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Evaluation of drug-drug interactions in hospitalized patients on medications for OUD

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Abstract

Introduction: Medications used to treat OUD have common metabolic pathways and pharmacodynamic properties that can lead to drug-drug interactions (DDIs) that may go unnoticed in the inpatient setting. The purpose of this study was to identify the frequency of DDIs between medications prescribed for OUD and commonly used inpatient medications.

Methods: This was a retrospective review of orders for buprenorphine, buprenorphine-naloxone, and methadone to identify potential DDIs. Adult inpatients with an order for one of these medications for OUD were included. Medication regimens were evaluated throughout the inpatient stay and on day of discharge for DDIs. DDIs were classified by severity and type of interaction (increased risk of QT prolongation, additive CNS effects/respiratory depression, and opioid withdrawal). The primary endpoint was the number of potential DDIs. Other endpoints included number of each classification/severity of DDI, duration of therapy of interacting medications, and modifications made to OUD medications because of DDIs.

Results: A total of 102 patients were included, with 215 inpatient interactions and 83 interactions at discharge identified. While inpatient, 85% of patients were on an interacting medication, and 46% of patients were on an interacting medication at discharge. The most common classification of DDI was additive CNS effects/respiratory depression (68.8% inpatient, 50.6% discharge), followed by QT prolongation (24.2% inpatient, 45.8% discharge). The majority of DDIs were classified as requiring close monitoring rather than contraindicated.

Discussion: There are opportunities to optimize the prescribing practices surrounding OUD medications in both the inpatient setting and at discharge to ensure patient safety.

Keywords: methadone, buprenorphine, OUD, opioid use disorder, drug-drug interactions

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Introduction

Buprenorphine, buprenorphine-naloxone, and methadone are medications commonly used for the management of OUD.[1,2] These medications have common metabolic

pathways and pharmacodynamic properties that result in several potential drug-drug interactions (DDIs) that may go unnoticed. Methadone and buprenorphine are metabolized by the liver, primarily by the cytochrome P450 (CYP) 3A4 enzyme.[1] CYP enzymes are responsible for the metabolism of many other medications, and both inhibition and induction of these enzymes play a major role in DDIs and may lead to changes in duration and intensity of drug effects.[3] The CYP enzymes that are most active in opioid metabolism include 3A4, 2B6, 2C19, 2C9, 2D6, and 2C8, leading to a large number of potential DDIs.[1]

Beyond DDIs due to common metabolic pathways, pharmacodynamic interactions may also contribute to potential harm. Potential risks of these pharmacokinetic and/or pharmacodynamic interactions include an increased risk of QT prolongation, additive CNS effects and respiratory depression, and/or opioid withdrawal symptoms.[1,2] Methadone may cause QT prolongation, potentially leading to fatal arrhythmias including Torsades de Pointes, whereas buprenorphine does not.[2,4-6] The effect of methadone on the QT interval is likely dose-related, so any DDI that can increase plasma concentrations of methadone increases this risk.[1] Opioid overdose toxicities, including altered mental status and respiratory depression, are concerns when considering potential DDIs with methadone and buprenorphine as these can also be life-threatening.[1] Lastly, interactions with OUD medications can lead to changes in serum concentrations of the OUD medication, potentially leading to opioid withdrawal or possibly death if significant changes in concentration occur.[2] A study by Brugal et al[7] reported that methadone overdose was often associated with specific drug combinations including opioids (86%) or benzodiazepines (59%). Subsequent opioid withdrawal as a result of a DDI may increase risk of relapse and use of illicit substances to relieve withdrawal symptoms. Following a relapse, patients inherently have a higher risk of opioid overdose since they are no longer tolerant to previously used illicit substances.[1]

Because of the significance of these DDIs and the increased use of medications for OUD, healthcare providers, including pharmacists, should be able to identify and manage possible DDIs. Pharmacists may help address potential DDIs by recommending changes in therapy, providing education to other healthcare providers, and educating patients on adverse effects and when to seek medical care. To determine the incidence of these DDIs, this study was designed to identify and classify potential DDIs between buprenorphine, buprenorphine-naloxone, and methadone and commonly used inpatient medications. Classifying the incidence and severity of these interactions will lead to a better understanding of when therapy modification is necessary and serve as an additional resource for pharmacists.

Methods

This was a retrospective review of orders for buprenorphine, buprenorphine-naloxone, and methadone that was approved by Atrium Health's IRB and identified potential DDIs (Table) at a large academic medical center between July 1, 2018 and July 1, 2019. Adult inpatients who received 2 or more doses of buprenorphine, buprenorphine-naloxone, or methadone for the management of OUD were included with a target enrollment of 100 patients. Patients receiving these medications for other indications were excluded, as were patients who were pregnant. Each patient's therapy was evaluated throughout the inpatient stay and on the day of discharge (per the discharge medication reconciliation) for identifiable DDIs. The primary endpoint was the number of potential DDIs identified. Secondary endpoints included the number of each classification of DDI, severity of identified interactions, duration of interactions, and modifications to OUD medications because of interactions.

DDIs were classified as potentially resulting in an increased risk of QTc prolongation, additive CNS effects or respiratory depression, or withdrawal symptoms. Potential DDI severity was classified as either level 1 or 2 as indicated in the Table. Lee et al[2] used Micromedex, Lexicomp Lexi-Interact, and published studies[1,8,9] to define levels of severity that have been adapted to fit this evaluation (Table). For this evaluation, a level 1 interaction was defined as drugs that should not be coadministered, and a level 2 interaction was defined as potential interactions that may require dose adjustment and close monitoring. Lastly, the duration of therapy of inpatient interacting medications was classified as either $<$3 days, 3 to 7 days, or $>$7 days.

Results

The review included 102 patients, with an average age of 38.6 years and 48% were men. Of these patients, 39.2% received methadone, 54.9% received buprenorphine-naloxone, and 5.9% received buprenorphine for OUD. In total, 89.2% of patients were prescribed medications during their inpatient stay or at discharge that were classified as a potential DDI. While inpatient, 85% of patients received an interacting medication, and 46.1% of patients were prescribed interacting medications at discharge for a total of 215 inpatient and 83 discharge interactions.

A summary of DDIs by classification can be seen in Figure 1. The most common classification of DDI was additive

TABLE: Classification and severity of identified drug-drug interactions (DDIs) with medications used in the treatment of opioid use disorder[1,2,8,9]

Drug/Class	Classification[a]	Severity
Amiodarone	Increased/additive CNS effects and respiratory depression; QT prolongation	Level 2
Amitriptyline	Increased/additive CNS effects and respiratory depression; QT prolongation	Level 2
Atazanavir (unboosted)	Increased/additive CNS effects and respiratory depression; QT prolongation	Level 1; guidelines state "do not coadminister" with buprenorphine
Atazanavir/ritonavir	Opioid withdrawal; Increased/ additive CNS effects and respiratory depression; QT prolongation	Level 2; buprenorphine dose adjustments may be necessary; dose adjustment not usually required for methadone (increase if needed)
Atazanavir, darunavir, lopinavir, tipranavir/cobicistat	Increased/additive CNS effects and respiratory depression	Level 2
Azithromycin, clarithromycin, erythromycin	QT prolongation	Level 2
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, lorazepam, midazolam, oxazepam, temazepam)	Increased/additive CNS effects and respiratory depression	Level 2
Carbamazepine, fosphenytoin, phenobarbital, phenytoin	Opioid withdrawal	Level 2
Chlorpromazine	Increased/additive CNS effects and respiratory depression; QT prolongation	Level 1
Ciprofloxacin, levofloxacin, moxifloxacin	Increased/additive CNS effects and respiratory depression; QT prolongation	Level 1
Darunavir, lopinavir, tipranavir/ ritonavir	Opioid withdrawal	Level 2
Dexamethasone	Opioid withdrawal	Level 2
Diltiazem, verapamil	Increased/additive CNS effects and respiratory depression	Level 2
Fluconazole, ketoconazole	Increased/additive CNS effects and respiratory depression; QT prolongation	Level 1; contraindicated
Fluoxetine	QT prolongation	Level 2
Fluvoxamine	QT prolongation; opioid withdrawal	Level 2
Nafcillin	Opioid withdrawal	Level 2
Nonnucleoside reverse transcriptase inhibitors – efavirenz, nevirapine, rilpivirine	Opioid withdrawal; QT prolongation	Level 2
Opioids (codeine, fentanyl, hydrocodone, hydromorphone, meperidine, morphine, oxycodone)	Increased/additive CNS effects and respiratory depression	Level 2
Prochlorperazine	Increased/additive CNS effects and respiratory depression; QT prolongation	Level 2
Promethazine	Increased/additive CNS effects and respiratory depression; QT prolongation	Level 2
Quetiapine	Increased/additive CNS effects and respiratory depression; QT prolongation	Level 2
Rifabutin, rifampin	Opioid withdrawal	Level 1
Tramadol	Opioid withdrawal	Level 1
Voriconazole, posaconazole, itraconazole	Increased/additive CNS effects and respiratory depression; QT prolongation	Level 1

[a]When QT prolongation is noted, this refers to a DDI with methadone.

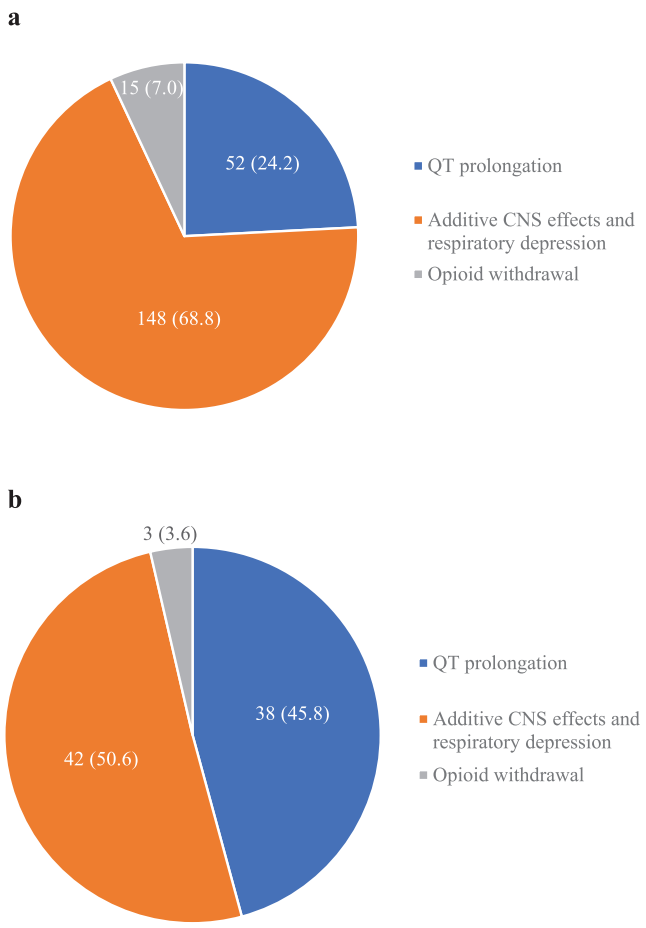

FIGURE 1: a. Classification of drug-drug interactions (DDIs), n (%), inpatient; b. Classification of DDIs, n (%), discharge

CNS effects/respiratory depression (68.8% inpatient, 50.6% at discharge), followed by QT prolongation (24.2% inpatient, 45.8% at discharge). Both inpatient and at discharge the highest number of concomitant QT prolonging medications prescribed was 3 (for 1 patient). Inpatient, the highest number of concomitantly prescribed medications with additive CNS effects/respiratory depression was 6 (2 patients), whereas at discharge it was 3 medications (1 patient). There was only one instance of a patient having more than 1 opioid withdrawal DDI, and this occurred in the inpatient setting.

The 4 most common medication classes with a risk of DDI in the inpatient setting were opioids, benzodiazepines, antipsychotics, and anti-infectives. The most frequently prescribed interacting medications while inpatient were oxycodone (29), quetiapine (20), hydromorphone (19), lorazepam (13), and morphine (12). The most frequent interacting medications at discharge were quetiapine (15), fluoxetine (10), oxycodone (5), promethazine (4), and clonazepam (3).

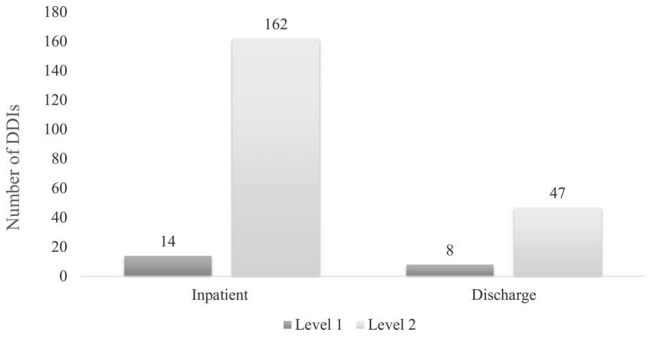

FIGURE 2: Severity of drug-drug interactions (DDIs)

Severity of DDI classification can be seen in Figure 2. The majority (90.5%) of DDIs were classified as requiring close monitoring rather than being contraindicated. Of the inpatient level 1 DDIs identified, 1 patient had 3 level 1 interactions while all others had only 1. The most common medications leading to level 1 DDIs while inpatient were tramadol (3), fluconazole (3), ciprofloxacin (2), and levofloxacin (2). The most common medications leading to level 1 DDIs at discharge were fluconazole (3), ciprofloxacin (2), levofloxacin (2), and rifampin (1). Of the inpatient level 2 DDIs collected, 3 patients had 5 DDIs (from different classifications), but most patients only had 1 DDI.

On average, each patient had 2 DDIs while inpatient and 1 DDI at discharge. Dose adjustments were made to OUD medications in 38.2% of patients. Buprenorphine was dose adjusted in 22 of 63 patients (34.9%), and methadone was dose adjusted in 18 of 40 patients (45%). Of these, 24.5% of doses were increased and 13.7% were decreased (Figure 3). The duration of potential interacting medications was variable, with 49.4% of patients on interacting medications for <3 days, 33.3% for 3 to 7 days, and 17.2% for >7 days.

Discussion

The number of DDIs identified in this evaluation indicates a potential lack of awareness of the impact of commonly used medications given in combination with an OUD medication. The most common classification of DDI was additive CNS effects and respiratory depression, of which, oxycodone, quetiapine, hydromorphone, lorazepam, and morphine were most frequently prescribed in our study. Increased CNS effects and respiratory depression may present additional complications while caring for patients and highlights the need for close monitoring, such as increased frequency of nursing checks to review vital signs and mental status. The high frequency of opioid use in patients with OUD emphasizes the complexity of pain management in these patients. Education regarding OUD

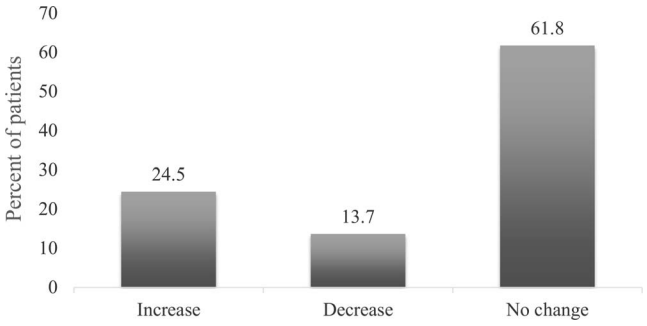

FIGURE 3: Incidence of opioid use disorder medication dose changes

medications, their individual differences, and the varying risks associated with DDIs for the most commonly used medications/medication classes may help optimize prescribing patterns. Pharmacists can also provide guidance to providers on alternative agents to minimize potential DDIs when possible. Additionally, the Centers for Disease Control and Prevention naloxone prescribing guidelines should be followed by offering naloxone when indicated.[10] Addiction medicine specialists are a rare resource, but if available, should be involved in the prescribing of opioids/benzodiazepines in patients with OUD.

While most patients received an interacting medication for less than 7 days, 50.5% of patients were on interacting medications for more than 3 days. As additive risk for adverse outcomes is likely with higher number of concomitant DDIs with similar classifications (eg, CNS effects), increased duration of overlap between interacting medications may also lead to further increased risk of DDIs. Fewer patients received interacting medications at discharge, indicating patients were less commonly prescribed interacting medications for long-term use in a potentially unmonitored setting. Efforts should be made by inpatient pharmacists to evaluate discharge medications to ensure patients are sent home only on essential medications. Pharmacist involvement in discharge medication reconciliation and medication education has previously been shown to decrease medication errors, decrease hospital readmissions, and lead to cost savings.[11-16] Time and pharmacy resources may be limiting factors, but pharmacist-led discharge medication reconciliations or transitions of care programs should be considered to target decreased DDIs on discharge. Patient and family education about adverse effects and when to contact a provider is also important and presents another opportunity for pharmacist involvement.

Over a third of patients had a dose adjustment made to their OUD medication. It is possible that some dose adjustments were made preemptively based on known CYP interactions, though the rationale for these changes was difficult to interpret because of the retrospective nature of this study. The variability of onset/resolution of DDIs prohibits clear guidance regarding therapy modifications during initiation/discontinuation of concomitant CYP medications and is dependent upon drug half-life and natural degradation time.[17-19] Interpatient variability in CYP inhibition/induction has also been reported, emphasizing the complexity of DDI assessment.[20] This further supports the need for ongoing medication review by pharmacists, as some effects of DDIs may not occur for weeks (eg, CYP induction).[17-20]

The most common classifications of DDIs noted in this evaluation were additive CNS effects/respiratory depression, followed by QT prolongation. Given the retrospective nature of this study it was difficult to determine if there were any instances of adverse effects recorded. An opportunity still exists to ensure that providers are aware of potential adverse effects and are appropriately monitoring. Pharmacists at an inpatient psychiatric facility developed a protocol for QTc-interval monitoring.[21] Although developed for a specific patient population, this is generalizable to other patient populations. Factors such as sex, age, electrolytes, medications, and cardiac status were included in their patient screening process. Ultimately, if the patient was found to be an appropriate candidate for an EKG using their algorithm, a pharmacist contacted the provider to recommend obtaining an EKG.[21] When considering the number of DDIs classified as QT prolongation in this evaluation, implementing this intervention tool at other institutions may be beneficial.

While we were not able to capture actual versus theoretical adverse effects related to DDIs in this evaluation, the potential for harm still exists and increased awareness of these DDIs is crucial. Medications that treat OUD decrease risk of fatal overdoses, and although these medications are currently underused, recent increases in awareness and advocacy for use are likely to increase prescriptions for medications for OUD.[22-25] With this in mind, DDIs are an issue that will only become more common, and pharmacists undoubtedly have a role in optimizing care for patients with OUD. In fact, a recent paper delineates a number of evidence-based areas for pharmacist involvement beyond management of DDIs.[26] This study is limited by its retrospective and single-center nature; further studies should be considered to identify patients most at risk for adverse effects from DDIs related to OUD as this may help prescribers in appropriately managing these patients.

Conclusion

Overall, opportunities exist to optimize the prescribing practices surrounding OUD medications in both the

inpatient setting and at discharge. The large number of DDIs identified may demonstrate a lack of awareness of the impact that commonly used medications can have when used in combination with an OUD medication. Education to pharmacists and providers regarding OUD medications and the risks associated with potential DDIs for both specific medications and drug classes should be implemented to improve current prescribing patterns.

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