Prescription Drug Abuse:
Who, What & What to do

The Nonmedical Use of Prescription Medications
Benzodiazepines

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Medical Indications for Use

- **Anxiolytic** – chronic / phobic anxiety & panic attacks
- **Sedative and hypnotic** – sleep disturbance & anaesthesia / premed
- **Anticonvulsant** – status epilepticus, myoclonic & photic epilepsy
- **Muscle relaxant** – muscle spasm / spasticity
- **Alcohol withdrawal**.
Benzodiazepine metabolism

Long-acting BDZs

<table>
<thead>
<tr>
<th>Half-life (h)</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–100</td>
<td>Chlordiazepoxide</td>
</tr>
<tr>
<td>70–160</td>
<td>Flurazepam</td>
</tr>
<tr>
<td>20–100</td>
<td>Diazepam</td>
</tr>
<tr>
<td>50–100</td>
<td>Chlorazepate</td>
</tr>
</tbody>
</table>

Active metabolites

Conjugation

BDZ + UDP-O

Inactive metabolite

Excreted

Short-acting BDZs

<table>
<thead>
<tr>
<th>Half-life (h)</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–24</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>8–35</td>
<td>Midazolam</td>
</tr>
<tr>
<td>2–5</td>
<td>Temazepam</td>
</tr>
</tbody>
</table>
Washington State 06
Top Therapeutic Class of Drugs
Medicaid Clients Death Related to Prescription Opioids

1. Analgesics, Narcotics
2. Anticonvulsants (Clonazepam and Gabapentin)
3. Selective Serotonin Reuptake Inhibitor (SSRIS)
4. Anti-anxiety Drugs
5. Muscle Relaxants
6. Gastric Acid Secretion Reducers
7. NSAIDS
8. Beta-Adrenergic Agents
9. Antipsychotic, Atypical
10. Penicillin
Comparison of the fatal toxicity index of zopiclone with benzodiazepines.

Reith DM, Fountain J, McDowell R, Tilyard M.

RESULTS: Of the 200 poisoning deaths in NZ for 2001, 39 involved hypnosedatives, and zopiclone was involved in 12.

Hypnosedatives were the sole agents in only one death and were the primary agents in eight deaths. Zopiclone was the sixth most commonly involved agent in poisoning deaths in NZ in 2001.

The relative rate of death per prescription (95% CI) and DDD (95% CI) of zopiclone compared with benzodiazepines were 1.04 (0.49-2.05) and 0.59 (0.28-1.16), respectively. The relative rates of death per DDD (95% CI) for alprazolam and chlormethiazole compared with the other sedatives/anxiolytics were 6.2 (1.6-17.0) and 20.9 (2.5-79.8) respectively.

CONCLUSIONS: The fatal toxicity for zopiclone was not significantly different from that for benzodiazepines as a group when adjusted for usage, whereas alprazolam and chlormethiazole had greater toxicity. Hypnosedatives are contributory factors rather than primary substances in poisoning deaths.
Benzo’s the Hidden Drug

• While there are hundreds of recent articles on Prescription Opiate problems-
  • Most literature on Benzo Abuse/Dependence is > 10 years old
  • Toxicology studies of Opiate deaths usually find Benzo’s too – respiratory depression is additive.
  • Sales of Benzo’s are also increasing dramatically
  • Simple Tox screens often miss Clon- and Alprazolam
  • Benzo withdrawal is among the most dangerous, and can occur behind or on top of other drugs and can be missed
Oxycodone Involvement in Drug Abuse Deaths: A DAWN-Based Classification Scheme Applied to an Oxycodone Postmortem Database Containing Over 1000 Cases*

Authors: Cone E.J.¹; Fant R.V.¹; Rohay J.M.¹; Caplan Y.H.²; Ballina M.³; Reder R.F.³; Spyker D.³; Haddox J.D.

Of 1014 cases:

- 30 (3.3%) involved oxycodone as the single reported chemical entity; of these,

- The vast majority (N = 889, 96.7%) were multiple drug abuse deaths

  The most prevalent drug combinations were oxycodone in combination with benzodiazepines, alcohol, cocaine, other narcotics, marijuana, or antidepressants.
Deaths per 100,000 related to unintentional overdose and annual sales of prescription opioids by year, 1990 - 2006

Source: Paulozzi, CDC, Congressional testimony, 2007
While Opiates have grown fastest, Benzos are not far behind

Source: SAMHSA, OAS, NSDUH data, July 2007
<table>
<thead>
<tr>
<th>Drug</th>
<th>Estimated visits</th>
<th>Percentage</th>
<th>95% CI Lower bound</th>
<th>95% CI Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opiates/opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiates/opioids</td>
<td>172,726</td>
<td>32.2%</td>
<td>136,497</td>
<td>208,956</td>
</tr>
<tr>
<td>Oxycodone/combinations</td>
<td>41,701</td>
<td></td>
<td>28,915</td>
<td>54,487</td>
</tr>
<tr>
<td>Hydrocodone/combinations</td>
<td>39,844</td>
<td></td>
<td>30,154</td>
<td>49,535</td>
</tr>
<tr>
<td>Methadone</td>
<td>38,806</td>
<td></td>
<td>28,151</td>
<td>45,461</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>46,526</td>
<td>26.8%</td>
<td>33,960</td>
<td>59,091</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>28,178</td>
<td></td>
<td>21,721</td>
<td>34,635</td>
</tr>
<tr>
<td><strong>Muscle relaxants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>14,736</td>
<td>4.8%</td>
<td>10,047</td>
<td>19,426</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>6,183</td>
<td></td>
<td>4,430</td>
<td>7,935</td>
</tr>
<tr>
<td><strong>All ED visits involving nonmedical use of pharmaceuticals</strong></td>
<td>536,247</td>
<td>100.0%</td>
<td>448,688</td>
<td>623,806</td>
</tr>
</tbody>
</table>

**GABA$_A$ Receptor**

- Transmembrane pentamer composed of 2 $\alpha$, 2 $\beta$, and 1 $\gamma$ or $\delta$ subunits
  - Each has a binding site for GABA
- Benzodiazepines
  - Bind a cleft of $\alpha$ and $\gamma$ subunits
  - Increases frequency of channel opening
- Barbiturates, (propofol)
  - Bind $\alpha$ subunit
  - Increase duration of channel opening
- Agonist: muscimol
- Antagonist: bicuculine
Benzodiazepines: Major Adverse Effects

- Abuse liability
- Sedation
- Psychomotor impairment
- Cognitive impairment (retrograde amnesia)
- Physiologic dependence/withdrawal
Different BZD Dosing Intervals: Different Rate of Onset

BZD Sedative and Euphoric Effects: Depend on Rate of Plasma Level Rise

Euphoria MBG Scale

Mean Score (Change from Baseline)

Time

† Significant vs placebo
* Significant FAST > Slow or placebo

Sedation PCAG Scale

Mean Score (Change from Baseline)

Time

MBG=Morphine-benzedrine group; PCAG=Phenobarbital-chlorpromazine-alcohol group.

Benzodiazepine Psychoactive Effects

- Prescribed range= anti-anxiety, sedation
- Higher range= euphoria
- Intoxication (double therapeutic range and up) similar to alcohol intoxication, loss of inhibition etc
- Higher level intoxication- ataxia, amnesia, stupor
- Delerium- impaired consciousness, nystagmus
Dose-dependent effects of CNS depressants on levels of consciousness.
Benzodiazepine: Risks of Fall in Elderly

- Increased with short half-life BZDs (but short half-life confounds potency with half-life)
- Increased with high dose
- Falls also increased with SSRIs for unclear reasons (odds ratio 1.8)\(^1\)
- SSRI fall rate close to that of BZDs in one study\(^2\)

BZDs=benzodiazepines; SSRIs=selective serotonin reuptake inhibitors.

Benzodiazepines: Cognitive Effects

- Anterograde amnesia (new learning)
- Not retrograde amnesia (old information)
- Not procedural learning
- Unrelated to sedation
- Worse with high potency
- Transient global amnesia with triazolam
BZD-Induced Cognitive Impairment: Dependent on Age, Dose, and Task

Low Dose

High Dose

“Easy” Task

“Difficult” Task

Minutes post-administration

RMS Deviation

Placebo

ALP 0.75

ALP 0.25

Young

Elderly


ALP=alprazolam.
Benzodiazepine Discontinuation: Treatment Factors

- Duration of use (6 months vs 1 month)
- Dose
- Rate of taper
- Half-life
Determining if Benzodiazepine Use is Safe or Risky

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.
Total 24-hour Dose Levels for the Most Commonly Used Benzodiazepines

<table>
<thead>
<tr>
<th>Drug</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>

Prescription Use Behavior Questionnaire

discriminated between two groups

- Use *more* than prescribed
- Use *more often* than prescribed
- Called for *early refills*
- Rx obtained from >> 1 physician/doctor shopping
- Use *when feeling upset*
- Used to *get high* or for euphoria
Urine toxicology in monitoring (cont.)

Test for what you’re seeking:
- Immunoassays typically miss synthetics, semi-synthetics – SO ASK FOR THEM!
- GC/MS detects these
- May need to specify compounds sought (e.g. methadone)

Use “therapeutic drug monitoring” codes:
- e.g., treat the test clinically like a Digoxin or aminophyline level.
Comparison of clonazepam compliance by measurement of urinary concentration by immunoassay and LC-MS/MS in pain management population.


Samples from 180 patients met these medication criteria:

- Positivity rates were 21% (38 samples) by immunoassay.
- The positivity rate was 70% (126 samples) if the LC-MS/MS cutoff was set at 200 ng/mL.
- Positivity rate was 87% (157 samples) if the LC-MS/MS was set at 40 ng/mL. Concentration distributions revealed a significant fraction (7%) in the 40 - 100 ng/mL range.
BZP withdrawal

- Like alcohol withdrawal, but variable in terms of length - longer for longer acting agents
- More likely to have Seizures
- Rebound and recurrence of Anxiety or sleep disorders
- Taper over Months, vs Crash 3 DAY WD using Anticonvulsants (Depakote, Carbamazepine GabaPenting)
1. **Taper over Months:**
   1. Convert to longer acting agent like Clonazepam or Diazepam
   2. Taper gradually while starting alternative therapies if needed (months)

2. **Use of Anticonvulsants:**

   **Use of anticonvulsants in benzodiazepine withdrawal.** Pages KP, Ries RK. University of Washington, Department of Psychiatry and Behavioral Sciences, Harborview Medical Center, Seattle, Washington 98104, USA.
   1. start high dose Depa or Carba, or Gaba
   2. Taper Benzo by 1/3 each day til DC

The differential effects of medication on mood, sleep disturbance, and work ability in outpatient alcohol detoxification.

A double-blind, randomized controlled trial of patients (n = 136) meeting DSM-IV criteria for alcohol withdrawal and stratified based on detoxification history were treated with carbamazepine or lorazepam for 5 days on a fixed dose tapering schedule. Mood symptoms improved for all subjects regardless of medication or detoxification history.

--- main effect favoring carbamazepine in reducing anxiety (p = 0.0007).

---main effect on sleep that again favored carbamazepine (p = 0.0186).

In this study of outpatients with mild to moderate alcohol withdrawal, carbamazepine was superior to lorazepam in reducing anxiety and improving sleep.
What do you do about Psychiatric Disorder Rebound?
Paroxetine, Imipramine, Benzodiazepine in GAD

**Graph:**
- **Y-axis:** Mean Hamilton Rating Scale for Anxiety
- **X-axis:** Baseline, Week 2, Week 4, Week 8
- **Legend:**
  - Paroxetine (N=30)
  - Imipramine (N=26)
  - 2′-Chlordesmethyl-diazepam (N=25)

**Annotations:**
- *P*<0.05 vs benzodiazepine
- GAD=generalized anxiety disorder.
Phase II Cross-National Comparison of Alprazolam, Imipramine, and Placebo (N=1080)*

Clinical Outcome Measures

- **Alprazolam**
- **Imipramine**
- **Placebo**

Mild

Moderate

Marked

Weeks

Baseline

1

3

4

6

8

EP

*Global improvement, panic attacks, anticipatory episodes, overall phobia, work, social and leisure life disability, depression (Hamilton Depression Scale, not Symptom Checklist 90) all significantly different between both drugs and placebo (de la Fuente, APA, 1988).
Social phobia: Phenelzine, Alprazolam, CBT, and Placebo

Social Phobia Score (Fear Questionnaire)

Phenelzine (n=13)  Alprazolam (n=12)  CBT (n=17)  Placebo (n=17)

Pretest  Posttest  Follow-up

CBT=cognitive-behavioral therapy.
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