



Brief Report

Descriptive study of drug-drug interactions attributed to prescriptions written upon discharge from the emergency department

Tara Jawaro, PharmD^a, Patrick J. Bridgeman, PharmD, BCPS^{b,*}, Jude Mele, MD^c, Grant Wei, MD^c^a University of New Mexico Hospital, Albuquerque, NM, United States of America^b Department of Pharmacy Practice and Administration, Rutgers, Ernest Mario School of Pharmacy, Piscataway, NJ, United States of America^c Department of Emergency Medicine, Rutgers, Robert Wood Johnson Medical School, Piscataway, NJ, United States of America

ARTICLE INFO

Article history:

Received 25 September 2018

Received in revised form 26 January 2019

Accepted 28 January 2019

Keywords:

Patient Safety

Drug interactions

Discharged emergency department patients

Pharmacist

ABSTRACT

Objective: The primary purpose of this study was to identify the most common drug-drug interactions (DDI'S) in patients prescribed medications upon discharge from the emergency department.

Methods: We conducted a respective chart review of patients discharged home with a prescription from an academic emergency department. The study period was from August 1, 2015 to August 31, 2015. Patients will be excluded if they meet the following criteria: age under 20 years; discharge home without a prescription; inpatient hospital admission; transfer to another inpatient facility; or sign out against medical advice. The primary endpoint is the identification and characterization of drug-drug interactions caused by discharge prescriptions written by the treating physician.

Results: A total of 500 patient charts were included, with 38% having at least one DDI. Overall, there were 429 DDIs among 858 prescriptions written. 15.6% ($n = 67$) of the DDI's were classified as B, no modification of therapy needed. 60% ($n = 260$) of the DDIs were risk-rating category C, requiring monitoring of therapy. 22% ($n = 95$) of the DDI's identified were category D, which are consider modification of therapy. Lastly, we identified 1.6% ($n = 7$) category X DDI's. The top 3 most commonly associated drugs were oxycodone/acetaminophen, ibuprofen, and ciprofloxacin.

Conclusion: DDIs are occurring upon discharge from a large, urban, tertiary care, academic medical center. Many of the DDI's identified do not require any modification to therapy. However, 23.6% of identified DDI's required modification or were contraindicated. A majority of the category X drug interactions involved QT prolongation.

© 2019 Published by Elsevier Inc.

1. Background

Adverse drug reactions (ADRs) occur in approximately 25% of patients in the ambulatory care setting. Of these adverse drug reactions, 39% are preventable or ameliorable with most preventable ADRs being the result of drug-drug interactions (DDIs) [1]. DDIs result from a combination of at least two drugs leading to a change in potency, safety, or efficacy of one drug because of another drug [2].

The rate of DDI introduction in the emergency department (ED) is estimated to occur anywhere from 3% to 47% [3–6]. DDIs occurring upon receipt of a prescription upon discharge from an ED are less likely to be monitored as patients may not make or keep follow up appointments, and follow up typically occurs with a physician who did not prescribe the medication in the ED [3].

In 2002, Gaddis et al. conducted a retrospective chart review of 200 outpatient ED visits to evaluate if medication prescribed, administered,

or dispensed by emergency medicine physicians had become the most common cause of DDIs. They evaluated patients at high-risk for DDIs, including patients ≥ 60 years old taking three or more medications or patients taking five or more medications regardless of age. On average patients were $64.5 (\pm 17.1)$ years old and were taking 7.2 medications. Out of the 200 patients evaluated, 50 had at least one DDI prior to the emergency department visit. Only 7 DDIs occurred in 140 patients who received a new medication from an emergency medicine physician. The drugs implicated in these seven interactions were as follows: four incidences of meperidine-promethazine, one incidence of warfarin-aspirin, one incidence of theophylline-diazepam, and one incidence of aspirin-antacids [7].

Similarly, in 2013, De Paepe et al. evaluated DDIs and ADRs in patients ≥ 65 years old admitted to the ED to characterize drugs most frequently prescribed by emergency medicine physicians leading to ADRs. In total, 55 patients received a medication in the ED resulting in 39 interactions in 23 patients. Majority of the DDIs were risk rating C (62%) followed by B (31%) followed by D (7%). All D interactions were considered benefit greater than risk by an expert panel. None of the C interactions were considered unjustified by the same expert panel.

* Corresponding author.

E-mail addresses: Patrick.bridgeman@pharmacy.rutgers.edu (P.J. Bridgeman), meleju@njms.rutgers.edu (J. Mele), weigr@rwjms.rutgers.edu (G. Wei).

The most common drugs occurring from most often to least often were as follows: beta2 agonists, ACE inhibitors, coumarin anticoagulants, digoxin, and NSAIDs [8].

Given the focus of prior studies on high risk or elderly populations, this study was undertaken to estimate the occurrence and severity of DDIs resulting from medications prescribed in the ED to a more generalized population.

1.1. Objective

The objective of this study is to identify and characterize the most common DDIs attributable to medications prescribed upon discharge from the ED.

2. Methods

The study was a retrospective chart review performed at large, urban, tertiary care, academic medical center. The study was approved by the institutional review board. A patient list of all adult ED visits between August 1st 2015 and August 31st 2015 which met study criteria was generated using a query of the electronic medical record. Patients who were discharged home from the ED with a prescription for medication(s) were included in the query. Patients were excluded if they met the following criteria: discharged home without a prescription; inpatient hospital admission; transferred to another inpatient facility; or signed out against medical advice. Patients who left against medical advice were excluded due to the inability to perform proper medication reconciliation prior to discharge. As this study was performed in an adult ED, charts belonging to patients under the age of 20 were not included in the analysis. Patients under the age of 20 were excluded based on logistics as they are seen in a separate pediatric ED at our facility. In order to observe consistency in prescribing practices we chose to exclude this age group. A convenience sample of the first 500 charts was used.

Lexicomp interaction analysis was utilized to identify DDIs between at home and newly prescribed medications, and to determine DDI severity. DDI severity was classified per the risk-rating category, a risk rating of A translates into no known interaction, a risk rating of B identifies an interaction which requires no clinical action, a risk rating of C identifies an interaction that requires clinical monitoring, a risk rating of D identifies the need to consider therapy modifications, and finally a risk rating of X represents therapies that are contraindicated (see Table 1). Baseline demographic data including age, gender, home medications, and medications prescribed upon discharge were extracted from the medical record. All data was analyzed using descriptive statistics.

3. Results

A patient list was generated using the Emergency Department Information Management Solution (EDIMS) to identify patients with the above inclusion and exclusion criteria from ED visits spanning August 1st 2015 to August 31st 2015. The first 500 charts from the generated list were evaluated. Patients were 42 years of age on average and mostly female (58.8%). Among the 500 patients, a total of 858 prescriptions were written upon discharge. Of the 500 patient charts reviewed, 38% ($n = 190$) of patients had at least one DDI of risk rating B or greater.

Table 1

Lexicomp Online® Severity Scoring System using Risk Rating Category and subsequent DDI management recommendation.

Risk rating category	Recommendation
A	No known interaction
B	No action needed
C	Monitor therapy
D	Consider therapy modification
X	Avoid combination

Of the 190 patients who had a DDI on review of their chart, the largest group, or 45.3% ($n = 86$) had only one DDI with the subsequent breakdown illustrated in Fig. 1.

There were a total 429 DDIs identified among the 190 patients. Out of a total of 429 DDIs, 15.6% ($n = 67$) of the DDIs were classified as B, “requiring no intervention”, 60% ($n = 260$) of the DDIs classified as a C, “requiring therapeutic monitoring”, 22% ($n = 95$) of the DDIs identified were category D, which are “consider modification of therapy.” Lastly, 1.6% ($n = 7$) category X DDIs or contraindicated combinations were identified. The study results of DDI classification by risk rating are highlighted in Fig. 2.

The top five drugs implicated in the 429 DDIs were oxycodone-acetaminophen (18%), ibuprofen (10%), ciprofloxacin (9%), prednisone (9%), and albuterol (9%). The top five drug interactions for category C and D interactions which require clinical attention and all category X interactions which are contraindicated are reported in Table 2.

4. Discussion

To our knowledge, this is the first retrospective chart review to evaluate DDIs occurring at discharge from an ED visit in a sample of patients who are not age or risk stratified. The first 500 adult patient visits were included regardless of age or number of home medications, giving an overall prevalence of DDIs occurring upon discharge. As such, this study provides a more generalizable assessment of the prevalence of DDIs resulting from emergency department prescriptions.

Themes were identified in the risk rating DDI severity, for example many of the top interactions identified involved prolongation of the QTc, increased bleeding risks, and CNS depression. Our study found that the top drug implicated was oxycodone/acetaminophen, which was not seen in the De Paepe study. This reflects the overall increase in opioid use in the United States which increased dramatically throughout the 1990's through 2012. However, opioid prescriptions appear to have crested in the 2010–2012 period and started declining in 2012, furthermore, additional initiatives have been launched in the last 2 years to further decrease opiate prescriptions [9]. Similar to the De Paepe study, NSAIDs and beta2 agonist were once again among the most common drugs involved in the DDIs. Furthermore, the DDI combinations identified in the 2002 study by Gaddis et al. have changed as the use of medications like theophylline and meperidine have decreased.

The majority of DDIs identified in this study fell into category C, with recommended monitoring of therapy. This finding highlights the importance of considering a patient's outpatient follow up when prescribing in the ED. The prevalence of category C DDIs in this and previous studies

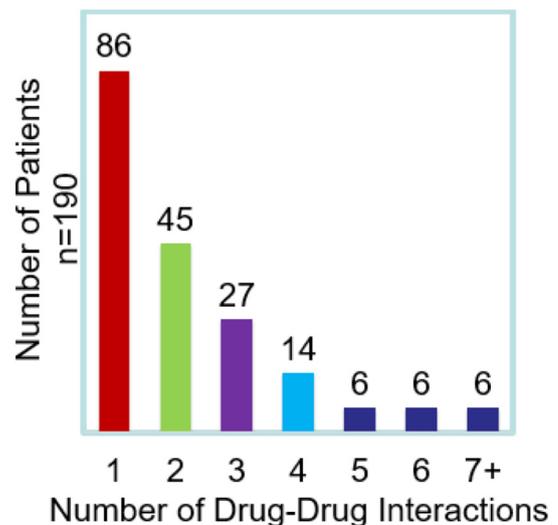


Fig. 1. Number of drug-drug interactions experienced by patients.

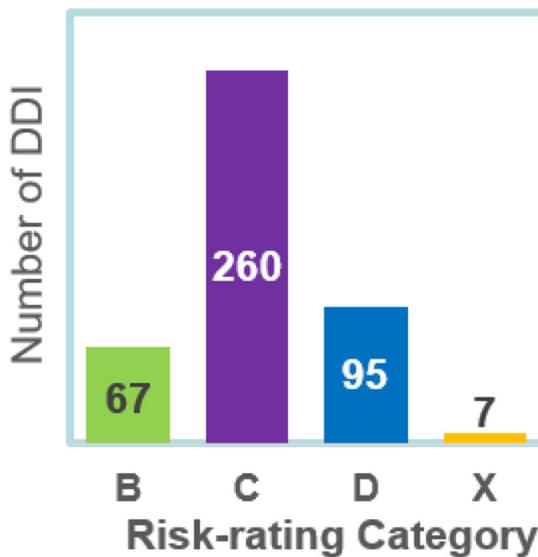


Fig. 2. Number of DDI per Risk-rating category.

such as the one by De Paepe evidence the necessity of reconciling a patient's discharge medication according to their access to primary care in addition to their current medication list.

Category C drug interactions accounted for the largest proportion of interaction identified and may be encountered more frequently by emergency medicine physicians. Therefore, further discussion of the clinical context of the drug interactions is warranted to assist emergency medicine physicians in performing a risk benefit analysis. Oxycodone/acetaminophen and ciprofloxacin were identified as a category C drug interaction, with an increased risk of myoclonus being the main concern. This DDI is derived from a single case report of an 80 year old female initiated on ciprofloxacin and oxycodone and subsequently developed myoclonus after 7 days of treatment [10]. Both opioids and fluoroquinolones been associated with neurologic adverse events such as seizures, delusions and hallucinations. Myoclonus may be a concern when these two medications are utilized together particularly in patients at higher risk for neurologic adverse events. Potential risk factors for higher risk of adverse neurologic effects are extremes of age, renal disease, history of neurologic disease, or impaired blood brain barrier integrity [11]. The potential clinical effect resulting from the ciprofloxacin and metronidazole drug interaction is additive qt prolongation.

Since completion of data collection and analysis the category C designation was removed from the Lexicomp database. Additionally, the metronidazole and ciprofloxacin drug interaction we removed as a

category C interaction [12]. However, both interactions are still listed as major drug interaction in a database by a separate publisher [13]. There is a case report that demonstrates metronidazole may prolong the qt interval and a separate case report where an occurrence of torsade's des pointes (tdp) occurred which was attributed to concomitant administration of metronidazole and amiodarone. There have not been any documented case reports of tdp caused by concomitant administration of ciprofloxacin or ondansetron and metronidazole, although theoretically the risks does exist.

When evaluating the oxycodone/acetaminophen and hydrochlorothiazide drug interaction there are three possible orthostatic hypotension, hyponatremia and reduced efficacy of diuretics. Opioids may increase excretion of antidiuretic hormone causing a pharmacodynamic drug interaction possibly augmenting naturetic effects of diuretics and decreasing a diuretics effectiveness. Hyponatremia caused by opioids is an extremely rare side effect, but should be taken into consideration if a patients sodium begins to decrease while taking opioids [14]. The increased risk of orthostatic hypotension may predispose patients to a fall when these medications are taken together. Communicating this risk to patients will allow them to implement strategies at home that may decrease their risk of fall if these medications are deemed required to be used concomitantly.

Lisinopril and ibuprofen was the final category C drug interaction identified in the study patient population. Overall the data supporting this interaction is more robust when compared to the other category C drug interactions identified. Increased rates of acute kidney injury and worsening of renal function have been identified with concurrent use of non-steroidal anti-inflammatory drugs (NSAID's) and ACE inhibitors. The risk of is further increased with concurrent use if diuretics [15,16]. Additionally, the antihypertensive effects of ACEi's may be attenuated with concurrent use of NSAID's. Therefore, the use of NSAID's with ACE's should be discouraged especially in patients with pre-existing renal dysfunction, the elderly, or those otherwise at risk for acute kidney injury. Alternative agents should be utilized for pain control such as acetaminophen. If the ACEi's and NSAID's are deemed necessary to be utilized together renal function and blood pressure should be assessed more frequently than if the agents.

The category D interactions should make clinicians consider selecting another equivalent therapy that avoids the identified interaction taking the clinical situation into account. The first two interaction identified were oxycodone/acetaminophen and either diazepam or cyclobenzaprine. In a safety statement from FDA concurrent use of opioid pain medications and benzodiazepines or CNS depressants is discouraged and should be avoided if possible. According to the FDA statement there is increased risk of overdose death when these types of medications are used together. Additionally, black box warnings are going to be added to the labeling for opioids and benzodiazepines. These statements are consistent with guidance provided by CDC regarding opioid and benzodiazepine or CNS depressant use [17]. Additionally, when diazepam or placebo in addition to naproxen was evaluated for the treatment of lower back no additional benefit was observed [18]. Another trial evaluated naproxen with either acetaminophen/oxycodone or cyclobenzaprine or placebo and found no difference at 1 week in pain or functionality [19]. The category D interaction of ibuprofen or another NSAID and aspirin may be a frequently encountered drug interaction for emergency medicine physicians. When considering prescribing ibuprofen to patients currently taking aspirin there may be an increased risk of gastrointestinal bleeding. Additionally, NSAID's may decrease aspirin's cardioprotective efficacy. Thus, it is reasonable to avoid chronic use of NSAID's for patients who also take aspirin for cardioprotection [20].

In the setting of an ED patient it may be reasonable for a short course of an NSAID if required for pain control. However, an alternative agent such as acetaminophen should be considered for use in this patient population. Patients should be advised to observe for any signs of gastrointestinal bleeding.

Table 2
Top Five interactions for risk-rating category C & D and all X.

Risk rating category	Most common DDI
C	<ul style="list-style-type: none"> • Metronidazole + ciprofloxacin • Oxycodone/acetaminophen + ciprofloxacin • Oxycodone/acetaminophen + HCTZ • Lisinopril + ibuprofen
D	<ul style="list-style-type: none"> • Ondansetron + metronidazole • Oxycodone/acetaminophen + diazepam • Oxycodone/acetaminophen + cyclobenzaprine • Aspirin + ibuprofen • Ciprofloxacin + ondansetron • Ibuprofen + sertraline
X	<ul style="list-style-type: none"> • Levofloxacin + citalopram • Ciprofloxacin + escitalopram • Ciprofloxacin + sotalol • Fluoxetine + ondansetron • Docusate + mineral oil • Celecoxib + naproxen • Dextromethorphan/quinidine + ondansetron

Generally, the category X interactions identified should prompt the provider to prescribe an alternative agent that does not expose the patient to unnecessary risk. Combinations of the identified medications should be avoided. A majority of the identified category X interactions involved prolongation of the qt interval and increased risk of tdp. The identified interaction of mineral oil and Colace is based on the possible risk for increased absorption of mineral oil leading to systemic toxicity. It is important to note this particular drug interaction is dependent on the route of mineral oil administration. It is not recommended to administer the oral formulation of mineral oil [21]. The combination of ibuprofen and sertraline has been identified to possibly increase the risk of bleeding through a number of cases and clinical trials. This interaction may be generalizable to NSAID's and SSRI's. The data is conflicting regarding the actual occurrence of bleeding associated with concurrent use of these medications. Taking this information into account it is reasonable to avoid the combination of these two medication classes [22].

There are important limitations of our study that need to be noted. This study was confined to a single, urban, academic tertiary care facility and so the prevalence of DDIs noted in this study may not be generalizable across all practice settings. A multicenter study would be likely to provide a more accurate estimation of DDI prevalence and severity relating to medications prescribed in the emergency department.

We utilized only one drug interaction checker to evaluate discharge drug interactions. There are other programs available to evaluate drug interactions that may differ on their classification and severity. Therefore, the results may differ if another drug interaction checking software is utilized. Due to the fact this was a retrospective chart review we were not able to ascertain if patients actually filled the original discharge prescription. It is possible that an intervention to avoid a drug interaction occurred upon presentation to an outpatient pharmacy.

Our data may also be limited as we excluded patients <20 years old. At our institution patients in this age range are seen in a separate pediatric emergency department. We decided to exclude this patient population as different physicians see these patients and it may have introduced prescribing practices that were not reflective of the adult ED population at our facility.

In addition, medication reconciliation was performed using medication lists provided by patients. Prior studies have demonstrated that elderly patients and those with poor health literacy are often unable to provide complete medication lists [4,23]. As such it is possible that our results are an underestimation of actual DDIs resulting from ED prescriptions.

We also did not convene an expert panel, as previous studies have done, to evaluate the clinical applicability of the identified drug interactions. Our overall goal was to make prescribers aware of the most common DDI's and allow them to provide education to patients regarding the need for increased monitoring for adverse events.

The results of this study suggest that both patients and providers in the emergency department may benefit from the implementation of a drug interaction screening check prior to discharge. As such, this study fills a current gap in the literature and elucidates an area of current practice which can be improved to reduce adverse outcomes.

Disclosures

The authors declare no potential conflicts of interest.

References

- [1] Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med* 2003;348(16):1556–64.
- [2] Ellenhorn MJ, Sternad FA. Problems of drug interactions. *J Am Pharm Assoc* 1966;6(2):62–5 [passim].
- [3] Beers MH, Storrie M, Lee G. Potential adverse drug interactions in the emergency room. An issue in the quality of care. *Ann Intern Med* 1990;112(1):61–4.
- [4] Hancock D, Kennington JM, Beckner RR, Quick G. Emergency department medication and drug interaction evaluation. *Hosp Pharm* 1992;27(2):129–32.
- [5] Herr RD, Caravati EM, Tyler LS, Iorg E, Linscott MS. Prospective evaluation of adverse drug interactions in the emergency department. *Ann Emerg Med* 1992;21(11):1331–6.
- [6] Goldberg RM, Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. *Am J Emerg Med* 1996;14(5):447–50.
- [7] Gaddis GM, Holt TR, Woods M. Drug interactions in at-risk emergency department patients. *Acad Emerg Med* 2002;9(11):1162–7.
- [8] De Paep P, Petrovic M, Outtier L, Van Maele G, Buylaert W. Drug interactions and adverse drug reactions in the older patients admitted to the emergency department. *Acta Clin Belg* 2013;68(1):15–21.
- [9] Guy Jr GP, Zhang K, Bohm MK, et al. Vital signs: changes in opioid prescribing in the United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017;66(26):697–704.
- [10] Kango Gopal G, Hewton C, Pazhvoor SK. Myoclonus associated with concomitant ciprofloxacin and oxycodone in an older patient. *Br J Clin Pharmacol* 2014;77(5):906–7.
- [11] Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. *Br J Clin Pharmacol* 2011;72(3):381–93.
- [12] Lexicomp Inc. Lexidrugs; 2018 [Accessed September 10th, 2018].
- [13] Truven Health Analytics. Metronidazole and Ciprofloxacin drug interaction results. <http://www.micromedexsolutions.com>; 2018, Accessed date: 10 September 2018.
- [14] Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis* 2008;52(1):144–53.
- [15] Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ* 2013;346:e8525 (Clinical research ed).
- [16] Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int* 2015;88(2):396–403.
- [17] FDA. Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning [press release]. August 31st, 2016; 2016.
- [18] Friedman BW, Irizarry E, Solorzano C, et al. Diazepam is no better than placebo when added to naproxen for acute low Back pain. *Ann Emerg Med* 2017;70(2):169–76 [e161].
- [19] Friedman BW, Dym AA, Davitt M, et al. Naproxen with cyclobenzaprine, oxycodone/acetaminophen, or placebo for treating acute low Back pain: a randomized clinical trial. *JAMA* 2015;314(15):1572–80.
- [20] Lexicomp Inc. Ibuprofen and aspirin drug interaction results; 2018 [Accessed September 10th, 2018].
- [21] Langhorne, PA: Insight Pharmaceuticals Corp. Kondremul (mineral oil) [prescribing information]; 2013.
- [22] Lexicomp Inc. Sertraline and ibuprofen drug interaction results; 2018 [Accessed September 10th, 2018].
- [23] Persell SD, Osborn CY, Richard R, Skripkauskas S, Wolf MS. Limited health literacy is a barrier to medication reconciliation in ambulatory care. *J Gen Intern Med* 2007;22(11):1523–6.