Benzodiazepines and Buprenorphine

What’s the problem?

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Disclosure of Relevant Financial Relationships
Content of Activity:
PCSS-O Buprenorphine/Benzodiazepine Presentation

<table>
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<th>Name</th>
<th>Commercial Interests</th>
<th>Relevant Financial Relationships: What Was Received</th>
<th>Relevant Financial Relationships: For What Role</th>
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<td>Stephen A. Wyatt, DO</td>
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None
Why are we talking about them?
"Bluelight"

- "Most "heroin overdoses" are actually polydrug ODs involving benzos, booze or some combo thereof. If you're going to do harm reduction, one of the best ways to minimize the risk of opiate use is to avoid mixing CNS depressants.......no one should tell you in good conscience that mixing benzos and opiates is a good idea so long as you're cautious. It's a risky and potentially fatal move at best."
Treatment Admissions

- Number of benzodiazepine and opiate combination admissions: 2000 to 2010
  Increased from 5,032 to 33,701

- 61.2 percent of benzodiazepine and opiate combination admissions reported daily use of any substance compared with 34.6 percent of other admissions

SAMHSA Treatment Episode Data Set (TEDS), 2000 to 2010.
Epidemiology of Benzodiazepines

- Chlordiazapoxide available in 1957
- A well-established pattern of higher sales among shorter-acting agents as compared to longer-acting ones
- Zolpidem prescriptions, have nearly doubled over the past 5 years
Epidemiology

• “The most widely used tranquilizer in America is more addictive than Valium and is often less effective than nondrug treatments for anxiety”

  Consumer Reports, January 1993
Epidemiology

- BZs are the most prescribed CNS depressants
  - Estimated past year prevalence of BZ use in the USA = 12.9%
  - 14.2% of these have taken the drug ≥ 12 mo
- 118.4 million prescriptions of the five most prescribed benzodiazepines were distributed in 2009 (Drug Enforcement Administration, 2010)
Epidemiology of Benzodiazepines

- About 30% of psychiatric patients receive benzodiazepines
- Greatest use in patients with affective disorders, long duration of mental illness, and high users of psychiatric services
- Generally most patients tend to decrease anxiolytic doses over time.
- The use of antidepressants to treat anxiety has increased in recent years and the proportion of patients treated with anxiolytics has fallen slightly
- There are certain groups of high-risk patients where long-term use, misuse, and abuse is greater than in patients with anxiety disorders.
Sedative Hypnotics

- Effective in modulating gamma aminobutyric acid (GABA)
- GABA is the major inhibitory neurotransmitter.
- Suppress central nervous system (CNS) activity
- Medical uses include
  - anxiolytic
  - hypnotic
  - anticonvulsant
  - muscle relaxant
  - anesthesia induction agent
Mechanism of Action - $\text{GABA}_A$ Receptor

- The $\text{GABA}_A$ receptor
  - An ionotropnic receptor and ligand-gated ion channel.
  - Activation, selectively conducts $\text{Cl}^-$ through its pore, resulting in hyperpolarization, of the neuron.
- Resulting in an inhibitory effect on neurotransmission by diminishing the chance of a successful action potential occurring.
**Mechanism of Action - GABA<sub>A</sub> Receptor**

- GABA<sub>A</sub> receptor is the binding site for GABA
- Different allosteric binding sites modulate the activity
  - Direct agonists
  - Enhanced GABA binding
- The allosteric sites are the targets of various drugs,
  - benzodiazepines,
  - nonbenzodiazepines,
  - barbiturates,
  - ethanol
  - neuroactive steroids,
  - inhaled anaesthetics
Pharmacokinetics Benzodiazepines

- **Adverse Effects**
  - **Cardiovascular**
    - Hypotension and bradycardia with rapid IV injection of Diazepam
  - **Respiratory depression**
    - Clinically relevant in patients with respiratory disease, in overdose situations and when combined with alcohol or opiate/opioids
Cognition

Results from the 13 studies in the meta-analysis:

- Benzodiazepines use
  - the duration between 1 and 34 years (mean 9.9 years)
  - average dose equivalent was 17.2 mg/day of diazepam

- Results suggested decline in all the cognitive domains measured: visuospatial, attention/concentration, problem solving, general intelligence, psychomotor speed, sensory processing, verbal memory, non-verbal memory, speed of processing, motor control/performance, working memory, and verbal reasoning.

Most abused benzodiazepines

- Short-acting
  - rapid onset
- Highly lipophilic
  - e.g., diazepam
- Short half-life and high potency
  - lorazepam, alprazolam
- Clonazepam – high potency, long half-life
  - Perceived as "safe"
  - Frequently abused as a street drug

Benzodiazepine Use Patterns

- Recreational abuse of BZs alone is uncommon
  - Commonly taken as part of polysubstance abuse

- Motivations
  - Euphoria
  - Augment euphoriant effect of other drugs, especially opiates
  - Up to 80% of opiate abusers have taken BZs
  - To ease the "crash" from cocaine
  - 29%-33% of alcohol abusers take BZs

Benzodiazepine Abuse

Note: Percentages may not sum to 100 percent due to rounding.
Source: SAMHSA Treatment Episode Data Set (TEDS), 2008.
Street Market

- Diazepam and clonazepam ≈ $2.00-$4.00/pill
- Many who seek these drugs for a "high" quickly move on to other agents
- High risk for continued misuse of BZs:
  - Heroin dependent / methadone or buprenorphine maintenance
    - 75%+ admitted taking BZs to enhance intoxication or treat withdrawal
  - Alcoholic
    - Perhaps for anxiety, insomnia, withdrawal sx$s$

How reinforcing are Benzodiazepines?

- Animals
  - Oral BZs
    - 8/18 studies in primates and rats did not show evidence of reinforcement
  - IV
    - Reinforcement demonstrated with a variety of benzodiazepines
- Humans
  - Normal (light drinkers without anxiety or insomnia)
    - BZ (diazepam, lorazepam, flurazepam) not preferred to placebo
  - Moderate social drinkers, no hx alcohol problems
    - Benzodiazepines (po) are reinforcers
    - Three studies confirm

Pharmacokinetics Benzodiazepines

• Physical Dependence
  • Becomes apparent when withdrawal occurs upon discontinuation of the drug
    • on withdrawal compensatory changes reduced GABA receptor function manifested as anxiety, insomnia, autonomic hyperactivity and possibly seizures.
  • Can occur after continued use over 2 to 4 months
  • Reported in 50% of patients on treatment for > 4-6 months

Six deaths linked to concomitant use of buprenorphine and benzodiazepines

M REYNAUD et.al, Centre Medico-Psychologique and the Institut de Medecine Legale of Centre Hospitalo-Universitaire de Clermont-Ferrand, France

Results

Benzodiazepine ± buprenorphine associations were found in every case (norbuprenorphine was found less systematically). No other substance that could account for the death was found (e.g. illicit poisons, psychotropics, other drugs).
Pharmacodynamics - Animal Model

- Animal model using median lethal doses of morphine, buprenorphine, and methadone alone and in animals pretreated with flunitrazepam (40mg/kg.)
- Buprenorphine had a significantly higher lethal dose.
- Buprenorphine/flunitrazepam cohort had a significant lengthening of the time to death.

SW Borron, et.al., Human Exp. Toxicology 2002, Nov
Pharmacodynamics - Animal Model

- Four benzodiazepines used intravenously at equi-efficacious doses in rats, alone and in combination with buprenorphine:
  - Outcomes: sedation, respiratory rate, arterial blood gases.
- Results:
  - Buprenorphine no significant change in sedation, respiratory rate, blood gases.
  - Buprenorphine / benzodiazepine: no significant effects on RR or blood gases
  - Buprenorphine / benzodiazepine: significantly deepened sedation.
- Effects of these combinations are rather mild.

Pirnay SO. et.al, Basic & Clinical Pharmacology & Toxicology. 103(3):228-39, 2008 Sep
Epidemiology of:

Buprenorphine and Benzodiazepines

- N = 170 buprenorphine treated patients
  - 54% no use / 15% were simple users (statistically similar)
  - 31% were problematic users. (DSM IV abuse or Dependence)
    - Used higher dosages of benzodiazepines than simple users.
    - Problematic users of benzodiazepines: higher depression and anxiety levels, correlated with quality of life impairment and precariousness.

- Factors associated independently with re-incarceration were prior imprisonment and benzodiazepine use.
- Though maintenance therapy has risen, the risk of re-imprisonment or death remains high among opioid-dependent prisoners.

Marzo JN. et.al., Addiction 104(7) 1233-40 2009 Jul
Epidemiology of: 

Buprenorphine and Benzodiazepines

- Buprenorphine abusers who were concomitantly using BZDs were significantly:
  - Younger
  - Earlier age of onset of illicit drug abuse
  - More likely to share syringes ($x^2 = 5.8, P = 0.02$)
  - More likely to be seropositive for hepatitis C virus ($x^2 = 4.3, P = 0.04$).

- Benzodiazepines complicate the work of substance abuse treatment providers.

Ng WL. et.al., Annals of the Academy of Medicine, Singapore. 36(9):774-7, 2007 Sep.
Pharmacodynamics

- Combining buprenorphine and diazepam single doses at 10 and 20mg.
  - Minimal effect on physiologic parameters
  - Significant on performance and subjective effects.
- Co-administering diazepam with methadone or buprenorphine under high dose conditions.
- Four methadone- and seven buprenorphine-prescribed patients without concurrent dependence on other substances or significant medical co-morbidity.

Pharmacodynamics

- Outcomes:
  - Physiological (pulse rate, blood pressure, pupil size, respiratory rate and peripheral SpO2), subjective (ARCI, VAS ratings)
  - Performance (reaction time, cancellation task and Digit Symbol Substitution Test, DSST) measures were taken prior to and for 6h post-dosing.

- High dose diazepam in both methadone and buprenorphine patients was associated with intensity of subjective drug effects and decreases in psychological performance.

Benzodiazapine plus: Buprenorphine vs. Methadone

- Five needle syringe programs and five opioid substitution treatment services.
- N=250 people who had experience with methadone or buprenorphine
- Structured questionnaire covering: concurrent use of buprenorphine and benzodiazepines:
  - route of administration,
  - source of medications;
  - opioid toxicity symptoms reported in association with methadone and buprenorphine consumption.

Benzodiazapine plus: Buprenorphine vs. Methadone

- Two-thirds reported concurrent benzodiazepine use, approx. 30 mg diazepam equiv.
- A greater number of opioid toxicity symptoms were reported in relation to methadone compared with buprenorphine.
- Those reporting toxicity with buprenorphine were more likely to report intravenous use compared with those reporting toxicity with methadone.
- The risk of opioid toxicity appeared greater with methadone compared with buprenorphine, despite high levels of benzodiazepine consumption and injection being reported in relation to buprenorphine use.

Combined Benzodiazepines and Buprenorphine

- Cohort study of 325 buprenorphine with past year benzodiazepine use and misuse.
- Not associated with treatment retention or illicit opioid use (urine toxicology screens)
- No greater overdose rate.
- Greater accidental injury related ED visits (>females)

Z Schuman-Olivier, et al., Drug and Alcohol Dependence, October 2013
Withdrawal

Many AEDs permit patients to comfortably and rapidly reduce / eliminate BZs, Soma, and non- hypnotics

- Examples
  - Pregabalin
  - Valproic acid
  - Gabapentin
  - Carbamazepine

- Extended use may be required for subtle protracted withdrawal

Benzodiazepine - Withdrawal treatment

- Prolonged Withdrawal
  - Correlates to the degree of psychopathology prior to use.
    - Mood and Anxiety disorders
    - Personality disorders
    - Concurrent substance use
- Treatment
  - Alternative medication strategies
  - Cognitive Behavioral Treatments
Prolonged Withdrawal

- The worst candidates are prescribed the most sedatives
- This probably worsens functional impairment and quality of life
- Management should include weaning. Replacement with alternate therapies for anxiety, sleep
Antidepressants for GAD

- Review of RCTs
  - Imipramine
  - Venlafaxine
  - Paroxetine
- All superior to placebo

TCAs for Anxiety

- **Strongly anxiolytic**
  - Doxepin is as anxiolytic as diazepam

- **Additional benefits**
  - Promote sleep
  - Reduce neuropathic pain, fibromyalgia and migraine

- Improve mood
An approach to talking to patients about anxiety.

- Avoid the word anxiety.
- Instead talk about the stress response (SR).
- Describe what is meant by the SR.
- Describe the importance of the SR.
- Describe how their SR might be used in a positive way, normalizing the response.
An approach to talking to patients about panic.

- Use much of the same approach as in the anxious patient.
- Talk to them about the importance of not panicking!
- Explain the experience of panic and the physiology of hyperventilation.
  - SOB
  - Numbness and tingling of mouth and fingers
  - Upset stomach
  - Chest heaviness
  - Visual abnormalities
  - Fainting
Summary

- The use of illicit administration of a benzodiazepine with buprenorphine is:
  - Dangerous primary due to the sedation and cognitive changes in a person that is already experiencing respiratory compromise.
  - Is an indication of:
    - Worse drug problems
    - Underlining mood and anxiety problems
    - High risk behavior