Pragmatic Approaches to Concurrent Benzo/Sedative Use: Data, Scripts, and Clinical Approaches

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Brian Grahan, MD, PhD, FACP, FASAM

Medical director, Addiction Medicine office-based services

Director, Integrated Opioid & Addiction ECHO

Disclosures

- We have no financial conflicts of interest.

- We will not be discussing off-label use of medications

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- Some slides were borrowed from ECHO presentations by:
  - George Dawson, MD – Benzodiazepines in Opioid Use Disorder. October 22, 2020

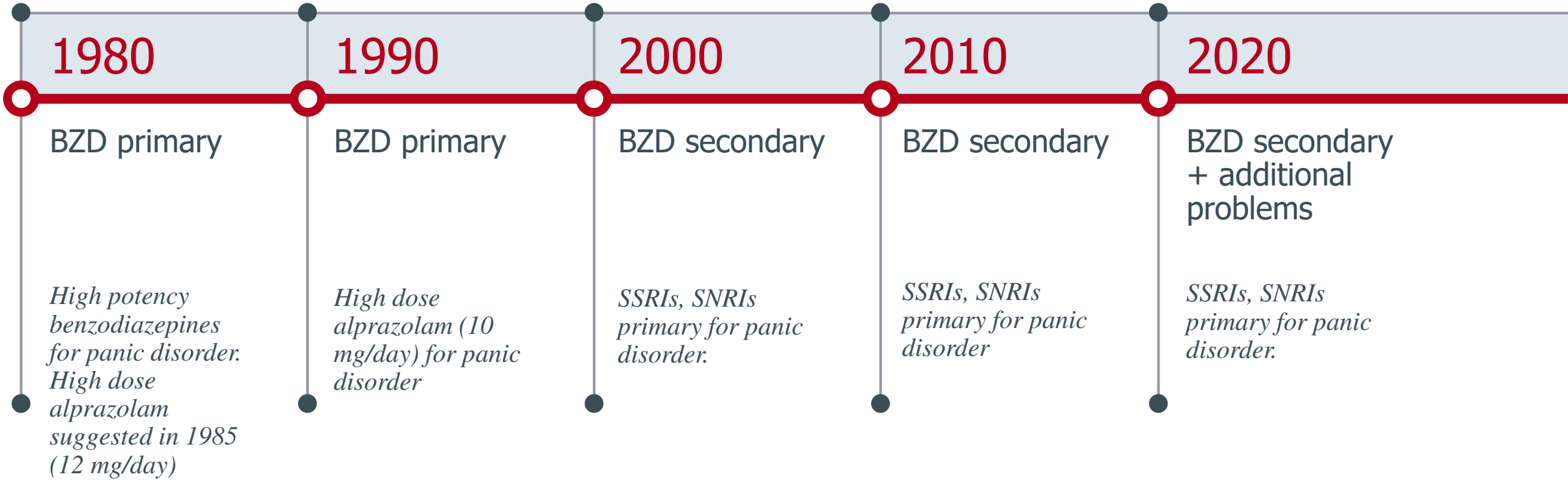
I encourage people to review these presentations in their entirety at the [Hennepin ECHO Resource Page]

Learner objectives

1. Describe clinical pharmacology of benzodiazepines
2. Assess risk-benefit of concurrent benzodiazepine and buprenorphine prescriptions
3. Consider when to adopt benzodiazepine prescription and work on taper vs decline/defer

Benzodiazepine Use

Clinical Use Over Time



The Politics of Benzodiazepines

(very similar to the politics of opioids)

Restrictive	Permissive
Fail non pharmacological treatments first	Initial goal of pharmacological maintenance
Time limited – careful selection of maintenance cases	Broad consideration of maintenance
Pharmacological strategies to minimize BZD use	BZD are mainstay of pharmacology
No concurrent opioids and BZD except for detox	BZD for anxiety and insomnia in OUD and MAT
Taper and DC BZD if any other SUD	Rx BZD if co-occurring SUD for common indications
No stimulant Rx for ADHD in SUD	Rx BZD to counteract ADEs from prescribed stimulants for ADHD
Bridging strategies – clear time to DC BZD	Polypharmacy strategies

Risks have been well defined…

Relationship between opioid MME and death

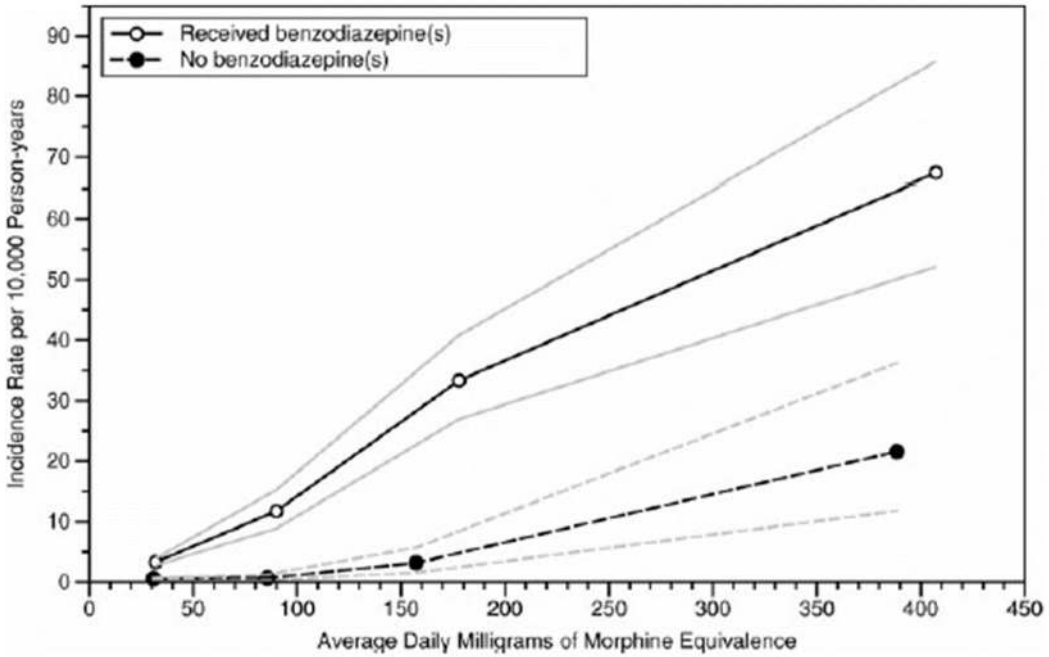


Table 3. Risk of Death Associated with Periods of Concomitant Therapy with MAT and Benzodiazepines or Non-benzodiazepine Hypnotic Drugs in Sweden, July 2005-December 2012*

	Adjusted Hazard Ratio (95% Confidence Interval)		
	Overdose Mortality	**Non-overdose Mortality**	**All-cause Mortality**
Benzodiazepine Treatment	1.05 (0.51-2.15)	1.74 (1.00-3.01)	1.44 (0.93-2.23)
Non-benzodiazepine Hypnotic Drug Treatment	2.34 (1.37-3.99)	1.25 (0.71-2.20)	1.66 (1.12-2.45)

*The table is based on the paper by Abrahamsson et al.[4] Benzodiazepines included in the study were diazepam, oxazepam, lorazepam, alprazolam, nitrazepam, flunitrazepam, triazolam, midazolam, and clonazepam. The non-benzodiazepine hypnotic drugs included in the study were zopiclone, zolpidem, and zaleplon.

Dasgupta N, Pain Medicine 2016;17:85-98

FDA Guidance for Health Care Professionals

- Educating patients about the serious risks of combined use, including overdose and death, that can occur with CNS depressants even when used as prescribed, as well as when used illicitly.
- **Developing strategies to manage the use of prescribed or illicit benzodiazepines** or other CNS depressants when starting MAT.
- **Tapering** the benzodiazepine or CNS depressant **to discontinuation if possible**.
- Verifying the diagnosis if a patient is receiving prescribed benzodiazepines or other CNS depressants for anxiety or insomnia, and considering other treatment options for these conditions

Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. Published online 9/20/2017

TABLE 1. The use of benzodiazepines in patients with substance use disorders

Acute/Subacute

1. **Detoxification.** Benzodiazepines remain the drugs of choice for alcohol and sedative-hypnotic detoxification. Many treatment facilities have withdrawal protocols that use anticonvulsants or phenobarbital, but benzodiazepines have the widest safety margin and may address some symptoms of the withdrawal syndrome such as anxiety better than non-benzodiazepine options. Benzodiazepines with long half-lives are generally preferable to other agents, but familiarity with options for patients with severe liver disease is also necessary.
2. **Short-term bridging to a more effective long-term plan for treating anxiety or anxiety and depression.** Withdrawal syndromes in patients with a chronic and complicated history of use can be more difficult to treat than textbook scenarios based on the pharmacological properties of the medications being used. In many situations, it is difficult to know if the withdrawal syndrome has been adequately treated, whether the underlying anxiety or sleep disorder is surfacing, or there is a new substance-induced disorder—or some combination of these processes.

3. **Short-term bridging in the case of polypharmacy in which alternative medications are less safe.** Many of the non-benzodiazepine medications that are used to treat depression, sleep, and anxiety disorders have risk in a polypharmacy environment. A common flag is problems with cardiac conduction. In many of these situations, it is best to avoid any medications that target the patient's anxiety or insomnia but potentially complicate other problems and to use benzodiazepines temporarily.
4. **Acute catatonia, agitation, akathisia, or transient anxiety due to brief severe stressors.** In residential treatment centers, that agitation is more likely associated with complex withdrawal states that include severe anxiety states. Benzodiazepines are useful medications to alleviate akathisia that can result from treatment with SSRIs or antipsychotic medications.

Long term

1. **Severe treatment-refractory insomnia.**[a]
2. **Severe treatment-refractory anxiety disorders,** including mixed anxiety and bipolar states and mixed anxiety and depressed states.[a]

[a] Only in situations in which the abuse potential (dose escalation, multiple prescribers, additional illegal intoxicants) can be contained.

TABLE 2. Tips for benzodiazepine prescribing: interpersonal dimension

1. Avoid emotional prescribing based on how stressful the situation is or on patient characteristics.
2. Have a well thought-out general approach to prescribing and do not deviate from that plan.
3. Be aware of how prescribing a controlled substance can affect your decision-making and the relationship with the patient.
4. Maintain a conservative prescribing bias in general and especially in the case of a suspected substance use disorder.
5. Maintain a teaching role with the patient that includes a detailed risk-to-benefit discussion and the rationale for prescribing or not prescribing the benzodiazepine; include a discussion of informed consent, addiction risk, and prevention.
6. Consult with colleagues in difficult situations and avoid professional isolation. Solicit feedback on how colleagues would make similar decisions. In group practices, controlled substance prescribing can be the basis of a quality improvement initiative and process.

Most of us won’t start prescribing benzodiazepines or z-drugs…

…but what should we do for people who are already on chronic benzo/sedatives?

•. 2013 Oct 1;132(3):580-6
•. 2013 Oct 1;132(3):580-6

Benzodiazepine use during buprenorphine treatment for opioid dependence: clinical and safety outcomes

Zev Schuman-Olivier [1], Bettina B Hoeppner, Roger D Weiss, Jacob Borodovsky, Howard J Shaffer, Mark J Albanese

Affiliations + expand

PMID: 23688843 PMCID: PMC3916951 DOI: 10.1016/j.drugalcdep.2013.04.006

Free PMC article

Abstract

Background: Prescribing benzodiazepines during buprenorphine treatment is a topic of active discussion. Clinical benefit is unclear. Overdose, accidental injury, and benzodiazepine misuse remain concerns. We examine the relationship between benzodiazepine misuse history, benzodiazepine prescription, and both clinical and safety outcomes during buprenorphine treatment.

Methods: We retrospectively examined outpatient buprenorphine treatment records, classifying patients by past-year benzodiazepine misuse history and approved benzodiazepine prescription at intake. Primary clinical outcomes included 12-month treatment retention and urine toxicology for illicit opioids. Primary safety outcomes included total emergency department (ED) visits and odds of an ED visit related to overdose or accidental injury during treatment.

Results: The 12-month treatment retention rate for the sample (N=328) was 40%. Neither benzodiazepine misuse history nor benzodiazepine prescription was associated with treatment retention or illicit opioid use. Poisson regressions of ED visits during buprenorphine treatment revealed more ED visits among those with a benzodiazepine prescription versus those without ($p<0.001$); benzodiazepine misuse history had no effect. The odds of an accidental injury-related ED visit during treatment were greater among those with a benzodiazepine prescription (OR: 3.7, $p<0.01$), with an enhanced effect among females (OR: 4.7, $p<0.01$). Overdose was not associated with benzodiazepine misuse history or prescription.

Conclusions: We found no effect of benzodiazepine prescriptions on opioid treatment outcomes; however, benzodiazepine prescription was associated with more frequent ED visits and accidental injuries, especially among females. When prescribing benzodiazepines during buprenorphine treatment, patients need more education about accidental injury risk. Alternative treatments for anxiety should be considered when possible, especially among females.

"naturalistic, quasi-experimental design, we attempted to evaluate the relationship between benzodiazepine prescribing and clinical and safety outcomes during buprenorphine treatment"

Retrospective study of sequential admissions

Identified 328 opioid + BZD users – 172 with no BZD misuse (140 no Rx + 32 Rx) and 152 with BZD misuse (130 no Rx + 156 Rx)

Outcomes:

1. **No effect on 12 month treatment retention**
2. **More frequent ED visits and accidental injuries**

Slide courtesy of George Dawson, MD. 10/22/2020
Schuman-Olivier Z, et al. Drug Alcohol Depend. 2013 Oct 1;132(3):580-6

Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment-A nation-wide register-based open cohort study

Tove Abrahamsson [1], Jonas Berge [1], Agneta Öjehagen [1], Anders Håkansson [2]

Affiliations + expand

PMID: 28315808 DOI: 10.1016/j.drugalcdep.2017.01.013

Free article

Abstract

Background: Use of sedatives may increase risk of death in opioid users. The aim of the study was to assess whether prescription of sedatives may be associated with mortality in patients in opioid maintenance treatment.

Methods: This retrospective register-based open cohort study included nation-wide register data including all individuals who were dispensed methadone or buprenorphine as opioid maintenance treatment for opioid dependence between July, 2005 and December, 2012 (N=4501). Outcome variables were overdose mortality and non-overdose mortality, respectively. Extended Cox regression analyses examined associations between type of sedative prescriptions and death, controlling for sex, age, previous overdoses and suicide attempts, psychiatric in-patient treatment and opioid maintenance treatment status. Opioid maintenance was assumed to last for 90days (or 30days in a sensitivity analysis) after the last methadone or buprenorphine prescription.

Results: Benzodiazepine prescriptions were associated with non-overdose death (HR: 2.02, 95% CI: 1.29-3.18) but not significantly associated with overdose death (1.49, 0.97-2.29). Z-drug (1.60, 1.07-2.39) and pregabalin prescriptions (2.82, 1.79-4.43) were associated with overdose death. In the sensitivity analysis, all categories of sedatives, including benzodiazepines, were significantly associated with overdose death.

Conclusions: Caution is advised when prescribing sedative drugs, including benzodiazepines, z-drugs and pregabalin, to patients in opioid maintenance treatment.

"retrospective Swedish register based open cohort study of all people treated with methadone or buprenorphine between the years 2005 and 2012"

In Sweden – OMT is mandated only for OUD
Most patients are heroin dependent
People are discharged if they are unable to comply with tx regulations and cannot return for 3 months.

N=4501: 1280 MMT + 2369 buprenorphine + both during the study interval

32.4% BZD Rx
40.8% z-drug Rx
22.2% pregabalin Rx

Outcomes:

1. **Benzo Rx did not increase fatal overdose rate**
2. **Increase in all-cause mortality rate**
3. **Z-drug and pregabalin increased fatal overdose rate**

Slide courtesy of George Dawson, MD. 10/22/2020.
Abrahamsson T, et al. Drug Alcohol Depend. 2017 May 1;174:58-64

Associations between prescribed benzodiazepines, overdose death and buprenorphine discontinuation among people receiving buprenorphine

Tae Woo Park [1 2], Marc R Larochelle [2 3], Richard Saitz [2 3 4], Na Wang [5], Dana Bernson [6], Alexander Y Walley [2 3]

Affiliations

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Free PMC article

Abstract

Background and aims: Benzodiazepines are commonly prescribed to patients with opioid use disorder receiving buprenorphine treatment, yet may increase overdose risk. However, prescribed benzodiazepines may improve retention in care by reducing buprenorphine discontinuation and thus may prevent relapse to illicit opioid use. We aimed to test the association between benzodiazepine prescription and fatal opioid overdose, non-fatal opioid overdose, all-cause mortality and buprenorphine discontinuation.

Design and setting: This was a retrospective cohort study using five individually linked data sets from Massachusetts, United States government agencies.

Participants: We studied 63 389 Massachusetts residents aged 18 years or older who received buprenorphine treatment between January 2012 and December 2015.

Measurements: Filled benzodiazepine prescription during buprenorphine treatment was the main independent variable. The primary outcome was time to fatal opioid overdose. Secondary outcomes were time to non-fatal opioid overdose, all-cause mortality and buprenorphine discontinuation. We defined buprenorphine discontinuation as having a 30-day gap without another prescription following the end date of the previous prescription. We used Cox proportional hazards models to calculate hazards ratios that tested the association between receipt of benzodiazepines and all outcomes, restricted to periods during buprenorphine treatment.

Findings: Of the 63 345 individuals who received buprenorphine, 24% filled at least one benzodiazepine prescription during buprenorphine treatment. Thirty-one per cent of the 183 deaths from opioid overdose occurred when individuals received benzodiazepines during buprenorphine treatment. Benzodiazepine receipt during buprenorphine treatment was associated with an increased risk of fatal opioid overdose adjusted hazard ratio (HR) = 2.92, 95% confidence interval (CI) = 2.10-4.06, non-fatal opioid overdose, adjusted HR = 2.05, 95% CI, 1.68-2.50, all-cause mortality, adjusted HR = 1.90, 95% CI, 1.48-2.44 and a decreased risk of buprenorphine discontinuation, adjusted HR = 0.87, 95% CI, 0.85-0.89.

Conclusions: Benzodiazepine receipt appears to be associated with both increased risk of opioid overdose and all-cause mortality and decreased risk of buprenorphine discontinuation among people receiving buprenorphine.

Retrospective cohort study of adults (N=63,389) in Massachusetts who received buprenorphine for OUD 2012-2015

Primary outcome: fatal overdose
Secondary outcomes: non-fatal overdose, all-cause mortality, buprenorphine discontinuation (defined as 30-day gap in Rx)

Benzodiazepine receipt was associated with…

- Increased fatal opioid OD: aHR 2.92
- Increased non-fatal OD: aHR 2.05
- Decreased risk of buprenorphine discontinuation: aHR 0.87

Park TW, LaRochelle, et al. Addiction. 2020 May;115(5):924-932

“Mary”

- 63 yr old woman with insomnia, GAD, OUD, and trigeminal neuralgia on carbamazepine. Cares for 3 teenagers, 2 of whom have significant neurodevelopment delays with behavioral challenges.
    - 24mg total daily buprenorphine (w naloxone)
    - 10mg diazepam at bedtime for insomnia

Consistent regimen for the past 7 years. Transfers to your clinic because new insurance won’t cover previous clinic.

- Would you prescribe a benzo for her?
- If so, what regimen for what time period (e.g. 10mg x28 days, 5mg x20 days [weekdays], etc)?
- If not, would you be concerned about withdrawal?

“Katie”

- 34 yr old woman with GAD on chronic benzo, OUD on bup. Involved in an abusive relationship. Cares for 1 teenagers and a 1 yr old daughter.
  - 24mg total daily buprenorphine (w naloxone)
  - 3mg clonazepam total daily, #90/month
  - 37.5mg Effexor XR daily

Consistent regimen for the past 12 years per outside clinic notes and PDMP. Has tried to taper off Effexor multiple times without success due to withdrawal symptoms (“brain zaps”). Transfers to your clinic because new insurance won’t cover previous clinic.

- Would you prescribe the clonazepam at same dose (with counseling on intent to taper)?
- Would you work to taper Effexor (managing withdrawal symptoms) or focus on benzo taper given SNRI indicated for anxiety?

“Kelsie”

- 30-something yr old transgender female with PTSD and GAD on chronic prescribed alprazolam, HIV, OUD, IVDU who has history of overdose and IV-associated abscesses.
  - 2mg alprazolam TID from another prescriber
  - 20mg escitalopram
  - 24mg total bup/nlx daily

Three months since last admission for IVDU complication, now in sober housing affiliated with an outpatient program. Feels comfortable with you and asks if you would adopt the alprazolam prescription to consolidate care. Insists that benzo is only med that’s ever worked for her anxiety.

  - Would you prescribe alprazolam? Another benzo?

Brian.Grahan@hcmed.org

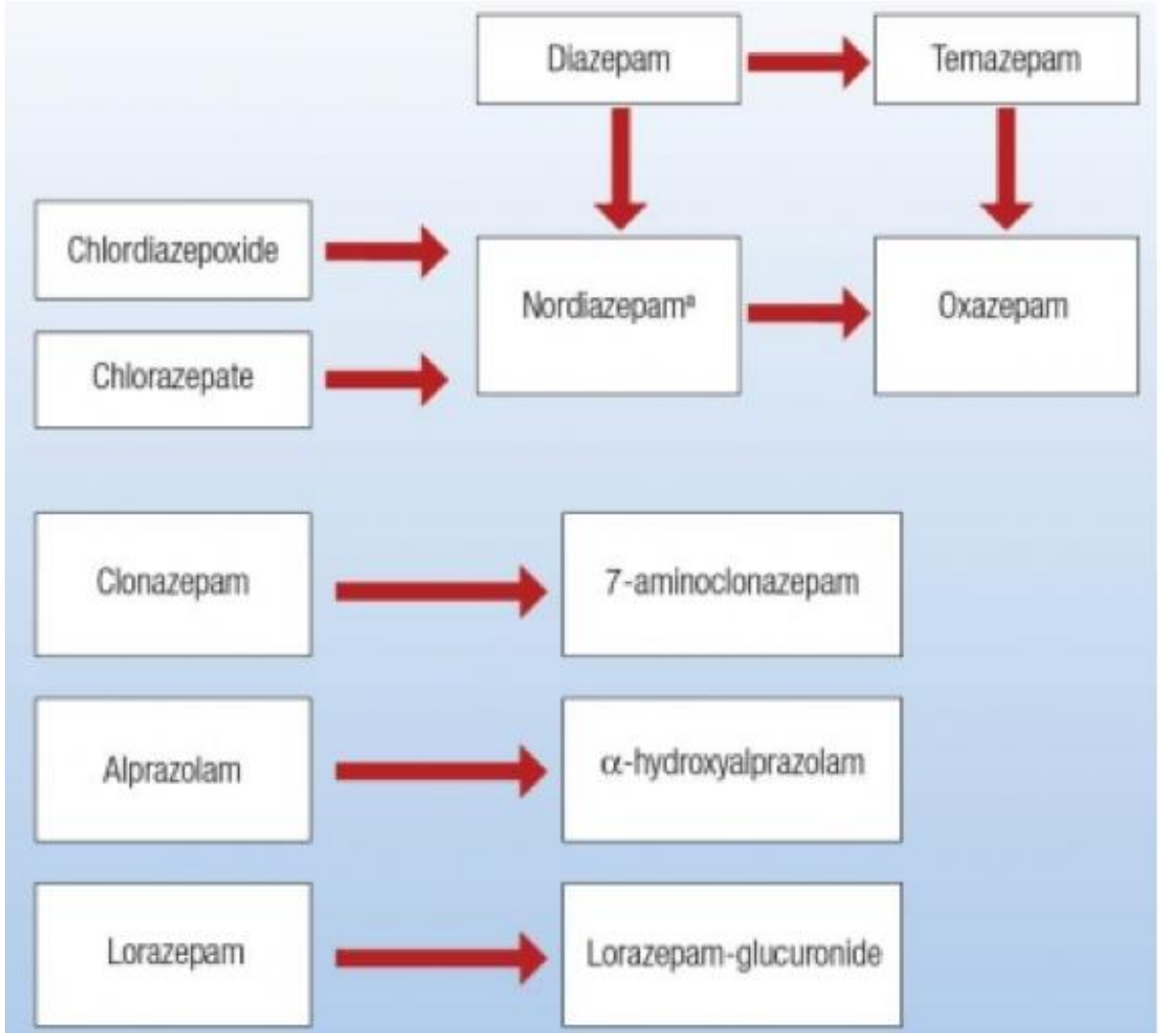
www.HennepinHealthcare.org/ECHO

Office: 612-873-5597

Clinic: 612-873-5500

Questions?

Benzodiazepine Metabolism



- Basic urine drug screen tests for nordiazepam & oxazepam
- May miss
  - Alprazolam (Xanax)
  - Clonazepam (Klonopin)
  - Lorazepam (Ativan)

http://www.practicalpainmanagement.com/