Al-Mukhtar Journal of Sciences 39 (3): 164-171, 2024
Doi: https://doi.org/10.54172/f4r0h750

Research Article **Open Access**

Exploring the Side Effects and Drug-Drug Interactions Resulting from Polypharmacy: A Case Study from Cardiovascular Pharmacotherapy

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Received:
27 August 2024

Accepted:
05 September 2024

Publish online:
10 October 2024

Abstract

In clinical practice, it is standard procedure to assess potential drug-drug interactions (DDIs) when prescribing multiple medications to a single patient. The prevalence of DDIs escalates with an increased number of concurrently prescribed drugs. Polypharmacy, as defined by the World Health Organization, entails the administration of numerous medications simultaneously, or an excessive number of medications. We postulate a close association between polypharmacy and DDIs. This study presents a singular case investigation encompassing a comprehensive review of all prescribed and over-the-counter medications, medical history, and laboratory results, coupled with an extensive cross-referencing with existing literature to identify DDIs associated with polypharmacy. Our findings underscore a robust positive correlation between polypharmacy and DDIs, with a total of 83 documented instances. Notably, antibiotics emerged as the medication class responsible for the highest number of DDIs, accounting for 13 cases.

Keywords: Drug-drug interactions, Polypharmacy, Drug Side Effects, Case Study.

INTRODUCTION

Drug-drug interactions (DDIs) refer to adverse effects that arise when two medications are concurrently administered to the same patient (Seymour & Routledge, 1998). These interactions can occur through various mechanisms and range from mild effects that may not require adjustments to high-risk situations where modification or cessation of one medication is necessary.

While adding a medication is typically intended to improve a patient's health, it also increases the potential for DDIs and drug-disease interactions. Clinically significant DDIs can manifest as reduced therapeutic effects of a drug, increased occurrences of adverse drug reactions, and compromised treatment outcomes (Hines & Murphy, 2011). Severe DDIs are those that pose life-threatening risks or necessitate medical intervention to minimize or prevent severe adverse effects.

Polypharmacy encompasses the prescription of more medications than typically recommended in the literature, often exceeding six drugs concurrently (Johnell & Klarin, 2007). Specifically, polypharmacy is defined as the simultaneous use of five or more medications, while hyper-polypharmacy denotes the concurrent use of ten or more medications (Masnoon et al., 2017). The

prevalence of polypharmacy varies across different populations and tends to rise with age. In a comprehensive study involving 1,742,336 older adults, polypharmacy affected 44% of the population (Khezrian et al., 2020). According to Scottish Polypharmacy Guidance, up to 11% of unplanned hospital admissions were linked to adverse effects stemming from polypharmacy, with approximately 50% of these incidents deemed preventable (Khezrian et al., 2020). Furthermore, a prospective study of 5052 older adults in Spain concluded that polypharmacy was associated with nearly a 1.8 times higher risk of mortality (Gómez et al., 2015).

Cardiovascular disease (CVD) is a group of disorders affecting the heart and blood vessels, including coronary heart disease, cerebrovascular disease, hypertension, peripheral arterial disease, heart failure, and arrhythmias. According to the American Heart Association (AHA), the incidence of CVD in the US is approximately 75% among individuals aged 60 to 79 years and rises to 86% among those aged 80 and older (Yazdanyar & Newman, 2009). Evidence-based practice for treating CVD typically involves using combinations of medications tailored to specific diseases (Fleg et al., 2011). Consequently, polypharmacy and potential drug-drug interactions (DDIs), along with their associated consequences, are common among older adults with CVD.

Many treatment regimens for cardiovascular conditions require prescribing multiple medications simultaneously, targeting various organs and necessitating multifaceted treatment approaches. For instance, congestive heart failure (CHF) affects organs such as the lungs, kidneys, and liver, with medication regimens aimed at preventing complications and enhancing quality of life. Depending on the disease stage and individual condition, patients with CHF may be prescribed up to eight medications (AHA). Moreover, CHF patients often present with concurrent conditions that require separate treatment, further increasing the complexity and number of medications administered. In such cases, the side effects of one medication may be mistaken for signs or symptoms of another condition, potentially leading to additional prescriptions.

Considering these factors, polypharmacy in cardiovascular medicine may indeed, elevate the incidence of drug-drug interactions (DDIs) and compromise the overall quality of life for patients. The simultaneous use of multiple medications in the treatment of cardiovascular diseases increases the complexity of managing potential interactions between drugs. These interactions can range from mild to severe, impacting the effectiveness of treatment and potentially leading to adverse effects or reduced therapeutic outcomes.

Furthermore, polypharmacy can contribute to medication adherence challenges and increase the risk of adverse drug reactions, particularly in older adults who may be more vulnerable due to age-related physiological changes and comorbidities. The need for careful monitoring and management of medication regimens is crucial to minimize the risks associated with polypharmacy in cardiovascular care.

In summary, while polypharmacy is often necessary to address the multifaceted nature of cardiovascular conditions, healthcare providers must remain vigilant in assessing and mitigating the risks of drug interactions to optimize patient outcomes and maintain quality of life.

MATERIALS AND METHODS

Hypothesis

Polypharmacy has the potential to precipitate serious complications, resulting in an escalation of prescribed medications and subsequent drug-drug interactions. This cascade can exacerbate existing

health issues, introduce additional complications, and potentially contribute to the onset of new medical conditions.

Methods

This study is a single case investigation involving a comprehensive review of the patient's medication record, encompassing approximately 32 prescriptions and over-the-counter (OTC) medications. The aim is to thoroughly analyze potential polypharmacy issues and their associated consequences, including drug-drug interactions, undertreated or overtreated conditions, and contraindications.

To identify the most prevalent drug-drug interactions and understand their pharmacological mechanisms, references from authoritative sources were consulted. The following texts and applications were utilized:

- Martindale: The Complete Drug Reference. 37th edition, edited by Sean C Sweetman.
- The British National Formulary (BNF). 69th edition. British Medical Association and Royal Pharmaceutical Society, 2015.
- Medscape drug-drug interactions checker.
- Drugs.com drug-drug interactions checker.

These resources were selected for their reliability in providing up-to-date information on pharmacological interactions and guidelines for medication management.

Case Presentation

HA, an 84-year-old female, presented with multiple intermittent complaints, including swelling of the lower limbs limiting daily movement, muscle pain and cramps, dizziness, fatigue, vomiting, nausea, vertigo, hearing loss, difficulty swallowing, persistent cough, and trouble breathing. She had no history of diabetes or hypertension.

Patient's Medical History

- **History of Most Recent Illnesses:**
  - Pneumonia with pleural effusion
  - Lower limb edema
  - Asthma
  - Cardiomyopathy (conflicting data regarding ischemic heart disease)
  - Dehydration
  - Renal artery spasm

- **Past Medical History:**
  - Rheumatoid arthritis with leukocytoclastic vasculitis (LCV) since 1992
  - Old infarctive cerebrovascular accident (CVA or stroke)
  - Secondary epilepsy due to CVA on January 26, 2013
  - Kidney stones: underwent left kidney shock wave lithotripsy (SWL)
  - Surgical: bilateral total knee replacement

Patient's List of Medications

Table: (1). List of drugs used by the patient under study

Brand Name	Generic Name	Duration/ Time
Nexium 40mg	Esomeprazole	Long Term Use
Aspirin 75mg	Acetyl Salicylic Acid	Long Term Use
Vastarel MR 35mg	Trimetazidine	Long Term Use
Carvedilol 6.25mg	Carvedilol	Long Term Use
Lasix 40mg	Furosemide	Long Term Use
Spironolactone 25mg	Spironolactone	Long Term Use
Atorvastatin 10mg	Atorvastatin	Long Term Use
Bisacodyl 5mg	Bisacodyl	Long Term Use
Madopar 125mg	Levodopa/carbidopa	Long Term Use
Allopurinol 300mg	Allopurinol	Long Term Use
Perindopril 5mg	Perindopril	Alternating with lisinopril
Lisinopril 5mg	Lisinopril	Alternating with Perindopril
Depakine Chrono 500mg	Sodium valproate	Long Term Use
Kaleorid 600mg	Potassium chloride	Long Term Use
Gemifloxacin	Gemifloxacin	13/4/2016
Bisolvon syrup	Bromhexine	13/4/2016
Clarithromycin 500mg	Clarithromycin	12/12/16
Trifid tablet	Triprolidine/pseudoephedrine	12/12/16
Night nurse syrup	Promethazine HCL/paracetamol/dextromethorphan/ ethanol alcohol	12/12/16
Rocephin IM inj.	Ceftriaxone	12/12/16
Gemifloxacin	Gemifloxacin	20/12/2016
Rapidus 50mg	Diclofenac potassium	20/12/2016
Levofloxacin 750mg	Levofloxacin	23/4/2017
Mucosolvon syrup	Ambroxol HCl	23/4/2017
Ventolin nebulizer	Salbutamol	23/4/2017
Pulmicort nebulizer	Budesonide	23/4/2017
Seroflo 250/5mg	Salmeterol/fluticasone	23/4/2017
Avamys nasal spray	Fluticasone furoate	30/4/2017
Aerius Syrup	Desloratadine	30/4/2017
Betaserc 16mg	Betahistine HCL	30/4/2017
B-comp syrup	Vitamin B Supplement	30/4/2017
Motilium 10mg	Domperidone maleate	15/5/2017
Cortigen B6 inj.	Pyridoxine and suprarenal cortex extract	15/5/2017

RESULTS AND DISCUSSION

After a comprehensive analysis of potential polypharmacy and drug-drug interactions, the results confirm varying definitions of polypharmacy, often defined as exceeding the upper limit of concurrent medications, typically more than six drugs. This study identified instances of unnecessary medications, drug-drug interactions (DDIs), drug-disease interactions, and exacerbation of the patient's medical condition, necessitating additional prescriptions to manage complications possibly induced by unstudied medication combinations. This cascade effect contributed to an escalation in both the quantity and adverse effects of prescribed medications.

All identified DDIs were categorized based on their impact on exacerbating the patient's condition.

DDIs Resulting in Inappropriate Treatment Indications

Trimetazidine-induced Parkinson-like Syndrome: Trimetazidine, a metabolic agent, affects glucose metabolism and is used to protect against myocardial ischemia. Following a safety review by the European Medicines Agency on June 21, 2012, concerns were raised about its effectiveness and

reports of movement disorders resembling Parkinson's symptoms. The Committee for Medicinal Products for Human Use (CHMP) concluded that while the benefits outweigh the risks in patients with angina pectoris, treatment should be restricted to add-on therapy for patients inadequately controlled by or intolerant to other angina treatments. In this case, the addition of Trimetazidine led to six additional drug-drug interactions after the patient developed Parkinsonian symptoms and required treatment with Madopar.

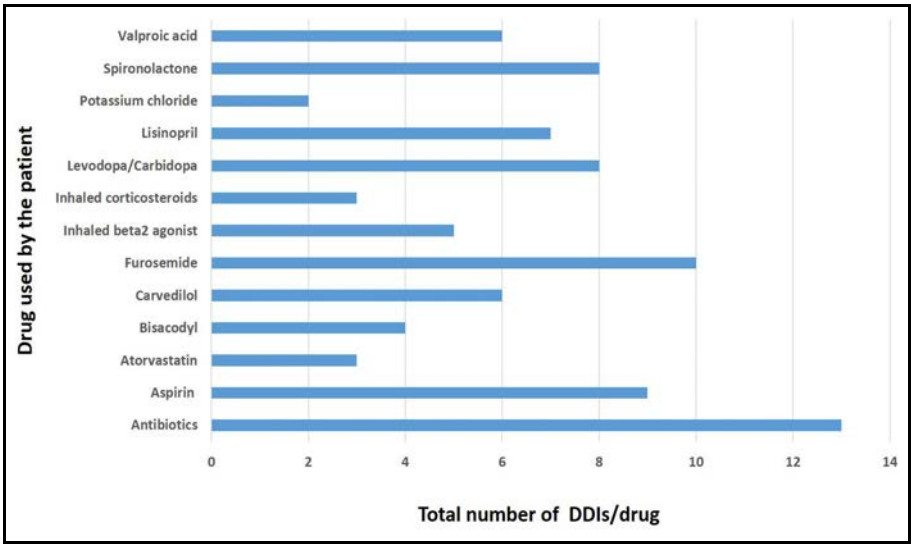

Figure: (1). Number of drug-drug interactions caused by each drug used by the patient.

DDIs Resulting in Therapeutic Failure: Beta2 Agonists and Non-Selective Beta Antagonists

Beta-blockers can antagonize the effects of beta-2 adrenergic bronchodilators, potentially precipitating acute, life-threatening bronchospasm in patients with asthma or other obstructive airway diseases. This drug-drug interaction (DDI) resulted in five prescriptions, multiple hospital visits, and trials of five respiratory antibiotics, which collectively contributed to thirteen DDIs. One of these interactions posed a major risk, involving substantial consequences. Additionally, trials of two different inhaled beta2 agonists introduced five more DDIs, while the use of three inhaled corticosteroids added approximately three additional DDIs. Over-the-counter cough remedies combining antihistamines exacerbated this issue, leading to synergistic sedative effects and nine additional DDIs. Lastly, a trial of Desloratadine, intended for vertigo and hearing loss, antagonized Betahistine, the recommended treatment for these conditions.

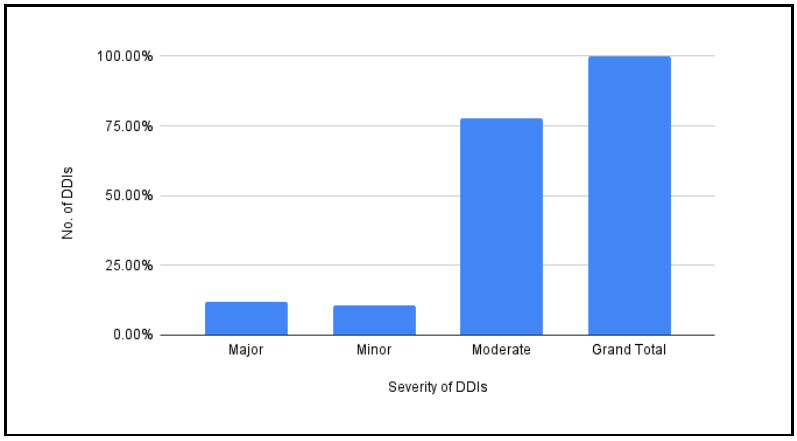

Figure: (2). Number of DDIs versus their deverity as a percentage of the grand total of DDIs

DDIs Contributing to Statin-Induced Myalgia: Atorvastatin, Clarithromycin, and Esomeprazole

Certain macrolide antibiotics such as troleandomycin, erythromycin, and clarithromycin inhibit the enzyme CYP450 3A4. This inhibition can lead to elevated plasma concentrations of HMG-CoA reductase inhibitors (statins) metabolized by this isoenzyme, potentially contributing to statin-induced myalgia.

This revision clarifies the relationship between macrolide antibiotics and statin metabolism, highlighting how these interactions may affect patient outcomes, particularly in terms of myalgia associated with statin therapy.

DDIs Resulting in QT Interval Prolongation:

- Antibiotics: levofloxacin, gemifloxacin, and clarithromycin.
- Beta2 agonists: salmeterol and albuterol.
- Bisacodyl.
- Furosemide.
- Promethazine.

DDIs Adversely Affecting Renal Function:

- **Hyperkalemia:** Caused by the combination of Spironolactone, ACE inhibitors (ACEIs), and Potassium Chloride. Concurrent use of Spironolactone and potassium supplements can lead to severe and life-threatening hyperkalemia.
- **Hyperuricemia:** Induced by the combination of Furosemide, Levodopa, and low-dose salicylates. Hyperuricemia can manifest as an asymptomatic condition characterized by elevated serum uric acid levels, with a urate concentration above 7.0 mg/dl indicating an increased risk of gout. Diuretics, salicylates, and levodopa, all taken concurrently by our patient, can reduce uric acid clearance through various mechanisms. Test results from 2016 showed a significant increase in serum urea, exceeding the upper limit by three-fold in October 2016. By April 2017, urea levels remained elevated, accompanied by an increase in uric acid to 10.5 mg/dl. Discontinuation of furosemide resulted in improved renal function, with subsequent tests in May 2017 revealing reduced urea levels to 61 mg/dl and uric acid levels to 8.14 mg/dl, confirming furosemide's contribution to elevated serum uric acid levels.

DDIs Resulting in Central Nervous System Adverse Drug Reactions: Valproic Acid and Aspirin

- Salicylates, particularly aspirin, have been implicated in displacing valproate from protein-binding sites and inhibiting its clearance. This interaction can lead to a four-fold increase in the free fraction of valproate, potentially amplifying therapeutic and toxic effects. The risk of this interaction is heightened with large or prolonged doses of salicylates, particularly in children.

DDIs resulting in unwanted additive effects:

- Additive lowering in blood pressure; hypotension: Concomitant administration of:
    - Furosemide + spironolactone + carvedilol + levodopa + promethazine.
    - Furosemide + spironolactone + carvedilol + lisinopril + promethazine.

CONCLUSION

The results demonstrate an undeniably strong positive correlation between polypharmacy and drug-drug interactions. This connection is primarily influenced by the following factors:

1. The increasing number of drugs and their pharmacological interactions.
2. Prolonged treatment durations without adequate follow-up and monitoring.
3. Use of over-the-counter (OTC) medications without medical advice.
4. Multiple physicians managing distinct medical conditions simultaneously without coordination.
5. Insufficient collaboration among healthcare team members in medication documentation and patient file updates.

These factors collectively contribute to the complexity and risks associated with polypharmacy, highlighting the critical need for improved medication management practices and interdisciplinary communication within healthcare settings.

It can be inferred that with each additional medication, the possibility of drug-drug interactions increases. Logically, these medications are taken by the same person, sharing the same metabolic environment and exerting their effects on interconnected physiological systems within the body. Therefore, medications taken concurrently are pharmacologically connected.

Based on the results, it is recommended to implement stringent guidelines for checking drug-drug interactions before dispensing medications. The severity and detrimental effects of these interactions on the patient's condition should always be evaluated. Many of the mentioned drug-drug interactions could potentially be avoided through monitoring, risk assessment, and evaluating the necessity and true indication of each prescribed medication.

Establishing stronger communication and collaboration between physicians and pharmacists may help mitigate discrepancies in medication regimens, reduce the prevalence of drug-drug interactions, and ultimately enhance the overall quality of life for patients.

Contribution: This research contributes to the understanding of the relationship between polypharmacy and drug-drug interactions (DDIs) by demonstrating a strong positive correlation between the two. Through a detailed case study, the research highlights the significant prevalence of DDIs in patients subjected to polypharmacy as a result of treating cardiovascular diseases, with antibiotics identified as the most frequent contributors to these interactions. This study highlights the importance of careful medication management and monitoring in patients receiving multiple drugs to mitigate the risk of DDIs.

Conflict of interest: The authors declare they have no conflict of interest related to this study. All authors have reviewed and approved the final version of the manuscript, and there are no financial, personal, or professional relationships that could be perceived as influencing the research or its outcomes.

Funding: This research was funded solely by the authors.

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