MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Benzodiazepine: Are they all the same, are they all bad?

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Disclosures

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"My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

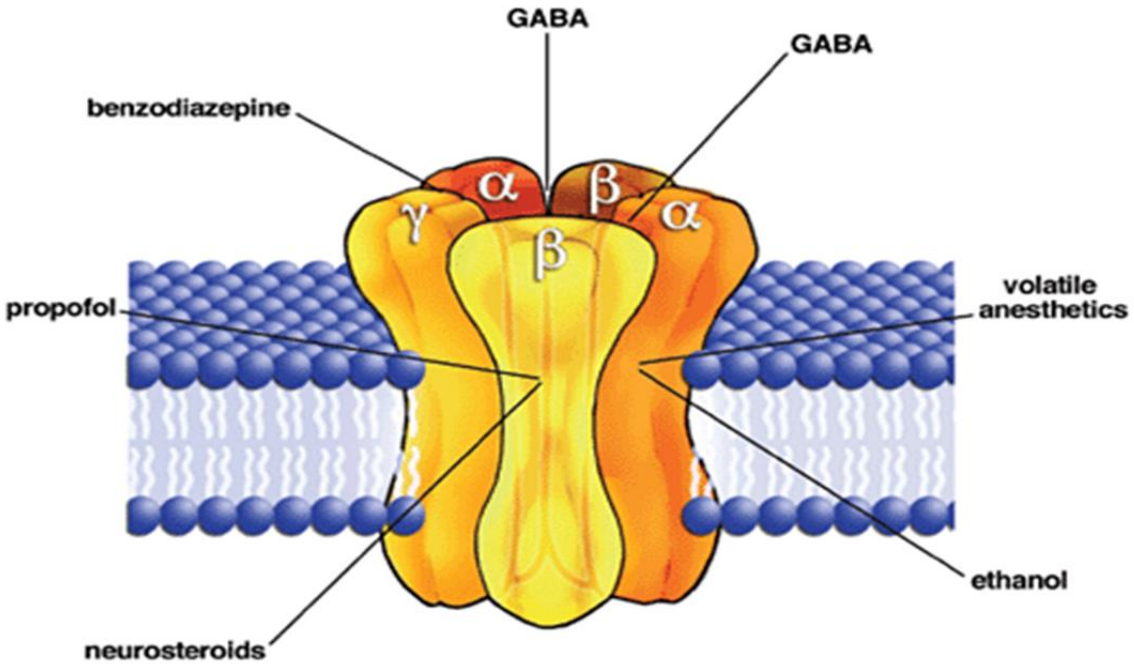
I am the author of the book "Almost Depressed" and have received payments from Harvard health Publications

Benzodiazepines Augment the Effects of GABA

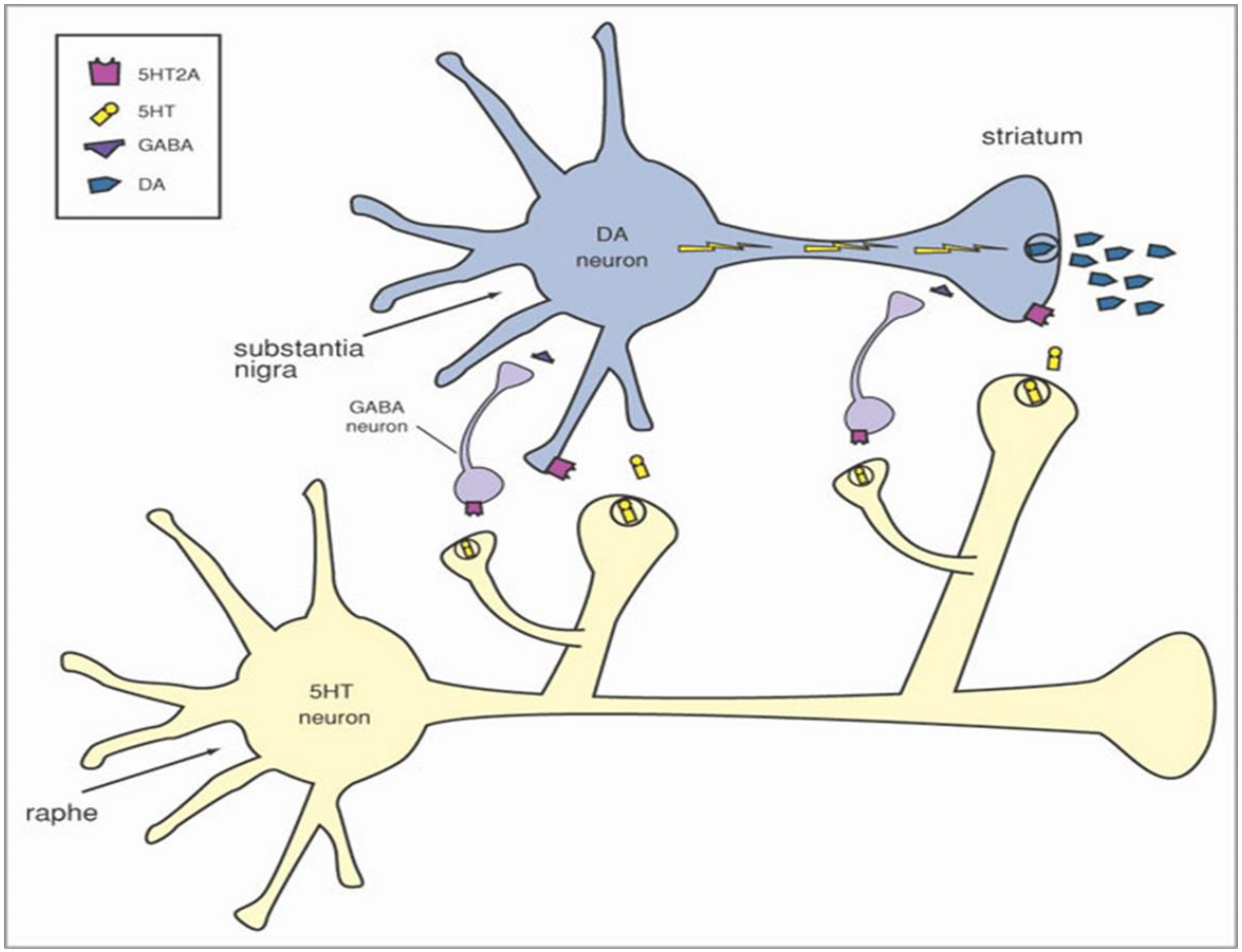
- GABA is the main inhibitory neurotransmitter in the brain.
- Benzodiazepines increase the affinity of GABA receptors for GABA; the effect of which increases Cl^- conductance resulting in hyperpolarizing
- Benzodiazepines exert their action only in the presence of GABA – for this reason they are called positive allosteric modulators (PAMs); acting as *indirect agonists* of the GABA receptor

Benzodiazepines are Positive Allosteric Modulators (PAMs) of GABA-A Receptors

- Allosteric sites are all receptor sites where GABA itself **does not** bind.
- Allosteric modulators can be positive or negative.



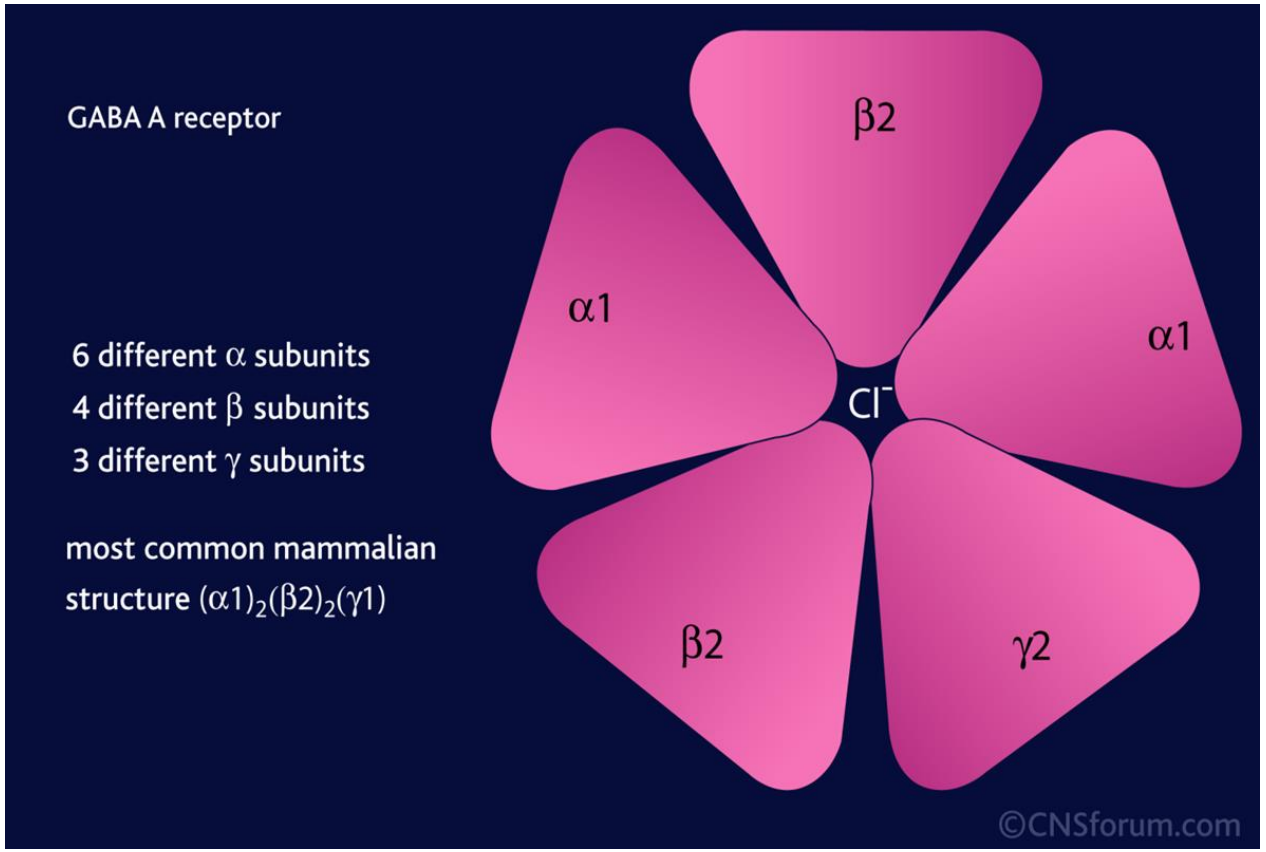
GABA Cells are Inter-neurons



Selectivity for GABA-A Receptor Subunits

GABA A Receptors containing Alpha 1 subunits are involved in SLEEP MODULATION

GABA A Receptors containing alpha 2 or alpha 3 subunits are involved in EXPERIENCES of ANXIETY



Existing Benzodiazepines are Non-selective

- Benzodiazepines bind to GABA-A alpha subunits: 1, 2, 3 and alpha 5.
- Each of subunits is associated with different effects
- Benzodiazepines are/can be/cause:
  - Sedating
  - Anxiolytic
  - Muscle relaxation
  - Potentiate effects of Alcohol

Benzodiazepines are Anxolytic & Hypnotic

- ANXIOLYTIC EFFECT: By binding at GABA- A receptors in the amygdala, Benzodiazepines inhibit the activation of amygdala.

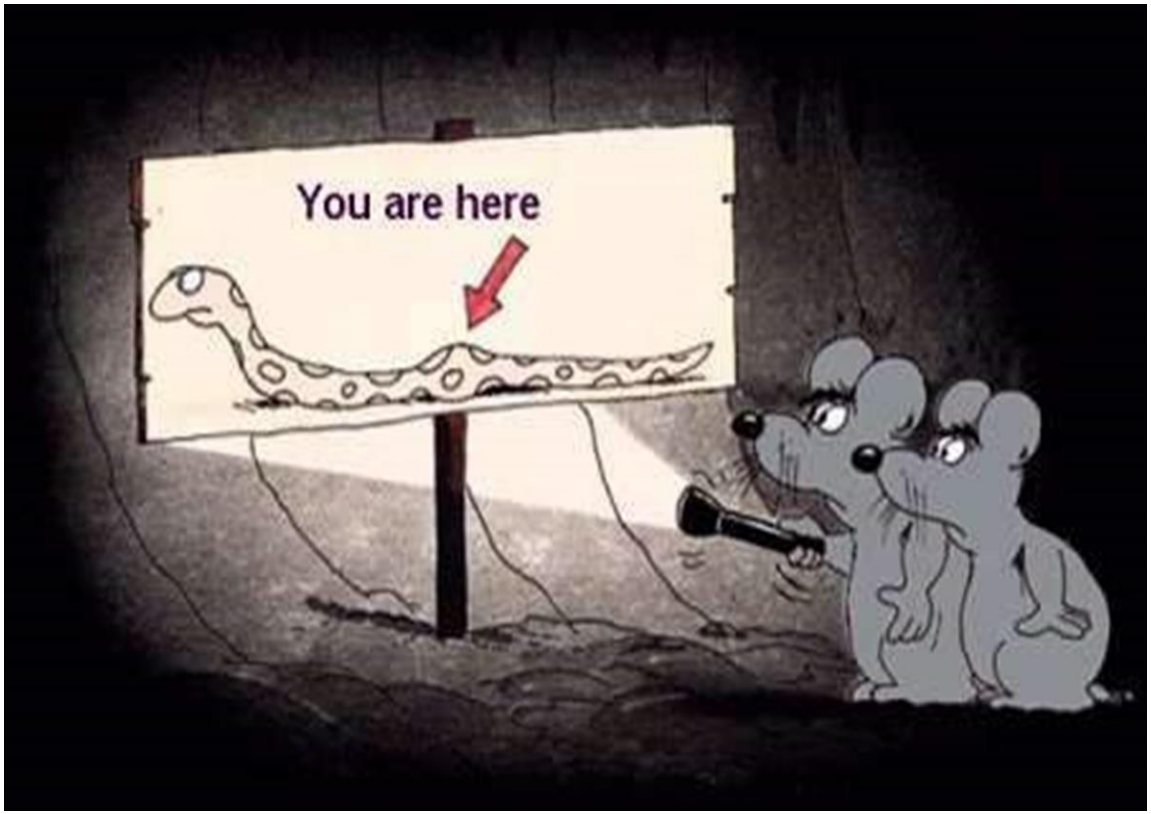
- HYPNOTIC EFFECT: Benzodiazepines promote sleep by binding at GABA-A receptors in the VLPO, causing sleepiness.

Amygdala Activated by Experience and/or Environment

Monoamines from the locus coeruleus activate amygdala causing

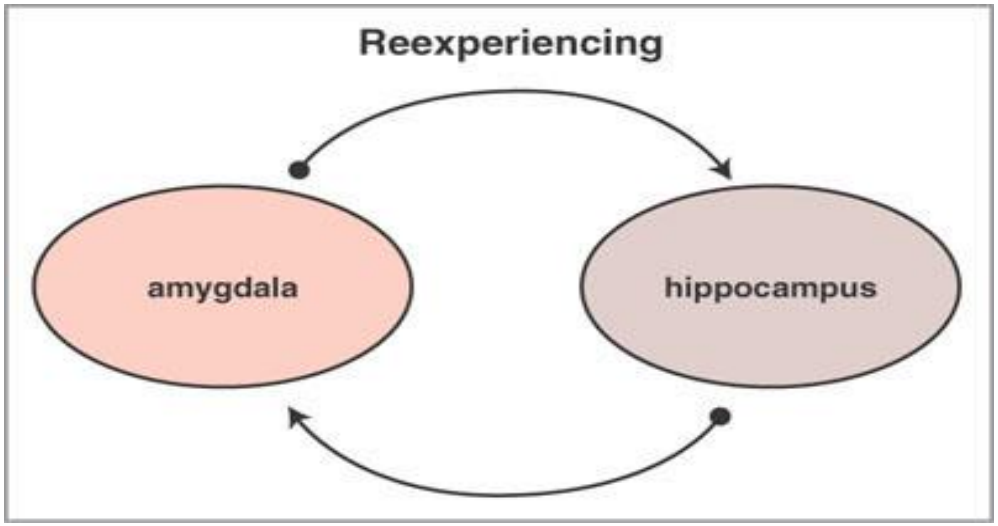
- anxiety,
- panic attacks,
- tremors,
- sweating,
- tachycardia,
- hyperarousal and
- nightmares

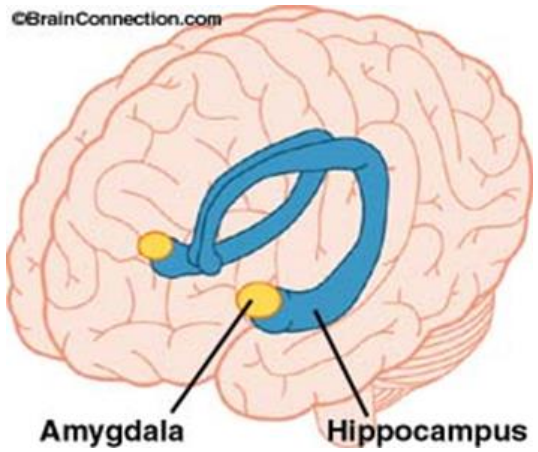
Benzodiazepines inhibit activation of amygdala



Reexperiencing - Activation of the Amygdala by Inner Cues

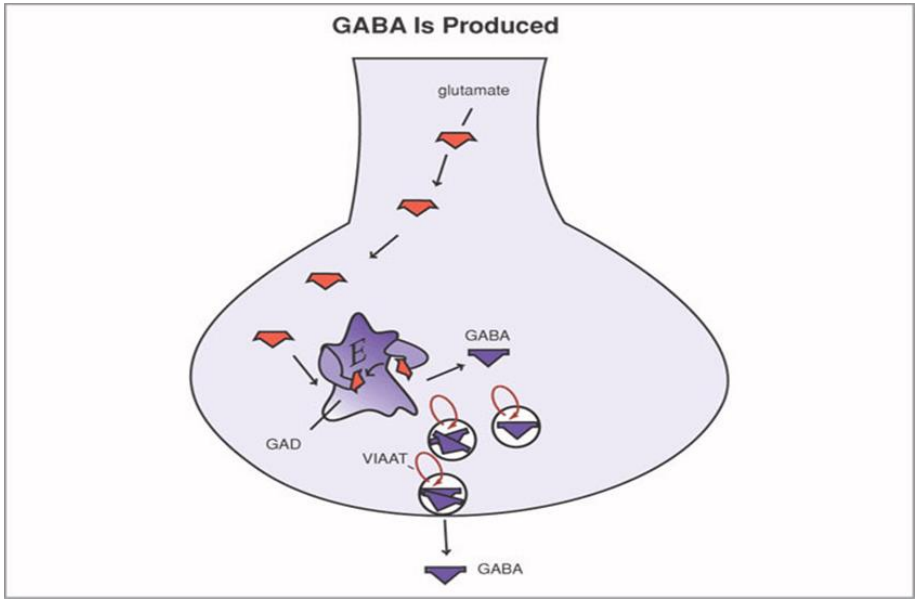
Traumatic memories can activate the amygdala, causing the amygdala in turn to activate the hippocampus and generate a fear response, **REEXPERIENCING, Hypervigilance, Intrusive memories** (AKA Acute Stress Disorder and/or Posttraumatic Stress Disorder





Exogenous GABA Does Not Cross the Blood Brain Barrier(BBB)

- GABA is produced in GABA-ergic neurons from the excitatory neurotransmitter Glutamate by the enzyme GAD (glutamic acid decarboxilase)



Benzodiazepine FDA Indications

- Anxiety, for muscle tension, insomnia, status epilepticus(diazepam), myoclonic epilepsy(clonazepam), preoperative anesthesia, and alcohol witdhrawal.

- Two benzodiazepines: alprazolam and lorazepam have FDA indication for **anxiety associated with depression.**

- Clonazepam and Alprazolam are indicated in the treatment of **panic disorder**.

Benzodiazepine Properties

The effects of benzodiazepines depend on their properties:

- half-life
- liposolubility
- receptor affinity

Liposolubility

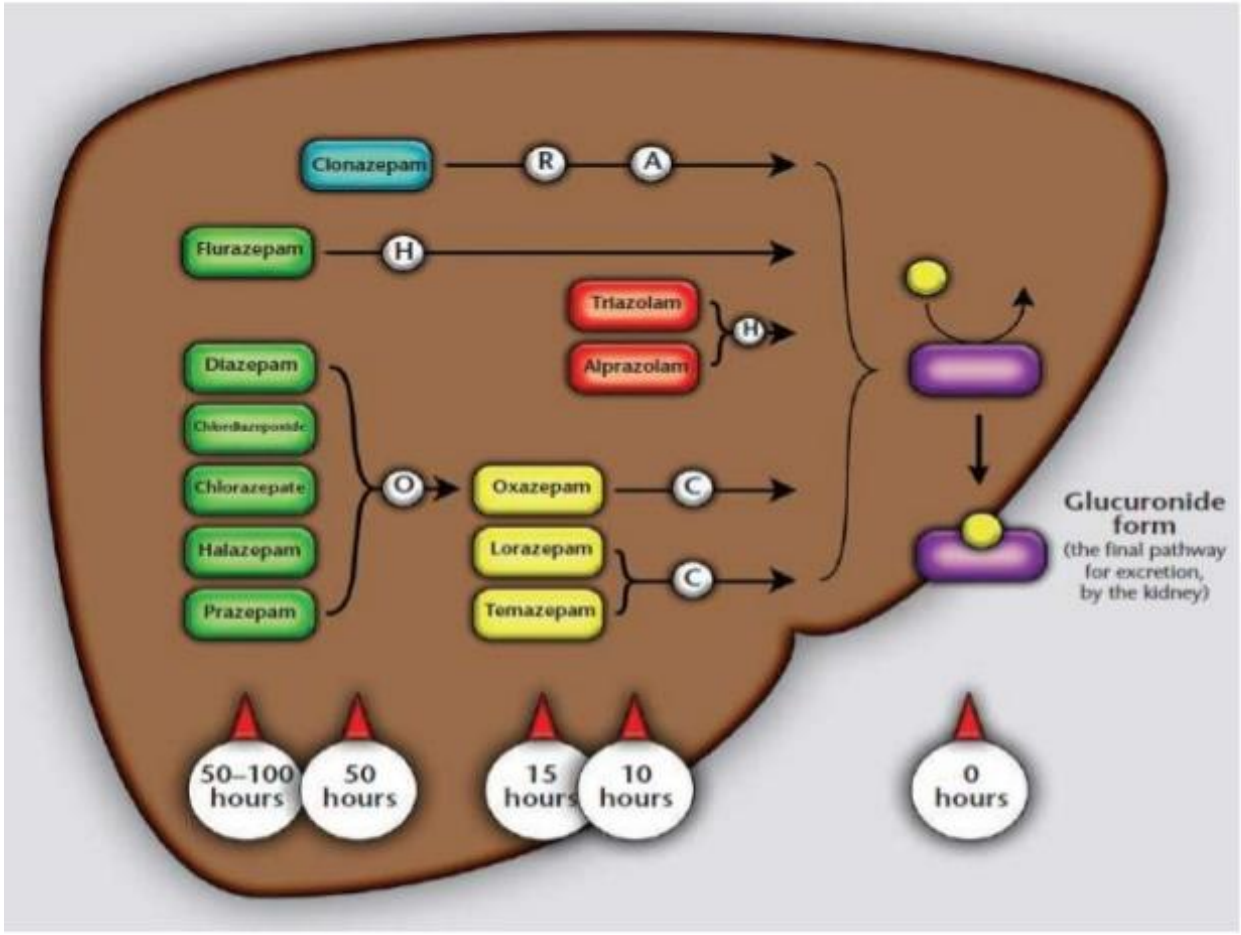
- Highly lipophilic benzodiazepines such as diazepam enter the brain more quickly, “turning on” the effect promptly, but “turning off” the effect more quickly as well as they disappear into body fat.

- Less lipophilic compounds such as lorazepam produce clinical effects more slowly, but may provide more sustained relief in spite of shorter half life.

Relative Receptor Affinity

- The higher their affinity for GABA-A receptors, the more intense withdrawal symptoms they cause.
- High potency benzodiazepines such as lorazepam and alprazolam have high receptor affinity – intense withdrawal symptoms.
- Oxazepam has low receptor affinity – fewer withdrawal symptoms.

Benzodiazepine Metabolism



Hepatic metabolism of BZDs

Benzodiazepines - Subclasses

2-keto (chlordiazepoxide, clonazepam, clorazepate, diazepam, halazepam, prazepam, and flurazepam)

- The 2-keto drugs and their active metabolites are oxidized in the liver, and because this process is relatively slow, these compounds have relatively long half-lives.

3-hydroxy (lorazepam, oxazepam, temazepam)

- The 3-hydroxy compounds are metabolized via direct conjugation with a glucuronide radical, a process that is more rapid than oxidation and does not involve the formation of active metabolites.

Triazolo (alprazolam, adinazolam, estazolam, and triazolam)

- The triazolo compounds are also oxidized, however they have a more limited active metabolites and thus shorter half-lives.

Prescribing Recommendations

- Address the cause of symptoms
- Psychotherapeutic guidance – Listen to the patient
- Has the patient tendency to misuse drugs/alcohol?
- Ensure dose is correct
- Prescribed for as long as necessary, aiming for shortest time
- Rebound anxiety, tapering dose, support
- Reduction/Discontinuation – Careful medical supervision & appropriate psychological interventions

Before prescribing benzodiazepines

- Take a full history including an alcohol and licit and illicit drug history.
- Inform the patient of the side-effect profile of benzodiazepines and offer education.
- Consider and treat, if possible, any underlying causes.
- Consider referral to other/additional services.
- Consider alternative sources of support for and with the patient

When prescribing for the 1st time

- Initiate with the lowest recommended dose, but this may need to be adjusted depending on patient's response.
- Usually prescribe for up to 4 weeks.
- Use phased dispensing where possible.
- Ensure that agreements between doctor and patient are documented.
- Record all details of medication prescribed and duration of treatment.
- Clear, effective and speedy communication concerning benzodiazepine usage should always take place between the prescribing professionals both within and between services.

Benzodiazepine dependent patients or pts in receipt of continuing prescribing

- Issue small quantities at a time Review regularly – monthly
- Use a long acting benzodiazepine in dosages no higher than diazepam 5 mg three times daily (or equivalent)
- Make patients aware of the risks of long term benzodiazepine use and document this communication.
- Encourage dependent pts to withdraw, offer them a detoxification program at regular intervals (at least annually) and document
- A significant number of requests for repeat benzodiazepine prescribing are associated with addiction problems, primarily alcohol, or in urban areas, opiate misuse. A doctor who suspects this is the case should seek specialist advice

Benzodiazepines – Adverse Effects

- Sedation
- Lethargy
- Dependency/Withdrawal
- Respiratory depression
- Possible cognitive impairment.
- May be Safe in overdose: up to 30 times the normal daily dose.
  - Usual symptoms of overdose include sedation, drowsiness, ataxia, and slurred speech.
  - May result in respiratory depression in combination with other CNS depressants.
  - Management includes gastric lavage, forced emesis, and assisted ventilation.

- Medication interactions:
  - Medications that increase benzodiazepine levels include P4503A4 inhibitors, ketoconazole, fluconazole, nefazodone.
  - Medications that decrease benzodiazepine levels include P4503A4 inducers such as carbamazepine.

How Addictive are Benzodiazepines?

- How long does one have to take a benzodiazepine before withdrawal is seen with discontinuation?

- Studies in animals have indicated that benzodiazepines can reinforce use and can produce physical dependence and tolerance.

- Available data seem to reveal that benzodiazepines are rarely sought after or craved in the sense that heroin or cocaine are. Rather, they are used as part of a polysubstance abuse pattern to modulate the effects of primary drug of abuse(e.g. cocaine) or as a backup drug when more euphoriant drugs are not available.

Tapering off of Benzodiazepines

- Should be carefully planned and structured, the aim being to gradually reduce to zero the amount of drug being taken.

- Gradual Dose Reduction
  - Recommended reduction rate: no more than 10% per day.

- Consider Substitution
  - Dose reduction then immediate substitution
  - Greater flexibility in dosing of longer acting Diazepam

- Adjuvant pharmacotherapy
  - Reduce the physical symptoms of withdrawal
  - Tremor, Sweating, Insomnia. Convulsions

Factors that MAY make benzodiazepine withdrawal more difficult include

- higher daily dose
- shorter half-life
- longer duration of prior benzodiazepine therapy
- more rapid taper

- Patient Characteristics:
  - a diagnosis of panic disorder,
  - higher pre-taper levels of anxiety or depression,
  - Characterological/relational challenges and/or personality disorder,
  - concomitant alcohol or substance abuse