviews with patients on benzos can be frustratingly circular and nonproductive.

You might find yourself repeating the same conversation every time and not "getting anywhere"

You may need to interrupt them, and end the conversation

Write down anything important

You might need to be rude to get out of the room

BZD OD deaths

These are probably mixed overdoses

Opioid rates many times (>10X) higher

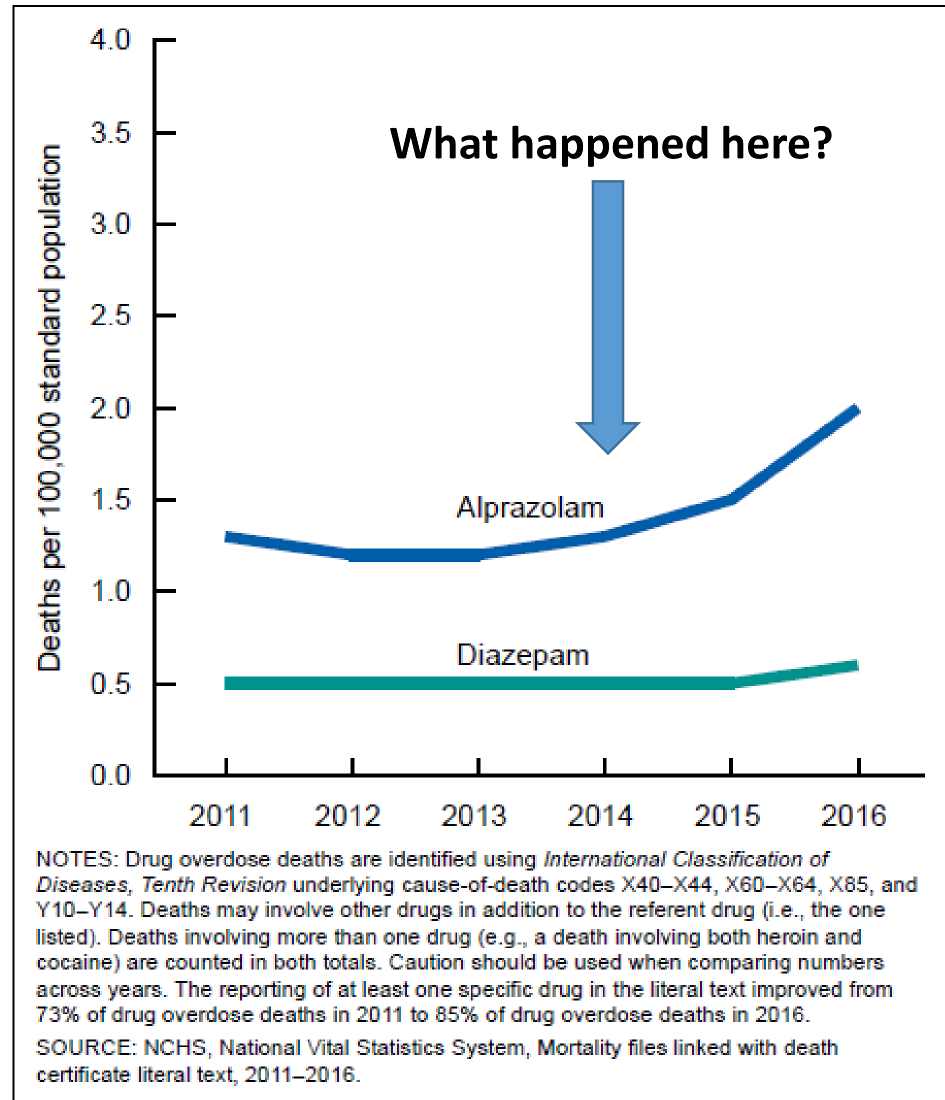
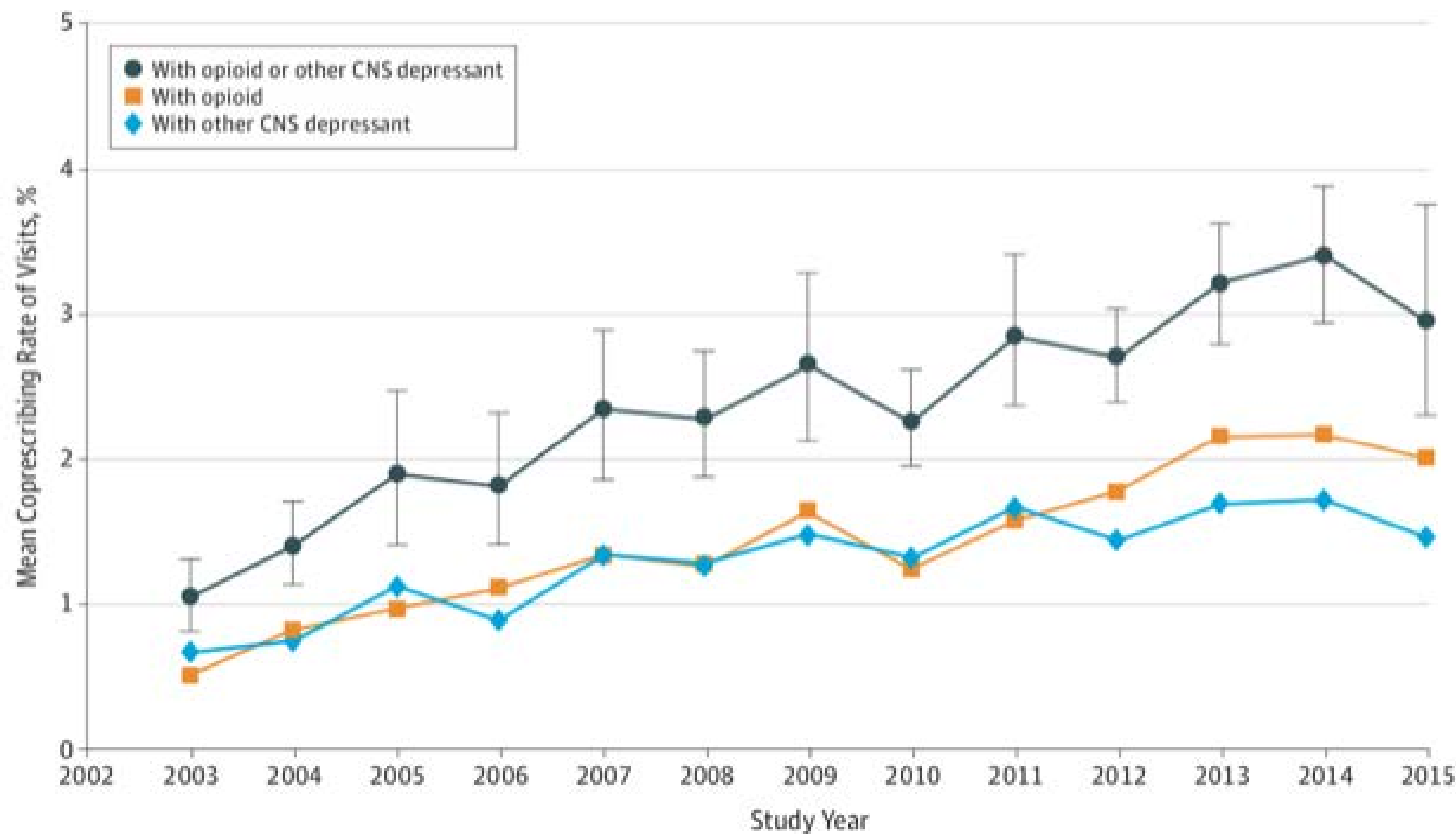



**Figure 2. Age-adjusted rates for drug overdose deaths involving selected benzodiazepines, 2011–2016**

National Vital statistic report
Vol 67, no 9 2018

Figure 3. Coprescribing Rate for Benzodiazepines With Opioids and Other Central Nervous System (CNS) Depressants




JAMA Network Open. 2019;2(1):e187399. doi:10.1001/jamanetworkopen.2018.7399

# Benzo Overdose

- Therapeutic index is very high
- Main risk is trauma/accidents
- Dangerous overdoses are coingestions (etoh, opioids)
- Support/monitor the patient
- Intubate if necessary
- Reversal of opioids with naloxone
- Reversal of benzos with flumazenil

# Common nonbenzo sedatives

- Carisoprodol, “Soma” or pro-meprobamate.
  - Barbiturate
- Butalbatol, “Fiorinol”
  - Barbiturate
- Phenobarbitol
  - long acting non-euphoric barbiturate used for tapers
- Propofol– cross tolerant with benzos
- GHB “Xyrem”
  - Powerful short acting sedative
- “Z drugs”:  zolpidem, eszopiclone, zaleplon
  - Ambien lunesta sonata
  - Mild benzo-like drugs for sleep



- Alcohol!

# Cautions with z-drugs

- Falls in hospital
- Falls at home
- Hip fracture
- Car accidents the next morning
- Amnesia during the night

POLL!

# Online synthetic benzos

- Available on the dark web *e.g.*
  - Etizolam
  - Flubromazolam
  - Clonazolam
- Recall that much street “alprazolam” is actually fentanyl
- Some may not trigger a bzd screen

Benzo Cessation Syndromes

Recurrence

Rebound

Withdrawal

# Lucinda’s Case

# Benzo withdrawal

- True benzo withdrawal is life threatening, requires close monitoring and detoxification
- Seizures, including status epilepticus
- Delirium and psychosis
- May start one week after last dose and continue for weeks
- Medical complications of withdrawal, like pneumonia

# Likelihood of true withdrawal

- Past withdrawal (including seizure)
- Short acting meds
- Concomitant heavy alcohol use
- Concomitant medical illness
- High dose

# Risk assessment for withdrawal

- Benzo exposure sufficient for physiologic dependence is highly variable!
  - 6 months daily use moderate dose
  - 3 months daily use 3X normal dose
  - Any duration in an alcohol/barbiturate dependent patient

# Post cessation anxiety recurrence

- People who love benzos have anxiety disorders
- Benzos only hide the anxiety disorder– it is still there waiting to return after benzos
- While on benzos they don't learn appropriate coping mechanisms
- After benzos stopped, the insomnia and anxieties return
- This is universal and very distressing to benzo patients.

# Benzo rebound anxiety

- Recurrence of anxiety symptoms *with a vengeance*
- If before benzos the patient had 1 panic attack a week, after benzos they will have panic attacks daily for a few weeks
- Reassure them that their anxiety will calm down in a few weeks

Benzo detox

Optimize non-bzd treatment for anxiety and counsel al patients

No hx addiction

Failed first attempt

Benzo addiction

Leave bzd the same and slowly decrease by 10% increments over months

Change bzd to long activing, shorten prescription duration, increase visit frequency, and try again

Inpatient therapy at a facility with medical detox; often require commitment; may want to restrict rpoviders

# Summary

- Benzos are sedative drugs with characteristic effect
- Benzos can be helpful for select conditions, but usually avoid for ongoing prescriptions
- Understand benzos based on their pharmacologic properties
- Identify benzo intoxicated patients
- Use special care with elderly and addicted patients
- Benzo withdrawal life threatening; benzo “rebound” troublesome and common