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Review of Pharmaceutical Drug Interactions in Gastrointestinal Disorders Therapy: Evidence and Mechanism

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Abstract

Drug-drug interactions significantly contribute to the occurrence of negative reactions in polypharmacy, with the frequency of these interactions increasing in direct correlation with the number of drugs involved. This study focused on identifying the primary drug-drug interactions that arose during the treatment of gastrointestinal symptoms using proton pump inhibitors and histamine H2-receptor antagonists. The two categories of agents, employed in the treatment of gastroesophageal reflux and ulcer disease, can be obtained over-the-counter upon the pharmacist's recommendation, therefore increasing the likelihood of drug-drug interactions.

Drug-drug interactions may arise from the decrease in gastric acidity, which might modify the biotransformation or excretion of the co-administered drug, resulting in reduced effectiveness. An increase in pH might potentially impact the absorption of some medicines, leading to a decrease in absorption for drugs such as ketoconazole, itraconazole, atazanavir, vitamin B_{12}, and magnesium, or an increase in absorption for drugs like triazolam and midazolam. Additionally, it is necessary to consider the potential interaction with drugs that have a restricted therapeutic index, such as warfarin, phenytoin, and theophylline. This is important due to the danger of toxic or adverse consequences resulting from the buildup of these drugs.

Keywords: Drug-drug interactions – warfarin – phenytoin – gastric acidity – restricted therapeutic index – histamine H2-receptor antagonists

Introduction

Drug interaction refers to alterations in the patient's reaction to a medication due to the administration or simultaneous exposure to another medication or substance. Approximately 20-30% of adverse medication reactions can be attributed to drug interactions. The prevalence of this occurrence is rising among the older population and individuals concurrently taking two or more medications. Modern therapy has revolutionized the management of diseases and has led to notable improvements in life expectancy, thus reducing both morbidity and mortality rates. Although there are numerous advantages, the occurrence of negative responses resulting from drug interactions is a frequent and avoidable cause of illness, impairment, and even mortality. In addition to the intrinsic danger of the drug, individuals may have a specific and unpredictable susceptibility to various medications. Furthermore, when multiple medications are prescribed, there is always the potential for drug interactions that may have adverse effects (Farrell et al., 2017; Holtmann et al., 2011).

The pharmacist plays a crucial role in the field of pharmaceuticals, specifically in detecting issues connected to the use and interactions through pharmaco-epidemiological investigations. Doctors and pharmacists are the primary health professionals who regularly report adverse responses to drugs. Continued monitoring and reporting of negative reactions to drugs remain crucial following the approval of medications and their utilization in real-life situations.

Drug-drug interactions (DDI) are a prevalent issue in clinical practice and can manifest through several mechanisms, such as pharmacokinetic and pharmacodynamic interactions (de Oliveira et al., 2021; Aljadani & Aseeri, 2018; Tragni et al., 2013; Vonbach et al., 2008). The American Association of Poison Control Centers received 18,988 inquiries for DDI information and documented 3,541 instances of therapeutic mistakes by medical staff resulting from DDI in 2020 (Gummin et al., 2021). The occurrence of drug-drug interactions is particularly frequent in emergency Departments where the time available for treatment is limited and quick access to therapy is crucial (Dookeeram et al., 2017). A recent observational study discovered that up to 38% of prescriptions issued upon release from the Emergency Department (ED) contain at least one DDI (Jawaro et al., 2019).

Prior research has similarly shown elevated drug-drug interactions among patients with polypharmacy (Bachmann et al., 2022; Stassen et al., 2022; de Oliveira et al., 2021; Okoli et al., 2020; Doan et al., 2013; Lin et al., 2011). The prevalence of polypharmacy in older adults is high as a result of the treatment of numerous preexisting medical problems. Over 50% of elderly people who are admitted to the hospital are subjected to at least one possible drug-drug interaction, while 20% experience at least one potentially serious DDI (Pasina et al., 2013). Additionally, the elder patient is particularly susceptible to experiencing a potential drug-drug interaction compared to other age groups in the ED as a result of polypharmacy (Dookeeram et al., 2017). Approximately 15% of pediatric patients who visited the emergency department had serious drug-drug interactions (Lombardi et al., 2018).

Healthcare professionals in the ED frequently encounter urgent situations and may provide medications to patients before a formal prescription is entered into the computer system. This approach circumvents the automated DDI checking software in the computerized prescribing system, which aims to mitigate simple and frequent DDIs. Furthermore, several EDs with limited resources lacked the presence of pharmacists. As a result, they kept emergency medication readily accessible on their local shelves for patients in need of urgent medical attention. In this context, the pharmacists in the central pharmacy department of the hospital were unable to perform a secondary check prior to the physicians administering these prescriptions to their patients (Dookeeram et al., 2017).

Drug interactions can occur due to mechanisms including pharmacokinetics, pharmacodynamics, or a combination of both. Understanding the mechanism by which drug interactions occur is valuable in a clinical setting. This knowledge can impact the progression of therapeutic outcomes over time. Additionally, it can provide opportunities to prevent or even utilize interactions to enhance the effectiveness of therapy. Drug interactions can arise in the context of mood-altering medications due to both internal (endogenous) and external (exogenous) variables (Palleria et al., 2013).

There are various categories of drug interactions: (i) pharmaceutical drug interactions, which involve in vitro interactions or incompatibilities; (ii) pharmacokinetic drug interactions, which pertain to the processes of absorption, distribution, metabolism, and excretion; (iii) pharmacodynamics drug .

interactions, which occur at the molecular or cellular level and affect anatomical-physiological systems; (iv) interactions between drugs and food, beverages, or medicinal plants (Tangsuwanaruk & Wittayachamnankul, 2022). Table (1) presents the most common interactions observed while treating gastrointestinal symptoms with proton pump inhibitors (PPIs) and histamine H2 receptor antagonists.

Table 1: the most common interactions observed while treating with PPIs and H2 antagonists

Drugs	Major drug interactions	Moderate drug interactions	Minor drug interactions
Proton pump inhibitors: omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole	atazanavir clopidogrel citalopram erlotinib methotrexate nelfinavir tacrolimus	alprazolam atorvastatin cisplatin diazepam digoxin ketoconazole itraconazole phenytoin simvastatin levothyroxine naproxen warfarin voriconazole theophylline rifampicin	aspirin ciprofloxacin clarithromycin cannabidiol cyanocobalamin glipizide phenobarbital rosuvastatin duloxetine valdecoxib tolbutamide
H2 receptor antagonists: cimetidine, ranitidine, famotidine	atazanavir astemizole cisapride citalopram eliglustat loperamide hydrocodone tamoxifen terfenadine	aminophylline amiodarone codeine cefpodoxime donepezil glipizide ivabradine ketoconazole metformin phenytoin quinidine warfarin zolpidem	acetaminophen caffeine cyclosporine diclofenac digoxin estradiol ketoprofen nicotine nifedipine piroxicam phenobarbital zidovudine

The objective of this research is to review the evidence and mechanisms of pharmacological medication interactions in the treatment of gastrointestinal illnesses. The study aims to systematically review the current literature on drug interactions in the management of gastrointestinal diseases, ascertain the mechanisms by which these interactions take place, and assess the therapeutic importance of these interactions.

The importance of this research is in its potential to profoundly influence patient safety and treatment results. Gastrointestinal diseases are prevalent and frequently necessitate prolonged treatment with numerous drugs. Comprehending the possible interactions among various medications is vital for healthcare practitioners to reduce the likelihood of negative effects and enhance the effectiveness of treatment. This research seeks to offer significant insights to healthcare practitioners regarding medication

management for patients with gastrointestinal conditions by examining the evidence and mechanisms of drug interactions.

Literature review

Drug interactions caused by proton pump inhibitors

Proton pump inhibitors (PPIs) are the preferred medications for treating gastric reflux disease and ulcers. They belong to a group of therapeutic pharmaceuticals that can be obtained without a prescription, based on the advice of a pharmacist. Global sales data indicate that omeprazole ranks among the top-selling medications in the overall pharmaceutical sector. The compounds offer a significant advantage in terms of their elevated therapeutic potential and the patient's enhanced compliance, which is facilitated by the administration of a single daily dose (Shin & Kim, 2013).

The use of omeprazole can affect the absorption of certain substances that rely on the acidity of the stomach for absorption, either by increasing or decreasing their absorption. Due to its primary metabolism by CYP2C19, omeprazole can lead to the accumulation of compounds that undergo similar biotransformation, such as warfarin, diazepam, or phenytoin. This accumulation can result in specific side effects. Furthermore, the use of medications such as clarithromycin and voriconazole, which hinder the activity of this liver enzyme, will lead to an elevation in the level of omeprazole in the bloodstream, resulting in a diminished therapeutic outcome. Rifampicin, a drug that induces liver enzymes, can decrease the concentration of omeprazole in the blood by enhancing its metabolism. Studies conducted on individuals without health issues revealed a pharmacokinetic/pharmacodynamic interaction between clopidogrel and omeprazole. This interaction resulted in a 46% reduction in the amount of the active form of clopidogrel in the body and an average decrease of 16% in the maximum inhibition of platelet aggregation caused by ADP (Li et al., 2013).

Patients receiving pantoprazole together with warfarin or fenprocoumon should undergo regular monitoring to detect any elevation in INR levels and prothrombin time. Clinical investigations have demonstrated diverse pharmacokinetic interactions with oral contraceptives that contain levonorgestrel and ethinyl estradiol. However, as of now, there is a lack of trustworthy data that strongly prohibits their

combination. Pantoprazole's potent and enduring suppression of stomach acid production can impede the absorption of other medications that rely on gastric pH for optimal oral availability, such as azole antifungals (ketoconazole, itraconazole, posaconazole) and erlotinib. Studies investigating the interactions of pantoprazole have demonstrated that it does not impact the metabolism of biotransformed active compounds via CYP1A2 (caffeine, theophylline), CYP2C9 (piroxicam, diclofenac, naproxen), and CYP2D6 (metoprolol) (Wedemeyer & Blume, 2014).

Caution should be exercised by specialists when co-administering this drug with protease inhibitors. The simultaneous use of tacrolimus and esomeprazole resulted in elevated levels of tacrolimus in the bloodstream. Intensive monitoring of tacrolimus plasma concentrations, renal function (creatinine clearance), and appropriate adjustment of tacrolimus dosage are required. On the other hand, studies have demonstrated that esomeprazole can disrupt laboratory examinations. To avoid potential interference with investigations for neuroendocrine tumors, it is advisable to temporarily discontinue therapy with esomeprazole for a minimum of 5 days before evaluating Chromatogranin A levels (Wedemeyer & Blume, 2014; Kalaitzakis & Björnsson, 2007).

Long-term administration of medications that reduce the production of acids can result in impaired absorption of cyanocobalamin (vitamin B12). Patients with Zollinger-Ellison syndrome and other hypersecretory clinical disorders that require long-term care should be evaluated for cyanocobalamin insufficiency. Furthermore, it has been demonstrated that lansoprazole has the ability to impede the function of P-glycoprotein in laboratory settings. Due to the fact that sucralfate/antacids reduce the amount of lansoprazole that can be absorbed by the body, it is recommended to wait at least one hour after taking these drugs before administering lansoprazole (Wedemeyer & Blume, 2014).

Use caution while using rabeprazole with protease inhibitors, ketoconazole, or itraconazole. Prolonged use of rabeprazole has been associated with the occurrence of severe hypomagnesemia in patients for a minimum duration of 3 months. In cases of hypomagnesemia, individuals may experience severe symptoms like weariness, tetany, psychosis, convulsions, dizziness, and ventricular arrhythmia. However, these symptoms can manifest gradually and may go unnoticed (Wedemeyer & Blume, 2014; Pace et al., 2007).

H2-receptor antagonists

H2-receptor antagonists reduce the production of stomach acid by competitively inhibiting the histamine H2 receptors on the gastric parietal cell. These medications are utilized to treat gastric and duodenal ulcers, gastroesophageal reflux, and Zollinger Ellison syndrome (Shim & Kim, 2017). The H2-receptor antagonists now available are cimetidine, famotidine, and ranitidine. Typically, these medications are administered orally. However, for immediate inhibition of stomach acid production, there are also injectable versions available (such as famotidine and ranitidine). Oral administration can be done once or twice a day, either when symptoms start or at least 30 minutes to 1 hour before symptoms occur (Voropaiev & Nock, 2021).

Often, it is preferable to administer these medications as a solitary dose before going to bed in order to inhibit the production of stomach acid during the night. This approach is supported by studies indicating that it is most effective in promoting the healing of peptic ulcers. The primary adverse effects caused by H2-receptor antagonists include central nervous system manifestations (such as headache, drowsiness, and confusion), cardiac effects (including bradycardia, hypotension, and heart block), hyperprolactinemia, acute pancreatitis, elevated levels of hepatic transaminases, increased alcohol dehydrogenase activity, thrombocytopenia, agranulocytosis, and interstitial nephritis. Disruption of drug metabolism by cytochrome P450 (Cooke & Giovannitti, 2017; Bansi & Louis-Auguste, 2012).

Interactions within this category of drugs primarily arise from the modification of absorption or the inhibition of the hepatic microsomal enzyme cytochrome P450, as well as the reduction of the urinary excretion of other pharmaceuticals. The frequency of interactions is greater for cimetidine and lesser for ranitidine and famotidine (Cooke & Giovannitti, 2017).

Cimetidine, the initial H2-receptor antagonist employed in treatment, has a database that reveals a total of 422 medications known to interact with it, out of which 29 are classified as causing significant interactions. Similar to proton pump inhibitors (PPIs), cimetidine, and other H2-receptor antagonists, prolonged and high-dose usage of these medications can have a considerable impact on the absorption of vitamin B12 (Aronson, 2016). While vitamin B12 insufficiency is commonly found in individuals with low body stores, such as vegetarians, it is worth mentioning that taking vitamin B12 supplements can be

beneficial in reducing the antiandrogenic effects of cimetidine (Beltrame et al., 2019).

The administration of cimetidine or other stomach acid-reducing medicines can increase the pH level, which may impact the absorption of calcium, iron, zinc, folic acid, vitamin D, and lower the bioavailability of certain weak base pharmaceuticals. The literature extensively discusses the impact of increasing pH on the solubility and absorption of antifungal medications, specifically ketoconazole and itraconazole, at the stomach level (Wanamaker & Grimm, 2004). To mitigate the impact of elevated pH, it is recommended to take the antifungal medications 2 hours prior to H2-receptor antagonists or 10-12 hours after the H2-receptor antagonists (Khawaja et al., 2022; Patel et al., 2020).

The primary significance of cimetidine lies in its ability to inhibit hepatic P450 isoenzymes, specifically CYP1A2, CP2C19, CYP2D6, and CYP3A4 (Waller & Sampson, 2018). Therapeutic drugs with a low therapeutic index and a hepatic metabolism can lead to a hazardous quantity in the plasma, such as warfarin, theophylline, and phenytoin. Additional significant interactions resulting from the inhibitory activity of cimetidine on CYP isoenzymes include beta-blockers (metoprolol or propranolol), lidocaine, quinidine, or nifedipine (Preston, 2016; Doligalski et al., 2012). When cimetidine is taken together with metoprolol or propranolol, it might cause significant slowing of the heart rate and low blood pressure. However, there is no documented interaction between cimetidine and the beta-blockers atenolol or nadolol (Lepist & Ray, 2016).

Cimetidine can competitively inhibit renal transporters, which are the principal route of excretion for H2-receptor antagonists, at the renal level, affecting active tubular secretion. These interactions are categorized as minimal or moderate, and they can be clinically significant when dealing with drugs that have a narrow therapeutic range, such as antiarrhythmic and cancer medications. They are also essential in populations where the use of multiple medications (polypharmacy) is widespread, such as the elderly and diabetics (Lepist & Ray, 2016). Furthermore, the intravenous injection of cimetidine leads to an elevation in its systemic concentration, which can be further enhanced by the use of renal P-glycoprotein inhibitor medicines such itraconazole (Karyekar et al., 2004).

Ranitidine is an H2-receptor antagonist that has a weaker attraction to the CYP enzymes and has fewer side effects when compared to cimetidine. Nevertheless, ranitidine is contraindicated in cases of acute

porphyria (Bystrak et al., 2011). Close monitoring of prothrombin time is important when using ranitidine concurrently with coumarin anticoagulants (such as warfarin) due to their narrow therapeutic index. There have been reports of an increased risk of bleeding or blood clot in such cases (Preston, 2016).

In addition, ranitidine elevated the levels of metoprolol and nifedipine in the bloodstream. However, these interactions seem to have little impact on clinical outcomes. Ranitidine can elevate the plasma concentrations of midazolam, triazolam, or glipizide by enhancing their absorption. Additionally, in high doses, ranitidine can impact the renal clearance of procainamide, hence raising the likelihood of side effects for the aforementioned drugs (Preston, 2016).

Management of Drug-Drug Interactions

Pharmaceutical treatment is a vital component of healthcare that facilitates the remedy and prevention of numerous medical disorders. Nevertheless, drug-related disorders (DRPs) are prevalent and result in patient distress, as well as significant expenses for society (Hakkarainen, 2014; Salvi et al., 2012; Jönsson et al., 2010; Jönsson et al., 2009). Drug-related problems (DRPs) are a frequent cause of hospitalization and can occasionally result in death (Westerlund et al., 2013; Salvi et al., 2012; Taché et al., 2011; Jönsson et al., 2009; Wester et al., 2008). A drug-drug interaction refers to the alteration of one medication's effects (either increased, decreased, or modified) due to the presence of another medication when taken together or in succession (Askari et al., 2013; Sjöqvist & Böttiger, 2010). Drug-drug interactions are often observed in hospitalized elderly patients, with reported occurrence rates ranging from 8% to 100%. These interactions have the potential to impair patient safety (de Oliveira et al., 2021).

Access to necessary information is crucial for effective drug therapy. This includes providing the relevant parties, such as prescribers, pharmacists, and patients, with the required information (Remen & Grimsmo, 2011; Forni et al., 2010). The understanding and awareness of pharmaceuticals are always expanding and evolving due to the emergence of new treatments and changes in research or clinical practice, which in turn alter previous guidelines (Eiermann et al., 2010).

eHealth solutions possess the capacity to tackle the issue of drug-drug interactions and enhance medication management in general. This is achieved through the provision of digital services for healthcare

professionals and patients. The implementation of eHealth interventions will persist in revolutionizing several aspects of medication management, shifting from traditional consultations with healthcare experts to acquiring knowledge about medications and their administration in everyday life (Car et al., 2017).

Managing drug-drug interactions is an intricate procedure that necessitates evaluating the risks and benefits of the medications involved. Clinical Decision Support Systems (CDSSs) are utilized in the drug management process to enhance the quality and efficiency of healthcare (de Oliveira et al., 2021; Car et al., 2017; Askari et al., 2013; Westerlund et al., 2013; Remen & Grimsmo, 2011; Eiermann et al., 2010; Forni et al., 2010).

A Clinical Decision Support System can assist healthcare professionals, including physicians and pharmacists, in identifying possible DDIs by connecting patient-specific variables and existing drugs with a library of knowledge. Creating a comprehensive and reliable knowledge database for drug-drug interactions necessitates substantial effort, ongoing updates, and expert evaluations (Böttiger et al., 2009). Subsequently, this knowledge database can be utilized across various applications and interfaces. Several studies have examined and assessed CDSS that notify professionals about drug-drug interactions, by elucidating the effects and factors to consider when creating and implementing DDI alerts for professionals, mostly physicians (Jung et al., 2020; Tolley et al., 2018; Payne et al., 2015). However, there is limited knowledge regarding the provision of drug-drug interaction services for patients.

It is widely accepted that patient empowerment promotes patient autonomy, self-care, and self-confidence (Risling et al., 2017). In order to ensure patient safety and compliance with drug therapy, it is crucial to give clear and tailored information that meets the specific informational requirements of each patient (Kusch et al., 2018). In addition to the fundamental information requirements, such as the specific medication, its administration method, and timing, patients may need supplementary information to assess the advantages of the recommended prescription and carefully consider this information in relation to their apprehensions. Patients who possess a robust conviction in the advantages of a treatment are more likely to adhere to it.

Conversely, possessing a strong "concern belief" can result in patients intentionally deciding not to comply to their treatment regimen. Subjectively wanted information about drugs is regarded to have the potential to alleviate patients' anxieties. Despite the high need for Drug-Drug Interaction information, there is still limited knowledge on how to tailor this information to meet the specific needs of patients (Kusch et al., 2018).

Prior research has demonstrated a deficiency in meeting patients' information requirements about drug-drug interaction information, as well as a disparity between patient expectations and the information provided by healthcare providers (Kim et al., 2020).

Physicians and pharmacists, together with other healthcare professionals, play crucial roles in ensuring the safety and appropriateness of patients' treatments, such as by preventing drug-drug interactions. Nevertheless, drug-drug interactions continue to pose a significant challenge, suggesting that they are occasionally overlooked by healthcare practitioners (Zheng et al., 2018). Possible causes for overlooking a potential drug-drug interaction include insufficient understanding of DDIs, absence of suitable clinical decision support systems in the utilized information system, incomplete information regarding a patient's current medications, or divergent perspectives on accountability and time constraints that hinder interaction checks (Hammar et al., 2014).

DDIs can also arise due to patient self-medication, including the use of Over the Counter (OTC) pharmaceuticals or herbal remedies that patients purchase themselves, or due to the unauthorized reuse of prescription drugs or the use of nutritional supplements. Patients need to be well informed about drug-drug interactions, particularly in relation to self-medication (Vacher et al., 2020).

Medication information provided to patients, such as patient information leaflets (PIL) and internet sources, occasionally contain DDI information (Panich et al., 2019). Health care providers have expressed concerns over the dissemination of DDI information to patients. The explanations encompass the apparent intricacy of information, apprehension over the potential creation of patient anxiety resulting in non-compliance with medicine, and the escalation of concerns and superfluous inquiries directed towards healthcare personnel (Hamrosi et al., 2013). Several apps or services already exist for patients to assess

DDI, suggesting a clear need or demand among patients (Vingen et al., 2020; Kim et al., 2018).

Methodology

The objective of this study is to perform a narrative review on a topic that has not been thoroughly studied before, in order to present a full overview of the area and highlight any research deficiencies in the current literature. Only scholarly publications or conference papers that have undergone peer review and are written in the English language were considered for inclusion in this study. Both research papers and review papers were considered eligible, whereas opinion publications were specifically excluded. The search encompassed all documents until January 2023, without any lower restriction in the time period, ensuring eligibility with respect to time.

Furthermore, the papers must specifically concentrate on providing information regarding drug-drug interactions (DDI) that is intended for patients. The papers can elucidate patients' requirements, utilization, and comprehension about the accessible DDI information, as well as the impacts of disseminating the information to patients, as specified in the study questions. The research questions further specify that we included studies that address the design quality, content, and usability of interactive DDI services.

In addition, articles that provided a broader description of patient needs for drug-drug interaction (DDI) information, rather than specifically focusing on DDI services, could be considered for inclusion in the review if the authors determined that these papers contained pertinent knowledge related to the review issue. Excluded were papers that solely concentrated on DDI services for healthcare professionals, as well as studies that specifically addressed oral communication about DDI between patients and healthcare providers.

In order to discover pertinent papers, we conducted searches in the following databases: ACM, Google Scholar, IEEE (Institute of Electrical and Electronics Engineers), and PubMed. Furthermore, the reference lists of the chosen publications were examined using the identical eligibility criteria employed for the database search.

Results and Discussion

Upon examination, a total of 11 publications with pertinent findings were identified in this study. They employ diverse methodologies and encompass various viewpoints pertaining to patient requirements, utilization, comprehension, and potential ramifications of utilizing DDI information. There is only one research paper that examines the actual experiences of patients who have used a digital drug-drug interaction (DDI) service that is now accessible. The study conducted by Justad et al. (2021) involved administering a questionnaire to patients who had utilized the Swedish DDI service Janusmed encounters. This service is specifically intended for and tailored to healthcare professionals. Patients reported use the service to assess potential drug-drug interactions (DDIs) not only between prescribed medications, but also with over-the-counter (OTC) medications, herbal treatments, food, and alcohol. They provided various justifications for desiring to personally verify DDIs, such as harboring doubts about the ability of healthcare experts to ensure the absence of interactions. Several individuals utilized it to verify potential drug-drug interactions for their acquaintances or relatives. The patients were surveyed about their potential response upon discovering a drug-drug interaction (DDI) among other factors. While most respondents indicated they would consult with the doctor, a few mentioned they might modify the dosage or discontinue the prescription, depending on the situation and whether the drug interaction involved over-the-counter or prescribed medications.

Additional studies explore the viewpoints of patients on drug-drug interaction (DDI) information, both in a general context and within different environments. Four publications elucidate the necessity for DDI information among patients, employing both qualitative and quantitative methodologies. Kusch et al. (2018) conducted a literature analysis to outline the specific drug information that patients seek. This evaluation included 12 studies that examined inquiries made to drug information hotlines, as well as 15 qualitative studies that assessed patients' demands for medication information. The researchers discovered that the topic most commonly asked by patients was information regarding adverse drug reactions (ADRs) and drug-drug interactions (DDIs).

Haverhals et al. (2011) conducted a qualitative study on older patients with multi-morbidity to explore their information needs regarding drug-drug interactions. The study also emphasized significant variations among individuals in relation to this topic. It was shown that a significant number of patients expressed concern over physicians prescribing drugs without adequately taking into account potential drug-drug interactions (DDIs). A significant number of patients utilized the package leaflet to seek out potential side effects and drug interactions, while a portion of them actively sought information online. A significant number of individuals desired to maintain their autonomy and actively engage in the decision-making process, while others unquestioningly adhered to the advice provided by physicians. The researchers discovered that the individuals in their study occasionally made independent choices to discontinue or modify their drugs. Nevertheless, the paper did not explicitly cite fear of drug-drug interactions (DDIs) as a cause for non-adherence. Instead, the reasons provided included the occurrence of side effects or the perception of being on an excessive number of prescriptions. Occasionally, people engaged in discussions over this matter with their doctor, while others proceeded without seeking the doctor's advice. Their findings indicate that personal health applications designed for the elderly to assist with medication management should provide hyperlinks to authoritative and dependable information regarding side effects and drug interactions, among other essential factors.

Mutebi et al. (2013) administered a questionnaire among registered users of an online medication monitoring service to assess the patient's information needs about drug-drug interactions. The purpose of the study was to gather data that would help in developing educational resources for the future. The researchers discovered that the users' primary concerns included: identifying interacting medications, understanding the severity of drug-drug interactions, recognizing interactions with over-the-counter medications, being aware of interactions with foods, managing exacerbation of existing medical conditions, addressing short- and long-term adverse effects, understanding the signs and frequency of DDIs, and learning strategies to minimize adverse effects. The study revealed a correlation between gender, prescription count, and the number of over-the-counter drugs and the perceived significance of various types of drug-drug interaction (DDI) information.

The study conducted by Indermitte et al. (2007) focused on the patient's understanding of drug-drug interactions, particularly in relation to self-medication and OTC medication. This study served as the concluding paper, highlighting the importance of DDI information. Patients frequently lacked awareness or had insufficient understanding of DDIs. In addition, they frequently fail to inform prescribing physicians regarding the utilization of OTC and herbal treatments. The authors found that potential significant outcomes may arise from interactions between OTC and prescribed medications, as they are not usually purchased simultaneously.

In their study, Dohle et al. (2017) conducted an experiment to examine the impact of risk presentation on patients' adherence to precautions in the context of dosing behavior. Researchers noted that informing participants about the heightened likelihood of adverse consequences resulting from a drug-drug interaction (DDI) did result in an amplified perception of risk and negative impact. However, it did not prompt them to modify their dosage behavior. Dohle et al. determined that individuals may encounter difficulties in applying their understanding of DDI risks to their decision-making actions.

Heringa et al. (2018a) conducted a qualitative study to investigate the factors that affect patients' preferences for information about drug-drug interactions (DDIs) and the alternatives available for managing them. Researchers discovered that patients possessed a restricted understanding of drug-drug interactions (DDI) and that their preferences were strongly influenced by the information they received. They discovered that specific cognitive, emotional, personal, and situational factors were linked to the preferences.

In a parallel investigation conducted by Heringa et al. (2018b), it was discovered that the preferences of drug-drug interaction (DDI) management vary across pharmacists and patients. For instance, several groups prioritized the avoidance of medication switching while deciding between various therapeutic choices, whilst others placed greater value on illness eradication or minimizing additional blood samples. The Summary of Product Characteristics (SPCs) serves as the main reference for healthcare professionals on DDIs. Regrettably, it is not possible to provide a comprehensive listing of DDI. As a result, the information on potential drug-drug interactions (DDIs) may be inadequately explained due to the

restricted amount of space in the Summary of Product Characteristics (SPC). According to cross-sectional study, it was discovered that 3.0% of individuals who use PPIs were at risk of potential DDIs within one year of follow-up, based on the risk outlined in the Italian Summary of Product Characteristics (SPCs) for PPIs. However, this proportion increased three-fold to 9.0% when considering information about DDI risk with PPIs reported in Drugdex (Trifirò, et al., 2006). Hence, assessments of DDI that incorporate several sources and are regularly updated with current evidence from the literature can be valuable in assessing the potential risk of DDI, especially in older patients receiving multiple medications.

Furthermore, while not always accessible and practical, implementing therapeutic drug monitoring protocols in the aforementioned patients (i.e., elderly individuals with multiple comorbidities undergoing treatment with multiple medications) should be regarded as a crucial measure to reduce the frequency and severity of drug-drug interactions that may result in both increased healthcare expenses and legal liability for healthcare providers. Thus, we expect the National Health System to devise a strategic intervention plan to ensure that clinicians are sufficiently informed about potential drug-drug interactions, especially those involving commonly prescribed pharmaceuticals. Nevertheless, it would be beneficial to have reports on DDIs that take into account many sources and are regularly updated with current evidence from the literature. This would help assess the potential danger of DDIs, especially in older patients who are taking multiple medications. Prior studies have indicated that the genetic variation in CYP enzymes has a notable impact on the clinical outcomes of pharmacological therapy and the occurrence of DDIs.

Considering the potential limitations, it is important to recognize the value of implementing therapeutic drug monitoring in patients receiving multiple drug treatments and utilizing in vitro techniques to predict the impact of CYP enzyme polymorphism on drug-drug interactions. These approaches can significantly reduce the occurrence and severity of such interactions.

Conclusion

Drug-drug interactions (DDIs) are frequently seen in clinical practice when managing patients receiving multiple medications. It should be emphasized that only two medications have the ability to cause a drug-drug interaction (DDI), and this clinical significance is associated with the pharmacology of each drug. Indeed, a drug-drug interaction (DDI) can elicit a clinically significant impact when combined with medications that have a narrow therapeutic range, a prolonged elimination half-life, and a greater affinity for plasma proteins.

Furthermore, it is crucial to emphasize that the occurrence of drug-drug interactions (DDI) is not a general issue affecting an entire class of drugs, but rather specific to individual drugs. It is possible for this problem to be underestimated if just the Summary of Product Characteristics (SPC) is considered. The treatment of gastrointestinal conditions using proton pump inhibitors (PPIs) or histamine H2-receptor antagonists might potentially lead to several drug-drug interactions, particularly in cases of polypharmacy and in patients who are more susceptible to side effects (such as the elderly or those with cancer). It is crucial to exercise caution in order to avoid the toxic and adverse effects, as well as to prevent the reduction in effectiveness, while delivering subtherapeutic amounts. Gaining a comprehensive comprehension of the pathways through which various agents may interact would facilitate enhanced identification, prevention, and management of drug interactions.

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