

Opiates and psychotropics: Pharmacokinetics for practitioners

Aaron M. Pierce, DO, and Nancy C. Brahm, PharmD, MS, BCPP

As prescribed by his internist, Mr. G, age 44, takes 10 mg of methadone every 4 hours for chronic back pain secondary to a work-related injury 3 years ago. He experiences minimal sedation. Mr. G presents for psychiatric evaluation with complaints of increasing irritability, poor focus, low energy, and lack of interest in usual activities. The psychiatrist diagnoses him with depressive disorder not otherwise specified, and prescribes fluoxetine, 20 mg/d. Three weeks later, Mr. G's wife contacts the psychiatrist reporting that her husband seems "overmedicated" and describes excess drowsiness and slowed thought processing.

After discussion with Mr. G's internist and pharmacist, the psychiatrist decides that this oversedation may represent a drug-drug interaction between methadone and fluoxetine resulting in higher-than-expected methadone serum levels. Mr. G is instructed to stop fluoxetine with no taper, and his methadone dose is lowered with good results. Over the next 2 weeks Mr. G is titrated back to his original methadone dose and is re-evaluated by the psychiatrist to discuss medication options to address his depression.

Psychiatrists commonly encounter patients who receive opiate medications for chronic pain. Being aware of potential drug-drug interactions between opiate medications and

psychotropics can help avoid adverse effects and combinations that may affect the efficacy of either drug. Pharmacokinetic interactions may affect your choice of psychiatric medication and should be taken into account when addressing adverse effects in any patient who takes opiates and psychotropics.

Metabolic pathways

The primary metabolic pathways for opiate metabolism are the cytochrome P450 (CYP) 2D6 and 3A4 isoenzymes. Depending on the agent used, prescribers may need to consider interactions for both pathways (*Table 1*,^{1,2} *page 84* and *Table 2*,¹ *page 85*). For example, oxycodone is metabolized via 2D6 and 3A4 isoenzymes and is a potent analgesic with oxymorphone and nor-oxycodone as its active metabolites. These

Practice Points

- When choosing pharmacologic therapy, **make sure that all medications your patient takes are documented**, consider drug-drug interactions, and instruct the patient to notify you of any new medications.
- In addition to toxicity, **loss of efficacy of some opiate drugs** may occur as a result of **metabolic inhibition or induction by psychotropic medications**.
- **Collaborate with the physician who is prescribing the opioid** if psychotropic choices are limited. The patient's pain may be treated adequately with another analgesic that does not interact with the psychotropic that has been chosen.



Vicki L. Ellingrod,
PharmD, BCPP, FCCP
Series Editor

Dr. Pierce is Medical Director, Psychiatry Clinic, Assistant Professor, Department of Psychiatry, University of Oklahoma School of Community Medicine, Tulsa, OK. Dr. Brahm is Clinical Associate Professor, Department of Pharmacy Practice: Clinical and Administrative Sciences-Tulsa, University of Oklahoma College of Pharmacy, Tulsa, OK.

Table 1

Cytochrome P450 isoenzymes inhibited and induced by psychotropics

Isoenzyme	Potency	Psychotropic(s)
2B6 inducer	Moderate	Carbamazepine
2B6 inhibitors	Mild to moderate	Fluoxetine, fluvoxamine
	Moderate	Sertraline
	Potent	Paroxetine
2D6 inhibitors	Mild	Venlafaxine
	Mild to moderate	Citalopram, escitalopram, fluvoxamine, risperidone
	Moderate	Duloxetine
	Moderate to potent	Bupropion
	Potent	Fluoxetine, haloperidol, paroxetine
	Dose-dependent	Sertraline
3A4 inducer	Potent	Carbamazepine
3A4 inhibitors	Mild	Sertraline
	Mild to moderate	Fluoxetine, fluvoxamine

Source: References 1,2

Clinical Point

Remain vigilant for possible opiate toxicity when administering oxycodone with 3A4 inhibitors

metabolites, however, make a negligible contribution to oxycodone's analgesic effect.^{3,4} Metabolism by the 3A4 isoenzyme is the principal oxidative pathway and the 2D6 site accounts for approximately 10% of oxycodone metabolism. A randomized, placebo-controlled, crossover study showed that 2D6 inhibition by paroxetine had no significant effect on oxycodone levels; however, a combination of paroxetine and itraconazole, a potent 3A4 inhibitor, resulted in substantial increases in oxycodone plasma levels.⁵ Remain vigilant for possible opiate toxicity when administering oxycodone with 3A4 inhibitors.

Methadone and meperidine also involve dual pathways. Methadone is metabolized primarily by 3A4 and 2B6, with 2D6 playing a smaller role.⁶ CYP2D6 seems to play an important part in metabolizing the R-enantiomer of methadone, which is largely responsible for the drug's opiate effects, such as analgesia and respiratory depression.^{7,8} Induction of the 3A4 isoenzyme may result in methadone withdrawal, and inhibition may cause methadone toxicity.⁹ Inducers of 3A4, such as carbamazepine, and inhibitors, such as fluoxetine and fluvoxamine, should be avoided or used very cautiously in patients taking methadone. The 2B6 and 2D6 isoenzymes also may

increase or decrease methadone levels and should be treated similarly. In Mr. G's case, fluoxetine inhibited all 3 isoenzymes that are primarily responsible for methadone metabolism. A better antidepressant choice for Mr. G may have been venlafaxine, which is known to only mildly inhibit 2D6, or mirtazapine, which does not seem to inhibit the major CYP isoforms to an appreciable degree.¹⁰

Although the full scope of meperidine metabolism has not been identified,⁹ an *in vitro* test demonstrated that 2B6 and 3A4 play important roles in metabolizing meperidine to normeperidine, its major metabolite.¹¹ Normeperidine does not provide analgesia and is associated with neurotoxicity, including anxiety, tremor, muscle twitching, and seizure.¹² Agents that induce 3A4—such as carbamazepine or St. John's wort—may contribute to neurotoxicity.⁹ Inhibition of these isoenzymes may increase meperidine levels and lead to anticholinergic toxicity or respiratory and central nervous system depression.^{13,14}

Opiates metabolized by the 2D6 isoenzyme include codeine, hydrocodone, and tramadol. The analgesic effect of codeine seems dependent on 2D6 metabolism. Via this pathway, codeine is converted into morphine, which has a 300-times stronger

Table 2

Cytochrome P450 isoenzymes inhibiting and inducing opiate metabolism

Isoenzyme	Opiates
2B6 inducer	Methadone
2B6 inhibitors	Meperidine, methadone
2D6 inhibitors	Codeine (may involve loss of efficacy as well as toxicity), methadone, tramadol (may involve loss of efficacy)
3A4 inducer	Meperidine, methadone
3A4 inhibitors	Fentanyl, oxycodone, meperidine, methadone

Source: Reference 1

affinity for the μ opioid receptor compared with codeine. 2D6 poor metabolizers have shown codeine intolerance and toxicity.³ Psychotropics known to strongly inhibit 2D6 isoenzyme processes—such as paroxetine, fluoxetine, and bupropion—should be avoided in patients taking codeine to prevent adverse effects and potential loss of efficacy. Better antidepressant choices include citalopram or venlafaxine, which inhibit 2D6 to a lesser degree.

Hydrocodone may be a viable option for patients taking 2D6 inhibitors. Hydrocodone is metabolized by 2D6 into hydromorphone, which is 7 to 33 times more potent than hydrocodone.¹⁵ Unlike codeine, 2D6 inhibition may have little effect on hydrocodone's analgesic properties. Animal studies have shown that inhibition of the CYP analog to 2D6 does not affect analgesic response. In humans, 2D6 inhibition does not seem to affect hydrocodone's abuse liability.¹⁶ Two case reports describe known 2D6 poor metabolizers who showed at least a partial response to hydrocodone.^{15,16}

Tramadol's analgesic properties may be related to serotonin and norepinephrine reuptake inhibition. It is less potent than codeine but is metabolized via the 2D6 isoenzyme into 0-desmethyltramadol, which is up to 200 times stronger than its parent compound.¹⁷ Clinicians should be aware that tramadol's efficacy may be decreased when coadministered with 2D6 inhibitors. In a randomized, placebo-controlled trial, paroxetine, a potent 2D6 inhibitor, was shown to lessen the analgesic effect of tramadol.¹⁸

The 3A4 site is the primary pathway for fentanyl metabolism. Agents that inhibit 3A4 could increase fentanyl plasma concentration, leading to respiratory depression.¹⁹ Examples of 3A4 inhibitors include fluoxetine and fluvoxamine.

Psychotropics may inhibit or induce P450 isoenzymes to varying degrees. For example, paroxetine and citalopram are known to inhibit 2D6 but paroxetine is a stronger inhibitor; therefore, a significant drug-drug interaction is more likely with paroxetine and a 2D6 substrate than the same substrate administered with citalopram.

Other considerations

In addition to pharmacokinetic interactions, it is important to consider synergistic effects of some opiates and psychotropics. Examples include:

- additive effect on respiratory depression by benzodiazepines and opiates
- increased risk of serotonin syndrome and seizure when using tramadol with selective serotonin reuptake inhibitors or tricyclic antidepressants
- additive prolongation of the QTc interval by methadone when used with psychotropics known to prolong the QTc, such as ziprasidone.^{9,17,20}

Careful attention to these interactions and collaboration among providers can ensure the best outcome for our patients. In Mr. G's case, collaboration with his internist would be in order, particularly if antidepressant choices are limited. In consultation with the psychiatrist, the

Clinical Point

Agents that inhibit 3A4 could increase fentanyl plasma concentration, leading to respiratory depression

Clinical Point

Use of SSRIs or tricyclic antidepressants with tramadol may increase risk for serotonin syndrome

Related Resources

- Indiana University School of Medicine drug interactions: cytochrome P450 drug interaction table. <http://medicine.iupui.edu/clinpharm/ddis/table.asp>.
- Ferrando SJ, Levenson JL, Owen JA, eds. *Clinical manual of psychopharmacology in the medically ill*. Arlington, VA: American Psychiatric Publishing, Inc; 2010.

Drug Brand Names

Bupropion • Wellbutrin, Zyban	Methadone • Dolophine, Methadose
Carbamazepine • Tegretol	Mirtazapine • Remeron
Citalopram • Celexa	Morphine • Avinza, Duramorph, others
Duloxetine • Cymbalta	Oxycodone • OxyContin, Roxicodone
Escitalopram • Lexapro	Paroxetine • Paxil
Fentanyl • Duragesic, Actiq	Risperidone • Risperdal
Fluoxetine • Prozac	Sertraline • Zoloft
Fluvoxamine • Luvox	Tramadol • Ultram
Haloperidol • Haldol	Venlafaxine • Effexor
Hydrocodone • Lortab, Vicodin, others	Ziprasidone • Geodon
Itraconazole • Sporanox	
Meperidine • Demerol	

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The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

internist might choose another opiate to treat Mr. G's pain that would not interact with fluoxetine. If Mr. G and his physician have struggled to manage his pain and if he is stable on the current regimen, selecting a different antidepressant may be warranted.

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