PALLIATIVE CARE SECTION

Original Research Article

Actual and Potential Drug Interactions Associated with Methadone

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ABSTRACT

Objective. To identify and characterize methadone-related drug interactions, as well as factors accounting for the variability in manifesting these interactions clinically.

Design. Systematic review of the primary literature.

Methods. Over 200 articles, reports of clinical trials, and case reports were reviewed. Studies and case reports were included if they revealed either quantitative or qualitative methods to identify, evaluate severity of, or compare methadone-related drug interactions.

Results of Data Synthesis. The evidence base associated with methadone drug interactions is underdeveloped in general, as the majority of references found were case reports or case series. Most of the studies and reports focused on inpatients receiving methadone maintenance treatment (MMT) that were between 20 and 60 years of age, taking 200 mg/day of methadone or less. Evidence supporting the involvement of lesser known cytochrome P450 enzymes such as 2B6 is emerging, which may partially explain the inconsistencies previously found in studies looking specifically at 3A4 in vitro and in vivo. Genetic variability may play a role in the pharmacokinetics and pharmacodynamics of many medications, including methadone.

Conclusions. Drug interactions associated with methadone and their clinical significance are still poorly understood in general. Many tertiary drug information references and review articles report interactions associated with methadone in a general sense, much of which is theoretical and not verified by case reports, much less well-designed clinical trials. The majority of drug interaction reports that do exist were performed in the MMT population, which may differ significantly from chronic pain or cancer pain populations.

Key Words. Methadone; Drug Interactions; Pain; Systematic Review; Cytochrome P450

Introduction

The use of methadone for pain management and maintenance of opioid withdrawal has been well established. Although morphine remains the “gold standard” by which other opioid analgesics are compared for analgesia, methadone is gaining a wider acceptance in both the chronic pain and palliative care settings as a unique, cost-effective alternative. Methadone is a synthetic opioid structurally dissimilar to morphine with a unique pharmacokinetic and pharmacodynamic profile. Several characteristics make methadone a valuable therapeutic agent and attractive drug. However, some of these same characteristics can make standardized use of methadone difficult, particularly in pain management [1]. Barriers to the widespread use of methadone include large inter-
individual variability in methadone pharmacokinetics, lack of reliable equianalgesic conversion ratio to and from other opioids, and the potential for multiple drug interactions [2].

The purpose of this article is to review the drug interactions found to be associated with methadone, as well as the pharmacokinetics and pharmacodynamics associated with them. This will allow the reader to interpret actual and potential interactions that exist between methadone and other medications.

Methods

This article is based on a systematic review of the literature on potential and actual drug interactions that involve methadone. This was done by conducting a search of the MEDLINE database for relevant articles published from January 1966 through October 2005 using the key words “methadone” and “drug interactions.” This yielded a total of 81 references. Additional relevant literature was found by following the reference citations from retrieved articles and by hand searching articles that each of the authors have in their personal libraries.

Two authors (D.J.W. and K.T.B.) reviewed over 200 articles, reports of clinical trials, and case reports. These resources included data regarding in vitro and in vivo drug interactions, including both animal and human studies, published in English language. Studies and case reports were included if they revealed either quantitative or qualitative methods to identify, evaluate severity of, or compare methadone-related drug interactions; 101 articles directly examining methadone drug interactions were selected for inclusion in this review. The quantitative and qualitative methods contained in the articles were then examined and grouped for likeness based on several key characteristics: study design, medication(s) studied with methadone, and population studied. After grouping the methods according to these characteristics, two distinct general approaches for assessing methadone-related drug interactions were identified: pharmacokinetic mechanisms of drug interactions and pharmacodynamic mechanisms of drug interactions. For the purposes of classifying the studies analyzed in this review, pharmacodynamic studies were considered to be those in which the outcomes of a study monitor for physiological change, as opposed to pharmacokinetic studies that focus on metabolism and excretion of the target drug. Additionally, previously published reviews and textbook articles were cross-checked for consistency of findings. Posters and published abstracts were omitted from the review. This review summarizes the findings of the literature identified.

Mechanisms of Drug Interactions with Methadone

A drug interaction is defined as “the possibility that one drug may alter the intensity of pharmacological effects of another drug given concurrently” [3,4]. Drug interactions can either predominantly affect the pharmacokinetics or pharmacodynamics of the drug. Pharmacokinetic interactions are those in which one drug affects the disposition of another [4], and most important pharmacokinetic drug interactions occur at the level of drug metabolism or protein binding. Pharmacodynamic interactions occur at the site of action, such as a receptor [4], and may or may not elicit a physiological change. It is important to remember that although many drug interactions are possible with methadone, the significance in any given patient may or may not be clinically important [2,5]. Overall, drug interactions may be agent or dose specific and can vary considerably between individuals. Table 1 highlights some of the difficulties with interpreting drug interaction data.

<table>
<thead>
<tr>
<th>Table 1 Factors influencing drug interactions [4]</th>
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</thead>
<tbody>
<tr>
<td>The concentration needed to achieve inhibition or induction in vitro may not be achievable in the clinical setting</td>
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<tr>
<td>Interactions may be seen in vivo that are not seen in vitro due to a metabolite that is active</td>
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<td>Findings in animal models may not necessarily translate over to human subjects</td>
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<tr>
<td>Drugs may vary in their affinity or potency for the enzyme system</td>
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<tr>
<td>The agent's therapeutic index may influence the frequency or severity of the interaction</td>
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<td>Interindividual variability (in enzyme concentration, metabolism, and/or clearance)</td>
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<tr>
<td>1. Genetic polymorphism (e.g., CYP2D6)</td>
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<tr>
<td>(a) Poor metabolizers</td>
</tr>
<tr>
<td>(b) Extensive metabolizers</td>
</tr>
<tr>
<td>(c) Very extensive (ultrarapid) metabolizers</td>
</tr>
<tr>
<td>2. Age-related changes in physiology</td>
</tr>
<tr>
<td>(a) There is a decline in P450 enzymes with age</td>
</tr>
<tr>
<td>Characteristics of cytochrome P450 metabolism</td>
</tr>
<tr>
<td>1. Some substrates are metabolized by more than one CYP450 enzyme</td>
</tr>
<tr>
<td>2. Many inducers and some inhibitors can affect more than one isozyme</td>
</tr>
<tr>
<td>3. Enantiomers may be metabolized by different CYP450 enzymes</td>
</tr>
<tr>
<td>4. Differences in inhibition may exist within the same class of agents</td>
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</tbody>
</table>
Pharmacokinetic Parameters

Numerous studies demonstrate that differences exist in the mean estimates of methadone's pharmacokinetic parameters [6]. Analgesic effects of methadone occur within 30–60 min and peak on average between 2.5 and 4.0 hours [6–8]. Methadone has a very long elimination half-life (t1/2; about 22 hours [6,9], range: 4.2–190.0 hours, depending on the literature that is reviewed [7]), even though its duration of action as an analgesic is markedly shorter (6–8 hours [2]). In addition, methadone's analgesic activity varies with repeated dosing—approximately 3–6 hours with initiation of methadone and 8–12 hours with repeated dosing. Thus, methadone can be used as an around-the-clock analgesic as well as on an as needed basis. By comparison, the duration of analgesia for oral morphine (4–6 hours) does not change with repeated dosing. The reader is directed to the accompanying Appendix for a list of key pharmacokinetic terms used throughout the article.

Absorption

Methadone is rapidly absorbed from the stomach, with little absorption occurring beyond the pylorus [9]. Its absorption is mediated by gastric pH and P-glycoprotein, a transport protein [9]. P-glycoprotein is an important drug efflux transporter in the intestine, liver, and brain, as well as other tissues and it is associated with many clinically significant drug interactions [5]. Methadone's high, but unpredictable, oral bioavailability (F) is close to 80% (range: 40–99%), which is approximately threefold that of oral morphine [10,11]. Following the oral administration of equal methadone doses in different subjects, significantly different blood concentrations may be obtained [8]. Although medications such as verapamil or quinidine may interfere with methadone's gastric absorption (see below), the major factor believed to be responsible for the variations of methadone F is the interindividual difference in the expression of intestinal CYP3A4 [8].

Distribution

Methadone is highly lipophilic, and, at physiological pH, 86% of the drug is bound to plasma proteins, predominately α1-acid glycoprotein (AAG). AAG is an acute-phase reactive protein and plasma levels of AAG can fluctuate with various physiological and pathological conditions such as stress, opioid addiction and withdrawal [12,13], cancer [14], and concomitant administration of certain medications (e.g., amitriptyline) [2,15]. For instance, nearly a fourfold difference in the free fraction of methadone was seen among cancer patients, as compared with a twofold difference in controls secondary to differences in AAG levels [16]. Elevated AAG levels may decrease the effects of methadone, leading to inadequate analgesia or even opioid withdrawal [2,10]. Conversely, conditions or medications that lower AAG concentrations or compete for binding sites can increase free circulating methadone levels, thereby increasing methadone's effect and potential for toxicity [10].

Methadone has a large volume of distribution (Vd) in humans that varies depending on patient characteristics. The Vd in patients with chronic pain ranges between 1.71 and 5.34 L/kg, whereas patients with opioid addiction may have a Vd of 4.2–9.2 L/kg [10,15]. Tissue binding predominates over binding to plasma proteins [9,15], and accumulation of the drug occurs in these tissues with repeated dosing. Methadone reabsorption from the tissues may continue for weeks after administration has ceased [9]. Delayed adverse effects may be experienced due to methadone accumulation during chronic administration. Although not a direct drug–drug interaction per se, systemic toxicity occurs more frequently in patients previously exposed to high dosages of opioids [9]. The authors believe that this is related to the N-methyl-d-aspartate (NMDA) receptor antagonist properties of methadone [2,10,17]. The NMDA receptor is involved in the development of opioid tolerance [18,19]; therefore, this antagonism may initiate a partial reversal of opioid tolerance. This causes the patient to respond to the much lower methadone doses than would be expected considering their prior high doses of a different opioid. This is particularly worrisome, as rotation to methadone is frequently performed in patients with uncontrolled pain despite escalating doses of opioids.

Metabolism

Methadone is metabolized almost exclusively by the liver by the Type I cytochrome P450 (CYP450) group of enzymes. Methadone does not have active metabolites; its primary metabolite is 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) [2]. The main enzyme responsible for N-demethylation of methadone is CYP3A4 [20], with lesser involvement from CYP1A2 and CYP2D6; CYP2B6 may play a significant role in metabolism as well [2]. Isoforms such as CYP2C9 and CYP2C19 might also be implicated in methadone metabolism but their in vivo relevance remains to
be demonstrated [6]. As mentioned previously, CYP3A4 is also found in the small intestine; therefore, it affects both the intestinal and hepatic metabolism of methadone [6,8]. Additionally, the activity of CYP3A4 varies greatly among individuals—from one- to 30-fold in the liver and one- to 11-fold in the gut [6,8]. Furthermore, the level of CYP3A4 mRNA in the liver can vary by more than 50-fold from one patient to another [21]. Variations of CYP3A4 and CYP2D6 levels and expression account for the large individual variations associated with methadone pharmacokinetics [2].

Inducers, inhibitors, or substrates of the CYP450 enzyme system may affect the metabolism of methadone. The process of induction is an important component of the body’s defense mechanisms against foreign xenobiotics. Induction is an increase in the production of enzymes secondary to the body’s exposure to a substance that stimulates this process (an inducer). More specifically, inducers stimulate enzyme synthesis via stimulation of new mRNA and protein. This occurs through the activation of nuclear receptors (NR) that regulate the amount of mRNA produced by a gene [22]. Each of the major isoforms of CYP450 has its own corresponding NR: polycyclic aromatic hydrocarbon-like (CYP1); phenobarbital-like (CYP2), also referred to as constitutively active receptor (CAR); glucocorticoid-like (CYP3), also referred to as pregnane X receptor (PXR); and clofibrate-like drugs (CYP4). In other words, PXR regulates the expression of 3A genes; CAR regulates the expression of 2B genes. The discovery of PXR was an important step forward in the understanding of the activity of the P450 system, and the underpinnings of the body’s defense system in general [21]. While an in-depth discussion of NR is beyond the scope of this review, it is important to know that many compounds known to be inducers of 3A metabolism are now known to activate PXR.

In general, metabolic induction is typically delayed (approximately 1–2 weeks) following the repeated administration of a drug [8]. Of particular importance, methadone can induce its own metabolism in a time-dependent fashion via CYP3A4 [2], thus increasing its clearance over time [10,15]. On the other hand, enzymatic inhibition develops quickly [8]. This inhibition can be either secondary to competition between drugs or their metabolite(s) for the same binding site or irreversible effects of a reactive metabolite [22]. Methadone itself can inhibit CYP2D6 and therefore it may affect the levels of drugs metabolized by this enzyme (i.e., substrates) [11,23]. In some cases, it may not be the addition of a CYP450 active drug that causes problems but rather the discontinuation of the active inhibitor or inducer [2]. Lastly, when two or more drugs that are metabolic substrates of the same CYP450 are administered concurrently, the drug that has the greatest affinity for that cytochrome can prevent in part the metabolism of the other drugs [8].

Elimination
Methadone has a prolonged and variable elimination phase that is dependent on single vs multiple dosing, individual adipose stores, and protein binding [7]. Methadone undergoes a biphasic pattern of elimination: slow distribution or α-elimination phase (8–12 hours) and a β-elimination phase (30–60 hours) [2]. The β-elimination phase correlates with the duration of analgesia, whereas plasma levels in the β-elimination phase are subanalgesic but sufficient to prevent withdrawal symptoms. Methadone’s slow clearance (CLR) from the body provides the rationale for dosing it once per day in methadone maintenance treatment (MMT) [10], compared with the three or four times daily dosing typically needed when prescribed for analgesia [2]. Clearance of methadone varies widely among individuals, ranging from 0.96 to 5.1 mL/min/kg [8]. Plasma protein binding should be considered a potential factor responsible, at least in part, for the interindividual variations in CLR [15]. Therefore, as aforementioned, medications that affect protein binding have the potential to interact with methadone.

Methadone is predominantly excreted in the feces. It does not accumulate in renal failure and does not appreciably filter during hemodialysis [10]. Unlike morphine, it is usually not necessary to adjust the dosage of methadone in patients with renal insufficiency [9]. However, renal excretion is variable and is pH dependent [2]. Methadone is a lipophilic basic drug with a dissociation constant (pKa) of 9.2 [2,6,10,15]. Therefore, agents that change the pH of the urine may affect methadone elimination. Acidification of the urine (i.e., pH < 6), for instance, will increase renal excretion of methadone [7] with a subsequent decrease in methadone concentration/effects. On the other hand, urinary alkalinizers may increase circulating methadone levels. Varying the pH also changes the t1/2 and Vd of the drug [8]; more detail regarding this interaction is provided below.
Pharmacodynamics
Methadone is primarily a mu opioid agonist that exists (commercially in the United States) as a racemic mixture of two enantiomers, R-methadone (l-isomer) and S-methadone (d-isomer). R-methadone is thought to be responsible for most of the activity at the opioid receptor, whereas S-methadone is a noncompetitive NMDA antagonist and inhibits reuptake of monoamines (e.g., 5-hydroxytryptamine, norepinephrine)—pharmacological actions that result in additional analgesia [2,10,17]. In addition, methadone binds to delta and to a lesser extent kappa opioid receptor sites [7]. By virtue of its mechanism of action, methadone may cause sedation and/or respiratory depression. Thus, additive effects would be anticipated when combined with other central nervous system (CNS) depressant drugs.

Medication Classes Known or Suspected to Interact with Methadone
Following is a detailed description of therapeutic classes and medications that have been reported to interact with methadone. Table 2 summarizes specific medications that have been studied directly with methadone, which are particularly relevant to the pain medicine practitioner. The authors caution the reader that this table is not meant to serve as a stand-alone guideline; rather, it should be used to compliment the contextual information provided in this discussion.

Antibiotics
Rifamycins
One of the first drug interactions discovered to be associated with methadone was with the use of rifampin in MMT patients receiving treatment for tuberculosis. Kreek et al. [24] found that plasma methadone levels were consistently lower (33–68%) at each time point measured except where methadone levels were at the lower limit of detection. Opioid withdrawal symptoms appeared within 5 days of initiating rifampin therapy. Similar findings were reported in other case reports in the same population [25,26] and in MMT patients with HIV [27]. Of note, it is now known that rifampin is an inducer of PXR expression [28], and an inducer of CYP2B6 [22]. However, Kharasch et al. [29] reported that although rifampin decreased F and increased CLr of methadone, studies with the CYP3A4 inhibitors troleandomycin and grapefruit juice did not produce similar findings compared with rifampin. Therefore, these findings suggest that there was no correlation between methadone CLr and hepatic CYP3A4 activity. Rather, greater effects seen with rifampin (as compared with troleandomycin and grapefruit juice) suggest a major role for intestinal transporters and for other P450 enzymes such as CYP2B6.

These findings are consistent with those reported for rifabutin, another antibiotic that is a potent CYP3A4 inducer. One study investigating this interaction [30] found no significant differences in methadone pharmacokinetics in the presence of rifabutin, as the mean day 14 : day 1 ratios for the maximum concentration (Cmax), area under the curve (AUC), and CLr were not significantly different; however, 18 of the 24 patients enrolled in this study reported at least one symptom consistent with opioid withdrawal. Of these 18 patients, 10 were found to have a decrease in methadone AUC; only five of which had a decrease >30%.

Fluoroquinolones
Moody et al. [31] used ciprofloxacin to determine if methadone is a CYP1A2 substrate in vitro. They found that some inhibition of methadone N-demethylation occurred secondary to ciprofloxacin; however, this activity was significantly less as compared with ketoconazole, which is a potent CYP3A4 inhibitor. In a case report [32], increased sedation and confusion was seen with the combination of methadone and ciprofloxacin in one patient. This interaction was subsequently rechallenged three times thereafter with the same result; the last of which required naloxone. The exaggerated response seen with the final rechallenge may have been secondary to the introduction of fluoxetine concurrently [32]. Inhibition of CYP1A2 and/or 3A4 may have been responsible for this interaction. While data related to a specific drug–drug interaction are not available for the other fluoroquinolones, many of these antibiotics prolong the QT interval (gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, ofloxacin, sparflloxacin) [33]. Therefore, caution is advised when using any of these fluoroquinolones in combination with methadone, particularly at higher doses (refer to QT prolongation section).

Macrolides
Significant inhibition of methadone metabolism was seen in vitro with the potent CYP3A4 inhibitor troleandomycin, which inhibited the formation of EDDP by up to 80% [20,34,35]. However, in vivo, Kharasch et al. [29] found that while
Table 2  Selected methadone drug interactions in pain medicine

<table>
<thead>
<tr>
<th>Medication Class Specific Agent(s)</th>
<th>Effect of Interaction(s)</th>
<th>Level of Evidence*</th>
<th>Potential Alternative Agent(s)</th>
<th>Reference Page No. in Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td></td>
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<tr>
<td>Phenytoin</td>
<td>Decreased ME levels/induction of ME metabolism/opioid withdrawal</td>
<td>4 (case report [67], case series [88]) 2 (observational study [70])</td>
<td>Valproic acid, gabapentin, lamotrigine, levetiracetam</td>
<td>10–11</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Increased ME CLr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Decreased ME levels/induction of ME metabolism/opioid withdrawal</td>
<td>4 (case report [69])</td>
<td>Valproic acid, gabapentin, lamotrigine, levetiracetam</td>
<td>11</td>
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<tr>
<td>Antidepressants</td>
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<td>SSRIs</td>
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<tr>
<td>Fluvoxamine</td>
<td>Increased ME levels/inhibition of ME metabolism</td>
<td>4 (case series [72], case report [74]/in vitro [23,35])</td>
<td>Sertraline, citalopram, escitalopram</td>
<td>11–12</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Opioid toxicity</td>
<td>4 (case report [73])</td>
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<tr>
<td>TdP</td>
<td>Increased ME levels/inhibition of ME metabolism</td>
<td>4 (case series [75,76])</td>
<td>Sertraline, citalopram, escitalopram</td>
<td>12</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Decreased hepatic metabolism</td>
<td>In vitro [35]</td>
<td></td>
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<tr>
<td>Sertraline</td>
<td>Increased ME levels/inhibition of ME metabolism</td>
<td>2 (prospective, observational study [80])</td>
<td>Sertraline, citalopram, escitalopram</td>
<td>12</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Increased ME levels/autoinduction</td>
<td>1 (prospective, RCT [82])</td>
<td>Citalopram, escitalopram</td>
<td>12–13</td>
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<td>TCAs</td>
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<tr>
<td>Desipramine</td>
<td>Inhibition of ME metabolism/ inhibition of ME urinary excretion</td>
<td>Animal study [84]</td>
<td>Sertraline, citalopram, escitalopram</td>
<td>13</td>
</tr>
<tr>
<td>Increased desipramine levels/ inhibition of desipramine metabolism</td>
<td>2 (observational study [85], case series [86])</td>
<td></td>
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<tr>
<td>Amitriptyline</td>
<td>Increased ME CLr</td>
<td>2 (observational study [70])</td>
<td>Sertraline, citalopram, escitalopram</td>
<td>13</td>
</tr>
<tr>
<td>Increased AAG levels</td>
<td>TdP/ prolonged QT</td>
<td>2 (observational study [87])</td>
<td>Sertraline, citalopram, escitalopram</td>
<td>13</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Displacement of ME from AAG</td>
<td>3 (case–control study [16])</td>
<td>Sertraline, citalopram, escitalopram</td>
<td>13</td>
</tr>
<tr>
<td>Anti-inflammatory NSAIDS</td>
<td>Enhanced analgesia/ opioid-sparing effect</td>
<td>1 (randomized controlled trial [96], observational study [97])</td>
<td>N/A</td>
<td>15</td>
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<tr>
<td>Anxiolytics</td>
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<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Alprazolam</td>
<td>CNS depression/sedation/overdose rather than opioid-like</td>
<td>4 (case series [102])</td>
<td>Buspirone, LOT‡</td>
<td>16</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Inhibition of ME metabolism</td>
<td>In vitro [20,23]</td>
<td>Buspirone, LOT‡</td>
<td>16</td>
</tr>
</tbody>
</table>

* Generally, drug interaction data are reported in the form of in vitro studies and/or case reports/series, and are seldom subjected to confirmatory investigation. Therefore, although the level of evidence to support a drug interaction is not comparable to meta-analyses or randomized controlled trials, it still merits consideration, and, in most cases, careful monitoring. The authors used the grading system developed by the Oxford Center for Evidence-based Medicine (http://www.cebm.net/levels_of_evidence.asp) to rate the level of evidence associated with methadone drug interactions.

† Although the lack of evidence precludes making definitive alternative recommendations, in anticipation or in the presence of a drug interaction with methadone the following agent(s) may be considered. The clinician is encouraged to use caution when methadone is used concomitantly with a medication from a drug class known to interact with methadone; close monitoring is recommended and periodic adjustment of or altering therapy may be required (refer to Theoretical Interactions with Methadone section).

‡ These agents have been weakly associated with TdP and/or QT prolongation in some reports (with and without concurrent methadone use), but they are unlikely to cause TdP when used in usual recommended dosages in patients without other risk factors (e.g., electrolyte disturbances) [33].

§ Although in vivo data indicate that a pharmacodynamic interaction can occur with methadone and the benzodiazepines, in vitro modeling suggests that kinetic interactions are possible as well. Therefore, benzodiazepines that do not undergo phase I metabolism (i.e., glucuronidation instead) may be preferred when used concomitantly with methadone, albeit additive depressant effects are still possible with these agents.

ME = methadone; CLr = clearance; TdP = Torsades de Pointes; RCT = randomized controlled trial; AAG = α1-acid glycoprotein; LOT = lorazepam, oxazepam, triazolam; BZ = benzodiazepine; N/A = not applicable.
troleandomycin decreased the EDDP/methadone AUC ratio after oral methadone, this decrease did not occur when methadone was administered intravenously. In addition, they found that troleandomycin had no effect on methadone plasma concentration, CLr, or other pharmacokinetic parameters. These and other results of this study prompted the authors to conclude that there was no correlation between methadone CLr and hepatic CYP3A4 activity [29], and perhaps alternate metabolic pathways better explain their findings.

It is well known that erythromycin, clarithromycin, and telithromycin are potent inhibitors of CYP3A4, and therefore are responsible for numerous drug–drug interactions with medications metabolized through this and other pathways [36]. Additionally, they all can prolong the QT interval [33]. However, these macrolides have not been specifically studied in combination with methadone. One case report by Piguet et al. [37] described asymptomatic QT prolongation in a patient administered clarithromycin in combination with methadone, which subsequently resolved secondary to the macrolide’s discontinuation. Despite the lack of evidence specific to methadone with all macrolides, caution is advised when administering them in combination with methadone.

Miscellaneous

Sulfaphenazole is a sulfonamide antibiotic that is often used in laboratory settings as a marker of CYP2C9 inhibition. The role of CYP2C9 in the metabolism of methadone is unclear, as it has been found to have both negligible [20,35] and significant activity [31,34]. One explanation for this discrepancy may be the differences in concentration of methadone used during testing, as Iribarne et al. [20] used a 50-fold higher concentration than what was used by Moody et al. [31]. Sulfamethoxazole is also known to be an inhibitor of CYP2C9 [38]. While there are no reports of a pharmacokinetic drug interaction between methadone and cotrimoxazole (sulfamethoxazole and trimethoprim), trimethoprim alone decreased the hepatic metabolism of R,S-methadone via CYP2C8 inhibition in vitro [35]. It is also believed that cotrimoxazole may prolong the QT interval [33]. The combination of methadone and cotrimoxazole may have contributed to QT prolongation in two patient cases, one of which subsequently developed ventricular tachycardia and Torsades de Pointes (TdP) [37]. While other contributors may have been more directly responsible for the TdP in this particular patient case, caution may be warranted when prescribing this therapy combination.

Although some clinicians have suggested an interaction between methadone and metronidazole, little evidence exists supporting this relationship. Once believed to be a strong CYP3A4 inhibitor [1], a study by Wang et al. [39] demonstrated a lack of effect in vitro and in vivo when metronidazole was combined with midazolam, a CYP3A4 substrate. It is now believed that inhibition of the CYP2C9 pathway may be more significant for metronidazole, which is a minor pathway of methadone, if at all.

Similar uncertainty exists for isoniazid, which is a potent CYP3A4 inhibitor. Despite the frequent use of this antibiotic in the MMT population, no interactions with methadone have been reported to date. Another potent CYP3A4 inhibitor that has not been studied in combination with methadone thus far is quinupristin/dalfopristin. However, caution is warranted until more clinical experience is gained with this particular drug combination.

Antiretroviral Therapies

Protease Inhibitors

Conflicting results regarding metabolic induction and inhibition are seen with many antiretroviral therapies; this is especially true with protease inhibitors. Although usually considered to be a CYP3A4 inhibitor, nelfinavir demonstrated induction of methadone metabolism in rats [40] and in patients with HIV [41,42]. In one case report, for instance, opioid withdrawal was experienced by a 40-year-old male who received methadone for 13 years prior to the introduction of nelfinavir [41]; however, in subsequent case series by the same investigators [42] no withdrawal or toxicity was seen despite significantly decreased AUC, Cmax, and minimum concentration (Cmin), as well as increased CLr. In contrast, nelfinavir was specifically cited as potentially being contributory in methadone-related TdP case reports [43,44], suggesting CYP3A4 inhibition, not induction. Although the exact mechanism by which nelfinavir may interact with methadone has not been established, increased expression of intestinal P-glycoprotein and hepatic CYP3A may be responsible.

When investigating amprenavir in rats, the Cmax and AUC of methadone decreased significantly by day 14 of therapy relative to baseline [40]. Increased intestinal P-glycoprotein and hepatic CYP3A protein levels were also observed;
however, no changes in intestinal CYP3A levels were seen. Despite significant increases (151%) in hepatic CYP3A protein levels, amprenavir treatment did not result in a significant increase in hepatic CYP3A activity [40]. In the HIV patient population, the combination of methadone, amprenavir, and abacavir may have precipitated opioid withdrawal [45]. Exposure to this combination for a median period of 14 days resulted in a significant reduction of methadone concentration, with a median decrease to 35% of the original concentration (range: 28–87%) [45]. Unlike amprenavir, abacavir is not associated with significant P450 activity, and thus was an unlikely contributory factor; however, the authors were unable to determine which antiretroviral was responsible for the interaction observed. Similarly, Hendrix et al. [46] found that the coadministration of amprenavir with methadone resulted in a decrease in AUC, Cmax, and Cmin for both the R- and S-methadone enantiomers.

Interactions between methadone and ritonavir are also inconsistent, whether ritonavir is prescribed alone or in combination with another protease inhibitor. An in vitro study of ritonavir resulted in a complete prevention of methadone N-dealkylation via competitive inhibition [47]. These in vitro findings are not consistent with a case report of opioid withdrawal 1 week after the initiation of ritonavir [48]. Opioid withdrawal symptoms in this patient resolved secondary to increasing the methadone dose from 90 mg/day to 100 mg/day and eventually up to 130 mg daily. A pharmacokinetic/pharmacodynamic study [49] performed subsequent to this case report found that ritonavir administration for a period of 7 days had no significant effect on methadone pharmacokinetics in 15 patients studied; methadone concentrations were modestly but not significantly increased. No patients receiving ritonavir therapy experienced opioid withdrawal symptoms.

Iribarne [47] investigated the inhibition of methadone by saquinavir in vitro, and concluded that the interaction is not likely to be of clinical significance. This was confirmed in two subsequent studies performed in vivo. When methadone was administered concomitantly with saquinavir, Gerber et al. [50] found a 40% decrease in total S-methadone AUC and a 32% decrease in R-methadone AUC. This change in methadone AUC was not associated with opioid withdrawal, and no modification of methadone dose was required. In a prospective, observational study [51] of 12 HIV patients the combination of once daily saquinavir and “minidose” ritonavir was well tolerated and was not associated with any clinically significant interactions. Although there was a small reduction in unbound concentrations of methadone, likely due to a slight increase (14%) in AAG observed, effects on other pharmacokinetic parameters (e.g., AUC) of the stereoisomers were unchanged.

When prescribed in combination with lopinavir, ritonavir reduced the mean methadone AUC by approximately 36%; a 44% reduction in Cmax was also seen [52]. Despite these findings, none of the patients experienced opioid withdrawal, and no methadone dosage adjustment was necessary. A subsequent study by Stevens et al. [53] also found an apparent lack of clinical significance associated with this drug interaction. This contrasts with a study performed by McCance-Katz et al. [49] in which lopinavir/ritonavir (L/R) substantially altered the pharmacokinetics of methadone, with a 26% decrease in AUC. The CLr of oral methadone also increased with L/R treatment; Cmax and Cmin each decreased by 28%. Additionally, there was a significant increase in the number of opioid withdrawal symptoms [49]. Thus, lopinavir appears to be a potent inducer of methadone metabolism, and treatment with the L/R combination requires clinical monitoring and increased methadone doses in some patients. Because of the inconsistency associated with this class of medications, Gerber et al. suggest that the CYP3A4 pathway may not be as significant as previously believed and alternate pathways, including CYP2B6, may be of greater significance [54].

Non-Nucleoside Reverse Transcriptase Inhibitors
The drug interactions associated with non-nucleoside reverse transcriptase inhibitors (NNRTIs) and methadone are somewhat more straightforward when compared with the protease inhibitors. The NNRTI nevirapine consistently induces methadone metabolism and precipitates opioid withdrawal in the majority of patients prescribed this combination [55–60]. Patients required methadone dose increases of between 15% [60] and 100% [57] when taking this combination. Nevirapine induces both CYP3A4 and CYP2B6 enzymes [22], and the induction of one or both of these enzymes is believed to be responsible for this interaction.

The addition of efavirenz to MMT precipitated opioid withdrawal in two case studies [58,61].
Likewise, Clarke et al. [59] demonstrated a marked decrease in methadone mean Cmax and decrease in mean AUC in the presence of efavirenz. Nine of the 11 patients in the study described symptoms of withdrawal and received dose increases of methadone. The mean dose increase necessary was 22%, although the mean reduction in AUC was >50% [59]. Boffito et al. [62] reported that dose increases between 66% and 133% of initial methadone doses were necessary to stabilize three MMT patients starting efavirenz therapy. While symptoms of opioid withdrawal occurred 3–7 days after initiating efavirenz therapy, subsequent methadone dosage adjustments were necessary over a 5- to 6-week period of time. Plasma methadone levels available from one patient showed a 70% reduction on day 6 of efavirenz therapy, which coincided with overt symptoms of opioid withdrawal. Transient symptomatic recovery for this patient was achieved on day 14 with a 66% increase in dose, but opioid withdrawal reappeared by day 28 (with a methadone concentration drop of 50% with the current dose). This patient was ultimately stabilized at 133% of their original methadone dose [62]. Efavirenz, like nevirapine, also induces CYP2B6 [22], which may explain the interaction reported between methadone and this agent.

**Nucleoside Reverse Transcriptase Inhibitors**

The interaction between methadone and zidovudine (ZDV) is not completely understood. Schwartz et al. [63] found that serum ZDV levels were significantly higher in methadone patients, with a 43% increase over the mean AUC observed in control patients. No significant differences were seen between the methadone and control groups regarding time to maximum concentration (Tmax), serum 1/2, glucuronidation, or urinary excretion [63]. These findings were consistent with a study by McCance-Katz et al. [64], which demonstrated that methadone treatment increased ZDV AUC and reduced the CLR of ZDV, regardless of route of administration or acute vs chronic administration. ZDV did not have a significant effect on methadone’s metabolism or CLR in either study [63,64].

Methadone does appear to affect the F of didanosine (ddI) and stavudine (d4T) as well. Methadone reduced the measured AUC for ddI and d4T, extrapolated AUC for full dosing interval, and peak drug concentrations [65]. Methadone’s effects on ddI and d4T appeared to result primarily from decreased F. Methadone also was found to delay drug absorption. Similar to the aforementioned ZDV data, trough levels for methadone did not differ significantly from those in historical controls, suggesting that ddI and d4T did not alter methadone’s disposition.

There does not appear to be a significant drug interaction between methadone and tenofovir disoproxil fumarate, as the mean R-methadone, S-methadone, and total methadone systemic exposures, AUC, and Cmax differed by 5% or less when methadone was dosed with tenofovir [66].

Although in vivo data are lacking, current evidence suggests that there is no clinically significant interaction between zalcitabine (ddC) and methadone, and data from in vitro studies suggest this interaction is negligible [34,35].

**Anticonvulsants**

Although many anticonvulsants have significant P450 induction capabilities, few case reports or clinical trials exist in the literature investigating drug interactions associated with these agents in combination with methadone. Finelli [67] submitted a case report in 1976, detailing opioid withdrawal in one patient within 4 days of starting phenytoin. This interaction was subsequently confirmed with a rechallenge of phenytoin. Tong et al. [68] also found similar results in a case series of five MMT patients who experienced opioid withdrawal within 3–4 days of starting phenytoin. Induction of methadone metabolism was confirmed by decreased methadone trough plasma levels and AUC.

Phenobarbital is an inducer of CYP1A2, 2B6, 2C, as well as 3A4 enzymes [22], and is known to activate both CAR and PXR [28]. Consistent with this enzyme profile, opioid withdrawal occurred in an MMT patient that abused this barbiturate; plasma levels and AUC returned to baseline 6 weeks after the discontinuation of phenobarbital [69]. Similarly, a case report of accelerated methadone CLR secondary to amobarbital (amylobarbitone) was described by Plummer et al. [70]; induction of methadone metabolism was attributed to this change in CLR.

Resolution of opioid withdrawal symptoms occurred in two patients taking methadone when converted from carbamazepine or phenytoin (both inducers of CYP3A4 and CYP2B6 [22]) to valproic acid [71]. The switch performed in the patient receiving carbamazepine required tapering the daily methadone dose from 120 mg to 60 mg daily; the dose of methadone was decreased from 110 mg to 70 mg daily in the patient switched...
from phenytoin. Both patients tolerated the combination of valproic acid and methadone well, and the serum valproic acid levels were within normal limits; no methadone serum levels were measured [71]. Another patient with AIDS who received valproic acid and methadone concurrently experienced QT prolongation, ventricular tachycardia, and TdP; however, this patient was also reported to have chronic alcoholism, which may have been contributory [37]. Therefore, while there does not appear to be an overt drug interaction between methadone and valproic acid, close monitoring of both medications is prudent.

Although not specifically studied with methadone, caution should be exercised when the following CYP3A4-inducing anticonvulsants are initiated, titrated, or discontinued in patients receiving methadone: felbamate, fosphenytoin, oxcarbazepine, and topiramate. Clinically significant interactions with myriad other medications metabolized by CYP3A4 and these anticonvulsants have been well documented.

**Antidepressants**

**Selective Serotonin Reuptake Inhibitors**

Fluvoxamine potently inhibits P450 3A4, 1A2, and 2C19; 2D6 inhibition is thought to be less significant [22]. In vitro studies have demonstrated that fluvoxamine does inhibit the metabolism of methadone [23,35]. In vivo experience with this combination confirms the significance of this interaction. Five MMT patients started on fluvoxamine experienced significant increases in methadone plasma levels [72]. Additionally, clinical manifestations of opioid withdrawal were seen when stopping fluvoxamine in one of these patients. An increase in methadone serum levels occurred in an MMT patient exposed to fluvoxamine, resulting in hypoventilation, hypoxemia, and hypercapnia [73]. In a case of an MMT patient who could not achieve stabilization with methadone alone, the known interaction between methadone and fluvoxamine was used to achieve therapeutic blood levels and prevent opioid withdrawal [74]. While no pharmacokinetic or controlled clinical trials have been performed outlining this particular drug interaction, current evidence suggests that the interaction between methadone and fluvoxamine is very significant clinically and achieved at therapeutic doses of both agents. Downward titration of methadone dose and frequent monitoring is necessary when initiating fluvoxamine therapy for patients prescribed methadone, and therapeutic drug monitoring of methadone blood levels may be prudent in those patients requiring this particular drug combination.

Fluoxetine is a potent inhibitor of the P450 enzymes 3A4, 2D6, and 2C19, among others [22]. It would therefore be expected that a drug interaction between fluoxetine and methadone would be clinically significant. An in vivo study conducted by Eap et al. [75] indicated that the R-methadone levels of seven MMT patients were increased preferentially by fluoxetine, while fluvoxamine increased the levels of both enantiomers. These results suggest that CYP2D6 preferentially metabolizes R-methadone, whereas CYP1A2 metabolizes both enantiomers, and that the role of CYP3A4 in this interaction is relatively minor. Bertschy et al. [76] also studied this interaction in nine MMT patients and found that the plasma level to dose ratio increased in three patients, did not change in four patients, and decreased in two patients, suggesting that fluoxetine was not a potent inhibitor of methadone metabolism. However, numerous confounders were present in this group of patients, limiting the interpretability of these findings. The combination of methadone and fluoxetine was also implicated as being contributory in multiple case reports of TdP [43,44,77,78]; however, other predisposing factors were present in all of these cases.

Only one prospective, randomized, double-blind study [79] has been carried out with the combination of methadone and fluoxetine, and the primary endpoint of this study was the efficacy of fluoxetine in treating depression when administered in combination with methadone. The investigators found that both fluoxetine and placebo groups experienced improvement in depression symptoms; tolerability and plasma levels were not assessed. In summary, while caution is indicated with the combination of methadone and fluoxetine, the nature and significance of this interaction is still largely unknown; patient-specific factors such as CYP2D6 phenotype may be responsible for clinically significant pharmacokinetic changes and subsequent adverse drug reactions.

Significant CYP2D6 inhibition is associated with paroxetine, which appears to result in a clinically relevant drug interaction with methadone; however, paroxetine's CYP3A4 inhibition in vivo is not believed to be significant. In vitro data demonstrated that paroxetine decreases the hepatic metabolism of R,S-methadone by 41% and 77%, respectively, suggesting stereoselective inhibition of methadone metabolism [35]. A prospective
studied the interaction of paroxetine with methadone in 10 MMT patients and found that paroxetine significantly increased the concentrations of RS-methadone in the entire group, with the degree of increase dependent on whether the patient was a poor or extensive metabolizer [80]. Thus, there appears to be a significant interaction between methadone and paroxetine, although some patients may tolerate this combination without a problem. Similar to fluoxetine, these findings also illustrate the potential significance and utility of CYP2D6 phenotyping in patients receiving this or similar medication regimens.

Sertraline is a mild inhibitor of CYP1A2 and CYP2C19 inhibition and has little if any effect on P450 3A4, 1A2, 2C9, or 2C19 enzymes [22,81]. The interaction between methadone and sertraline was investigated in a prospective, randomized, controlled clinical trial of MMT patients with depression [82]. Sertraline modestly increased methadone serum levels over a 6-week period; however, between weeks 6 and 12 methadone plasma levels decreased back toward baseline and did not significantly differ from placebo at week 12. Sertraline and placebo groups did not differ in reported side-effects or dose adjustments throughout the study. The authors believe that autoinduction of methadone’s metabolism might have been responsible for this observation [82]. This combination has also been cited in TdP case reports [37,77], but, consistent with most interactions highlighted in these citations, other contributors were also present. Therefore, while a drug interaction between methadone and sertraline does appear to exist, it is much less clinically significant than either fluvoxamine or fluoxetine.

Citalopram has not been specifically studied with methadone for a potential drug interaction, but this combination was also present in one patient experiencing TdP [37]. Citalopram is a weak CYP2D6 inhibitor; it also has some weak CYP1A2 and CYP2C19 inhibition in vitro [83]. Like sertraline, while clinical significance of this interaction is unknown, it is generally considered to be one of the safer selective serotonin reuptake inhibitors (SSRIs) to be used in combination with methadone.

Tricyclic Antidepressants

Although the tricyclic antidepressants (TCAs) are well-known inhibitors of CYP2D6 (some also inhibit CYP1A2 to a lesser degree), few studies thus far have looked specifically at pharmacokinetic changes when used with methadone. That said, while not fully elucidated, methadone and TCAs may interact with each other on a number of different levels.

Desipramine was found to potentiate and prolong methadone analgesia by increasing the brain concentration and inhibiting the hepatic metabolism of methadone in rats [84]. Methadone concentrations were higher in the kidneys and lower in the lungs, suggesting a possible inhibition of methadone urinary excretion. In an unrelated study, methadone was found to inhibit the metabolism of desipramine in human subjects, possibly due to inhibited hydroxylation via CYP2D6 [85]. Similarly, significantly higher desipramine serum levels were seen in MMT patients coadministered methadone as compared with those patients taking desipramine alone [86]. In the case of the latter, the authors suggest that monitoring of desipramine serum levels may be beneficial when concomitantly administered with methadone [86]; however, the practicality and feasibility of this in clinical practice is not established.

In a model developed by Plummer et al. [70], amitriptyline was believed to inhibit methadone CLR in cancer patients; however, other confounding variables may have played an important role and the potential mechanism of this interaction was not reported. Alternatively, TCAs may have a pharmacodynamic interaction with methadone via AAG induction. One prospective observational study, for instance, found increased AAG levels during treatment with amitriptyline in 13 of the 16 patients, albeit none of these patients received methadone [87]. However, Abramson found that imipramine displaced methadone from AAG binding sites in advanced cancer patients on methadone therapy compared with controls [16]. Despite these findings, the author concluded that the level of displacement of methadone by imipramine is not likely to be of clinical significance.

Although not studied specifically with methadone as a substrate, TCAs and fluoxetine had minor direct effects on opioid receptor binding in the thalamus in vitro [88]. This interaction was more pronounced with the kappa opioid receptor subtype. All TCAs except clomipramine had a higher affinity for the kappa receptor; clomipramine was equally selective for both mu and kappa receptors. Fluoxetine was also included in this investigation and had less affinity for the opioid receptor in comparison with the TCAs studied. The implications of these findings in clinical practice remain to be established.

Tricyclic antidepressants are known to be effective for the management of multiple types of neu-
ropathic pain, and are generally considered to be first-line agents for the treatment of peripheral neuropathic pain [89]. Methadone is also believed to be especially suited to the treatment of refractory pain, namely neuralgia. Thus, some clinicians use both agents concomitantly, and, in low doses, the combination may be well tolerated by many patients. However, in addition to potential interactions discussed thus far, clinicians should also keep in mind that TCAs can prolong the QT interval. The combination of methadone and TCAs resulting in TdP was seen in case reports of patients prescribed amitriptyline [43,44] and trazodone [78]. The potential for additive prolongation of the QT interval and (fatal) cardiac arrhythmias does exist for the combination of TCAs and methadone. Therefore, this combination should only be used with caution and careful monitoring.

Monoamine Oxidase Inhibitors

Because the monoamine oxidase inhibitors (MAOIs) are infrequently used in clinical practice in comparison with other classes of antidepressants available, interactions with methadone have not been characterized. However, despite the paucity of evidence that exists outlining a drug interaction between the MAOIs (as a medication class) and methadone, the use of this therapy combination should probably be avoided if possible. Although the chemical structure and classification of methadone (a diphenylpropylamine) differs from meperidine (a 4-phenylpiperidine), they are related compounds. Meperidine, when used in combination with MAOIs, can produce serotonin syndrome and has resulted in fatality [4].

Miscellaneous

Four MMT patients with depression that failed one or more agents previously were successfully treated with nefazodone, a strong CYP3A4 inhibitor [90]. No signs or symptoms of sedation or other opioid-related adverse effects were present in three of the four patients; the fourth patient complained of sedation that resolved by decreasing the dose of nefazodone. Concomitant substance abuse either improved (two patients) or stopped completely (two patients). No blood levels of methadone were drawn and no opioid-specific assessment tools were used to assess methadone. Therefore, it is plausible that the decline in substance abuse may have been secondary to increased pharmacological effects of methadone secondary to an inhibition of its metabolism.

Interestingly, the patient reporting sedation was prescribed the lowest daily dose of nefazodone (50 mg); the remaining three patients tolerated nefazodone doses in the range of 300–400 mg daily [90].

The effects of St. John’s wort on serotonin and monoamine oxidase inhibition are similar to, but thought to be less significant than, that which occurs with the SSRI and MAOI class of antidepressants, respectively [91,92]. Eich-Hochli et al. reported a significant interaction between methadone and St. John’s wort [93]; a significant decrease in methadone concentration-to-dose ratio was seen in all patients included in this study, with a mean decrease of 47% of the original concentration. Additionally, two patients reported symptoms consistent with opioid withdrawal. Induction of CYP3A4 and/or P-glycoprotein was believed to play a role in this interaction [93], albeit it is not possible at this time to identify with certainty the mechanism associated with this interaction.

No references were found that specifically outlines an interaction between the SSRI duloxetine and methadone. Duloxetine is both a substrate and an inhibitor of CYP2D6 [94]. Therefore, duloxetine and methadone may inhibit each other’s metabolism, increasing serum levels of both drugs and potentially resulting in adverse effects and/or toxicity. This combination should be avoided, if possible. Similarly, the combination of methadone and venlafaxine has not been studied thus far. Venlafaxine mildly inhibits CYP2D6 in vivo, and therefore may inhibit methadone’s metabolism [95]. Because venlafaxine is also a substrate of CYP2D6, levels of venlafaxine may be increased when coadministered with methadone [96]. Patients should be monitored closely if taking these agents concurrently.

Antifungal Agents

Some of the most fundamental drug interactions reported in the literature occur with the azole antifungal agents. Iribarne et al. found that up to 84% of methadone metabolism was inhibited by ketoconazole in vitro [20], and confirmed that methadone is N-demethylated by P450 3A4 by at least 72%, based on ketoconazole data associated with a subsequent study [23]. Other studies report similar findings of inhibited metabolism [31,34,35]. While none of these studies were performed in vivo, there is enough evidence to suggest that the interaction between ketoconazole and methadone is clinically significant, and meth-
Actual and Potential Drug Interactions Associated with Methadone

An in vivo pharmacokinetic study with fluconazole and methadone [97] found a mean increase of 35% in serum methadone AUC; methadone's Cmax and Cmin increased by 27% and 48%, respectively, and the CLR of methadone decreased by an average of 24%. While CYP3A4 inhibition was believed to be the primary mechanism behind this interaction, the authors could not rule out possible contributions of alternate pathways such as CYP2D6 and/or 2C. Case reports of this interaction document the occurrence of respiratory depression in one patient receiving intravenous fluconazole [98], and QT prolongation in two AIDS patients, one of which developed ventricular tachycardia and TdP [37]. In the patient that developed TdP, discontinuation of the fluconazole and other potentially contributory medications helped decrease the QT interval; it remained unchanged in the asymptomatic patient despite the discontinuation of fluconazole [37].

While no data exist specific to itraconazole and methadone, the former also is a potent CYP3A4 inhibitor [1]. Thus, the significant nature of the interactions seen with both ketoconazole and fluconazole must also be assumed to be present with itraconazole. Caution and significant adjustments in the dose of methadone should be performed when attempting to use anyazole antifungal in a patient prescribed methadone therapy.

**Anti-Inflammatory Agents**

The combination of methadone with nonsteroidal anti-inflammatory (NSAID) agents appears to result in analgesic synergy. In a prospective, randomized, double-blind, crossover trial of 28 patients with cancer pain, Ferrer-Brechner and Ganz [99] found that the combination of methadone and ibuprofen significantly increased analgesia measured via three different pain intensity scales. Pain severity ratings showed a statistically significant difference in pain scores when ibuprofen was added at the 2-hour interval, which persisted for 4 hours. This regimen seemed to be most effective in patients with visceral/bone pain. Similar results were seen with diclofenac; significantly less methadone was consumed in the diclofenac group at the time of therapy combination and final assessment [100]. Methadone plasma levels were also monitored in this study, and decreases in methadone levels seen did not reach statistical significance [100]. The combination of NSAID and methadone was also well tolerated in both of these studies.

Corticosteroids are frequently used in combination with opioid therapy, especially in palliative care. While dexamethasone is an inducer of CYP3A4 [101] and CYP2B6 [22], there is no evidence currently available demonstrating an interaction between dexamethasone and methadone. The potential for an interaction does exist, but may be dependent on the dose of dexamethasone. For instance, an increase in cyclophosphamide's clearance was seen when used in combination with high doses of dexamethasone [102,103]. However, when combining low-dose dexamethasone with triazolam (a CYP3A4 substrate), no statistically significant effects on triazolam were seen [104]. The authors did suggest, however, that more pronounced changes in triazolam metabolism were possible when using dexamethasone at higher doses or over prolonged periods of time. While the potential for an interaction between methadone and dexamethasone does exist, it is not easily characterized by using the current literature. Studies are warranted investigating this particular combination, especially in the cancer and/or palliative care populations.

**Benzodiazepine Agonists and Antagonists**

Medications with CNS depressant effects, such as the benzodiazepines, may have additive adverse consequences when combined with methadone. It is common for patients subject to long-term MMT to simultaneously use benzodiazepines [20]. In a case series study of three patients with history of drug abuse, including one patient on MMT, fatal overdoses were attributed to the combination of methadone and alprazolam [105]. These overdoses occurred with serum drug levels lower than what is usually considered to be fatal, and all three patients had deaths certified as accidental multiple drug overdose.

The synergy between methadone and diazepam was evaluated in a prospective, double-blind, crossover study of five adult male patients on MMT with histories of diazepam abuse [106]. The combination of methadone at 150% of the maintenance dose with 40 mg of diazepam induced increases in pupil constriction and scores on a subjective response scale greater than those induced by either drug dose alone. Plasma level analysis does not indicate a pharmacokinetic interaction between diazepam and methadone as demonstrated in two small-scale studies of MMT patients. The first of these investigations, per-

formed by Pond et al. [107], showed that blood concentrations and plasma protein binding of methadone were not altered in any of the four subjects receiving diazepam concomitantly. In a case series study of five patients on MMT who received diazepam, no significant differences were seen in methadone or diazepam/N-methyl diazepam time-course or AUC when compared with either drug alone [108]. The authors point out that the methadone concentration present in the brain and/or liver may be higher than seen in the plasma, providing one explanation for what may be seen pharmacodynamically. An in vitro study conducted using human liver microsomes [20] showed that N-demethylation of methadone by CYP3A4 was competitively inhibited by diazepam. Modeling of in vitro data according to Iribarne et al. [23] predicts that coadministration of diazepam with methadone would inhibit the metabolism by 10–20%. Such an inhibition in vivo could enhance methadone’s effects leading to overdose symptoms. This may explain why benzodiazepines were found in 74% of deaths related to methadone in one study [109].

In a double-blind, placebo-controlled study of 71 adult patients undergoing dental surgery, the effects of flumazenil, a benzodiazepine antagonist, on morphine analgesia was evaluated [110]. Flumazenil significantly enhanced morphine analgesia compared with placebo. Specifically, ibuprofen usage was significantly higher in the placebo group at 18 and 30 hours post procedure and there was no difference in the amount of hydrocodone used between the two groups. No significant differences were seen with any vital sign parameter. Postdischarge pain levels did not differ between the two groups. Although this study used morphine as the opioid analgesic, findings suggest that gamma-aminobutyric acid (GABA) antagonism may enhance opioid-mediated analgesia. The authors were unable to find any studies evaluating flumazenil and methadone specifically.

**Cardiac-Related Medications**

**Antiarhythmic**

Despite quinidine’s well-known ability to inhibit CYP2D6 metabolism, in vitro studies have demonstrated that the activity of quinidine on methadone’s metabolism is not significant [20,31,34], suggesting that the P450 2D6 pathway is not a significant one for methadone’s metabolism. However, quinidine also inhibits P-glycoprotein in the intestinal cell wall, which can lead to enhanced absorption of oral methadone. Bouer et al. [111] demonstrated this in rats, as a 2.14-fold increase in intestinal methadone absorption was seen after quinidine was administered. Thus, the variability in methadone F may be attributed to inhibition of P-glycoprotein in intestinal tissue.

Torsades de Pointes secondary to methadone, fluoxetine, and mild hypokalemia progressed to ventricular fibrillation in one patient that was administered a lidocaine infusion [77]. Magnesium sulfate was subsequently administered and the lidocaine infusion was stopped. A short run of ventricular tachycardia occurred 30 minutes later, followed by a spontaneous conversion back to normal sinus rhythm. No further rhythm abnormalities were seen in this patient.

While no cases have been reported thus far of TdP secondary to coadministration of methadone and quinidine or other antiarrhythmic medications, many of these medications are metabolized via the P450 system and can interact with methadone at this level, as well as secondary to additive QT prolongation. Clinicians should be aware of the hazards associated with this interaction and avoid such drug combinations wherever possible.

**Calcium Channel Blockers**

Both verapamil and diltiazem are potent inhibitors of CYP3A4 [38] and therefore coadministration with methadone would be expected to result in elevated methadone plasma levels. However, the pharmacokinetics and pharmacodynamics associated with this theoretical interaction have not been studied thus far. Interestingly, Plummer et al. found that verapamil increased the CLr of methadone in patients with cancer pain [70]. The alteration of methadone F secondary to intestinal P-glycoprotein inhibition was also studied with verapamil [111]; methadone’s systemic absorption was increased 1.6-fold in rats secondary to this pathway. The effects of diltiazem on methadone’s F have not been investigated and the clinical consequences of such an interaction have not been fully elucidated.

Both methadone and nifedipine are substrates of and compete for the same P450 3A4 enzyme according to their different affinities, with a theoretical risk of diminished methadone metabolism [23].

**Miscellaneous**

Patients receiving methadone for cancer pain had increased methadone CLr when coadministered spironolactone, suggesting P450 enzyme induction [70]. Eap et al. [6] also suggests that CYP3A4 induction secondary to spironolactone may be
responsible for this finding, which makes sense as spironolactone is also recognized to activate PXR [112].

Propranolol, like methadone, is a basic drug that is highly bound to AAG. Abramson found that propranolol displaces methadone from AAG binding sites in patients with advanced cancer [16]. It is not known whether this or other AAG-based interactions are clinically significant; the author suggests that supratherapeutic levels of methadone would be necessary for such an interaction to be of clinical significance.

Patients receiving opioid therapy may respond differently from aspirin as compared with drug-free populations. One study demonstrated that patients receiving methadone experienced a paradoxical activation of platelet receptors after the digestion of a single 325 mg aspirin tablet as compared with the control group [113]. However, no detail was provided regarding methadone daily dose or the concomitant drug therapy of either study group. The anticoagulant coumarin was also investigated in vitro as a marker of CYP2A6 metabolism, and did not have a significant impact on EDDP formation [34].

Chemotherapeutic Agents

Patients receiving methadone therapy for cancer pain may receive chemotherapy concomitantly, especially in earlier stages of the disease. Although not studied directly with methadone, Aguirre et al. [114] demonstrated that treatment of cancer patients with the alkylation agents carmustine and mechlorethamine could alter serum proteins and modify their binding capacity. The authors specifically state that these findings should be taken into account when treating patients receiving alkylating agents simultaneously with other basic drugs such as methadone.

More recently, increased sedation and confusion was seen with the combination of methadone and the epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib [115]. The patient was a 50-year-old man with end-stage lung cancer who took oral methadone for 30 years; his daily dose at the time of the event was 240 mg. He was admitted to the hospital secondary to dyspnea and change in consciousness and was found to have pulmonary embolism and diuretic-induced hypovolemia. Gefitinib was started 50 days prior to admission. During the hospital admission, gefitinib was stopped and subsequently rechallenged; tachypnea and dyspnea resulted 7 days later. The patient died of respira-

tory failure on day 15 of hospitalization. Multiple confounding medications and medical conditions made it impossible to attribute the methadone drug interaction to the ultimate demise of the patient. If a drug interaction between methadone and gefitinib did play a role then it was one that was delayed. No gefitinib levels were reported in this case study. So, while it is unlikely that an interaction between methadone and gefitinib alone resulted in mortality, clinicians should be aware that the potential for such an interaction exists, particularly if other P450 active medications are administered concomitantly.

CNS Depressants

Alcohol

Some CNS active medications may also induce or inhibit methadone’s metabolism via the CYP3A4 pathway. While the administration of ethanol slows down methadone’s metabolism on an acute basis, it could induce methadone’s metabolism when administered chronically [116,117]. This interaction may be of particular concern in the MMT population.

Chlorzoxazone

Using human liver microsomes to evaluate methadone’s stereoselectivity, Foster et al. [34] found that EDDP formation from S-methadone, but not R- or racemic methadone, was significantly inhibited by chlorzoxazone. These data along with in vitro experiments from Iribarne et al. [23] indicate that CYP2E1 is not involved in methadone N-demethylation.

Tetrahydrocannabinol

Low doses of tetrahydrocannabinol (Δ9-THC) enhanced antinociceptive effects of several opioids, including methadone, in rats [118]. While Δ9-THC alone did not elicit any antinociceptive effects, methadone analgesia was enhanced fourfold by an inactive dose of Δ9-THC. The shift in response curves was found to be parallel with methadone. Other opioids that experienced an enhancement in potency included morphine, codeine, oxymorphone, hydromorphone, l-alpha-acetylmethadol (LAAM), heroin, meperidine; no antinociceptive benefit was seen with pentazocine. These findings suggest synergy between the cannabinoid and mu (and possibly delta) opioid receptors.

Neuroleptics

Despite the frequent concomitant use of methadone and neuroleptic agents such as haloperidol,
there are few studies performed either in vitro or in vivo that provide evidence that is helpful to the clinician. Older typical neuroleptics such as chlorpromazine, thioridazine, and prochlorperazine were also included in Abramson’s study of methadone displacement [16]. All three neuroleptics significantly displaced methadone from AAG. As stated previously, while these results were statistically significant, the clinical signiﬁcance of these findings is still largely unknown.

Case reports of risperidone administration precipitating opioid withdrawal occurred in two patients, one of which was prescribed methadone [119]. Risperidone is a CYP2D6 and 3A4 (weak) substrate and a weak CYP2D6 inhibitor. Thus, the P450 profile of this neuroleptic would not appear to be consistent with such an outcome. The authors also suggest that this reaction was not P450-mediated due to the rapid onset of opioid withdrawal.

Olanzapine has been implicated as a potential contributor in methadone-associated TdP case reports [43,44,78]. Olanzapine is not a signiﬁcant inhibitor of P450, and its effects on the QT interval are believed to be mild and not clinically signiﬁcant [78,120,121]. Therefore, more evidence needs to emerge to conﬁrm or refute the potential for additive QT prolongation with this therapy combination.

Opioid Agonists

Methadone N-demethylation occurs via CYP3A4 and not CYP2D6 [23]. Dextromethorphan, an agent occasionally used for refractory neuropathic pain but more commonly for cough suppression, is a known substrate of the 2D6 isozyme. As such, one would predict that this drug does not influence methadone biotransformation. When administered at a low concentration in vitro dextromethorphan did not inhibit methadone N-demethylation; conversely, it did at a high concentration, which may have resulted in selective affinity for CYP3A4 metabolism [23]. On the other hand, methadone has been previously demonstrated to inhibit dextromethorphan O-demethylation, mediated by CYP2D6, in vivo [122]. The inhibition of CYP2D6 activity by methadone in vivo is incomplete, but still may result in clinically significant drug interactions that may contribute to exaggerated response or unexpected toxicity from drugs that are CYP2D6 substrates, such as dextromethorphan [122]. In a prospective, double-blind, placebo-controlled study of 15 patients on MMT, Cornish et al. [123] found no significant differences in methadone plasma levels between the dextromethorphan and placebo groups. However, patients in the dextromethorphan group had mild but signiﬁcant elevations in heart rate and temperature. Dextromethorphan did not cause any changes in respiration, pupil diameter, or subjective drug effects. The authors concluded that dextromethorphan is generally well tolerated in patients receiving methadone; however, coadministration of these agents did result in more side-effects over placebo, especially sleepiness and drowsiness. Lot-rich and colleagues [124] describe a case report of an 83-year-old woman prescribed methadone and dextromethorphan. The patient, who was previously ambulatory and interactive, became lethargic and delirious secondary to the addition of dextromethorphan to the medication profile. Complete reversal of delirium, along with depression, sedation, and loss of appetite occurred within 7 days of discontinuing dextromethorphan.

Although the mechanism proposed was inhibition of dextromethorphan metabolism via inhibition of CYP2D6 by methadone, the patient was also prescribed escitalopram (a weak CYP2D6 inhibitor), metoclopramide (a CYP2D6 substrate), had mild dehydration on admission, and had mild baseline dementia. The role of dextromethorphan as the reason for delirium was rated as probable via the Naranjo ADR Probability scale.

Tramadol, a CYP2D6 substrate, is another agent that is frequently used for treating nociceptive and neuropathic pain. As methadone is known to be an inhibitor of CYP2D6 metabolism, the potential exists for adverse drug events and/or toxicity secondary to a combination of these two agents. Cami et al. [125] studied the effects of short-term parenteral tramadol administration on a group of MMT patients, looking at subjective, behavioral, and physiological markers as endpoints. The study was a double-blind, placebo-controlled design, using tramadol doses of 100 and 200 mg in patients receiving 30 mg of methadone daily. Their results indicated that tramadol neither produced opioid agonist activity nor precipitated opioid withdrawal and its behavioral and physiological effects were not significantly different from placebo. However, patient tolerability was only assessed via an addiction-related tool; other side-effects may not have been captured. Therefore, while this therapy combination appears to be well tolerated after single doses of tramadol are administered, we do not know how this differs with long-term administration. Simi-
larly, tolerability may also be different in those patients requiring a daily methadone dose in excess of 30 mg. Another consideration is that the analgesia associated with tramadol was not assessed in this investigation. Because the biotransformation of tramadol to O-desmethyl-tramadol (a mu opioid receptor agonist) is dependent on CYP2D6 metabolism, prevention of this metabolite’s formation secondary to methadone exposure would theoretically impact tramadol’s analgesia.

**Opioid Antagonists, Mixed Agonist Antagonists**

As would be expected, opioid withdrawal is demonstrated secondary to opioid antagonists as well as partial antagonists when coadministered with methadone. A methadone/naloxone preparation precipitated severe opioid withdrawal in two patients and milder withdrawal in three patients; the remaining patients could not differentiate between the dosage forms [126]. Interestingly, four of the eight patients receiving the methadone/naloxone combination experienced higher plasma levels of methadone 6 hours post ingestion. Thus, although naloxone may have affected the absorption of methadone systemically, the precipitation of opioid withdrawal was not related to a lowering of methadone plasma levels, as the levels observed at 2 hours were within the range of those observed at 24 hours when there were no symptoms of opioid withdrawal [126].

Methadone acted as the control in a study investigating whether or not naltrexone modulates the subjective and physiological effects of oral THC in patients that were heavy marijuana smokers [127]. Naltrexone administration resulted in decreased ratings of “good drug effect,” “high,” and “stimulated” when administered with a 10 mg dose of methadone; naltrexone did not affect these ratings at the 5 mg dose level. An ultra low dose of naltrexone (1 µg orally twice daily) was also tried in combination with methadone in a patient with peripheral diabetic neuropathy [128]. Prior to the initiation of naltrexone, the patient was taking methadone 60 mg four times daily, methylphenidate 30 mg twice daily, and gabapentin 3,600 mg/day. The patient’s pain score dropped from a 9/10 to a 3/10 within 24 hours of starting the opioid agonist/antagonist combination. In addition, his methadone dose was titrated down to 50 mg four times daily, remaining stable for 1 month thereafter. No opioid withdrawal was experienced, and his chronic nausea resolved. Thus, the combination of methadone and ultra low dose naltrexone resulted in improved analgesia, methadone dose reduction, decreased sedation, and resolution of opioid-related side-effects. The mechanism responsible as suggested by the authors was that opioid antagonism at low doses may shorten the action potential duration in dorsal root ganglia, which may correlate with analgesia [128].

Walsh [129] found that abruptly transitioning a patient receiving MMT to buprenorphine produced patient discomfort that was positively related to both methadone and buprenorphine dose; buprenorphine had greater antagonistic effects in the 60 mg/day MMT group, whereas methadone extra doses had greater agonist effects in the 30 mg/day MMT group. Another study examined the combination of intravenous buprenorphine and naloxone, naloxone alone, and buprenorphine alone in MMT patients stabilized on 40–60 mg/day [130]. Opiate withdrawal scores were seen with both naloxone alone and the buprenorphine/naloxone combination; no differences were observed between buprenorphine alone and placebo for these subjective measures. Similarly, the naloxone conditions resulted in a significant increase in both systolic and diastolic blood pressure; buprenorphine alone produced no effect on systolic and diastolic blood pressure different from placebo. There was no significant difference between any of the groups in the measurement of skin temperature, pupil size under dim, dark, or light conditions. Additionally, there was no significant difference in heart rate between all groups; however, a tendency for heart rate to remain higher in both naloxone groups was observed [130].

**Miscellaneous**

**pH**

Factors that affect systemic or urinary pH may have significant effects on methadone excretion and blood levels. This important effect is not well known by clinicians. Urinary pH is a major factor in the renal CLr of methadone. Bellward et al. [131] found that at low pH there was nearly a threefold increase in renal CLr, which was associated with a decreased major metabolite to methadone ratio. The urinary pH in the high CLr group was below 6.0, whereas the low CLr group had a pH that was found to be considerably higher. Nilsson et al. [132] confirmed these findings with a prospective crossover study using the urinary acidifier ammonium chloride and alkalizer sodium hydrogen carbonate. Alkaline urine increased methadone’s t1/2 and Vd, and decreased methadone’s body CLr. During alkaline condi-
tions, only a small amount of methadone was excreted in urine, suggesting almost complete resorption by the kidneys; with acidic urine, about 34% of the administered dose was excreted as urinary methadone [132]. Thus, coadministration of methadone with agents that change urine pH, such as acetazolamide and thiazides (alkalinate urine) or high doses of ascorbic acid (acidify urine) [133], can have profound effects on the distribution and elimination pharmacokinetics of methadone.

Changes in systemic pH also appear to influence methadone pharmacokinetics and pharmacodynamics. de Castro et al. [134] found that methadone-induced respiratory depression was more pronounced in rats administered omeprazole as compared with placebo. Omeprazole pretreatment produced a marked and significant increase in the respiratory depressant effect of methadone. A significant decrease in pO2, increase in pCO2, and decrease in blood pH was also seen. All changes were most pronounced at the 120-minute interval after methadone dose administration. Additional cohorts analyzed modification of gastric pH via coadministration of methadone with sodium bicarbonate, omeprazole, and an acidic solution of methadone (pH = 2). The Cmax and AUC of the omeprazole and bicarbonate groups increased at least threefold as compared with placebo, and there were no significant differences between these two groups. Changes in Cmax and AUC in the acidic group did not differ significantly from placebo. Significant respiratory depression was seen in the bicarbonate cohort. These results confirm that pH, not P450 involvement, was the mechanism behind the changes seen with the omeprazole group. As this was a single-dose study, it is therefore unlikely that P450 enzymes played a role in the results found [134]. The authors suggest that although the majority of methadone is absorbed in the small intestine, small changes or interindividual differences in gastric pH may influence plasma methadone concentrations [134].

**QT Prolongation**

Methadone may prolong the QT interval, which may then lead to the development of TdP. The evidence for QT prolongation and cardiotoxicity from oral methadone is lacking and remains limited to case reports of oral administration of doses greater than 200 mg/day [2,17]. The risk appears to be the greatest with intravenous administration and medical conditions or medications that predispose patients to QT interval prolongation [2].

In a recent cohort study of 118 patients receiving MMT [135], methadone induction and maintenance resulted in a modest but statistically significant mean increase in QT dispersion and QTc interval. The magnitude of the change in repolarization with methadone was similar to that associated with other nonantiarrhythmic drugs (e.g., cispapride), but substantially less than that associated with most antiarrhythmic agents. Concurrent antidepressant therapy was associated with a greater increase in QT dispersion, albeit the authors did not report specific antidepressants used. No QT dispersion value exceeded 100 milliseconds, which would be indicative of high arrhythmia risk. The patients studied were relatively free of structural heart disease and received a mean ± SD methadone daily dose after 6 months of therapy of 80 ± 32 mg (range: 20–180 mg). In this large, prospective study, no episodes of TdP, cardiac arrhythmia, or sudden death were documented, despite a high prevalence of tobacco and cocaine use self-reported by patients. Findings suggest that methadone results in clinically less significant cardiac repolarization effects than antiarrhythmic agents. Nonetheless, clinicians treating patients with methadone should be aware of the potential cardiac effects of this drug, particularly when prescribing it for patients receiving other QT-prolonging agents, such as antidepressants [135].

Some clinicians have postulated that the cause of cardiotoxicity in patients treated with parenteral methadone may be due to chlorobutanol, a preservative used in this formulation, rather than methadone itself [17]. Kornick et al. [136] investigated the ability of parenteral methadone to prolong the QT interval as compared with parenteral morphine. Findings of this in vitro study demonstrate that both methadone and chlorobutanol independently block human ether-a-go-go-related gene current (I_{HERG}) in a concentration-dependent manner. Chlorobutanol potentiated methadone's ability to block I_{HERG}, and this combination was found to be associated with QTc interval prolongation. Therefore, patients receiving parenteral methadone may be more likely to experience TdP as compared with patients receiving oral therapy at equivalent doses [136].

A few reports exist of MMT patients experiencing QT prolongation and/or TdP while using cocaine concomitantly with methadone [37,43,44,78,136]. However, only one of these patients...
had a baseline QT interval recorded at some time in the past [78]. Because cocaine itself can prolong the QT interval, it is difficult to know to what degree methadone contributed to this adverse event, if at all. However, as many patients receiving MMT have a history of cocaine abuse, clinicians should be aware of the potential consequences of this combination.

**Somatostatin**

Antagonism of analgesia was experienced by three patients previously well controlled on opioid therapy secondary to the introduction of somatostatin [137]. One 20-year-old patient with chondrosarcoma was prescribed oral methadone 12 mg daily prior to starting somatostatin therapy. Her pain control worsened during and after the start of somatostatin therapy, and a subsequent dose increase of methadone to 30 mg/day was ineffective. The patient was consequently rotated from methadone to morphine via both subcutaneous and intraspinal routes of administration, which also was ineffective. Pain relief was ultimately achieved with complete anesthesia of the legs secondary to hyperbaric bupivacaine. After somatostatin therapy was discontinued, a reduction in spinal morphine dose by more than 50% was achieved approximately 10 days later. Based on their findings, the authors suggest that somatostatin might interfere with opioid analgesia [137]. More studies are necessary to confirm this drug interaction and the mechanism(s) responsible.

**Disulfiram**

The proposed mechanism by which disulfiram may interact with methadone is through inhibition of hepatic microsomal enzymes. Although reviews of methadone occasionally cite disulfiram as an agent that may interact with methadone [1,8], this interaction does not appear to be substantiated in the literature. In a small study of participants in a methadone maintenance program, there was no significant interaction between disulfiram and methadone at doses used for management of alcoholism [138].

**Cigarette Smoking, Nicotine**

Results from several studies examining the effects of methadone on smoking and vice versa have shown that each drug influences use of the other. Specifically, methadone can increase the rate of smoking [139–141]. The influence of tobacco use on methadone has only recently been established. In a small experimental study of five methadone-maintained patients with a history of smoking, Spiga and colleagues [142] demonstrated that nicotine leads to heightened consumption of methadone. Tacke et al. [143] examined the relationship between subjective symptoms of inadequacy (“not holding”) of methadone dose and tobacco smoking among 50 patients participating in MMT. The investigators found that methadone patients who smoke more are significantly more likely to report problems of not feeling “held” by their methadone dose.

While behavioral mechanisms, in part or in whole, may account for these effects, a pharmacokinetic interaction between methadone and nicotine may exist. Cigarette smoke has been well characterized as a CYP1A2 inducer [22]. To our knowledge this potential pharmacokinetic interaction has been unexplored. Nonetheless, the prevalence of smoking in the MMT population is extremely high (around 90%) [144,145], and thereby this interaction may have important clinical implications. When investigating tobacco smoking in MMT patients, additional factors common to this patient population shown to influence smoking behavior, such as marijuana and alcohol use, also need to be considered [143].

**Dihydroergotamine**

Dihydroergotamine (DHE) is an ergot alkaloid used for the treatment of headaches. DHE is a reversible, selective inhibitor of the P450 3A enzymes [20] Using in vitro techniques to identify the hepatic P450 enzyme(s) involved in the major metabolic pathway of methadone, Iribarne et al. [20] found that DHE inhibited the N-demethylation of methadone by approximately 60%.

**Theoretical Interactions with Methadone**

The liver metabolizes many drugs, including methadone, and biotransformation via the cytochrome P450 system can potentially lead to drug interactions. Changes in the metabolism and elimination of methadone are mainly caused by inhibition or induction of CYP450, with a consequent increase or decrease of the amount of drug levels in blood and tissues [8]. Thus far we have described known drug interactions of methadone; however, many interactions are not clinically apparent because plasma concentrations with therapeutic doses are lower than those used to cause the interaction in vitro [8], although other pharmacological and genomic factors may play a role. Other pharmacokinetic drug–drug interactions of methadone have been postulated based on...
metabolic enzyme induction, inhibition, or competition for binding sites. Various CYP450 enzyme tables exist (e.g., http://medicine.iupui.edu/flockhart), which may aid the clinician in anticipating potential drug interactions; however, many of the drugs listed in these tables have not been studied directly with methadone.

There is no guarantee that because two medications share a common metabolic pathway that they will have a clinically significant pharmacokinetic interaction when coadministered in a particular patient [5]. Drug-specific factors such as route of administration, oral bioavailability, hepatic extraction ratio, active metabolite formation, therapeutic index, acute vs chronic administration, timing of administration, and the existence of alternate metabolic pathways available for a drug to undergo metabolism also play a role in the determination of whether a drug interaction will manifest itself and to what degree. Because an interaction with methadone has not been reported in the literature the clinician should not automatically discount its potential; rather, the patient should be carefully observed and, if necessary, the daily dose of methadone or the concomitant therapy should be adjusted on the basis of clinical signs and symptoms manifested by the patient. Clinicians should be suspicious of a drug interaction if the patient experiences exaggerated drug effects or reduced responses when methadone therapy is initiated or titrated, or when other medications are added to or eliminated from the patient’s regimen.

**Generalized Findings Related to P450**

The vast majority of drug interactions reported in this review are related to the cytochrome P450 system. CYP3A4 is the most common cytochrome P450 enzyme involved in drug metabolism, as approximately 60% of all medications are metabolized via this pathway, at least in part [146,147]. It affects both hepatic and intestinal metabolism, accounting for 60% of the P450 enzymes in the liver and 70% of those located in the gut wall [148–151]. CYP3A4 is the predominant enzyme responsible for the biotransformation of methadone to EDDP, and interindividual variability of CYP3A4 and other CYP enzymes accounts for a large part of the variation of methadone blood concentration for a given dosage [6]. It is of particular concern therefore that relatively few of the CYP3A4 inducers or inhibitors that have been identified have specifically been studied for their pharmacokinetic and/or pharmacodynamic effects on methadone, either *in vitro* or *in vivo*. Complicating matters is the fact that while some 3A4-based interactions occur predictably (e.g., ketoconazole), many do not (e.g., diazepam, ritonavir), which can be particularly frustrating for clinicians. Aside from alterations in activity secondary to liver disease or dietary influences such as grapefruit juice (a CYP3A4 inhibitor), significant variability within the P450 system itself may explain these discrepancies, at least partially.

The hepatic content of CYP3A4 varies at least 20-fold among individuals, and the activity associated with this enzyme varies 10-fold [147,152]. Similarly, small bowel 3A4 content varies 11-fold [147]. Ethnic and cultural differences are believed to be partially responsible for the interindividual variability seen, as well as age [153], and possibly gender [154], among other factors [147]. Additionally, many medications inhibit both 3A4 and P-glycoprotein in the gut, blurring the distinction of which mechanism is responsible for changes in a substrate’s bioavailability. The findings related to the variability in clinical relevance associated with methadone drug interactions also may be partially explained by other P450 enzymes such as 2B6, 2C8, and 3A5. These P450 isoforms are not as extensively studied as 3A4, 2D6, 1A2, 2C9, and 2C19, and may be underappreciated in general [5].

The emergence of evidence supporting the role of CYP2B6 as a contributing enzyme in methadone metabolism is of particular interest. Gerber et al. [54] found that the hierarchy of EDDP generation in vitro was 2B6 > 2C19 ≥ 3A4. A second experiment demonstrated that CYP2B6 formed EDDP many times more rapidly as compared with CYP2C19 and 3A4. Finally, in liver microsomes with high and low CYP2B6 expression and equivalent CYP3A4 expression, Gerber et al. found that microsomes with a high CYP2B6 expression generated twice the amount of EDDP as compared with microsomes that have five times less 2B6 expression [54]. Kharasch et al. [29] found that in vitro 2B6 was the second most active CYP450 enzyme at low (2.5 µM/L) methadone concentrations, and its activity was equivalent to 3A4 at higher concentrations (150 µM/L). The importance of CYP2B6 in the metabolism of methadone was recently confirmed in vivo by Crettol et al. [155]. Furthermore, polymorphisms are associated with CYP2B6, and the poor metabolizer genotype (*6/*6) was associated with higher S- and R,S-methadone plasma levels. Because of the selectivity toward the S- (i.e., nonopioid) enantiomer, the authors concluded that this genotype is more likely to have a minor, as opposed to significant,
influence on the metabolism of methadone [155]. The confirmation of CYP2B6 as a metabolic pathway of methadone, as well as the recognition of this enzyme’s induction potential for many medications (e.g., carbamazepine, dexamethasone, efavirenz, nevirapine, phenobarbital, and rifampin) helps explain inconsistencies found with drug interactions associated with methadone and CYP3A4 induction.

Another aspect of the complex interplay between methadone and enzyme inducers and inhibitors is the PXR/CAR pathway. While the activation of PXR regulates the expression of the CYP3A4 enzyme, “cross-talk” occurs between the PXR and CAR NR [21]. For example, CAR activation by phenobarbital can result in the transactivation of CYP3A4 expression and vice versa, providing a degree of functional redundancy. Thus, these NR may play a complementary role in the body’s defense against foreign xenobiotics [21]. Additionally, PXR polymorphisms have also been discovered, some of which have resulted in missense mutations leading to variant PXR proteins. More studies are required to determine whether the polymorphisms identified or yet unknown will be able to reliably predict CYP3A4 activity in vivo [21].

CYP2D6 is also significantly involved in the biotransformation of methadone. This enzyme is mainly expressed in the liver, and while not inducible like CYP3A4, it is subject to significant genetic variability secondary to polymorphism of this allele. Those patients that are homozygous with defective 2D6 alleles or heterozygous with a combination of two defective alleles are considered to be poor metabolizers (PM), whereas those individuals that are homozygous for the wild-type allele or heterozygous with one defective allele are considered to be extensive metabolizers (EM). Additionally, patients with a duplication or multiplication of the 2D6 allele are referred to as ultra metabolizers (UM). These polymorphisms can result in a more than 100-fold difference in CYP2D6 activity [6,156]. PM status is present in approximately 7% of white people [154,155], and 1–2% of Chinese or Japanese individuals [157–161]; UM status is found in 1–7% of white people [158,162,163], and may be as high as 29% in persons of Ethiopian decent [164]. The polymorphic nature of CYP2D6 must therefore be considered a variable in drug interactions, particularly those associated with methadone.

Inconsistency exists with in vitro studies investigating CYP2D6 N-demethylation of methadone [20,31,34]. Eap et al. [165] demonstrated the involvement of CYP2D6 in the metabolism of methadone in vivo by comparing MMT patients having PM, EM, or UM status. Significant differences were found between the genotypes and methadone concentrations to dose-to-weight ratios for R-, S-, and R,S-methadone. Therefore, 2D6 metabolizer status does impact methadone blood concentrations achieved at steady state [165]. A study by Begre et al. [80] demonstrated that paroxetine significantly inhibits the metabolism of methadone, with stereoselectivity toward the R-enantiomer. Paroxetine significantly increased the concentrations of R,S-methadone in the whole group and in the group of eight EMs; in the two subjects that were PM, only S-methadone concentrations were increased by paroxetine. These findings confirm the stereoselectivity of CYP2D6 metabolism of methadone, as well as the significance of patient genotype in predicting the manifestation of a drug interaction via the P450 pathway. It is also important to note that genotype does not necessarily equal phenotype. A study by Shiran et al. [166] illustrated this discrepancy as only three of 34 MMT patients were deemed to be PM by genotype, whereas 16 of 28 were PM by phenotype; eight patients that were genotyped as EM were assigned PM status by phenotype. The number of 2D6*4 alleles and sex were significant determinants of CYP2D6 activity in MMT patients; methadone dose, age, and weight did not contribute [166].

No studies have been identified by the authors that specifically evaluate methadone analgesia by differences in phenotype or genotype. Stamer et al. [167] investigated the impact of the PM phenotype on postoperative tramadol analgesia and found a higher percentage of nonresponders in the PM group as compared with the EM group. In addition, patients with the PM genotype required higher loading doses and more rescue medication. The results are largely due to patients’ inability to metabolize tramadol into O-desmethyltramadol (a mu opioid agonist) via the CYP2D6 pathway. Because methadone is not exclusively metabolized via CYP2D6 and does not require conversion to active metabolites, it would be expected that the difference in analgesia secondary to the PM phenotype would not be as pronounced as seen with tramadol. However, this assumption has yet to be confirmed.

Less is known about CYP1A2 and its role in the metabolism of methadone. This enzyme is similar to CYP3A4 in that it is not subject to genetic polymorphism and its activity varies significantly...
among individuals [8]. In vitro data suggest that CYP1A2 is a minor pathway of methadone metabolism with much less significance as compared with CYP3A4 [31,34]. However, CYP1A2 induction is known to occur secondary to cigarette smoking, and, as described previously, methadone consumption or control can be modified by the presence of nicotine [142,143]. It is more difficult to assess CYP1A2 inhibition of methadone metabolism, as many drugs known to be inhibitors of CYP1A2 also inhibit other P450 enzymes, such as 3A4 and/or 2D6. More in vivo studies are needed to confirm or refute the role of CYP1A2 in the metabolism of methadone. In the meantime, clinicians should be aware of the potential for such an interaction, particularly in patients taking methadone and actively smoking tobacco, as well as those considering smoking cessation.

The enzymes 2C9 [31,34] and 2C19 [54] have been implicated to be significant in the metabolism of methadone in vitro. Both CYP2C9 and CYP2C19 have genetic polymorphisms, with *2 and *3 alleles indicating PM status. Crettol et al. [155] investigated the significance of these two enzymes and associated polymorphisms, and found that neither CYP2C9 nor CYP2C19 genotypes influenced methadone levels in vivo, as there was no significant difference in the methadone blood levels for PM and EM of either enzyme. Therefore, drug interactions mediated via the CYP2C9 or 2C19 pathway alone are unlikely to be of clinical significance.

AAG Binding

As mentioned throughout this review, some uncertainty exists surrounding the potential or actual clinical impact AAG binding has on methadone and medications that compete for these binding sites. In vitro studies have demonstrated that two classes of binding sites exist for basic and neutral drugs [16,168]. Abramson [16] suggested that a methadone concentration of 4,600 ng/mL would be necessary to achieve half-saturation. Typical therapeutic concentrations for MMT are between 100 and 200 ng/mL. When methadone is used for analgesia, a range of 100–800 ng/mL is considered therapeutic; levels in excess of 800 mg/mL have also been reported. Thus, one would not expect to achieve even half-saturation of binding sites with doses of methadone used in clinical practice.

Within each individual, there is a genetic polymorphism of AAG; however, the pharmacological consequences and clinical significance of this polymorphism remains to be elucidated [6]. For instance, a drug interaction between methadone and imipramine secondary to AAG binding displacement may not be of significance in 85% of the population; however, the remaining 15% with a phenotypic variation may be at risk for its clinical manifestation. It also is unclear whether changes in AAG concentrations lead to variations in the relative concentrations of its variants. If this is the case (e.g., with inflammatory conditions), functional heterogeneity of AAG may alter drug binding in various disease states [169].

Difficulty in Extrapolating In Vitro Data to In Vivo Applications

The relevance of in vitro findings needs to be carefully interpreted in the in vivo environment [5], as a number of different factors may misrepresent the severity or significance of a drug interaction seen at the in vitro level. Many drug interactions have only been demonstrated in vitro or in animal studies, and may not become apparent clinically because plasma concentrations associated with therapeutic doses are lower than those used to precipitate the interaction in vitro [8]. It is important to bear in mind that drug interactions reported in vitro and based upon the competition for the same P450 isoform, do not allow for extrapolation to in vivo [23]. The extent of in vivo drug interactions is dependent upon the drugs’ relative affinity and inhibitory constants, their relative doses, and their plasma levels, among other factors [23]. For example, as aforementioned, plasma concentrations of methadone during MMT have been reported to be about 100–200 ng/mL, which are many orders of magnitude lower than its affinity for CYP3A4 [23]. At this concentration, for instance, methadone would be predicted to inhibit less than 2% of nifedipine’s metabolism [23]. The clinical significance of such interactions therefore remains questionable unless shown in a clinical study [170]. The substrate concentration must also be considered when interpreting in vitro results. For example, the discrepancy seen in sulfaphenazole’s ability to inhibit EDDP formation may have been secondary to Iribarne et al. [20] using a methadone concentration of 500 µM, whereas Moody et al. used 10 µM, which is much more close to physiological levels [31]. Thus, very high concentrations of methadone may have obscured the CYP2C9 activity that was evidenced at lower concentrations. Time-dependent inhibition of P450 enzymes by the candidate drug also may not be captured by an in vitro test, complicating the prediction of the
extent of drug–drug interactions in vivo [5]. Therefore, drug–drug interactions predicted from in vitro data may underestimate the true interaction that could occur in the presence of a time-dependent inhibitor [5].

**Limitations of Current Evidence Base**

The majority of references included in the evidence base specific to drug interactions with methadone are case reports or case series. Therefore, by definition, the level of evidence and grade of recommendation for these citations is 4C, using the system developed by the Oxford Center for Evidence-based Medicine (http://www.cebm.net/levels_of_evidence.asp). Very few double-blind, placebo-controlled studies exist focusing solely on methadone and drug interactions. For those citations that are clinical trials or studies, the enrollment is generally very small; no study included in this review exceeded a sample size of 260 patients [165], and the majority had less than 50 subjects enrolled. Due to this comparatively low enrollment, as well as the heterogeneity of study design and outcomes measured in these reports, a systematic review, rather than a meta-analysis, was performed.

Most of the data regarding the use of methadone have been generated from younger adults on MMT. These patients often have concomitant HIV disease with complicated medication regimens and a history of drug abuse, both of which further obscure methadone pharmacotherapy. They also differ physiologically from other populations. As mentioned previously, MMT patients have a higher Vd of methadone than adults not receiving methadone maintenance [10,12]. There also are some differences with regards to protein binding. Patients undergoing opioid withdrawal were found to have significantly higher AAG serum concentrations and less unbound methadone as compared with a control group [13]. Finally, as seen throughout the previous sections of this report, MMT patients frequently consume tobacco, illicit substances such as cocaine or marijuana, benzodiazepines, and/or alcohol concomitantly with methadone. This fact makes it difficult not only to generalize findings specific to a particular drug interaction reported in studies completed, but also to extrapolate those findings to patients not consuming these medications—even on a periodic basis.

There is a dearth of data regarding methadone’s clinical utility in the elderly population. Because the majority of published studies and case reports are specific to the MMT population, most studies do not include individuals that are 65 years of age or older. Older adults are particularly vulnerable to drug interactions and adverse effects from pharmacotherapy due to multiple, coexisting chronic illnesses that require complex drug regimens, sensory and motor deficits, and physiological changes associated with aging. It is well known that some medications may alter the absorption or metabolism of methadone and their concurrent use may require dosing adjustments. However, the extent and clinical significance of these interactions are largely unknown. There also is believed to be an age-related decline in P450 activity as well [171]. While the CLr of methadone does not appear to be affected by age significantly [6,172,173], these patients may be more susceptible and sensitive to an interaction that alters methadone’s metabolism or results in a synergistic effect such as additive drowsiness. More studies are warranted to ensure the safe and appropriate use of methadone in this vulnerable population.

Only a few studies in this base of evidence included patients who were taking daily methadone doses in excess of 200 mg [37,43,44,60,74,77,115,128,155,165,174]. One possible explanation for this finding may be attributed to the dosing limitations associated with many MMT programs. Higher daily doses of methadone are sometimes necessary when using this opioid in the treatment of pain. For example, one analysis of outpatient methadone prescribing found that 5% of hospice patients were prescribed daily doses in the range of 201–300 mg; 4% were prescribed daily doses in excess of 300 mg [175]. Although many in vitro studies were performed with multiple concentrations of methadone, some of which being supra-therapeutic, it is not known if very high serum levels will precipitate the materialization of drug interactions not commonly seen at lower doses of methadone. There does appear to be such a relationship present with methadone dose and the precipitation of TdP. However, similar to the drug interaction evidence base, the evidence base outlining this relationship is under-developed in general and filled with confounders, making it difficult to assign causality to methadone dose alone.

**Conclusion**

While many medications have been reported to interact with methadone, the evidence base asso-
cient with this topic is underdeveloped in general. The majority of studies and reports outlining these drug interactions are with patients receiving MMT for opioid addiction. Similarly, the majority of patients comprising these reports are between 20 and 60 years of age. Another potential confounder is that many of these patients were smokers and were allowed to consume tobacco, a CYP1A2 inducer, during the drug interaction studies and reports. Significant variability in patient response can occur with methadone, and may be partially explained by genetic differences between individuals. Polymorphisms associated with CYP2D6, other CYP enzymes, and perhaps AAG can influence methadone’s metabolism as well as the manifestation and/or severity of a drug interaction. Pharmacogenomic testing may be a useful strategy in patients with either an incomplete or an exaggerated response to methadone.

The use of methadone is rapidly expanding outside of the MMT population for the management of chronic nonmalignant pain as well as for cancer pain. These patient populations differ significantly from the typical MMT patient. Therefore, caution is advised when interpreting and applying the current methadone interaction evidence base to these patients. Additionally, the majority of studies and reports reviewed in this article included patients taking methadone doses of 200 mg/day or less. Very high doses of methadone, while not commonly prescribed, are sometimes necessary for patients with intractable pain or high tolerance to opioids. Therefore, interactions studied at lower methadone doses and believed not to be of clinical significance may become significant at higher daily doses. Finally, while the evidence base associated with methadone conversion ratios also continues to mature, very few studies investigating these ratios and associated dosing schemes mention or take into account drug interactions present during these investigations. The authors recommend that the continued use of methadone be encouraged; however, clinicians should exercise due diligence when prescribing and monitoring this unique, yet complicated therapy.

References

18 Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: A current view of
Actual and Potential Drug Interactions Associated with Methadone


107 Preston KL, Griffiths RR, Cone EJ, Darwin WD, Gorodetzky CW. Diazepam and methadone blood levels following concurrent administration of diaz-


Appendix

Abbreviations and acronyms associated with pharmacokinetic terms used in this review

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Translation</th>
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<tbody>
<tr>
<td>$t_{1/2}$</td>
<td>Elimination half-life</td>
</tr>
<tr>
<td>$F$</td>
<td>Bioavailability</td>
</tr>
<tr>
<td>$V_d$</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>NR</td>
<td>Nuclear receptor(s)</td>
</tr>
<tr>
<td>CYP1</td>
<td>Polycyclic aromatic hydrocarbon-like</td>
</tr>
<tr>
<td>CYP2 or CAR</td>
<td>Phenobarbital-like or constitutively active receptor</td>
</tr>
<tr>
<td>CYP3 or PXR</td>
<td>Glucocorticoid-like, also referred to as pregnane X receptor</td>
</tr>
<tr>
<td>CYP4</td>
<td>Clofibrate-like</td>
</tr>
<tr>
<td>CLr</td>
<td>Clearance</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum concentration</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>Cmin</td>
<td>Minimum concentration</td>
</tr>
<tr>
<td>Tmax</td>
<td>Time to maximum concentration</td>
</tr>
<tr>
<td>PM</td>
<td>Poor metabolizer(s)</td>
</tr>
<tr>
<td>EM</td>
<td>Extensive metabolizer(s)</td>
</tr>
<tr>
<td>UM</td>
<td>Ultra metabolizer(s)</td>
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</tbody>
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