Benzodiazepine Use

Trip Gardner, MD
Chief Psychiatric Officer
Medical Director Homeless Health Services
Penobscot Community Health Care

THE FACTS

You can’t see her face, but you can help her feel less anxious.

Barbital 1903
Phenobarbital 1912
Chlordiazepoxide 1957
Diazepam 1963
Several Thousand, 35 Clinically

“MOTHER’S LITTLE HELPER”

Sweet, refreshing...

VALIUM

ALCOHOL

Table Title:
Prevalence of Any Benzodiazepine Use, Long-acting Benzodiazepine Use, and Use of Long-Acting Benzodiazepines by Sex and Age Group in the United States in 2008

Percentage of Population in the United States in 2008 With Any Benzodiazepine Use by Sex and Age

Figure Legend:
Percentage of Population in the United States in 2008 With Any Benzodiazepine Use by Sex and Age

From: Benzodiazepine Use in the United States

Copyright © 2015 American Medical Association. All rights reserved.

From: Benzodiazepine Use in the United States

Copyright © 2015 American Medical Association. All rights reserved.

DISCLOSURES

None
ILLIGITIMATE BENZO USE
- 7.9% took a benzo illegitimately 2011
  - 2.6% of children 12-17
  - 11.6% of young adults 18-25
  - 8.0% of adults > 26

- 20.4 million over 12 - lifetime misuse of a benzo

WHO'S PRESCRIBING NATIONALLY
Roughly 9 of 10 older adults who use benzodiazepines on a
long-term basis have their prescriptions written exclusively by primary care
physicians or other non-psychiatrists


HOW DO BENZOS WORK?

- They're anti-anxiety pills...
- But I'm afraid to take them!!

MECHANISM OF ACTION
- Benzodiazepines potentiate the effects of endogenous GABA, the main inhibitory neurotransmitter
- Alcohol potentiates the effects of endogenous GABA, the main inhibitory neurotransmitter

IMS HEALTH’S 2011 STATISTICS

<table>
<thead>
<tr>
<th>Psychotropic Ranked by Sales:</th>
<th>Numbers Prescribed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanax 49 million</td>
<td>Ativan 27.6 million</td>
</tr>
<tr>
<td>Ativan 27.6 million</td>
<td>Klonopin 26.9 million</td>
</tr>
<tr>
<td>Klonopin 26.9 million</td>
<td>Valium 15 million</td>
</tr>
</tbody>
</table>

Benzo’s are 10th most commonly prescribed therapeutic class...

BUT... Benzo’s are not first-line therapy for any common psychiatric disorder

11/9/2015
Main inhibitory neurotransmitter 50% of the inhibitory synapses
GABAergic inhibition is seen at all levels of the CNS, 40% of all neurons respond
Consequences of GABA inhibition
• Decreased excitatory transmission
• Decreased NE, 5HT, ACH, DA
• Decreased anxiety
• Decreased alertness
• Decreased emotional response
• Decreased endocrine secretion
• Decreased muscle tone
• Decreased memory
• Decreased new learning

ONSET

<table>
<thead>
<tr>
<th>Drug (Dose)</th>
<th>Time to Peak</th>
<th>Onset (Time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>1.5-2H IR; 5-11H ER</td>
<td>15-60min</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>1-2H</td>
<td>15-30min</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>0.5-5H</td>
<td>20-30min</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>1-4H</td>
<td>20-60min</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>2H</td>
<td>20-60min</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>2H</td>
<td>30-45min</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>2-3H</td>
<td>45-60min</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>2-4H</td>
<td>60-120min</td>
</tr>
</tbody>
</table>

Faster onset = higher risk of abuse
Slower onset = lower risk of abuse

Commonly Prescribed Benzodiazepines: A Comparison Chart


Also relevant to the potential for psychiatric disorders and substance use disorders.

CLINICAL USES

Vallium (Valium)

Reduce psychic tension

Clinical Information

- Efficacy and safety in the treatment of anxiety and related symptoms
- May be effective in the management of symptoms associated with anxiety disorders
- Used in the treatment of alcohol withdrawal symptoms

Side Effects

- Drowsiness
- Fatigue
- Headache
- Dizziness
- Nausea
- Constipation
- Dry mouth
- Sexual dysfunction

Contraindications

- Hypersensitivity to benzodiazepines
- Active liver disease
- OB/NE: Use only if potential benefit outweighs risk to mother and fetus

Warnings

- Benzodiazepines can cause drowsiness, dizziness, and impaired coordination
- Should be used with caution in patients with a history of drug or alcohol abuse

Precautions

- Benzodiazepines should be used with caution in elderly patients
- Use with caution in patients with a history of suicidal ideation or behavior

Dosage and Administration

- Oral: Adults: 5-10 mg/day in divided doses; Children: 0.5-1.0 mg/kg/day
- Intravenous: Adults: 0.02-0.1 mg/kg, Children: 0.01-0.02 mg/kg

Adverse Reactions

- Sedation
- Dizziness
- Nausea
- Drowsiness
- Headache
- Fatigue

Overdose

- Symptoms: Drowsiness, slurred speech, paradoxical excitation, respiratory depression
- Management: Supportive care, gastric irrigation, activated charcoal, flumazenil (benzodiazepine antagonist)

Drug Interactions

- Benzodiazepines should be used with caution when administered concomitantly with other CNS depressants
- May potentiate the effects of other centrally acting drugs

Pregnancy

- Category D: Use only if potential benefit outweighs risk to mother and fetus

Lactation

- Excretion in breast milk: Unknown

Pediatrics

- Use with caution in children

Geriatric Use

- Use with caution in elderly patients

Allergies

- Hypersensitivity: Use with caution

Reference

SHORT TERM USES

- Excessive Anxiety
- Muscle Relaxation
- Alcohol/Benzo Withdrawal
- Insomnia
- Acute Psychosis
- Acute Mania
- Acute Agitation
- Sedation for office procedure
- Catatonia
- Seizures and neurological disorders

Royal College of Psychiatrists
“In all the conditions in which they are used, benzodiazepines tend to produce dependence and withdrawal reactions. So - Benzodiazepines should only be used for periods of up to 4 weeks”
http://www.rcpsych.ac.uk/healthadvice/treatmentswellbeing/benzodiazepines.aspx

CONTINUING BEYOND 4 WEEKS

- May result in:
  - Loss of effectiveness
  - Tolerance
  - Dependence
  - Withdrawal
  - Persistent adverse effects
  - Interference with preferred medication and counseling

SHORT TERM ANXIETY ADJUNCT GREAT IDEA?

- Can Be Used during initial treatment as adjunct
  - while waiting for definitive therapy of long-term meds/counseling
- Addition to initial antidepressants only increased adequate duration time from 39.3% to 42.4%
  - In those that received both, 14.1% still on it after 1 year
- In Panic Disorder - Augmenting acute-phase antidepressant treatment with 4-6 weeks of clonazepam/alprazolam resulted in faster symptom resolution compared to placebo augmentation BUT no difference by 8 to 12 weeks

ADVERSE EFFECTS AND CONTRA-INDICATIONS

- Most common subjective effect
- Tolerance appears to develop after a few weeks, but residual effects remain
- Higher doses lead to unsteadiness, slurring of speech, disorientation
- Heightened when BZDs are combined with alcohol

Sedation

- When used to treat acute anxiety


GUIDELINES FOR THE USE OF BENZODIAZEPINES IN OFFICE PRACTICE IN THE STATE OF MAINE
http://www.benzos.une.edu/documents/prescribingguidelines26-08.pdf
**PSYCHOMOTOR EFFECTS**

- Impaired ability to perform simple repetitive tasks
- Related to speed of execution: studies have shown persons on BZDs slow down to maintain accuracy of performance
- Size of effect is dose related
- Despite tolerance, impaired performance on simple repetitive tasks persists up to 1 year after long-term use

Lader M. Benzodiazepines revisited—will we ever learn? Addiction. 2011 Dec;106(12):2086-109

**COGNITIVE EFFECTS**

- Inhibit learning of alternatives
- Impaired higher brain functions
  - Learning
  - Anterograde memory
- Magnified by the addition of alcohol
- Dose related
- Effects after BZD discontinuation
  - Impairment did not fully resolve within 6 months for those on high dose diazepam (mean dose 48mg)

**DISINHIBITION**

- Elderly
- Children
- Developmentally Disabled
- Borderline PD
- Alcohol-use Disorders
- Traumatic Brain Injury
- Disorders with impulse control problems

**PSYCHOLOGICAL DEPENDENCE**

- Overreliance on the need for the agent
- Loss of self confidence
- Learn no other skills
- Drug-seeking behavior and aberrant drug-taking behavior
- Block healthy development socially, cognitively, emotionally, behaviorally
- Misplaced fears of anticipatory anxiety

**TOLERANCE**

- Long term use may decrease efficacy of GABA-A receptor
- When discontinued, down regulated inhibitory system is uncovered and hyperexcitability ensues
- Hypnotic rapidly
- Anxiolysis slowly
  - But little evidence retain efficacy > 6mos
  - Often continued to suppress withdrawal states which mimic anxiety
  - Dose escalation maintains dependency

**INCREASED RISK OF DEPENDENCE**

- Short Duration of Action (ALPRAZOLAM)
- Long-term Use
- High Dose
- High Potency (ALPRAZOLAM/CLONAZEPAM)
- Alcoholism/Drug Dependency
- Personality Disorders
- Use Without Medical Supervision
- The risk of dependence led the Committee on Safety of Medicines to recommend that benzodiazepines should be restricted to severe need and that treatment should be at the lowest dose possible and not be continued beyond 4 weeks


Chronic BENZOS lead to ANXIETY
Use Reduces receptor’s affinity
In France Psychosis
Somatization
Breathing drops PCO2 levels while simultaneously increasing including alcohol
More prone to confusion, paradoxical excitation
Cardiopulmonary Overall odds ratio
Medullary desensitizing drugs like 
Increased heart rate
COPD causes a chronic retention of CO2 and over time can lead to Increased respiratory rate
When PCO2 increases, the medulla stimulates the pulmonary 
DELIRIUM COPD causes a chronic retention of CO2 and over time can lead to Increased respiratory rate
Medullary desensitizing drugs like 
Increased respiratory rate
COPD causes a chronic retention of CO2 and over time can lead to Increased respiratory rate
DELIRIUM COPD causes a chronic retention of CO2 and over time can lead to Increased respiratory rate
Metabolism
Increased body temp
Increased sensitivity
Increased body temp
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increased sensitivity
Increase
DANGER WITH ADDICTION DISEASE VULNERABILITY

- Addiction is a disease process similar no matter the substance.
- Greater risk for inappropriate benzo use.
  - Personal history of any substance/alcohol use disorder
  - Family history of any substance/alcohol use disorder
  - Those who cope chemically

- Leads to more violence, other drugs, memory impairment for events, disorganized, confused, overdose, jail.

“HELPING” CAN BE HARMFUL

Emergency Contraindications to Continued Prescribing (above all, first do no harm)

- Altering a prescription = FELONY
- Selling prescription drugs = DRUG DEALING
- Accidental/intentional overdose = DEATH
- Threatening staff = EXTORTION
- Too many scams = OUT OF CONTROL

THE HARM

BECAUSE THEY DON’T PAY YOU ENOUGH TO PUT UP WITH ALL THIS SHIT...

NON-ADVISED/ILLICIT USES

- “Top off”
- Potentiate Methadone
- Relieve Cocaine’s Side Effects
- Augment Alcohol Effects
- Alcohol Withdrawal
- Facilitate Sexual Assault
- Treat Excess Anxiety
- Over-treat Normal Anxiety
- Numbing from Trauma
- Take Excess Rx Doses
- Give to Others
- Income Production

DIVERSION

From 2014 federal, state and local forensic labs:
1. 43,000 oxycodone
2. 40,747 alprazolam
3. 33,132 hydrocodone
4. 15,209 buprenorphine
5. 11,797 clonazepam
6. 5559 methadone
7. 5446 diazepam

- Alprazolam #1, hydrocodone #2, oxycodone #3 in 2006 DEA Office of diversion control report.
- Alprazolam increased 75% from 2001 to 2005, clonazepam doubled.
- Diazepam, alprazolam, morphine and oxycodone had the highest ratios of drugs reported in forensic labs per prescriptions.

USE ➔ ER VISITS

From 1996-2011:
- The number of emergency department visits related to benzodiazepine or opioid intake increased by 106%.
- Benzodiazepine-related visits increased by 108%.
- Opioid-related visits increased by 101%.

USE ➔ ER VISITS

From 1996-2011:
- The number of emergency department visits related to benzodiazepine or opioid intake increased by 106%.
- Benzodiazepine-related visits increased by 108%.
- Opioid-related visits increased by 101%.


**ACCIDENTS AND INJURIES**

- Increased likelihood of MVA, injury, falls
  - 50% increase in elderly hip fracture
  - 60-80% increase in MVA
  - 7.7 fold increase in odds of an accident when taken with alcohol

- Epidemiological studies indicate 3-6% drivers involved in fatal car crashed had used a benzo

**MAINE IMPAIRED DRIVER URINALYSIS TOXICOLOGY SCREENS: BENZODIAZEPINES**

<table>
<thead>
<tr>
<th>Year</th>
<th>Clonazepam</th>
<th>Ativan</th>
<th>My BZD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>8%</td>
<td>5%</td>
<td>40%</td>
</tr>
<tr>
<td>2010</td>
<td>5%</td>
<td>17%</td>
<td>40%</td>
</tr>
<tr>
<td>2011</td>
<td>12%</td>
<td>20%</td>
<td>45%</td>
</tr>
<tr>
<td>2012</td>
<td>8%</td>
<td>40%</td>
<td>45%</td>
</tr>
</tbody>
</table>

**ER VISITS FROM BENZO/OPIOIDS**

![Chart showing ER visits from benzodiazepines and opioids]

**BENZOS AND OPIOIDS**

- 33% LT CNCP Opioid users reporters recent Benzodiazepine use, 53% of those daily
  - >pain, pain interference with life, lower self efficacy
  - On >200mg MED
  - Also on antidepressants or antipsychotics
  - Had SUDs
  - More ER, ambulance
  - Use inconsistent with CNCP and all Chronic MH condition guidelines

- Benzodiazepine and narcotic combination substance abuse treatment admissions
  - 5,032 in 2000 to 33,701 in 2010 - 569.7%
  - all others substances declined 9.6%

- 38.7% started both in the same year
- 34.1% started the narcotic pain reliever first
- 27.1% started the benzo first

**BENZO/OPIOID COMBO THERAPY**

- Additive sedation
- Decreased psychomotor performance and attention
- Increased impaired episodic memory
- Metabolism interference
- Enhanced “boosting” of their high
- Increased accidents, injuries, ER visits
- Death

**Number of deaths caused by pharmaceuticals and/or illicit drugs: 2010–2014**

- From 2011 to 2014, Maine observed a 34% increase in the number of all drug related overdose deaths.
- In 2014, most (89%) drug overdose deaths involved pharmaceutical drugs.
- There was a 54% increase in the number of illicit drug related overdose deaths was observed from 2011 to 2014.

*Source: Office of the Chief Medical Examiner*
From presentation by Tim Diomede, MPPM, State Epidemiological Outcomes Workgroup Maine DHHS Special Report October 2015

11/9/2015

**Benzos**

- Accidental or deliberate overdose
- Injuries
- Delay return of normal sleep pattern
- Mask underlying pathology
- Dependence, Abuse, Addiction and Stimulating the brain's previously controlled addiction disease
- Diversion
- Fall Risk
- Vehicle accident risk
- On opioids
- Safe Environment
- Decreasing response to other treatments
- Drug interactions
- Cognitive impairment
- Respiratory Depression and other condition interactions
- Diversion
- Fall Risk
- Vehicle accident risk
- On opioids
- Safe Environment
- Decreasing response to other treatments
- Drug interactions
- Cognitive impairment
- Respiratory Depression and other condition interactions

**Questions Before Prescribing**

- What is the diagnosis and is there an indication?
  - “Anxiety” is not a diagnosis, it is a bodily function
  - Without a bodily function, there is no diagnosis
  - Is this just a normal anxiety response to situation?
- Have more preferred treatments had adequate trials?
- Am I following clinically established guidelines of care or am I following the patient’s or the marketer’s or the “customer is always right” guideline of care?
- Does immediate benefit outweigh the immediate and long-term risk?
- Has education been provided about the risks?
- Has an exit strategy been agreed upon?

**Number of drug deaths involving specific drug types**: 2014

- More than one in three overdose deaths involved benzodiazepines.
- More than one in four overdose deaths involved heroin/morphine.

**Number of drug deaths involving specific drug types**: 2010–2014

- In 2014, there were 57 deaths involving heroin/morphine: a 53% increase since 2011.
- Fentanyl related deaths increased by 377% from 2013 (9) to 2014 (43)

**Calls to Poison Center**

- Substances most frequently requested for verification by non-law enforcement, by drug type: (NNEPC, 2014)

**PUTTING IT INTO PRACTICE**

- Xanax adds a unique dimension to your patient management
- For anxiety associated with depression
- “Anxiety” is not a diagnosis, it is a bodily function
- Without a bodily function, there is no diagnosis
- Is this just a normal anxiety response to situation?
- Have more preferred treatments had adequate trials?
- Am I following clinically established guidelines of care or am I following the patient’s or the marketer’s or the “customer is always right” guideline of care?
- Does immediate benefit outweigh the immediate and long-term risk?
- Has education been provided about the risks?
- Has an exit strategy been agreed upon?
NO good evidence supports long-term use for any mental health indication for most people.

During prescription renewal or medication review, the prescriber should discuss the risks of chronic benzodiazepines and the benefits of discontinuation (on cognition, mood, sleep, and energy level) and advise the patient to consider reduction or discontinuation.

Patients often do not recognize their own impairment.

Intent→ Are you treating a diagnosis or creating one (addiction)?

Effect→ Does the benzod improve the patient’s functional status?

Taper 10% starting dose every 1-2 weeks

Decrease taper amount and lengthen interval for final 25-35% of taper down to no more than 5% every 2-4 weeks for the last 20%.

Consider switching to long-acting benzodiazepine at equivalent dose like diazepam but no significant difference between short and long acting in taper study. If a switch is made, it should be stepwise—one dose every one to two weeks if the patient is on multiple daily doses.

Earlier withdrawal easier to tolerate than later

Be flexible→ may stay put longer, but try not go backwards

Rate of tapering individualized

Duration of Rx dependent on reliability/severity of addiction

Withdrawal sx may resemble sx of anxiety or insomnia

May not feel better until off, don’t stop

Use scheduled rather than p.r.n. doses

F/U visits q. 1-2 weeks and ask patient about the benefits of tapering (e.g., increased energy, increased alertness)

Most still off benz after 3y and have lower levels of depression/anxiety

Long-term use rarely justified as most patients show improvement when benz is withdrawn—cognitive functioning, memory, balance

SSRIs and CBT have clinically significant long-term benefits established by rigorous studies with better toleration without abuse/dependence

Impaired performance on simple repetitive tests for 1y and on tests of attention for several years in long-term benz users

Cognitive function improved at 6 months
Normal Anxiety = Normal Motivation

Too Little Anxiety = Frozen by lack of drive

Too Much Anxiety = Frozen by fear

Borwin Bandelow et al Guidelines for the pharmacological treatment of anxiety disorders, obsessive–compulsive disorder and posttraumatic stress disorder in primary care
International Journal of Psychiatry in Clinical Practice 2012 16:2, 77-84

Receipt of CBT-oriented, quality psychosocial (but not pharmacologic) care showed a strong dose-response relationship with satisfaction with mental health care for anxiety disorder.
GENERALIZED ANXIETY DISORDER

- First Line → SSRI and/or CBT
- Nonresponse after adequate SSRI trial → try CBT and/or a different SSRI
  - Adequate = 6 - 12 weeks, moderate dose at least
- If still nonresponsive → try SNRI
- If still nonresponsive → try Pregabalin, SNRI, buspirone, TCA, or mirtazapine
- If partial response → augment with CBT, buspirone or hydroxyzine
- Exercise has been shown to be effective as well

GENERALIZED SOCIAL ANXIETY DISORDER

- First-line treatment → SSRI/SNRI and/or cognitive behavioral therapy
- Other agents with some support for efficacy include MAOIs, Gabapentin and Pregabalin
- SSRI, SNRIs, and MAOIs may take four to six weeks for an initial response and 12 to 16 weeks for full response

PANIC DISORDER

- SSRIs and/or CBT as first-line treatment
- Next choices are 2nd SSRI, SNRIs, TCAs, MAOIs
- CBT and antidepressant medication have been shown in controlled trials to be equally effective for panic d/o
- Combination of CBT and antidepressant treatment has shown a small advantage over either therapies alone

PTSD

- First Line → Trauma-focused psychotherapy (prolonged exposure, cognitive processing therapy, eye movement desensitization and reprocessing) and/or SSRI/SNRI
- Partial response → Trauma-focused psychotherapy as adjunct in patients who have only partial response to SSRI/SNRI
- Trauma-focused psychotherapy can replace SSRI/SNRI in those nonresponsive to an adequate trial of medication
- Next → trial of a different Trauma-focused psychotherapy or different SSRI
- Consider prazosin for patients that experience sleep disruption or nightmares

PTSD PHARMACOTHERAPY GUIDELINES VA/DOD

- First Line → Exposure and Response Prevention Cognitive-Behavioral Therapy, an SSRI, or both
- Long duration, > 6 weeks at high dose of SSRI
- If no response → try a different SSRI, Venlafaxine, Clomipramine
- If SSRI/SNRI results in partial response → augment with CBT or antipsychotic

OCD

- First Line → Exposure and Response Prevention Cognitive-Behavioral Therapy, an SSRI, or both
- Long duration, > 6 weeks at high dose of SSRI
- If no response → try a different SSRI, Venlafaxine, Clomipramine
- If SSRI/SNRI results in partial response → augment with CBT or antipsychotic
AMYGDALA = “ANXIETY BUTTON”

Cognitive Therapy (+)

SLEEP WITHOUT PILLS? NO WAY!!!

- **Stimulus Control**
- **Relaxation Training**
  - Progressive muscle relaxation, guided imagery, or abdominal breathing
- **Cognitive Behavioral Therapy for Insomnia**
  - Seeks to change patient’s unrealistic expectations about sleep
- **Sleep Restriction**
- **Paradoxical Intention**
  - Patient is trained to confront fear of staying awake; objective to eliminate anxiety about sleep performance
- **Biofeedback Therapy**
  - Teaches patient to control some physiologic variable through visual or auditory feedback. The objective is to reduce somatic arousal
- **Sleep Hygiene**

**INSOMNIA THERAPIES**

**Stimulus control therapy rules**
1. Go to bed only when sleepy.
2. Do not watch television, read, eat, or warm while in bed. Use bed only for sleep and sex.
3. Get out of bed if unable to fall asleep within twenty minutes and go to another room. Return to bed only when sleepy. Repeat this step as many times as necessary throughout the night.
4. Set an alarm clock to wake up at a fixed time each morning including weekdays.
5. Do not take a nap during the day.

**Ten basic rules for a good night’s sleep**
- Sleep only as much as you need to feel rested and then get out of bed
- Keep a regular sleep schedule
- Avoid napping
- Get up at the same time every day
- Avoid caffeinated beverages after lunch
- Avoid alcohol near bedtime: no “nightcap”
- Avoid smoking, especially in the evening
- Do not go to bed hungry
- Adjust bedroom environment
- Deal with your worries before bedtime

**WHY NOT RELAXATION OR EXERCISE?**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SOL (min)</th>
<th>WASO (min)</th>
<th>Sleep Efficiency (%)*</th>
<th>Total Sleep Time Increase (min)</th>
<th>Sleep Quality (SMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpharmacologic</td>
<td>-19.7 to -24</td>
<td>-22.5</td>
<td>24.3 to 32</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Relaxation</td>
<td>-14.5</td>
<td>-1.6</td>
<td>23.0</td>
<td>0.37</td>
<td>-</td>
</tr>
<tr>
<td>Exercise</td>
<td>-12</td>
<td>-2</td>
<td>0.32</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>-12.2 to -16.7</td>
<td>-23.1</td>
<td>39.1 to 61.8</td>
<td>0.28</td>
<td>-</td>
</tr>
<tr>
<td>Nonbenzodiazepines</td>
<td>-15.1</td>
<td>12.6</td>
<td>18.0</td>
<td>0.38</td>
<td>-</td>
</tr>
</tbody>
</table>

SOL = sleep-onset latency; mean difference from placebo in minutes
WASO = wakefulness after sleep onset
SMD = standardized mean difference from placebo: the greater the difference, the more effective the medication
* Amount of time spent asleep as a percentage of total time spent in bed

**References**
- Bonnet M, Arand D. “Treatment of insomnia” Up to Date Feb 2013 http://www.uptodate.com/contents/treatment-of-insomnia?topicKey=PULM%2F7691&elapsedTimeMs=10&source=search_result&searchTerm=Hypnotics&selectedTitle=1%7E124&view=print&displayView=full
**GUIDE FOR PRESCRIBING HYPNOTICS**

<table>
<thead>
<tr>
<th>Prescribe the lowest effective dose</th>
<th>Risks of rebound effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribe for short durations (two to four weeks) and intermittently (duration based on patient's return to an acceptable sleep cycle)</td>
<td>Hypnotics should be discontinued gradually; physician should be alert for adverse effects (especially rebound insomnia) and withdrawal phenomena</td>
</tr>
<tr>
<td>Watch for requests for escalating doses or resistance to tapering or discontinuing</td>
<td>Long term treatment is of un-established efficacy and tolerance probably occurs</td>
</tr>
<tr>
<td>Risk benefit ratio for the benzos becomes adverse for many beyond 2 - 4 weeks</td>
<td>Avoid if patient has a hx of substance abuse, COPD, myasthenia gravis, respiratory impairment, or acute CVA</td>
</tr>
</tbody>
</table>

Identify and address behaviors, circumstances, and underlying disorders contributing to insomnia


KALYANAKRISHNAN RAMAKRISHNAN, MD, and DEWEY C. SCHEID, MD, MPH, "Treatment Options for Insomnia." American Family Physician. 2007 Aug 15;76(4):517-26