CENTER FOR CARE INNOVATIONS

BENZODIAZEPINES AND BUPRENORPHINE - SAFETY DRIVEN MEDICATION MANAGEMENT

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EVERYONE IS MUTED

CHAT IN YOUR QUESTIONS!

SLIDES AND RECORDING WILL BE SENT OUT THIS WEEK

Benzodiazepines and Buprenorphine - Safety Driven Medication Management

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No disclosures

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

This provides updated information to the FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning issued on August 31, 2016.

Safety Announcement

[9-20-2017] Based on our additional review, the U.S. Food and Drug Administration (FDA) is advising that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks. We are requiring this information to be added to the buprenorphine and methadone drug labels along with detailed recommendations for minimizing the use of medication-assisted treatment (MAT) drugs and benzodiazepines together.

https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm

Quick Review

Opioids

- Agonists at opioid receptors:
  - Pain
  - Anesthesia
  - Cough suppression
  - Diarrhea suppression

Benzodiazepines

- Agonists at chloride channel (GABA) receptors:
  - Anxiolytic
  - Hypnotic
  - Anticonvulsant
  - Muscle relaxant
  - Anesthesia
  - Catatonia treatment
  - Alcohol (or Rx sedative) withdrawal management

Quick Review

Opioids

- Side Effects:
  - Sedation
  - Dizziness
  - Nausea
  - Vomiting
  - Constipation
  - Respiratory depression
  - Confusion / Delirium
  - Tolerance + Withdrawal

Benzodiazepines

- Side Effects:
  - Sedation
  - Dizziness
  - Impaired coordination
  - Blurry vision
  - Depressed mood
  - Respiratory depression
  - Confusion / Delirium
  - Tolerance + Withdrawal

Synergistic Effects

Opioids

- Side Effects:
  - Sedation
  - Dizziness
  - Nausea
  - Vomiting
  - Constipation
  - Respiratory depression
  - Confusion / Delirium
  - Tolerance + Withdrawal

Benzodiazepines

- Side Effects:
  - Sedation
  - Dizziness
  - Impaired coordination
  - Blurry vision
  - Depressed mood
  - Respiratory depression
  - Confusion / Delirium
  - Tolerance + Withdrawal

FDA News Release

FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use

Action to better inform prescribers and protect patients as part of Agency's Opioids Action Plan

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

For Immediate Release August 31, 2016

Release

En español

After an extensive review of the latest scientific evidence, the U.S. Food and Drug Administration announced today that it is requiring class-wide changes to drug labeling, including patient information, to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and a class of central nervous system (CNS) depressant drugs called benzodiazepines.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.htm

FDA News Release

FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use

Action to better inform prescribers and protect patients as part of Agency's Opioids Action Plan

- Opioids + benzos result in serious side effects, including respiratory suppression and death.
- Limit prescribing opioid pain medicines with benzodiazepines or other CNS depressants only to patients for whom alternative treatment options are inadequate
- If prescribed: limit the dosages and duration of each drug to the minimum possible

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.htm

Benzos Commonly Prescribed

- Retrospective observational study of benzodiazepine use from composite retail pharmacy records from 2008.
- 5.2% of US adults used benzodiazepines
- Three quarters of individuals receiving a benzodiazepine received a short acting benzodiazepine.
- % in long term benzo treatment increased by age group 14.7% (18-35 years) to 31.4% (65-80 years),

Olfson, M., King, M., & Schoenbaum, M. (2015). Benzodiazepine use in the United States. *JAMA psychiatry*, *72*(2), 136-142.

Benzos Commonly Prescribed

- Study of 65,912 primary care patients
- Benzodiazepine prescription was issued to 15 % (9821); of these patients, 44 % received at least one benzodiazepine prescription from their PCPs.
- High-dose benzodiazepines more frequently to patients at higher risk for benzodiazepine-related adverse events

Kroll, D. S., Nieva, H. R., Barsky, A. J., & Linder, J. A. (2016). Benzodiazepines are prescribed more frequently to patients already at risk for benzodiazepine-related adverse events in primary care. *Journal of general internal medicine*, *31*(9), 1027-1034.

Who Is At Risk?

- Depression (OR, 2.7; 95 % CI, 2.6–2.9)
- Substance use disorder (OR, 2.2; 95 % CI, 1.9–2.5),
- Tobacco use disorder (OR, 1.7; 95 % CI, 1.5–1.8),
- Osteoporosis (OR, 1.6; 95 % CI, 1.5–1.7)
- Chronic obstructive pulmonary disease (OR, 1.6; 95 % CI, 1.5–1.7)
- Alcohol abuse (OR, 1.5; 95 % CI, 1.3–1.7)
- Sleep apnea (OR, 1.5; 95 % CI, 1.3–1.6)
- Asthma (OR, 1.5; 95 % CI, 1.4–1.5)

Kroll, D. S., Nieva, H. R., Barsky, A. J., & Linder, J. A. (2016). Benzodiazepines are prescribed more frequently to patients already at risk for benzodiazepine-related adverse events in primary care. *Journal of general internal medicine*, *31*(9), 1027-1034.

High Dose Benzos

- Non-alcohol substance use disorder (OR, 7.5; 95 % CI, 5.5–10.1)
- Disordered alcohol use (OR, 3.2; 95 % CI, 2.2–4.5)
- Tobacco use disorders (OR, 2.7; 95 % CI, 2.1–3.5),
- Chronic obstructive pulmonary disease (OR, 1.5; 95 % CI, 1.2–1.9).

Kroll, D. S., Nieva, H. R., Barsky, A. J., & Linder, J. A. (2016). Benzodiazepines are prescribed more frequently to patients already at risk for benzodiazepine-related adverse events in primary care. *Journal of general internal medicine*, *31*(9), 1027-1034.

Benzos Unusual to be Primary Substance of Preference

- In alcohol abstainers without AUD or light drinkers without anxiety or insomnia:
  - Diazepam, lorazepam, flurazepam not preferred to placebo
- Moderate social drinkers, no hx alcohol problems
  - Benzodiazepines (po) are reinforcing
- Route of administration matters:
  - IV benzos much more reinforcing than PO

Griffiths, R. R., & Weerts, E. M. (1997). Benzodiazepine self-administration in humans and laboratory animals–implications for problems of long-term use and abuse. *Psychopharmacology*, *134*(1), 1-37.

Benzos and Opioid Users

- Benzos amplify the euphoriant effect of opioids
- 80% of people with opioid use disorder have taken benzos.

American Psychiatric Association. (1990). *Benzodiazepine dependence, toxicity, and abuse: A task force report of the American Psychiatric Association*. American Psychiatric Publishing.

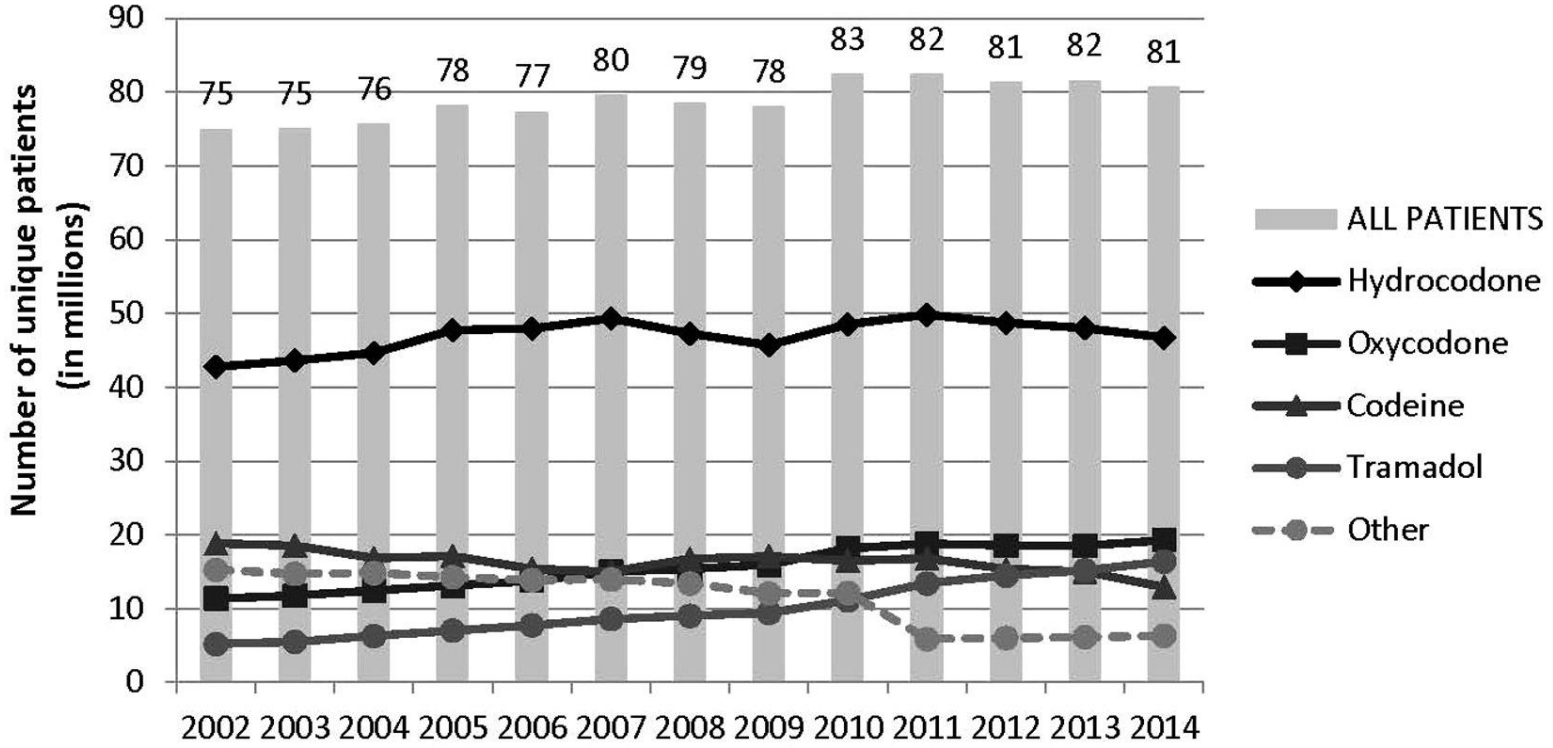
Specific Drug Involvement in Pharmaceutical Overdose Deaths, United States, 2010

	No. (%)[a]		
	Drug Involvement in Pharmaceutical Overdose Deaths	Specific Drug Involvement in Opioid Analgesic–Related Overdose Deaths	Opioid Analgesic Involvement in Deaths for Specific Drugs, No./Total (%)
Rx Opioids	16 651 (75.2)	16 651 (100.0)	16 651/16 651 (100.0)
Rx Benzos	6497 (29.4)	5017 (30.1)	5017/6497 (77.2)

Jones, C. M., Mack, K. A., & Paulozzi, L. J. (2013). Pharmaceutical overdose deaths, united states, 2010. *Jama*, *309*(7), 657-659.

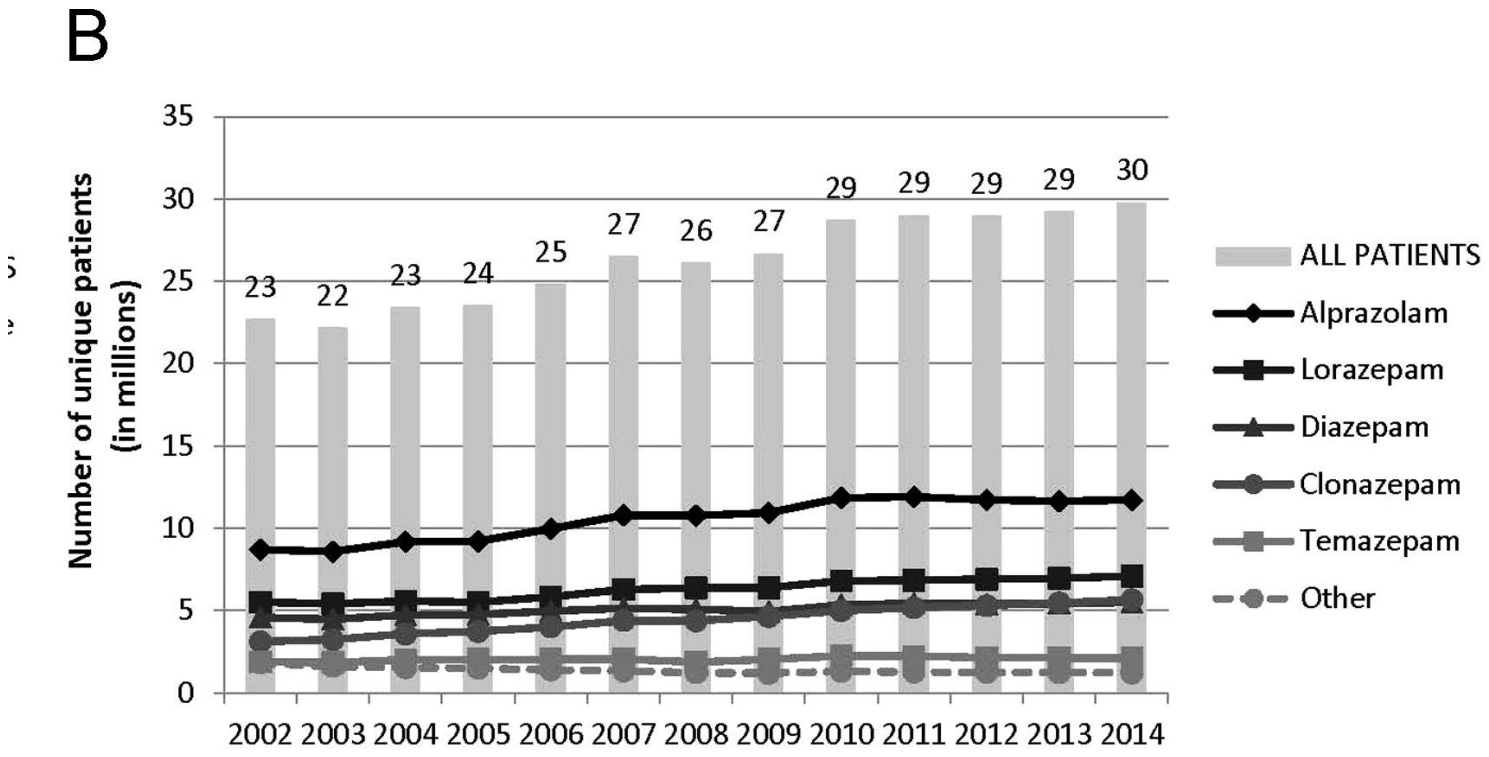
Rx Opioids

A



Hwang, C. S., Kang, E. M., Kornegay, C. J., Staffa, J. A., Jones, C. M., & McAninch, J. K. (2016). Trends in the Concomitant Prescribing of Opioids and Benzodiazepines, 2002–2014. *American journal of preventive medicine*, *51*(2), 151-160.

Rx Benzos



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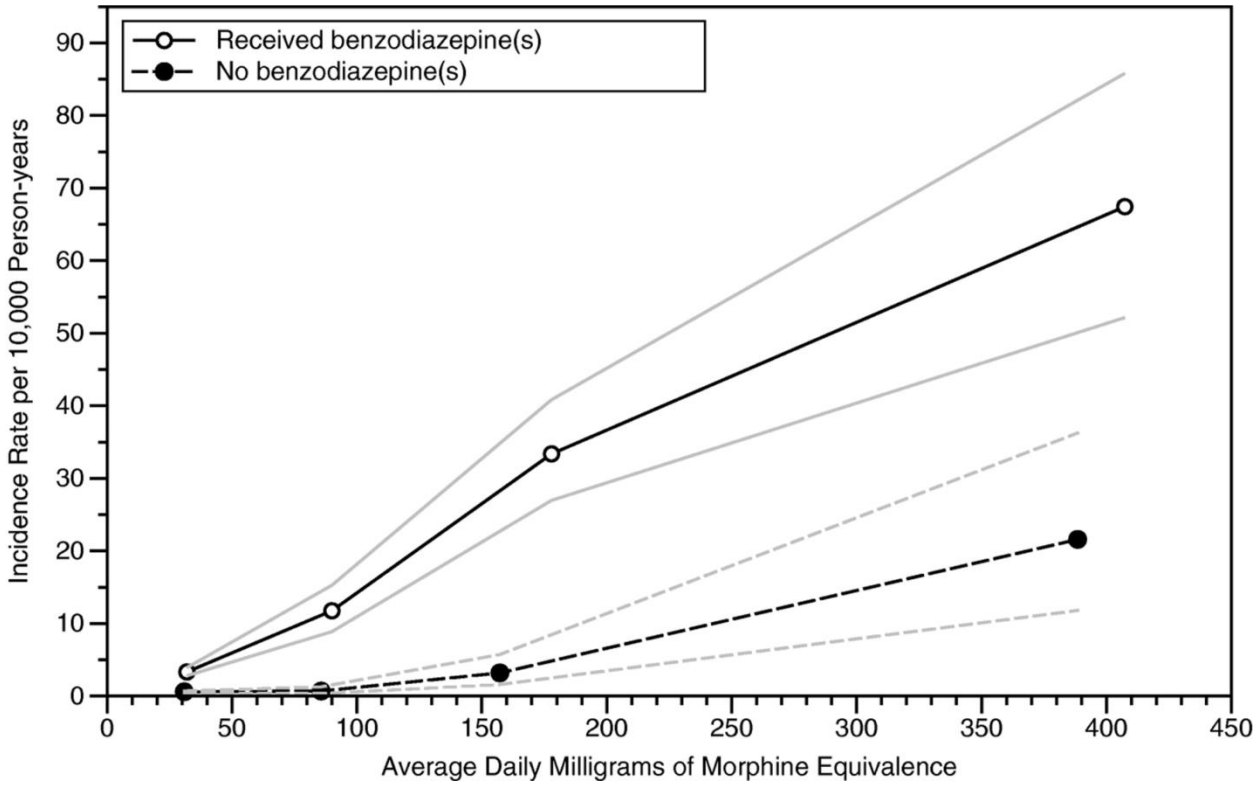
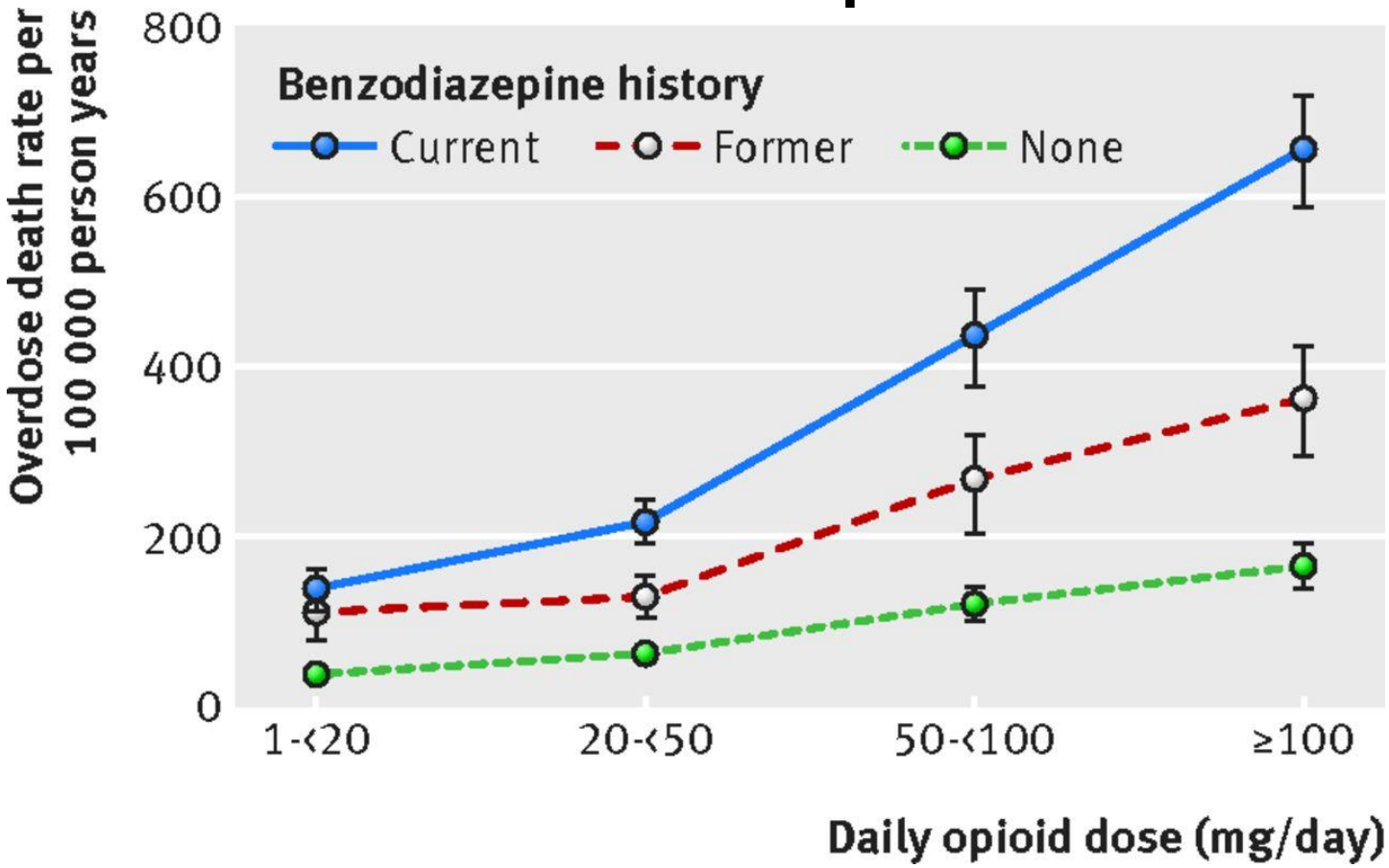
Overdose from Opioids and Benzodiazepines



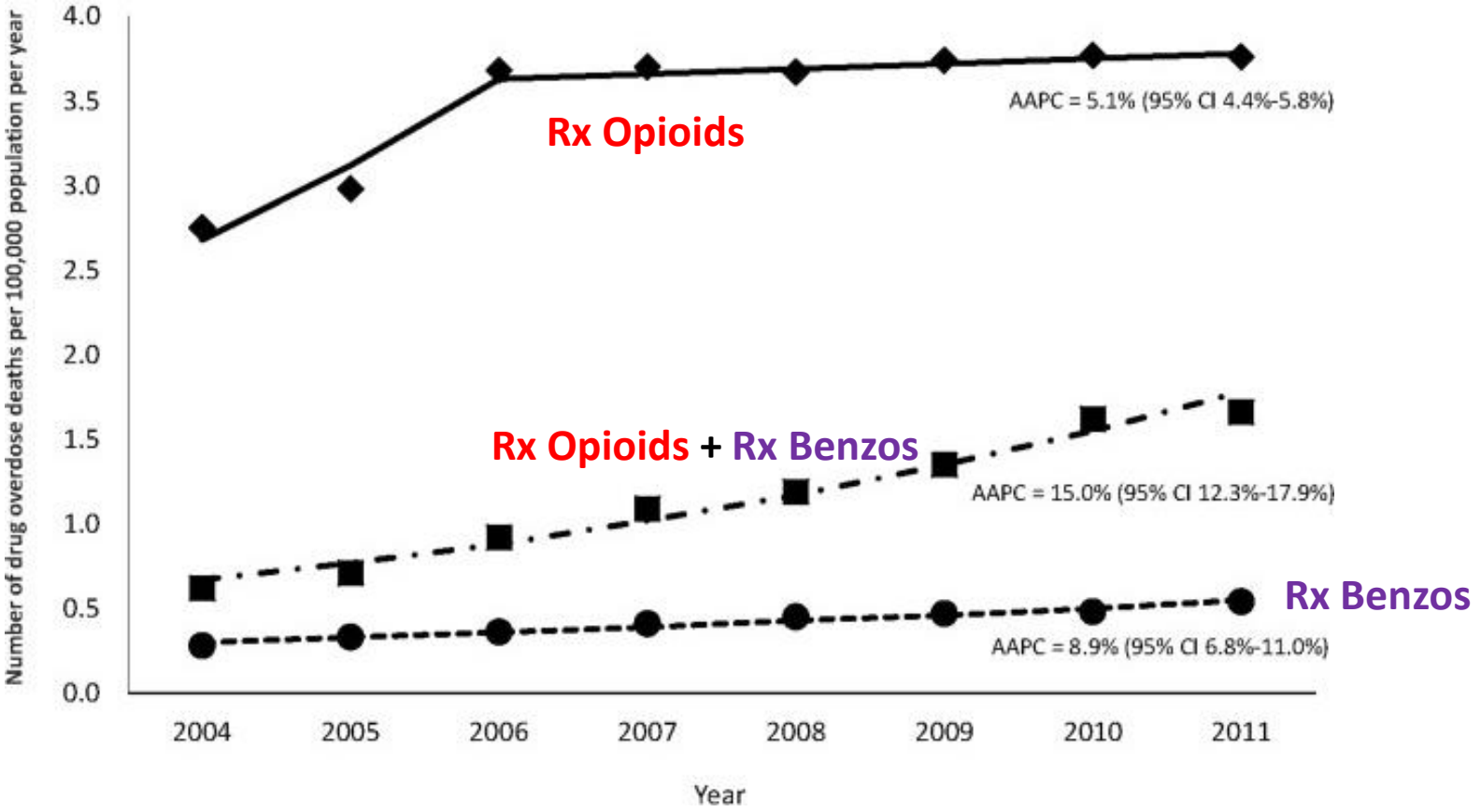
Dasgupta, N., Funk, M. J., Proescholdbell, S., Hirsch, A., Ribisl, K. M., & Marshall, S. (2016). Cohort study of the impact of high-dose opioid analgesics on overdose mortality. *Pain medicine*, *17*(1), 85-98.

Death Rate from Opioids and Benzodiazepines



Park, T. W., Saitz, R., Ganoczy, D., Ilgen, M. A., & Bohnert, A. S. (2015). Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *Bmj*, *350*, h2698.

Death Rate from Opioids and Benzodiazepines



Jones, C. M., & McAninch, J. K. (2015). Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *American journal of preventive medicine*, *49*(4), 493-501.

Alcohol Involvement in Rx Opioid and Benzodiazepine Related ED Visits and Drug-Related Deaths

- Alcohol commonly involved in ED visits resulting from use of Rx opioids + benzodiazepines, and in death related to these drugs.

Jones, C. M., Paulozzi, L. J., Mack, K. A., & Centers for Disease Control and Prevention (CDC). (2014). Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths-United States, 2010. *MMWR Morb Mortal Wkly Rep*, *63*(40), 881-5.

What About Opioid Maintenance Medications?

- Buprenorphine and methadone, when taken as prescribed: hypothesized to be a lower risk than that associated with heroin or short-acting rx opioids:
  - Slower absorption
  - Longer duration of peak effects
  - Slower metabolism

Toxicity of nonmedical use of benzodiazepines with buprenorphine or methadone

- National Poison Data System: 692 methadone-BZD cases and 72 BUP-BZD cases from 2002-2010

METHADONE

- lethargy (71.1%)
- respiratory depression (29.0%)
- coma (22.4%)
- respiratory arrest (4.5%)
- hypotension (11.8%)
- cardiac arrest (1.9%)

BUPRENORPHINE

- lethargy (59.7%)
- respiratory depression (15.3%)
- coma (5.6%),
- respiratory arrest (0)
- hypotension (2.8%)
- cardiac arrest (0)

Lee, S. C., Klein-Schwartz, W., Doyon, S., & Welsh, C. (2014). Comparison of toxicity associated with nonmedical use of benzodiazepines with buprenorphine or methadone. *Drug and alcohol dependence*, *138*, 118-123.

Toxicity of nonmedical use of benzodiazepines with buprenorphine or methadone

- National Poison Data System: 692 methadone-BZD cases and 72 BUP-BZD cases from 2002-2010

METHADONE

- 16 Deaths

BUPRENORPHINE

- Zero Deaths

Lee, S. C., Klein-Schwartz, W., Doyon, S., & Welsh, C. (2014). Comparison of toxicity associated with nonmedical use of benzodiazepines with buprenorphine or methadone. *Drug and alcohol dependence*, *138*, 118-123.

Toxicity buprenorphine with benzodiazepines

- Study of French Cases:
  - High dose buprenorphine
  - IV injection of crushed buprenorphine tablets
  - IV benzodiazepine administration
  - Lack of buprenorphine / naloxone formulation

Kintz, P. (2001). Deaths involving buprenorphine: a compendium of French cases. *Forensic Science International*, *121*(1), 65-69.

Opioid Agonist OUD Maintenance Pharmacotherapy Plus Benzos

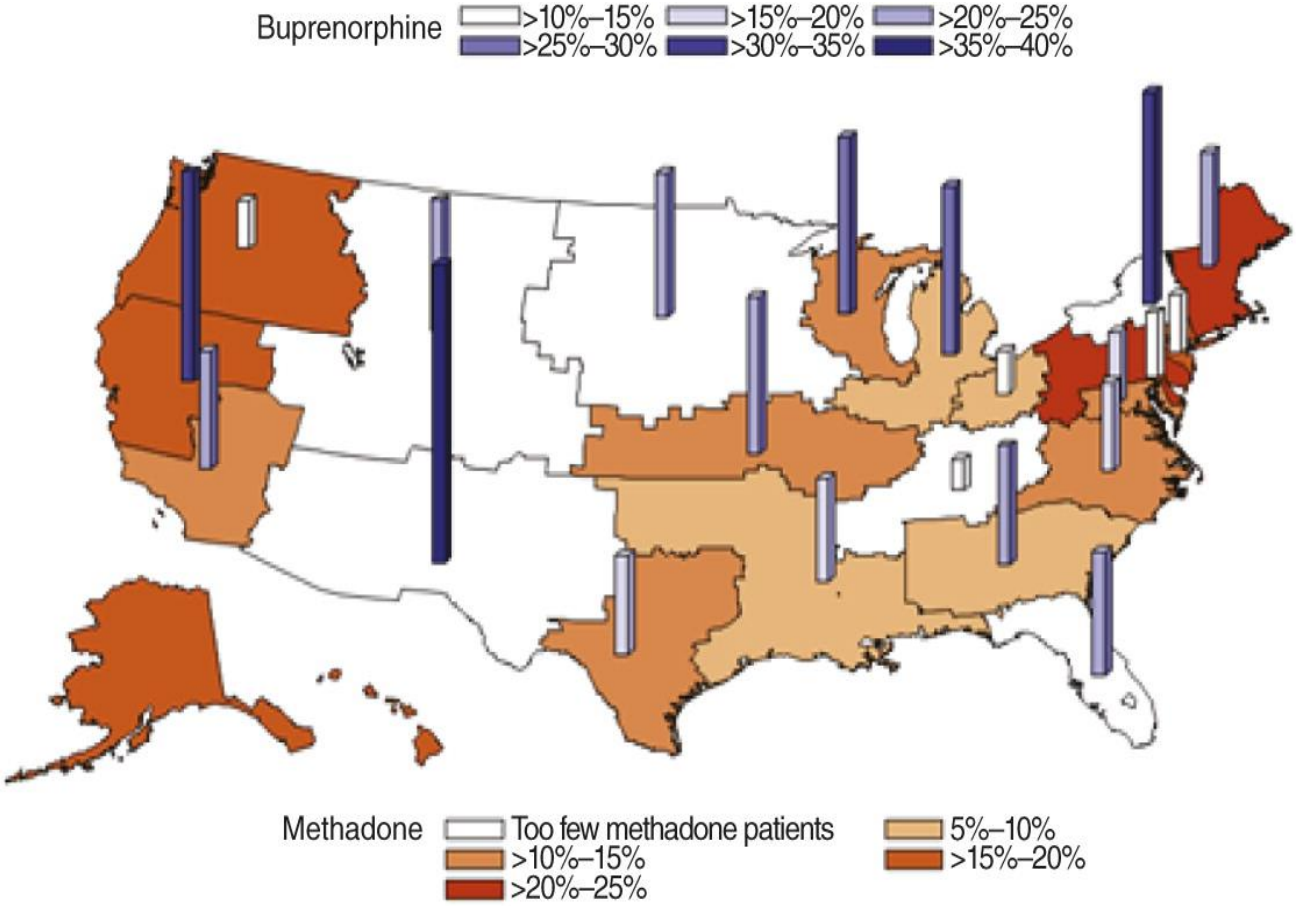


Figure 1 Percentages of patients on opioid agonist therapy in the Veterans Health Administration who were prescribed benzodiazepines, fiscal year 2010

Park, T. W., Bohnert, A. S., Austin, K. L., Saitz, R., & Pizer, S. D. (2014). Datapoints: Regional variation in benzodiazepine prescribing for patients on opioid agonist therapy. Psychiatric Services, 65(1), 4-4.

Benzos During Opioid Agonist Maintenance Treatment

- Benzodiazepines significantly associated
  - Non-overdose death (HR: 2.02, 95% CI: 1.29–3.18)
  - All-cause mortality (1.75, 1.28-2.39)
  - No significant association with overdose death.

Abrahamsson, T., Berge, J., Öjehagen, A., & Håkansson, A. (2017). Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment—A nation-wide register-based open cohort study. *Drug and Alcohol Dependence*, *174*, 58-64.

Benzodiazepine use during buprenorphine treatment for opioid use disorder

- Study of 328 buprenorphine outpatients:
  - 12-month treatment retention rate for the sample (*N* = 328) was 40%.
  - Benzos did not change treatment retention.
  - More ED visits among those with a benzodiazepine prescription versus those without, but not among users of non-prescribed benzodiazepines
  - ED visits were for accidental injury

Schuman-Olivier, Z., Hoeppner, B. B., Weiss, R. D., Borodovsky, J., Shaffer, H. J., & Albanese, M. J. (2013). Benzodiazepine use during buprenorphine treatment for opioid dependence: clinical and safety outcomes. *Drug and alcohol dependence*, *132*(3), 580-586.

Drugs Involved in Overdose Deaths: United States, 2010-2014

- Top 10 included heroin, oxycodone, methadone, morphine, hydrocodone, fentanyl, alprazolam and diazepam;
- Drug overdose deaths involving heroin more than tripled
- The rate of drug overdose deaths involving fentanyl more than doubled in a single year (from 2013 to 2014)

Warner, M., Trinidad, J. P., Bastian, B. A., Miniño, A. M., & Hedegaard, H. (2016). Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2010-2014. *National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System*, *65*(10), 1-15.

Opioid agonist maintenance of OUD Reduces Long-Term Mortality

- Controlling for all other factors in the model:
- Exposure methadone or buprenorphine treatment lasting longer than 7 days, reduces the risk of death by 28% [95% confidence interval (CI) 7–44%].

Gibson, A., Degenhardt, L., Mattick, R. P., Ali, R., White, J., & O'brien, S. (2008). Exposure to opioid maintenance treatment reduces long-term mortality. *Addiction*, *103*(3), 462-468.

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Drug Safety Communications

FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

- Buprenorphine or methadone should not be categorically denied to patients taking benzodiazepines.
- Despite benzo-bup risks, creating barriers to MAT poses an even greater risk of morbidity and mortality due to the opioid use disorder.

https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm

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Drug Safety Communications

FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

- Educate patients about the risks
- Develop strategies to manage use of prescribed or illicit benzodiazepines
- Tapering off benzodiazepines or other CNS depressants is preferred in most cases of concomitant use with MAT medicines
- Patients may require MAT medications indefinitely, and should continue as long as benefits > harms.

https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm

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Drug Safety Communications

FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

- Benzodiazepines are not the treatment of choice for anxiety or insomnia
- Ensure that all clinicians prescribing benzodiazepines or other CNS depressants are aware of the patient's methadone or buprenorphine treatment and coordinate care to minimize the risks associated with concomitant use

https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm

Practical Strategies

- Avoid prescribing on benzodiazepines or z-drug sedative-hypnotics.
- First line is non-medication approaches:
  - CBT for anxiety: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4610618/
  - Sleep Hygiene for insomnia: https://sleepfoundation.org/sleep-topics/sleep-hygiene

Practical Strategies

If using a medication other than a benzodiazepine or $GABA_A$ agonist, there are two compatible strategies:

- Long acting agents:
  - SSRIs
  - SNRIs
  - Buspirone
  - TCAs
  - Anticonvulsants
    - Valproate
    - Carbamazepine
- Short Acting (prn) agents:
  - Clonidine
  - Propranolol
  - Gabapentin
  - Pregabalin
  - Trazodone
  - Anticholinergics and antihistamines
  - Suvorexant (?)

Non-benzo prescription medications

- Despite the "nonaddictive nature" of some medications (eg, gabapentin, clonidine), high rates of medication misuse in opioid dependent patients admitted for detoxification was found and appeared similar to rates of misuse among controlled substances such as clonazepam and amphetamine salts.

Wilens, T., Zulauf, C., Ryland, D., Carrellas, N., & Catalina-Wellington, I. (2014). Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. The American journal on addictions. 2015 Mar;24(2):173-7

When to use a benzo?

Typically focus on function

- Supported when:
  - Validated, objective symptoms
  - Interfere with recovery or quality of life
- Less Supported When:
  - Vague
  - Subjective
  - No functional implication

General Principles

- Coordinate care
- Always check CURES
- Non-confrontive curiosity stance with patients
- BUT: I control the Rx
- “I am here to offer my best medical opinion, which is __”

If Using Benzo, Not All Are Equal:

Take absorption and duration of action into account:

- Avoid:
  - Alprazolam
  - Diazepam
  - Temazepam
- Consider:
  - Chlordiazepoxide
  - Lorazepam
  - Clonazepam

Short term treatment better than long term
Lower doses safer than higher doses
Smaller quantities safer than higher quantity

Cosci, F., Guidi, J., Balon, R., & Fava, G. A. (2015). Clinical methodology matters in epidemiology: not all benzodiazepines are the same. *Psychotherapy and psychosomatics*, *84*(5), 262-264.

What About Those Inherited on Benzos

- Steve Wyatt: Speak about ‘stress response’, not anxiety
- Validation of symptoms and experience
- The longer someone’s been on a benzo, the longer the taper
- Cross-taper to longer acting benzodiazepine
- Offer non-benzo alternative alongside taper of longer acting benzodiazepine
- Taper to low benzo doses, limit duration of prescriptions, and schedule frequent follow-up visits.

Toxicology Monitoring of Benzodiazepines

- When managing benzos for a patient, similar principles to good toxicology monitoring for buprenorphine – a good option with new patients and those with changes in clinical status is ‘no urine, no Rx.’
- Urine should be positive for prescribed medications and negative for other substances.
- When new patient being evaluated for buprenorphine tests positive for benzos, can start bup induction, but bring back to clinic sooner (eg/ 3 days instead of 7 days), don’t escalate dose as quickly, and don’t proceed to longer quantity prescriptions as quickly.

Toxicology Monitoring of Benzodiazepines

- Note that lorazepam and clonazepam are frequently false-negative on screening immunoassays.
- In the case of worrisome negative or unexpected positive, recommend sending for definitive confirmatory testing that offers quantitative and itemized benzo results.

Mikel, C., Pesce, A. J., Rosenthal, M., & West, C. (2012). Therapeutic monitoring of benzodiazepines in the management of pain: current limitations of point of care immunoassays suggest testing by mass spectrometry to assure accuracy and improve patient safety. *Clinica Chimica Acta*, *413*(15), 1199-1202.

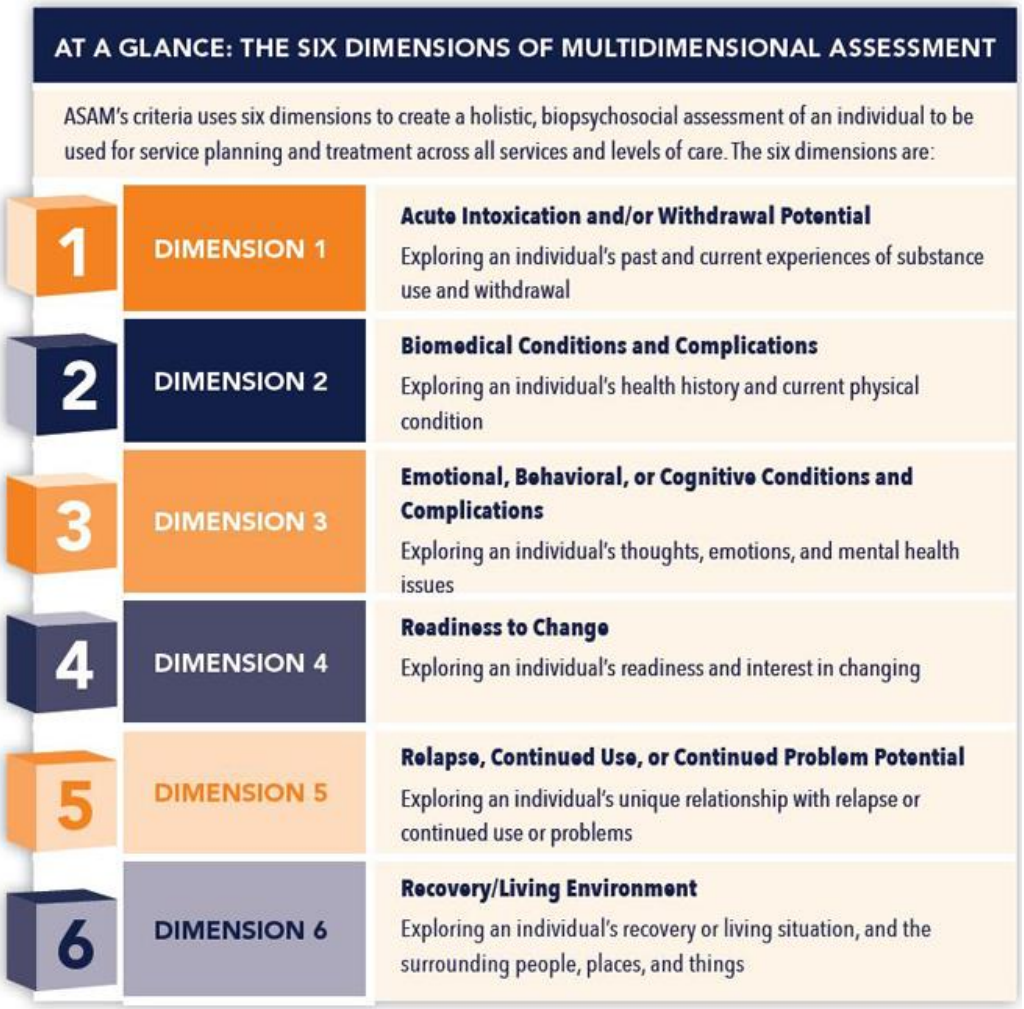
Toxicology Monitoring of Benzodiazepines

- Recommend confirmatory testing whenever suspect non-prescribed benzo use on top of prescribed benzo use – eg/ clinical exam or collateral report suggestive of sedation out of proportion to prescribed medication regimen.
- See: http://bit.ly/DrugTestingDownload

What About Those Inherited on Benzos

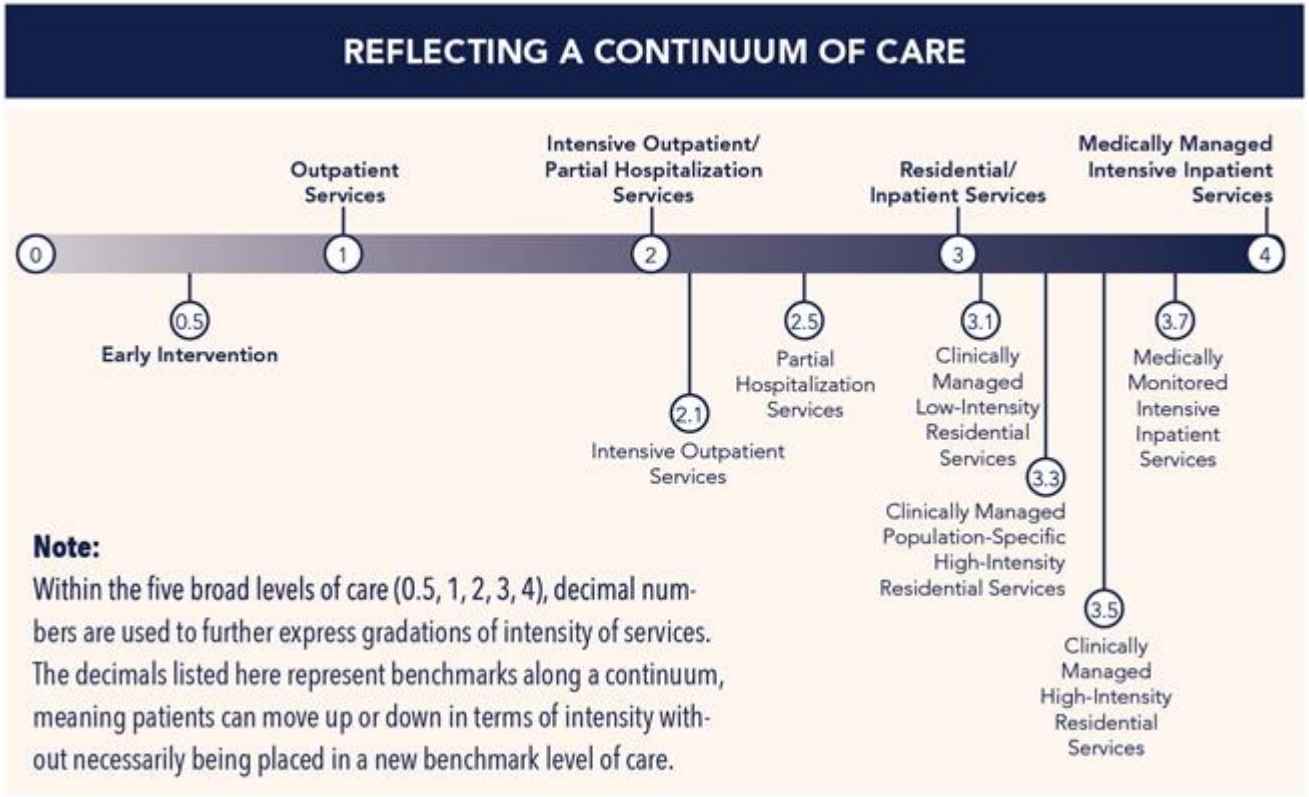
- Additional References on Benzo Taper interventions / approaches:
  - Lader, M., & Kyriacou, A. (2016). Withdrawing benzodiazepines in patients with anxiety disorders. *Current psychiatry reports*, *18*(1), 8.
  - Parr, J. M., Kavanagh, D. J., Cahill, L., Mitchell, G., & Young, R. M. (2009). Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis. *Addiction*, *104*(1), 13-24.
  - Lader, M., Tylee, A., & Donoghue, J. (2009). Withdrawing benzodiazepines in primary care. *CNS drugs*, *23*(1), 19-34.

Consider Level of Care



https://www.asam.org/resources/the-asam-criteria/about

Consider Level of Care



https://www.asam.org/resources/the-asam-criteria/about

Other Learning Opportunities

- AAAP in December in San Diego
  - www.aaap.org
- ASAM in April in San Diego
  - www.asam.org
- CSAM State of the Art in August 2018
  - www.csam-asam.org

QUESTIONS?

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