Sedative/Hypnotics (*e.g.* Benzodiazepines)

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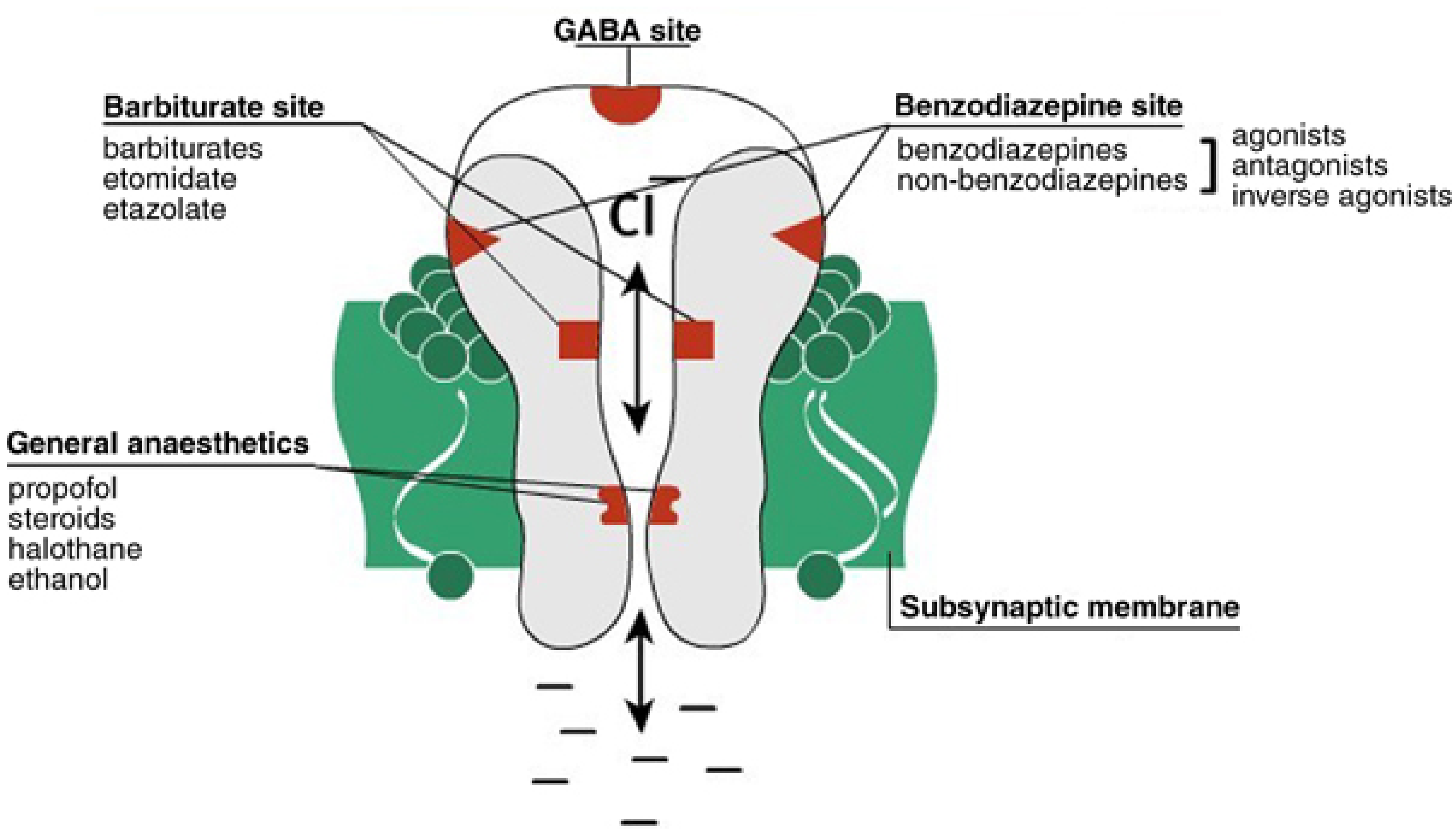
Learning Objectives

- Evaluate the pharmacologic properties that differentiate one benzo from another
- Describe common indications for benzos, and which benzos are appropriate for those indications
- List the contraindications and harms of benzodiazepines
- Benzo withdrawal and taper protocols

Sedative/Hypnotics

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

GABA receptor
gabaergic drugs have incomplete cross tolerance



Benzo effects

- Euphoria
- Antiseizure
- Amnesia
- Muscle relaxation
- Clumsiness, visio-spatial impairment
- Soporific
- Respiratory suppression
- Anxiolysis/disinhibition

Tolerance to benzo effects?

- **Rapid tolerance (weeks)**
  - **Euphoria**
  - **Antiseizure**
- Incomplete tolerance
  - Amnesia
  - Muscle relaxation
  - clumsiness, visio-spatial impairment
  - Soporific
- *Least Tolerance (sustained effect)*
  - *Respiratory suppression*
  - *Anxiolysis/disinhibition*

Rapid dose escalation (2 weeks): consider euphoria seeking patients

Which person is on benzos?

What else dilates pupils?

- Anticholinergics
- Opioid wd
- Stimulants
- Darkness

- …And some people just have large pupils

Mental status benzo intoxication

- Emotional lability
- Rambly, 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?

Assure safe transit home (car keys!)

When I talk to BZD intoxicated patients, I may go into “bartime” mode: Loud, interruptive, simply directive thoughts

I am not being rude….

They are blacking out!

Alternatively when I talk to a bzd intoxicated patients I may take the opportunity to ask them questions they normally would not answer….

They are disinhibited!

Benzo Pharmacology

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

BENZODIAZEPINE (BZ) COMPARISON CHART www.RxFiles.ca Brent Jensen BSP Jul 03

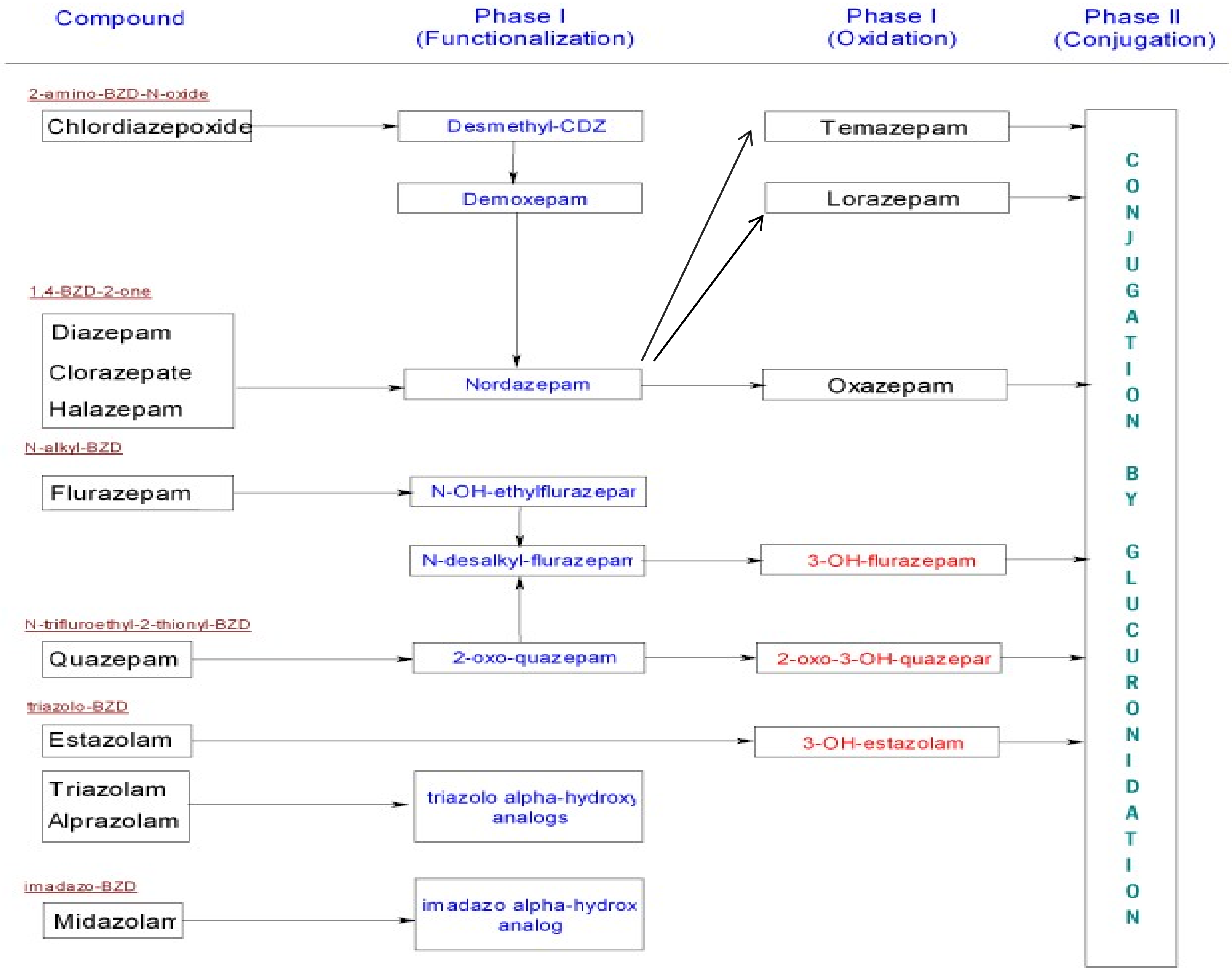
Name Generic -TRADE	Equivalent Dose/Class	Peak Level/ ABSORPTION RATE	Average Half-life (hr)	Active Metabolites	Comments (√ = therapeutic use)	INITIAL & MAX DOSE	USUAL DOSE RANGE	$ /Month
SHORT ACTING: more rebound anxiety effect & withdrawal reactions, **better sedative/hypnotic**; preferred over long 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	15 15
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	10 12
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	11 12 14
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	10 11 17
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	11 11
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	9 10
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	20 32
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	0.25mg 10-20mg Used for BZ withdrawal	0.5mg po tid 1mg po bid 2mg po tid	15 21 20
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	13 18 26
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	2mg 40mg Used for BZ withdrawal	2mg po tid 5mg po tid 10mg po tid	15 17 19
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	10 11
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	11 12

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.

Half Life and metabolites

- High variability half life between benzos
  – Midazolam… 1 hours
  – Lorazepam… 15 hours
  – Diazepam… >50 hours
- Certain benzos have active metabolites:
  – Diazepam and chlordiazepoxide
  – Liver disease and elderly - they become very very long acting

Active Metabolites



Onset of action

- Independent of half life
  - Diazepam acts more quickly than lorazepam
- More euphoria if rapid
- Clinical utility if rapid
  - Breaking a seizure
  - Panic disorder

Benzo variables

- Potency differences
- Time of onset
- Half life
- Active metabolites

Commonly used benzos and why

- Clonazepam for **GAD/SAD**
  - Longer action, less euphoria
- Lorazepam for **panic/specific phobia**
  - More rapid onset, shorter half life, less euphoria
- Diazepam for alcohol **detoxification**
  - Self tapering, rapid onset, long half life
- 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?

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, fractures and death!

Organ toxicity from benzos?

Organ toxicity from benzos?

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

Benzos and Addiction

- Benzos are not that addictive
- 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
- A true benzo addict is incredibly complex and challenging: risk to themselves and others

Benzo Overdose

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

Common nonbenzo sedatives

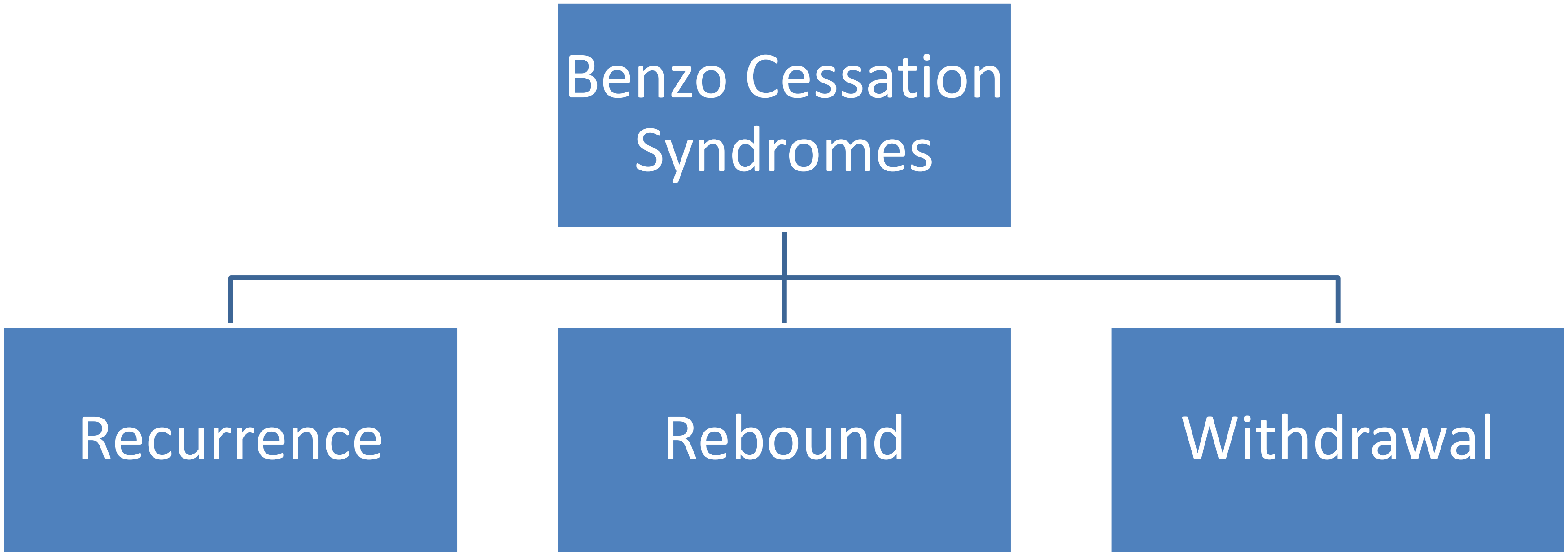
- Carisoprodol, “Soma” or pro-meprobamate.
  - Barbiturate
- Butalbatol, “Fiorinol”
  - Barbiturate
- Phenobarbitol
  - long acting non-euphoric barbiturate used for tapers
- Propofol– cross tolerant with benzos
- GHB “Xyrem”
  - Powerful short acting sedative
- “Z drugs”: zolpidem, eszopiclone, zaleplon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

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

Benzo withdrawal is life threatening and requires close monitoring and detoxification

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

Benzo addicts are notoriously poor historians, and unreliable pill takers

They are not lying!
They just don’t remember

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

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

Failed first attempt

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

Benzo addiction

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

See attachment on benzos and MAT….

Thank you!
Questions?