Exploring Potential Drug-Drug Interactions in Outpatients with Chronic Diseases in Najran

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List of abbreviations:

DDI	Drug-Drug interaction.
pDDI	potential drug-drug interaction.
HTN	Hypertension
DM	Diabetes Mellitus.

Abstract:

Drug-drug interactions (DDIs) are a major cause for concern in patients with chronic diseases due to multiple co-existing conditions and the wide class of drugs they receive. The objective of our study was to identify potential drug-drug interactions among outpatients with common chronic diseases like diabetes (DM), hypertension (HTN), hypothyroidism, and hyperlipidemia. A retrospective observational study was carried out among 140 outpatients with chronic diseases in Najran city. Chronic patients prescribed at least two drugs. The prescriptions were analyzed for potential DDIs using Micromedex multidrug interaction checker tool. Descriptive statistics, Inferential statistics and p value were used to analyze the results. The incidence of potential DDIs was 67% major interactions, 47% moderate interactions and there is no minor interactions with 140 prescriptions having at least one potential DDI. The top major interacting pairs were Metformin HCL and Glipizide 56 (15.3%). The top moderate interaction Metformin HCL and Lisinopril (21 [5.7%]). Drugs most commonly involved were Metformin HCL, Glipizide, insulin, aspirin and Lisinopril. The risk factors found associated with the potential DDIs Were Age, polypharmacy. The findings highlight the urgent need for enhanced patient education, collaborative care models, and targeted research to mitigate polypharmacy risks, ultimately improving patient safety and treatment outcomes.

Keywords: DDIs, Micromedex, Chronic diseases.

1.1. Introduction:

The examination of drug-drug interactions (DDIs) in outpatients with chronic conditions such as diabetes, hypertension, hypothyroidism, and hyperlipidemia in Najran City has advanced considerably. The increase in polypharmacy has been driven by improvements in chronic disease management, leading to higher rates of DDIs, especially in outpatient settings ((José Luís Blanco et al., 2020), (Maziyyah N et al., 2018)).

For example, a recent study indicated that patients with diabetes and hypertension frequently encounter DDIs due to overlapping medications, necessitating better prescribing practices ((Ponikowski P et al., 2016)).

Certain combinations of antihypertensives and antidiabetics have been shown to significantly elevate the risk of adverse effects ((T Choi et al., 2023)).The active involvement of healthcare professionals, particularly pharmacists, in medication reconciliation is crucial for addressing these challenges ((A Kotalczyk et al., 2022)).A focus on targeted interventions is essential to enhance medication adherence and minimize DDIs among chronic disease outpatients ((D Day et al., 2022)).As the literature from Najran expands, it highlights the need for systematic screening methods for potential interactions to promote safe prescribing and improve patient outcomes ((Ahmed M Badheeb et al., 2024)).Understanding the dynamics of DDIs in outpatient populations remains a critical area for ongoing research ((Hamid AMA et al., 2017)).

2.1. Research Problem:

The prevalence of drug-drug interactions among outpatients with common chronic diseases.

2.2. Aim of the study:

The study aims to identify potential drug-drug interactions among outpatients with common chronic diseases like diabetes, hypertension, hypothyroidism, and hyperlipidemia.

2.3. Study objective:

- Assess the severity of risk of this interaction.

- Assess the correlation between number of drugs prescribed, comorbidities and the incidence of DDIs.

2.4. Literature review

Investigating drug-drug interactions (DDIs) among outpatients with chronic conditions such as diabetes and hypertension in Najran City is increasingly vital, as these patients often face a higher risk of adverse interactions due to polypharmacy. For instance, a study indicated that 90.1% of diabetic patients lacked proper self-care, mainly due to inadequate medication knowledge, highlighting the urgent need for improved medication management education (Sheikh S Abdullah et al., 2024).Diabetes management frequently includes antihypertensive medications, which can negatively impact thyroid disorder treatments. Research shows that certain antihypertensive drugs can lead to significant DDIs, especially with hypothyroidism medications(X Ni et al., 2022). Therefore, it is crucial to monitor prescriptions closely to prevent serious side effects. Factors like age and the number of prescriptions are linked to an elevated risk of DDIs in chronic disease patients(Stremoukhov A et al., 2022).Older adults managing hypertension and hyperlipidemia are particularly at risk, emphasizing the necessity for clinical awareness (J Burton et al.,

2022).As the population ages, healthcare systems must devise effective strategies for managing polypharmacy and related DDIs, especially in resource-limited settings like Najran City(Infrastrukturnta MW et al., 2024).Research predominantly utilizes quantitative observational methods to identify high DDI prevalence rates in hypertensive patients, including combinations like furosemide and ramipril (Infrastrukturnta MW et al., 2024). Studies using electronic health records can analyze large data sets to gauge DDI prevalence and severity, establishing a significant link between polypharmacy and adverse interactions (Paul K Whelton et al., 2017). Complementary qualitative methods, such as interviews, enrich quantitative findings by exposing gaps in patient understanding of medication interactions (M Rasool et al., 2023). Employing methodological triangulation that merges qualitative and quantitative strategies provides a comprehensive view of factors impacting DDIs, facilitating enhanced patient outcomes through tailored interventions (X Ni et al., 2022).Thus, diverse methodologies in DDI research reflect the complexities faced by outpatients with chronic illnesses in Najran City, underscoring the need for integrated care strategies that address both clinical and patient-centered needs. Frameworks focused on DDIs are essential for ensuring medication safety in chronic disease management, as many conditions necessitate multiple medications, heightening the risk of adverse interactions. The socio-ecological model illustrates how medication practices are shaped by broader social and healthcare dynamics, emphasizing the need for interventions that consider these elements(Sheikh S Abdullah et al., 2024).Additionally, medication reconciliation is key to preventing DDIs, requiring thorough medication assessments and educational

initiatives from healthcare providers, particularly in outpatient settings (X Ni et al., 2022), (Stremoukhov A et al., 2022).This is crucial in Najran City, where chronic diseases are prevalent and healthcare resources are scarce (J Burton et al., 2022). Empirical evidence indicates a strong link between polypharmacy and moderate to severe DDIs in chronic disease patients (Infrastrukturnta MW et al., 2024), (Bektay MY et al., 2024).Risk factors, such as age and comorbidities, exacerbate this issue, as older adults are more susceptible to the adverse effects of multiple medications. By integrating various theoretical frameworks into chronic disease management, research highlights the need for proactive strategies to minimize DDI risks and foster safer, personalized treatment approaches for patients in Najran City (M Rasool et al., 2023), (Wafaa T Elgzar et al., 2023).

3.1. Materials and methods:

3.2. Study design, population and data collection

A retrospective observational study were carried out for a period of 8 months (April –Novmber 2024) in a primary care enter**.**

3.3. Study type

retrospective observational study.

3.4. Study area

Saudi Arabia, Najran Region.

3.5. Sample size:

140 prescriptions were analyzed during the study period**.**

Certain demographic characteristics were studied to find out the predictors of DDIs, such as patient characteristics [gender, age (more than 18 years old) and

concurrent morbidities], drug characteristic (number of drugs).

3.6. Inclusion Criteria:

- All outpatients aged 18 years and older than that.

- Patients with at least one chronic disease.

3.7. Exclusion Criteria:

- All patients under 18 years of age.

- Patients with no chronic diseases.

3.8. Classification and analysis of the drug – drug interactions

Each patient's electronic medication list and medication orders in the chart were evaluated. Micromedex interaction databases were used to provide an objective and consistent assessment of the presence and clinical significance of potential drug-drug interactions. When a potential drug-drug interaction were identified by the Micromedex databases, the interacting drugs, doses, routes of administration and the database severity rating were recorded. The patient's sex and age will be also recorded.

3.9. Data Analysis

After a potential drug-drug interaction were identified, a severity assessment was conducted with the Micromedex databases. The mean age and sex of the patients in the study were determined. Descriptive statistics were performed on the collected data to enable the development of a list of the most frequently occurring and clinically significant potential drug-drug interactions.

Results were expressed as percentage for age, gender, diagnosis, number of drugs prescribed, severity and risk involved. Chi-square test were done to study

the association of comorbidities and sex with pDDI.

Table 1: severity Risk:

Major	Effects may result in death, hospitalization, permanent injury, or therapeutic failure
Moderate	Medical intervention needed to treat effects; effects do not meet criteria for major
Minor	Effects would be considered tolerable in most cases; no need for medical intervention

4.1. Results:

Table 2: Demographic characteristics (Gender)

	Frequency	Percent	Valid Percent	Cumulative Percent
Male	89	63.6	63.6	63.6
Female	51	36.4	36.4	100

Figur1:
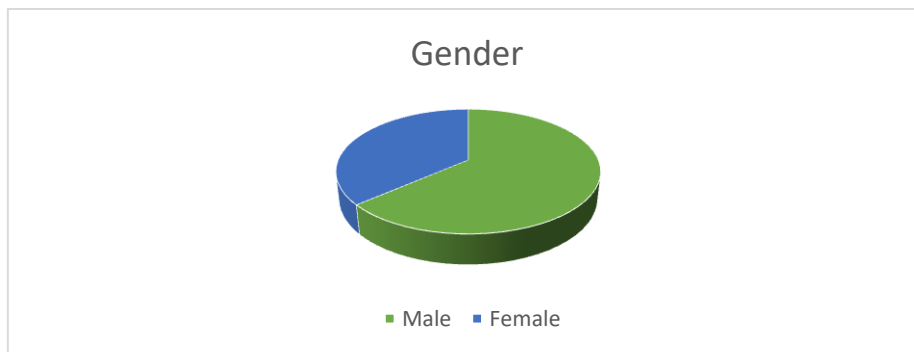
Table 3: Age

Cumulative Percent	Valid Percent	Percent	Frequency	
0.6	0.6	0.6		valid
7	6.4	6.4	9	19-30
8.4	1.4	1.4	2	31-40
26.8	18.4	18.4	26	41-50
47.4	20.6	20.6	29	51-60
78.7	31.3	31.3	44	61-70
100	21.3	21.3	30	more than 70
	100	100	140	**TOTAL**

Figure 2:
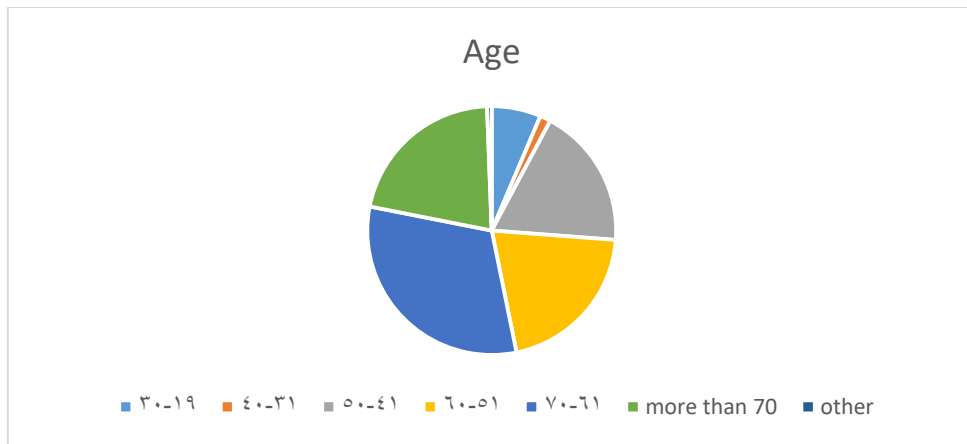
Table 4: the Number of drugs prescribed

		Frequency	Percent	Valid Percent	Cumulative Percent
Number of drugs	1-3	48	34.3	34.3	34.3
	4-6	59	42.1	42.1	76.4
	7-9	28	20	20	96.4

				3.6	100
	more than10	5	3.6	3.6	100
TOTAL		140	100	100	

Figure 3 : Number of drugs prescribed for the patients

This figure showed that the Number of drugs prescribed to the chronic patients when the most patients take 4-6 drugs were 42 % then 1-3 drugs in 34% and 7-9 drugs 20% then more than 10 were 4%.
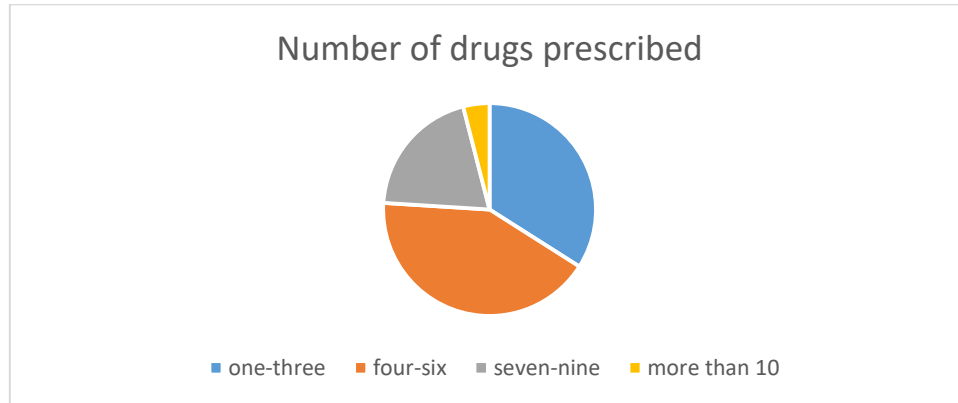

Table 5: severity of the pDDIs:

		Frequency	Percent	Valid Percent	Cumulative Percent
Major interaction	Yes	95	67.4	67.4	67.4
	No	45	32.6	32.6	100
Moderate interaction	Yes	66	47.2	47.2	47.2
	No	74	52.8	52.8	100
Minor interaction	Yes	0	0	0	0
	No	140	100	100	100

Figure 4: severity of the pDDIs

This figure showed that the severity of DDI in 140 patients. Major DDI it is the most common 67.4% then Moderate DDI is present in 47.2 % and there is no minor DDI in the patients.
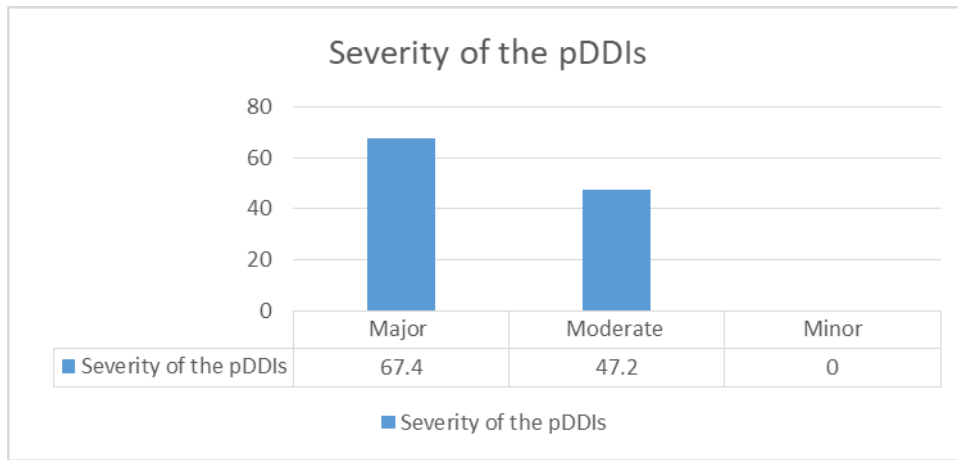
(Figure 4)

Table 6: The most commonly prescribed drugs

		Frequency	Percent	Valid Percent	Cumulative Percent
Nitrates	yes	1	0.7	0.7	0.7
	no	139	99.3	99.3	100
Antiplatletes	yes	30	21.4	21.4	21.4
	no	110	78.6	78.6	100
Diuretics	yes	5	3.6	3.6	3.6
	no	135	96.4	96.4	100
ACE.inhibitors	yes	26	18.6	18.6	18.6
	no	114	81.4	81.4	100
ARB	yes	10	7.1	7.1	7.1
	no	130	92.9	92.9	100
Calcium.channel.blocker	yes	25	17.9	17.9	17.9

	no	115	82.1	82.1	100
Adrenergic.inhibitors	yes	0	0	0	0
	no	140	100	100	100
Beta.Blockers	yes	14	10	10	10
	no	126	90	90	100
HMG.CoA.reductase.inhibitors or stains	yes	59	42.1	42.1	42.1
	no	81	57.9	57.9	100
Thyroid.Agents	yes	13	9.3	9.3	9.3
	no	127	90.7	90.7	100
Vitamin.B.COMPLEX	yes	99	70.7	70.7	70.7
	no	41	29.3	29.3	100
Insulin	yes	72	51.4	51.4	51.4
	no	68	48.6	48.6	100
SGLT2.inhibitors	yes	5	3.6	3.6	3.6
	no	135	96.4	96.4	100
DPP.4	yes	45	32.1	32.1	32.1
	no	95	67.9	67.9	100
Sulfonylurea	yes	65	46.4	46.4	46.4
	no	75	53.6	53.6	100
Biguanides	yes	100	71.4	71.4	71.4
	no	40	28.6	28.6	100

Figure 5: The most commonly prescribed drugs

This figure showed that most commonly prescribed drugs Biguanides, Vitamin.B.COMPLEX (71.4%, 70.7%) respectively. (Figure 5)
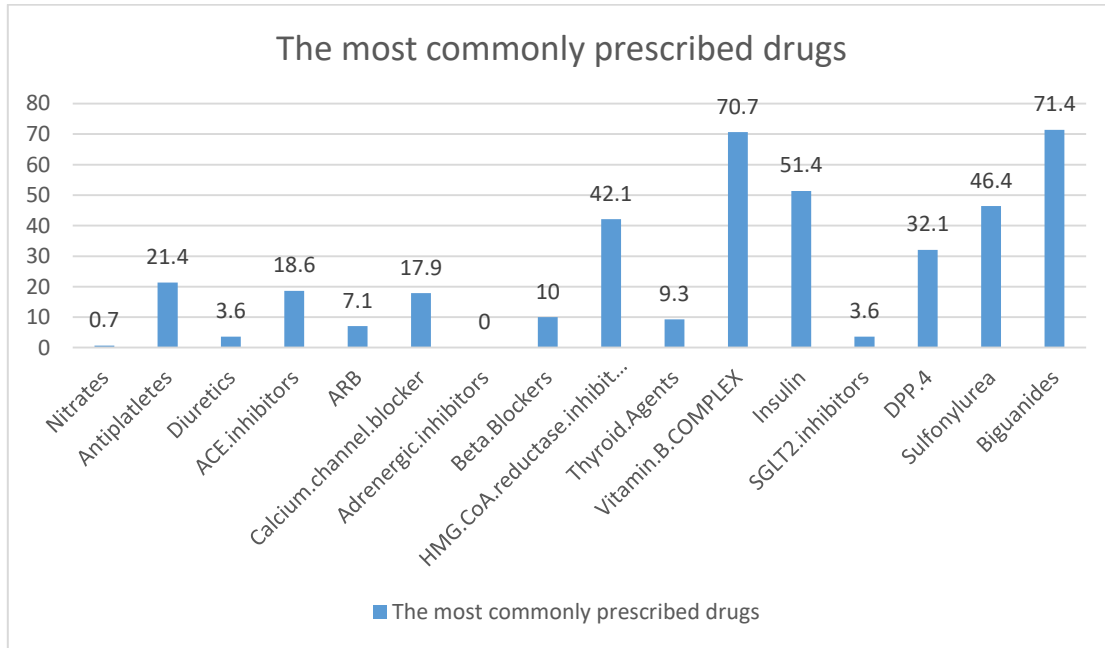

Table 7: most common diagnosis diseases

		Frequency	Percent	Valid Percent	Cumulative Percent
Hypertension	yes	69	49.1	49.1	49.1
	no	71	50.9	50.9	100
Diabetes mellitus	yes	140	100	100	100
	no	0	0	0	100
Hypothyroidism	yes	14	10	10	10
	no	126	90	90	100
Hyperlipidaemia	yes	35	25	25	25
	no	105	75	75	100

This table shows the most common diagnosis diseases in the patients. Diabetes mellitus disease 100 % , Hypertension disease 49.1 % , Hyperlipidaemia 25%.

Figure 6: The Diagnosis

This figure showed that the most common chronic diseases in the patients. Diabetes mellitus disease 100 % then Hypertension disease 49.1 %. Finally, Hyperlipidaemia 25% and Hypothyroidism came in 10%. (Figure 6)
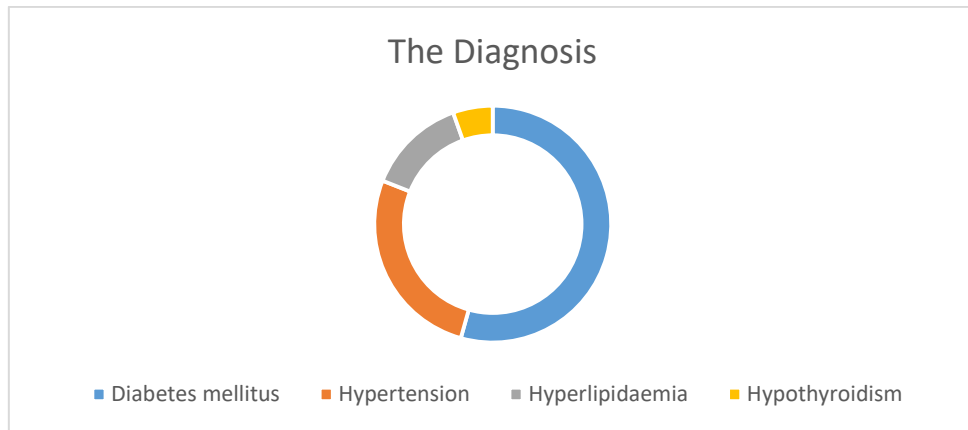

The Diagnosis

■ Diabetes mellitus ■ Hypertension ■ Hyperlipidaemia ■ Hypothyroidism

Table 8: The most common comorbidities in patients with pDDIs

	Frequency	Percent	Valid Percent	Cumulative Percent
Asthma	18	12.5	12.5	12.5
Chronic Ischaemic heart disease	1	0.7	0.7	13.2
Glaucoma	1	0.7	0.7	13.9
Hyperplasia of prostate	1	0.7	0.7	14.6
Parkinson disease	1	0.7	0.7	15.3
NO comorbiditie	118	84.7	84.7	100

Figure 7: The most common comorbidities in patients with pDDIs

This figure showed that the most common comorbidities in patients with pDDIs is Asthma Disease (12.5%). (Figure 7)
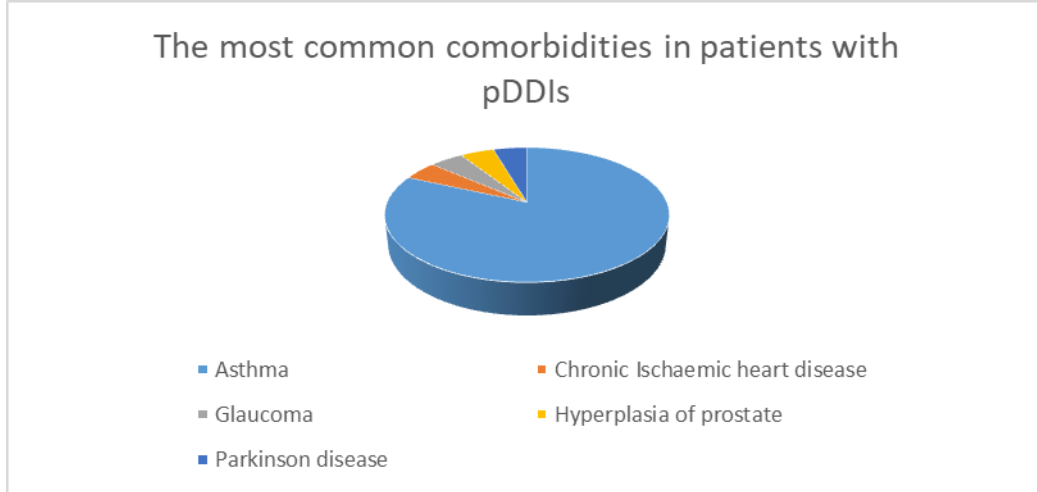
The most common comorbidities in patients with pDDIs

- Asthma
- Chronic Ischaemic heart disease
- Glaucoma
- Hyperplasia of prostate
- Parkinson disease

Table 9: Top 10 major interaction

Interact	Frequency	Percent
Metformin HCL and Glipizide	56	15.3
Metformin HCL and Sitagliptin	41	11.2
Insulin Aspart and Metformin HCL	30	8.2
Glipizide and Sitagliptin	29	7.9
Insulin Degludec and Metformin HCL	26	7.1
Aspirin and Metformin HCL	23	6.3
Insulin Aspart and Sitagliptin	17	4.6
Insulin Glargine and Metformin HCL	15	4.1
Insulin Degludec and Sitagliptin	14	3.8
Aspirin and Glipizide	11	3

Table 10: Top 10 moderate interaction

Interact	Frequency	Percent
Metformin HCL and Lisinopril	21	5.7
Insulin Aspart and Aspirin	20	5.4
Insulin Degludec and Aspirin	17	4.6

Amlodipine Besylate and Metformin HCL	16	4.4
Insulin Aspart and Lisinopril	10	2.7
Insulin Glargine and Aspirin	9	2.5
Insulin Degludec and Lisinopril	9	2.5
Glipizide and Lisinopril	9	2.5
Levothyroxine Sodium and Metformin HCL	7	1.9
Insulin Degludec and Levothyroxine Sodium	7	1.9

Figure 8: Relationship between number of Drugs prescribed and the pDDIs.

This figure showed that the number of drugs that used by the patients increase the risk of
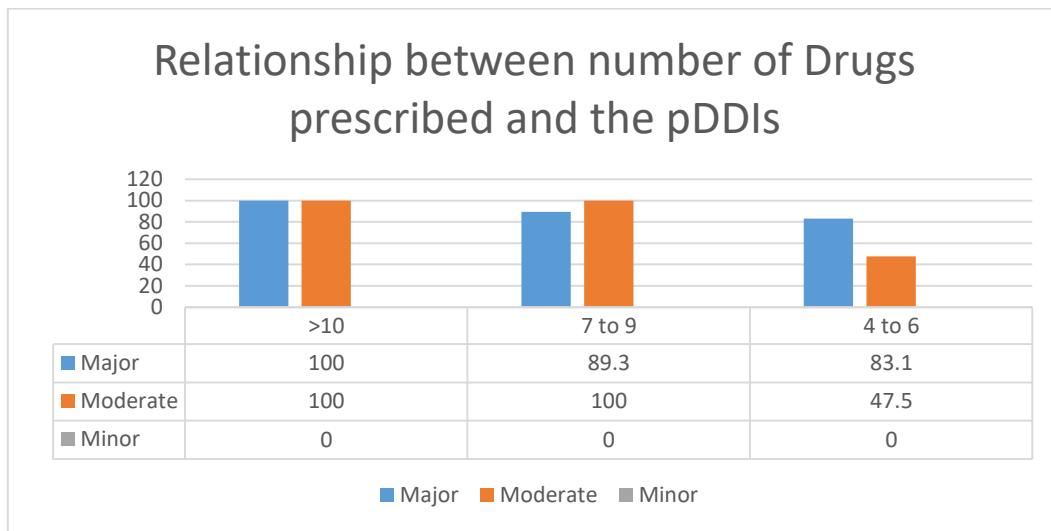
DDIs increased. (Figure 8)

Relationship between number of Drugs prescribed and the pDDIs

	>10	7 to 9	4 to 6
Major	100	89.3	83.1
Moderate	100	100	47.5
Minor	0	0	0

Figure 9: Relationship between the age and potential Major DDIs

This figure showed that Relationship between the age and potential Major DDIs with 31.6%
of Major DDIs in patients with 61-70 years and 0% in patients between 30 and 40 years old.
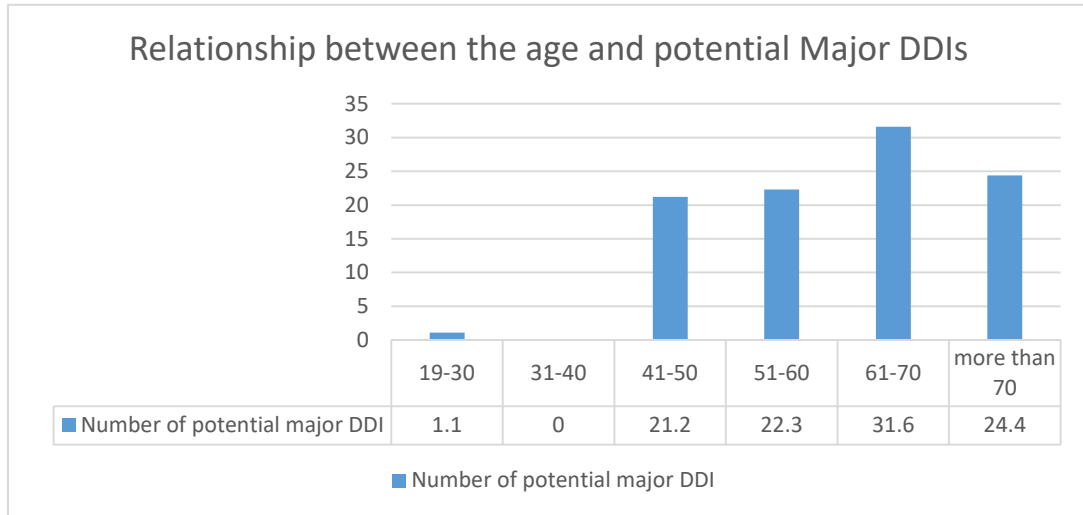(Figure 9)

Relationship between the age and potential Major DDIs

	19-30	31-40	41-50	51-60	61-70	more than 70
Number of potential major DDI	1.1	0	21.2	22.3	31.6	24.4

Figure 10 : Relationship between the age and potential Moderate DDIs

This figure showed that 39% of Moderate DDIs in patients 61-70 years and 0% in patients 19-30 years and 30- 40 years old. (Figure 10)
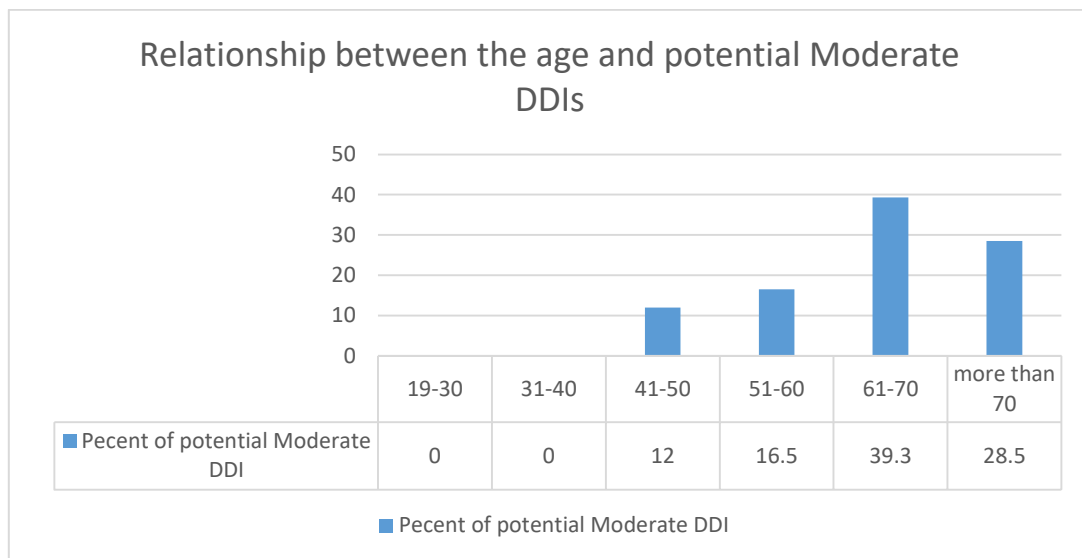

Relationship between the age and potential Moderate DDIs

	19-30	31-40	41-50	51-60	61-70	more than 70
Pecent of potential Moderate DDI	0	0	12	16.5	39.3	28.5

Table 11: Relationship between Gender and the Diseases

	Diseases	Chi-square	p-value
Gender	Hypertension	0.082	0.77
	Diabetes mellitus	0	1
	Hypothyroidism	1.97	0.16
	Hyperlipidaemia	0.83	0.36

Table 12: Relationship between Gender and Severity of pDDI

	Severity of pDDI	Chi-square	p-value
Gender	Major	7.46	0.023
	Moderate	5.64	0.059
	Minor	5.25	0.072

Table 13: Relationship between Diseases and Severity of pDDI

Diseases	Severity of pDDI	Chi-square	p-value
Hypertension	Major	9.007	0.011
	Moderate	43.46	3.642
	Minor	9.810	0.007
Diabetes mellitus	Major	0	1
	Moderate	0	1
	Minor	0	1
Hypothyroidism	Major	6.744	0.034
	Moderate	9.509	0.008
	Minor	1.115	0.572
Hyperlipidaemia	Major	18.52	9.478
	Moderate	12.10	0.002
	Minor	4.329	0.114

5.1.Discussion:

Investigating drug-drug interactions (DDIs) in outpatients with chronic diseases like diabetes, hypertension, hypothyroidism, and hyperlipidemia is crucial for patient safety and treatment effectiveness. Identifying DDIs is important due to the complexity of medication regimens patients need to manage their conditions. Among the 140 prescriptions analyzed, the majority (31%) were in the age group of 61-70 years then (20%) 51-60 years. The most common diagnosis was Asthma 12%, then Glaucoma and Parkinson disease came in 0.7 %. The most common drugs prescribed in our study were Biguanides (100 [71.4%]), Vitamin.B.COMPLEX (99 [70.7%]), Insulin (72 [51.4%]).On analyzing the severity of the interactions, majority of the identified pDDIs were of significant grade (67%), moderate (47%) and there is no minor interactions. The top major interacting pairs were Metformin HCL and Glipizide 56 (15.3%). The top moderate interaction Metformin HCL and Lisinopril (21 [5.7%]). Relation between number of drugs and majority of drug-drug interactions, we found that the increase of the number of drugs increases DDI and majority. More than 10 drugs major interactions were 100%. The number of drugs prescribed to the chronic patients when the most patients take more than 10 drugs, 100%, then 9-7 drugs in 89% and 6-4 drugs 83%, because the patients diagnosed with disease such as hypertension, diabetes mellitus, hypothyroidism ,etc. The risk factors found associated with the potential DDIs Were Age, polypharmacy. Monitoring and continuous follow up over longer durations are required to identify of DDI. Patients should be aware of potential DDIs to actively participate in their health management. Healthcare providers face challenges managing DDIs due to time constraints and the vast pharmacological data available. Cultural considerations

in Najran City affect how patients perceive treatments and may impact DDIs. Future research should focus on specific DDIs in the local population. Policy recommendations include implementing guidelines for medication reconciliation during outpatient visits. Exploring DDIs is essential for improving patient outcomes and public health strategies in Najran City by promoting patient-provider communication and ongoing education on medication safety to reduce risks associated with polypharmacy.

6.1. Conclusion:

- The high prevalence and clinical significance of drug-drug interactions (DDIs) among outpatients with chronic diseases in Najran City.

- The findings highlight the urgent need for enhanced patient education, collaborative care models, and targeted research to mitigate polypharmacy risks, ultimately improving patient safety and treatment outcomes.

6.2. Recommendation:

- One of the ways to minimize the consequences of DDIs would be to use the DDI database freely available online, by the healthcare providers.

- We recommend to add a new feature to suggest safe alternative medication to healthcare provider as a basic part in the health care system.

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