

Methadone and Buprenorphine: Clinical Impact of Drug Interactions

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Disclosures

None

Adverse Drug Interactions

- Accidents: leading cause of death in the USA in those aged 1–44 with highest rates in 25–44 y.o.
- Poisoning: a leading cause of accidental deaths in the US
 - 145% increase in 1999–2007
 - Opioids most frequently named drugs in poisonings
- DDIs: a leading cause of accidental poisoning deaths in the USA (CDC, 2011)
 - Those exposed to DDIs between CYP450-metabolized opioids and other medications have higher medical costs (Summers et al, 2011)

Underlying Reasons for DDIs

- Many with opioid dependence have co-occurring medical and / or mental disorders
- Patients believe prescribed drugs are 'safe'
- Lack of patient education about adverse events that can occur
- May not understand need to take as prescribed
- Sharing / selling

Pathophysiology of DDIs

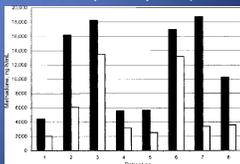
- Pharmacokinetic (PK)
 - What you do to the drug (or not)
 - With PK interactions, one drug causes an alteration in the concentration of another drug increasing risks of side effects or reduced effectiveness of the drug
- Pharmacodynamic (PD)
 - What the drug or drugs do to you
 - With PD interactions, two drugs have additive effects or antagonistic effects

Pharmacodynamic Interactions

- PK interactions may have associated PD consequences
- PD interactions can occur in the absence of a PK interaction
- Two drugs with similar pharmacological characteristics interact synergistically
 - Increases potential toxicity of drug
 - Opioids and benzodiazepines
 - Eg diazepam with buprenorphine
 - Opioids and alcohol

Pharmacokinetic Interactions

- A drug in presence of other drugs
 - May be better absorbed; eg slowed GI motility
 - Altered efflux (P-glycoprotein [Pgp] effects)
 - Inhibition or induction of metabolism of CYP enzymes (eg methadone and HIV medications such as nevirapine) or glucuronidation effects (eg atazanavir / buprenorphine)
- Specific to opioids:
- Net increase in exposure to drug(s) or reduction to the point of inducing physical withdrawal



Clarke SM et al. Pharmacokinetic Interactions of Nevirapine and Methadone and Guidelines for Use of Nevirapine to Treat Injection Drug Users. Clin Inf Dis. 2001; 33(9):1595-1597.

Question

- What kind of interaction is there between **methadone** and **lopinavir/ritonavir**?

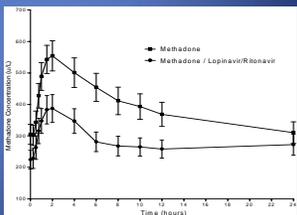
1. Pharmacokinetic
2. Pharmacodynamic
3. No documented interaction

Question

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- Lopinavir is a potent inducer of CYP2C19 and Pgp
 - 2C19 contributes to methadone metabolism; Pgp is an efflux transporter
- Methadone plasma levels reduced
 - Withdrawal symptoms requiring methadone dose increases



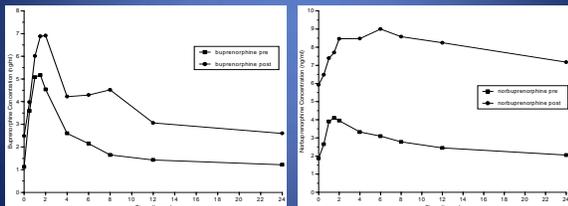
Question

- What kind of interaction is there between **buprenorphine** and **atazanavir**?
1. Pharmacokinetic
 2. Pharmacodynamic
 3. No reported interaction

Question

- What kind of interaction is there between **buprenorphine** and **atazanavir**?
1. Pharmacokinetic
 2. Pharmacodynamic
 3. No reported interaction

- Atazanavir inhibits CYP3A4 and UGT1A1 glucuronidation
 - Buprenorphine is mainly metabolized by CYP3A4 and by glucuronidation
- Buprenorphine plasma levels are increased
 - Increased drowsiness has been reported as well as increased bilirubin



McCabe-Katz EF et al. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. Drug Alcohol Depend. 2007; 91:269-278.

Question

- What kind of interaction is there between **buprenorphine** and **sertraline**?

1. Pharmacokinetic
2. Pharmacodynamic
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Methadone only (38%)	Buprenorphine+naloxone only (40%)	
other anticonvulsant (7% of deaths)	alcohol	risperidone
alcohol (7% of deaths)	alprazolam	quetiapine
alprazolam	bupropion	zolpidem
carisoprodol	carisoprodol	
clonazepam	clonazepam	
cocaine (7% of deaths)	clonidine	
duloxetine, amitriptyline (8% deaths)	cocaine	
SSRIs (8% of deaths)	cyclobenzaprine	Methadone and Buprenorphine Adverse Events
heroin	fentanyl	
hydrocodone (7% of deaths)	heroin	
marijuana	hydrocodone	
MDMA (Ecstasy)	hydromorphone	
methamphetamine	lithium	
morphine	lorazepam	
narcotic analgesics (8% of deaths)	marijuana	
olanzapine	methadone	
oxycodone	modafinil	
quetiapine (9% of deaths)	other benzodiazepines	
benzodiazepines (52% of deaths)	oxycodone	
zolpidem	paroxetine, trazodone, sertraline	

Opioids and Other Drugs: Basis of Adverse Events

- Why are we seeing greater numbers of adverse events and increasing deaths in methadone-using individuals who co-consume psychotropics: SSRIs, antipsychotics?
- Not formally studied, but...
 - DAWN and ME data describe increasing numbers
 - Methadone metabolized by CYP3A4, 2D6, 2B6, buprenorphine metabolized by mainly 3A4
 - Some SSRIs and some antipsychotics can inhibit metabolic enzymes
 - May lead to increased plasma concentrations of drugs and associated toxicities
 - Fluoxetine and fluvoxamine inhibit both 3A4 + 2D6
 - Paroxetine, sertraline, citalopram and escitalopram: inhibit CYP2D6 only

Opioids and Other Drugs: Basis of Adverse Events

- As methadone concentrations rise; risk of adverse events increases
 - High dose (>100 mg/d methadone)
 - Drug interactions that increase methadone exposure through inhibition of methadone metabolism
 - Eg fluvoxamine/methadone interaction
 - Ciprofloxacin/methadone interaction
 - Drug interactions that occur when an inducing drug is given
 - Methadone dose increased to maintain efficacy but not decreased once drug is withdrawn
 - Eg lopinavir/ritonavir/methadone interaction

Consequences of Undetected Drug Interactions

- Non-compliance with opioid dependence treatment
- Lack of efficacy
- Illicit drug use
- Opioid toxicity
- Non-adherence to treatments for co-occurring conditions
- Viral resistance (in HIV / HCV)

Case

- 45-year-old man with HIV and opioid dependence
- Currently treated with antiretroviral therapy (ART) and methadone 160 mg daily
- No other medications, known allergies or illnesses
- Recent laboratory evaluation shows
 - ↓ CD4 of 50 cells/mm³
 - ↑ Viral load of 5 logs
- ART discontinued; patient evaluated for new regimen
- 10 days later, he has a sudden syncopal episode
- Examination shows the following results:
 - Vital signs: 124/86, 74, afebrile;
 - Normal: CK, CKMB, troponin
 - Hemoglobin: 11.2; Hematocrit: 33; Glucose: 75
 - Cardiogram: PR: 0.12, QRS: 0.08, QTc: 580 msec, normal sinus rhythm
 - Plasma methadone concentration: 1100 ng/mL

Question

What was the most likely cause of the patient's syncopal episode?

1. Anemia
2. Cryptococcosis with brain abscess
3. Myocardial infarction
4. Prolonged cardiac QT interval
5. Hypoglycemia

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- 1. Allergy to new HIV ART
- 2. Cardiac effects of HIV infection
- 3. Familial long QT syndrome
- 4. Toxicity related to methadone

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Which of the following ARTs are most likely to have contributed to these symptoms?

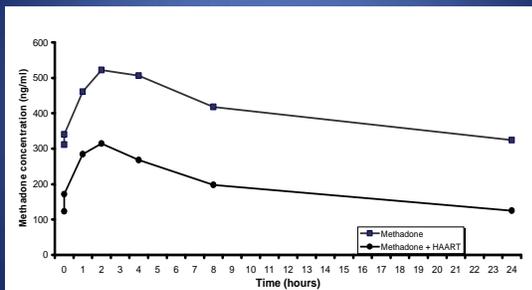
1. Atazanavir
2. Tenofovir
3. Efavirenz
4. Didanosine
5. Nelfinavir

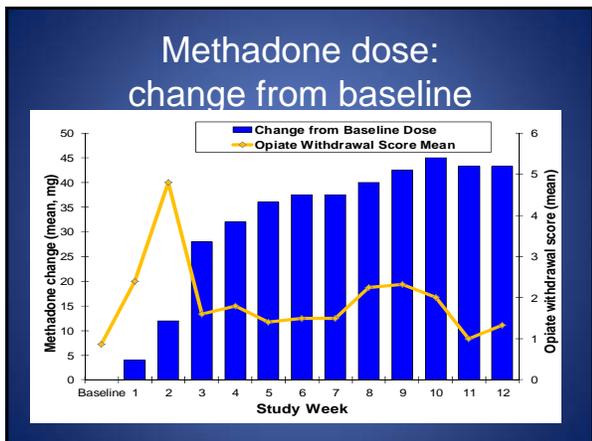
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4. Didanosine
5. Nelfinavir

Effect of Efavirenz on Methadone Concentrations





Question

How could this drug–drug interaction be avoided?

1. Never use medications that induce methadone metabolism and would result in a need for higher daily methadone doses
2. Monitor cardiogram monthly in those receiving medications that are known to alter methadone metabolism
3. Monitor for the need for increased methadone dose with ART known to induce methadone metabolism. When such medications are stopped, taper patient back to the methadone dose on which they were formerly stable
4. Do not use methadone in patients with HIV / AIDS because many ART affect methadone metabolism

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Case

A patient is maintained and stable on buprenorphine/naloxone 12/3 mg/d. The patient has a recent diagnosis of tuberculosis and is started on tuberculosis treatment. Five days later the patient complains of mild nausea, night sweats and malaise. On examination, blood pressure is 140/88, pulse 88, the patient is mildly tremulous and pupils are dilated at 4 mm.

Question

What is the most likely cause of the patient's presentation?

1. Exacerbation of tuberculosis
2. Superinfection with influenza
3. Opiate withdrawal syndrome
4. Allergy to medications given to treat tuberculosis

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Question

Which tuberculosis medication is most likely to be responsible for these symptoms?

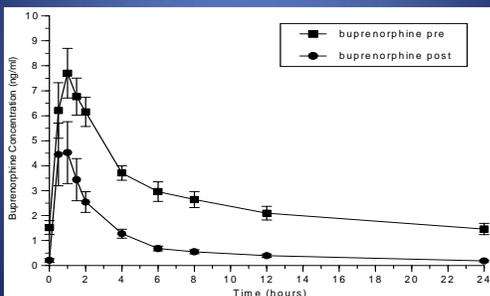
- 1. Rifampin
- 2. Isoniazid
- 3. Pyridoxine
- 4. Ethambutol

Question

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- 1. Rifampin
- 2. Isoniazid
- 3. Pyridoxine
- 4. Ethambutol

Effect of Rifampin on Buprenorphine



Question

Which of the following interventions would be the best choice in treating this patient?

1. Switch from buprenorphine/naloxone to methadone
2. Alter dosing of buprenorphine/naloxone from once daily to split twice-daily dosing
3. Change from rifampin to rifabutin
4. Stop rifampin; add cycloserine and streptomycin

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Summary: Opioid Interactions with ARV or TB Medications

- Methadone
 - Potential to be clinically significant
 - AZT
 - DDI
 - d4T
 - Nevirapine
 - Efavirenz
 - Delavirdine
 - Lopinavir/ritonavir
 - Rifampin
 - PK interaction, but not likely to be clinically significant
 - Saquinavir/ritonavir
 - Nelfinavir
 - Abacavir
 - Rifabutin
- Buprenorphine
 - Potential to be clinically significant
 - Atazanavir/ritonavir
 - Rifampin
 - Not clinically significant
 - AZT
 - Efavirenz
 - Delavirdine
 - Nevirapine
 - Ritonavir
 - Rifabutin
 - No effect
 - Lopinavir/ritonavir
 - Nelfinavir
 - Buprenorphine does not affect most ARV PK

Question

Which of the following antidepressants inhibits the function of CYP450 3A4 and would be expected to increase plasma concentrations of methadone or buprenorphine?

1. Fluoxetine
2. Mirtazepine
3. Sertraline
4. Venlafaxine

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1. Fluoxetine
2. Mirtazepine
3. Sertraline
4. Venlafaxine

Fluoxetine Inhibits CYP3A4 and 2D6

- Buprenorphine interactions
 - Buprenorphine metabolism inhibited in vitro by norfluoxetine¹; adverse opioid events were not observed in a clinical trial²
- Methadone interactions
 - Fluoxetine inhibits methadone N-demethylation in vitro¹
 - Increased methadone plasma levels have been observed in co-treated patients³

1. Iribarne et al. In vitro interactions between fluoxetine or fluvoxamine and methadone or buprenorphine. *Fundam Clin Pharmacol.* 1998; 12(2):194–199. 2. Oliveto et al. Desipramine, amantadine, or fluoxetine in buprenorphine-maintained cocaine users. *J Subst Abuse Treat.* 1995; 12(6):423–428. 3. Eap et al. Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. 1997; 17(2):115–117.

Question

Which of the following anticonvulsants has been associated with an adverse interaction with methadone?

1. Valproate
2. Gabapentin
3. Carbamazepine
4. Topiramate

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Carbamazepine Induces CYP3A4

- Buprenorphine interactions
 - No serious adverse events reported in two clinical trials^{1,2}, but buprenorphine levels would be expected to be decreased with concurrent administration
- Methadone interactions
 - Reduced plasma methadone levels have been observed with carbamazepine³
 - Withdrawal symptoms and 60% decrease in trough methadone levels reported in a clinical trial⁴
 - Case report of respiratory depression after carbamazepine cessation in a co-prescribed cancer patient⁵

1. Paetzold et al. Detoxification of poly-substance abusers with buprenorphine. Effects on affect, anxiety, and withdrawal symptoms. *Nervenarzt*. 2000; 71(9):722-729. 2. Seifert et al. Detoxification of opiate addicts with multiple drug abuse: a comparison of buprenorphine vs. methadone. *Pharmacopsychiatry*. 2002; 35(6):152-164. 3. Saxon et al. Valproic acid, unlike other anticonvulsants, has no effect on methadone metabolism: two cases. *J Clin Psychiatry*. 1989; 50(6):228-229. 4. Kuhn et al. Carbamazepine treatment of cocaine dependence in methadone maintenance patients with dual opiate-cocaine addiction. *NIDA Res Monogr*. 1989; 95:316-317. 5. Benitez-Rosario et al. Methadone-induced respiratory depression after discontinuing carbamazepine administration. *J Pain Symptom Manage*. 2006; 32(2):99-100.

Summary: Opioid Interactions with Psychotropics

Medication	Metadone plasma concentrations	Buprenorphine plasma concentrations
Antipsychotics		
Quetiapine	↑	Not clinically studied
Antidepressants		
Fluoxetine	↑	No reported interaction
Fluvoxamine	Possible ↑ metabolism (associated with onset of opioid withdrawal)	Not clinically studied
Amitriptyline	Could be associated with increases in plasma methadone concentrations	Single report of serotonin toxicity
St. John's Wort	↑ metabolism and elimination	↑ metabolism and elimination
Desipramine	Associated with increased desipramine levels	No reported interaction
Anxiolytics		
Diazepam	Associated with increased sedation and impaired performance on psychological tests	Associated with increased sedation and impaired performance on psychological tests
Alprazolam	Associated with fatalities	Associated with fatalities
Anticonvulsants		
Carbamazepine	Opiate withdrawal	Not clinically studied
Phenytoin	Opiate withdrawal	Not clinically studied
Phenobarbital	Opiate withdrawal	Not clinically studied

Case

A patient has been stable on a 90 mg daily dose of methadone. She is started on an antibiotic for a urinary tract infection. Three days later she complains of sedation and “fuzzy thinking”.

Question

Which of the following antibiotics is most likely to cause the symptoms described?

1. Amoxicillin
2. Ciprofloxacin
3. Streptomycin
4. Trimethoprim/sulfamethoxazole

Question

Which of the following antibiotics is most likely to cause the symptoms described?

1. Amoxicillin
2. Ciprofloxacin
3. Streptomycin
4. Trimethoprim/sulfamethoxazole

Ciprofloxacin Inhibits CYP3A4 and 1A2

- Co-administration with methadone can decrease methadone metabolism and increase plasma levels¹
- Sedation and confusion¹ and TdP² have been reported in patients taking both methadone and ciprofloxacin

1. Herlin K et al. Methadone, ciprofloxacin and adverse drug reactions. Lancet. 2000; 356(9247):2069-2070. 2. Nair et al. Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient. Addiction. 2008; 103(12):2062-2064.

Drug Interactions: Antibiotics

	Methadone plasma concentrations	Buprenorphine plasma concentrations
Voriconazole	↑	Not studied
Ciprofloxacin	↑	Not studied
Clarithromycin	↑	Not studied
Fluconazole	↑	Not studied

Question

Diazepam has a pharmacodynamic interaction with methadone and buprenorphine. This interaction is greater with:

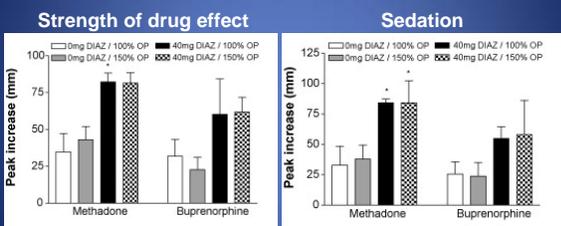
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- A. Methadone
- B. Buprenorphine

Differences in methadone and buprenorphine effects with diazepam¹



1. Lintzeris et al. Drug Alcohol Depend. 2007; 91(2-3):187-194.

Case

A 26-year-old man with opioid dependence, but otherwise in good health, is receiving treatment with buprenorphine/naloxone at a daily dose of 16/4 mg. He is found unresponsive and later dies at the hospital emergency department. A toxicology screen is obtained. Buprenorphine blood levels are substantially higher than expected with the man's dose if taken sublingually as prescribed. A second illicit substance is detected in the blood.

Question

What is the most likely illicit substance to have been identified in this person?

- 1. Heroin
- 2. Methamphetamine
- 3. Oxycodone
- 4. Alprazolam
- 5. Cocaine

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Question

The autopsy provides evidence for circumstances leading to this death. Which of the following findings at autopsy would explain the blood level of buprenorphine and the death?

1. Dilated pupils
2. Congestion in the lungs
3. Fresh needle marks in the left forearm
4. Enlarged, fatty liver

1. Neilsen S, et al. Concurrent buprenorphine and benzodiazepines use and self-reported opioid toxicity in opioid substitution treatment. *Addiction*. 2007; 102(4):616-622.

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Avoiding Adverse Interactions

- Think about metabolic interactions
- Warn patients / families about signs of opioid toxicities: cognitive impairment, increased sedation, slowed, loud breathing
- If concomitant medications needed, use those less likely to impair opioid metabolism
 - Methadone: venlafaxine, bupropion, mirtazepine, sertraline
 - Buprenorphine: mainly 3A4 substrate; avoid fluoxetine / fluvoxamine
- Buprenorphine appears in some situations to be preferable to methadone in those needing other medications (fewer expected interactions)
- Little data to say this with certainty
- Low funding for drug interaction studies in this area

Strategies

- Training of prescribers
 - Safe prescribing
 - Avoid polypharmacy whenever possible
- Public outreach and education
 - Eg important information on DDIs including basic opioid pharmacology
 - No medication sharing
 - Safe medication disposal
- Physicians' Clinical Support System – Medication Assisted Treatment
- Prescribers' Clinical Support System – Opioids
- Research

Physicians' Clinical Support System – Medication Assisted Treatment

Prescribers' Clinical Support System – Opioids

Sponsored by U.S. Center for Substance Abuse Treatment / Substance Abuse and Mental Health Services Administration



From www.PCSSMAT.org and www.PCSS-O.org

- Download clinical tools, forms and concise guidances (like FAQs) on specific questions regarding opioid dependence, use of approved pharmacotherapies for treatment of opioid addiction, safe use of opioids, training opportunities and peer support

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