FULL REVIEW

Pharmacokinetic drug interactions and adverse consequences between psychotropic medications and pharmacotherapy for the treatment of opioid dependence

Ali S. Saber-Tehrani, M.D., Robert Douglas Bruce, M.D., M.A., M.Sc. and Frederick L. Altice, M.D, M.A.

Yale University AIDS Program, Section of Infectious Diseases, Department of Internal Medicine, Yale School of Medicine, Yale University, New Haven, CT, USA

Background: Psychiatric comorbidities among opioid-dependent patients are common. Many medications used to treat both conditions are metabolized through complimentary cytochrome P450 isoenzymes. When medication-assisted treatment for opioid dependence is concurrently used with psychotropic medications, problematic pharmacokinetic drug interactions may occur.

Methods: We reviewed relevant English language articles identified through the MedLine, Scopus, and Embase databases from 1950 to December 2009 using the specific generic names of medications and keywords such as pharmacokinetics and drug interactions with buprenorphine, methadone, and naltrexone. Selected references from these articles were reviewed. Additionally, a review was conducted of abstracts and conference proceedings from national and international meetings from 1990 to 2009. A total of 60 studies were identified and reviewed.

Results: Clinical case series and carefully controlled pharmacokinetic interaction studies have been conducted between methadone, buprenorphine, or naltrexone and some psychoactive medications. Important pharmacokinetic drug interactions have been demonstrated within each class of medications affecting either methadone and buprenorphine or psychoactive drugs. Few studies, however, have been conducted with naltrexone.

Conclusions and Scientific Significance: Several interactions between methadone, buprenorphine, or naltrexone and psychoactive medications are described and may have important clinical consequences. To optimize care, clinicians must be alerted to these interactions.

Keywords: methadone, buprenorphine, naltrexone, psychoactive medications, drug interactions

INTRODUCTION

Opioid dependence remains a major global health issue that is associated with significant negative medical and social consequences. Methadone, buprenorphine, and naltrexone are evidence-based pharmacological treatments for opioid dependence and have consistently been demonstrated to be safe and effective. Although pharmacokinetic interactions between pharmacological therapies for opioid dependence and HIV therapies have been reviewed, there remains a paucity of information in the interactions between these therapies and the treatment of a more prevalent condition, mental illness (1,2). The prevalence of comorbid psychiatric illnesses is many times greater among patients with opioid dependence than among the general population, thus requiring concomitant treatment for both conditions (co-occurring disorders) to achieve optimal outcomes. Despite this urgent clinical need, continued concerns regarding the misuse of methadone or buprenorphine when combined with other psychotropic medications persist (1).

Methadone-maintained patients are often concomitantly prescribed psychotropic medications because of the high prevalence of psychiatric comorbidity observed among individuals with opioid dependence (3–5). Furthermore, some psychotropic medications have the...
potential for abuse and there are reports in the literature that some methadone-maintained patients may abuse or be prescribed by a clinician a psychoactive medication such as benzodiazepines (6), selective serotonin reuptake inhibitors (SSRIs) (7–9), antipsychotics (10), tricyclic antidepressants (11), and others that have been associated with altered metabolism or synergistic toxicities (e.g., prolongation of the QT interval) with medication-assisted therapy, such as methadone.

Case series, for example, from methadone maintenance programs suggest that approximately one-third of patients use benzodiazepines in any given month (12–14). Although these medications are sometimes prescribed for the treatment of anxiety disorders in patients, they are frequently taken in excess of prescribed doses or purchased for self-consumption (6,15). Although the etiology of this use is diverse, potential explanations include the high level of underlying anxiety disorders such as post-traumatic stress disorder or self-management of concomitant stimulant use (15). More concerning is that benzodiazepines have been identified in 50–80% of heroin-related deaths (16), in 63.7% of methadone-related deaths (17), and in up to 80% of buprenorphine-related deaths (18).

Appropriate clinical use of these medications requires an understanding of the principles of both pharmacokinetics and pharmacodynamics. Pharmacokinetics, described as what the body does to the drug, includes processes such as absorption, distribution, localization in tissues, biotransformation, and excretion, whereas pharmacodynamics, or what the drug does to the body, refers to the physiological effects of a drug and the body’s compensatory homeostatic adjustments to the presence of the drug (19). Given the potential for the serious adverse events, it is important to better understand the relative safety of methadone, buprenorphine, and naltrexone when taken in combination with other psychoactive drugs. We therefore review the clinical and pharmacokinetic data between the treatments for opioid dependence (methadone, buprenorphine, and naltrexone) and a list of broadly prescribed psychotropic medications that may be commonly coadministered.

METHODOLOGY

We reviewed relevant English language articles identified through the MedLine, Scopus, and Embase databases from 1950 to December 2009 using specific medication names and keywords such as pharmacokinetic or drug interactions and buprenorphine, methadone, and naltrexone. Selected references from these articles were reviewed. Additionally, abstracts and conference proceedings from national and international meetings from 1991 to 2009 were reviewed using conference proceedings citation index provided by Web of Science. A total of 60 studies were identified and reviewed.

Detailed metabolism of each of these medications has been reported previously (2,20). Briefly, methadone undergoes oxidative metabolism through multiple cytochrome P450 isoenzymes, including CYP 2B6, 3A4, 2C19, 2D6, and 2C8 (21–24). Methadone is a racemic mixture of R and S enantiomers, of which (R)-methadone is the most active compound (25). Metabolism at CYP 2B6 and CYP 2C19 is stereo-selective, and this may explain why the plasma concentration ratio of R/S-methadone is variable (22,26). Methadone is metabolized to an inactive metabolite – a risk for opioid withdrawal when given with inducing medications. The most important dose-dependent adverse effects of methadone are respiratory depression and cardiac rhythm disorders related to QT interval prolongation (27) with, in some cases, sudden death through polymorphic ventricular tachycardias such as torsade de pointes (28).

Buprenorphine is N-dealkylated to norbuprenorphine primarily by CYP 3A4 and CYP 2C8 (29–31). Both buprenorphine and norbuprenorphine are glucuronidated by uracil diphosphate–glucuronosyl transferases (UGTs). The role and importance of UGT has been described previously (32–39). Although there were limitations to some of these reports (34), such as not being conducted under predefined conditions that compare one isoform to another, other studies conducted under uniform conditions provide further insight into UGT’s pharmacological mechanisms with buprenorphine (38,39). For example, UGT 1A8 does not appear to be involved in the glucuronidation of either buprenorphine or norbuprenorphine (38,39). Buprenorphine glucuronidation is, however, principally glucuronidated by UGT 1A3 with less involvement by 2B6 and 1A1 and much less involvement by 2B17. Norbuprenorphine glucuronidation is also principally glucuronidated by UGT 1A3 with less involvement from 1A1 and much less from 2B17 and 2B7 (38,39). The relative lack of metabolism of norbuprenorphine by UGT 2B7 is a major difference between parent compound and oxidative metabolite. Two in vitro studies suggest that buprenorphine and its major active metabolite norbuprenorphine are inhibitors of CYP 2D6 and CYP 3A4; however, because of relatively high dissociation constant (K_i) for inhibition, they are not predicted to cause clinically important drug interactions with other drugs metabolized by major hepatic P450 isoenzymes at therapeutic concentrations (40,41).

Naltrexone, available in both oral and injectable formulations, is highly bioavailable orally (42) and is not metabolized through cytochrome P450 isoenzymes. Instead, it is predominantly reduced to 6-β-naltrexol hepatically by dihydrodiol dehydrogenase (43,44). Conjugated naltrexone and conjugated 6-β-naltrexol are then excreted in the urine (42). There are reports of liver toxicity caused by naltrexone (45,46). Clinicians should keep this fact in mind when they prescribe naltrexone with other medications associated with
potential liver toxicity. With the exception of diazepam, there is little, if any, expected pharmacokinetic interactions with naltrexone. There are, however, case reports of interactions between thioridazine and naltrexone (47).

Benzodiazepine Metabolism
Benzodiazepines are conjugated hepatically by multiple UGT enzymes to form pharmacologically inactive, water-soluble glucuronide metabolites that are then excreted in the urine. The 3-hydroxy benzodiazepines, oxazepam, lorazepam, and temazepam, by virtue of their 3-hydroxy group, can be conjugated directly. The 2-keto benzodiazepines, such as chlordiazepoxide, clorazepate, and diazepam, must first be oxidatively metabolized into 3-hydroxy derivatives before they can be conjugated. The 7-nitro benzodiazepines, clonazepam and nitrazepam, are metabolized by reduction of the 7-nitro substituents to form inactive amines that are then acetylated before excretion (19).

Other studies have indicated that CYP 2C19 is involved in the metabolism of diazepam, and CYP 3A4 is involved in the metabolism of alprazolam, clonazepam, midazolam, and triazolam (48–54). Flunitrazepam is also metabolized by CYP 3A4 in humans (48).

Benzodiazepine Interactions
The epidemiology of benzodiazepine use among opioid-dependent persons and the interactions between benzodiazepines with methadone or buprenorphine have recently been reviewed by Lintzeris et al. (55). We therefore limit our review on this topic and only provide explanatory mechanisms essential for understanding these interactions.

Benzodiazepine Interactions with Methadone
Safety concerns about benzodiazepines and methadone coadministration (55–57), including potentially fatal central nervous system (CNS) depression, are raised by practitioners and policy-makers alike (58). During coadministration, the CNS depressive effects may be more synergistic than additive. Data regarding interactions between benzodiazepines and methadone are varied, in part due to the use of in vitro animal studies and nontherapeutic doses of medication. Diazepam has been studied most for its interactions with methadone (57,59–61). One in vitro study (24) demonstrating competitive inhibition of diazepam on methadone N-demethylation was limited by supratherapeutic dosing confirmed by a Ki of 50 μM; this finding has not been confirmed clinically by such interactions in humans (60,61). Flunitrazepam has also been reported to lower the intravenous minimum lethal dose of methadone in rats (62). The differences between rats and humans, however, may preclude extrapolation of these results to humans for clinical purposes (62). Table 1 summarizes these interactions. Further studies are needed to determine whether this effect is a pharmacokinetic interaction or a pharmacodynamic one.

Benzodiazepine Interactions with Buprenorphine
As buprenorphine (63) and most benzodiazepines (50–54) undergo extensive metabolism by cytochrome P450 (CYP 3A4), metabolic interactions are plausible. Chang and Moody (64), however, demonstrated that benzodiazepines are not potent inhibitors of buprenorphine metabolism using human liver microsome. Of note, evidence for the metabolically activated inhibition of nor-buprenorphine has been shown in the case of midazolam and zolpidem (64,65).

In rats, high doses of midazolam or buprenorphine alone have limited effects on respiratory depression, measured using arterial blood gases, whereas midazolam and buprenorphine appear to be additive or synergistic in depressing their respiration and inducing hypoxia (66). The concomitant injection of buprenorphine with midazolam has recently been reported in Southeast Asia (67,68). The studied subjects have suggested that injecting midazolam “boosted” and prolonged the effects of buprenorphine (67). The clinical importance of CYP 3A4 inhibition is not established in detail and further studies are needed to assess the in vivo inhibition potential.

Although flunitrazepam is rarely detected in clinical settings due to its rapid degradation in vitro, it is suspected to be involved in a large number of buprenorphine intoxications and adverse consequences (18,69,70). Studies performed on human microsome preparations have predicted the absence of in vivo metabolic interactions between buprenorphine and flunitrazepam when dosed at therapeutic concentrations (40,71,72).

In humans, both CYP 3A4 and 2C19 are involved in the metabolic pathways of flunitrazepam to desmethyl flunitrazepam and to the third flunitrazepam metabolite, 3-OH flunitrazepam (73). This mechanism, however, is not entirely elucidated in rats. Megarbane et al. (74) demonstrated that rat pretreatment with flunitrazepam alters neither plasma nor striatal buprenorphine distribution. Pretreatment with buprenorphine has had no effects on flunitrazepam disposition, while inducing a threefold increase in its main active metabolite, desmethyl flunitrazepam, plasma concentration (75). The desmethyl flunitrazepam AUC/flunitrazepam AUC ratio, named the “metabolism index,” has been increased by 41% in buprenorphine-pretreated rats when compared with 15% in controls (75). This difference resulted in a significant decrease in PaO2 and an increase in PaCO2 levels in rats, confirming increased respiratory depression (75).

As there are differences among species in metabolism, human studies are needed before extrapolating these findings to humans. Similar studies in humans examining flunitrazepam and desmethyl flunitrazepam kinetics, however, have not been performed.

Under pharmacological conditions, projected in vivo inhibition of CYP 3A4-mediated metabolism of flunitrazepam by buprenorphine is ~1.2–2.5%. Estimated inhibition of buprenorphine N-dealkylation by flunitrazepam in vivo is ~0.08% (72). These results are not significant and do not support a buprenorphine–flunitrazepam metabolic interaction at the concentrations that occur in humans. Of
TABLE 1. Interactions between psychotropic medications and methadone or buprenorphine.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Buprenorphine</th>
<th>Methadone</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>No effect (64)</td>
<td>Not studied</td>
<td>Risk of additive effects on respiratory depression and psychomotor impairment</td>
</tr>
<tr>
<td>Diazepam</td>
<td>No effect (64)</td>
<td>Inhibition of methadone N-demethylation with the K_i of 50 μM (24)</td>
<td>Both human in vitro studies</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>↓ FZ Metabolism by .1–2.5% (72)</td>
<td>↓ MTD MLD</td>
<td>Human in vitro study</td>
</tr>
<tr>
<td>Midazolam</td>
<td>IC_50 for N-BPN formation = 20.25 μM (65)</td>
<td>Not studied</td>
<td>Human in vitro study</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Not studied</td>
<td>(R)-MTD metabolism by 41% and (S)-MTD metabolism by 77% (21)</td>
<td>Human in vitro study</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>No effect (90)</td>
<td>(R)-MTD metabolism (89)</td>
<td>Human in vivo study</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>↓ BPN metabolism</td>
<td>↓ (R)- and (S)-MTD metabolism (23)</td>
<td>Opioid withdrawal symptoms have been described at the sudden stop of fluvoxamine (96)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Not studied</td>
<td>3–33% ↑ in (R)-MTD dose (10)</td>
<td>Varies with poor versus extensive metabolizers</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Not studied</td>
<td>No effect (106)</td>
<td>Human in vivo study</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Not likely</td>
<td>↓ MTD levels (122)</td>
<td>Risk of MTD overdose on sudden cessation of carbamazepine</td>
</tr>
<tr>
<td>Valproate</td>
<td>No effect</td>
<td>No effect</td>
<td>Human in vivo study</td>
</tr>
<tr>
<td>Lithium</td>
<td>Not studied</td>
<td>No effect</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td></td>
<td>↑ TCA toxicity (130)</td>
<td>Increased risk of QT prolongation with MTD, risk of withdrawal syndromes with sudden cessation</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Not studied</td>
<td>↓ MTD metabolism (11)</td>
<td>Human in vivo study</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Not studied</td>
<td>↓ MTD metabolism (133)</td>
<td>Animal in vivo study</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td></td>
<td>Contraindicated</td>
<td>Potential for serotonin syndrome</td>
</tr>
</tbody>
</table>

Note: MLD, minimum lethal dose; MTD, methadone; BPN, buprenorphine.

High-dose diazepam has been associated with time-dependent increases in the intensity of subjective medication effects and decreases in psychological performance in buprenorphine-maintained patients (55). Buprenorphine, when combined with clonazepam, nordiazepam, oxazepam, or bromazepam at therapeutic doses, has not influenced respiration or arterial exchange in rats, when compared with buprenorphine alone. Combinations of oxazepam or nordiazepam with buprenorphine, however, have significantly deepened sedation in rats (78). These differences are probably because of the unique properties of each benzodiazepine.
molecule. However, to date, the molecular basis for these observations remains to be determined.

With the exception of midazolam, these results strengthen animal studies and observations in humans that suggest the adverse interactions between benzodiazepines and buprenorphine most probably arise from a pharmacodynamic mechanism rather than a pharmacokinetic one (66,79).

Given the disparity between the findings from in vitro and in vivo studies and the clinical findings reported from the case series, pharmacodynamic studies examining the safety of escalating doses of benzodiazepines in buprenorphine-maintained patients are needed.

**Benzodiazepine Interactions with Naltrexone**

There seems to be little likelihood of pharmacokinetic drug interactions occurring in vivo between naltrexone and most benzodiazepines. The studies on human liver microsomal preparations demonstrate that benzodiazepines inhibit dihydrodiol dehydrogenase, the enzyme responsible for the formation of 6-β-naltrexol from naltrexone (44), by less than 20% (44). Moreover, as a complete μ-opioid receptor antagonist, one might not anticipate any pharmacodynamic interactions.

Interestingly, naltrexone does increase the sedative effects of diazepam and delay the time to reach peak blood diazepam levels. The precise mechanism by which naltrexone alters the time to peak concentration is not known, but it is possibly due to a delay in diazepam absorption (80). Naltrexone increases the half-life of diazepam from 4.0 h to 4.3 h, but the area under the curve (AUC) remains unchanged (80), perhaps suggesting that this would not result in any clinically significant pharmacodynamic interaction.

**SSRIs Metabolism**

Pharmacokinetic interactions caused by metabolic inhibition of CYP isoenzyme activity represent the majority of the interactions reported with the SSRIs (81). Although members of this class of medications are quite similar in their antidepressant activity and side effect profiles (82), they differ substantially in their chemical structure, metabolism, pharmacokinetics, and their inhibitory effects on the cytochrome P450 system.

Fluoxetine is mainly excreted in urine, with less than 10% excreted unchanged or as fluoxetine N-glucuronide (83). It has been suggested that CYP 2C9 plays a pivotal role in the N-demethylation of fluoxetine with a possible contribution of the CYP 2C19 and a CYP 3A4 isoform (83). Fluoxetine strongly inhibits CYP 2D6 (84). Norfluoxetine, a major metabolite of fluoxetine, is also a strong inhibitor of CYP 3A4 (85).

Fluvoxamine’s main route of elimination is through hepatic metabolism that has been found to be associated with CYP 2D6 polymorphism and also CYP 1A2 activity. Paroxetine undergoes extensive metabolism in the liver to form more hydrophilic excretable compounds (83). Paroxetine is the most potent inhibitor of CYP 2D6 among all SSRIs (86) but, unlike fluoxetine and fluvoxamine, paroxetine is also a mild inhibitor of CYP 1A2, CYP 2C9, CYP 2C19, and CYP 3A4 (84).

The metabolism of citalopram leads to two pharmacologically active metabolites with two enantiomers for each. It has been shown that CYP 2C19 and CYP 2D6 each play a role in the biotransformation of citalopram (83). The N-demethylation of sertraline correlates with the activity of CYP 3A4 (87).

**SSRIs Interactions**

**SSRIs Interactions with Methadone**

Depressive disorders are highly prevalent among those with substance use disorders (88), and patients prescribed methadone are also commonly prescribed SSRIs. There are reports of pharmacodynamic interactions between methadone and different SSRIs. For example, fluoxetine significantly increases (R)-methadone concentrations (84,89). It inhibits CYP 3A4 and CYP 2D6, both of which are involved in methadone metabolism (84,90), although CYP 3A4 is considered to have a more prominent role compared with CYP 2D6 (21,91–93). Fluvoxamine is a nonselective inhibitor of CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, and CYP 3A4 and increases concentrations of both (R)- and (S)-methadone (89,90,94,95). Additionally, opioid withdrawal symptoms have been described when fluvoxamine is suddenly stopped, because fluvoxamine continues inhibiting 2D6 and 3A4, allowing for increased metabolism of methadone and development of withdrawal symptoms (96).

Paroxetine inhibits CYP 2D6 more than fluoxetine or norfluoxetine (50) and is also an inhibitor of CYP 3A4 (21,84). Paroxetine significantly increases the concentrations of both enantiomers of methadone (23), which is due to inhibition of not only CYP 3A4 but also CYP 2D6 and, to a minor extent, CYP 2C8 (21). Whether discontinuation of paroxetine can result in withdrawal is yet to be studied. Pharmacodynamic studies, however, have yet to examine the association between paroxetine and increased methadone levels and until they are done, clinicians should be alert to the effects of SSRIs on serum methadone levels and the possible need for adjusting the methadone dose, especially after sudden discontinuation of SSRI medications.

**SSRIs Interactions with Buprenorphine**

Buprenorphine is metabolized primarily through cytochrome P450 3A4, whereas fluoxetine and fluvoxamine inhibit 2D6 and 3A4 in vitro. Iribarne et al. (90), however, demonstrated that fluoxetine does not inhibit buprenorphine dealkylation in vitro but norfluoxetine inhibits buprenorphine metabolism. Fluvoxamine, on the contrary, has been shown to inhibit buprenorphine dealkylation uncompetitively. There have been instances of drug interactions such as the interaction between delavirdine and buprenorphine that can cause a change in the buprenorphine metabolism but does not result in any clinical manifestations (97). Further studies are
Antipsychotic Medication Metabolism

One of the major advantages of novel antipsychotics over classical compounds is their negligible effect on hepatic drug-metabolizing enzymes (98). Unlike older antipsychotics, such as phenothiazines, which are potent inhibitors of CYP 2D6 (99), novel antipsychotics are only weak in vitro inhibitors of P450 isoenzymes at therapeutic concentrations (100, 101).

The major metabolic pathways of olanzapine include direct N-glucuronidation, mediated by UGT 1A4, and N-demethylation, mediated by CYP 1A2 (102). Minor pathways of olanzapine biotransformation include N-oxidation, catalyzed by flavin-containing monoxygenase-3 system, and 2-hydroxylation, metabolized by CYP 2D6 (101, 102). Olanzapine does not inhibit P450 isoenzymes (102) and therefore should not have any significant pharmacokinetic interactions.

Quetiapine, a dibenzothiazepine derivative, is extensively metabolized in the liver by sulfoxidation to form its major, but inactive, sulfoxide metabolite. Eleven metabolites have been identified. N- and O-dealkylation also occur as lesser metabolic pathways (103). Quetiapine and its metabolites were found to be weak inhibitors of the activity of cytochrome P450 enzymes (CYP 1A2, 2C9, 2C19, 2D6, and 3A4) and are, therefore, not expected to produce clinically relevant inhibition in vivo (104).

Antipsychotic Medication Interactions

Uehlinger et al. (10) demonstrated that quetiapine increases plasma concentrations of (R)-methadone, which is speculated to be due to an interaction with CYP 2D6 or the P-glycoprotein transporter system or both. In this particular study, however, no pharmacodynamic signs of oversedation caused by increased methadone plasma concentrations were described. There are reports of quetiapine abuse especially among inmates with a history of drug dependence (105). Further studies are needed to confirm the presence of a pharmacodynamic or pharmacokinetic interaction between quetiapine and other opioids. Opioid withdrawal symptoms might theoretically occur when quetiapine treatment is abruptly interrupted, but remain unknown until empirically studied.

The addition of olanzapine to patients on stable methadone doses has not resulted in clinical withdrawal in patients. Moreover, no change in plasma methadone ratio has been observed in relation to the dose before and during the treatment, which suggests a lack of pharmacokinetic interaction between methadone and olanzapine (106).

Recent studies document methadone’s ability to prolong the QT interval that can result in torsade de pointes (107–109). Psychotropic medications such as chlorpromazine, intravenous haloperidol, ziprasidone, levomepromazine, aripiprazole, and sulproide have been found to significantly lengthen the QT interval, whereas oral haloperidol, bromperidol, olanzapine, quetiapine, risperidone, and zotepine do not (110). Studies examining the potential interactions of methadone and antipsychotic medications on QT prolongation are needed to explore the safety of concomitant administration because of concerns that these various medications may have additive effects on QT prolongation when coadministered.

Furthermore, members of SSRI family, especially fluoxetine, paroxetine, and sertraline, have been associated with cardiac rhythm disturbances such as prolonged QT interval (111–113). Moreover, tricyclic antidepressants have been found to cause defects in the cardiac conduction due to the slowdown in the cardiac depolarization and expansions in the QT interval that predispose the patients to cardiac arrhythmias (114–116). Considering methadone’s effects on QT interval (107) and the potential for additive effects, caution should be advised on coadministration of these medications and methadone.

Prescribing higher doses of methadone to improve treatment outcomes for opioid dependence in recent years and the frequent addition of psychotropic medications to treatment regimens are two of the reasons why clinicians should be more aware of the possible additive effects between antipsychotic medications and methadone. It would be advisable to take careful medical history screening for known cardiac risk factors, perform baseline and follow-up electrocardiograms, and watch for potential additive effects.

Metabolism of Mood Stabilizers

Mood stabilizers are medications used to treat mood disorders characterized by intense and sustained mood shifts such as in bipolar disorder. Lithium, the first mood stabilizer, is not metabolized by the liver. Other described “mood stabilizers,” most of which are also categorized as anticonvulsants, include carbamazepine (CBZ), lamotrigine, and valproic acid.

CBZ is extensively metabolized in the liver, with only about 3% being excreted unchanged in the urine (117). The main metabolic pathway of CBZ (to its active 10,11-epoxide, CBZ-E) appears to be mediated primarily by CYP 3A4, with a minor contribution by CYP 2C8 (118). This epoxide pathway accounts for about 40% of CBZ disposition. More important, however, is the impact of CBZ on inducing CYP 3A4, resulting in many potential pharmacokinetic interactions (117). CBZ decreases the plasma levels of not only CBZ itself (autoinduction) but also many other medications (heteroinduction). Moreover, if CBZ is discontinued, plasma levels of these other medications can rise, leading to toxic effects from these agents (119).
Valproic acid is a fatty acid with biochemical properties such as blocking sodium channels and modulating GABAergic function. Valproic acid is extensively metabolized with less than 3% being excreted unchanged in the urine. There are three principal routes of metabolism: (1) conjugations to inactive glucuronides (50%); (2) β-oxidation in the mitochondria (40%); and (3) cytochrome P450 oxidation (10%) (117). Valproic acid may cause clinically relevant pharmacokinetic interactions by inhibiting the metabolism of selected substrates, most notably phenobarbital and lamotrigine (120).

**Mood Stabilizers Interactions**

The main biotransformation of methadone is the N-demethylation by CYP 3A4 and CYP 2B6 (21–24). CBZ strongly induces CYP 3A4 activity (121) and consequently accelerates methadone metabolism. In a study on 12 methadone maintenance patients, CBZ resulted in a significant reduction in methadone trough levels, resulting in mild opioid withdrawal symptoms over 7–10 days (122). At the cessation of CBZ, there is a reduction in the metabolism of methadone with a resultant increase in plasma methadone levels, thereby increasing the risk of overdose, an unfortunate adverse event that has been documented with CBZ cessation (123). Further pharmacokinetic studies are needed to determine the extent of this effect. Stopping CBZ in the setting of methadone treatment should include close observation of the patient for oversedation and opioid overdose and a need for methadone dosage modification.

The induction of CYP 3A4 by CBZ could lead to a significant reduction of the mean terminal elimination half-life of buprenorphine and methadone that is speculated to be clinically relevant (40,41), yet confirmatory studies are still needed.

Surprisingly, the number of pharmacokinetic studies on valproic acid and buprenorphine or methadone interactions is very limited. Kristensen et al. (124) measured buprenorphine levels before and after receiving valproic acid in 12 patients and have concluded that no significant interactions between the two medications occur.

The studies performed on potential interactions between lithium and opioid maintenance drugs are limited. In a study in 1978 (125), seven methadone-maintained patients were treated with lithium for a month, which resulted in a significant decrease in the methadone dose needed for maintenance. Further studies are needed in this field.

**Tricyclic Antidepressants**

Antidepressant medications are used in the treatment of major depression, neurosis, panic disorder, and chronic pain and tricyclics are one of the most commonly used amongst them (126).

Inactivation of tricyclics occurs largely through cytochrome P450 enzymes, by demethylation of tertiary tricyclics to their secondary amine metabolites, hydroxylation, then glucuronidation, and excretion in the urine (127). Tricyclic antidepressant medication metabolism depends, to different degrees, upon the isoenzymes CYP 2D6 (127,128).

Methadone maintenance therapy patients have been found to use amitriptyline to achieve euphoria (6,129). Increased tricyclic antidepressant (TCA) toxicity with methadone coadministration has been reported (130–132). In a retrospective study, decreased methadone clearance was found in patients receiving amitriptyline (11). Liu et al. (133) have shown that desipramine significantly reduces the analgesic ED₉₀ of methadone in rats. Desipramine treatment has also been found to significantly reduce the LD₉₀ of methadone. The addition of desipramine to microsomal incubations from normal rat liver has resulted in inhibition of methadone N-demethylation proportional to the desipramine concentration (133). Because of the differences among species in their metabolism, human studies are needed before extrapolating these findings to humans. Further studies are required to better understand the underlying mechanism of these interactions.

**Monoamine Oxidase Inhibitors**

The administration of opioid agonist medications and monoamine oxidase inhibitors (MAOIs) within 2 weeks of each other is contraindicated. MAOIs can cause a serotonin-like syndrome especially when coadministered with some SSRIs (134). Many questions have been raised regarding the safety of opioid analgesics in patients who were taking MAOIs (135–137).

To the best of our knowledge, there are no serotonin toxicity reports of methadone and MAOI combination treatments (134) and although methadone is a weak non-SSRI (138), such reactions are considered unlikely (134). The same is true in the coadministration of buprenorphine and MAOIs. There are no reports on serotonin syndrome caused by interaction of buprenorphine and MAOIs and such interactions are not likely (134).

**CONCLUSIONS**

*In vitro* and well-designed and conducted pharmacologic studies in humans have defined an array of pharmacokinetic and pharmacodynamic interactions with variable clinical impact between opioid agonist therapies and psychoactive medications. Being cognizant of possible synergistic effects of psychotropic medications and methadone on QT prolongation and the risks involved are necessary in today’s clinical practice. Careful medical history taking, risk stratification, and obtaining a baseline and a follow-up electrocardiogram after a month of initiating therapy are examples of practices that can help clinicians address such risks. Considering the current gaps in knowledge on pharmacokinetic and pharmacodynamic interactions between opioid agonist therapies and psychoactive medications and the potential for serious consequences, further human subject studies are required to better understand the underlying mechanism of these interactions.
Declaration of Interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

REFERENCES
46. Bishop WP, Tephly TR. The glucuronidation of exogenous and endogenous compounds by stably expressed rat liver microsomes and comparison with hepatocytes and in vivo. Drug Metab Dispos 2010; 38(9):1449–1455.
57. Borron SW, Monier C, Risede P, Monier C, Buneaux F, Debray M, Baud FJ. Buprenorphine and midazolam act in


100. Shin JG, Soukhova N, Flophart DA. Effect of antipsychotic drugs on human liver cytochrome P-450 (CYP) isoforms in...


