


I love you, I love you not...

Benzodiazepine use and abuse



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Case study

35 yr/o white female in a methadone clinic was referred to the psychiatrist by her counselor to evaluate a history of anxiety. She has c/o anxiety attacks since she was 13 years old. She has the following symptom: acute onset of anxiety, shortness of breath, feeling faint, tremor, feeling unreal, need to escape, hands going numb and some nausea. She has these attacks about 3 times a week and they last 5-10 minutes. The attacks are severe and frightening; she feels like she will die. She was placed on Xanax by her family doctor and continues to use this medication 1mg three times a day. She also obtains Ambien for sleep.


She has a history of past drug abuse including IV heroin abuse since age 18, last use about one year ago when she was placed on methadone maintenance. She has also abused cocaine and alcohol. When she comes in for dosing with methadone the nurses have noted that she has been overly sedated and they have not given her methadone on those occasions.

She has a medical history of hypertension, hepatitis C and chronic back pain. Her doctor has her on blood pressure medication and hydrocodone for pain.

What's a person to do ????

Benzodiazepine Abuse

- Deliberate, compulsive abuse to get high
- Unintentional abuse by patients prescribed Bz and than use inappropriately



■ O'Brien, 2005

Pharmacologic Dependence vs Addiction


- Pharmacologic (dependence)
 - Physiologic adaption to use of drug
 - 2 weeks
 - 16 weeks (50% withdrawal)
- Addiction Substance Dependence
 - Loss of control
 - Compulsive drug-seeking to get high
 - Continued use despite Consequences
 - DSM-IV



O'Brien, 2005

Abuse Liability

- Benzodiazepines lower abuse potential than other drugs of abuse (Rickels et al. 1999)
- Abused with other drugs (polyabuse)
 - Rare by itself




Abuse Liability

- Less reinforcing than other drugs of abuse (Griffiths and Weerts, 1997)
- Only class of abused drugs that decreases dopamine in mesolimbic system (Finley et al., 1992)
- Subpopulation of sedative hypnotic and alcohol drinkers with HX of drug use at risk
 - (Chutuape and de Wit 1994)

Abuse Liability

- Faster onset may be more reinforcing
 - Alprazolam (Xanax)
 - Diazepam (Valium)
- Slow onset less reinforcing
 - Oxazepam (Serax)
 - Chlordiazepoxide (Librium)
- Relative High
 - Diazepam, alprazolam > oxazepam, chlordiazepoxide



Griffiths et al., 1984, 1988


Table 2. Street Value and "Use Again" Value of Benzodiazepines^a

Benzodiazepine	Street Value	"Use Again" Value ^b
Methaqualone 300mg	\$3.00	12.2
Diazepam 20mg	\$1.60	8.7
Diazepam 10mg	\$0.70	6.3
Lorazepam 4mg	\$0.80	6.8
Lorazepam 2mg	\$0.30	6.0
Alprazolam 2mg	\$0.70	8.0
Praxepam 40mg	\$0.60	7.1
Placebo	\$0.20	3.3

^aData from Cole
^b"Use Again" values are rated on a 16 point scale, where 0 indicates "would never use the drug again", 8 indicates "maybe", and 16 indicates "would definitely enjoy using drug again"


Abuse Liability

- **Opioid dependent** patients on methadone
 - Lifetime use 66-100%
 - Current use 51-70% (positive UDS)
 - Abuse/dependence 18-50%
 - Lintzeris, 2010
- Reinforce opioid high and treat withdrawal




Abuse Liability

- Pharmacologic and behavioral link
 - Reinforcing effect of Bz may be mediated by opioid mechanism
 - Anxiolytic & positive subjective effect of bz blocked by mu receptor antagonist--naltexone, (Duka, 1982)
 - Bz may substitute for heroin (Spiga et al., 2001)



Intensity of withdrawal

- Time on medication
- Dose of medication
- Half- life



O'Brien, 2005

Some common benzodiazepine withdrawal symptoms


Symptoms common to all anxiety states	Symptoms less common in anxiety states--relatively specific to benzodiazepine withdrawal ^a
Anxiety, panic attacks, agoraphobia	Perceptual distortions, sense of movement
Insomnia, nightmares	Depersonalization, derealization
Depression, dysphoria	Hallucinations (visual, auditory)
Excitability, restlessness	Distortion of body image
Poor memory and concentration	Tingling, numbness, altered sensation
Dizziness, light headedness	Formication (skin 'crawling')
Weakness, 'jelly legs'	Sensory hypersensitivity (light, sound, taste, smell)
Tremor	Muscle twitches, jerks, fasciculation
Muscle pain, stiffness	Tinnitus
Sweating, night sweats	Psychotic symptoms ^a
Palpitations	Confusion, delirium ^a
Blurred or double vision	Convulsions ^a

^a Usually only on rapid or abrupt withdrawal from high doses of benzodiazepines

Ashton, 2005

How to stop??

- Rapid taper generally not successful
- Gradual and staged approach more successful (Rickel, 1999)
- Switch to long acting bz:
 - clonazepam
 - chlordiazepoxide
- Taper 6-12 mo (Ashton, 2005)



Approximate equivalent doses and elimination half-lives of benzodiazepines


Benzodiazepine	Approximately equivalent dosage (mg) ^a	Elimination half-life (h) (active metabolite)
Alprazolam	0.5	6-12
Chlordiazepoxide	25	5-30 (36-200)
Clonazepam	0.5	18-50
Diazepam	10	20-100 (36-200)
Flunitrazepam	1	6-12
Flurazepam	15-30	(40-250)
Loprazolam	1	6-12
Lorazepam	1	10-20
Loxmetazepam	1	10-12
Nitrazepam	10	15-38
Oxazepam	20	4-15
Temazepam	20	8-22

^a Clinical potency for hypnotic or anxiolytic effects may vary between individuals; equivalent doses are approximate


Ashton, 2005

How to stop??

- Adjunctive medication??
- Carbamazepine (Tegretol) best supported (Cochrane review) data insufficient for recommendation for use (Denis, 2006; Parr et al., 2008)
- If patient addicted to multiple drugs may need to admit to inpatient unit to withdraw, outpatient much less successful.



Dutch Chronic Bz Work Group 2001, 36 GPs




- 436 eligible patients
- 230 consented

70 paroxetine	129 placebo
36, 50% completed	70, 43% completed

2-3 year f/u

13% Bz free

Prescribe or not to prescribe Bz that is the Question??




Alternative to Bz

- GAD
- Panic Attack Disorders
- Social Anxiety Disorders
- PTSD
- OCD
- SSRI, venlafaxine, pregabalin, buspirone
- SSRI, venlafaxine, mirtazapine
- SSRI, propranolol
- SSRI, prazosin
- SSRI, clomipramine



When to use Bz in substance abusing population??


- Remote history of abuse
- Past history of successful use without abuse
- Family history of response without abuse



Harvard Algorithm Project, Psych Annuals, 1999

When to use Bz in substance abusing population??


- High likelihood of relapse if Bz not used.
- High functioning, well motivated, sustained period of abstinence and mild level of dependence
- High risk suicide, accompanying dysphoria



Harvard Algorithm Project, Psych Annuals, 1999

Safeguards

- Coordinate providers (ROIs)
 - One doctor
 - One pharmacy
- Use Bz with less abuse potential
 - oxazepam (Serax)
 - chlordiazepoxide (Librium)
- Limit access to Bz
 - Daily or frequent dispensing
 - Lost meds not replaced



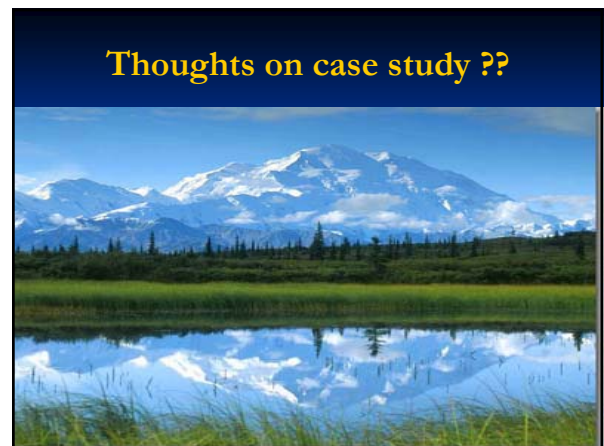

Safeguards

- Regular patient monitoring
 - Refills in person
 - No refills early
 - UDS, (GCMS)
 - Family/collateral observe and attend sessions
 - Prescription Monitoring Program



Safeguards

- Document treatment decisions
- Identify & address aberrant drug behaviors in treatment
- Patients on methadone, dose at window
- Sign written agreement
 - Lintzeris, 2010; Dupont, 2005



Withdrawal symptoms Ashton, 2005

Table 3. Some common benzodiazepine withdrawal symptoms

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Dizziness, light headedness	Formication (skin 'crawling')
Weakness 'jolly legs'	Sensory hyper-sensitivity (light, sound, taste, smell)
Tremor	Muscle twitches, jerks, fasciculation
Muscle pain, stiffness	Tinnitus
Sweating, night sweats	Psychotic symptoms*
Palpitations	Confusion, delirium*
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Equivalent doses Ashton, 2005

Table 4. Approximate equivalent doses and elimination half-lives of benzodiazepines

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Flunitrazepam	1	18–28 (36–200)
Flurazepam	15–30	(40–250)
Loprazolam	1	6–12
Lorazepam	1	10–20
Lormetazepam	1	10–12
Nitrazepam	10	15–38
Oxazepam	20	7–15
Temazepam	20	6–22

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