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# Risk and Benefit of the Concomitant Use of Benzodiazepines and Opiates

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# Disclosure

- I have no actual or potential conflict of interest in relation to this activity.
- I do plan on discussing unlabeled or investigational uses of a commercial product.

## **Goal:**

To describe the risks associated with the concomitant use of opiate and benzodiazepine medications.

## **Objectives:**

List the pharmacodynamic interactions between the opiate and benzodiazepine (BZD) class of drugs,

Identify the physiological presentation of benzodiazepine and opiate combination use, Describe possible benefit of this combination of medications, and

Explain when this combination of medication classes presents a risk to the patient.

# Frequency of concomitant use

- In patients abusing opiates rates are nearly 75% concomitant use.
- 72% of methadone users who were coprescribed BZDs found the BZD enhanced the opiate effect.
  - More commonly seen in in-treatment patients compared to untreated heroin users.
- In methadone maintenance treatment pts rates are over 50%.
  - Buprenorphine treated pts have similar rates.
- Some pts are legally prescribed BZDs but most are using illegally.
  - Also results in worse w/d syndrome.
- In chronic pain approximately 33% opiate and BZD coprescribed.

Backmund M. J Addict Dis. 2005.

Jones JD. Drug Alc Dep. 2012.

Manchikanti L. Pain Physician. 2013.

# Increase in prescribing

- 2002-2009 Primary care clinics are increasing BZD and opiate prescriptions, both monotherapy and as combination therapy.
  - 12% increase in coprescribing.
  - Same trend is also seen in ED rxs.
    - 6.4% inc in coprescribing.
- Often started from 2 separate prescribers then continued by new prescriber.

Kao M. Poster presentation AAPM 30<sup>th</sup> Annual Meeting. 2014.

# Agonism at specific opiate receptors

- $\mu$ 
  - Analgesia
  - Decreased respiratory function
  - Decreased GI motility
  - Increased feeding
  - Increased sedation
  - Increased prolactin release
  - Increased growth hormone release
  - Inhibit acetylcholine release
  - Inhibit DA release

Goodman and Gilman's Pcol Basis of Therapeutics. 11<sup>th</sup> ed.2006

# Agonism at specific opiate receptors

- $\kappa$ 
  - Analgesia
  - Decreased GI motility
  - Psychotomimesis
  - Increased feeding
  - Increased sedation
  - Increased diuresis
- $\delta$ 
  - Analgesia
  - Increased feeding
  - Increased growth hormone
  - Inhibit DA release

Goodman and Gilman's Pcol Basis of Therapeutics. 11<sup>th</sup> ed.2006.



# GABA agonism

- Not as easily defined as with opiate subtypes
  - Approx 19 subtypes
  - GABA<sub>A</sub>
    - $\alpha$  1-6,  $\beta$  1-3,  $\gamma$  1-3,  $\delta$ ,  $\epsilon$ ,  $\theta$ ,  $\pi$ ,  $\rho$  1-3
      - $\rho$  1-3 sometimes referred to as GABA<sub>C</sub>
  - GABA<sub>B</sub>
    - 1 and 2

Rudolph U. Curr Opin in Pharmacol. 2006.  
Whiting PJ. Curr Opin in Pharmacol. 2006.  
Bowery NG. Curr Opin in Pharmacol. 2006.

# GABA receptor subtype and effect

- GABA<sub>A</sub>
  - $\alpha 1$ 
    - Sedative/hypnotic, reinforcing
  - $\alpha 2$  and 3
    - Anxiolytic, anticonvulsant ( $\alpha 2$ )
  - $\alpha 5$ 
    - Learning and memory
  - $\beta 3$ 
    - Respiratory drive, hypnotic
- GABA<sub>B</sub>
  - Muscle relaxant

Fradley RL. J Psychopharmacology. 2007.  
Rudolph U. Current Opin Pharmacology. 2006.  
Bowery NG. Current Opin Pharmacology. 2006.

# Dynamic effects of opiate and benzodiazepine (BZD)

- Respiratory depression
  - Most significant harm related to combo use.
  - Due to 2 mechanisms.
    - Primary: Additive effect on lowering respiratory drive.
      - Both through GABA effects and possible pro opiate effects from the BZD.
    - Possible increase in opiate levels (kinetic).
- Diazepam and methadone combination produced greater miosis (pupillary constriction) than either monotherapy.

Preston KL. Clin Pharmacol Ther. 1984.  
Kapur BM. Critical Rev in Clin Lab Sci. 2011.  
Jones JD. Drug Alc Dep. 2012.  
Backmund M. J Addict Dis. 2005.

# Physiological effects of combo

placebo v alprazolam 0.5mg v oxycodone 10mg v combo.

- Miosis (mm)
  - pl 6.7, alpraz 6.6, oxy 5.5, combo 5.1
- SaO<sub>2</sub>
  - Pl 97.9, alpraz 97.6, oxy 97.7, combo 96.9
- Altered sense
  - Feeling high (0-100)
    - Combo increased 33% compared to oxy mono
    - Combo increased 500% compared to alpraz mono

Zacny JP. Drug Alc Dep. 2012

# Opiate kinetics

- CYP 3A4
  - Methadone
  - Buprenorphine
  - Oxycodone to oxymorphone
  - Fentanyl
- CYP 2D6
  - Codeine
  - Hydrocodone to hydromorphone
- Glucuronidation
  - Morphine
  - Oxymorphone
  - Hydromorphone

Armstrong SC. Psychosomatics. 2009.  
Pergolizzi JV. JMCP. 2014.  
Overholser BR. Amer J Manag Care. 2011.

# BZD pharmacokinetics

- CYP 450 3A4
  - Alprazolam
  - Midazolam
  - Triazolam
  - Chlordiazepoxide
- CYP 450 2C19
  - Diazepam (and 3A4)
- Glucuronidation
  - Oxazepam
  - Lorazepam

Textbook of Psychopharmacology 4<sup>th</sup> ed. 2009.

# Opiate and BZD kinetic interactions

- Midazolam and diazepam increase methadone and buprenorphine.
  - Not considered a potent effect.
  - Some studies have shown no kinetic effect with diazepam and methadone.
- Clonazepam increased oxycodone levels.
  - Case report

Jones JD. Drug and Alcohol Dep. 2012.  
Burrows DL. J Forensic Sci. 2003.

# Assessment Question

Which of the following is true regarding pharmacokinetic interactions with opiates and benzodiazepines?

- A. Diazepam has shown to increase methadone and buprenorphine in some studies but not all.
- B. Lorazepam consistently increases blood levels of oxycodone.
- C. Pharmacokinetic interactions may exist but are not likely the major reason for risks associated with combination therapy.
- D. A and C only.



# Answer

Which of the following is true regarding pharmacokinetic interactions with opiates and benzodiazepines?

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- D. *A and C only.*

# Dynamic effect of opiate and BZD on memory

- BZD can worsen short term memory.
- In patients using methadone or buprenorphine and concomitant BZD working memory (9 months) worsened compared to baseline.
  - Worsened compared to normal controls.
    - Methadone a little worse than buprenorphine.
  - Diazepam accounted for nearly half of BZD.

Rapeli P. Substance Abuse Treatment, Prevention, Policy. 2009.

# Dynamic misuse risk

- Increased euphoria ‘high’ compared to opiate alone.
  - At least 25% of opiate users also use a BZD recently and >50% in the last year.
  - Diazepam is frequently reported as a preferred agent.
- Often used to diminish opiate withdrawal effect.
  - Technically misuse.

DuPont RL. Am J Drug Alcohol. 1988.  
Bramness JC. Drug Alcohol Depend. 2007.  
Jones JD. Drug Alc Dep. 2012.  
Textbook of Psychopharmacology 4<sup>th</sup> ed. 2009.

# Benzodiazepine (BZD) pharmacology

- Abuse seems to be related to a combination of all  $\alpha$  receptors, specifically  $\alpha 1$
- BZDs also agonizes opiate receptors
  - Primarily  $\kappa$  receptors
    - Midazolam may have additional  $\delta$  receptor agonism.

Ator NA. CNS Spectrums. 2005.  
Cox RF. Anesth Analg. 2001.

# Bluelight.org

- I took 30mg hydrocodone and need help falling asleep. Took 2mg etizolam 10 minutes ago and plan on feeling good for a little while then passing out. Is this combination really that bad?

[www.bluelight.org/vb/threads](http://www.bluelight.org/vb/threads). 25-04-2012.

## Bluelight.org - responses

- I died for almost a minute on the combination.
- I really blacked out and woke up from a dream realizing I just smashed my car.
- I did 8mg of Xanax and 40mg Opana no problem. I did 13mg of Xanax and 40mg Opana and woke up with a doctor staring down at me amazed I was still alive.
- I have overdosed and actually died due to benzos and opiates.

## Bluelight.org - responses

- If you know your limits it can go fine.
- If you are tolerant to opiates and benzos, and dose accordingly, you are not guaranteed death. Plenty of us combine the two.
- Even now I don't leave home without washing 4mg of clonazepam with methadone syrup.
- I usually find the heroin in the UK so weak I won't bother getting heroin unless I got some benzos.

# Overdose risk

- OD fatality from opiates (mono) primarily from respiratory depression.
  - Initiating long acting has higher rates than initiating with short acting.
- OD fatality from BZDs (mono) are rare but also from respiratory depression, decreased cardiac contractility and vasodilation.
- Diazepam, midazolam and flunitrazepam have been shown to lower threshold for respiratory depression with buprenorphine.

Goldfrank's Toxicologic Emergencies 10<sup>th</sup> ed. 2015.

Miller M. JAMA Int Med. 2015.

Jones JD. Drug and Alc Dep. 2012.



# Frequency of OD with opiate and BZD

- DAWN network calculated that polypharmacy resulted in a 37% inc. in having a serious event compared to BZD only.
- 50% of OD involve opiate and BZD.
- Heroin users report up to 80% of their non fatal ODs involved a BZD.
- BZDs are involved in 50-80% of methadone related fatal ODs.
- 30% of fatal opiate ODs had a concomitant BZD in 2010.
  - 77% of fatal BZD ODs also included opiates.

SAMHSA DAWN report. 12/18/2014.  
Jones JD. Drug Alc Dep. 2012.  
Jones CM. JAMA.2013.

# BZD and opiate

- Australian survey in chronic pain pop.
- BZD and opiate combo use correlated with:
  - Increased dose of opiate
  - Increased use of medical services
    - ED visits, ambulance use
    - Accidental OD (10% for opiate only v 26% for combo)
  - History of substance use disorder diagnosis (387% increase) and use of illicit drugs.

Nielsen S. Pain Medicine. 2014.

# Genetic risks

- Genetic differences of the mu opioid receptor correlates with risk of toxic OD.
  - A118G variation on the mu opiate receptor gene results in greater risk of experience toxicity.
  - Correlates with increased opioid requirements.

Manini AF. J Med Toxicol. 2013.  
Klepstad P. Acta Anaesthesiol Scand. 2004.

# Benefits of adding opiates and BZDs

- Preoperatively
  - Hypnotic and analgesic
- Agitation in the ICU
  - Ventilated patients
- Few published reports of using both together for maintenance purposes.
- Anxiety guidelines rarely recommend the use of daily BZDs.
  - Contrarily, chronic pain guidelines do suggest that patients may require daily opiate therapy.
    - Most warn against combo use.

# Guideline recommendations Generalized Anxiety Disorder

- British Association of Psychopharmacology (2014)
  - Acute phase
    - Start SSRIs, TCAs and add BZD if necessary
  - Prophylaxis
    - SSRIs, SNRIs, buspirone, pregabalin
- NICE (2007)
  - SSRIs for 12 weeks then switch to another for at least 6 mos.
    - Benzos for no more than 4 weeks
  - Venlafaxine second line (dose 75mg or less)

# Guideline recommendations Generalized Anxiety Disorder

- Canadian Psychiatric Association (2006)
  - SSRIs and venlafaxine.
  - Second line
    - Buspirone, pregabalin, imipramine
    - Bupropion XL
  - Benzos in the acute phase.
    - Have shown long term benefit in some studies.

# Assessment Question

LJ is a 35 yo female who is admittedly uses oxycodone recreationally. She has been diagnosed with generalized anxiety disorder (GAD) and is expecting to be prescribed diazepam. Which of the following is the most appropriate treatment for her GAD?

- A. Diazepam is the most appropriate treatment.
- B. Initiate escitalopram (an SSRI), low dose and taper up as needed.
- C. Initiate lorazepam low dose and taper up as necessary.
- D. Prescribe the oxycodone on a scheduled basis.

# Answer

LJ is a 35 yo female who is admittedly uses oxycodone recreationally. She has been diagnosed with generalized anxiety disorder (GAD) and is expecting to be prescribed diazepam. Which of the following is the most appropriate treatment for her GAD?

- A. Diazepam is the most appropriate treatment.
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- C. Initiate lorazepam low dose and taper up as necessary.
- D. Prescribe the oxycodone on a scheduled basis.



# Guideline recommendations

## Panic Disorder

- British Association for Psychopharmacology (2014)
  - Acute phase treatment
    - SSRIs, TCAs, venlafaxine
      - With BZDs if necessary
  - Prophylaxis
    - SSRIs, TCAs
- NICE (2007)
  - SSRIs for 12 weeks to assess efficacy
    - Duration of therapy at least 6 months
  - TCAs if multiple SSRIs fail
  - BZDs not recommended for prophylaxis

# Guideline recommendations

## Panic Disorder

- American Psychiatric Association (APA-2008)
  - SSRIs and SNRIs
  - TCAs
  - BZDs for the first 4-6 weeks of treatment only.
- Canadian Psychiatric Association (2006)
  - First line SSRIs and venlafaxine
  - Second line TCAs
  - BZDs for acute treatment only

# Guideline recommendations PTSD

- British Association of Psychopharmacology (2014)
  - Acute
    - SSRIs, venlafaxine
  - Prophylaxis
    - SSRIs
    - Augmentation with an atypical antipsychotic, prazosin
- NICE (2005)
  - SSRIs and mirtazapine
  - TCAs

# Guideline recommendations PTSD

- APA (2006)
  - SSRIs
  - TCAs and other antidepressants
  - Benzos not recommended as main treatment but as PRN
- VA/DoD (2010)
  - SSRIs and SNRIs
  - Mirtazapine, TCAs, nefazodone, MAOIs
    - Prazosin for nightmares
  - No benefit BZDs (harm), valproate, risperidone, topiramate

# conclusion

- Concomitant use has little data for support in maintenance therapy.
- Frequent concomitant use from legal prescriptions and obtained illegally.
- Kinetic interactions exist but unlikely to have a dramatic impact.
  - Watch for CYP 450 3A4 combos
- Dynamic interaction results in substantial reduction in respiratory drive.
  - Combination often sought after due to dynamic interaction of a subjective experience of more intense euphoria.
- Should place more vigilance on concomitant use to verify benefit is worth the risk.

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