

MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

Current Understanding of the Interaction of Benzodiazepines and Buprenorphine

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Frances Levin, MD is a consultant for GW Pharmaceuticals and receives study medication from US Worldmed.

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- American Academy of Addiction Psychiatry designates this enduring material educational activity for a maximum of 1 (one) *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.
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System Requirements

- In order to complete this online module you will need Adobe Reader. To install for free click the link below:
 - <http://get.adobe.com/reader/>

Target Audience

- The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

Educational Objectives

- At the conclusion of this activity participants should be able to:
 - Understanding of the basic pharmacology of benzodiazepines.
 - Understand the effects of opiates on respiratory function.
 - Understanding of the hazards of combining benzodiazepines and buprenorphine.
 - Know of alternatives to the treatment of anxiety in the opiate dependent patient.

Buprenorphine and Benzodiazepines

- Buprenorphine and benzodiazepines are both known to have relatively wide margins of safety. However there is evidence of greater toxicity when these medications are used or abused concurrently. This module will review the pharmacology of these medications and the evidence of the hazards of using them together.
- There will also be suggestions of non-BZD alternatives to treatment of anxiety in the BUP maintained patient.

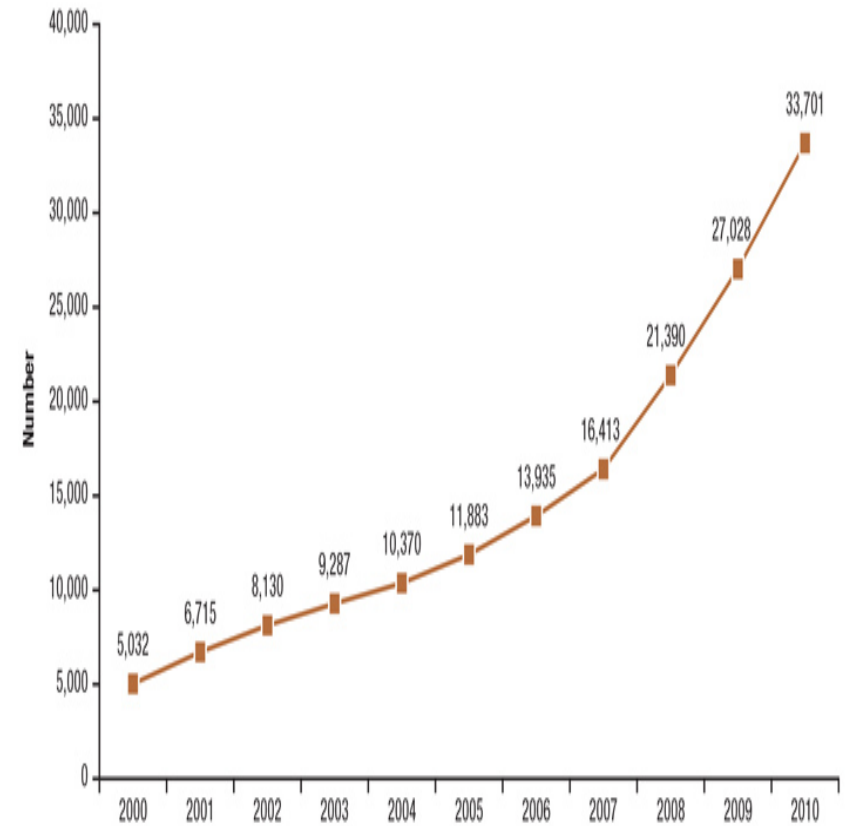
Benzodiazepines and Buprenorphine

- There is forensic evidence of the association of increased mortality in the concurrent use of BUP and a benzodiazepine (BZD)¹
- Six deaths linked to concomitant use of buprenorphine and benzodiazepines
- 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)²

1. Kintz, 2001; 2. Reynaud et al., 1998

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



Source: SAMHSA Treatment Episode Data Set (TEDS), 2000 to 2010.

Buprenorphine

- Buprenorphine (BUP) is known to have a higher affinity and slower dissociation than full opiate agonists contributing to the efficacy of this medication in the treatment of opiate dependent patients.
- There is a plateau of respiratory depression est. in both rat and human models contributing to the reduced toxicity of BUP.¹⁻⁴
- However worsening safety profile of BUP is associated with injection use or concurrent use of other psychoactive drugs. ⁵⁻⁹

1. Cowan et al., 1977; 2. Dahan et al., 2005; 3. Nielsen and Taylor, 2005; 4. Walsh et al., 1994; 5. Kintz 2001; 6. Lai et al., 2006; 7. Pirnay et al., 2004; 8. Reynaud et al., 1998; 9. Tracqui et al., 1998

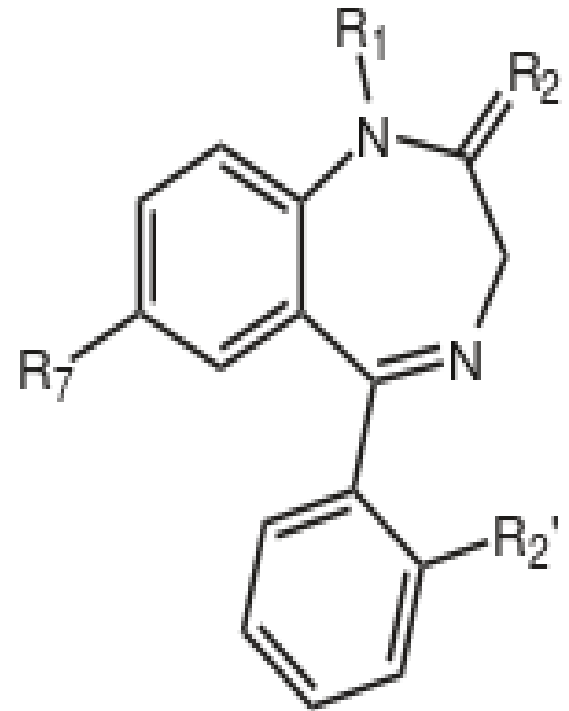
Benzodiazepine

- Benzodiazepines also have an improved safety profile over other sedative, sedative/hypnotics.
- However there is a rich and longstanding literature identifying the misuse and abuse of these medications.¹⁻³

Epidemiology of Benzodiazepines

- Chlordiazapoxide available in 1957
- They are now highly prevalent:
 - A well-established pattern of higher sales among shorter-acting agents as compared to longer-acting ones
 - Zolpidem, a para-benzodiazepine prescriptions, have nearly doubled over the past 5 years

1,4 benzodiazepine ring



Epidemiology

- BZs are the most prescribed CNS depressants
 - Estimated past year prevalence of BZ use in the USA = 12.9%
 - 14.2% of these patients have taken the drug ≥ 12 mo¹
- 118.4 million prescriptions of the five most prescribed benzodiazepines were distributed in 2009 (Drug Enforcement Administration, 2010)

1. Barker et al., 2004

Epidemiology

- “(Alprazolam) The most widely used tranquilizer in America is more addictive than Valium and is often less effective than nondrug treatments for anxiety”¹
- Alprazolam, remains the 13th most commonly sold medication in 2012, and was the psychiatric medication most commonly prescribed in 2011. ²

XANAX

1. Consumer Reports, January 1993; 2. SAMHSA, DAWN Report, 2014

Epidemiology of Benzodiazepines

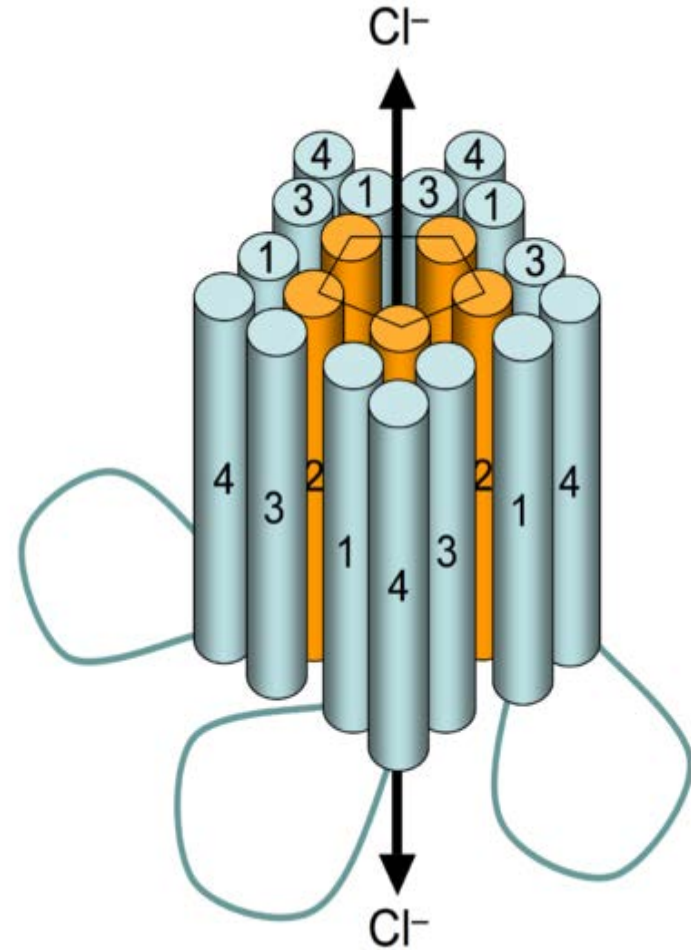
- About 30% of psychiatric patients receive benzodiazepines
- Greatest use in patients with affective disorders, long duration of mental illness, and high users of psychiatric services
- Generally most patients tend to decrease anxiolytic doses over time.
- The use of antidepressants to treat anxiety 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.

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 – GABA_A Receptor

- The **GABA_A receptor**
 - An ionotropic receptor and ligand-gated ion channel.
 - Activation, selectively conducts 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.

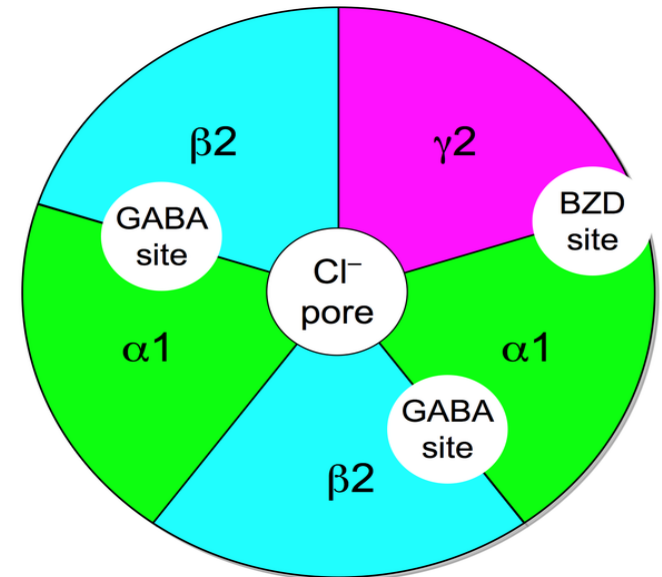


Mechanism of Action – GABA_A Receptor

- GABA_A 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,
non-benzodiazepines,
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

Benzodiazepines: 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.

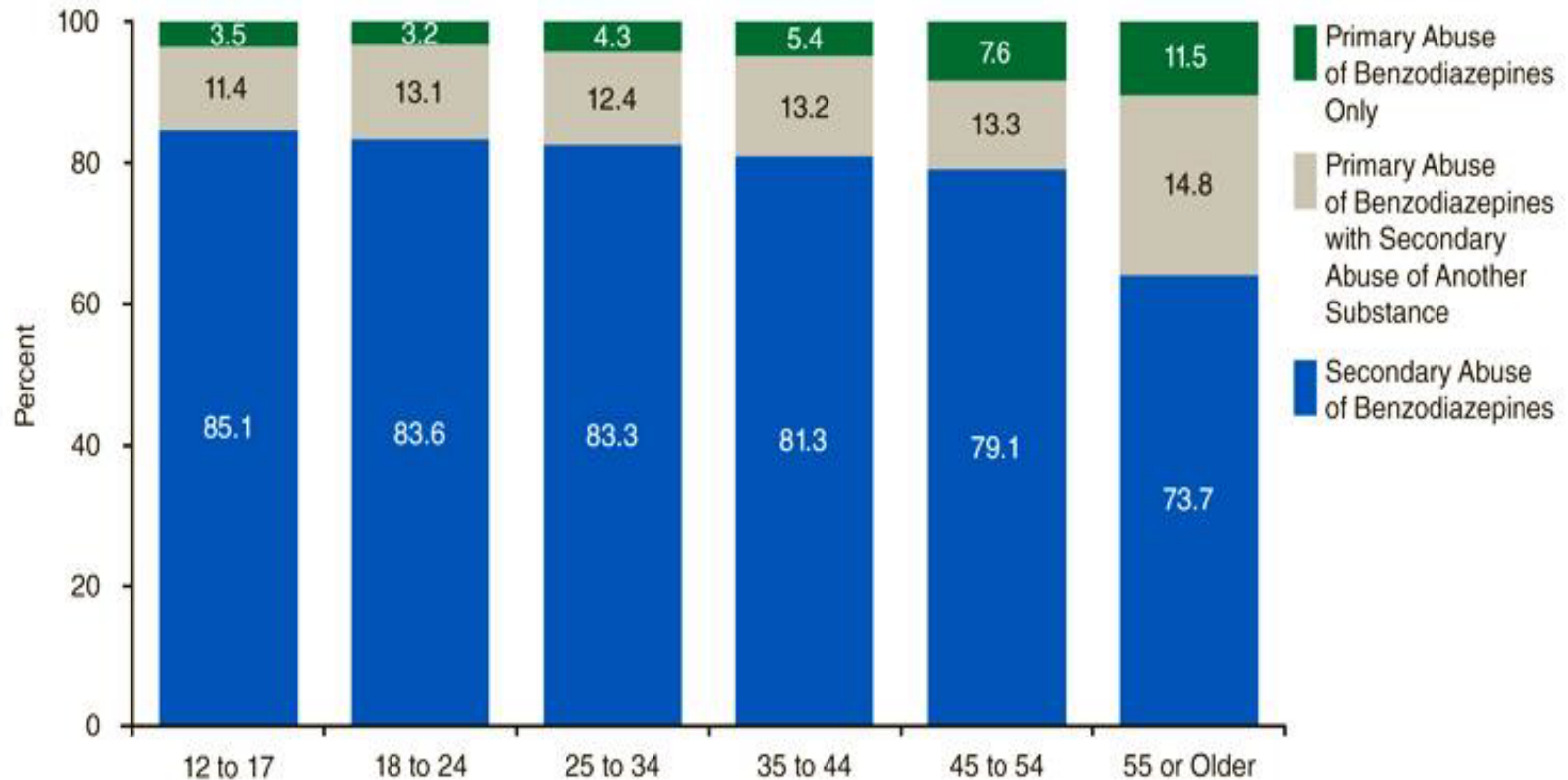
Most Abused Benzodiazepines

- 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

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

Opiate/Opioid Toxicity

- Opioid medications and illicit drugs are well known to significant toxicity.
- In recent years there has been a rise in the unintentional deaths due to these drugs.
- The mortality is worsened when combined with other drug use including alcohol and benzodiazepines.

Opiate/Opioid Toxicity

- Pathophysiology
 - Histaminic effects resulting in increased respiratory congestion.
 - Sedation
 - Potential bronchospasm
 - Elevation of CO₂ secondary to the decreased sensitivity in the centrally located respiratory center

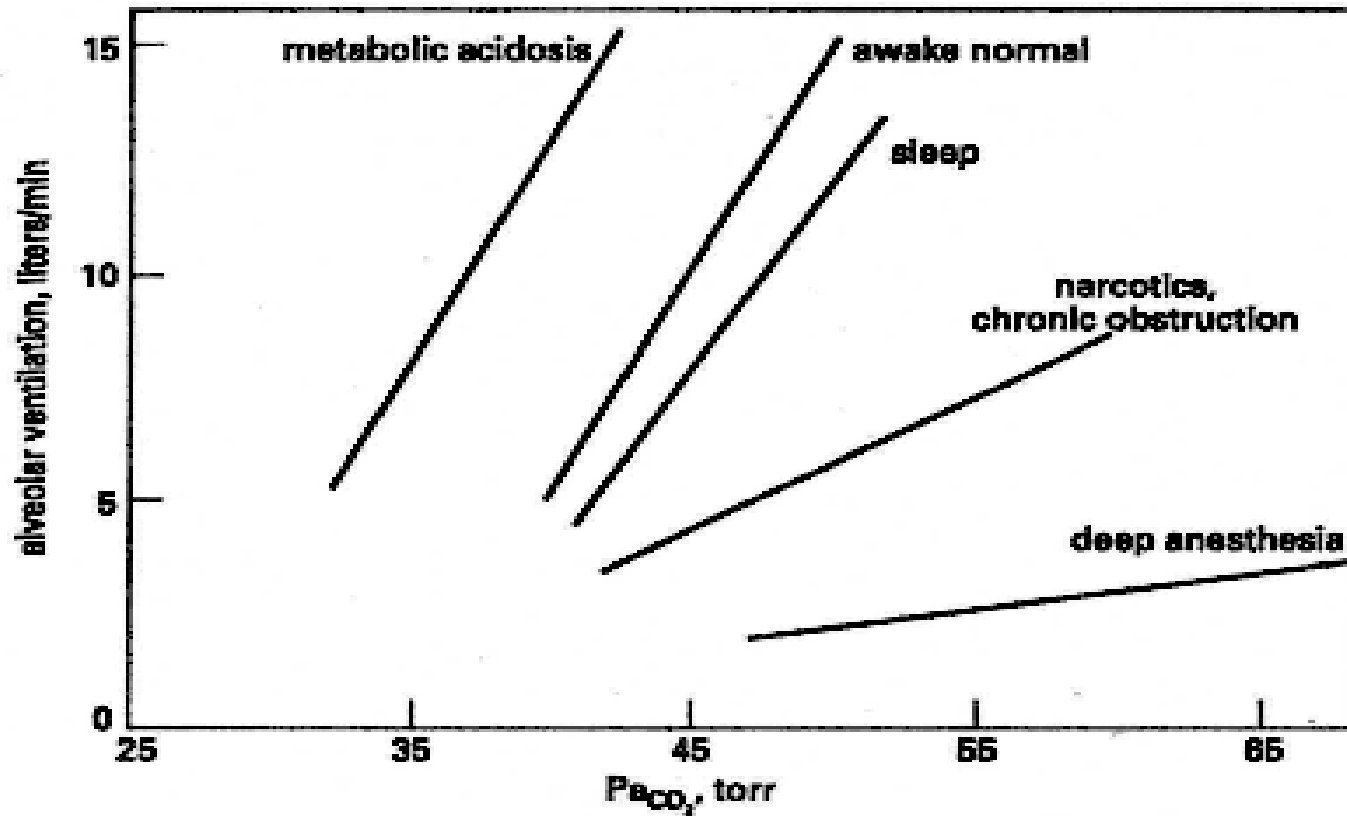
Opiate/Opioid Toxicity

- These problems are compounded by:
 - Nausea/Vomiting
 - Respiratory illnesses
 - Cardiovascular disease
 - Sleep Apnea
 - Obesity

Opiate/Opioid Toxicity

- Respiratory depression:
 - There is an altered sensitivity to CO₂ in the respiratory center within the medulla.
 - This results in the slowing and potential discontinuation of the drive to breathe.
 - Full opiates can cause both hypoxia and hypercapnia, while buprenorphine has been identified in rat models to only cause hypoxia from a slowing of respiration.

Opiate/Opioid Toxicity



Note how the negative effects of narcotics can be further altered in sedation or sleep.

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.

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.

Pharmacodynamics - Animal Model

- Evidence of an alteration in metabolism of a BZD contributing to toxicity.
 - Sprague-Dawley rat study of IV infusion of various doses of flunitrazepam and BUP.
 - High dose combinations appeared to result in an increase in respiratory toxicity (\uparrow pO₂ and \downarrow pO₂) and this was mediated by the increased concentrations of the BZD metabolite desmethylflunitrazepam.

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.

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.

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)

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

Antidepressants for GAD

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

Kapczinski et al., 2003

TCA's 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 hyperventilation.
 - SOB
 - Numbness and tingling of mouth and fingers
 - Upset stomach
 - Chest heaviness
 - Visual abnormalities
 - Fainting

Summary

- The administration of a benzodiazepine with buprenorphine is:
 - Poorly understood in both animal and human studies, though there is evidence of negative respiratory effects when used concurrently.
 - Clearly dangerous due to the drug effects of sedation and worsening cognition in a person already experiencing moderate slowing of respiration.
 - The illicit use of these drugs is an indication of:
 - Complicated drug problems
 - Underlying mood and anxiety problems
 - High risk behavior

Benzodiazepines and Buprenorphine - Vignette

- Patient is a 37 year old Caucasian, married, female with past history of depression, anxiety, and polysubstance use, presents with a complaint of recent panic episodes. There is maternal family history of bipolar disorder in her mother and a great aunt who was hospitalized multiple times. There is extensive paternal history of alcohol use disorders. She describes herself as having been a shy child. She first saw a counselor while in elementary school for behavioral problems. There was an attempt at treatment with a psycho-stimulant and antidepressants on entering middle school but she was inconsistent in taking them. She first started smoking cigarettes at 10 years. She was given marijuana by her older brother when 12 and smoked daily until quitting high school in her junior year. This also marked the onset of her use of opioid pain medications. By 19 she was using heroin by injection. She describes when first trying opiates she felt "normal", a state she believed other people feel like all the time. However, her opioid dependence caused her problems in multiple domains.

Benzodiazepines and Buprenorphine – Vignette

- She had her first child at 23 and second at 25 by her current husband. She got her GED at 27 and has worked as a manager at a body shop for 7 years. She was in multiple opiate medical withdrawal programs from 22 to 32 and on methadone during both her pregnancies. The use of alcohol and benzodiazepines have often been associated with her relapses. She had one unintentional overdose at 28 involving a mix of drugs but cleared with naloxone. Following this trauma her children were put in the custody of her sister in law by child protective services for two years. Her husband has been maintained on methadone since she was 29 and has not relapsed. He is working and she describes him as a supportive husband. She was first prescribed buprenorphine/naloxone at 32 and has been opiate free since then. She has always been troubled by her anxiety and struggled with sleep maintenance. Since being on buprenorphine her life has stabilized but she believes she needs benzodiazepines for control of her anxiety. She has problems with feeling nervous in a variety of social settings.

Vignette Question 1:

Is this woman a candidate for a benzodiazepine?
If so which benzodiazepine would be indicated?

- A.** Yes, a short acting benzodiazepine only as needed would be the best then she might not get dependent.
- B.** No
- C.** Yes, It would be best to treat her with a short acting benzodiazepine every 6 hours to resist her abusing a PRN.
- D.** Yes, A long acting Benzodiazepine every 12 hours would be indicated.
- E.** Yes, a long acting benzodiazepine as needed would be indicated.

Complete Post-test for answer

Vignette Question 2:

The most therapeutic treatment for this patient's anxiety would be?

- A.** A benzodiazepine
- B.** An SSRI
- C.** A tricyclic antidepressant
- D.** A combination of cognitive behavioral therapy plus either B or C
- E.** Cognitive behavioral therapy

Complete Post-test for answer

Vignette Question 3:

Your patient was prescribed a benzodiazepine by a psychiatrist in the community. She does well for the first month but quickly falls into an abuse pattern of use. She presents for a refill of her buprenorphine clearly disinhibited. You encourage her to stop the use of this medication. Your attempts at speaking to her psychiatrist fails. You reduce the quantities of her buprenorphine prescriptions in an attempt more frequent observation and engagement. There is recognition of a worsening affect and engagement with treatment. Her husband calls describing an incident at home involving her combined use of buprenorphine, benzodiazepines and alcohol. This all takes place within two months of starting the benzodiazepine. At her next presentation you inform her she is:

- A. Discharged from your practice.
- B. To stop the benzodiazepines and you will continue to treat her.
- C. To go to inpatient for benzodiazepines and buprenorphine withdrawal treatment.
- D. To go to methadone maintenance treatment.
- E. To go inpatient for alcohol withdrawal treatment.

Complete Post-test for answer

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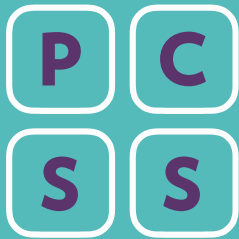
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PCSS-MAT Mentoring Program

- PCSS-MAT Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.
- PCSS-MAT Mentors comprise a national network of trained providers with expertise in **medication-assisted treatment, addictions and clinical education.**
- Our 3-tiered mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.
- The mentoring program is available, at no cost to providers.

For more information on requesting or becoming a mentor visit:

pcssmat.org/mentoring



MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

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For More Information: www.pcssmat.org

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