LOOK BEFORE YOU LEAP
Short acting Benzodiazepine use

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MISSING LINK

Outline

- Benzodiazepine
- Introduction
- History
- Common Uses Today
- Pattern of use
- PK/PD
- Adverse effects
- Tolerance
- Withdrawal

Introduction

- Benzodiazepines (BZDs) are some of the most commonly prescribed medications in the world.
- However, they are commonly used in ways not supported by the literature.
- Here, we review their historical and common uses, and the evidence for and against the use of benzodiazepines

- Reduce the inappropriate prescribing of BZD
- Understand the indications, long term indications and contraindication
- Identifying and treating physical dependence and withdrawal of BZD's

History

- The first benzodiazepine (benzo) was synthesized by an Austrian scientist named Dr. Leo Sternbach in the mid 1950's while working at Hoffman-La Roche.
- The new compound's potential as a pharmaceutical was not initially recognized, however, Dr. Sternbach's persistent research eventually uncovered it's efficacy as a tranquilizer. In 1959, chlordiazepoxide (Librium) was introduced as the first of many benzos to come. Just four years later, in 1963, diazepam (Valium) came on the market.
- Clinicians quickly recognized the potential of benzos as a safer alternative to the barbiturate class of anxiolytics.

Issues in General

Benzodiazepines

- One of the most commonly prescribed classes of psychotropic medications.
- Benzodiazepine seeking is common and this challenges person centered treatment approaches
- In 2008, roughly 1 in 20 adults filled a BDZ Rx
- Long Term use (120 day supply within 1 year)
  - Characteristic of 0.4% population ages 18-35
  - 2.7% populations ages 65-80
- Vast majority of Rx written by non-psychiatrists

Issues in General

- BDZs - widely prescribed in almost all psychiatric conditions, as well as in many other medical disorders.
- Often prescription practices do not align with current evidence.
- Scientific literature provides conflicting recommendations regarding the continued role of BDZs in ongoing treatment, with varying interpretations of the benefits and risks associated with their prescription.
- Paucity of guidelines focusing specifically on BDZs usually confined to disorder-specific treatment guidelines that very rarely provide specifics on dosage, selection of appropriate BDZ or specific length of treatment.
- All guidelines contend prescribers should employ BDZs as primarily a short-term, stabilizing intervention
- Require significant monitoring of a range of possible adverse side-effects, including the potential for tolerance, dependency, rebound symptoms and withdrawal.

Benzodiazepines

- Benzodiazepines bind to GABA receptors and depress the central nervous system.
- They are prescribed for their sedative-hypnotic, antianxiety, muscle relaxant, and anticonvulsant effects.

Mechanism of Action

- Modulate GABA-A receptor
- Boosting GABA affinity
- GABA - chief inhibitory neurotransmitter
- >>BZDs slow the brain down
- GABA receptor density low in respiratory brainstem > limiting the incidence of respiratory depression

Alprazolam

- Alprazolam is a short-acting high potency BZD with an elimination half-life of 6-27 hours.
- Commonly prescribed for panic disorders and anxiety.
- For anxiety starts with 0.25-0.5 mg tablets, administered by mouth 3 times per day. The maximum recommended daily dose of alprazolam for anxiolysis should not exceed 4 mg.
- A common issue with alprazolam is rebound anxiety that occurs with abrupt discontinuation because of the drug's short elimination half-life.

Clonazepam

- Second high-potency BZD discovered.
- Has anticonvulsant and anxiolytic effects.
- Clonazepam proved as effective for treating panic disorders as alprazolam, and termination did not cause rebound anxiety symptom because of clonazepam's long elimination half-life.
- Less likely to cause anterograde amnesia compared to the other high-potency BZDs.
- The maximum daily dose should not exceed 1-4 mg.

Lorazepam

- Slightly less lipid soluble compared with alprazolam, suggesting a lower risk of amnesic side effects compared to alprazolam.
- Binds GABA-A with less affinity than alprazolam but with greater affinity than clonazepam.
- Effective as an anticonvulsant and also works well as an adjunct to antipsychotics in the treatment of acute agitation and mania.
- Lorazepam can be used in patients with hepatic or renal dysfunction with only minor effects on the drug's pharmacokinetics.

Lorazepam

- Lorazepam dosing largely depends on the indication.
- For alcohol withdrawal, clinicians prescribe 2 mg tablets orally every 6 hours for a total of 4 doses, followed by 1 mg every 6 hours for a total of 8 doses.
- For anxiolysis, dosing begins with 2-3 mg/d orally, divided into 3 doses per day. Maximum daily doses should not exceed 10 mg.
- The safety and effectiveness of oral forms have not been established in children under the age of 12.
- However, the same dosing recommendations for adults apply to children over the age of 12. For sedation, such as in the intensive care unit (ICU), 0.01-0.1 mg/kg/h intravenously is recommended

Midazolam

- Short-acting BZD, is roughly 1.5-2 times as potent as diazepam17 and has a greater hypnotic effect than diazepam because it interferes with GABA reuptake.
- It is available in intravenous, intramuscular, oral, sublingual, rectal, and intranasal preparations.
- This lipophilia accounts for midazolam's rapid absorption and crossing of the blood brain barrier and, hence, the rapid onset of clinical effects.
- Midazolam is rapidly redistributed, leading to a short duration of action and a short elimination half-life.
- Recommended dosing of midazolam in the preoperative setting for sedation/anxiolysis is usually 1-5 mg intravenously up to 1 hour before surgery in otherwise healthy patients.

Benzodiazepine Receptors

- Type 1:
  - Most common throughout CNS, mediates SEDATION: Tolerance
- Type 2:
  - Hippocampus, striatum, spinal cord, mediates ANXIOLYSIS
- Type 3:
  - Cerebellar granule cells

BZD: Pharmacokinetics

- Lipid-soluble: fast cross blood-brain-barrier: rapid onset of action.
- Persist longer in high fat-to-lean body mass
  - Obese, elderly
  - Abuse liability (Valium)
- Biotransformation & Half-Life:
  - Hepatic oxidation: long-t½, active metabolites
  - Glucuronidation: short-t½, no active metab.

Classification- based on elimination half life

Short acting (1-2 hours) Half life	**Triazolam Midazolam**	**1.5 to 5.5 ½ life**
Intermediate acting (12-40 hours)	Alprazolam Clonazepam Lorazepam Oxazepam Temazepam	11.2 12-50 10-20 8.2 8.8
Long acting (40-250 hours)	Chlordiazeporide Diazepam Hurazepam	24-48 up to 100 hours 47-100
Z- drugs Zaleplon Zolpidem Eszopiclone		

BZD: Interactions

CNS Depressants

- p450 2C9
  - Diazepam, TCAs, Warfarin, phenitoin. (luvoxinhibit)
- p450 3A4
  - Triazolam, Midazolam, Alprazolam, CBZ, Quinidine, Terfenadine, Erythromycin, (Luvox, Sserzone inhibit)
  - Disulfiram & Cimetidine ↑BZD levels

Interactions between Benzodiazepines and select common medications

Interaction	Medication Class	Examples
Increased serum Levels (CYP450 inhibition)	Antifungals Macrolides SSRIs Histamine-2 blockers	Ketoconazole Itraconazole Clarithromycin Erythromycin Fluoxetine Paroxetine Cimetidine
Increased sedative effects of benzodiazepines	Opioids Antipsychotics Barbiturates Sedating antihistamines	Oxycodone Chlorpromazine Clozapine Phenobarbital Secobarbital Diphenhydramine Hydroxyzine

Guideline Sample - The Jewish Board, NY, NY

- Generally agreed upon indications in psychiatry
  - Anxiety: Acute and chronic (especially PD, GAD, SAD)
  - Acute insomnia
  - Acute agitation particularly in mania and psychosis
  - Acohol withdrawal
  - Akathisia
  - Catatonia
  - Co-prescription during initiation phase of antidepressant in PD and GAD
  - Tremor

Guidelines Sample - The Jewish Board, NY, NY

- Disputed indications in psychiatry
  - Acute stress disorder
  - Posttraumatic stress disorder
  - Chronic insomnia

BZD: Adverse Effects

- BZD vs other psychotropics have few SE Sedation, CNS Depression
- Worse if combined with EtOH Behavioral Disinhibition
- Irritable, excitement, aggression (<1%), rage Psychomotor & Cognitive Impairment
- Coordination, attention (driving)
- Poor visual-spatial ability (not aware of it)
- Ataxia, confusion

BZD: Adverse Effects cont…

- Amnesia
- Disinhibition
- Delirium
- Depression

BZD: Adverse Effects

- Overdose: Rare fatalities if BZD alone
- Severe CNS & Respiratory Depression if combined with:
  - Alcohol
  - Opiates
  - Heroin
  - Barbiturates
  - Narcotics
  - Tricyclic Antidepressants

Dependence and Withdrawal

- Most people will become dependent after > 6 weeks continuous use
- Only 30% of benzodiazepine dependent people ever get off them completely
- Methadone patients at high risk of benzodiazepine abuse (25 - 65%)

BZD: Withdrawal

- Worse if stop abruptly
- Symptoms:
  - GI Sx, Diaphoresis, pulse, BP
  - Tremor, lethargy, dizziness, headaches
  - Restlessness, insomnia, irritability, anxiety
  - Depersonalization, perceptual disturbances
- Also: depression, tinnitus, delirium, panic, hallucinations, abnormal muscular movs.
- Seizures: Abrupt discount of short acting
- Treatment: Long half-life benzo

Dependence/Withdrawal, cont.

- Rarely - seizures, delirium, confusion, psychosis
- Triggering of depression, mania, OCD
- 90% of long-term users (>8mo-1yr) experience significant withdrawal
- Insignificant wd if used less than 2 weeks
- Mild-moderate if used >8 weeks
- Slow taper (>30days) with +/- carbamazepine, valproic acid, trazodone, imipramine
- CBT effective in dc-ing benzos and controlling panic/anxiety

Predictors of severe withdrawal

- High-potency-quickly eliminated (e.g. alprazolam, lorazepam, triazolam)
- Higher daily dose
- More rapid rate of taper (esp last 50%)
- Diagnosis of panic disorder (not GAD)
- High pretaper levels of anxiety and depression
- ETOH or other substance dependence/abuse
- Personality pathology -e.g. neurotic or dependent.
- Not motivated to discontinue use.

Anxiety symptoms

Common to all anxiety	Specific to withdrawal
Agitation	Perceptual distortions, depersonalization
Panic attacks	Hallucinations (visual and auditory)
Agoraphobia	Tingling and loss of sensation, formication (a feeling of ants crawling over the skin)
Insomnia	Sensory hypersensitivity
Nightmares	Muscle twitches and fasciculation
Depression	Psychotic symptoms, confusion, convulsions (rare)
Poor memory	
Loss of concentration	

How long do symptoms last?

- Up to 15% of people develop protracted withdrawal symptoms (months or years)
- Anxiety: Gradually diminishes over 1 year
- Insomnia: Gradually diminishes over 6–2 months
- Depression: May last a few months responds to antidepressants
- Cognitive impairment: Gradually improves, but may last for >1 year
- Perceptual symptoms: (e.g. tinnitus, paraesthesia, pain (usually in limbs) Gradually recedes, but may last for at least 1 year and occasionally persist indefinitely
- Motor symptoms: (e.g. muscle pain, weakness, tension, painful tremor, jerks) Usually gradually recede, but may last for >1 year
- Gastrointestinal symptoms: Gradually recede, but may last for at least 1 year and occasionally persist indefinitely

Common problems when detoxing

- Symptoms of depression
- Symptoms of anxiety
- Insomnia
- Worsening of pre-existing mental health problems
  - OCD
  - Panic attacks
  - Psychotic symptoms

What has been tried?

NO EVIDENCE for:

- Antipsychotics – makes it worse!!
- Antidepressants
- Buspirone

SOMEO evidence for:

- Propranolol
- Valproic acid

Suggested principles

- Where possible change to a long acting drug – usually diazepam
- Avoid extra medication
- Antidepressants only useful for clinical depression or panic attacks
- SUPPORT.. SUPPORT.. SUPPORT!
  – Family, friends, help lines, addiction or GP staff

Why use diazepam?

- Withdrawal is most easily managed from diazepam because:
- Diazepam and its metabolites (desmethyldiazepam and nordiazepam) have long half-lives (between 20 hours and 200 hours), which ensures a gradual fall in blood concentrations. The blood level of its longest active metabolite for each dose falls by a half in about 8 days [Micromedex, 2006]

Detox regimens

- Be flexible in following the schedule
- For people taking 40 mg per day of diazepam or less, a typical withdrawal schedule that is tolerated by most people would be to:
  - Reduce by 2 mg to 4 mg every 1–2 weeks to 20 mg per day
  - Reduce by 1 mg to 2 mg every 1–2 weeks to 10 mg per day
  - Reduce by 1 mg every 1–2 weeks to 5 mg per day
  - Reduce by 0.5 mg to 1 mg every 1–2 weeks until completely stopped.
- Total withdrawal time from diazepam 40 mg per day might be 30
- 60 weeks; withdrawal from diazepam 20 mg per day might take 20
- 40 weeks.
- Stopping the last few milligrams is often seen by patients as being particularly difficult but this is usually an unfounded fear derived from long-term psychological dependence on benzodiazepines.

Behavioral and Cognitive Therapy
And
Psychodynamic Psychotherapy

Benzodiazepines in older Adults

- Benzodiazepine treatment in patients aged 65 and older can increase risk for2,5-7,9,11,12,15,42-45:
  - Falls and hip fractures
  - Possible cognitive impairment
  - Negative interactions with other medications
  - Daytime fatigue
  - Confusion and delirium
- Initiate treatment at one-half the standard adult starting dose.
- Monitor response to treatment and minimize dosage and/or frequency to avoid adverse effects. In older adults, benzodiazepines should never be used as first-line treatment for insomnia, agitation, or delirium, and long-acting benzodiazepines should not be used for any indication.

Benzodiazepines during Pregnancy and Lactation

- Benzodiazepine use during pregnancy is associated with risks to the newborn 2,12:
  - Respiratory depression
  - Poor temperature regulation
  - Hypotonicity
  - Neonatal abstinence syndrome
- Patients planning a pregnancy, gradually discontinue benzodiazepine treatment and consider other options.
- If postpartum benzodiazepine treatment is being considered, explain that benzodiazepine metabolites can be found in breast milk.

If prescribing…

Consider when prescribing benzos

Intent

- Are you treating a diagnosed medical problem?

Effect

- Does the medication improve the patient's functional status or worsen it?

Monitoring

- Are you assessing the patient at the peak or trough effect of the medication?

Myths

- First line treatment for anxiety and depression
- First line treatment for insomnia
- Low dose benzodiazepines are non addictive
- Safe with most medical illnesses
- Safe in elderly
- Safe in pregnancy
- No interactions with other drugs
- Less abuse potential


Questions

For Reading

https://benzo.org.uk/manual/contents.htm


THANK YOU