PAIN TREATMENT TOPICS

Methadone-Drug* Interactions

(*Medications, illicit drugs, & other substances)

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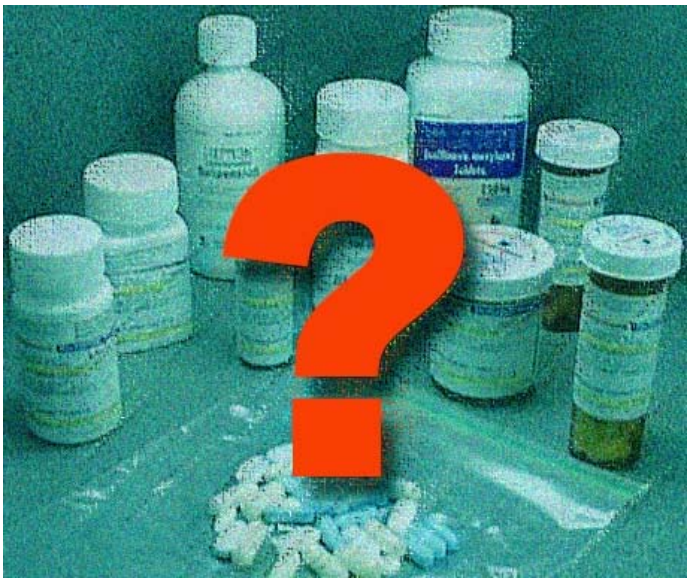

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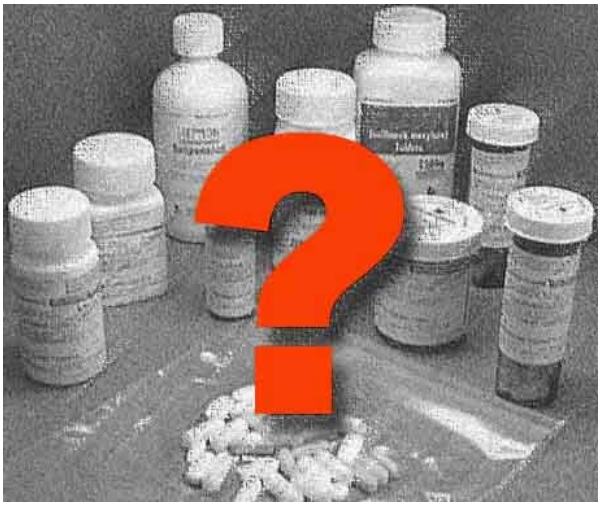
Section Contents

Understanding Methadone Metabolism & Drug Interactions

The Importance of Drug Interactions



Each year in the U.S. there are innumerable adverse drug reactions, broadly defined as any unexpected, unintended, undesired, or excessive response to a medicine. Such reactions may require discontinuing or changing medication therapy. Furthermore, greater than 2 million of those are serious reactions resulting in hospitalization and/or permanent disability, and there are more than 100,000 deaths annually attributed to reactions involving prescribed medications (Cohen 1999; Wilkinson 2005).

Three-fourths of those adverse reactions relate to *drug interactions*, which occur when the amount or action of a drug in the body is altered – usually increased or decreased – by the presence of another drug or multiple drugs (Bochner 2000; Levy et al. 2000; Piscitelli and Rodvold 2001). Avoiding these can be difficult, since the number of potential interactions among diverse drugs used in clinical practice can be overwhelming; more than 2,000 such interactions have been described in the literature and new cases appear monthly (Levy et al. 2000). As the tables in this document indicate, there are more than100 substances – medications, illicit drugs, OTC products, etc. – that can interact in some fashion to affect a patient's response to methadone.

Pharmacotherapy is increasingly complicated by the introduction of new drugs and the use of multidrug regimens – called "polypharmacy" – for acute or chronic disease, which can result in clinically important drug interactions. While multiple drugs often are necessary for treating complex or resistant conditions, side effects of the drugs themselves may induce symptoms rather than any pathological processes (Farrell et al. 2003). This is of vital importance for patients receiving methadone analgesia regimens, since these individuals often have co-morbid physical and/or mental disorders requiring multiple medications.

Methadone History

Methadone was discovered in Germany in the late 1930's by Max Bockmühl and Gustav Ehrhart, working for the German chemicals conglomerate IG Farberindustrie. They were exploring synthetic compounds with a structure similar to Dolantin®, which was an opioid analgesic (later marketed as Pethidine®, Demerol®, and others) similar to morphine that was discovered earlier at the same company (Bäumler 1968, Chen 1948; Ehrhart 1956; Eichler and Farah 1957; Erhart and Ruschig 1972; Payte 1991; Preston 2003).

Bockmühl and Ehrhart synthesized a compound that was both analgesic and spasmolytic, which they called “Hoechst 10820” and for which they filed a patent application in September 1941. This agent was found to be at least as powerful as morphine and 10 times more potent than Dolantin; however, its pharmacology was different and little was known about how to best prescribe the new agent. Consequently, Hoechst 10820 was not effectively used as an analgesic during the war years, allegedly because the very high initial doses typically administered at that time produced intolerable side effects (Bäumler 1968, Chen 1948; Ehrhart 1956; Eichler and Farah 1957; Erhart and Ruschig 1972; Payte 1991; Preston 2003).

As part of the “spoils of war,” the formula for Hoechst 10820 became available to other countries worldwide and was further tested and used for analgesia. It soon became generically known as methadone and trade names in the U.S. include Dolophine® and Methadose®; other brands have been developed outside the U.S. (Bäumler 1968, Chen 1948; Eichler and Farah 1957; Ehrhart 1956; Erhart and Ruschig 1972; Payte 1991; Preston 2003; Velten 1992).

Initially, methadone was widely used in clinical medicine as an analgesic and antitussive, for which it was approved in the U.S. in 1947. Early indications for its use included: migraine, dysmenorrhea, labor pain, painful nerve disorders, advanced cancer or tuberculosis, and tetanus, among others. However, at this time, relatively little was known about methadone pharmacology and how best to prescribe it. Due to improper prescribing and/or misuse, there were deaths associated with methadone in the late 1940’s and the 1950’s, and a number of those fatalities were reported in England and Germany among young children exposed to methadone in cough syrups. Similar deaths in children and adults, or cases of near-fatal respiratory depression, soon occurred in other countries where methadone was widely prescribed. Consequently, due to its perceived toxicity and the potential for methadone to produce physiologic dependence, it fell into disuse as an analgesic by the early 1960’s (Harding-Pink 1993; Payte 1991; Preston 2003; Rettig and Yarmalonsky 1995).

In the mid-1960’s, Vincent P. Dole, MD, and his team at Rockefeller University in New York City began research on a new method for treating heroin addiction. Methadone was chosen for experimentation in treating opioid addicts because it was known to be long-acting, could be taken orally, and had been previously used in analgesia and for withdrawing opioid-addicted persons from heroin. Dole and colleagues found that, once opioid tolerance was established to a methadone dose of 80-120 mg/day, patients were able to function normally, without drug craving (Dole 1988; Joseph and Appel 1993; Joseph et al. 2000; Kreek 1993; McCann et al. 1994; Nadelman and McNeely 1996; Parrino 1993).

During clinical use in the maintenance treatment of opioid addiction spanning more than 40 years, hundreds of studies have examined the pharmacology and efficacy of oral methadone and it has proven to be a well-tolerated medication with minimal adverse reactions when properly prescribed in appropriate doses (Kreek 1973; Novick et al. 1993). However, there are potential methadone-drug interactions – involving other prescribed medications, illicit drugs, OTC products, and other substances – which sometimes can be difficult to predict. Such interactions may be potentially harmful

and/or can lead to treatment failures, whether methadone is used as a component of addiction treatment or as an analgesic (Harrington et al. 1999; Levy et al. 2000).

Metabolic Basics

Most drugs are foreign to the human body and are metabolized by chemical reactions into molecules that can be more easily eliminated (Flexner and Piscitelli 2000). A primary metabolic pathway involves the actions of proteins, called cytochrome P450 (CYP450) enzymes, that facilitate those chemical reactions. These enzymes evolved as a protective mechanism more than 3 billion years ago to cope with a growing number of naturally occurring environmental chemicals and toxins (Hardman et al. 1996; Richelson 1997).

There are more than 28 CYP enzymes encoded by 57 different human genes (Flexner and Piscitelli 2000; Shannon 1997; Wilkinson 2005). Each is designated by a combination of numbers and letters: for example, 3A4 and 2B6 which are important in methadone metabolism. CYP enzymes reside mainly in the liver, but also are present in other organs. Substances that interact with the CYP450 system usually do so in one of three ways: 1) by acting as a substrate, 2) through inhibition, or 3) through induction.

- A ***substrate*** is any drug metabolized by one or more CYP enzymes, and more than half of all medications that undergo metabolism are CYP3A4 substrates (Piscitelli and Rodvold, 2001).
- Some drugs are ***inhibitors*** of specific CYP enzymes and thereby slow the metabolism of drugs that are substrates for those particular enzymes, which may result in excessively high drug levels and related toxic effects (Levy et al. 2000).
- Other drugs are ***inducers***; they boost the activity of specific CYP enzymes resulting in more rapid metabolism of substrate drugs, which may result in lower than expected levels of the substrate drugs (Flexner and Piscitelli 2000).

A drug can at the same time be a substrate for and induce or inhibit one or more CYP enzymes. Co-administered drugs that merely share the same metabolic pathway – that is, are substrates for the same CYP enzymes – may compete with each other. The “winning drug” could garner more enzyme activity, thus diminishing metabolism of the other drug and intensifying its effects (Hardman et al. 1996). Readers may wish to consult current sources listing drugs that are CYP450-enzyme substrates, inducers, or inhibitors; such as at http://drug-interactions.com (Flockhart 2003).

Methadone Metabolism

Methadone is usually readily absorbed, with about 80% of the administered dose passing into the bloodstream during stabilized, steady-state dosing and the remainder metabolized in the GI tract and liver; although, for reasons described below, bioavailability can range from 35% to 100% (Eap et al. 2002, Moolchan et al. 2001). The three available formulations of oral methadone – solid tablets, dispersible tablets, and liquid concentrate – have been demonstrated as intrinsically equal in terms of their bioavailability and metabolism (Gourevitch et al. 1999); however, patient reactions to each formulation may vary, possibly due to psychosomatic factors in some cases.

The most important enzymes in methadone metabolism are CYP3A4 and CYP2B6. Secondarily CYP2D6 appears to have a role, and CYP1A2 may possibly be involved (see ***Table***).

CYP450 Enzymes Metabolizing Methadone	
CYP3A4	Important methadone metabolizer (can also be induced by methadone during the early start-up phase of therapy).
CYP2B6	Relatively recently discovered as an important methadone metabolizer.
CYP2D6	Secondary role (methadone can inhibit this enzyme in some cases and this enzyme is particularly involved in the metabolism of the active R-methadone enantiomer).
CYP1A2	Possibly involved (clinical significance still under investigation).
Note: Previously CYP2C9 and 2C19 were thought to be involved, but this has not been confirmed (Crettol et al. 2005). Borg and Kreek 2003; Eap et al. 2002; Gerber 2002; Gerber et al. 2004; Iribarne et al. 1997; Kharasch et al. 2004a; Leavitt et al. 2000; Moolchan et al. 2001; Shinderman et al. 2003; Wu et al. 1993	

CYP3A4, the most abundant metabolic enzyme in the body, can vary 30-fold between individuals in terms of its presence and activity in the liver (Eap et al. 2002; Leavitt et al. 2000). This enzyme also is found in the gastrointestinal tract, so methadone metabolism actually can begin before the drug enters the circulatory system (Hardman et al. 1996). The amount of this enzyme in the intestine can vary up to 11-fold, partially accounting for some individual differences in the breakdown and absorption of methadone (Levy et al. 2000).

Fairly recently, CYP2B6 has been discovered as playing a prominent role in methadone metabolism (Gerber 2002; Gerber et al. 2004; Kharasch et al. 2004a, Rotger et al. 2005), and especially but not exclusively metabolism of the inactive S-enantiomer (Crettol et al. 2005, in press; Totah et al. 2004). Effects of CYP2B6 were demonstrated in laboratory experiments and also helped account for certain otherwise unexplained methadone-drug interactions during human trials. At present, relatively few agents have been identified as inducers or inhibitors of CYP2B6 (Faucette et al. 2004; Flockhart 2005), and there also can be individual differences in activity of this enzyme (Kharasch et al. 2004a; Rotger et al. 2005). However, as research continues, many agents currently thought to be interacting with methadone primarily via other P450 enzymes also may be identified as CYP2B6 substrates, inducers, or inhibitors. Therefore, in many cases, the most that can be stated with certainty at present is that CYP450 enzymes are involved in a methadone-drug interaction, without always knowing the relative roles of exact enzymes (personal communication, E. Kharasch, October 2005).

Another metabolic protein of some importance is P-glycoprotein (P-gp), which is found in the intestine, along the blood-brain barrier, and in other tissues (Matheny et al. 2001, Wang et al. 2004). This substance functions as a pump, transporting methadone *out* of cells lining the intestinal wall and back into the lumen. Thus, some of the methadone absorbed by the intestine is pumped back out before it ever enters the circulation. There is up to a 10-fold variation in the amount of intestinal P-gp expressed by individuals (Hall et al. 1999, Leavitt et al. 2000), and some interactions originally considered solely due to intestinal CYP3A4 may involve P-gp as well (Dresser et al. 2000; Eap et al. 2002; Kharasch et al. 2004b). Some evidence suggests that expression of P-gp in the blood-brain

barrier, which can vary across individuals, may play a role in the access and effects of methadone in the brain and the potential for adverse effects (Wang et al. 2004). Although, one clinical study found that P-gp may not be a significant factor in this regard (Kharasch et al. 2004b).

Drugs or other agents that ***induce*** the activity of enzymes involved in methadone metabolism can accelerate its breakdown, increase its rate of clearance, abbreviate the duration of methadone's effects, lower the serum methadone level (SML), and possibly precipitate opioid-withdrawal syndrome. Conversely, CYP-enzyme ***inhibitors*** may slow methadone metabolism, raise the SML, extend the duration of its effects, and possibly cause methadone-related toxicity such as oversedation and/or respiratory depression (Eap et al. 2002; Leavitt et al. 2000; Methadose PI 2000; Payte et al. 2003; Wolff et al. 2000).

Genetic factors also can act on certain enzymes to affect methadone metabolism. For example, CYP2D6 is entirely absent in a significant portion of the population (1 out of 15 persons), resulting in increased sensitivity to methadone's effects; conversely, some persons have high activity of this enzyme and are rapid metabolizers of methadone (Eap et al. 2002).

The variability of CYP-enzyme presence and activity means that SMLs can differ significantly even in the absence of interacting substances; some persons can naturally be either extensive (rapid) or poor (slow) metabolizers of methadone. When interactions with other drugs occur on top of this it could further influence problematic methadone under- or overmedication (Eap et al. 2002; Leavitt et al. 2000; Richelson 1997).

Methadone-Drug Interactions

When co-prescribing medications with methadone, and a suspected drug interaction occurs, the time course of sign/symptom development can be a guide as to whether enzyme induction or inhibition is involved. *Overmedication* reactions are likely due to *CYP inhibition that develops quickly;* within a few days after concurrent drug administration. In contrast, *CYP induction is slower to emerge*, commonly taking about a week to produce significant *withdrawal* signs/symptoms (Antoniou and Tseng 2002; Faragon and Piliero 2003; Gourevitch and Friedland 2000; Hansten 1995; Wolff et al. 2000). In the presence of strong CYP inducers, merely increasing the methadone dose may be insufficient and an increase plus more frequent daily dosing may be necessary.

Potential effects on methadone metabolism also should be considered when *discontinuing* medications. If a drug that inhibits CYP enzymes is stopped, methadone serum levels may decrease and cause opioid withdrawal that requires increased methadone dose. Conversely, if a CYP inducer is discontinued, metabolizing-enzyme levels will diminish and SMLs may rise to toxic levels unless careful methadone dose reductions are implemented in response to clinical signs of overmedication.

Some methadone-drug interactions primarily relate to how certain drug combinations may adversely affect physiological response in the patient (pharmacodynamics) and have little to do with altered pharmacokinetics. For example, the *additive effects* of methadone combined with other central nervous system (CNS) depressants may cause hypotension, sedation, respiratory depression, or

coma (Leavitt 2003; Methadose PI 2000). Also, polysubstance abuse in certain patients may put them at greater risk of adverse additive interactions with other CNS-active drugs (Antonio and Tseng 2002; Harrington et al. 1999; Quinn et al. 1997).

Another concern involves the recognition of methadone's potential to affect heart rhythm under certain circumstances (Leavitt and Krantz 2003). Researchers studying patients attending methadone maintenance programs for addiction have reported relatively small but statistically significant QT interval increases; however, the QT measurements generally remained within acceptable limits (Maremmani et al. 2005; Martell et al. 2005). Often, these heart rhythm changes were in patients taking medications or drugs in addition to methadone, or having cardiac risk factors that might normally be of concern (Leavitt and Krantz 2003).

In the largest retrospective investigation to date, researchers examined all adverse events associated with methadone officially reported to the FDA during a 33 year period (Pearson and Woosley 2005). Of 5,503 incidents, only 16 noted QT interval prolongation and 43 indicated torsade de pointes (TdP). Most cases involved methadone used in pain management – at doses ranging from 29 to 1,680 mg/day – and it could not be determined that methadone was a direct cause. Five cases (0.09%) were fatal; however, 3 of those involved pre-existing factors known to influence arrhythmia.

The conclusions and recommendations of all major investigations to date concur that the risk of TdP is likely to be small, should not deter healthcare providers or patients from using methadone, and it is premature to suggest routine ECGs before or during methadone therapy. However, it would be advisable to take careful medical histories screening for known cardiac risk factors and it would be prudent not to co-prescribe methadone with other drugs known to prolong the QT interval because of the potential for additive effects (Krook et al. 2004; Leavitt and Krantz 2003; Maremmani et al. 2005; Martell et al. 2005; Pearson and Woosley 2005; Piquet et al. 2004). Thus, comedications that might produce acute elevations of serum methadone concentrations or may in themselves contribute to dysrhythmias should be used only after considering the risks versus benefits.

In cases of patients on elaborate drug regimens – such as multidrug therapies for HIV/AIDS, hepatitis, and/or severe mental illness – outside consultation with specialists in such pharmacotherapies might be advised. For example, many drugs used for HIV/AIDS therapy interact with each other (Chrisman 2003; Schütz 2002) and their combined effects on methadone can be complex (Antoniou and Tseng 2002; Faragon and Piliero 2003).

Putting Concepts Into Practice

Methadone works best when administered in *adequate* therapeutic doses (Leavitt 2003). However, given the individual variability in methadone absorption and metabolism, it becomes difficult to accurately predict the effects of drug combinations in any one patient (Harrington et al. 1999), or how methadone dosing may need adjustment to compensate for metabolic inducers or inhibitors (Wolff et al. 2000). If a patient is responding unexpectedly or unfavorably to methadone – with signs/symptoms of under- or overmedication – a search for potentially interacting substances

(prescribed medications, illicit drugs, OTC products, or other agents) would be appropriate. Taking a comprehensive history from the patient can be important in this search (Kramer 2000).

When prescribing comedications the potential for certain drugs and drug combinations to interact with methadone requires careful consideration. Furthermore, polysubstance abuse may place patients at risk for hazardous interactions of methadone with other opioids and drugs such as alcohol, cocaine, barbiturates, and benzodiazepines. Clinical experience, intuition, and common sense can be valuable tools for practitioners in taming drug interactions and the following ***Table*** lists some suggestions.

Clinical Suggestions for Minimizing Methadone-Drug Interactions

1. Maintain an accurate, updated profile for each patient that includes all prescribed drugs and OTC products (including herbal remedies and dietary supplements).
2. Use alternative, non-interacting, drugs whenever possible.
   Usually, there are differences in the interactive properties of at least some members of any drug class. For example, the macrolide antibiotic erythromycin is a strong CYP3A4 inhibitor, likely to possibly interact with methadone, whereas the macrolide azithromycin does not appear to have this effect.
3. If a potentially interacting drug is used with methadone, it is better to adjust the methadone dose based on patient response rather than in advance based on an expected interaction.
   The magnitude of drug interactions varies dramatically from patient to patient, and it is unlikely that the selected methadone dosage adjustment would exactly offset the actual effect of the second drug.
4. Signs/symptoms of either opioid withdrawal or overmedication (e.g., sedation), and their severity, can help gauge serum methadone level (SML) adequacy in the presence of an interacting drug. Adjustments of methadone or concomitant drug(s) may be appropriate to overcome such adverse reactions.
5. If there are concerns about adverse effects of increased methadone concentrations, patients should be advised in advance of physical signs/symptoms of overmedication that might occur and what to do. It may be desirable to temporarily monitor SMLs in certain cases.
6. Whenever possible, avoid concurrent administration of drugs with overlapping adverse-effect profiles. Otherwise, signs/symptoms of major variations in methadone concentration may be confused with side effects of concomitantly administered drugs, and vice versa.
7. Consider preexisting disease states.
   For example, conditions associated with impaired renal or hepatic function may significantly alter drug metabolism and excretion. Patients with preexisting cardiovascular conditions – particularly those with congestive heart failure or left ventricular systolic dysfunction – may be more sensitive to potential arrhythmogenic effects of certain drugs (including methadone).
8. In some cases, adverse drug reactions can be resolved by prescribing a medication with or without food, by altering dosing schedules, or by splitting doses into smaller increments.
9. Unreported or seemingly inconsequential factors may play a role in drug interactions.
   For example, grapefruit juice can hinder metabolism and increase methadone serum levels.
10. Patients may not adhere to prescribed medication regimens, which could affect adverse reactions, and the more complicated the regimen the less likely that the patient will adhere to it. This can be important in methadone-maintained patients prescribed multiple medications.

Adapted from: Chung 2002; Cohen, 1999; Kramer 2000; Levy et al., 2000; Piscattelli and Rodvold, 2001

The traditional advice when adding drugs to a therapeutic regimen is to *start low, go slow, and monitor closely*. This may be especially prudent with methadone analgesia, since many commonly prescribed drugs are associated with dose- and concentration-dependent toxicities, and individual response may vary by several orders of magnitude. Potential adverse reactions also can be minimized by using the smallest effective doses for drugs added to methadone therapy. In many cases, doses of adjunctive medications lower than those recommended by the manufacturer may be sufficient for desired therapeutic effect (Cohen, 1999).

It has long been recognized that *patient education* is essential for successful outcomes with methadone and this should be initiated early in treatment. Better informed patients can partner more effectively with clinic staff regarding their pharmacotherapy. However, as with all other aspects of pain management, this relies on mutual trust and effective communication. Several important points need to be emphasized with patients regarding potential interactions of methadone with other substances and to help them avoid all drug interactions, as noted in the ***Table*** below.

Helping Patients Avoid Drug Interactions

- Patients maintained on methadone should be cautioned to consult healthcare professionals before taking any OTC products, herbal remedies, or dietary supplements.
- Patients should provide to their healthcare providers and pharmacist an updated list of all medical products used.
- Patients should understand their prescriptions and the dosage, and be able to cross-check what was prescribed with what they receive from the pharmacist.
- For each prescribed medication, patients should be *verbally* instructed on what the drug is used for, how to take it, and how to reduce the risk of side effects or drug interactions. It cannot be assumed that patients will read or understand product labels or written information provided with medications or other healthcare products.
- Compliance with prescribed medication regimens should be emphasized. Patients need to understand the importance of taking all medications exactly when, how, and in the quantities specified.
- Patients should be educated on the hazards of taking excess medication or sharing medicines with anyone else. They should be reminded about safe storage of medications and proper disposal of unused portions.
- Patients should be counseled on the importance of quickly reporting any sudden or unexpected signs/symptoms of either methadone withdrawal or overmedication, as this could indicate a potentially hazardous interaction with another drug or substance.
- Special consideration and instruction will be required for patients with physical conditions that may cause or exacerbate drug interactions, such as: liver or kidney disorders, pulmonary or heart ailments, pregnancy, etc.
- Patients taking multiple medications should be assisted in keeping a journal or chart listing the name, purpose, and dose schedule for each drug.
- Patients should be instructed in advance on what to do in the event of an ***emergency*** if their supply of methadone and/or other medications runs out and they do not have access to their usual source of supply. Ideally, such instructions also would be provided in writing.

Adapted from: FDA/CDER 2000; NCPIE 2003.

Theoretically, any drug or substance metabolized by the same CYP enzymes as methadone, or affecting their expression by inhibition or induction, might interact with methadone; although, many of these interactions would not be clinically important. Just because certain drugs *can* interact does not mean that they *will*, or to *what extent*.

The methadone-drug interaction ***Tables*** below list only drugs and substances *specifically mentioned in the scientific literature* that either: A) should definitely be avoided with methadone, B) may influence unexpected results or are themselves altered by their combination with methadone, or C) raise or lower SMLs and increase or decrease methadone's effects, respectively. Due to space limitations, earlier editions of this document most extensively cited literature-review articles in reporting sources of information. This current document retains those references but is greatly expanded to also include citations of the primary studies and articles.

There have been a limited number of clinical studies investigating methadone interactions with specific drugs; therefore, some interactions are predicted based on lower levels of evidence, such as case reports, laboratory experiments, or pharmacologic principles. The various levels of evidence are denoted in the ***Tables*** by different colors and typefaces as follows:

- **Interaction demonstrated via published clinical studies and/or by the well-established and specific pharmacology of methadone metabolism.**
- *Based on published clinical case series reports and/or laboratory investigations in animals or tissues (in vitro).*
- *Proposed in the literature, but predicted from general pharmacologic principles and/or sporadic anecdotal cases.*

To simplify the presentation, only substances reported or proposed as interacting in a substantive way with methadone are included in the ***Tables***. In some cases, the interaction potential of certain drugs may have been examined but no clinically significant interaction was found; therefore, these drugs are not listed in this document.

Furthermore, enzymes involved in methadone-drug interactions are often broadly indicated here as part of the CYP450 family, without specifying the *exact* enzymes. As noted above, this is an ongoing area of investigation and many agents currently thought to be interacting with methadone via specific P450 enzymes may be otherwise identified as time passes. Therefore, the most that often can be stated with certainty is that CYP450 enzymes are involved in a methadone-drug interaction. Clinically, this is still helpful in understanding the possible interaction and suggesting when therapeutic adjustments of methadone and/or the interacting agent(s) might be appropriate.

Finding Drugs/Substances of Interest in this Document

While viewing this Adobe Reader® PDF document, use the "Search" function to easily and quickly locate a drug/substance within the document. Click on the "Search" button icon (***graphic at left***) on the menu bar. This function also is available under the "Edit" menu, or by pressing the "Control [Ctrl]" plus the "F" keys simultaneously on the keyboard.

In the panel that appears along the right side of the document (***graphic at right***), enter the name of the drug or substance of interest or concern and click on the search button. All instances of the named drug/substance in the document will be listed and these can be selected individually for viewing.

Table Legend

Table Abbreviations, Data Sources, & Notes

Abbreviations: NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SML = serum methadone level; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

♥ Denotes drugs that have been associated in the literature with cardiac rhythm disturbances (prolonged QTc interval and/or torsade de pointes [TdP]) and should be used cautiously with methadone. For regularly updated information on TdP risk, see: http://QTdrugs.org (Woosley 2003). Also see, Leavitt and Krantz 2003.

Reference Sources: The original document (2004) principally cited current *review articles* specifically mentioning methadone-drug interactions. This revision/update (2005) now also includes references to primary studies, if available, demonstrating the methadone-drug interaction.

Note: Drug brand names are registered trademarks of their respective manufacturers. Additional brands may be on the market and the tables may not be all-inclusive of drugs/brands that might be contraindicated or interact with methadone. Clinical experiences with drugs may differ, as there are often individual patient variations in methadone metabolism and reactions to any drug or combination of therapies.

Levels of Evidence (The following colors/typefaces are used in the tables to designate the certainty of interactions)**:**

- **Interaction demonstrated via published clinical studies and/or by the specific pharmacology of methadone.**
- *Based on published case series reports and/or laboratory investigations in animals or tissues (in vitro).*
- *Proposed in the literature, but predicted from general pharmacologic principles and/or sporadic anecdotal cases.*

Table 1

Drugs That Are *CONTRAINDICATED* with Methadone (May Precipitate Opioid Withdrawal)

Generic Name	Brands/Examples	Actions/Uses	Notes/References
agonist/antagonist analgesics buprenorphine, butorphanol, dezocine, nalbuphine, pentazocine	**Buprenex, Subutex, Suboxone, Stadol, Dalgan, Nubain, Talwin**	**Opioid analgesics with some opioid-antagonist activity.**	**Can displace methadone on μ-opioid receptors to cause acute withdrawal (DeMaria 2003; Kalvik et al. 1996).**
monoamine oxidase (MAO) inhibitors	*Nardil, Parnate, others*	*Antidepressants.*	*Contraindicated with methadone due to potential adverse reactions (Methadose® PI 2000).*
opioid antagonists naltrexone, nalmefene, naloxone	**Depade, ReVia, Revex, Narcan**	**Blockade or reversal of opioid effects or treatment of alcoholism.**	**Interaction displaces methadone on μ-opioid receptors, causing severe acute withdrawal (DeMaria 2003; Kalvik et al. 1996, Strang 1999).**
tramadol	*Ultram, Ultracet*	*Synthetic analgesic.*	*Potentially may cause withdrawal in persons already taking opioids (Ultram PI 1998); anecdotal cases have been reported..*

Table 2

Drugs That May Result in Altered Metabolism or Unpredictable Interactions in Combination with Methadone

Generic Name	Brands/Examples	Actions/Uses	Notes/References
benzodiazepines *alprazolam, clorazepate, estazolam, flurazepam, midazolam, triazolam, zopiclone*	*Xanax, Tranxene, ProSom, Dalmane, Versed, Halcion, Imovane*	*Sedatives.*	*Potential interaction due to common CYP450 metabolic pathway with methadone (Harrington et al. 1999). May cause additive CNS depression (Strang 1999); potentially fatal (Ernst et al. 2002). Note: Diazepam has been more thoroughly studied and increases methadone effects (see Table 4).*
cannabis	*Marijuana, hash, hemp, pot*	*Psychotropic agent.*	*Interaction proposed due to common CYP450 metabolic pathway with methadone (Harrington et al. 1999).*
chloral hydrate ♥	*Noctec, Somnote, others.*	*Sedative hypnotic.*	*Case report of additive effects with methadone causing fatal adverse event (Thurau et al. 2003).*
chlormethiazole (clomethiazole)	*Distraneurin, Hemineurin, Heminevrin*	*Sedative-hypnotic, anticonvulsant.*	*Enhanced sedative effects due to additive CNS depression noted anecdotally (Physeptone 2000).*
cyclizine (meclizine)	*Antivert, Bonine, Emoquil Marezine, Marzine*	*Antivertigo, antiemetic.*	*If abused, increased sedative effects due to additive CNS depression noted anecdotally (Physeptone 2000).*
didanosine (ddI, buffered tablet)	**Videx**	**NRTI antiretroviral.**	**Buffered tablet: decrease in ddI concentration (Rainey et al. 2000). Enteric coated (EC) capsule: effect not seen (Friedland et al. 2002).**
dextromethorphan	*Robitussin, Vicks, Delsym, Touro DM*	*Cough medicine.*	*Possible increase in levels/effects of dextromethorphan proposed (Levy et al. 2000).*
interferon-alfa + ribavirin	*Rebetron (possibly also pegylated interferon, e.g., Pegasys)*	*Antihepatitis C treatment.*	*Side effects can mimic opioid withdrawal symptoms and methadone dose is often increased (Schafer 2001; Sylvestre 2002).*
methylphenidate	*Ritalin, Ritalin SR, Concerta*	*Stimulant used for treating AD/HD.*	*CYP2D6 inhibition (Flockhart 2005) might slightly increase methadone effects. Anecdotal reports only (Leavitt 2005).*
nifedipine	*Procardia, Adalat*	*Cardiac medication (Ca^{++} blocker).*	*Possible increase in nifedipine proposed (Levy et al. 2000; Strang 1999).*
opioids **alfentanil, hydrocodone, fentanyl, meperidine, morphine, oxycodone, propoxyphene**	**Alfenta, Vicodin, Sublimaze, Demerol, Duramorph, MS Contin, OxyContin, Darvon**	**Analgesics.**	**Common CYP450 pathways with methadone; however, interaction probably occurs due to possible additive opioid effects. Long-acting excitatory metabolites of meperidine and propoxyphene can reach toxic levels (Harrington et al. 1999).**
promethazine	*Insomn-eze, Mepergan, Phenergan, others*	*Antihistamine.*	*Increased methadone effect mentioned only anecdotally, possibly due to CYP2D6 inhibition (Brown and Griffiths 2000) or synergistic sedation (Phenergan PI 2000). Effects with other phenothiazines (Thorazine, Stelazine) not reported.*
stavudine (d4T)	**Zerit**	**NRTI antiretroviral.**	**Decrease in d4T concentration; no effect on methadone (Rainey et al. 2000). Clinical significance in d4T decrease unclear; no dosage adjustments necessary.**
TCAs *amitriptyline♥, desipramine♥, imipramine♥, nortriptyline♥, protriptyline♥*	*Elavil, Norpramin, Tofranil, Pamelor, Trimipramine, Sinequan, Vivactil, and other brands*	*Tricyclic antidepressants (TCAs).*	*Combination with methadone increases TCA toxicity (DeMaria 2003; Maany et al. 1989; Quinn et al. 1997; Richelson 1997). Mixed reports of methadone increase or decrease (Eap et al. 2002; Moolchan et al. 2001; Strang 1999; Venkatakrishnan et al. 1998). Caution might be advised when using the drugs in combination with methadone due to possible proarrhythmic effects.*

Table 2 CONTINUED: Drugs That Result in Altered Metabolism / Unpredictable Interactions

zidovudine (AZT)	**Retrovir, AZT combinations (e.g., Combivir, Trizivir)**	**NRTI antiretroviral.**	**AZT concentration increased significantly with methadone; more frequent AZT side effects are possible, but no effect on methadone (McCance-Katz et al. 1998, 2001; Rainey et al. 2002; Retrovir PI 2001; Schwartz et al. 1992; Trepnell et al. 1998).**

Table 3

Drugs That May *LOWER* SML and/or *DECREASE* Methadone Effects

Generic Name(s)	Brands/Examples	Actions/Uses	Notes/References
abacavir (ABC)	**Ziagen**	**NRTI antiretroviral.**	**Methadone level mildly decreased; also reduces ABC peak concentration (Bart et al. 2001; Gourevitch 2001; Sellers et al. 1999; Ziagen PI 2002).**
amprenavir	**Agenerase**	**PI antiretroviral.**	**CYP3A4 enzyme induction may decrease methadone levels (Agenerase PI 1999; Bart et al. 2001; Chrisman 2003; Eap et al. 2002), but no adjustment in methadone dose required (Henrix et al. 2000, 2004). Amprenavir levels also may be reduced but the clinical significance is unclear.**
barbiturates *amobarbital, amylo-barbitone butabarbital, mephobarbital,* **pheno-barbital**, *pentobarbital, secobarbital, others*	*Amytal, Butisol, Fioricet, Fiorinal, Lotusate, Luminal, Mebaral, Nembutal,* **Pheno-barbital**, *Seconal, Tal-butal, Tuinal, and others*	*Barbiturate sedatives and/or hypnotics.*	*CYP450 enzyme induction (Kreek 1986).* **Phenobarbital, the most studied, can cause sharp decrease in methadone (Alvares and Kappas 1972; Faucette et al. 2004; Gourevitch 2001; Liu and Wang 1984; Plummer et al. 1988) A methadone dose increase may be required.**
carbamazepine	**Atretol, Tegretol**	**Anticonvulsant for epilepsy and trigeminal neuralgia.**	**Strong CYP3A4 and** *CYP2B6* **enzyme induction may cause withdrawal (Bochner 2000;** *Faucette et al. 2004;* **Kuhn et al. 1989).** *Effect not seen with valproate (Depakote; Saxon et al. 1989).*
cocaine♥	*Crack, coke, others*	*Illicit stimulant.*	*Accelerates methadone elimination (Moolchan et al. 2001).*
dexamethasone	*Decadron, Hexadrol*	*Corticosteroid.*	*CYP3A4 and CYP2B6 enzyme inducer (Eap et al. 2002; Faucette et al. 2004); cases reported in pain patients (Plummer et al. 1988).*
efavirenz	**Sustiva**	**NNRTI antiretroviral.**	**Due to CYP3A4 and/or CYP2B6 induction (Barry et al. 1999; Boffito et al. 2002; Clarke et al. 2000, 2001a; Eap et al. 2002, Gerber et al. 2004; Marzolini et al. 2000; McCance-Katz et al. 2002; Pinzanni et al. 2000; Rotger et al. 2005; Tashima et al. 1999). Methadone withdrawal is common and a significant methadone dose increase is usually required.**
ethanol (chronic use)	*Wine, beer, whiskey, etc.*	*Euphoric, sedative.*	*CYP450 enzyme induction (Borowsky and Lieber 1978; Kreek 1976, 1984; Quinn et al. 1997).*
fusidic acid	*Fucidin*	*Steroidal antibacterial.*	*CYP450 enzyme induction (Eap et al. 2002; Van Beusekom and Iguchi 2001); reports of opioid withdrawal symptoms after 4-weeks of therapy (Reimann et al. 1999).*
heroin	*Smack, scat, others*	*Illicit opioid.*	*Decreases free fraction of methadone (Moolchan et al. 2001).*

Table 3 CONTINUED: Drugs That May Lower SML and/or Decrease Methadone Effects

lopinavir + ritonavir	**Kaletra**	**PI antiretroviral.**	**Combination lowers SML (Clarke et al. 2002), although there is some evidence to the contrary (Stevens et al. 2003). Withdrawal symptoms might occur requiring methadone dose increase; however, side effects of Kaletra may mimic GI side effects of opioid withdrawal. *Most* but not all research suggests this effect is not seen with ritonavir alone or ritonavir/saquinavir combination (Beauverie et al. 1998; Chrisman 2003; Geletko and Erickson 2000; Gerber et al. 2001; Hsu et al. 1998; Kharasch and Hoffer 2004; McCance-Katz et al. 2003; Munsiff et al. 2001; Shelton et al. 2001, 2004)** *although ritonavir induces CYP 2B6 (Faucette et al. 2004).*
nelfinavir	**Viracept**	**PI antiretroviral.**	**CYP3A4 and P-gp induction (Beauverie et al. 1998; Eap et al. 2002), but clinical methadone withdrawal is rare (Brown et al. 2001; Hsyu et al. 2000; Maroldo et al. 2000; McCance-Katz et al. 2004); however, manufacturer suggests methadone may need to be increased (Viracept PI 2000). Interaction may (Chrisman 2003) or may not (McCance-Katz et al. 2004) occur to decrease nelfinavir, which also is a potent inhibitor of CYP2B6 (Antoniou and Tseng 2002).**
nevirapine	**Viramune**	**NNRTI antiretroviral.**	**CYP3A4 and/or 2B6 enzyme induction reduces methadone level and precipitates opioid withdrawal. Methadone dose increase necessary in some patients (Altice et al. 1999; Clarke et al. 2001; Eap et al. 2002; Gerber et al.; Heelon et al. 1999; Otero et al. 1999; Pinzanni et al. 2000; Rotger et al. 2005; Staszewski et al. 1998).**
phenytoin	**Dilantin**	**Control of seizures.**	**Sharp decrease in methadone due to CYP3A4 and *CYP2B6* enzyme induction (Eap et al. 2002; *Faucette et al. 2004*; Finelli 1976; Kreek 1986; Tong et al. 1981).**
primidone	*Myidone, Mysoline*	*Anticonvulsant.*	*Proposed in the literature (Vlessides 2005) due to CYP450 enzyme induction (Michalets 1998) including CYP2B6 (Brown & Griffiths 2000) but not clinically verified.*
rifampin (rifampicin) and rifampin/isoniazid	**Rifadin, Rimactane Rifamate**	**Treatment of pulmonary tuberculosis.**	**Induces CYP450 enzymes; cases of severe withdrawal reported (Bending and Skacel 1977; Borg and Kreek 1995; Eap et al. 2002; Faucette et al. 2004; Holmes 1990; Kreek 1986; Kreek et al. 1976). Effect not seen with rifabutin (Mycobutin: Brown et al. 1996; Gourevitch 2001; Levy et al. 2000).**
spironolactone	*Aldactone*	*K^+-sparing diuretic.*	*Possible CYP450 induction (Eap et al. 2002). Effect observed in patients receiving methadone for cancer pain (Plummer et al.).*
St. John's wort (Hypericum perforatum)	*Ingredient in various OTC products*	*Herb used as antidepressant.*	*Induces CYP3A4 and P-gp; 47% decrease in methadone noted in one study (Eich-Höchli et al. 2003; Scot and Elmer 2002).*
tobacco	*Various brands*	*Habitual smoking.*	*Some mixed reports, but most indicate reduced effectiveness of methadone, possibly due to CYP1A2 induction (Eap et al. 2002; Moolchan et al. 2001; Tacke et al. 2001).*
urinary acidifiers (e.g., ascorbic acid)	*Vitamin C (extremely large doses); K-Phos*	*Dietary supplement; keeps calcium soluble.*	*Proposed, methadone excreted by kidneys more rapidly at lower pH (Nillson et al. 1982; Strang 1999).*

Table 4

Drugs That May *RAISE* SML and/or *INCREASE* Methadone Effects

Warning: Acute increases in serum methadone concentration may produce significant signs/symptoms of methadone overmedication, possibly resulting in overdose. Recent data suggest that in susceptible individuals acutely elevated methadone levels – alone or, more commonly, in combination with other drugs and/or cardiac risk factors – may influence cardiac rhythm disturbances (prolonged QTc interval and/or torsade de pointes; see Leavitt and Krantz 2003).

Generic Name	Brands/Examples	Actions/Uses	Notes/References
Asthma Medications zafirlukast, zileuton	*Accolate, Zyflo*	*Prevention and control of asthma symptoms.*	*Proposed in the literature (Vlessides 2005) due to CYP450 inhibition (Flockhart 2005), but not clinically verified.*
Cardiac Medications amiodarone♥, diltiazem quinidine♥	*Cordarone, Cardizem, Diltia, Tiazac, Cardioquin, Quinaglute, Dura-Tabs, others*	*Heart rhythm stabilizers, antihypertensives.*	*Recently proposed in the literature (Vlessides 2005) possibly due to CYP450 inhibition (Flockhart 2005), but not otherwise verified.*
cimetidine	*Tagamet*	*H_2-receptor antagonist for GI disorders.*	*CYP450 enzyme inhibitor (Bochner 2000; Dawson and Vestal 1984; Sorkin and Ogawa 1983; Strang 1999).*
ciprofloxacin	*Cipro*	*Quinolone antibiotic.*	*Inhibition of select CYP450 enzymes (Eap et al. 2002; Herrlin et al. 2000).*
delavirdine	*Rescriptor*	*NNRTI antiretroviral.*	*Predicted effect due to CYP450 enzyme inhibition (Gourevitch 2001; McCance-Katz et al. 2004, 2005); manufacturer suggests methadone dose may need to be decreased (Rescriptor PI 2001).*
diazepam	*Dizac, Valium, Valrelease*	*Control of anxiety and stress.*	*Mechanism undetermined (Eap et al. 2002; Iribarne et al. 1996; Preston et al. 1984, 1986) but unlikely due to metabolic interaction (Foster et al. 1999; Pond et al. 1982) and effect sporadic (Levy et al. 2000).*
dihydroergotamine	*D.H.E., Migranal*	*Migraine treatment.*	*Predicted due to CYP3A4 enzyme inhibition (Van Beusekom and Iguchi 2001).*
disulfiram	*Antabuse*	*Alcoholism treatment.*	*Sedation in patients noted with higher doses of disulfiram (Bochner 2000), but some reports inconclusive (Tong et al. 1980).*
ethanol (acute use)	*Wine, beer, whiskey, etc.*	*Euphoric, sedative.*	*Competition for CYP450 enzymes or CYP450 inhibition (Borowsky and Lieber 1978; Kreek 1976, 1984; Quinn et al. 1997).*
fluconazole	**Diflucan**	**Anti-fungal antibiotic.**	**CYP450 enzyme inhibition (Eap et al. 2002); increased methadone levels (Cobb et al. 1998; Gourevitch 2001); clinical significance uncertain (Levy et al. 2000, Tamuri et al. 2002).** *Other azole antifungals may potentially influence opioid toxicity: e.g., itraconazole, ketoconazole♥, voriconazole.*
grapefruit	**juice or whole fruit**	**Food.**	**Inhibits intestinal CYP3A4 (Bailey et al. 1998; Dresser et al. 2000; Hall et al. 1999) and P-gp (Benmebarek et al. 2004; Dresser et al. 2000; Eagling et al. 1999; Eap et al. 2002); although, there is some conflicting evidence (Kharasch et al. 2004). This effect is not expected with other fruits/juices (Karlix 1990).**

Table 4 CONTINUED: Drugs That May Raise SML and/or Increase Methadone Effects

macrolide antibiotics *erythromycin♥, clarithromycin♥*	*EES, Erythrocin, Eryzole, Ilosone, Prevpac, Biaxin*	*Anti-infective.*	*Predicted due to strong inhibition of CYP3A4 enzyme. Cardiac and metabolic effects not expected with azithromycin (Eap et al. 2002).*
moclobemide	*Aurorix, Manerix*	*MAO-inhibitor (antidepressant).*	*Case reported, possibly due to CYP450 enzyme inhibition (Eap et al. 2002; Gram et al. 1995).*
metronidazole	*Flagyl*	*Anti-infective.*	*Proposed in the literature (Vlessides 2005) due to CYP3A4 inhibition (Michalets 1998), but unverified.*
"natural" supplements *uncaria tomentosa, matricaria recutita, echinacea angustifolia, hydrastis canadensis, quercetin*	*Cat's claw, Chamomile, Echinacea, Goldenseal (may be ingredient in various product brands)*	*Herbal products used for gastrointestinal therapy, immune system enhancement, others.*	*Not studied specifically with methadone – predicted potential effect due to strong CYP3A4 enzyme inhibition (Scott and Elmer 2002, Van Beusekom and Iguchi 2001).*
omeprazole	*Prilosec*	*Treatment of acid-related GI disorders.*	*In animal studies, possibly affects methadone absorption (de Castro et al. 1996; Strang 1999).*
SSRIs *fluoxetine♥,* **fluvoxamine,** *paroxetine♥, nefazodone, sertraline♥*	*Prozac,* **Luvox,** *Paxil, Serzone, Zoloft*	*Treatment of depression and compulsive disorders.*	*Possible mild elevations of SML due to variable inhibition of CYP450 enzymes (Begre et al. 2002; Batki et al. 1993; Bertschy 1996; Eap et al. 2002; Hamilton et al. 1988, 2000; Levy et al. 2000; Richelson 1997).* **Strongest effect seen with fluvoxamine (Alderman and Frith 1999; Bertschy et al. 1994; DeMaria and Serota 1999; Eap et al. 1997).**
troleandomycin	*TAO*	*Antibiotic (similar to erythromycin).*	*Expected due to CYP450 enzyme inhibition (Beusekom and Iguchi 2001).*
urinary alkalinizers (e.g., sodium bicarbonate)	**Bicitra, Polycitra**	**Treatment of kidney stones, gout therapy.**	**Alkaline (higher pH) urine decreases methadone excretion by kidneys (Kalvik et al. 1996; Strang 1999).**
verapamil	*Calan, Covera-HS, Isoptin*	*Cardiac drug (Ca^{++}-channel blocker).*	*Predicted effect due to CYP450 enzyme and strong P-glycoprotein inhibition (Levy et al. 2000).*

Table 5

Methadone-Drug Interactions
Alphabetical Listing by Generic & Brand Names

NOTE: Drug *Brand Names* begin with capital letters and are registered trademarks of their respective manufacturers. All others are generic agents.

The listings here may not be all-inclusive of drugs/brands that might be contraindicated or interact with methadone. Furthermore, clinical experiences with medications may differ, as there are often individual variations in methadone metabolism and reactions to any drug, substance, or combination of therapies.

Interactions resulting in acute SML increases are of special concern, since they may produce signs/symptoms of overmedication and possible overdose. In individuals with cardiac risk factors, methadone's combination with other drugs having arrhythmogenic potential may influence cardiac rhythm disturbances.

Symbols:

⃠ = contraindicated with methadone (may cause opioid withdrawal, possibly severe).

↕ = may result in altered metabolism or unpredictable interactions with methadone.

↑ = increases serum methadone level (SML) and/or increases methadone effects.

↓ = decreases serum methadone level (SML) and/or decreases methadone effects.

♥ = drug has been associated with cardiac rhythm disturbances (prolonged QTc interval and/or torsade de pointes) and should be used cautiously with methadone. For latest listings see: http://Qtdrugs.org.

Levels of Evidence *(The following colors/typefaces are used in the tables to designate the certainty of interactions)*:

■ **Interaction demonstrated via published clinical studies and/or by the specific pharmacology of methadone.**

■ *Based on case series reports and/or laboratory investigations in animals or tissues (in vitro).*

■ *Proposed in the literature, but predicted from general pharmacologic principles and/or sporadic anecdotal cases.*

Drug/Substance	Effect With Methadone	
abacavir (ABC)	↓	**Also decreases ABC peak concentration.**
Accolate	↑	*Proposed due to CYP450 inhibition.*
Adalat	↕	*Nifedipine increase proposed.*
Agenerase	↓	**Also may decrease Agenerase (amprenavir).**
Aldactone	↓	*Possible CYP450 induction.*
Alfenta	↕	**Common CYP450 pathway; possible additive effects with methadone.**
alfentanil	↕	**Common CYP450 pathway; possible additive effects with methadone.**
alprazolam	↕	*Potential interaction, additive CNS depression.*
Alurate	↓	*Due to CYP450 enzyme induction.*
amiodarone ♥	↑	*Proposed due to CYP450 inhibition.*
amitriptyline ♥	↕	*Possible increased TCA toxicity; uncertain effect on methadone.*
amobarbital	↓	*Due to CYP450 enzyme induction.*
amprenavir	↓	**Also may decrease amprenavir.**
amylobarbitone	↓	*Due to CYP450 enzyme induction.*
Amytal	↓	*Due to CYP450 enzyme induction.*
Antabuse	↑	*Sedation reported.*
Antivert	↕	*Increased sedative effects if abused.*
aprobarbital	↓	*Due to CYP450 enzyme induction.*
ascorbic acid	↓	*Proposed due to more rapid urinary excretion.*
Atretol	↓	**May cause opioid withdrawal.**

Aurorix	↑	*Possible due to CYP450 inhibition.*
Aventyl ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
AZT (zidovudine)	↓↑	**AZT concentration increased and side effects common.**
barbiturates	↓	*Due to CYP450 enzyme induction.*
benzodiazepines	↓↑	*Potential interaction, additive CNS depression.*
Biaxin ♥	↑	*Strong CYP3A4 inhibition.*
Bicitra	↑	**Decreases methadone urinary excretion.**
Bonine	↓↑	*Increased sedative effects if abused.*
Buprenex	⊘	**Displaces methadone on μ-opioid receptors.**
buprenorphine	⊘	**Displaces methadone on μ-opioid receptors.**
butabarbital	↓	*Due to CYP450 enzyme induction.*
butalbital	↓	*Due to CYP450 enzyme induction.*
Butisol	↓	*Due to CYP450 enzyme induction.*
butorphanol	⊘	**Displaces methadone on μ-opioid receptors.**
Calan	↑	*Predicted due to CYP450 inhibition.*
cannabis	↓↑	*Proposed interaction, common CYP450 pathway.*
carbamazepine	↓	**May cause opioid withdrawal.**
Cardioquin	↑	*Proposed due to CYP450 inhibition.*
Cardizem	↑	*Proposed due to CYP450 inhibition.*
Cat's claw	↑	*Predicted due to CYP450 inhibition.*
Chamomile	↑	*Predicted due to CYP450 inhibition.*
chloral hydrate	↓↑	*Additive effects, possibly fatal.*
chlormethiazole	↓↑	*Enhanced sedative effects.*
cimetidine	↑	*CYP450 enzyme inhibitor.*
Cipro	↑	*CYP3A4 and/or CYP1A2 inhibition.*
ciprofloxacin	↑	*CYP3A4 and/or CYP1A2 inhibition.*
clarithromycin ♥	↑	*Strong CYP3A4 inhibition.*
clomethiazole	↓↑	*Enhanced sedative effects.*
clorazepate	↓↑	*Potential interaction, additive CNS depression.*
cocaine ♥	↓	*Methadone elimination accelerated.*
coke (cocaine) ♥	↓	*Methadone elimination accelerated.*
Combivir	↓↑	**AZT concentration increased.**
Concerta	↓↑	*Possible CYP2D6 inhibition.*
Cordarone ♥	↑	*Proposed due to CYP450 inhibition.*
Covera-HS	↑	*Predicted due to CYP450 inhibition.*
crack (cocaine) ♥	↓	*Methadone elimination accelerated.*
cyclizine	↓↑	*Increased sedative effects if abused.*
D.H.E.	↑	*CYP450 enzyme inhibition.*
Dalgan	⊘	**Displaces methadone on μ-opioid receptors.**
Dalmane	↓↑	*Potential interaction, additive CNS depression.*
Darvon	↓↑	**Possible opioid additive effects; long-acting toxic metabolites.**
Decadron	↓	*CYP450 induction.*
delavirdine	↑	*Due to CYP450 inhibition.*
Delsym	↓↑	*Increased dextromethorphan effects proposed.*
Demerol	↓↑	**Possible opioid additive effects; long-acting toxic metabolites.**
Depade	⊘	**Displaces methadone on μ-opioid receptors.**
desipramine ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
dexamethasone	↓	*CYP450 induction.*
dextromethorphan	↓↑	*Increased dextromethorphan effects proposed.*

dezocine	⊘	**Displaces methadone on μ-opioid receptors.**
diazepam	↑	*Effect sporadic, unknown mechanism.*
didanosine (ddI buffered tab)	↓↓	**Decrease in ddI (effect not seen with enteric-coated).**
Diflucan	↑	**CYP3A4 inhibition.** *Case reports requiring dose reduction reported.*
dihydroergotamine	↑	*CYP450 enzyme inhibition.*
Dilantin	↓	**Sharp decrease, CYP3A4 induction.**
Diltia	↑	*Proposed due to CYP450 inhibition.*
diltiazem	↑	*Proposed due to CYP450 inhibition.*
Distraneurin	↓↓	*Enhanced sedative effects.*
disulfiram	↑	*Sedation reported.*
Dizac	↑	*Effect sporadic, unknown mechanism.*
doxepin ♥	↓↓	*Possible increased TCA toxicity; uncertain effect on methadone.*
Duramorph	↓↓	**Common CYP450 pathway; possible additive effects with methadone.**
Dura-Tabs	↑	*Proposed due to CYP450 inhibition.*
E.E.S., Eryped ♥	↑	*Strong CYP3A4 inhibition.*
Echinacea	↑	*Predicted due to CYP450 inhibition.*
Emoquil	↓↓	*Increased sedative effects if abused.*
efavirenz	↓	**Due to CYP3A4/2B6induction, methadone withdrawal common.**
Elavil ♥	↓↓	*Possible increased TCA toxicity; uncertain effect on methadone.*
Erythrocin ♥	↑	*Strong CYP3A4 inhibition.*
erythromycin ♥	↑	*Strong CYP3A4 inhibition.*
Eryzole ♥	↑	*Strong CYP3A4 inhibition.*
estazolam	↓↓	*Potential interaction, additive CNS depression.*
ethanol (acute use)	↑	*Competition for CYP450 enzymes.*
ethanol (chronic use)	↓	*CYP450 enzyme induction.*
fentanyl	↓↓	**Common CYP450 pathway; possible additive effects with methadone.**
Fioricet	↓	*Due to CYP450 enzyme induction.*
Fiorinal	↓	*Due to CYP450 enzyme induction.*
Flagyl	↑	*Proposed due to CYP450 inhibition but unverified.*
fluconazole	↑	**CYP3A4 inhibition.** *Case reports requiring dose reduction reported.*
fluoxetine ♥	↑	*Variable CYP450 enzyme inhibition.*
flurazepam	↓↓	*Potential interaction, additive CNS depression.*
fluvoxamine	↑	**Variable CYP450 enzyme inhibition.**
Fucidin	↓	*CYP450 induction.*
fusidic acid (systemic)	↓	*CYP450 induction.*
Goldenseal	↑	*Predicted due to CYP3A4 inhibition.*
grapefruit	↑	**Inhibition of intestinal CYP3A4 and P-gp.**
Halcion	↓↓	*Potential interaction, additive CNS depression.*
hash	↓↓	*Proposed interaction, common CYP450 pathway.*
hemp	↓↓	*Proposed interaction, common CYP450 pathway.*
Hemineurin	↓↓	*Enhanced sedative effects.*
Heminevrin	↓↓	*Enhanced sedative effects.*
heroin	↓	*Decreases methadone free fraction.*
Hexadrol	↓	*CYP3A4 induction.*
hydrastis canadensis	↑	*Predicted due to CYP3A4 inhibition.*
hydrocodone	↓↓	**Common CYP450 pathway; possible additive effects with methadone.**
Hypericum perforatum	↓	*Significant decrease; CYP3A4 and P-gp induction.*
Ilosone ♥	↑	*Strong CYP3A4 inhibition.*

imipramine ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
Imovane	↓↑	*Potential interaction, additive CNS depression.*
Insomn-eze	↓↑	*Possible increased sedation or methadone effects.*
interferon-alfa + ribavirin	↓↑	*Side effects may mimic opioid withdrawal.*
Isoptin	↑	*Predicted due to CYP450 inhibition.*
Kaletra	↓	**Effect not seen with ritonavir alone.**
ketoconazole ♥	↑	*Predicted due to CYP3A4 inhibition.*
K-Phos	↓	*Proposed due to more rapid urinary excretion.*
lopinavir + ritonavir	↓	**Effect not seen with ritonavir alone.**
Lotusate	↓	*Due to CYP450 enzyme induction.*
Luminal	↓	*Possibly sharp decrease in methadone.*
Luvox	↑	**Variable CYP450 enzyme inhibition.**
macrolide antibiotics	↑	*CYP3A4 inhibition (not azithromycin).*
Manerix	↑	*Possible due to CYP450 inhibition.*
MAO (monoamine oxidase) inhibitors	⊘	*Potential adverse interaction.*
Marezine (Marzine)	↓↑	*Increased sedative effects if abused.*
marijuana	↓↑	*Proposed interaction, common CYP450 pathway.*
matricaria recutita	↑	*Predicted due to CYP3A4 inhibition.*
Mebaral	↓	*Due to CYP450 enzyme induction.*
meclizine	↓↑	*Increased sedative effects if abused.*
Mepergan	↓↑	*Possible increased sedation or methadone effects.*
meperidine	↓↑	**Possible opioid additive effects; long-acting toxic metabolites.**
mephobarbital	↓	*Due to CYP450 enzyme induction.*
methylphenidate	↓↑	*Possible CYP450 inhibition.*
metronidazole	↑	*Proposed due to CYP3A4 inhibition but unverified.*
midazolam	↓↑	*Potential interaction, additive CNS depression.*
Migranal	↑	*Possible CYP450 enzyme inhibition.*
moclobemide	↑	*Possible due to CYP450 inhibition.*
morphine	↓↑	**Common CYP450 pathway; possible additive effects with methadone.**
MS Contin	↓↑	**Common CYP450 pathway; possible additive effects with methadone.**
Myidone	↓	*CYP450 induction proposed..*
Mysoline	↓	*CYP450 induction proposed..*
nalbuphine	⊘	**Displaces methadone on μ-opioid receptors.**
nalmefene	⊘	**Displaces methadone on μ-opioid receptors.**
naloxone	⊘	**Displaces methadone on μ-opioid receptors.**
naltrexone	⊘	**Displaces methadone on μ-opioid receptors.**
Narcan	⊘	**Displaces methadone on μ-opioid receptors.**
Nardil	↓↑	*Potential adverse interaction.*
nefazodone	↑	*Variable CYP450 enzyme inhibition.*
nelfinavir	↓	**Possible decrease also in nelfinavir; methadone increase rarely needed.**
Nembutal	↓	*Due to CYP450 enzyme induction.*
nevirapine	↓	**Frequent opioid withdrawal syndrome.**
nifedipine	↓↑	*Nifedipine increase proposed.*
Nizoral ♥	↑	*Predicted due to CYP450 inhibition.*
Noctec	↓↑	*Additive effects, possibly fatal.*
Norpramin ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
nortriptyline ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
Nubain	⊘	**Displaces methadone on μ-opioid receptors.**

omeprazole	↑	*Possibly affects methadone absorption.*
opioid analgesics	↓↑	**Common CYP450 pathway; possible additive effects with methadone.**
oxycodone	↓↑	**Common CYP450 pathway; possible additive effects with methadone.**
OxyContin	↓↑	**Common CYP450 pathway; possible additive effects with methadone.**
Pamelor ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
Parnate	↓↑	*Potential adverse interaction.*
paroxetine ♥	↑	*Variable CYP450 enzyme inhibition.*
Paxil ♥	↑	*Variable CYP450 enzyme inhibition.*
Pegasys	↓↑	*Side effects may mimic opioid withdrawal.*
pegylated interferon	↓↑	*Side effects may mimic opioid withdrawal.*
pentazocine	⊘	**Displaces methadone on μ-opioid receptors.**
pentobarbital	↓	*Due to CYP450 enzyme induction.*
Phenergan	↓↑	*Possible increased sedation or methadone effects.*
phenobarbital	↓	**CYP450 induction, possibly sharp decrease in methadone.**
phenytoin	↓	**Sharp decrease, CYP3A4 induction.**
Polycitra	↑	**Decreases methadone urinary excretion.**
pot (marijuana)	↓↑	*Proposed interaction, common CYP450 pathway.*
Prevpac ♥	↑	*CYP3A4 inhibition (contains clarithromycin).*
Prilosec	↑	*Possibly affects methadone absorption.*
primidone	↓	*CYP450 induction proposed..*
Procardia	↓↑	*Nifedipine increase proposed.*
promethazine	↓↑	*Possible increased sedation or methadone effects.*
propoxyphene	↓↑	**Possible opioid additive effects; long-acting toxic metabolites.**
ProSom	↓↑	*Potential interaction, additive CNS depression.*
protriptyline ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
Prozac ♥	↑	*Variable CYP450 enzyme inhibition.*
quercetin	↑	*Predicted due to CYP450 inhibition.*
Quinaglute ♥	↑	*Proposed due to CYP450 inhibition.*
quinidine ♥	↑	*Proposed due to CYP450 inhibition.*
Rebetron	↓↑	*Side effects may mimic opioid withdrawal.*
Rescriptor	↑	*Due to CYP450 inhibition.*
Retrovir	↓↑	**AZT concentration and related side effects increased.**
Revex	⊘	**Displaces methadone on μ-opioid receptors.**
ReVia	⊘	**Displaces methadone on μ-opioid receptors.**
ribavirin + interferon-alfa	↓↑	*Side effects may mimic opioid withdrawal.*
Rifadin	↓	**Possibly severe; CYP450 induction.**
Rifamate	↓	**Possibly severe; CYP450 induction (not seen with rifabutin).**
rifampicin	↓	**Possibly severe; CYP450 induction (not seen with rifabutin).**
rifampin	↓	**Possibly severe; CYP450 induction (not seen with rifabutin).**
rifampin/isoniazid	↓	**Possibly severe; CYP450 induction (not seen with rifabutin).**
Rimactane	↓	**Possibly severe; CYP450 induction (not seen with rifabutin).**
Ritalin, Ritalin SR	↓↑	*CYP450 inhibition.*
ritonavir + lopinavir	↓	**Effect not seen with ritonavir alone.**
Robitussin	↓↑	*Increased dextromethorphan effects proposed.*
scat (heroin)	↓	*Decreases methadone free fraction.*
secobarbital	↓	*Due to CYP450 enzyme induction.*
Seconal	↓	*Due to CYP450 enzyme induction.*
sertraline ♥	↑	*Variable CYP450 enzyme inhibition.*
Serzone	↑	*Variable CYP450 enzyme inhibition.*

Sinequan ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
smack (heroin)	↓	*Decreases methadone free fraction.*
sodium bicarbonate	↑	**Decreases methadone urinary excretion.**
Somnote	↓↑	*Additive effects, possibly fatal.*
spironolactone	↓	*Expected CYP450 induction.*
SSRI antidepressants	↑	*Variable CYP450 enzyme inhibition.*
St. John's wort	↓	*Significant decrease; CYP 3A4 and P-gp induction.*
Stadol	⊘	**Displaces methadone on μ-opioid receptors.**
stavudine (d4T)	↓↑	**Decreased d4T concentration (unclear clinical significance).**
Sublimaze	↓↑	**Common CYP450 pathway; possible additive effects with methadone.**
Suboxone	⊘	**Displaces methadone on μ-opioid receptors.**
Subutex	⊘	**Displaces methadone on μ-opioid receptors.**
Surmontil	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
Sustiva	↓	**Due to CYP3A4/2B6 induction, methadone withdrawal common.**
Tagamet	↑	*CYP450 enzyme inhibitor.*
talbutal	↓	*Due to CYP450 enzyme induction.*
Talwin	⊘	**Displaces methadone on μ-opioid receptors.**
TAO	↑	*Expected due to CYP450 inhibition.*
Tegretol	↓	**May cause opioid withdrawal.**
Tiazac	↑	*Proposed due to CYP450 inhibition.*
tobacco	↓	*Possible; reports mixed.*
Tofranil ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
Touro DM	↓↑	*Increased dextromethorphan effects proposed.*
tramadol	⊘	*Potential withdrawal in persons taking opioids.*
Tranxene	↓↑	*Potential interaction, additive CNS depression.*
triazolam	↓↑	*Potential interaction, additive CNS depression.*
tricyclic antidep.(TCAs) ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
trimipramine	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*
Trizivir	↓↑	**AZT concentration increased.**
troleandomycin	↑	*Expected due to CYP450 inhibition.*
Tuinal	↓	*Due to CYP450 enzyme induction.*
Ultram	⊘	*Potential withdrawal in persons taking opioids.*
Ultracet	⊘	*Potential withdrawal in persons taking opioids.*
Uncaria tomentosa	↑	*Predicted due to CYP450 inhibition.*
urinary acidifiers	↓	*Proposed due to more rapid urinary excretion.*
urinary alkalinizers	↑	**Decreases methadone urinary excretion.**
Valium	↑	*Effect sporadic, unknown mechanism.*
Valrelease	↑	*Effect sporadic, unknown mechanism.*
verapamil	↑	*Predicted due to CYP450 inhibition.*
Versed	↓↑	*Potential interaction, additive CNS depression.*
Vicks (cough med)	↓↑	*Increased dextromethorphan effects proposed.*
Vicodin	↓↑	**Common CYP450 pathway; possible additive effects with methadone.**
Videx (ddI buffered tablet)	↓↑	**Decrease in ddI (effect not seen with enteric-coated).**
Viracept	↓	**Possible decrease also in Viracept.**
Viramune	↓	**Frequent opioid withdrawal syndrome.**
vitamin C (very high dose)	↓	*Proposed due to more rapid urinary excretion.*
Vivactil ♥	↓↑	*Possible increased TCA toxicity; uncertain effect on methadone.*

wine, beer, whiskey (acute use)	↑	*Competition for CYP450 enzymes.*
wine, beer, whiskey (chronic use)	↓	*CYP450 enzyme induction.*
Xanax	↑↑	*Potential interaction, additive CNS depression.*
zafirlukast	↑	*Proposed due to CYP450 inhibition.*
Zerit (d4T)	↓↓	**Decreased d4T concentration (unclear clinical significance).**
Ziagen	↓	**Also decreases Ziagen peak concentration**
zidovudine (AZT)	↓↓	**AZT concentration increased and side effects common.**
zileuton	↑	*Proposed due to CYP450 inhibition.*
Zoloft ♥	↑	*Variable CYP450 enzyme inhibition.*
zopiclone	↑↑	*Potential interaction, additive CNS depression.*
Zyflo	↑	*Proposed due to CYP450 inhibition.*

Table 6

Drug Interactions Resources on the Internet

Note: All websites listed below were active on the date access was checked. However, the Internet is a dynamic environment with frequent changes – specific sites may be discontinued or moved without notice.

Disclaimer: *Pain Treatment Topics* does not endorse the contents provided through or referenced on the websites listed here, and does not make any assurances regarding the accuracy of information. Methadone-drug interactions is an ongoing area of scientific inquiry and some of the information provided at these websites may be out of date and/or invalid..

CYP450 Drug Interaction Reference Tables

http://drug-interactions.com

Flockhart D. Cytochrome P450 Drug Interaction Tables: Indiana University School of Medicine. Periodically updated. Access checked 9/6/05.

http://www.urmc.rochester.edu/urmc/AAPCC/tables.html

Cytochrome P450 Reference Tables. Adapted from: Michalets FL. Update: clinically significant cytochrome P-450 drug interactions. Pharmacotherapy. 1998;18(1):84-112. Access checked 9/19/05.

Cardiac Concerns

http://QTdrugs.org

Drugs that Prolong the Qt Interval and/or Induce Torsades de Pointes Ventricular Arrhythmia. Tucson, AZ: University of Arizona Center for Education and Research on Therapeutics (CERT). Periodically updated. Access checked 9/3/05.

http://www.atforum.com/cardiacmmt.shtml

Leavitt SB, Krantz MJ. Cardiac Safety in MMT. Addiction Treatment Forum. Special Report; October 2003. Access checked 9/5/05.

Drug Interactions Associated with HIV/AIDS Therapies

http://www.hivguidelines.org/public_html/sub-ddi/sub-ddi.pdf

Committee for the Care of the HIV-Infected Substance User: New York State Department of Health AIDS Institute. Drug-drug interactions between HAART, medications used in substance use treatment, and recreational drugs. August 2, 2005. Access checked 9/12/05.

http://www.nynjaetc.org/clinician.htm

Woo M, Sullivan L, Chang E, Kubin C. Pain Management/Addiction Management Medications and HIV Antiretrovirals: A Guide to Interactions for Clinicians. New York: New York / New Jersey AIDS Education and Training Center (AETC) at Columbia University; Fall 2004. Access checked 9/14/05.

Table 6 CONTINUED: Drug Interactions Resources on the Internet

http://depts.washington.edu/hivaids/drug/case3/index.html

Kosel BW. Drug-Drug Interactions, Case 3: Antiretrovirals and Methadone. HIV Web Study at University of Washington. Updated June 2004. Access checked 9/15/05.

http://www.medscape.com/viewarticle/461892/

Faragon JJ, Piliero P. Drug interactions associated with HAART: Focus on treatments for addiction and recreational drugs. AIDS Read. 2003;13(9):433-450. Access checked 9/6/05.

http://www.drugabuse.gov/MeetSum/CPHTWorkshop/Gerber.html

Gerber JG. Interactions between methadone and antiretroviral medications. Paper presented at: 3rd International Workshop on Clinical Pharmacology of HIV Therapy [NIDA-sponsored]; April 13, 2002; Washington, DC. Access checked 9/3/05

http://www.medscape.com/viewprogram/301_pnt

Flexner C, Piscitelli SC. Managing drug-drug interactions in HIV disease. Medscape. 2000. Access checked 9/6/05.

General Information About Drug Interactions

http://www.medscape.com/viewarticle/474163

Malone DC, Abarca J, Hansten PD, et al. Identification of serious drug-drug interactions: results of the partnership to prevent drug-drug interactions. J Am Pharm Assoc. 2004;44(2):142-151. Access checked 9/19/05.

http://www.atforum.com/SiteRoot/pages/addiction_resources/DosingandSafetyWP.pdf

Leavitt SB. Methadone dosing and safety in the treatment of opioid addiction. Addiction Treatment Forum. Special Report. 2003. Access checked 9/6/05.

http://www.nasmhpd.org/general_files/publications/med_directors_pubs/Polypharmacy.PDF

Medical Directors Council and State Medicaid Directors. Technical Report on Psychiatric Polypharmacy. Alexandria, VA: National Association of State Mental Health Program Directors (NASMHPD); 2001 (September). Access checked 9/19/05.

http://www.pai-ca.org/PUBS/702001.htm

Morrison L, et al. Psychiatric Polypharmacy: A Word of Caution. Sacramento, CA: Protection & Advocacy, Inc. (PAI); undated. Access checked 9/19/05.

Cited Resources

References

Agenerase® (amprenavir) [product information]. Research Triangle Park, NC: GlaxoSmithKline; **1999**. Available at: http://www.gsk.com/products/agenerase_us.htm.

Alderman CP, Frith PA. Fluvoxamine-methadone interaction. Aust and New Zealand J of Psych. **1999**;33:99-101.

Altice FL, Friedland GH, Cooney E. Nevirapine induced opiate withdrawal among injection drug users with HIV infection receiving methadone. AIDS. **1999**;13:957-962.

Alvares AP, Kappas A. Influence of phenobarbital on the metabolism and analgesic effect of methadone in rats. J Lab Clin Med. **1972**;79:439-451.

Antoniou T, Tseng AL. Interactions between recreational drugs and antiretroviral agents. Ann Pharmacother. **2002**;36:1598-1613.

Bailey DG, Malcolm J, Arnold O, et al. Grapefruit juice-drug interactions. Br J Clin Pharmacol. **1998**;46:101-110.

Barry M, Mulcahy F, Merry C, Gibbons S, Back D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. Clin Pharmacokinet. **1999**;36:289-304.

Bart PA, Rizzardi PG, Gallant S, et al. Methadone blood concentrations are decreased by the administration of abacavir plus amprenavir. Ther Drug Monit. **2001**;23:553-555.

Batki SL, et al. Fluoxetine for cocaine dependence in methadone maintenance: quantitative plasma and urine cocaine benzoylecgonine concentrations. J Clin Psychopharmacol. **1993**;13:243-250.

Bäumler E. A Century of Chemistry. Dusseldorf: Econ Verlag; **1968**.

Beauverie P, et al. Therapeutic drug monitoring of methadone in HIV-infected patients receiving protease inhibitors. AIDS. **1998**;12:2510-2511.

Begré S, von Bardeleben U, Ladewig D, et al. Paroxetine increases steady-state concentrations of (R)-methadone in CYP2D6 extensive but not poor metabolizers. J Clin Psychopharmacol. **2002**;22(2):211-215.

Bending MR, Skacel PO. Rifampin and methadone withdrawal. Lancet. **1977**;1:1211.

Benmebarek M, Devaud C, Gex-Fabry M, et al. Effects of grapefruit juice on the pharmacokinetics of the enantiomers of methadone. Clin Pharmacol Ther. **2004**;76(1):55-63.

Bertschy G, Eap CB, Powell K et al. Fluoxetine addition to methadone addicts: pharmacokinetic aspects. Ther Drug Monit. **1996**;18:570-572.

Bertschy G, et al. Probable metabolic interaction between methadone and fluvoxamine in addict patients. Ther Drug Monit. **1994**;16:42-45.

Bochner F. Drug interactions with methadone: pharmacokinetics. In Hummeniuk R, Ali R, White J, Hall W, Farrell M. Proceeding of Expert Workshop on the Induction and Stabilisation of Patients Onto Methadone. Monograph Series 39. Canberra: Commonwealth of Australia; **2000**: 93-110. Available at: http://www.health.gov.au.

Boffito M, et al. Undefined duration of opiate withdrawal induced by efavirenz in drug users with HIV infection and undergoing chronic methadone treatment. AIDS Res Hum Retro. **2002**;18(5):341-342.

Borg L, Kreek MJ. Clinical problems associated with interactions between methadone pharmacotherapy and medications used in the treatment of HIV-1-positive and AIDS patients. Curr Opin Psychiatry. **1995**;8:199-202.

Borg L, Kreek MJ. The pharmacology of opioids. In Graham AW, et al. (eds). Principles of Addiction Medicine. 3rd ed. Chevy Chase MD: American Society of Addiction Medicine; **2003**: 141-153.

Borowsky SA, Lieber CS. Interaction of methadone and ethanol metabolism. J Pharmacol Exp Ther. **1978**;207:123-129.

Brown FM, Griffiths PS. P450Guide: Comprehensive Enzymatic Drug Metabolism Reference. 2nd Ed. Montgomery, AL: P450Guide; **2000**.

Brown LS, Chu M, Aug C, Dabo S. The use of nelfinavir and two nucleosides concomitantly with methadone is effective and well-tolerated in HepC co-infected patients (abstract I-206). Presented at: 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, December 16–19, **2001**:311.

Brown LS, Sawyer RC, Li R, et al. Lack of pharmacologic interactions between rifabutin and methadone in HIV-infected former injection drug users. Drug Alcohol Depend. **1996**;43:71-77.

Chen KK. Pharmacology of methadone and related compounds. Annals NY Acad Sci. **1948**.

Chrisman CR. Protease inhibitor-drug interactions: proceed with caution. J Critical Illness. **2003**;18(4):185-188.

Chung EP. A review of clinically significant drug interactions. California Pharmacist. **2002** (Summer):56-65.

Clarke S, Mulcahy F, Bergin C, Reynolds H, Boyle N, Barry MG, et al. Absence of opioid withdrawal symptoms in patients receiving methadone and the protease inhibitor lopinavir–ritonavir. Clin Infect Dis **2002**;34: 1143-1145.

Clarke SM, Mulcahy FM, Tija J. The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase inhibitor efavirenz. Br J Clin Pharmacol. **2000**;51:213-217.

Clarke SM, Mulcahy FM, Tjia J, Reynolds HE, Gibbons SE, Barry MG, et al. The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase inhibitor efavirenz. Br J Clin Pharmacol. **2001a**;51:213-217.

Clarke SM, Mulcahy FM, Tjia J, Reynolds HE, Gibbons SE, Barry MG, et al. Pharmacokinetic interactions of nevirapine and methadone and guidelines for use of nevirapine to treat injection drug users. Clin Infect Dis. **2001**;33:1595-1597.

Cobb M, Desai J, Brown LS, et al. The effect of fluconazole on the clinical pharmacokinetics of methadone. Clin Pharmacol Ther. **1998**;45:921-925.

Cohen JS. Preventing adverse drug reactions before they occur. Medscape Pharmacotherapy [online serial]. **1999**. Available at http://www.medscape.com/viewarticle/408588

Crettol S, Deglon J-J, Besson J, et al. Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. Clin Pharmacol Ther. **2005**, in press.

Dawson GW, Vestal RE. Cimetidine inhibits the in vitro N-demethylation of methadone. Res Commun Chem Pathol Pharmacol. **1984**;46:301-304.

deCastro J, et al. The effect of changes in gastric pH induced by omeprazole on the absorption and respiratory depression of methadone. Biopharm Drug Dispos. **1996**;17(7):551-563.

DeMaria Jr PA. Methadone drug interactions. J Maint Addictions. **2003**;2(3):69-74.

DeMaria PA, Jr., Serota RD. A therapeutic use of the methadone fluvoxamine drug interaction. J Addict Dis. **1999**;18:5-12.

Dole VP. Implications of methadone maintenance for theories of narcotic addiction. JAMA. **1988**;260:3025-3029.

Dresser GK, Spence DJ, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet. **2000**;38(1):41-57.

Eagling VA, Profit L, Back DJ. The effect of grapefruit juice constituents on the CYP3A4-mediated metabolism and P-glycoprotein-mediated transport of saquinavir. Br J Clin Pharmacol. **1999**;47:593P.

Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet. **2002**;41(14):1153-1193.

Eap CB, et al. Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. J Clin Psychopharmacol. **1997**;17:113-117.

Ehrhart G, Ruschig H. Arzneimittel entwicklung wirkung darstellung, band 1, therapeutica mit wirkung auf das zentral nervensystem. Weinheim: Verlag Chemie; **1972**.

Ehrhart G. Some new analgesics and antispasmodics. ODC Bulletin on Narcotics (United Nations Office on Drugs and Crime). **1956**;1:28-32. Available at: http://www.unodc.org.

Eich-Höchli D, Oppliger R, Golay KP, Baumann P, Eap CB. Methadone maintenance treatment and St. John's wort. Pharmacopsychiatry. **2003**;36:35-37.

Eichler O, Farah A. Handbuch Der Experimentellen Pharmakologie. Berlin: Springer-Verlag; **1957**.

Ernst E, et al. Methadone-related deaths in Western Australia, 1993-1999. Australian and New Zealand Journal of Public Health. **2002**;26:364-370.

Faragon JJ, Piliero P. Drug interactions associated with HAART: Focus on treatments for addiction and recreational drugs. AIDS Read. **2003**;13(9):433-450. Available at: http://www.medscape.com/viewarticle/461892/.

Farrell VM, Hill VL, Hawkins JB, Newman LM, Learned RE. Clinic for identifying and addressing polypharmacy. Am J Health-Syst Pharm. **2003**;60(18):1830-1835.

Faucette SR, Wang H, Hamilton GA, et al. Regulation of CYP2B6 in primary human hepatocytes by prototypical inducers. Drug Metab Disp. **2004**;32(3):348-358.

FDA/CDER (Center for Drug Evaluation and Research). Drug Interactions: What You Should Know. Undated. Available at: http://www.fda.gov/cder/consumerinfo/druginteractions.htm.

Finelli PF. Phenytoin and methadone tolerance (letter). New Engl J Med. **1976**;294:227.

Flexner C, Piscitelli SC. Managing drug-drug interactions in HIV disease. Medscape. **2000.** Available at: http://www.medscape.com/viewprogram/301_pnt,

Flockhart D. Cytochrome P450 drug interaction table: Indiana University School of Medicine. Available at: http://drug-interactions.com. Updated June 14, **2005**.

Foster DI, Somogyi AA, Bochner F, et al. Methadone N-demethylation in human liver microsomes: lack of stereoselectivity and involvement of CYP3A4. Brit J Clin Pharmacol. **1999**;47:403-412.

Friedland G, Rainey P, Jatlow P, Andrews L, Damle B, McCance-Katz E. Pharmacokinetics (pK) of didanosine (ddI) from encapsulated enteric coated bead formulation (EC) vs chewable tablet formulation in patients (pts) on chronic methadone therapy (abstract TuPeB4548). Presented at: XIV International AIDS Conference, Barcelona, July 7–12, **2002**, vol 1:402-3.

Geletko SM, Erickson AD. Decreased methadone effect after ritonavir initiation. Pharmacotherapy. **2000**;20:93-94.

Gerber JG, Rhodes RJ, Gal J. Stereoselective metabolism of methadone N-demethylation by cytochrome P4502B6 and 2C19. Chirality. **2004**;16(1):36-44.

Gerber JG, Rosenkranz S, Segal Y, Aberg J, D'Amico R, Mildvan D, et al. The effect of ritonavir/saquinavir on the stereoselective pharmacokinetics of methadone: results of AIDS clinical trials group (ACTG) 401. J Acq Immune Def Synd. **2001**;27:153-160.

Gerber JG. Interactions between methadone and antiretroviral medications. Paper presented at: 3rd International Workshop on Clinical Pharmacology of HIV Therapy [NIDA-sponsored]; April 13, **2002**; Washington, DC. Available at: http://www.drugabuse.gov/MeetSum/CPHTWorkshop/Gerber.html.

Gourevitch MN, Friedland GF. Interactions between methadone and medications used to treat HIV infection: a review. Mt Sinai J Med. **2000**;67(5-6):429-436.

Gourevitch MN, Hartel D, Tenore P, et al. Three oral formulations of methadone. A clinical and pharmacodynamic comparison. J Subst Abuse Treat. **1999**;17(3):237-241.

Gourevitch MN. Interactions between HIV-related medications and methadone: an overview. Mt Sinai J Med. **2001**;68(3):227-228.

Gram LF, et al. Moclobemide, a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6, and CYP1A2 - A panel study. Clin Pharmacol Ther. **1995**;57:670-677.

Hall SD, Thummel KE, Watkins PB. Molecular and physical mechanisms of first-pass extraction. Drug Metab Disp. **1999**;27(2):161-166.

Hamilton SP, et al. The effect of sertraline on methadone plasma levels in methadone maintenance patients. Am J Addict. **2000**;9:63-69.

Hamilton SP, Klimchek C, Nunes EV. Treatment of depressed methadone maintenance patients with nefazodone. A case series. Am J Addictions. **1988**;7:309-312.

Hansten PD. Drug Interactions. In: Applied Therapeutics: The Clinical Use of Drugs. (Koda-Kimble MA, et al.eds.) Vancouver: Applied Therapeutics, Inc.; **1995**:1-3.

Harding-Pink D. Opioid toxicity. Lancet. **1993**;341:665-666.

Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG (eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill; **1996**:3-63.

Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and γ-hydroxybutyrate. Arch Intern Med. **1999**;159:2221-2224.

Heelon MW, Meade LB. Methadone withdrawal when starting an antiretroviral regimen including nevirapine. Pharmacotherapy. **1999**;19:471-472.

Hendrix C, Wakeford J, Wire MB, Bigelow G, Cornell E, Christopher J, et al. Pharmacokinetic and pharmacodynamic evaluation of methadone enantiomers following co-administration with amprenavir in opioid-dependent subjects (abstract 1649). Presented at: 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, September 17–20, **2000**:335.

Hendrix CW, Wakeford J, Wire MB, et al. Pharmacokinetics and pharmacodynamics of methadone enantiomers after coadministration with amprenavir in opioid-dependent subjects. Pharmacotherapy. **2004**;24(9):1110-1121.

Herrlin K, Segerdahl M, Gustafsson LL, Kalso E. Methadone, ciprofloxacin, and adverse drug reactions [letter]. Lancet. **2000**;356(9247).

Holmes V. Rifampin induced methadone withdrawal in AIDS (letter). J Clin Psychopharm. **1990**;10(6):443-444.

Hsu A, et al. Ritonavir does not increase methadone exposure in healthy volunteers. Proceeding of the 5th conference on retroviruses and opportunistic infections, Chicago, **1998**. Abstract 342

Hsyu PH, Lillibridge JH, Maroldo L, Weiss WR, Kerr BM. Pharmacokinetic (PK) and pharmacodynamic (PD) interactions between nelfinavir and methadone (abstract 87). Presented at: 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, **2000**.

Iribarne C, Dreano Y, Bardou LG, et al. Interaction of methadone with substrates of human hepatic cytochrome P450 3A4. Toxicology. **1997**;117:13-23.

Iribarne C, Dreano Y, Bardou LG, et al. Involvement of cytochrome P450 3A4 enzyme in the N-demethylation of methadone in human liver microsomes. Chem Res Toxicol. **1996**;9:365-373.

Joseph H, Appel P. Historical perspectives and public health issues. In: Parrino MW, chair. State Methadone Treatment Guidelines. Treatment Improvement Protocol (TIP) Series 1. Rockville, MD: U.S. Department of Health and Human Services; Center for Substance Abuse Treatment;**1993**:11-24 DHHS Pub# (SMA) 93-1991.

Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): a review of historical and clinical issues. Mt Sinai J Med. **2000**;67(5-6):347-364.

Kalvik A, Isaac P, Janecek E. Help for heroin dependence: what pharmacists need to know about methadone maintenance therapy. Pharmacy Practice. **1996**;12(10):43-54.

Karlix J. Pharmacists Corner [untitled discussion on fruit juice and medication levels in blood serum]. Prescription Plus. Ronkonkoma, NY: Lifecare Pharmaceuticals Services; **1990**:15.

Kharasch ED, Hoffer C, Whittington D, Sheffels P. Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. Clin Pharmacol Ther. **2004a**;76(3):250-269.

Kharasch ED, Hoffer C, Whittington D. The effect of quinidine, used as a probe for the involvement of P-glycoprotein, on the intestinal absorption and pharmacodynamics of methadone. Br J Clin Pharmacol. **2004b**;57(5):600-610.

Kharasch ED, Hoffer C. Assessment of ritonavir effects on hepatic and first-pass CYP3A activity and methadone disposition using noninvasive pupillometry. Clin Pharmacol Ther. 2004;75:P96.

Kramer TAM. Polypharmacy. Medscape Mental Health. **2000**;5(3). Available at: http://www.medscape.com.

Kreek MJ. A personal retrospective and prospective viewpoint. In: Parrino MW. State Methadone Treatment Guidelines. Treatment Improvement Protocol (TIP) Series 1. Rockville, MD: U.S. Department of Health and Human Services; Center for Substance Abuse Treatment;**1993**:133-143. DHHS Pub# (SMA) 93-1991.

Kreek MJ, Garfield JW, Gutiahr CL, et al. Rifampin-induced methadone withdrawal. N Engl J Med. **1976**;294:1104-1106.

Kreek MJ. Drug interactijons with methadone in humans. In: Braude MC, Ginzburg HM (eds). Strategies for Research on the Interactions of Drugs of Abuse. NIDA Research Monograph 68. **1986**:193-225.

Kreek MJ. Medical safety and side effects of methadone in tolerant individuals. JAMA. **1973**;223:665-668.

Kreek MJ. Metabolic interactions between opiates and alcohol. Ann N Y Acad Sci. **1976**;281:36-49.

Kreek MJ. Opioid interactions with alcohol. Advances in alcohol and substance abuse. New York, NY: The Haworth Press; **1984**.

Krook AL, Waal H, Hansteen V. Routine ECG in methadone-assisted rehabilitation is wrong prioritization [Article in Norwegian, English abstract]. Tidsskr Nor Laegeforen. **2004**;124(22):2940-2941.

Kuhn KL, Halikas JA, Jemp KD. Carbamazepine treatment of cocaine dependence in methadone maintenance patients with dual opiate-cocaine dependence. In Harris LS (ed). Problems of Drug Dependence. NIDA Res Mon 95. Rockville, MD: NIDA; **1989**.

Leavitt SB, Krantz MJ. Cardiac Considerations During MMT. AT Forum (special report). October **2003**. Available at: http://www.atforum.com/SiteRoot/pages/addiction_resources/CardiacPaper.pdf.

Leavitt SB, Shinderman M, Maxwell S, Eap CB, Paris P. When 'enough' is not enough: new perspectives on optimal methadone maintenance dose. Mt Sinai J Med. **2000**;67(5-6):404-411.

Leavitt SB. AD/HD: A common problem during MMT? Addiction Treatment Forum. **2005**(Summer);14(3). Available at: http://www.atforum.com/SiteRoot/pages/current_pastissues/summer2005.html#adhd.

Leavitt SB. Methadone dosing and safety in the treatment of opioid addiction. Addiction Treatment Forum. Special Report. **2003**. Available at: http://www.atforum.com/SiteRoot/pages/addiction_resources/DosingandSafetyWP.pdf.

Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum M (eds). Metabolic Drug Interactions. Philadelphia, PA: Lippincott Williams & Wilkins; **2000**.

Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum M, eds. Metabolic Drug Interactions. Philadelphia, PA: Lippincott Williams & Wilkins; **2000**.

Liu SJ, Wang RI. Case report of barbiturate-induced enhancement of methadone metabolism and withdrawal syndrome. Am J Psychiatry. **1984**;141:1287-1288.

Maany I, et al. Increase in desipramine serum levels associated with methadone treatment. Am J Psychiatry. **1989**;146:1611-1613.

Maremmani I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A. QTc Interval Prolongation in Patients on Long-Term Methadone Maintenance Therapy. Eur Addict Res. **2005**;11(1):44-49.

Maroldo L, Manocchio S, Artenstein A, Weiss W. Lack of effect of nelfinavir mesylate on maintenance methadone dose requirement (abstract WePeB4120). Presented at: XIII International AIDS Conference, Durban, South Africa, July 9–14, **2000**:60.

Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Am J Cardiol. **2005**;95(7):915-918.

Marzolini C, Troillet N, Telenti A et al. Efavirenz decreases methadone blood concentrations. AIDS. **2000**;14:129-132.

Matheny CJ, Lamb MW, Brouwer KLR, Pollack GM. Pharmacokinetic and pharmacodynamic implications of P-glycoprotein modulation. Pharmacotherapy. **2001**;21(7):778-796.

McCance-Katz EF, Gourevitch MN, Arnsten J, et al. Modified directly observed therapy (MDOT) for injection drug users with HIV disease. Am J Addict. **2002**;11(4):271-278.

McCance-Katz EF, Jatlow P, Rainey P, Friedland G. Methadone effects on zidovudine (AZT) disposition (ACTG 262). J Acquir Immune Defic Syndr. **1998**;18:435-443.

McCance-Katz EF, Rainey PM, et al. Effect of opioid dependence pharmacotherapies on zidovudine disposition. Am J Addict. **2001**;10:296-307.

McCance-Katz EF, Rainey PM, Friedland G, Jatlow P. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. CID. **2003**;37(4):476-482.

McCance-Katz EF, Rainey PM, Smith P, et al. Drug interactions between opioid and antiretroviral medications: Interaction between methadone, LAAM, and nelfinavir. Am J Addictions. **2004**;13:163-180.

McCance-Katz EF, Rainey PM, Smith P, et al. Drug interactions between opioid and antiretroviral medications: Interaction between methadone, LAAM, and delavirdine. Am J Addictions. **2005**, in press.

McCann MJ, Rawson RA, Obert JL, Hasson AJ. The treatment of Opiate Addiction with Methadone. Technical Assistance Publication (TAP) 7. Rockville, MD: Center for Substance Abuse Treatment; **1994**. Publication (SMA) 94-2061.

Methadose® Oral Concentrate [package insert]. St. Louis, MO: Mallinckrodt Inc; **2000**.

Michalets FL. Update: clinically significant cytochrome P-450 drug interactions. Pharmacotherapy. **1998**;18(1):84-112.

Moolchan ET, Umbricht A, Epstein D. Therapeutic drug monitoring in methadone maintenance: choosing a matrix. J Addict Dis. **2001**;20(2):55-73.

Munsiff AV, Patel J. Regimens with once daily ritonavir + Fortovase are highly effective in PI-experienced HIV-HCV co-infected patients on methadone (abstract 684). Presented at: 39th Annual Meeting of the Infectious Diseases Society of America, San Francisco, October 25–28, **2001**.

Nadelman E, McNeely J. Doing methadone right. The Public Interest. **1996**;123:83-93.

NCPIE (National Council on Patient Information and Education). Be MedWise®. **2003**. Available at: http://www.bemedwise.org/

Nillson MI, et al. Effect of urinary pH on the disposition of methadone in man. Eur J Clin Pharm. **1982**;22:337-342.

Novick DM, Richman BL, Friedman JM, et al. The medical status of methadone maintained patients in treatment for 11-18 years. Drug Alcohol Dep. **1993**;33:235-245.

Otero MJ, Fuertes A, Sanchez R, Luna G. Nevirapine-induced withdrawal symptoms in HIV patients on methadone maintenance programme: an alert. AIDS. **1999**;13:1004-1005.

Parrino MW. Overview: current treatment realities and future trends. In: Parrino MW. State Methadone Treatment Guidelines. Treatment Improvement Protocol (TIP) Series 1. Rockville, MD: U.S. Department of Health and Human Services; Center for Substance Abuse Treatment;**1993**:1-9. DHHS Pub# (SMA) 93-1991.

Payte JT, Zweben JE, Martin J. Opioid maintenance treatment. In: Graham AW, Schultz TK, Mayo-Smith MF, Ries RK, Wilford BB (eds). Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine; **2003**: 751-766.

Payte JT. A brief history of methadone in the treatment of opioid dependence: A personal perspective. J Psychoactive Drugs. **1991**;23:103-107.

Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. Pharmacoepidemiol Drug Saf. June **2005** [Epub ahead of print].

Phenergan® [package insert] Philadelphia, PA: Wyeth Pharmaceuticals; **2005**.

Physeptone® (methadone HCl). The Physeptone File [product information]. Essex, UK: Martindale Pharmaceuticals; **2000**.

Piguet V, Desmeules J, Ehret G, Stoller R, Dayer P. QT interval prolongation in patients on methadone with concomitant drugs [letter]. J Clin Psychopharmacology. **2004**[Aug];24(4):446-448.

Pinzanni V, Faucherre V, Peyiere H, et al. Methadone withdrawal symptoms with nevirapine and efavirenz. Ann Pharmacother. **2000**;34:405-407.

Piscitelli SC, Rodvold KA (eds). Drug Interactions in Infectious Diseases. Totowa, NJ: Humana Press; **2001**.

Plummer JL, et al. Estimation of methadone clearance: application in the management of cancer pain. Pain. **1988**; 33:313-322.

Pond SM, Tong TG, Benowitz NL, et al. Lack of effect of diazepam on methadone metabolism in methadone-maintained addicts. Clin Pharmacother. **1982**;31:139-143.

Preston A. The Methadone Briefing. Section 1: The history of methadone and methadone prescribing. Online edition, **2003**. Access checked January 2003. Available at: http://www.exchangesupplies.org/ publications/methadone_briefing/section1.html.

Preston KL, et al. Diazepam and methadone blood levels following concurrent administration of diazepam and methadone. Drug and Alcohol Dependence. **1986**; 18:195-202.

Preston KL, et al. Diazepam and methadone interactions in methadone maintenance. Clin Pharmacol Ther. **1984**;36:534-541.

Quinn DI, Wodak A, Day RO. Pharmacokinetic and pharmacodynamic principles of illicit drug use and treatment of illicit drug users. Clin Pharmacokinet. **1997**;33(5):344-400.

Rainey PM, Friedland G, McCance-Katz EF, et al. Interaction of methadone with didanosine and stavudine. J Acquir Immune Defic Syndr. **2000**;24(3):241-248.

Rainey PM, Friedland G, Snidow JW, et al. The pharmacokinetics of methadone following co-administration with a lamivudine/zidovudine combination tablet in opiate dependent subjects (NZTA4003). Am J Addictions. **2002**;11(1):66-74.

Reimann G, et al. Effect of fusidic acid on the hepatic cytochrome P450 enzyme system. Int J Clin Pharmacol Ther. **1999**;37:562-566.

Rescriptor® (delavirdine) [product information]. New York: Pfizer; **2001**. Available at: http:www.rescriptor.com.

Retrovir® (zidovudine) [product information]. Research Triangle Park, NC: GlaxoSmithKline, **2001**. Available at: http://www.retrovir.com.

Rettig RA, Yarmolonsky A (eds). Federal Regulation of Methadone Treatment. Committee on Federal Regulation of Methadone Treatment; Division of Biobehavioral Sciences and Mental Disorders; Institute of Medicine (IOM). Washington, DC: National Academy Press; **1995**.

Richelson E. Pharmacokinetic drug interactions of new antidepressants: a review of the effects on metabolism of other drugs. Mayo Clin Proc. **1997**;72:835-847.

Rotger M, Colombo S, Furrer H, et al. Swiss HIV Cohort Study. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenetics & Genomics. **2005**;15(1):1-5.

Saxon AJ, Whittaker S, Hawker CS. Valproic acid, unlike other anticonvulsants, has no effect on methadone metabolism: 2 cases. J Clin Psychaitry. **1989**;50:228-229.

Saxon AJ, Wittaker S, Hawker SC. Valproic acid, unlike other anticonvulsants, has no effect on methadone maintenance: two cases. J Clin Psychiatry. **1989**;50:228-229.

Schafer M. Psychiatric patients, methadone patients, and earlier drug users can be treated for HCV when given adequate support services. Presentation at: Digestive Disease Week, May 20-23, **2001**; Atlanta, Georgia.

Schütz M. Quick reference guide to antiretrovirals. Medscape HIV/AIDS [online]. June 1, **2002**.

Schwartz EL, Brechbuhl AB, Kahl P, Miller MA, Selwyn PA, Friedland GH. Pharmacokinetic interactions of zidovudine and methadone in intravenous drug–using patients with HIV infection. J Acquir Immune Def Syndr. **1992**;5:619-626.

Scott GN, Elmer GW. Update on natural product-drug interactions. Am J Health Syst Pharm. **2002**;59(4):339-347.

Sellers E, Lam R, McDowell J, Corrigan B, Hedayetullah N, Somer G, et al. The pharmacokinetics of abacavir and methadone following coadministration: CNAA1012 (abstract 663). Presented at: 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 26–28, **1999**:25.

Shannon M. Drug-drug interactions and the cytochrome P450 system: an update. Ped Emergency Care. **1997**;13(5):350-353.

Shelton MJ, Cloen D, Berenson C, Esch A, Brewer J, Hewitt R. Pharmacokinetics (PK) of once daily (QD) saquinavir/ritonavir (SQV/RTV): effects on unbound methadone and α-acid glycoprotein (AAG) (abstract A-492). Presented at: 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, December 16–19, **2001**:14.

Shelton MJ, Cloen D, DiFrancesco R, et al. The effects of once-daily saquinavir/minidose ritonavir on the pharmacokinetics of methadone. J Clin Pharmacol. **2004**;44(3):293-304.

Shinderman M, Maxwell S, Brawand-Amey M, Powell Golay K, Baumann P, Eap CB. Cytochrome P4503A4 metabolic activity, methadone blood concentrations, and methadone doses. Drug Alcohol Depend. **2003**;69;205-211.

Sorkin EM, Ogawa GS. Cimetidine potentiation of narcotic action. Drug Intell Clin Pharm. **1983**;17:60.

Staszewski S, Haberl A, Gute P, Nisius G, Miller V, Carlebach A. Nevirapine/didanosine/lamivudine once daily in HIV-1 infected intravenous drug users. Antiviral Ther. **1998**;3:55-56.

Stevens RC, Papaport S, Maroldo-Connelly L, Patterson JB, Bertz R. Lack of methadone dose alterations or withdrawal symptoms during therapy with lopinavir/ritonavir. J Acquir Immune Defic Syndr. **2003**;33(5):650-651.

Strang J (chair). Drug Misuse and Dependence - Guidelines on Clinical Management. The Scottish Office Department of Health. Welsh Office and the Department of Health and Social Services: Norwich, UK; **1999**. Available at: http://www.doh.gov.uk/drugdep.htm.

Sylvestre DL. Treating hepatitis C in methadone maintenance patients: an interval analysis. Drug Alcohol Dep. **2002**;67(2):117-123.

Tacke U, Wolff K, Finch E, Strang J. The effect of tobacco smoking on subjective symptoms of inadequacy ("not holding") of methadone dose among opiate addicts in methadone maintenance treatment. Addict Biol. **2001**;6(2):137-145.

Tamuri Y, Pereira J, Watanabe S. Methadone and fluconazole: respiratory depression by drug interaction. J Pain Symptom Manage. **2002**;23(2):148-153.

Tashima K, Bose T, Gormley J, et al. The potential impact of efavirenz on methadone maintenance. Ninth European Congress on Clinical Microbiology and Infectious Diseases. Berlin, Germany; March 21-24, **1999**. Abstract No. P0552.

Thurau K, Goerke R, Vogt S, Perdekamp MG, Weinmann W. Mixed fatal poisoning caused by taking L-methadone and chloral hydrate [German]. Arch Kriminol. **2003**;21(3-4):90-97.

Tong TG, Benowitz NL, Kreek MJ. Methadone:disulfiram interaction during methadone maintenance. J Clin Pharmacol. **1980**;10:506-513.

Tong TG, Pond SM, Kreek MJ, et al. Phenytoin induced methadone withdrawal. Ann Intern Med. **1981**;94:349-351.

Totah R, Roberts T, Sheffels P, et al. Determination of CYP2B6 protein expression levels in human liver microsomes and its potential role in methadone metabolism. Drug Metab Rev. **2004**;36(Suppl 1):73.

Trepnell CV, Klecker RW, et al. Glucuronidation of 3'-azido-3'-deoxythymidine (zidovudine) by human liver microsomes: relevance to clinical pharmacokinetic interactions with atovaquone, fluconazole, methadone, and valproic acid. Antimicrob Agents Chemother. **1998**;142(7):1592-1596.

Ultram® [tramadol HCL package insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; **1998**.

Van Beusekom I, Iguchi MY. A Review of Recent Advances in Knowledge About Methadone Maintenance Treatment. Cambridge, UK: Rand Europe; **2001**. Available at: http://www.rand.org/publications/MR/MR1396/.

Velten E. Myths about methadone. NAMA Eduction Series, Number 3. **1992**.

Venkatakrishnan K, et al. Five distinct human cytochromes mediate amitriptyline N-demethylation in vitro: dominance of CYP2C19 and 3A4. J Clin Pharmacol. **1998**;38:112-121.

Viracept® (nelfinavir) [product information]. Agouron Pharmaceuticals, **2000**. Available at: http://www.viracept.com/.

Vlessides M. Methadone continues return to favor for pain treatment. Anesthesiology News. **2005**(May).

Wang JS, Ruan Y, Taylor RM, Donovan JL, Markowitz JS, DeVane CL. Brain penetration of methadone (R)- and (S)-enantiomers is greatly increased by P-glycoprotein deficiency in the blood-brain barrier of Abcb1a gene knockout mice. Psychopharmacology. **2004**;173(1-2):132-138.

Wilkinson GR. Drug metabolism and variability among patients in drug response. NEJM. **2005**;352(21):2211-2221.

Wolff K, Rostami-Hodjegan A, Hay AWM, Raistrick D, Tucker G. Population-based pharmacokinetic approach for methadone monitoring of opiate addicts: potential clinical utility. Addicion. **2000**;95(12):1771-1783.

Woosley RL. Drugs that prolong the QT interval and/or induce torsades de pointes. Updated May 24, **2003**. University of Arizona Center for Education and Research on Therapeutics (CERT). Available at: http: www.QTDrugs.org.

Wu D, Otton SV, Sproule BA, et al. Inhibition of human cytochrome P450 2D6 (CYP2D6) by methadone. Br J Clin Pharmacol. **1993**;35(1):30-34.

Ziagen® (abacavir) [product information]. Research Triangle Park, NC: GlaxoSmithKline, **2002**. Available at: http://www.gsk.com/products/ziagen_us.htm.

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