TOWARDS SAFER PRESCRIBING OF SEDATIVE-HYPNOTICS

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Objectives

- To review the history & pharmacology of benzodiazepines and other sedative-hypnotics
- To educate prescribers about the indications for the proper use of benzodiazepines, including recent information about benzodiazepine use and abuse
- To educate prescribers about other treatments of anxiety disorders & insomnia besides benzodiazepines
Disclosures

- None
Several of you are about my age and, like me, are not in academics. We treat patients every day.

We keep up with advances and “state of the art” in our field. e.g. huge advances in joint replacement and cancer treatment.
Updates in the Last 30 Years

- Probably some basic conditions that all of us deal with regularly yet we haven’t kept up with all the advances over the years:
  - Hypertension
  - Anxiety disorders
  - COPD
  - Insomnia

- Much of our “education” on these topics is probably driven by pharmaceutical company influenced presentations.
Updates in the Last 30 Years

- Do your own internet search & review.
- Read some of the reviews or “state of the art” articles.
- This can be done at no cost and are free from commercial bias.
- This will also lead you to practice guidelines by a number of different organizations.
- Ask yourself:
  - What is really the gold standard?
  - What is acceptable practice?
  - What should I implement in my practice or how should I change what I am doing?
Updates in the Last 30 Years

- As part of my preparation for updating my talk this year I did this for you for:
  - Anxiety disorders
  - Insomnia
- I compiled some review articles, updates and practice guidelines.
- Almost all free and available for download
  - Printed copy of several
  - Reference List
  - Thumb drives
Because If You Don’t…

When something goes wrong ---
you can be assured that the expert witness hired by the plaintiff will be armed with these articles and practice guidelines.

“Your Honour, I call Nigel From The Pub ... expert witness on whatever you like.”
Big Take Home Points

- Benzos are not the first line treatment for either anxiety disorders or insomnia.
- For anxiety disorders - SSRI’s/SNRI’s and/or Cognitive Behavioral Therapy (CBT) are the first line treatment.
- Benzos can be used short-term (2-4 weeks) for relief of severe anxiety while waiting for the full treatment effect of the other modalities.
Big Take Home Points - Insomnia

- Several benzos and Z-drugs are indicated for short-term (1-2 weeks) use in insomnia.
- These drugs are neither indicated nor effective for the long-term treatment of insomnia.
- The gold standard for insomnia is improving sleep hygiene practices and cognitive behavioral therapies (CBT) plus treating the underlying contributing conditions.
Big Take Home Points

- The reason for the continuing increase in the number of benzodiazepine prescriptions and the increased complications are that more people are on chronic benzodiazepines.
- Benzodiazepine use and adverse effects are most prevalent in the elderly population.
Benzodiazepines should not be used in patients with a history of Substance Use Disorders (Addiction).
Big Take Home Points

- FDA Black Box Warning on all opioids and benzodiazepines. Prescribe them together at your own peril!
What we are going to cover

- What are Sedative Hypnotics/How they work
- History – Older Sedative-Hypnotics > BZ > Newer Drugs
- Pharmacology
- Differences in benzodiazepines (=benzos, = BZ)
- Clinical Use
- Safe Prescribing & Tapering
Sedative-Hypnotics

- Suppress CNS activity
- Pharmacologically diverse
- Cause effects along a continuum of: calming > sleep > unconsciousness > coma > death
- Uses:
  - Anxiolytics (among the “minor tranquilizers”)
  - Hypnotics/soporifics
  - Anti-convulsants
  - Muscle relaxants
  - Anesthesia induction
GABA System

- Most all of these sedative hypnotics act on this GABA system.
- Gamma-aminobutyric acid is the primary inhibitory neurotransmitter system in the CNS.
- There are GABA receptors with multiple sub-types in different regions, etc.
- GABA binds to these receptor sites causing a chloride ion channel to open and then all of these inhibitory things take place.
- Stimulation of the GABA receptors lead to all the effects we are talking about: sedative, anti-convulsant, hypnotic, amnestic
Y-aminobutyric acid = GABA

- Benzodiazepines bind at the alpha sub-unit to cause positive modulation of the GABA receptors - meaning that they augment the effect of GABA at the receptor.
- Barbiturates are GABA receptor agonists.
- Alcohol acts on the membrane wall to prolong opening of the chloride ion channel.

(http://www.neurocypres.eu/science)
History of Sedative-Hypnotics

- Alcohol is the oldest
- Very similar chemically to what we are talking about today
- ~10 million years ago – a genetic mutation that allowed humans to metabolize alcohol
- This allowed humans to come down out of the trees and eat fermented fruit that had fallen to the ground when other food sources were not available.
Alcohol in Biblical Times

- 6 Give strong drink unto him that is ready to perish, and wine unto those that be of heavy hearts.
- 7 Let him drink, and forget his poverty, and remember his misery no more.

Proverbs 31:6-7 King James Version (KJV)
Alcohol

- Hyrdomel/Mead
- Wine
- Distillation-introduced in the Medieval Period
Plants in the Middle Ages

often were the alkaloids from plants

- Opium
- Lavender
- Chamomile
- Belladonna
- Jimson weed
- Hemp
History – Late 1800’s

• Chloral hydrate©
  • ‘Mickey Finn’
• Paraldehyde
• Bromides
1864-Synthesis of Malonylurea

Barbituric acid

Adolph von Baeyer
Diethyl-barbituric acid
Patented 1903
Generic name changed to barbital after WWI

"Secure & Harmless"
During the 1920’s-1940’s dozens came on the market

now she can cope...

thanks to

**Butisol**

(SODIUM BUTABARBITAL)

“daytime sedative” for everyday situational stress

When stress is situational—environmental pressure, worry over illness—the treatment often calls for an anxiety-allaying agent which has a prompt and predictable calming action and is remarkably well tolerated. Butisol Sodium (sodium butabarbital) meets this therapeutic need.

After 30 years of clinical use, ... still a first choice among many physicians for dependability and economy in mild to moderate anxiety.

Contraindications: Porphyria or sensitivity to barbiturates.

Precautions: Exercise caution in moderate to severe hepatic disease. Elderly or debilitated patients may react with marked excitement or depression.

Adverse Reactions: Drowsiness at daytime sedative close levels; skin rashes, “hangover” and systemic disturbances are seldom seen.

Warning: May be habit forming.

**Usual Adult Dosage:** As a daytime sedative, 15 mg (1/4 gr.) to 30 mg (1/2 gr.) t.d.s. or q.i.d. Available for daytime solution: Tablets, 15 mg (1/4 gr.); 30 mg (1/2 gr.) Elmer, 30 mg per 5 cc. (alcohol 7%).

**Buticaff® (Capsules Butisol, Sodium sodium butabarbital))** 15 mg (1/4 gr.); 30 mg (1/2 gr.).

Early 1900’s-Barbiturates

- Clinically introduced in the early 1900’s for use as sedative-hypnotics.
- Problems with safety: Dependence and Overdose (death)
- Replaced in popularity in the 1950’s and 1960’s by the benzodiazepines because of safety concerns
Barbiturates

- Are actual agonists at the GABA receptor (not just modulators).
- Causes prolonged opening of the chloride ion channel of the GABA receptor
  - Paralysis of neurons responsible for respiratory drive
  - Fatal overdose
Barbiturates Today

• Phenobarbital-
  • Still in use as an anti-convulsant
  • Relatively low abuse potential
  • Dysphoria or at least not much euphoria
  • Stopping suddenly can lead to withdrawal seizures
  • Needs to be tapered

• Some ultra-short acting barbiturates used for anesthesia induction
1950’s- Minor Tranquilizers

- 1955- Meprobamate (Miltown©/Equanil©)
- Others: Methaqualone (Quaalude©)
- A pro-drug of meprobamate is still available as: Carisprodol (Soma©)
  - Marketed as a muscle relaxant.
  - Different than other skeletal muscle relaxants.
1960’s- Benzodiazepines

- 1957: chlordiazepoxide (Librium©) found to have hypnotic, sedative, and muscle relaxant effects
- Less toxic in overdose and fewer drug interactions than barbiturates
- Superior efficacy and safety compared to meprobamate
- In the 1960’s & 1970’s benzodiazepines became the sedative-hypnotics of choice
1970’s- Valium©

- 1963- Valium© (Diazepam) released.
- Became the most prescribed benzodiazepine by 1973
More Recent (1990’s)
Non-benzodiazepine Hypnotics—“The Z Drugs”

- Zolpidem = Ambien©
- Zaleplon = Sonata©
- Zopiclone –sold in U.S. only as the S-isomer – eszopiclone = Lunesta©
- Pharmacologically diverse but are not BZ
- Very similar effects and mechanism of action to BZ (at the GABA –α site)
- Brought to market as potentially safer and less addiction liability than BZ
  (Huedo-Medina et al., 2012)
Non-Benzodiazepine Hypnotics

- Zolpidem(Ambien®), Zaleplon(Sonata®), Eszopiclone(Lunesta®)- The Z-drugs
- Rapid onset(<one hour)
- Short half-lives
- Decrease sleep latency(time to onset of sleep)
- Little effect on other sleep stages (unlike benzos)
- Benzodiazepine effects on sleep: Prolong stage 1 and 2; shorten stages 3 and 4(deep sleep); Shorten duration of REM sleep

(Huedo-Medina et al., 2012; Ries, 2009)
Zolpidem (Ambien©)

- Zolpidem is the second most commonly prescribed hypnotic in the USA (alprazolam is number 1); approved by FDA in 1999.
- Limit use to ≤7 days, to avoid rebound insomnia
- Zolpidem can produce dependence and withdrawal delirium
- Do not use in patients with history of addiction

(Miller, 2002; Ries, 2009)
Zolpidem (Ambien©)

- Clearly is abused and can become dependent on it.
- Can cause amnesia and ‘complex sleep behaviors’.
- Very similar to benzodiazepines and we see very similar addiction syndrome/treat similarly.

(Olkkola, 2008)
Melatonin & MT Receptor Agonists

- Ramelton - sold in U.S. as Rozerem
- FDA indicated for longer term
GHB=gamma-hydroxy-butyric acid

- Is a chemical with sedating properties
- Popular as a chemical of abuse (bought via internet) 15 years ago
- Used as a date-rape drug
- The sodium salt of GHB is also known as sodium oxybate
- Schedule III indicated for daytime sleepiness in patients with narcolepsy
Suvorexant =

- Approved FDA August 2014
- First in kind mechanism of action
- Does not work via GABA, histamine or melatonin
- Is a DORA- dual orexin receptor antagonist

DEA Response to comment opposing Schedule IV: The DEA does not agree. Suvorexant is a novel, first in class, new chemical substance and information on actual abuse data is not currently available. The legislative history of the CSA addresses the assessment of a new drug's potential for abuse,\(^2\) and data from clinical studies investigating the abuse potential for suvorexant suggests that its effect is similar to zolpidem (schedule IV). Similarly, while the mechanism of action for suvorexant is distinct from any currently marketed drug for insomnia, human abuse potential studies demonstrated that suvorexant produced effects that were indistinguishable from zolpidem (schedule IV).

Future ???
Benzodiazepine Pharmacology

- 1, 4 benzodiazepine ring structure
- All have similar activity as modulators at the GABA receptor.
- Differences are the additions at sites around the ring
- The variations are in potency, efficacy and onset of action.
- Has to do with lipophilicity, whether metabolized to an active metabolite or not, half-life
Differences in Benzos

- Theoretically longer acting ones should be safer and with less addiction potential.
- Librium—“self-tapering”
Benzodiazepine Metabolism

- Hepatic metabolism involving oxidation by the cytochrome P-450 system
- Some are converted to an active metabolite which is then slowly cleared.
- Final phase involves conjugation with a glucuronide.
- Safest for use with impaired hepatic function, or liver failure: lorazepam (Ativan®), oxazepam (Serax®), and temazepam (Restoril®)- the “LOT” group
- Do not require hepatic oxidation, but only hepatic glucuronide conjugation, with rapid excretion.

(Page et al., 2002)
<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA-approved indication(s)</th>
<th>Onset of action</th>
<th>Approximate half-life (hours) in healthy adults</th>
<th>Approximate equivalent dose (mg)(^a)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Anxiety disorders, panic disorder</td>
<td>Intermediate</td>
<td>6.3 to 26.9 (IR), 10.7 to 15.8 (XR)</td>
<td>0.5</td>
<td>Increased risk for abuse because of greater lipid solubility</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Anxiety disorders, acute alcohol withdrawal, preoperative apprehension and anxiety</td>
<td>Intermediate</td>
<td>24 to 48</td>
<td>10</td>
<td>Risk for accumulation because of long-acting metabolites (desmeth/diazepam, oxazepam)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Seizure disorders, panic disorder</td>
<td>Intermediate</td>
<td>18 to 50</td>
<td>0.25 to 0.5</td>
<td>Use caution in patients with liver disease</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>Anxiety, seizures, acute alcohol withdrawal</td>
<td>Fast</td>
<td>40 to 50</td>
<td>7.5</td>
<td>Risk for accumulation because of long-acting metabolites (desmeth/diazepam, oxazepam)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Anxiety disorders, acute alcohol withdrawal, muscle spasms, convulsive disorders</td>
<td>Very fast</td>
<td>20 to 100</td>
<td>5</td>
<td>Risk for accumulation because of long-acting metabolites (temazepam, desmeth/diazepam, oxazepam), Increased risk for abuse because of quick onset</td>
</tr>
<tr>
<td>Estazolam</td>
<td>Insomnia</td>
<td>Intermediate</td>
<td>10 to 24</td>
<td>0.3 to 2</td>
<td>None</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Insomnia</td>
<td>Intermediate</td>
<td>47 to 100</td>
<td>30</td>
<td>Avoid in geriatric patients or patients with liver impairment</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Anxiety</td>
<td>Intermediate</td>
<td>10 to 20</td>
<td>1</td>
<td>Preferred for patients with liver impairment and geriatric patients</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Anxiety, acute alcohol withdrawal</td>
<td>Slow to intermediate</td>
<td>5 to 20</td>
<td>30</td>
<td>Preferred for patients with liver impairment and geriatric patients</td>
</tr>
<tr>
<td>Quazepam</td>
<td>Insomnia</td>
<td>Intermediate</td>
<td>39 to 73</td>
<td>5 to 15</td>
<td>Risk for accumulation because of long-acting metabolites (desmeth/diazepam, oxazepam)</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Insomnia</td>
<td>Intermediate</td>
<td>3.5 to 18.4</td>
<td>30</td>
<td>Preferred for patients with liver impairment and geriatric patients</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Insomnia</td>
<td>Fast</td>
<td>1.5 to 5.5</td>
<td>0.25</td>
<td>Lacks active metabolites</td>
</tr>
</tbody>
</table>

\( IR: \) immediate release; \( XR: \) extended release

*Interpret with caution, conflicting data exist

Source: References 2-6
### Benzodiazepines - Potency

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparative Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>diazepam</td>
<td>5mg</td>
</tr>
<tr>
<td>alprazolam</td>
<td>0.5mg</td>
</tr>
<tr>
<td>clonazepam</td>
<td>0.25mg</td>
</tr>
<tr>
<td>lorazepam</td>
<td>1mg</td>
</tr>
<tr>
<td>chlordiazepoxide</td>
<td>25mg</td>
</tr>
<tr>
<td>temazepam</td>
<td>10mg</td>
</tr>
<tr>
<td>estazolam</td>
<td>1mg</td>
</tr>
<tr>
<td>triazolam</td>
<td>0.25mg</td>
</tr>
</tbody>
</table>

(Adapted from Ries, 2009)
Adverse Effects

- Excessive sedation, fatigue/ psychomotor impairment
- Memory and other cognitive impairment
- Altered sleep physiology
- Ataxia with falls, especially in elderly
- Dysarthria
- Hypotonia
- Confusion
- Paradoxical excitement/ release of anxiety/ hostility

(Ries, 2009)
Short term indications: < 6-8 weeks

- Initial management of panic, GAD, severe anxiety associated with depression while waiting on full effect of the first line meds
- Insomnia -1-2 weeks
- Alcohol and other drug withdrawal
- Muscle relaxation/spasm
- Seizure prophylaxis
- Single use for phobias (e.g. flying)

(Ries, 2009)
Long term use of Benzodiazepines

- Long term use is $\geq 8-12$ months
- 90% experience withdrawal symptoms, whether withdrawn slowly or rapidly
- Gradual taper off alprazolam after long-term treatment of panic disorder results in rebound panic and anxiety, exceeding pretreatment levels in 50-90% of patients.

(Saddock et al., 2009)
Adverse Effects: Chronic

Increased rates of:

1) Accidents, falls (hip fractures etc.)
2) Motor vehicle accidents
3) General decline in functional status
4) Cognitive decline/memory impairment
5) Self poisoning
6) Withdrawal
7) Dependence

(Saddock et al., 2009)
Benzodiazepine Use & Risk of Alzheimer’s Disease

- Case control study in Quebec published in the British Medical Journal
- 1796 people who were diagnosed with Alzheimer’s and were followed for at least 6 years prior matched with 7184 controls
- Benzodiazepine use associated with increased risk of Alzheimer’s
- The strength of the association increased with long term exposures

(Billioti de Gage et al., 2014)
National Overdose Deaths
Number of Deaths from Prescription Drugs

Source: National Center for Health Statistics, CDC Wonder
National Overdose Deaths
Number of Deaths from Benzodiazepines

Source: National Center for Health Statistics, CDC Wonder
Benzodiazepine use: Mississippi

Data from 2015 MS PMP-Most Prescribed Drugs

- #1=Hydrocodone – 1.9 million rx’s = 116 million pills
- #2=Alprazolam (Xanax) – 580,000 rx’s = 34 million pills
- #3=Tramadol
- #4=Oxycodone
- #5=Amphetamine
- #6=Zolpidem (Ambien) - 444,000 rx’s = 14 million pills
- #7=Clonazepam (Klonopin)- 363,000 rx’s = 20 million pills

MS population 2015: approx. 3.0 million
Benzodiazepine use: Mississippi

Data from 2017 MS PMP-Most Prescribed Drugs

- Opiates = ~ 3.3 million prescriptions
- Benzodiazepines = ~1.4 million prescriptions

MS population 2017: approx. 3.0 million
% of Population in the U.S. With Any Benzodiazepine Use in 2008 By Age & Sex

(Olfson, 2015)
Table 1. Prevalence of Any Benzodiazepine Use, Long-term Benzodiazepine Use, and Use of Long-Acting Benzodiazepines by Sex and Age Group in the United States in 2008\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean age, y, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18-35</td>
</tr>
<tr>
<td><strong>US Population</strong></td>
<td></td>
</tr>
<tr>
<td>With any benzodiazepine use, y</td>
<td>2.6</td>
</tr>
<tr>
<td>Among men</td>
<td>1.7</td>
</tr>
<tr>
<td>Among women</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Among Persons With Any Benzodiazepine Use</strong></td>
<td></td>
</tr>
<tr>
<td>With long-term benzodiazepine use(^b)</td>
<td>14.7</td>
</tr>
<tr>
<td>Among men</td>
<td>15.6</td>
</tr>
<tr>
<td>Among women</td>
<td>14.2</td>
</tr>
<tr>
<td>With any long-acting benzodiazepine use, y</td>
<td>24.1</td>
</tr>
<tr>
<td>Among men</td>
<td>26.9</td>
</tr>
<tr>
<td>Among women</td>
<td>22.7</td>
</tr>
</tbody>
</table>

\(^a\) The data source was 2008 LifeLink Information Assets-LRx Longitudinal Prescription Database, 2008 (IMS Health Inc).

\(^b\) Long-term use defined as 120 days or more supply of benzodiazepine during 2008.

(Olfson, 2015)
Recent Trends - Positive

- Decrease in chronic opiate prescribing
- Recognition of the dangers of combining opiates and benzos
- Decrease in Soma use (\& less “Holy Trinity” combo)
- Don’t see a huge illicit supply - unlike opiates and amphetamines
- Realization that chronic opiate use and chronic benzo use just don’t work well to treat the conditions for which they are being used
- Lack of big pharma influence (My Opinion)
Recent Trends-Negative

- Continuing escalation of #'s of prescriptions
- Continuing increase in overdose deaths
- Increasing use among the elderly
- Patients more likely now to have illicit source of opiates. More potent heroin & more difficult to know they are on it.

(My Opinion)
Alcohol Analogy

- Talked about today that benzodiazepines and alcohol are similar and both work on the GABA receptor
- BZ and EtOH have similar effects on the body
- Can abuse and become dependent on both
- Both can lead to an addiction
- There are many people who socially consume alcohol over the course of their lives without any identifiable problem.
- In fact, there is some evidence that alcohol consumption in moderation can have health benefits
- So there are 4 groups of patients:
Group 1 – Pts. With SUD

- First, there is certainly debate about the best treatment for addiction
- But most of us would agree that:
  - Addiction is a chronic, brain disease
  - Once an “addiction switch” is flipped there is a change in circuitry which lasts a very long time
  - And that for the most part people suffering from alcoholism cannot ever successfully drink again
Group 1 – Pts. With SUD

- If asked for our medical opinion, I don’t think any of us would recommend that a person who has previously been treated for alcoholism to occasionally take a “little nip” to calm his nerves. We all know that is not going to work out well.
- Why would you do the same thing with benzos?
Group 1 – Pts. With SUD

- Doesn’t matter the addiction-- benzos and other substances trigger the same reward pathways and can lead to a full blown relapse quickly in someone who already has the disease of addiction.

• Like throwing gas on a fire
Thus...For Group 1

- Don’t prescribe benzodiazepines to patients with a history of Substance Use Disorders (SUD)
- (Excludes inpatient settings)
Continuing with the Alcohol Analogy

- Second, we know that there are many people who don’t ever develop addiction problems despite long-term social drinking.
- We don’t know all the factors - not have the right genes, etc.
Group 2 – Long-term Controlled Use

- If asked, you would not likely tell the old guy or woman in the retirement home that he/she can’t have her occasional glass of wine.
- Likewise, there are certainly patients who can go for a prolonged period using benzodiazepines sporadically or without ever showing any propensity to increase their dose or mis-use the medication.
Group 2 – Long-term Controlled Use

- Certainly, you want to check the PMP to make sure they are not getting more sedative-hypnotics from other providers, and
- You don’t want to encourage increasing the dose but
- Realistically, you are not going to try and stop this use
Continuing with the Alcohol Analogy

- So that’s two groups-- halfway there.
- Now the third group are people (mostly young persons) who have not ever been drinkers.

• If asked what to do because the person is anxious at their new job or they get anxious when they talk to their wife about money, most of you would not think it is a good idea to tell them to start drinking to help them deal with it.
Group 3- Not on Benzodiazepines

- Same with benzodiazepines, don’t start new patients on benzodiazepines except for very specific indications and for brief periods of time.
- Can avoid adding to problem we have with chronic benzodiazepine users
Continuing with the Alcohol Analogy

- So that leaves us with the fourth group:
- Chronic users whose use is becoming problematic
  - Increasing tolerance
  - Increasing symptoms
  - Decreasing effectiveness
Group 4- Chronic Users with Problems

- What to Do:
  - Maximize other treatment modalities
  - Taper off benzodiazepines

- See practice guidelines
  - Slow taper
  - Long time

- If getting the benzodiazepines from multiple providers or illicitly, then refer to a provider skilled in treating addiction
Practice Guidelines

- Reviewed at least 4 of them
  - JPS Health Network, Prescribing & Tapering Benzodiazepines, E-Resource
  - Safe Prescribing of BZ- State of Pennsylvania
  - Judicious Prescribing of Benzodiazepines- NYC
- Would encourage you to get them and review
- Incorporate ideas from each into your practice
<table>
<thead>
<tr>
<th>Generic (Brand) Approval Date</th>
<th>FDA Approval for Psychiatric Indications*</th>
<th>Tablet or Capsule Strengths</th>
<th>Average Dosage Range for Anxiety</th>
<th>Equivalent Dose (to lorazepam 1 mg)</th>
<th>Onset of Action After Oral Dose</th>
<th>Half Life (Hours)</th>
<th>Clinical Duration of Action (Hours)†</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax) 1981</td>
<td>• Anxiety • Panic disorder</td>
<td>0.25 mg, 0.5 mg, 1mg, 2 mg; orally disintegrating tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg; oral solution: 0.5 mg/5 ml</td>
<td>1–4 mg/day</td>
<td>0.5 mg</td>
<td>30 min</td>
<td>11–16</td>
<td>3–4</td>
<td>High abuse potential, some possibility of rebound anxiety if doses are spaced too far apart</td>
</tr>
<tr>
<td>Alprazolam XR (Xanax XR) 2003</td>
<td>• Panic disorder</td>
<td>0.5 mg, 1 mg, 2 mg, 3 mg</td>
<td>1–4 mg/day</td>
<td>0.5 mg</td>
<td>1–2 hours</td>
<td>11–16</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium) 1960</td>
<td>• Anxiety • Alcohol withdrawal • Preoperative anxiety</td>
<td>5 mg, 10 mg, 25 mg</td>
<td>15–100 mg/day</td>
<td>25 mg</td>
<td>2 hours</td>
<td>&gt;100</td>
<td>4–6</td>
<td>Often used for alcohol withdrawal, use caution in the elderly because of long half life and active metabolites</td>
</tr>
<tr>
<td>Clonazepam (Klonopin) 1975</td>
<td>• Panic disorder • Seizure disorder • Periodic leg movement • Neuralgia • Anxiety</td>
<td>0.5 mg, 1 mg, 2 mg; orally disintegrating formula, 0.25 mg, 0.5 mg, 1 mg, 2 mg</td>
<td>0.5–2 mg/day</td>
<td>0.25mg–0.5mg (sources differ on dose equivalence of clonazepam)</td>
<td>1 hour</td>
<td>20–80</td>
<td>6–8</td>
<td></td>
</tr>
<tr>
<td>Clorazepate (Tranxene) 1972</td>
<td>• Anxiety • Adjunctive therapy for partial seizures • Alcohol withdrawal</td>
<td>3.75 mg, 7.5 mg, 15 mg, Tranxene</td>
<td>15–60 mg/day</td>
<td>7.5 mg</td>
<td>30 min–1 hour</td>
<td>&gt;100</td>
<td>6–8</td>
<td></td>
</tr>
<tr>
<td>Clorazepate SD (Tranxene SD)</td>
<td>• Anxiety • Adjunctive therapy for partial seizures</td>
<td>11.25 mg, 22.5 mg</td>
<td>11.25–45 mg/day</td>
<td>7.5 mg</td>
<td>&gt;100</td>
<td></td>
<td>Information not available</td>
<td></td>
</tr>
<tr>
<td>Generic (Brand) Approval Date</td>
<td>FDA Approval for Psychiatric Indications*</td>
<td>Tablet or Capsule Strengths</td>
<td>Average Dosage Range for Anxiety</td>
<td>Equivalent Dose (to lorazepam 1 mg)</td>
<td>Onset of Action After Oral Dose</td>
<td>Half Life (Hours)</td>
<td>Clinical Duration of Action (Hours)†</td>
<td>Notes</td>
</tr>
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</tr>
<tr>
<td>Diazepam (Valium) 1963</td>
<td>• Anxiety • Alcohol withdrawal • Adjunctive therapy for seizure disorders, status epilepticus • Muscle spasms • Procedural or preanesthesia sedation</td>
<td>2 mg, 5 mg, 10 mg; oral solution: 5 mg/ml; injection: 5 mg/ml</td>
<td>5–40 mg/day</td>
<td>5 mg–10 mg (sources differ on dose equivalence of diazepam)</td>
<td>30 minutes</td>
<td>&gt; 100</td>
<td>4–6</td>
<td>Works quickly and has a long duration of action clinically, use caution in the elderly because of long half life and active metabolites</td>
</tr>
<tr>
<td>Estazolam (ProSom) 1990</td>
<td>• Sedative hypnotic</td>
<td>1 mg, 2 mg</td>
<td>1–2 mg/day</td>
<td>1 mg</td>
<td>2 hours</td>
<td>10–24</td>
<td>4–8</td>
<td></td>
</tr>
<tr>
<td>Flurazepam (Dalmane) 1970</td>
<td>• Sedative hypnotic</td>
<td>15 mg, 30 mg</td>
<td>15–30 mg/day</td>
<td>15 mg</td>
<td>2 hours</td>
<td>&gt; 100</td>
<td>4–6</td>
<td></td>
</tr>
<tr>
<td>Lorazepam (Ativan) 1977</td>
<td>• Anxiety • Chemo-related nausea/vomiting • Injectable form: epilepsy, preanesthesia</td>
<td>0.5 mg, 1 mg, 2 mg; oral solution: 2 mg/ml; sublingual version: 1 mg, 2 mg; injection: 4 mg/ml, 2 mg/ml</td>
<td>1–4 mg/day</td>
<td>1 mg</td>
<td>30–60 minutes</td>
<td>10–20</td>
<td>4–6</td>
<td>No active metabolites</td>
</tr>
<tr>
<td>Oxazepam (Serax) 1955</td>
<td>• Anxiety • Alcohol withdrawal</td>
<td>10 mg, 15 mg, 30 mg</td>
<td>30–120 mg/day</td>
<td>15 mg</td>
<td>2–4 hours</td>
<td>5–14</td>
<td>Information not available</td>
<td>No active metabolites, capsule only</td>
</tr>
<tr>
<td>Temazepam (Restoril) 1981</td>
<td>• Insomnia</td>
<td>7.5 mg, 15 mg, 30 mg</td>
<td>15–30 mg/day</td>
<td>15 mg</td>
<td>30–60 minutes</td>
<td>10–20</td>
<td>4–6</td>
<td>No active metabolites, used as a sedative and tranquilizer for sleep, capsule only</td>
</tr>
<tr>
<td>Triazolam (Halcion) 1982</td>
<td>• Insomnia</td>
<td>0.125 mg, 0.25 mg</td>
<td>0.25 - 0.5 mg/day</td>
<td>0.25 mg</td>
<td>30 min–1 hour</td>
<td>1.5–5</td>
<td>Information not available</td>
<td></td>
</tr>
</tbody>
</table>

*Many benzodiazepines were approved before DSM-III, and were therefore indicated for a miscellaneous array of anxiety disorders that are labeled differently in modern parlance. Most of these “anxiety” indications would correspond either to generalized anxiety disorder or for the short-term relief of anxiety symptoms.

†This is the answer to a patient’s question, “how long will it last?” assuming prn dosing. When dosed chronically, duration of action will usually be longer due to accumulation.
Clinical Practice Guideline

- Inquire about substance abuse history and do not prescribe benzos to those patients with SUD, even short term
- Don’t automatically continue hospital/ED prescriptions
- When starting a benzo, make clear that it will be for short term (maximum 2-4 weeks for anxiety, 7-14 days for insomnia) and stick to that

(JPSHealth, 2014)
Indications for long-term treatment with benzodiazepines:

- Benzodiazepines may be used for longer than 6 weeks in the terminally ill, in the severely handicapped patient, and in certain neurological disorders.
- Restless leg syndrome

(JPS Health, 2014)
Do not prescribe - No Effectiveness:

Clinical trials have shown no effectiveness with the use of benzodiazepines in the following condition:

- Tinnitus
- Chronic tension headache
- Essential Tremor
- Meniere’s
- Post-traumatic stress disorder (Provided a “D” rating as being of “No Benefit/Harm” classification by the VA/DOD official PTSD CPG)
- Concussion
- Evidence of substance abuse

(JPS Health, 2014)
If you follow these practice guidelines, that only leaves you with:

- Patients on long-term benzodiazepines that you already have or inherit
- Develop a plan to get as many off chronic benzodiazepines as you are able or at least examine each patient’s situation to reduce the quantity, etc.
Long Term Use Discontinuation Letter

Dear ______________,

I am writing to you because I note from our records that you have been taking _________ for some time now. Recently, doctors have become concerned about this kind of medication when it is taken over long periods. Our concern is that the body can get used to these tablets so that they no longer work properly. If you stop taking the tablets suddenly, you may experience unpleasant withdrawal effects. For these reasons, repeated use of the tablets over a long time is no longer recommended. More importantly, these tablets may actually cause anxiety and sleeplessness and they can be addictive.

At our next appointment we will evaluate your current prescription and the short and long term goals of treatment with ________.

It is important to work with me in the tapering or discontinuation of this medicine. Please do not discontinue this medication until we have an opportunity to discuss a plan. Any change in the medication would involve a plan to prevent and or reduce the likelihood of significant withdrawal symptoms.

We can discuss your prescription of _________ and alternative options that may be a good fit for your condition.

Yours sincerely,

Dr ______________

(JPS Health, 2014)
### Recommended durations for tapering benzodiazepines

<table>
<thead>
<tr>
<th>Duration of use</th>
<th>Recommended taper Length</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 to 8 weeks</td>
<td>Taper may not be required</td>
<td>Depending on clinical judgment and patient stability/preference, consider implementing a taper, particularly if using a high-dose benzodiazepine or an agent with a short or intermediate half-life, such as alprazolam or triazolam</td>
</tr>
<tr>
<td>8 weeks to 6 months</td>
<td>Slowly over 2 to 3 weeks</td>
<td>Go slower during latter half of taper. Tapering will reduce, not eliminate, withdrawal symptoms. Patients should avoid alcohol and stimulants during benzodiazepine withdrawal</td>
</tr>
<tr>
<td>6 months to 1 year</td>
<td>Slowly over 4 to 8 weeks</td>
<td></td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>Slowly over 2 to 4 months</td>
<td></td>
</tr>
</tbody>
</table>

(Bostwick, 2012)
Other Treatments for Anxiety

Pharmacologic:
1) Selective serotonin reuptake inhibitors (SSRIs)
2) Tricyclic antidepressants (TCAs)
3) Benzodiazepines
4) Monoamine oxidase inhibitors (MAOIs)
5) Other drugs- beta blockers, buspirone (buspar©)

Psychological:
1) Cognitive behavior therapy
2) Supportive and insight-oriented psychotherapy
3) Group therapy

(Ries, 2009)
Anxiety and CBT

- The majority of anxiety disorders are optimally treated with cognitive behavioral therapies (CBT).
- CBT and other psychological therapies are evidence based, effective interventions with a sustained impact on anxiety disorders.
- There is a considerable overlap in the symptoms of the major anxiety disorders.
- Effective treatments for one often address the other.
- Developing simple referral pathways with psychologists, primary care providers can begin to offer alternatives to benzodiazepines.
DSM-5 Changes

- Obsessive-Compulsive Disorder is no longer lumped in with the anxiety disorders. It has its own chapter “Obsessive-Compulsive and Related Disorders.”

- PTSD likewise is not included with the anxiety disorders. It has a new chapter on “Trauma and Stress or Related Disorders.”

- Benzodiazepines have not been shown to be effective in either of these conditions and should not be used. They may be harmful in PTSD.
Other Treatments for Insomnia

- Treat Underlying Conditions
  - Anxiety/Depression
  - Obstructive Sleep Apnea
  - GERD
  - CHF/COPD
- Sleep Hygiene
- Meds
  - Mirtazapine (Remeron©)
  - Trazodone
  - TCAs: Amitriptyline (Elavil©)
  - Hydroxyzine (Vistaril©/diphenhydramine (Benadryl©)
  - Melatonin
  - Ramelteon (Rozerem©)

(Ries, 2009)
And Please, Please Remember

- Benzodiazepine withdrawal can be deadly!!
- Can lead to delirium and status epilepticus.
- So if you are a provider in a (for instance) jail setting, don’t just say: “I don’t prescribe benzos”
- Or if you are an orthopedic doctor, don’t just presume that the little old lady you admitted for a hip fracture will be OK without her chronic Ativan because you don’t want to run afoul of the MS Board of Medical Licensure regulations
HOW TO PRESCRIBE BENZODIAZEPINES JUDICIOUSLY

• Provide appropriate first-line treatment for anxiety and insomnia.

• If benzodiazepines are clinically indicated:
  o fully assess your patient,
  o prescribe the lowest effective dose for the shortest duration—no more than 2 to 4 weeks,
  o talk to your patient about the benefits and risks of benzodiazepine treatment,
  o avoid co-prescribing with opioids or other CNS depressants because of the risk of fatal respiratory depression.
References

References

References

- Billioti de Gage, S et al. Benzodiazepine use and risk of Alzheimer’s disease: case-control study. BMJ. 2014;349:g5205