Overview

- Education on benzodiazepines - for patients and prescribers
- For prescribers
- Withdrawal symptoms and management
- Tapering strategies
- Medications to avoid in recovery
### Therapeutic Actions (in Short Term Use)

<table>
<thead>
<tr>
<th>Action</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiolytic - relief of anxiety</td>
<td>Anxiety and panic disorders, phobias</td>
</tr>
<tr>
<td>Hypnotic - promotion of sleep</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Myorelaxant - muscle relaxation</td>
<td>Muscle spasms, spastic disorders</td>
</tr>
<tr>
<td>Anticonvulsant - stop fits, convulsions</td>
<td>Fits due to drug poisoning, some forms of epilepsy</td>
</tr>
<tr>
<td>Amnesia - impair short-term memory</td>
<td>Premedication for operations, sedation for minor surgical procedures</td>
</tr>
</tbody>
</table>

**Other clinical uses, utilising combined effects:**

- Alcohol detoxification
- Acute psychosis with hyperexcitability and aggressiveness
Adverse effects

- Over sedation
- Memory impairment (anterograde amnesia)
- Paradoxical stimulant effects
- Drug interactions
- Depression/emotional blunting
- Elderly
- Pregnancy
- Tolerance and dependence
Tolerance to Side Effects

- Tolerance develops to
  - Sedation
  - Anxiolytic effects
  - Psychomotor effects

- Whether tolerance develops to cognitive side effects remains controversial.
Dependence

1. Therapeutic dose dependence
   - Taken as prescribed for several years
   - “Need” BZD’s to carry out daily activities
   - Continued despite original indication disappeared
   - Difficulty stopping/decreasing due to withdrawal symptoms
   - Develop anxiety between doses

2. Prescribed high dose dependence

3. Recreational use/abuse
Risk factors for dependence

- High doses (2 – 3 weeks) vs low doses (6 – 8 months)
- Longer duration (approx. 10 – 30% of long-term users develop dependence)
- High potency (Xanax, Ativan, Klonopin, Triazolam)
- Short half-life
- Long-term use (6 – 12 months) is not synonymous with dependence.
- A special characteristic of benzodiazepines is that physical and mental dependence can develop in the absence of tolerance (low-dose dependence).
FOR PRESCRIBERS
Total 24-hour dose levels for the most commonly used benzodiazepines

<table>
<thead>
<tr>
<th></th>
<th>Green Light Zone</th>
<th>Yellow Light Zone</th>
<th>Red Light Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>Up to 5 mg/d</td>
<td>&gt; 5 mg up to 10 mg/d</td>
<td>&gt; 10 mg/d</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Up to 2 mg/d</td>
<td>&gt; 2 mg and up to 4 mg/d</td>
<td>&gt; 4 mg/d</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Up to 20 mg/d</td>
<td>&gt; 20 mg up to 40 mg/d</td>
<td>&gt; 40 mg/d</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Up to 2 mg/d</td>
<td>&gt; 2 mg up to 4 mg/d</td>
<td>&gt; 4 mg/d</td>
</tr>
<tr>
<td>Alprazolam XR</td>
<td>Up to 3 mg/d</td>
<td>&gt; 3 mg up to 6 mg/d</td>
<td>&gt; 6 mg/d</td>
</tr>
</tbody>
</table>

RL Dupont Curr Med Res Opin. 2005
CSAM 2016
Determining if Benzodiazepine Use is Safe or Risky

(Dupont)

Green light zone: 1/2 or less of maximum dose listed in PDR
Nonaddictive patients with anxiety take benzodiazepines at low and stable doses

Yellow light zone: 1/2 up to maximum dose listed in PDR
Not many anxious patients in this zone

Red light zone: above maximum dose listed in PDR
Addictive patients reach this zone of dosing very quickly

PDR=Physicians’ Desk Reference.
Should be avoided...

- PTSD, OCD
- Chronic respiratory disease (COPD, sleep apnea)
- Receiving other CNS depressants (opioids)
- Substance use disorder
- History of TBI
- Dementia
- Elderly
Prescription use behavior questionnaire

- Use more than prescribed
- Use more often than prescribed
- Called for early refills
- Rx obtained from > 1 physician
- Used when feeling upset
- Used to get high/euphoria

ALWAYS CHECK DOPL BEFORE OR WHILE PRESCRIBING BENZODIAZEPINES.
Figure 1: Illustrations of benzodiazepine metabolism.
Arrows indicate metabolic pathways
*Nordiazepam is also a metabolite of halazepam, medazepam, prazepam, and tetrazepam
FALSE POSITIVES

- Sertraline

- Oxaprozin - NSAID used for RA and OA (tested positive for diazepam)
Drug interactions

- Antidepressants (e.g. amitriptyline, doxepin)
- Major tranquillizers
- Neuroleptics (e.g. prochlorperazine [Compazine], trifluoperazine
- Anticonvulsants (e.g. phenobarbital, phenytoin [Dilantin], carbamazepine
- Sedative antihistamines (e.g. diphenhydramine [Benadryl], promethazine [Phenergan])
- Opiates (heroin, morphine, meperidine), and,

*MOST IMPORTANTLY: ALCOHOL*
Equivalency chart

- Alprazolam 0.5 mg
- Chlordiazepoxide 25 mg
- Clonazepam 0.5 mg
- Diazepam 10 mg
- Lorazepam 1 mg
- Temezepam 20 mg
- Zaleplon (Sonata) 20 mg
- Zolpidem (Ambien) 20 mg
- Eszopiclone 3 mg
WITHDRAWAL SYMPTOMS
Acute withdrawal

- Increased anxiety, panic attacks (temporary)
- Vivid dreams, insomnia, nightmares
- Sensory hypersensitivity, hallucinations, illusions and perceptual distortions
- Depression, aggression and obsessions
- Muscle stiffness, tension headache, tremor, jerks, spasms
- Problems with balance
- Seizures
- Psychosis and delirium

**COURSE OF WITHDRAWAL: wax and wane**
Supportive medications

- Antidepressants (TCA’s – amitriptyline, doxepin and SSRI’s)

- Beta blockers – propranolol 10 mg TID

- NO barbiturates, chloral hydrate, Ambien/sonata/lunesta

- Insomnia – TCA’s, antihistamines, gabapentin, pregabalin
### Protracted withdrawal symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Usual Course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety</strong></td>
<td>- Gradually diminishing over a year</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>- May last a few months; responds to antidepressant drugs</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td>- Gradually diminishing over 6-12 months</td>
</tr>
<tr>
<td><strong>Sensory symptoms:</strong></td>
<td>- Gradually receding but may last at least a year and occasionally several years</td>
</tr>
<tr>
<td>- tinnitus, tingling, numbness, deep or</td>
<td></td>
</tr>
<tr>
<td>- burning pain in limbs, feeling of</td>
<td></td>
</tr>
<tr>
<td>- inner trembling or vibration, strange</td>
<td></td>
</tr>
<tr>
<td>- skin sensations</td>
<td></td>
</tr>
<tr>
<td><strong>Motor symptoms:</strong></td>
<td>- Gradually receding but may last at least a year and occasionally several years</td>
</tr>
<tr>
<td>- muscle pain, weakness, painful cramps,</td>
<td></td>
</tr>
<tr>
<td>- tremor, jerks, spasms, shaking attacks</td>
<td></td>
</tr>
<tr>
<td><strong>Poor memory and cognition</strong></td>
<td>- Gradually improving but may last at least a year and occasionally several years</td>
</tr>
<tr>
<td><strong>Gastrointestinal symptoms</strong></td>
<td></td>
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</tbody>
</table>
TAPERING STRATEGIES
Benzodiazepine discontinuation factors

- Duration of use (6 months vs 1 month)
- Dose
- Rate of taper
- Half-life
Tapering strategies

- Gradually taper the original benzodiazepine
  OR
- Substitute with a longer-acting benzodiazepine then gradually taper
  OR
- Taper to lower dose of original benzodiazepine then switch to a long acting benzodiazepine.

ASHTON MANUAL (benzo.uk.org)
1. Taper over Months:
   1. Convert to longer acting agent like Clonazepam or Diazepam
   2. Taper gradually while starting alternative therapies if needed (months)
   3. Rebound Psych meds for Anxiety/Sleep

2. Use of Anticonvulsants:
   **Use of anticonvulsants in benzodiazepine withdrawal.**
   1. Start high dose Depa or Carba, or Gaba
   2. Taper Benzo by 1/3 each day till DC
   3. Continue Anticonvulsant for at least one month, longer better.
   4. Check level of Depa and Carba after a week or two
   5. Start SSRI’s or other for Dep/Anxiety

CSAM 2017
Use of Anticonvulsants in Benzodiazepine Withdrawal.


1. Start high dose Depakote 500 tid
   or Carbamazepine 200 tid,
   or Gabapentin 800 tid
2. Taper Benzo by 1/3 each day til DC
3. Continue Anticonvulsant for at least one month, longer better.
4. Check level of Depa and Carba after a week or two
5. Start SSRI’s or other for Dep/Anxiety
6. If dependent on only short acting agents- alprazolam etc, might use a one day conversion to clonazepam or diazepam then taper 1/3rd dose each day

These are case series NOT RCT’s
Minimal educational interventions

- Discontinuation education letter/pamphlet.
- Single consultation with clinician to discuss risks of long term benzodiazepine use and benefits of discontinuation.
- Self help instructions (e.g. sleep hygiene).
- Prescribers could be encouraged or required to check their state’s prescription drug monitoring program (PDMP) before prescribing benzodiazepines.

Voluntary support groups (self help groups)
Management of Benzodiazepine (BZD) Withdrawal.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Treatment Approach</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach to BZD dependence in general</td>
<td>Gradual withdrawal over a period of several weeks or months</td>
<td>High</td>
</tr>
<tr>
<td>Use of several BZDs or sedatives</td>
<td>Switch to use of only one BZD for detoxification (diazepam)</td>
<td>Good</td>
</tr>
<tr>
<td>Choice of BZD for detoxification</td>
<td>Switch to a long-acting BZD (diazepam)</td>
<td>Low</td>
</tr>
<tr>
<td>BZD withdrawal in a patient receiving opioid maintenance therapy</td>
<td>Adjustment of opioid dose to prevent opioid withdrawal; switch to a partial agonist (buprenorphine)</td>
<td>Good for adjustment of opioid dose; moderate for switch to partial agonist</td>
</tr>
<tr>
<td>Concomitant pharmacotherapy for BZD withdrawal</td>
<td>Carbamazepine, 200 mg twice a day</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>Antidepressants, antihistaminergic drugs, melatonin; improved sleep hygiene, sleep restriction, relaxation techniques</td>
<td>Moderate</td>
</tr>
<tr>
<td>Other drugs for treatment of withdrawal symptoms</td>
<td>Pregabalin, gabapentin, beta-blockers, flumazenil</td>
<td>Low for pregabalin, gabapentin, and beta-blockers; experimental for flumazenil</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>Cognitive behavioral therapy and other approaches</td>
<td>Good</td>
</tr>
</tbody>
</table>
In September 2017, the FDA advised clinicians treating opioid use disorder not to withhold medication-assisted treatment with buprenorphine or methadone in patients concurrently prescribed benzodiazepines, arguing that the benefits of opioid-agonist therapy outweigh the risks of combining these opioids with benzodiazepines.
MEDICATIONS TO AVOID IN RECOVERY
1. Any alcohol containing liquid medications/OTC (Nyquil)
2. Sedative hypnotic medications – BZD’s, Zdrugs, Soma, Barbiturates
3. Opioid medications – Codeine, methadone, tramadol, buprenorphine
4. Stimulant medications – Ritalin, Adderall
5. Cannabinoids – Marinol, Cesamet