Diagnosis and Management of Benzodiazepine Dependence

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Disclosure

• AstraZeneca Pharmaceuticals
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Outline

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Benzodiazepine use and neurochemistry

On benzodiazepines

• There is a clinical role for the benzodiazepines in the short term for addressing anxiety and panic symptoms as well as inducing sleep.
• This class of drugs has relatively few drug interactions and primary care and ED prescribers use them often for addressing patient complaints.

Benzodiazepine use

• Benzodiazepines are widely prescribed, with four of them—alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium) and lorazepam (Ativan)—were listed among the top 100 most commonly prescribed medications in 1995, but the latest data show none in this class among the most commonly prescribed drugs, their ranks being filled by opiate pain medications and stimulants.(1)
• Benzodiazepines typically produce almost immediate effects, and thus may be prescribed for short-term, intermittent, “as-needed” use. Because many of the anxiety disorders wax and wane over time, patients with these disorders often prefer benzodiazepines because these agents can be taken intermittently, when patients feel the need to take them, and some patients can use benzodiazepines judiciously.(2)
• Benzodiazepines are also widely prescribed for other reasons, such as muscle spasticity, convulsive disorders, presurgical sedation, involuntary movement disorders, detoxification from alcohol and other substances, and anxiety associated with cardiovascular or gastrointestinal conditions.(3)

1. IMS National Prescription Audit, IMS Health 2013.
Benzodiazepine use (cont.)

- According to the APA report on benzodiazepines, 11-15 percent of the adult population has taken a benzodiazepine one or more times during the preceding year, but only 1-2 percent have taken benzodiazepines daily for 12 months or longer. (1)

- In psychiatric treatment settings and in substance-abuse populations, however, the prevalence of benzodiazepine use, abuse and dependence is substantially higher than that in the general population. (2, 3)


Neurochemistry

- Benzodiazepine receptors are ubiquitous throughout the central nervous system. Benzodiazepine receptors are linked predominantly to y amino butyric acid (GABA) receptors, which sensitize benzodiazepine receptors to the neurotransmitter GABA, the most prominent inhibitory neurotransmitter in the central nervous system.

- Activation of the benzodiazepine-GABA-chloride ionophor complex is responsible for producing the therapeutic anxiolytic effects of benzodiazepines and for mediating many of the side effects and, possibly, dependence and withdrawal from these drugs. (1)


Neurochemistry (cont.)

- There is a synergistic effect of benzodiazepines with barbiturates and other sedative-hypnotics, such as alcohol. (1)

- Benzodiazepines and barbiturates act at separate binding sites on the receptor to potentiate the inhibitory action of GABA.

- Alcohol modifies the receptor by altering the membrane environment so that it has increased affinity for GABA and the other sedative-hypnotic drugs.

- These related actions on a common receptor type help explain their pharmacologic use as well as cross tolerance.

Neurochemistry (cont.)

- With long-term high-dose use of benzodiazepines (or ethanol), there is an apparent decrease or down-regulation in the efficacy of GABA-A receptors, presumably the mechanism of tolerance.(1, 2)
- When high-dose benzodiazepines or ethanol are abruptly discontinued, this down-regulated state of inhibitory transmission is unmasked, leading to characteristic withdrawal symptoms such as anxiety, insomnia, autonomic hyperactivity and, possibly, seizures.

Benzodiazepine problems

- Benzodiazepines impair consolidation of memory and episodic memory.
- The elderly are most sensitive.
- Alcohol enhances the amnestic effects.
- Some recent evidence of increased risk of dementia with even episodic use.(1)

Benzodiazepine problems (cont.)

- These medications may impair psychomotor speed, coordination, and impair sustained attention.
- These effects are enhanced with increasing age, increasing peak drug level, alcohol use.
- In a meta analysis of studies from 1980-2000, long term benzodiazepine patients were consistently more impaired than control groups across all cognitive measures used.(1)
- In these studies, while patients who discontinued use noted improvement, this never rose to the level of cognitive performance of the control groups.
Benzodiazepine withdrawal information

The benzodiazepine receptor problem

- Benzodiazepines affect just about every part of the body.
- There are GABA receptors throughout the body including the gastrointestinal tract and most other organ systems in the body.
- For this reason there is a wide variety of withdrawal syndromes you may encounter in your patients.

Short term withdrawal

- Withdrawal effects from therapeutic dosages of benzodiazepines are predominately anxiety symptoms.\(^1\, 2\) In addition, autonomic instability (i.e., increased heart rate and blood pressure, tremulousness, diaphoresis), insomnia and sensory hypersensitivity are common.
- The most serious acute withdrawal symptoms are seizures and delirium tremens, which most commonly occur with abrupt discontinuation. The time frame for the emergence of acute withdrawal symptoms corresponds to the half-life of the particular agent being used.
- Some elements of withdrawal are believed to occur in a majority of patients who have taken therapeutic dosages of benzodiazepines for more than a few months, although the severity of withdrawal symptoms generally depends on the amount of the original dosage, the rate at which the dosage is tapered, the selection of patients and the definition of withdrawal symptoms.\(^1\, 3\)

Extended withdrawal

- A protracted abstinence syndrome has been described by some addiction specialists.(1)
- Symptoms include prolonged (i.e. several months) problems with anxiety, depression and insomnia. In addition, physical symptoms related to gastrointestinal, neurologic and musculoskeletal effects have been reported. This abstinence phenomenon may develop despite long, slow, judicious tapering of the dosage and is hypothesized to result from chronic neuroadaptation to the benzodiazepine.


Withdrawal is more likely with the following:

- Higher daily dose of benzodiazepine
- Using a benzodiazepine with a shorter half life
- The longer the duration of benzodiazepine therapy.
- The rapidity of the taper, especially the last 50%.
- Use of higher potency benzodiazepines.

Withdrawal is more likely with the following part 2:

- The diagnosis of panic disorder.
- A higher pre-therapy level of mood or anxiety symptoms.
- Current use of alcohol or recent substance abuse.
- Higher levels of personality psychopathology.
Important considerations about withdrawal

- The level of patient distress does not always correlate with the level or injury or disease.
- Anxiety and pain perception may be affected by multiple factors including mood, level of attention placed on the pain, etc.
- The severity of the withdrawal symptoms does not necessarily correlate with the inability to taper a patient off a benzodiazepine.
- Patients with co-morbid depression or personality pathology may be acutely sensitive to relatively minor cues of withdrawal and sabotage the taper.

Further important considerations

- If patients are able to taper off benzodiazepine therapy, 75% will be benzo-free 3 years out.
- In the cases of failed taper that resulted in 50% reduction of original dose, over 60% remained on benzodiazepines at 3 year follow up.
- Among patients who refused a taper, 86% continued daily benzodiazepine use.
- Patients who successfully remained benzodiazepine free at 3 year follow up reported lower level of anxiety and depression compared to patients who remained on active drug.


Hyperalgesia, dependence, addiction, and diversion
Hyperalgesia and tolerance

• Tolerance is the need to increase the dose to maintain equivalent analgesic effects over time.
• It may be linked to psychological factors, or it may involve down-regulation or desensitization of receptors, or both.
• Repeated administration of benzodiazepines may lead to desensitization or down-regulation of the receptor and subsequent sensitization to minor stimuli.
• A similar process may also occur spontaneously in anxiety and depressive illnesses (i.e. “depression hurts”).

Dependence

• Psychological dependence
  – Extreme behavior (craving) associated with procuring/consuming drug.
  – Withdrawal avoidance rather than chasing a “high”.
• Physical dependence
  – Class-specific withdrawal syndrome that can be produced by abrupt cessation or rapid dose reduction of a drug (or administration of an antagonist).

Addiction

• Physical and psychological dependence possible, but also a seeking of a “high” or preoccupation with sedative/numbing effects of the medication.
• Chronic relapsing disorder characterized by persistent drug-seeking and drug-taking behaviors.
• Impaired control over use, compulsive use, continued use despite harm and craving.
• Patients will often spend significant time in office visits bargaining, threatening, and pleading for the drug they are seeking.
Diversion

• Most controlled substance medications have significant street value.
• Consider diversion if:
  • Patients ask for name brand rather than generics.
  • Patients ask for immediate release rather than XR versions of controlled substances.
  • Patients ask you not to communicate with their other providers.
  • Negative drug screens even with regular filling of prescriptions.
  • Sign up for the SC DHEC prescription monitoring website at https://scpmpph.hidinc.com/

Benzodiazepine specific information

• Benzodiazepines are rarely the preferred or sole drug of abuse. An estimated 80 % of benzodiazepine abuse is part of polydrug abuse, most commonly with opioids. (1)
• A two-year treatment outcome study by the National Institute on Drug Abuse(2) found that 15 % of heroin users also used benzodiazepines daily for more than one year, and 73 % used benzodiazepines more often than weekly. Studies indicate that from 5-90 % of methadone users are also regular users of benzodiazepines. High-dose benzodiazepine abuse is especially prevalent in patients who are taking methadone. (3)


Benzodiazepine specifics (cont.)

• Studies indicate that 3 to 41 % of alcoholics report that they abused benzodiazepines at some time, often to modulate intoxication or withdrawal effects. (1)
• The alcoholic patient is usually a multiple-drug user. As many as 80 % of alcoholics under the age of 30 have been addicted to or use at least one other drug. (2)

Benzodiazepine specifics (cont.)

- Medical prescriptions constitute a primary source of supply for people who abuse benzodiazepines.
- Prescriptions have a street value, which encourages rerouting to illicit sources, with some name-brand pills selling for $5-10/pill.
- Benzodiazepines have multiple uses for addicts, including enhancing the euphoriant effects of opioids, to alleviate withdrawal or abstinence syndromes between fixes, to temper cocaine or methamphetamine highs, to augment alcohol synergistically and to modulate withdrawal states.

Benzodiazepine specifics (cont.)

- In general, short-acting benzodiazepines seem to be preferred among addicts because of their relatively rapid onset of action.\(^1\)
- In general, mood-altering substances are most highly reinforcing in patients with chemical dependence if the agent has a rapid onset of action, a high potency, a brief duration of action, high purity and water solubility (for intravenous use) or high volatility (ability to vaporize if smoked).\(^2\)
- Data suggest that highly lipophilic benzodiazepines (for example, those that cross the blood-brain barrier more rapidly), such as diazepam, and agents with a short half-life and high potency, such as lorazepam or alprazolam, are the most reinforcing benzodiazepines and, therefore, the ones most likely to be associated with abuse.\(^1\)

Benzodiazepine specifics (cont.)

- Clonazepam is a high-potency benzodiazepine with a long half-life. It is widely prescribed for a variety of psychiatric and neurologic conditions. Although clonazepam is perceived as “safe,” addiction medicine specialists have found that it is also increasingly also abused as a street drug.
- Compared with generic formulations, trade-name prescription drugs can be worth twice as much per tablet when they are sold on the street because they are readily recognizable as the “real thing”.

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Common behavior patterns among addicts or drug seekers

Drug-seeking scams

- You will encounter drug-seeking patients in your practice, without question.
- Seekers will commonly attempt scams to obtain the drug they are seeking.
- Be aware that often a patient will attempt to “push” the prescriber. Patient-generated pressure to prescribe in the face of the prescriber’s feeling of hesitancy is a classic indicator of a scam, so trust your “gut feelings”.
- Patients rarely self-medicate with prescribed agents that do not produce a “high” or reward, and they are often quite adept at projecting their misery and helplessness onto “prospective prescribers.”(1,2)

Drug-seeking (cont.)

- An initial “no” (refusal to prescribe by the prescriber) that eventually is changed to a “yes” (willingness to prescribe) in the face of pressure from the patient is considered by some experts to be pathognomonic of prescription drug abuse.
- Once a scam has worked in a given practice, that scam will likely continue to surface periodically in that office practice until the prescriber ceases to reinforce the scam. Dealing with scams consists of learning to recognize the common ones and refusing to give in to them.(1,2)
Drug-seeking routines in the office setting

- The clock king/queen
- The ellipse
- The SCUD
- The reluctant Guinea pig
- The stick up

Drug seeking (cont.)

- Chemically dependent patients may prey on the prescriber's helping instincts and discomfort with confrontation such that the initial "no" can be turned into a "yes" if enough pressure is applied.
- In such situations, a basic clinical survival skill is to mean "no" when saying "no" and to stick with it. You may be able to forestall further efforts by shifting the discomfort to the patient while still refusing to prescribe by making statements such as "I'm feeling pushed by you to write a prescription today that is not medically indicated and thus I'm concerned about you, and we need to talk about your use of alcohol (or other substances)."[1,2]
- Also, be aware that there are other external pressures that sometimes conspire to push you to prescribe controlled substances. As noted earlier, they have fewer drug interactions, they are inexpensive, and increasing pressure to see more patients in less time makes dealing with drug-seeking difficult.
- Many prescribers faced with such situations take the option to "write "(Rx)" than fight."

Office based strategies

References:
Practical suggestions for dealing with the patient with chronic anxiety

- Give the patient adequate time to discuss all concerns—consider scheduling extra time at another office visit.
- Forgo controlled substance use unless you are confident of what you are doing.
- Consider more regular scheduled office visits.
- Monitor drug usage.
- Recommend appropriate exercise.
- Refer for or suggest stress management techniques.

Consider different types of office visits

- Patients with chronic anxiety may respond better to regular, more frequent office visits.
- Remember to clarify your role up front and be clear if you intend to prescribe controlled substances or not.
- Remember these patients often think their providers do not take them or their problems seriously.
- If their anxiety causes significant impairment in leaving the home (such as agoraphobia), office visits may be a primary social outlet.
- If you cannot find any redeemable quality to an individual patient, consider referring to another provider.

Benzodiazepine equivalents
Benzodiazepine equivalents

- For benzodiazepines, it is sometimes useful to convert to a standard scale, keeping in mind relative potency and half life as well.
- What follows are the commonly used benzodiazepines with their relative dose equivalence to 10mg of Diazepam (Valium).
- This information can be useful when performing a gradual taper using a benzodiazepine.


High-potency benzodiazepines

- **Drugs with a short half-life**
  - Alprazolam (Xanax) – 0.5mg
  - Lorazepam (Ativan) – 1mg
  - Triazolam (Halcion) – 0.5mg
- **Drugs with a long half-life**
  - Clonazepam (Klonopin) – 0.5mg


Low-potency benzodiazepines

- **Drugs with a short half-life**
  - Oxazepam (Serax) – 20mg
  - Temazepam (Restoril) – 20mg
- **Drugs with a long half-life**
  - Chlordiazepoxide (Librium) – 25mg
  - Clorazepate (Tranxene) – 15mg
  - Diazepam (Valium) – 10mg
  - Flurazepam (Dalmane) – 30mg

Psychiatric medication options for benzodiazepine detox

Benzodiazepine tapers

- The use of benzodiazepines for detox has many benefits. You are typically gradually tapering either the original drug, or converting to either Clonazepam or Diazepam equivalents, then tapering.
- While some patients may succeed, this strategy often fails as patients will overtake the tapered dose. If you decide to pursue this strategy, close monitoring is key.


Benzodiazepine tapers (cont.)

- Typical tapers fall into rapid, stepwise, or gradual strategies.
- For rapid tapers, you would decrease the dose by 25% every week. This strategy has a high dropout rate in community patients as opposed to inpatient settings.
- For stepwise, rapid taper of 50% of pre-taper dose over the first 2-4 weeks, then taper the remaining 50% more slowly, typically 12-24 weeks.
- Gradual tapers are typically to decrease the starting dose by 10% every 1-2 weeks. This requires much patience on the part of both prescriber and patient, but may be a better option for patients who experience protracted withdrawal symptoms.
- In either setting, if the patient has a significant psychological dependence on their existing benzodiazepine, it can be useful to convert them first to an equivalent dose of either Clonazepam or Diazepam prior to initiating a taper.

Example taper with Valium

• Starting regimen 10mg QID.
• Rapid taper: decrease by 10mg/week for 4 weeks, with the last dose to be stopped QHS.
• Extended taper: decrease by 5mg/2-3 weeks, again with the final dose to be discontinued QHS.

Anticonvulsant tapers

• Anticonvulsant tapers have some benefits for select patients.
• They are less likely to overtake medication during the taper and the medication will prevent seizures without significant sedation for most patients.
• Anticonvulsants may also be used in conjunction with a benzodiazepine taper for patients who have failed prior taper attempts.

Utility in detox

• Can be very effective, particularly in place of a benzodiazepine for detox.
• Wide variation in use among addictions specialists, and use is off label.
• Mechanism of action is different from the benzodiazepines: inhibition of repeated neuronal discharges (carbamazepine), GABA mimetics (gabapentin, pregabalin).
• Gabapentin is frequently a first choice as levels do not need monitoring and it is inexpensive.
• Valproate has little clinical evidence for usefulness in this population and there have been few studies thus far for topiramate, but it may be promising.
Carbamazepine

• Some data on carbamazepine show benefit for benzodiazepine withdrawal. Adjunctive carbamazepine seems to reduce withdrawal severity in placebo-controlled studies when used in conjunction with a standard taper.

• There is also evidence that carbamazepine reduced benzodiazepine withdrawal in benzodiazepine-abusing populations.(1, 2, 3)


Carbamazepine (cont.)

• Dosing is individualized, 200-800mg daily.

• Continue pre-taper benzodiazepine for 1-2 weeks concurrently with Carbamazepine, then taper benzodiazepine by 25%/week for 4 weeks.

• Continue Carbamazepine alone for 2-4 weeks, then it may be either tapered as above or discontinued.

• Need to follow CBC and BMP routinely while on this medication.

Gabapentin

• Gabapentin has show efficacy in alcohol withdrawal and similarly may be useful for benzodiazepine detox. (1, 2, 3, 4)

• It is cleared via renal mechanisms, which may be of particular utility in patients with hepatic dysfunctions. It does not interact with liver enzymes thus decreasing the risk of pharmacokinetic interactions.

• Although it has no direct effect on GABA receptors or transporters, it has been shown to increase GABA turnover in various regions of the brain. It may influence the synthesis of glutamate and has been hypothesized that gabapentin may, through its GABAergic activity, restore the feedback inhibition from the nucleus accumbens after alteration through repeated cocaine use (5).

Gabapentin (cont.)
• It may be useful both as adjunctive therapy for a Clonazepam or Diazepam taper, or by itself.
• My standard dosing is 300mg BID-QID depending on how the pre-existing benzodiazepine was dosed, then taper by 25%/week once stabilized.

Naltrexone
• Naltrexone has been investigated for use in addictions other than opiate dependence.(1,2 3)
• There may be benefit in this medication for extended withdrawal syndromes and for relapse prevention.
• The dose is 50-100mg/day.

N-Acetylcystiene
• N-Acetylcystiene has been investigated in various psychiatric conditions.(1)
• There is evidence of its usefulness in addictions, particularly cravings.
• I have used this off-label for benzodiazepine detox with a dose of 600mg BID.
Patient practices for working with anxiety and stress

Basic Breathing Practice

• Sit up with a straight spine so that your back doesn’t contact the back of the chair
• Your eyes can be open or closed
• Gently close your mouth and breathe through your nose
• Relax the abdominal muscles and breathe through your diaphragm
• Focus on the sensation of the breath rising and falling, like the waves on the ocean

Box Breathing Practice

• Begin as in the basic breathing practice
• When you feel ready, begin to breathe to a rhythm of 4 counts to breathe in, hold for 4 counts, 4 counts to breathe out, hold out for 4 counts (i.e. the “box”)
• Try to breathe in time with your heart rate for an even more powerful relaxation response
• Continue this practice for up to 5 minutes at a time
Books to recommend

• Full Catastrophe Living by Jon Kabat-Zinn
• Loving What Is by Byron Katie

Websites and apps

• UCLA Mindful Awareness Research Center (MARC) http://marc.ucla.edu/
• Moodscope https://www.moodscope.com/
• Azumio’s “Stress Doctor” app for IOS (Android coming)
• Buddhify 2 app for IOS/Android and downloads of MP3 files
• De.stress.ify app for IOS/Android
Conclusion

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