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Drug-Drug Interactions and Prescription Appropriateness in COVID-19 ICU Patients in a Tertiary Care Hospital, Karnataka, India

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Abstract

Severe Coronavirus disease 2019 (COVID-19) management has been challenging due to varying treatment protocol. Additionally, co-morbidities and older age group receiving polypharmacy increases the risk for drug-drug interactions (DDIs).With limited DDI research studies in Indian setup, we aimed to assess the frequency and severity of potential DDIs in COVID-19 ICU patients. This was a retrospective, observational study conducted in a tertiary care hospital, Karnataka, India. Case record of all patients aged ≥18 years with COVID-19 disease admitted to the COVID-19 ICU during March 2021 to July 2021 and treated with two drugs at least were included. A total of one hundred ninety one medical records of COVID-19 patients confirmed by RTPCR were reviewed from medical record department. DDIs were assessed by validated INTERCheck® web system and prescription appropriateness by Beers criteria. Among 191 COVID-19 treated patients, a total of 1049 pDDIs were recorded. Thirty nine percent of the total interactions were classified as potentially severe (class C + class D). Severe pDDIs increased significantly (140 to 274; $p < 0.001$) during hospitalization. Consistently, a significant increase in drug interactions trend was observed during hospitalization (432 to 617; $p < 0.001$). Hence, this study concludes that the severe pDDIs increased significantly during hospitalization and consistent increase in overall (Class A, B, C D) drug interactions trend was observed during hospitalization largely because of the drugs managed to treat comorbidities. Therefore, web based system with multidisciplinary team of expertise may be adopted in hospitals for regulating the dosage of interacting drugs and selecting substitute for overall optimizing the therapy.

Keywords: COVID-19, Drug-drug interaction, Intensive care unit, Prescription appropriateness.

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Introduction

As of 6 February 2022, India reported more than 1,225,011 active cases and over 501,979 deaths related to COVID-19 infection1. Although risk factors associated with coronavirus 2019 disease (COVID-19) have been recognized, co-morbidities and aging are well-recognized self-determining drivers of the development of drug-drug interactions (DDIs)[2-4].

Age-related and age-unrelated co-morbidities usually require polypharmacy for its optimum control, thus aggregating the threat of potential drug-drug interactions (pDDIs), potentially inappropriate medications (PIMs) and drug-specific adverse events[5-7]. However, pDDIs may be intensified in patients with COVID-19 as the polypharmacy burden is increased by the addition of specific treatments along with the medications used for the management of underlying medical comorbidities8. In addition to these, a number of drugs like hydroxychloroquine, methylprednisolone, dexamethasone, prophylactic dose of LMWH (enoxaparin) and investigational therapies like remdesivir and tocilizumab have been recommended for the treatment of moderate to severe COVID-19 disease[9].

Taken together, this puts an extremely high risk of pDDIs, inappropriate medication prescriptions and adverse clinical outcomes, independent of the severity of COVID-19 infection. Therefore an optimized and safer prescription practice in multiple co-morbid conditions and older individuals is often a difficult task. However, to address these issues, various computerized prescription support systems have been developed and one such is INTERCheck® Web System, which stores information on pDDIs, PIMs, dose adjustment in renal impairment cases and modality for drug withdrawal[10,11]. With limited data in the Indian context which addresses the burden of pDDIs and PIMs in COVID-19 ICU patients, we intended to assess the frequency and severity of pDDIs in COVID-19 ICU patients and to evaluate PIMs in a subgroup of patients aged more than 65 years.

Methods

This was a retrospective, observational, single centered study conducted in a tertiary care hospital, in Karnataka, India.

Patients Characteristics

After the ethical approval from the Institutional Ethics Committee and registration in CTRI (No: CTRI/2022/09/045611); case records of all patients aged ≥18 years with COVID-19 disease admitted to the COVID-19 ICU from March 2021 to July 2021 and treated with two drugs at least were included. Patients transferred to other wards from the ICU or discharged/died within 24 hours of admission were excluded. A total of one hundred ninety-one (n = 191) medical records of COVID-19 patients confirmed by RTPCR were reviewed by the Medical Record Department to record the demographic details, co-morbidity conditions, ICU stay and the number and nature of drugs prescribed were collected upon admission and during hospitalization on a pre-designed case report form. The following parameters were evaluated.

Drug-Drug Interactions

It was assessed using a validated INTERCheck® Web System developed by the Istituto Di Ricerche Farmacologiche Mario Negri IRCCS which is updated weekly[12]. According to their clinical relevance; pDDIs are classified as: minor (A, interaction not clinically relevant); moderate (B, interaction associated with an uncertain or variable event); major [C, interaction associated with a serious event, but which can be managed (e.g. by adjusting the dose)]; contraindicated or very serious (D, interaction associated with

a serious event for which co-administration should be avoided or carefully monitored).

Prescription Appropriateness

Appropriateness of drug prescription was evaluated upon admission and during hospitalization by using an American Geriatrics Society 2019 Updated AGS Beers Criteria®[6]. The results were analyzed by using statistical SPSS software version 17.0. Descriptive statistics were used for the categorical variables, which were reported as frequencies and percentages. Mean with standard deviation was expressed for continuous variables. Qualitative variables were analyzed using the Chi-square test and Fischer's exact test. A p-value of ≤ 0.05 was considered statistically significant.

Results and Discussion

Patients Characteristics

One hundred ninety-one medical records of patients with confirmed COVID-19 were evaluated. Table 1 shows the patient's demographic and clinical characteristics. Of the total study population, male sex predominated (55.50%), and the mean age was 51.27 ± 15.66 years (range 18-87). The majority of the study population was in the age group 41-60 years attributing to 40.31%. The median number of medications administered during admission and upon hospitalization was 8 (IQR, 6-9) and 13 (IQR, 11-16) respectively. ARDS (20.42%) was the most common comorbidity, followed by diabetes with hypertension (16.23%) and hypertension (14.66%). Table 2 describes the drugs of different therapeutic classes. Two hundred forty-five prescriptions were antibiotics at the time of admission. Other frequently prescribed were PPIs (n = 158), antiviral drugs (n = 108) and systemic steroids (n = 98). During hospitalization, there was a significant increase in the use of anti-asthmatic drugs (20 to 77, $p < 0.001$), antiviral drugs [(108 to 142, $p < 0.03$; remdesivir (11 to 105; $p < 0.001$)], inhalational steroids (3 to 32, $p < 0.001$), LMWHs (68 to 106, $p < 0.003$) and systemic steroids (98 to142, $p < 0.00451$).

Drug-Drug Interactions

Among the 191 COVID-19 treated patients, a total of 1049 pDDIs were recorded. Thirty-nine percent of the total interactions were classified as potentially severe (class C + class D) with a twofold increase in class D DDIs (Table 3). Severe pDDIs increased significantly (140 to 274; $p < 0.001$) during hospitalization. Consistently, a significant increase in drug interactions trend was observed during hospitalization (432 to 617; $p < 0.001$).

Details of potentially severe DDIs and class B DDIs at admission and during hospitalization are described in Tables 4 & 5. The majority of the potentially severe DDIs observed at admission and during hospitalization increased the risk of QT prolongation attributing to 92.84% and 78.82% respectively. The main drivers for QT prolongation were ceftriaxone plus pantoprazole, ondansetron plus piperacillin, azithromycin plus piperacillin and azithromycin plus ondansetron. According to the credible Meds website, ondansetron, azithromycin, and levofloxacin are classified as 'known risk', piperacillin, pantoprazole, and metronidazole as 'conditional risk' for QT prolongation. DDIs observed due to different steroid administration increased the risk of tendon rupture (1.82%) in levofloxacin recipients, decreased the hypoglycaemic activity of antidiabetic agents (2.97%) and antagonized the action of antihypertensive drugs (1.47%). Table 6 describes the association between variables gender, age, ICU stay and pDDIs. A statistical significant association was found between ICU stay and pDDIs ($p < 0.003$).

Prescription Appropriateness

Of the 191 patients with COVID-19, 41 were aged more than 65 years (21.5%). Among them, 4 patients received only one PIM (9.8%), 9 received two PIMs (21.9%), 6 received three PIMs (14.6%), and 3 received four or more PIMs (7.3%). Among the varied of medications prescribed in study participants, 16 patients (39%) received medications that were categorized as medications potentially clinically important drug-drug interactions to be avoided, 11 patients (26.8%) received medications to be avoided in geriatrics regardless of medical conditions, and 6 patients (14.6%) received medications to be used with caution. The therapeutic classes of PIMs were corticosteroids (39%), non-steroidal anti-inflammatory drugs (39%), insulin (14.6%), diuretics (9.8%), antiplatelet medications (7.3%), anti-cholinergic medications (4.9%), and oral antidiabetes medications (2.4%).

The present study considered March-July 2021 as the study duration, as the larger number of COVID-19 patients required admission. The key finding of this study is that severe pDDIs increased significantly during hospitalization and consistent increase in overall (Class A, B, C D) drug interactions trend was observed during hospitalization largely because of the drugs managed to treat comorbidities and the secondary infection developed during the course of hospitalization.

Higher prevalence of poly-pharmacy (6-9 drugs) is notable in our study population. While concurrent use of five or more drugs is deemed polypharmacy in previous studies[13,14]; extensive polypharmacy is considered to be the use of 10 or more in adults[15].

Varied classes of drugs were used upon admission and during hospitalization (Table 2). An increasing trend in the use of some drugs like remdesivir because of antiviral property[16], systemic steroids because of anti-inflammatory properties and LMWHs due to their prophylactic role and curtailing viral persistence in COVID-19 patients[17] were proposed for treatment of SARS-C0V-2 infection. However, the increase in antibiotic consumption at admission in our study can partly be clarified by usage of azithromycin because of its immunomodulatory property[18] and hence suggesting its role in SARS-CoV-2 infection. We found that 39% of total interactions were potentially severe in nature with a twofold increase in potentially severe DDIs during hospitalization relating to combinations of drugs that should be evaded theoretically or managed by adjusting the dose or by monitoring carefully.

Considering varied of drug combinations which led to different adverse event (Table 4, 5); the most common was cardiac toxicity attributing to almost 80% of the pDDIs during hospitalization. This could due to increased risk of cardiovascular diseases in COVID-19 patients with reported decrease in potassium level leading to electrocardiographic changes[19-22]. Although, DDIs is a challenging task to recognize and to diagnose especially in clinical conditions with multiple comorbidities to clinicians, administration of non-specific drugs for COVID-19 such as azithromycin, pantoprazole, ondansetron, piperacillin with different inherent risk of prolonging QT interval prolongation could be attributable to increased trend in pDDIs during hospitalization as part of COVID-19 management[23]. Therefore, a high level of DDIs in our study could be attributable to several factors such as comorbidities, presence of extensive polypharmacy (median number of drugs prescribed during hospitalization 13; IQR 11-16), and longer hospital stay (median 11; IQR 7-17 days), and many others[24,25].

Although a significant use of remdesivir was observed in our study, it is noteworthy that no clinically important DDIs were noted; which encourages its use in terms of safety which corroborated with study conducted by Cattaneo D et al[12]. Another interesting finding was that the majority of the severe DDIs were determined by PPIs which could be attributable to its theoretical risk of electrolyte disturbances following its prolonged use. Yet the use of PPIs for causing clinically important DDIs is still undervalued[26-28].

Severe COVID-19 infection is linked with excessive inflammatory response which ensues endothelial and haemostatic activation leading to arterial and venous thrombotic state[29]. Therefore DDIs of oral anticoagulants must be anticipated while handling these clinical conditions. However, rivaroxaban and dabigatran were commonly ordered in our study. Among the direct oral anticoagulants (DOACs), rivaroxaban is a substrate for both CYP3A4 and P-glycoprotein (P-gp) transporter and in contrast dabigatran is a substrate only for P-glycoprotein transporter. Hence, co-administration with inhibitors of P-gp transporter and CYP3A4 (e.g., clarithromycin, fluconazole, verapamil) should be evaded due to raised serum concentration of rivaroxaban and dabigatran and hence tendency of bleeding[30]. Additionally COVID-19 patients with underlying cardiovascular diseases may use antiplatelets prophylactically and NSAIDs for symptomatic relief of fever and myalgia and therefore its administration with anticoagulants may escalate the threat of bleeding[31].

Analysis of variables like age, sex, and ICU stay with pDDIs revealed that the occurrence of DDIs is significantly associated with ICU stay which could be explained by the complicated conditions in critically ill patients and polypharmacy which corroborated with the study conducted by Amir Ali Mahboobipour and Shadi Baniasadi[32]. Nearing one-fourth of COVID-19 patients inducted in our study were aged more than 65 years, the threshold age for assessing PIMs. Among the varied PIMs of different therapeutic classes, the majority were corticosteroids and non-steroidal anti-inflammatory drugs. The majority of the patients received medications that were categorized as medications potentially clinically important drug-drug interactions to be avoided, followed by medications to be avoided in geriatrics regardless of medical conditions. This could be possibly explained by the fact that considering the severity of the COVID-19 patients, the treating physicians accepted the risk of DDIs but were not fully aware of the updated Beers criteria for optimizing drug prescriptions.

The strength of the study is that DDI studies among COVID-19 ICU patients are limited. Therefore, data provided by our research can encourage physicians to cautiously prescribe certain medications especially in older elderly and hence to optimize prescription in these set of patients. However, our study has certain limitations. First, the adverse event related to actual DDI was not evident in the patients' records and also the impact of DDIs on clinical outcomes could not be verified due to nature of study design. Second, although we found certain risk factors of DDIs in COVID-19 patients; causal inferences may not be ascertained considering the study design. Finally, it is important that as the new data emerge and constantly changing treatment protocols, physicians need to stay abreast with current trends and be vigilant while administering drugs.

Conclusion

Nearing forty percent of DDIs were severe in nature. Consequently, COVID-19 patients treated with medications with inherent

property of prolonging QT interval and cardiovascular comorbidity are at increased risks of cardiotoxicity. Therefore, web based system with multidisciplinary team may be adopted in hospitals for regulating the dosage of interacting drugs and selecting substitute for over all optimizing the therapy.

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Conflict of Interest
None declared.

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Table 1. Demographic and clinical characteristics of COVID-19 patients [N= 191]

Characteristics	Number (n)	(%)
Age (years)		
< 40	60	31.4
41-60	77	40.3
>61	54	28.3
Sex		
Male	106	55.5
Female	85	44.5
Comorbidities		
Acute Respiratory Distress Syndrome	39	20.4
Diabetes with Hypertension	31	16.2
Hypertension	28	14.7
Diabetes	27	14.1
Chronic Obstructive Pulmonary Disease	4	2.1
Asthma	3	1.6
Cerebrovascular Accidents	3	1.6
Chronic Kidney Disease	2	1.04
Deep Vein Thrombosis	2	1.04
Parkinson Disease	2	1.04
Hypothyroidism	1	0.5
Characteristics	**median (IQR)**	
Length of stay (in days)	11 (7-17)	
No of drugs prescribed,		
On admission	8 (6-9)	
During hospitalisation	13 (11-16)	

IQR:inter-quartile range

Table 2. Distribution of drug classes at admission and during hospitalization [N= 191]

Therapeutic class (examples of often-prescribed drugs	At admission n (%)**	During hospitalization n (%)**	p-value (Chi square/Fisher's exact test)
ACEI/ARBs (enalapril, telmisartan)	07 (3.6)	13 (6.8)	0.18
Antiasthmatic drugs (acebrophylline, formeterol, salmeterol and combinations withother antiasthmatic drugs)	20 (10.5)	77 (40.3)	<0.001*
Antibiotics (azithromycin, ceftriaxone, piperacillin+tazobactum)	245	160	<0.001*
Antiemetic drugs (ondansetron)	67 (35.1)	38 (19.9)	0.004*
Antiviral drugs (oseltamivir, remdesivir)	108 (56.5)	142 (74.3)	0.03*
CCBs	11 (5.8)	28 (14.7)	<0.001*
Inhalational steroids (budesonide, fluticasone)	03 (1.6)	32 (16.8)	<0.001*
LMWHs (enoxaparin, dalteparin)	68 (35.6)	106 (55.5)	<0.001*
PPIs (pantoprazole)	158 (82.7)	140 (73.3)	0.29
NSAIDs (paracetamol)	63 (32.9)	29 (15.2)	<0.001*
Systemic steroids (methylprednisolone, dexamethasone)	98 (51.3)	142 (74.3)	0.004*

*denotes p-value as statistically significant. ** Percentage may not add up to 100% because of multiple medications prescribed.

Direct Oral Anticoagulants (DOACs) and insulin was used only during the hospitalization i.e. in 26 and 13 patients respectively. Thus they were excluded from the analysis.
ARBs: angiotensin receptor blockers; ACEi:angiotensin converting enzyme inhibitors; CCBs:calcium channel blockers; LMWHs:low molecular weight heparin; PPIs:proton pump inhibitors; NSAIDs:non-steroidal anti-inflammatory drugs

Table 3. Distribution of pDDIs at admission and during hospitalization

Class	At admission	During hospitalization	p - value (Chi square/Fisher's exact test)
Class A	2	4	0.41
Class B	290	339	0.050*
Class C	50	78	0.013*
Class D	90	196	< 0.001*

*denotes p-value as statistically significant. pDDIs: potential drug-drug interactions

Table 4. Prevalence of the first 10 potentially severe drug-drug interactions (DDIs) at hospital admission and during hospitalization

Drug combination	Potential adverse events	Patients (n (%)) At admission	During hospitalization
Ceftriaxone + pantoprazole	Increased risk of cardiotoxicity i.e. QT interval prolongation, cardiac arrest, torsade de pointes,)	50 (35.7)	57 (20.8)
Ondansetron + piperacillin		23 (16.4)	42 (15.3)
Azithromycin + piperacillin		22 (15.7)	44 (16.1)
Azithromycin + ondansetron		28 (20.0)	37 (13.5)
Azithromycin + levofloxacin		03 (2.1)	08 (2.9)
Piperacillin + levofloxacin		03 (2.1)	08 (2.9)
Ondansetron + levofloxacin		01 (0.7)	09 (3.2)
Piperacillin + metronidazole		0	06 (2.2)
Metronidazole + ondansetron		0	05 (1.8)
Prednisolone + levofloxacin	Increased risk of tendon ruptures	0	05 (1.8)

Table 5. Prevalence of first 10 Class B DDIs at hospital admission and during hospitalization

Drug combination	Potential adverse event	Patients (n (%)) At admission	During hospitalization
Pantoprazole + ondansetron	Increased risk of cardiotoxicity i.eQT interval prolongation, torsade de pointes, cardiac arrest	64 (22.01)	88 (25.9)
Pantoprazole + piperacillin +		58 (20.0)	91 (26.8)
Azithromycin + pantoprazole		55 (18.9)	63 (18.6)
Pantoprazole + metronidazole		02 (0.7)	15 (4.4)
Pantoprazole + levofloxacin		04 (1.4)	11 (3.2)
Metformin + Prednisolone	Concomitant intake may decrease the hypoglycaemic activity of antidiabetic agents	0	05 (1.5)
Dexamethasone + Metformin		0	05 (1.5)
Dexamethasone + Telmisartan	Corticosteroids antagonize the action of antihypertensive drugs	0	05 (1.5)
Pantoprazole + dabigatran	Reduction of the absorption and bioavailability of dabigatran	0	04 (1.2)
Atorvastatin + clopidogrel	Possible reduction of the metabolic activation of clopidogrel and its therapeutic efficacy	0	02 (0.6)

Table 6. Association between variables gender, age, ICU stay and pDDIs [N= 191]

Variables	Interaction (n=166)	No interaction (n=25)	Odds ratio 95% CI	p-value (Chi square/Fisher's exact test)
Gender				
Male	93	13	0.85 (0.36-1.97)	0.71
Female	73	12		
Age				
< 60	103	16	1.08 (0.45- 2.6)	0.84
≥ 60	63	9		
ICU stay, days				
< 11	68	18	3.7 (1.46-9.35)	0.003*
≥ 11	98	7		

*denotes p-value as statistically significant.
ICU: intensive care unit; pDDIs: potential drug-drug interactions; CI: confidence interval

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Analysis of Waiting Times for Compound and Non-Compound Prescription Services At Al-Masoem Pharmacy in Cibiru, Bandung City

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Abstract

Prescription services at Al-Masoem Pharmacy, Cibiru should consider waiting time as one of the indicators for service provision to enhance service quality and ensure patient satisfaction. The aim of this research is to analyze the waiting time for prescription services at Al-Masoem Pharmacy, Cibiru and assess compliance with the Minimum Service Standards for Pharmacies outlined in Ministry of Health Regulation Number 73 of 2016. Observations of waiting times for prescription services at Al-Masoem Pharmacy, Cibiru, located in Bandung Regency, were conducted over 14 working days in February 2024, involving 365 prescriptions. This study utilized an observational method during the specified 14-day working period in February 2024, covering 365 prescriptions. The research findings indicate that prepared and unprepared prescription services align with the time range specified in Ministry of Health Regulation Number 73 of 2016, which is 15-30 minutes. Based on observational data, the average waiting time for 44 compound prescriptions was 14 minutes and 18 seconds, while the average waiting time for 321 non-compound prescriptions was 7 minutes and 10 seconds.

Keywords: Waiting Time, Prescription Services, Pharmacy

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Introduction

Pharmacies are facilities that provide pharmaceutical services and serve as practice venues for pharmacists. Pharmaceutical Service Standards are guidelines used by pharmaceutical personnel in delivering pharmaceutical services. Numerous studies and literature reviews have been conducted to evaluate the quality of health services and related issues, including patient dissatisfaction due to long waiting times, especially in prescription services at pharmacy[1,2]. The quality of service at the pharmacy significantly impacts patient satisfaction, especially concerning prescription waiting times[3,4]. This waiting time is influenced by several factors, such as the availability of human resources, medication, prescribing patterns of physicians, and standard operating procedures applied in the prescription service process at pharmacies[5].

Waiting time in healthcare services remains a prevalent issue, particularly in the prescription medication process at pharmacies. Delays can lead to patient dissatisfaction as they have to wait longer to receive prescribed medication. As part of the service process, this waiting time reflects the quality of the pharmacy staff's work, which should be adaptable to patients' needs and expectations. In striving for excellent service, it is crucial for pharmacy to optimize waiting times to be efficient, both in dispensing ready-made prescriptions and in preparing specialized medications[6,7].

Prescription waiting time is one of the indicators used to assess the quality of service at pharmacies. The typical duration for prescription service falls within the range of 15 to 30 minutes[8]. The waiting time for compounded prescription services refers to the specific time needed for pharmacists to prepare medication according to the doctor's prescription. Compounded prescription service usually takes longer compared to non-compounded prescription service because it involves mixing medication ingredients according to the prescription. This indicator reflects efficiency in meeting patient needs. The shorter the waiting time, the better the service provided. This is because patients receive medication faster without having to wait excessively.

Methods

This research was conducted using an observational design with descriptive analysis. Descriptive research aims to describe specific phenomena or subjects[9]. The observations were carried out at Al-Masoem Pharmacy, Cibiru over a period of 14 working days in February 2024. The research sample consisted of prescriptions received by Al-Masoem Pharmacy, Cibiru from Monday to Saturday, totaling 365 prescriptions, which were collected using accidental sampling. Quantitative data collection was performed by measuring the waiting time for both non-compounded and compounded prescription services using a stopwatch[10].

The waiting time for prescription services was calculated from the moment the patient submitted the prescription until the medication was handed over by the staff, including Drug Information Services. The variable in this study is a single variable, namely the waiting time for prescription services at Al-Masoem Pharmacy, Cibiru. The analysis of the collected data involved calculating the average waiting time for prescription services. The waiting time measurements in prescription services were presented in a table, and the results were considered satisfactory if they complied with the provisions of the Ministry of Health Regulation Number 73 of 2016 regarding Pharmaceutical Service Standards at Pharmacies.

Results and Discussion

The collaboration between Al-Masoem Pharmacy, Cibiru and several doctors forming the clinic has brought significant positive impacts. One of the impacts observed is the increase in the number of patients visiting the pharmacy. The collaboration between the pharmacy and the clinic allows patients to receive more integrated services, where prescriptions written by doctors can be filled and processed directly at the affiliated pharmacy[11]. From the research results, a total of 365 prescription samples were obtained. From the presented table, it is evident that (Table 1) the Analysis of Prescription Waiting Time is divided into two categories: waiting time for compounded and non-compounded prescriptions. All prescriptions collected in this study were from non-BPJS patients or patients who undergo health examinations using personal funds. Therefore, all patients paid in cash. Among the types of prescriptions obtained, the majority were non-compounded prescriptions, totaling 321 prescriptions. The use of compounded prescriptions at Al-Masoem Cibiru Clinic is more commonly prescribed for pediatric patients or for topical preparations that require more than one type of medication. The finding that the number of compounded prescriptions is relatively low indicates that the number of pediatric patients receiving prescriptions from doctors is lower compared to adult patients. Additionally, the disease patterns of patients consulting dermatologists indicate that many cases can be treated with only one type of topical medication.

Doctor Specializations at Al-Masoem Cibiru Clinic

In addition to serving prescriptions written by collaborating doctors, Al-Masoem Pharmacy, Cibiru also accepts prescriptions from other clinics or hospitals. This indicates that the pharmacy has become an important healthcare center in the area, not only for patients from the collaborating clinic but also for patients from various other medical institutions in the vicinity. The following table describes the distribution of prescription variations based on the specialization of the prescribing doctors served by Al-Masoem Pharmacy, Cibiru during the observation period.

Al-Masoem Pharmacy, Cibiru has established partnerships with various specialist doctors, including two general practitioners, two dermatologists, one ophthalmologist, one dentist, one obstetrician/gynecologist, one otolaryngologist, one pediatrician, and one internist (Table 2). Each doctor has their own practice schedule, meaning that the number of patients visiting the pharmacy each day cannot be precisely predicted. The variation in doctor specializations and their practice schedules can affect the number of prescription services provided at the pharmacy on any given day. The presence of more dermatologists and general practitioners who practice at Al-Masoem Pharmacy, Cibiru every day does indeed impact the number of prescriptions served. These doctors may prescribe medication more frequently because they serve a larger number of patients compared to other doctors. Additionally, the patient limit policy established by specific doctors each day also influences the number of prescriptions served.

Prescription Service Waiting Time

Prescription service waiting time refers to the total duration of medication service at Al-Masoem Pharmacy, Cibiru, starting from the moment the patient submits the prescription until the patient receives the medication. From the research findings, the average waiting time for 44 compounded medication prescriptions is 14 minutes and 18 seconds, while the average waiting time for 321 non-compounded medication prescriptions is 7

minutes and 10 seconds (Table 3 and 4). This difference indicates that the waiting time for compounded medication services tends to be longer than for non-compounded medications at Al-Masoem Pharmacy, Cibiru.

The prescribing patterns of each doctor have a significant impact on the waiting time for services at Al-Masoem Pharmacy, Cibiru. Each doctor tends to prescribe certain types of medication. For example, in non- compound prescriptions, ophthalmologists tend to prescribe only one or two types of eye drops. Patients receiving prescriptions for eye drops only need to wait for fewer preparations, which directly reduces their waiting time. In compound prescriptions, dermatologists tend to prescribe a combination of two or three brands of ointments and creams into one container. Consequently, patients receiving such prescriptions will experience shorter waiting times compared to patients receiving compounded prescriptions from other doctors who may require several different compounding steps. Based on the table above, the average waiting time for prescription services, both compounded and non-compounded, at Al-Masoem Pharmacy, Cibiru is below the maximum time limit set, which is 15-30 minutes[8]. This indicates that prescription services at the pharmacy are efficient, so patients do not have to wait too long to receive the medication they need.

Several factors contribute to the efficiency of prescription service waiting times at Al-Masoem Pharmacy, Cibiru. One of them is the availability of an adequate number of human resources. The allocation of human resources shifts at Al-Masoem Pharmacy, Cibiru is carried out in two shifts. Each shift has a minimum of two Pharmaceutical Technical Personnel and one Pharmacist. With an adequate number of human resources, the pharmacy can reduce the likelihood of prescription accumulation and improve prescription handling times[12]. Additionally, the skills of human resources in preparing prescriptions also play a crucial role. With trained and experienced human resources, the pharmacy can ensure that the prescription preparation process is carried out quickly and accurately. The combination of these two factors helps ensure that prescription service waiting times remain efficient and in line with established standards[13].

The availability of adequate medication, in accordance with the doctor's prescription, is also a factor in determining prescription service waiting times at the pharmacy[14]. Al-Masoem Pharmacy, Cibiru has sufficient medication stock and can serve patients more quickly and efficiently. When certain medications are not available, pharmacy staff must confirm the shortage with the doctor and adjust the dosage or find alternative medications that are suitable for the given prescription[15]. This process takes additional time and may delay service to patients.

Conclusion

Based on the research findings, it can be concluded that the waiting time for prescription services, both compounded and non-compounded, at Al-Masoem Pharmacy, Cibiru has exceeded the standards set in Minister of Health Regulation No. 73 of 2016, which is between 15 to 30 minutes. The average waiting time for compounded prescription services is 14 minutes and 18 seconds, while the average waiting time for non-compounded medication services is 7 minutes and 10 seconds. This indicates that the pharmacy has successfully provided efficient and timely services to patients.

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None declared.

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Table 1. Number of Compound and Non-Compound Prescriptions

Prescription Type	Quantity	Percentage
Compound prescriptions	44	12,33%
Non-Compound prescriptions	321	87,67%
Total	**365**	**100%**

Table 2. Prescription Variations Based on Doctor Specializations

Specialty	Compound Prescription Quantity	Non-Compound Prescription Quantity
Ophthalmology	-	11
Dentistry	1	23
Obstetrics/Gynecology	-	8
Otorhinolaryngology	2	19
General Practice	1	67
Pediatrics	5	26
Dermatology	37	127
Internal Medicine	-	14
External Prescriptions	-	26

Table 3. Average Prescription Service Waiting Time

Prescription Type	Average Waiting Time
Compound Prescription	0:14:53
Non-Compound Prescription	0:07:10

Table 4. Average Prescription Service Waiting Time by Doctor Specialization

Speciality	Average Service Waiting Time	
	Compound Prescription	Non-Compound Prescription
Ophthalmology	-	0:04:12
Dentistry	0:15:09	0:05:09
Obstetrics/Gynecology	-	0:05:10
Otorhinolaryngology	0:27:28	0:05:46
General Practice	0:23:47	0:07:11
Pediatrics	0:22:23	0:08:39
Dermatology	0:12:00	0:07:45
Internal Medicine	-	0:08:08
External Prescriptions	-	0:06:43

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Prescription Pattern Analysis in Patients of Alcohol Use Disorder coming to the Psychiatry OPD of a Tertiary Care Hospital in Mumbai district of Maharashtra, India: A Single Centre, Cross Sectional, Observational Study

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Abstract

Alcohol is the most common psychoactive substance used by Indians. The prevalence of alcohol dependence in India is estimated to be 2.7%. In Maharashtra, the prevalence of Alcohol Use Disorders (AUD) is about 4.9%. Prescription pattern monitoring studies are a tool for assessing the prescribing, dispensing, and distribution of medicines. They promote the appropriate use of drugs and reduction of their misuse. With changing guidelines and the availability of newer drugs, it is the need of time to monitor the prescriptions. So, this study was done from October 2019 to January 2021 in a tertiary care teaching institute in western India on 100 patients, which focuses on analyzing the prescribing pattern of drugs in AUD patients. Along with this, potential drug interactions were checked using the Medscape drug interaction checker. A comparison of prescriptions with 2018 APA guidelines was also done. An average 4.77 drugs were prescribed per patient per encounter. 65% of patients were prescribed anti-craving drugs as oral tablets. Only 11% of them were listed in the NLEM, but none were in the hospital drug formulary. The maximum prescribed drugs of other groups were Vitamins (25.7%), Benzodiazepines (22.3%) and Antipsychotics (20.6%). 53.3% of these drugs were from hospital formulary. Potential drug-drug interactions were found in 76%. Adherence to 2018 APA guidelines was present in 89% of cases. This study would provide insight into the trends of drug utilization and feedback to prescribers to create awareness about the rational use of drugs. The evaluation of potential drug interactions can help in solving the problem of polypharmacy.

Keywords: Alcohol dependence, WHO core prescribing indicators, Drug-drug interactions

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Introduction

Alcohol is the most common psychoactive substance used by Indians, followed by Cannabis and Opioids. In India, about 14.6% of the population (between 10 and 75year of age) uses alcohol and 19% of current users of alcohol consume it in a dependent pattern. The prevalence of dependent pattern of alcohol use in India is estimated to be 2.7%. In the state of Maharashtra, the prevalence of alcohol use disorders is about 4.9%[1]. DSM–IV described two distinct disorders, alcohol abuse and alcohol dependence, with specific criteria for each. As per DSM–V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), the two DSM–IV disorders- alcohol abuse and alcohol dependence, are integrated into a single disorder called Alcohol Use Disorder (AUD)[2].

The misuse of alcohol is one of the leading causes of preventable death, illness, and injury in many societies throughout the world. Pharmacotherapy along with behavioural therapy plays an important role in preventing alcohol addiction. Advances in neurobiology and associated neurotransmitter systems in development of AUD are also the potential targets for pharmacological approach[3]. Prescription pattern monitoring studies (PPMS) are a tool for assessing the prescribing, dispensing and distribution of medicines. They promote appropriate use of monitored drugs and reduction of their abuse or misuse[4]. These studies guide and support prescribers, dispensers, and general public on appropriate use of drugs, develop working relationship with other key organizations to achieve a rational use of drugs. They explain the extent and profile of drug use, trends, quality of drugs, and compliance with regional, state, or national guidelines. There is increasing importance of PPMS because of a boost in marketing of new drugs, variations in pattern of prescribing and consumption of drugs, growing concern about delayed adverse effects, cost of drugs and volume of prescription[3,4].

The core prescribing indicators of drug use recommended by WHO are calculated from the prescriptions. Prescribing indicators measure general prescribing tendencies within a given setting, independent of specific diagnoses[5]. With the changing guidelines and availability of newer drugs in AUD patients, it is the need of time to monitor the prescriptions[6]. Very few studies have been conducted in the past regarding PPMS of AUD, however no such recent study has been done in our institute. So, this study is done which focuses on analysing the prescribing pattern of drugs in patients of alcohol use disorders. Along with this, potential drug interactions are also checked using Medscape drug interaction checker.

Methods

This study was conducted from October 2019 - January 2021 in a tertiary care teaching institute in Mumbai district of Maharashtra, India. Its protocol was approved by the Institutional Ethics Committee prior to commencement of the study. As the prevalence of 4.9% of AUD in Maharashtra, the minimum sample size calculated was 72. So, 100 patients were taken as study population. The inclusion criteria were prescriptions of patients of either sex, 18-60 years of age coming to the Psychiatry OPD and diagnosed as a case of AUD. Pregnant alcoholic patients and those not interested in participating in the study were excluded. Patients were given patient information sheet and their informed consent was taken. The demographic profile, diagnosis, number, and type of anti-craving drugs and other classes of drugs along with their dose, frequency, duration was captured on a structured case record form and analysed.

The prescription pattern was then studied, as per WHO core prescribing indicators-

a. Average no. of drugs prescribed per encounter
b. Percentage of anti-craving drugs prescribed
c. Percentage of other classes of drugs prescribed
d. Percentage of different dosage forms prescribed
e. Percentage of drugs prescribed by generic name
f. Percentage of drugs prescribed by brand name
g. Percentage of drugs prescribed from National List of Essential Medicines (NLEM)
h. Percentage of drugs prescribed from available Hospital Drug Formulary

Potential drug interactions were checked using Medscape Drug Interaction checker. Comparison of prescriptions with 2018 APA (American Psychiatric Association) Guidelines for treatment of AUD was also done.

Results and Discussion

Total 100 prescriptions were analysed. The demographic profile shows that greater number of male (93%) suffered from AUD as compared to female (7%). Male preponderance has also been observed in other previous Indian studies[7-10]. This may be due to the sociocultural aspects of the country, where almost exclusively males are involved in alcohol intake[8]. Out of 100 patients enrolled, majority(32%) belonged to age group 31-40 years and the least number of patients were in the age group <21 years (Figure 1), mean age being 36.08 years. This coincides with the data from other similar Indian studies[7,9,11]. In a study done by Vijayan M et al, majority belonged to the age group 51–60 years, followed by 41–50 years[12].

Prescription Data

Average number of drugs prescribed per encounter

Average 4.77 drugs were prescribed per patient per encounter, which included drugs for treatment of AUD along with drugs for other associated conditions. This measures the degree of polypharmacy. According to WHO, it should be monitored to prevent over prescribing and to avoid the risk of drug-drug interactions. Therefore, it is advisable to keep the number of drugs as less as possible.

Percentage of anti-craving drugs prescribed

65% patients(n=100) were prescribed anti-craving drugs.

Prescribing pattern of anti-craving drugs

Out of 65 patients, 53(81.5%) were prescribed Acamprosate, 11(16.9%) were prescribed Baclofen and 1(1.5%) was prescribed Naltrexone. In a study done by Dube et al similar results were seen[8]. The anti-craving drugs were in tablet form. The results are in accordance with other similar Indian studies[13,14]. This pattern of prescribing anti-craving drugs is approved by the US FDA. Acamprosate is effective for both maintaining abstinence and for reducing heavy drinking days[15]. Acamprosate and Naltrexone have the best evidence for improving alcohol consumption outcomes for such type of patients[16]. Baclofen appears to delay return to drinking and help sustain abstinence, particularly in individuals who at baseline drink very heavily[17].

Percentage of other classes of drugs prescribed

A total of 412 other drugs were prescribed along with anti-craving drugs. They were prescribed for other comorbid conditions, substance abuse and psychiatric disorders.

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Classes of drugs prescribed

The different classes of drugs prescribed are shown in Figure 2. The maximum prescribed drugs were Vitamins, prescribed 107(25.7%) times, followed by Benzodiazepines, 93(22.3%) and Antipsychotics 86(20.6%) times. Our results are in line with a previous study done by Dube U et a[8]. As nutritional deficiency is common in patients of AUD, Vitamins were found to be the most prescribed drugs.

Prescribing patterns of Benzodiazepines

For decreasing the withdrawal symptoms, Benzodiazepines (BZDs) were prescribed. Among the BZDs, Lorazepam (83%) was the most prescribed drug, followed by Clonazepam (9%), Clobazam (6%) and Alprazolam (2%). Similar findings were also seen in a study done by Dube et al[8]. Benzodiazepines are effective because they stimulate the inhibitory GABA-signaling pathways. They suppress alcohol withdrawal symptoms and shorten the course of withdrawal, and they are the only agents that have been shown to prevent withdrawal associated seizures, delirium tremens, and death in patients undergoing alcohol withdrawal. Although many different benzodiazepines have been shown to be effective, lorazepam, chlordiazepoxide, oxazepam, and diazepam are the benzodiazepines most commonly used to treat alcohol withdrawal[18].

AUD with other substances of abuse

Out of 100 patients, 48% had other substance abuse along with AUD. Among these 48 patients, Nicotine was the most common substance of abuse and Amphetamine was the least common one. Among these 48 patients, 34(70.83%) had Nicotine, 7(14.58%) had Cannabis, 5(10.42%) had Opioid and 2(4.17%) had Amphetamine use disorder (Figure 3).

In a study done by Connor JP et al, it was found that at least half of the patients had nicotine use disorder[10]. In a similar study done by Arias F et al, cocaine, cannabis and opiate were the most abused substances along with alcohol[19]. It has been found that polysubstance abuse has higher risk of comorbid psychopathology, health problems and deficits in cognitive function[20]. Both alcohol and nicotine are highly comorbid and there is a strong correlation between alcohol and nicotine dependence. The patients with AUD are three times more likely to abuse nicotine than the general population[21]. Concurrent use of alcohol and nicotine may exacerbate the health effects of either substance alone, with increased risk for cancer of mouth, throat and liver[22,23]. Additionally, for alcohol-dependent individuals, it also increases the risk of nicotine-related diseases (heart and lung disease) and death from complications[24].

AUD with psychiatric conditions

Often individuals with mental health disorders use substances to reduce stress or relieve symptoms. Among the 100 patients enrolled for the study, 50% had AUD with psychiatric comorbidities. Personality disorder was the most common psychiatric comorbidity, affecting 24(48%) patients, mood disorders in 20(40%), psychosis in 4(8%) and substance induced behavioural disorders in 2(4%) patients. In a similar study done by Kessler RC et al, it was found that major depressive disorder was most common with AUD[25].

The prevalence of most mood, anxiety, substance, and thought disorders is higher in people with AUD than in the general population[26]. Given the high co-occurrence between AUD and mental health conditions, and the increased morbidity associated with the presence of co-occurring disorders, it is important to identify the co-occurring disorders and to address both disorders in treatment to improve treatment outcome. Treatment that addresses both disorders concurrently with the same provider is called integrated treatment[27].

Although pharmacological and psychosocial treatments for AUD and psychiatric disorders can be integrated to help these patients, relatively few clinical studies have tested these types of therapy. An approach to address this issue is seen in a study[28]. In our study also, other co-existent affective disorders were treated with antipsychotics and antidepressants.

Percentage of different dosage forms prescribed

All anti-craving drugs were prescribed in oral tablet form. This WHO indicator provides us the information regarding usage of various drug formulations.

Percentage of formulations of other classes of drugs prescribed

Out of the 412 other class of drugs prescribed, 356(86.5%) were in tablet form, 54(13.1%) injectables, 1(0.2%) capsule and 1(0.2%) syrup. This information regarding drug formulations can be considered as a basis of cost calculation and its comparison among various prescriptions and, subsequently the pharmacoeconomic burden on the patient.

Percentage of drugs prescribed by brand & generic names

Out of 65 anti-craving drugs prescribed, 56(86%) were prescribed by brand name and 9(14%) prescribed by generic name. Out of 412 other drugs prescribed, 206(50%) were prescribed by generic name and 206(50%) prescribed by brand name. Prescribing drugs by generic names makes the treatment cost-effective and avoids prescription errors[29]. Hence, we should encourage it as much as possible. This can be achieved by educational intervention methods and strict compliance with WHO drug policies. In a study done by Kolasani BP et al, percentage of drugs prescribed by generic name were 42.1% and brand name were 57.9%[7].

Presence of drugs in NLEM/ Hospital Drug Formulary

Essential medicines, as defined by WHO are those drugs that satisfy the health care needs of most of the population. They should, therefore, always be available, in adequate amounts and in the appropriate dosage forms, at a price the community can afford[29]. In our study, the percentage of drugs prescribed from NLEM, India was 56.1% which is higher than a study where it was 31.7%[30]. WHO recommends the drugs prescribed from NLEM to be 100%. So, there is a need to adhere to the NLEM while prescribing, as it does not only promote rational use of medicines, but also promotes prescription by generic names. Out of total 65 anti-craving drugs, only 11% were listed in the NLEM, but no drugs in Hospital Drug Formulary. Availability of drugs in hospital formulary is helpful for the prescribers to prescribe cost-effective drugs, which reduce financial burden to the patients. In our study, 53.3% drugs prescribed were from hospital formulary, which was little lesser compared to a similar study[8], where 60.9% drugs were from hospital formulary. By giving this feedback to the hospital administration, it will help in the procurement and utilization of drugs.

Potential drug-drug interactions

Out of 100 prescriptions, potential drug-drug interactions were found in 76%, of which 59% were minor. They were checked through Medscape drug interaction checker[31]. They ranged from minor, moderate, and major interactions, as follows

1. Major/Serious: Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit. Effects are potentially life threatening or capable of causing permanent damage.
2. Moderate: Moderately clinically significant. Use it only under special circumstances/ close monitoring required. Effects may cause deterioration in patients'

clinical status and additional treatment or extension of hospital stay.

3. Minor/ Mild: Minimally clinically significant. Interaction is unlikely to be clinically relevant. Effects are usually mild.

Polypharmacy is one of the major reasons for drug interaction. An idea regarding the potential drug interactions can help the prescribing physician to take care of untoward consequences. As this was a cross sectional, single encounter study, actual drug-drug interactions were not assessed.

Comparison of prescriptions with 2018 APA Guidelines for treatment of AUD

The observed patterns of drug use can be compared with the current recommendations and guidelines for the treatment of a certain disease. Hypotheses can then be generated to determine whether discrepancies represent less than optimal practice, whether pedagogic interventions (education) are required or whether the guidelines should be reviewed in the light of actual practice[4]. In this study, out of 100 prescriptions, adherence to 2018 APA, AUD guidelines was found in 89% cases. APA recommends (1B) that Naltrexone or Acamprosate be offered to patients with moderate to severe alcohol use disorder who have a goal of reducing alcohol consumption or achieving abstinence[6]. Acamprosate and Naltrexone were actually the anti-craving drugs prescribed, as per the guidelines. 11% patients were also prescribed Baclofen 30mg tablet. The frequency, dosage, and duration of drug therapy are the three important parameters, and if not clearly recorded, can result in indiscriminate, injudicious use of drugs and therapeutic failure. These parameters were in accordance with the guidelines.

Conclusion

This study was done to provide an insight into the trends of drug utilization and provide feedback to prescribers to create an awareness about rational use of drugs. The use of anti-craving drugs along with multivitamins and BZDs is the mainstay of treatment for these alcohol dependent patients. Anti-craving agents like Baclofen, Acamprosate and Naltrexone were prescribed in our study. AUD is seen to co-exist with other co-morbidities like psychosis, anxiety, and depression. Potential drug interactions were found in majority of the prescriptions. Educating the prescribing physicians about the potential drug interactions can help in solving the problem of polypharmacy.

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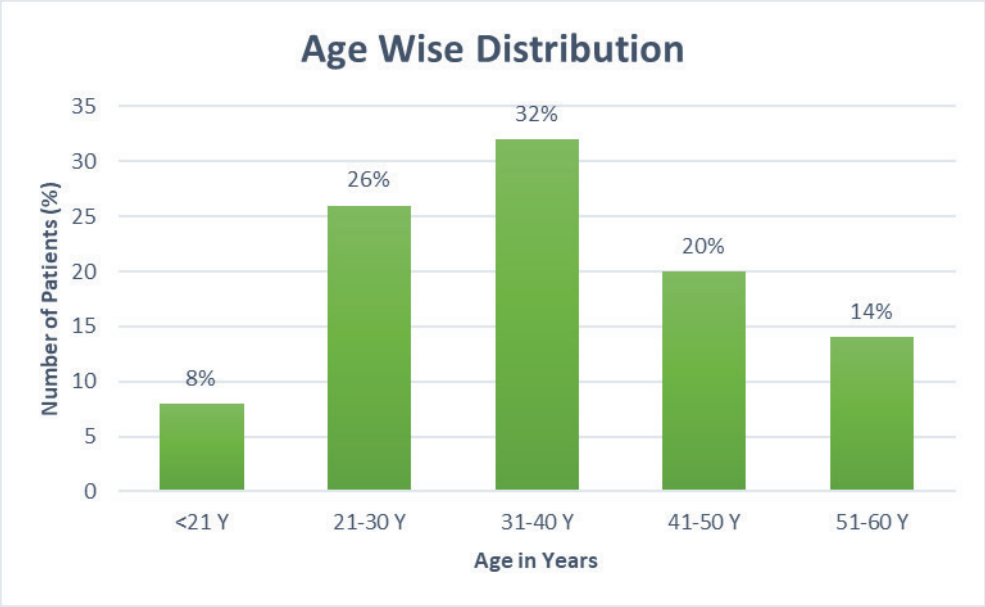

Figure 1. Age wise distribution of patients treated for AUD

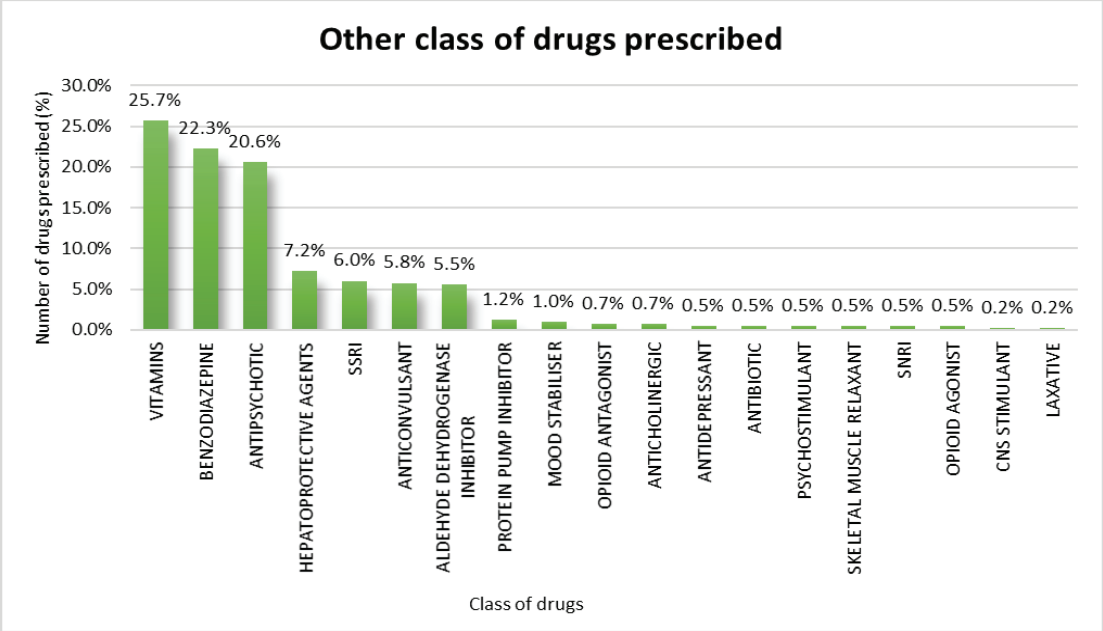

Figure 2. Other classes of drugs prescribed

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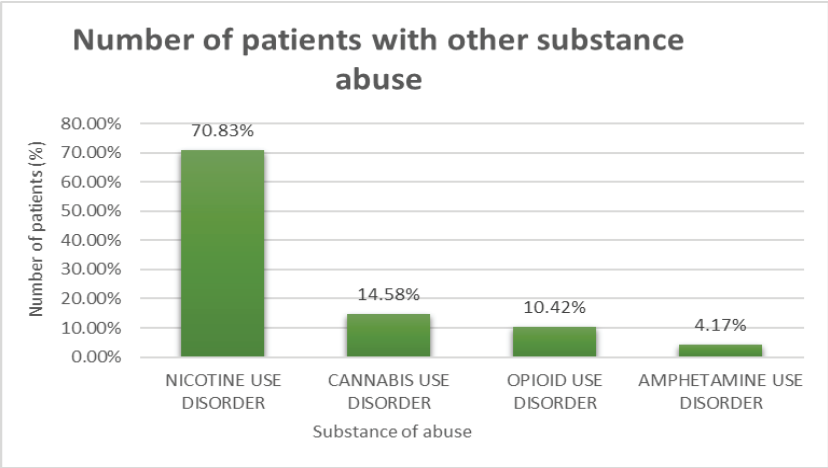

Figure 3. Number of patients with other substance abuse (n = 48)

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Relationship Between Knowledge and Adherence to Antihypertensive at Public Healthcare in Banjarmasin City, Indonesia

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Abstract

Hypertension is one of the world's most hazardous diseases since it harms the heart, brain, kidneys, and other organs. Patients' understanding of hypertension can be the key to successful treatment. Nonadherence with antihypertensive medication is a primary cause of therapeutic failure and is considered a serious issue. The purpose of this study is to examine the association between antihypertensive knowledge and adherence at public healthcare facilities. This study employed a quantitative approach using a cross-sectional design. The purposive sampling technique determined the sample, resulting in 100 hypertensive respondents from Public Healthcare. Knowledge is the independent variable in data collection; adherence to antihypertensive medications is the dependent variable; and demographic variables are the confounding variable. We employed the HFQ (Hypertension Fact Questionnaire) and MMAS-8 (Modified Morisky Adherence Scale-8) questionnaires as data-gathering instruments. We conducted univariate, bivariate, and multivariate analyses on the data using SPSS. Based on the study's findings, it is possible to conclude that there is a significant association between knowledge level and adherence with antihypertensive medicine use in public healthcare, with a p-value of 0.003. Comorbidities are a risk factor for hypertension that affects adherence, with a p-value of 0.007 and an OR of 0.801, indicating that patients are 0.801 times more likely to take their medicine.

Keywords: Hypertension, Knowledge, Adherence

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Introduction

Hypertension is a medical condition that can affect anyone, regardless of age. It is one of the most severe diseases in the world, causing serious damage to the heart, brain, kidneys, and other vital organs. Hypertension affects approximately 1.28 billion people aged 30-79 worldwide, with the vast majority (almost two-thirds) residing in low- and middle-income nations. An estimated 46% are unaware of their elevated blood pressure. Only around one in five people with hypertension appropriately manages their blood pressure, while less than half, 42%, have received recognition and treatment. Hypertension is a prominent cause of premature death worldwide. One of the global goals for managing noncommunicable illnesses is to lower the prevalence of hypertension by 33% between 2010 and 2030[1].

According to the 2018 RISKESDAS data, the prevalence of hypertension in Indonesia in the population aged 18 and overreached 34.1%. South Kalimantan has the highest prevalence at 44.1%, while Papua has the lowest at 22.2%. Estimates place the total number of hypertension cases in Indonesia at 63,309,620, and the number of deaths at 427,218. Hypertension is most common in 31-44 years old (31.6%), 45-54 years old (45.3%), and 55-64 years old (55.2%). We have identified only about 8.8% of all cases as hypertensive.

In 2022, data from the Banjarmasin City Health Office showed that essential hypertension ranked first in all health centers with 56,269 cases. This confirms that hypertension is still a significant problem for public health services and programs in Banjarmasin City. The patient's understanding of hypertension is an essential component for achieving successful therapy and effectively controlling blood pressure. Enhanced understanding of the illness increases the patient's consciousness of upholding a healthful way of life and following the prescribed drug regimen, leading to higher rates of adherence. Failure to comply with medical instructions may result in severe problems and impact blood pressure management. Adherence has a crucial role in the ongoing management of hypertension patients' long-term health. Non-adherence with antihypertensive medication is a primary reason for the failure of therapy, resulting in hypertension being the primary cause of mortality in Indonesia[2,3].

Healthcare practitioners perceive patient non-adherence to be a significant issue. A person's level of knowledge influences how well they adhere to their drug regimen. Hence, a comprehensive comprehension of antihypertensive medications is vital to facilitate effective treatment. Individuals with hypertension must possess awareness regarding the significance of consistently using antihypertensive medications. Additionally, they should comprehend the potential hazards and repercussions associated with non-adherence to antihypertensive treatment regimens[4].

According to data from the Banjarmasin City Central Bureau of Statistics for 2024, South Banjarmasin District has a high population density, reaching 167,928 people in 2022. This density is often a risk factor for various health problems, including hypertension. Preliminary studies show that the Healthcare in South Banjarmasin Subdistrict has the highest number of hypertensive patients, with 1,352 patients, many of whom have low education levels. Research on the relationship between knowledge level and adherence to taking antihypertensive medication at healthcare has never been conducted, so the descroption of the relationship is unknown.

Methods

This study employed a quantitative observational approach, utilizing a cross-sectional research design. The data collected in this study includes patient knowledge as the independent variable and patient adherence to therapy as the dependent variable. In this study, knowledge is defined as all information known by hypertensive patients about hypertention in response to the questions of HFQ, meanwhile patient adherence refers to the behavior of hypertensive patients that aligns with the recommendations provided by healthcare professionals. Confounding variables were also considered in this study, such as demographic features. The Public Healthcare conducted the study from February to April 2024.

The population in this study consisted of 1352 hypertension patients who received treatment at Public Healthcare between January and March. The data gathering technique to be employed is Purposive Sampling, which involves including all subjects who match the inclusion requirements and exist during a specified time frame, in order to ensure an adequate number of respondents. The study utilized a sample size of 100 respondents. The study included patients diagnosed with hypertension and receiving treatment at Public Healthcare. They were required to complete questionnaires and be willing to undergo therapy. The study excluded patients who were illiterate, elderly, pregnant with hypertension, or had mental and cognitive abnormalities. The study employed the HFQ (Hypertension Fact Questionnaire) and MMAS-8 (Modified Morisky Adherence Scale-8) questionnaires as data collection instruments. HFQ was validated and tested for reliability by Salem (2011) in Pakistan, obtaining a Cronbach's alpha of 0.70, which was considered valid. Subsequently, the HFQ questionnaire was adapted into Indonesian and revalidated by the researcher Hardiyani (2017), yielding a Cronbach's alpha of 0.707 (considered reliable when the Cronbach's alpha value is > 0.6). The psychometric analysis of the MMAS-8 Indonesian version shows strong reliability and validity. The internal consistency, evaluated using Cronbach's alpha coefficient, was found to be 0.824, while the test-retest reliability, assessed using Spearman's rank correlation, was 0.881. The data was analyzed using univariate analysis, bivariate analysis with chi-square test, and multivariate analysis with logistic regression test using SPSS.

Results and Discussion

The Research Ethics Commission of Muhammadiyah University Banjarmasin granted the study its ethical approval under the reference number 091/UMB/KE/III/2024. Patients with hypertension who signed an informed consent form were eligible for the research samples. Table 1 displays the sociodemographic data of 100 respondents. Table 2 displays the patient's condition, including the duration of hypertension and comorbidities.

The study's results were based on the respondents' gender, as shown in Table 1. The study reveals that 78% (78 respondents) are women. This shows that women tend to have higher hypertension than men. This is in line with research (Artaviachika, 2022) 5 which shows that the prevalence of hypertension in women is greater than men, namely the number of female respondents as many as 146 (73%), and male respondents as many as 54 (27%). One factor that remains constant is gender. Women have a higher risk of hypertension than men. Generally, women who enter old age will experience menopause, which can cause a decrease in estrogen and HDL (high-density lipoprotein) secretion, thus triggering an increase in blood

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pressure. In addition, obese women are more prone to hypertension. Obesity rates tend to be higher in women than in men. Therefore, the risk of hypertension in women can be related to reproductive age, fertility rate, and menopause[6].

According to Table 1, the study's results were based on the respondents' ages. The study reveals that 62 respondents, or 62%, are aged 51–60, while 2 respondents, or 2%, are the youngest, aged 20–30. This is in line with research Yunus, M et al (2021)[7], which shows that most respondents aged 51–60 were 135 patients (50.4%). According to the study's findings, aging can lead to a decrease in organ function and a weakening of the immune system, making people more susceptible to various diseases. Advancing age leads to physiological alterations in the body, including the thickening of the uterine wall caused by the buildup of collagen compounds in the muscle layer. As a result, blood vessels undergo constriction and rigidity, beginning at the age of 45. Furthermore, there is an increase in peripheral resistance and sympathetic activity, accompanied by a diminished baroreceptor sensitivity that regulates blood pressure as well as the functions of the gonads, blood flow, and glomerular filtration rate[8].

The study's findings reveal that 51 respondents, or 51%, had only completed elementary school. This is in line with research Mardiana, S.S et al (2021)[9] on the relationship between education level and adherence with taking medication in hypertensive patients at the Karangrayung II Health Center, which showed significant results. This finding states that the higher the patient's education level, the higher their adherence with taking antihypertensive medication.

The study's occupation-based results reveal that 81 respondents, or 81%, were housewives. This is in line with research conducted by Mayefis & Sari (2022)[11] which shows that most of the respondents are housewives. This shows that they tend to be more prone to stress, which results in non-adherence and a lack of attention to personal health. Women who are not working or housewives have a higher risk of suffering from hypertension compared to women who are working. This is due to a lack of physical activity, which increases the risk of being overweight and thus developing hypertension[12]. In addition, other possible factors, such as stress, can trigger an increase in sympathetic nerve activity, causing blood pressure to rise above normal.

According to Table 1, this study also examined the relationship between demographic characteristics and medication adherence. The results indicate that education and employment significantly influence patient adherence to antihypertensive therapy. Prior studies have reported a significant association between educational level and adherence[13], suggesting that lower educational levels may impede the acceptance of new information and health-related values, while higher educational attainment facilitates information processing and enhances knowledge. The findings of this study align with this, indicating that higher educational levels are associated with improved health knowledge. Employment status also significantly impacts adherence, as supported by previous studies, which indicate that employment can influence health behaviors, particularly adherence to hypertension management. Time availability appears to be a critical factor; employed individuals often have limited time to access healthcare services, potentially reducing their adherence to hypertension treatment. In contrast, unemployed individuals typically have greater flexibility, allowing more frequent engagement with available healthcare facilities for monitoring and treatment adherence.

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Based on the duration of hypertension, Table 2's results reveal that 57 respondents, or 57%, experienced hypertension for less than 5 years. This is in line with research conducted by Khansa et al. (2023)[14,15] based on the length of time spent suffering from hypertension, it is known that of the 79 respondents, most had hypertension for <5 years, as many as 44 respondents (55.7%). The time since a person received a diagnosis of hypertension is known as the duration of hypertension. Contributing factors closely influence the speed at which a person develops hypertension. The more risk factors a person has, the sooner they are likely to develop hypertension, compared to those with few or no risk factors. The adherence rate of hypertension patients in Indonesia for treatment and control is quite low. The longer a person suffers from hypertension, the lower their adherence rate tends to be, as most sufferers feel bored to keep seeking treatment[16].

The findings of this study indicate that comorbidities significantly influence patient adherence to treatment, as evidenced by a p-value of 0.009 ($p < 0.05$). Previous study has similarly demonstrated that comorbid conditions influence patient adherence to treatment[17]. The study's comorbidity-based results reveal that 91 respondents, or 91%, have no comorbidities. Respondents who had experienced hypertension-related complications showed a higher level of adherence to treatment than those who had not experienced issues. This may be because they are more aware of the serious consequences of hypertension, so they are more disciplined when undergoing treatment.

The results of the study based on the knowledge of respondents according to the results described in Table 3. It can be seen that the low category was 24 respondents (24%), the medium category was 56 respondents (56%) and the high category was 20 respondents (20%). Knowledge influences efforts to prevent the recurrence of hypertensive disease. Risk factors for hypertension can be prevented through primary prevention measures, such as maintaining a diet to maintain ideal body weight and prevent hypercholesterolemia, and diabetes mellitus; quitting smoking; changing eating habits by eating low-salt foods; and doing exercises to control body weight. If certain factors have already established a person's hypertension, secondary prevention becomes necessary. These measures include comprehensive management of the patient, both with medication and measures such as primary prevention, to keep blood pressure normal or stable, control other risk factors for ischemic heart disease, and limit activity[18].

The study's results on respondent adherence show that 77 respondents (77%) were non-adherence, while 23 respondents (23%) were adherence. Wulansari et al. (2024) found that out of 90 respondents, 84 had low results (92.3%), 4 had moderate results (4.4%), and 2 had high results (2.2%). Non-adherence will lead to suboptimal drug use. As a result, patients lose the benefits of therapy, and their condition may gradually deteriorate. Adverse reactions may occur if patients use an excessive dose or take the drug more frequently than recommended[20].

The results of the study were based on the knowledge of respondents, according to the results described in Table 3. Table 3 reveals that 24 respondents (24%), 56 respondents (56%), and 20 respondents (20%) belonged to the low category. Patients who possess knowledge about hypertension, including its causes, development, and control, along with the treatment process, can enhance their self-control and awareness, leading to greater adherence with their treatment regimen. In the

treatment of chronic diseases like hypertension, adherence is crucial as it enables the use of adherence antihypertensive drugs to produce long-term blood pressure control effects and prevent various potential complications[21].

Various factors can cause hypertension patients to not take their medication at the public healthcare facility. One of them is a lack of understanding about the importance of maintaining adherence in hypertension treatment. This study reveals that patient knowledge of hypertension significantly influences patient medication edherence to therapy. The more obedient or routine a person is in taking hypertension medication, the more he will realize that adherence with taking hypertension medication is very beneficial for his health.

The variables that will be analyzed multivariately are confounding factors, such as gender, age, education, occupation, length of suffering, and comorbidities, with the dependent variable being adherence to taking antihypertensive medication. The multivariate analysis will include education (p-value 0.041), occupation (p-value 0.024), and comorbidities (p-value 0.009) in Tables 1 and 2, as these variables have p-values less than 0.25. The results of the logistic regression analysis in the first step showed that the confounding variables, namely education (p-value 0.397) and occupation (p-value 0.394), were not significant because the p-value was greater than 0.05. The confounding variable is comorbidities (p-value 0.003), which is significant because the p value is less than 0.05.

Table 5 presents the final stage of the logistic regression analysis within the multivariate analysis. The results of this multivariate analysis indicate that the comorbidity variable has a significant impact on patient adherence to treatment, with a p-value of 0.007 ($p < 0.05$), demonstrating a statistically significant relationship. The regression coefficient (B) of -0.820 suggests a negative association, indicating that the presence of comorbidities tends to decrease patient adherence. The Odds Ratio (OR) of 0.441 indicates that patients with comorbidities are 0.441 times less likely to adhere to treatment compared to patients without comorbidities. The 95% Confidence Interval (CI) for the OR, ranging from 0.242 to 0.801, does not cross the value of 1, further supporting the significant association between comorbidities and adherence. Previous study have indicated that the number of comorbidities can increase the risk of patient non-adherence to treatment, patients with a higher burden of comorbidities tend to be less adherence[22].

Conclusion

This study concludes that patient knowledge about hypertension influences adherence to antihypertensives in public healthcare. Comorbidity, with a p-value of 0.007 and the highest OR of 0.801 times more obedient in taking medication, is the most influential risk factor.

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Conflict of Interest

None declared.

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Table 1. Socio-demographics of patient with hypertension

Sociodemographics data	Criteria	n(%)	P value
Gender	Man	22 (22)	0,534
	Women	78 (78)	
Age	20-30 Years	2 (2)	0,879
	31-40 Years	5 (5)	
	41-50 Years	31 (31)	
	51-60 Years	62 (62)	
Last Education	Primary school	51 (51)	0,041*
	Junior High School	16 (16)	
	Senior High School	27 (27)	
	College	4 (4)	
	No school	2 (2)	
Occupation	Civil Servant	3 (3)	0,024*
	Private Employee	4 (4)	
	Self-employed	2 (2)	
	Laborer	2 (2)	
	Retired	0 (2)	
	Housewife	81 (81)	
	Others	8 (8)	

*p-value < 0.05 indicates a significant association between patient demographic characteristics (last education and occupation) and adherence to antihypertensive medication

Table 2. Condition of patient with hypertension

Condition	Criteria	n(%)	P value
Duration of Hypertension	< 5 Years	57	0,136
	> 5 Years	43	
Comorbidities	Diabetes	6	0,009*
	Heart disease	1	
	Stroke	2	
	None	91	

*p-value < 0.05 indicates a significant association between patient comorbidities and adherence to antihypertensive medication.

Table 3. Category of Knowledge and Adherence to Antihypertensive

Data	Categories	N(%)
Knowledge	Low	24(24)
	Medium	56 (56)
	High	20 (20)
Adherence	Non-adherence	77 (77)
	Adherence	23 (23)

Table 4. Relationship between Knowledge Level and Adherence Level of Taking Anti-hypertensive Medication

Variables	Adherence		Non- Adherence		Total	p- value
	F	%	F	%		
Knowledge						
Low	8	8	16	16	24 (24%)	
Medium	6	6	50	50	56 (56%)	0,003*
High	11	11	9	9	20 (20%)	
Total	**25**	**25**	**75**	**75**	**100 (100%)**	

*p-value of <0.05 indicates a statistically significant association between knowledge and treatment adherence

Table 4. Relationship between Knowledge Level and Adherence Level of Taking Anti-hypertensive Medication

Variable	B	Wald	Sig.	OR	95% CI	
					Lower	Upper
Comorbidities	-0,820	7,217	0,007	0,441	0,242	0,801

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Identification of Probable Drug-Drug and Drug-Food Interactions in Hospitalized Patients With Chronic Renal Disease

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Abstract

Chronic renal disease is a substantial health challenge in numerous countries worldwide, including Indonesia. Chronic renal disease patients frequently experience comorbidities and require multiple medications (polypharmacy). In patients receiving polypharmacy, it is necessary to monitor the occurrence of drug interactions. The current study analyzed the most probable of drug-drug interactions based on severity and management. Furthermore, to analyze the most probable drug-food interactions based on severity and management in patients hospitalized with chronic renal disease. From September to October 2023, a cross-sectional study was carried out using retrospective data gathering. The present study population consists of hospitalized patients with chronic renal disease in 2022. The sampling methodology utilizes the saturated sample method. The tools utilized encompassed the Lexicomp® drug interaction checking application. The severity and management categories for probable drug-drug interactions and drug-food interactions are defined within the Lexicomp® application. The study analyzed medical data from 51 patients in total. The results of the current study showed that there were probable drug-drug interactions in 68.62% and drug-food interactions in 47.06% of patients hospitalized with chronic renal disease. Based on severity, the most probable drug-drug interaction and drug-food interaction is in the moderate category. Based on the management, the most probable drug-drug interaction needs to be monitored, and the most probable drug-food interaction needs to be avoided concurrent administration with food. In patients with chronic renal disease, it is crucial to minimize and handle probable drug-drug and drug-food interactions.

Keywords: Adverse Drug; Medication Interaction; Nutrition; Polypharmacy; Recommendation

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Introduction

The global prevalence of chronic renal disease in 2017 was 697.5 million cases[1]. Chronic renal disease has become a prominent factor contributing to death on a global scale[2]. In 2019, the World Health Organization announced that renal disease ranks among the top ten leading causes of mortality globally[3]. Chronic renal disease is a substantial health challenge in numerous countries worldwide, including Indonesia[4,5]. According from 2023 Health Survey Indonesia, the mean prevalence was 0.18%, indicating that 2 out of every 1,000 individuals were diagnosed with chronic renal disease. Chronic renal disease is a significant issue in Indonesia, ranking among the seven chronic diseases that contribute to the highest mortality rates and health expenditures[6].

Patients with chronic renal disease are one patient population that comes in the category of chronic diseases and requires special care during therapy. Chronic renal disease patients frequently experience comorbidities and require multiple medications (as is known in polypharmacy)[7]. In patients receiving polypharmacy, it is necessary to monitor the occurrence of drug interactions[8].

Drug interactions refer to the interactions that occur between a drug and other drugs that hinder the drug from achieving its desired effect. This concept encompasses the interactions between drugs and other drugs, drugs and food, and drugs and other substances[8,9]. Drug interactions can result in either a reduction or enhancement of the drug's effects[10–13]. The concurrent use of many pharmaceuticals was considered to have probable drug-drug interactions when the theoretical interactions between the prescribed medications were assessed, rather than based on their actual occurrence[11]. Furthermore, considering potential drug-food interactions is crucial for enhancing treatment efficacy[14]. Some food habits of patients, such as consuming green tea, coffee, soy, and grapefruit, had the capacity to interact with drugs[15].

Numerous studies have revealed that the probable of drug-drug interactions is common in chronic renal disease, with prevalence varying between 61.9% and 92.5% in different research[16]. Several studies have investigated probable drug interactions in Indonesian patients with chronic renal disease. However, previous research has mainly examined drug interactions considering their level of severity[7,17–22]. Current suggestions to mitigate probable drug interactions remain insufficient. In Indonesia, the www.drugs.com application is the most widely used device for studying probable drug interactions[7,18,19,21]. Furthermore, the studies conducted in Indonesia focus primarily on the examination of the possibility of drug-drug interactions, while the analysis of drug-food interactions in patients with chronic renal disease remains restricted[7,17–22].

Drug interactions can result in adverse side effects. Two-thirds of the patients had a suspected drug-drug interaction-related adverse reaction[17]. To reduce the occurrence of adverse effects caused by drug interactions, it is important to have more knowledge regarding drug interactions. In addition, suggestions for mitigating probable drug interactions could be improving the safety of clinical drug therapies. Drug interactions contribute significantly to hospital admissions, resulting in a significant financial burden[16].

The current study analyzed the most probable of drug-drug interactions based on severity and management. Furthermore, to analyzed the most probable drug-food interactions based on severity and management in patients hospitalized with chronic renal disease.

Methods

From September to October 2023, a cross-sectional study was carried out using retrospective data gathering. The study took place in a public hospital, Ansari Saleh. The hospital provide facility for patients with chronic renal disease in Banjarmasin, South Kalimantan. Electronic medical records were used to collect information such as age, gender, and therapy. The research has been authorized by the Lambung Mangkurat University Medical Faculty, The Committee on Medical Research Ethics on April 2023 (061/KEPK-FK ULM/EC/IV/2023).

The present study population consists of hospitalized patients with chronic renal disease in 2022. The hospitalized patients with chronic renal disease in 2022 that attains the study criteria as the research sample. The sampling methodology utilizes the saturated sample method. The current study included chronic renal disease patients who were getting more than one drug. The inclusion criteria required comprehensive medical records, including age, gender, and detailed information on the therapy, such as the drug name, rules of use, and dosage type. Patients under the age of 18 with chronic renal disease were not included in the study.

The tools utilized encompassed a data collection sheet and the Lexicomp® drug interaction checking application. Lexicomp® demonstrates extremely sensitive and consistently delivers excellent performance. Furthermore, it offers information on the seriousness of drug interactions and provides recommendations on how to prevent and handle drug interactions if they occur[16,23]. The Lexicomp® was utilized to analyze probable drug-drug and drug-food interactions. The software, encompassing all text and other content, is owned by Lexicomp® and is guaranteed by copyright (Copyright 2024 UpToDate Inc. All Rights Reserved) and intellectual property statutes[24].

The severity and management categories in probable drug-drug interactions and drug-food interactions are defined within the Lexicomp® application. The category of severity in probable drug interaction include 16:

1. Minor: relating to minor consequences that can be readily surmounted.
2. Moderate: indicating intermediate consequences that can result in harm to organs;
3. Major: signifying severe consequences that can result in death

Lexicomp® was used to gather management categories regarding probable drug-drug interactions and drug-food interactions. The management categories for handling probable of drug-drug interactions encompass: there is no need to take any action; medication monitoring; modification of the medication is recommended; and avoiding drug combinations is recommended. The management categories for handling probable of drug-food interactions encompass: there is no need to take any action; administer without regard to food; medication monitoring; take with food; administer 30 minutes before food; administer 30 minutes after food; and avoid concurrent administration with food[24].

Results and Discussion

The study analyzed medical data from 51 patients in total. The findings indicated that the age of patient from 18 to 79 years old. Patient characteristics showed that 51% were female and 49% were male, consistent with earlier investigations[25]. According to gender, female patients encountered a higher incidence of potential drug-drug interactions (62%) and food-drug interactions (52%). Previous studies explain that there is no correlation between gender and the occurrence of

potential drug interactions. Nonetheless, the practice of polypharmacy carries the risk of potential drug interactions[26]. Polypharmacy was observed during hospitalization and most of the patients received more than five drugs (Table 1).

The Probable of Drug-Drug Interaction

The results of the current study showed that there were probable drug-drug interactions in 68.62% (35 patients) of patients hospitalized with chronic renal disease. Total 60 various types of probable drug-drug interactions with 190 cases. The present study demonstrates that patients with chronic renal disease experience the highest number of probable drug-drug interactions ranging from 1 to 6 (Table 1). The most probable drug-drug interactions category was moderately severe and required medication monitoring (Table 1). Previous research has demonstrated comparable findings, indicating that most probable drug-drug interactions in patients with chronic renal disease fall into the moderate severity category[7,16,18,19,21,27].

The results of the analysis of this study showed that patients with chronic renal disease hospitalized with the most probable drug-drug interactions Domperidone-Ciprofloxacin at the minor category, Ceftriaxone-Furosemide drug interactions at the moderate category and Codeine-Cetirizine drug interactions at the major category (Table 2). The research conducted by Sari and Maulana in 2024 revealed that the most occurrence of drug interaction at major category was between Codeine and Cetirizine[16]. However, previous research revealed disparities in the probability of drug-drug interactions in the minor and moderate categories because the research examined drug-drug interactions in patients with outpatient chronic renal disease[16]. Prescription patterns vary between inpatients and outpatients, resulting in changes in the probable drug-drug interactions.

Codeine-Cetirizine was the most occurrence of drug at the highest level of severity. Cetirizine may enhance the sedative impact of codeine, possibly due to its depressive effect on the central nervous system. According to the Food and Drug Administration (FDA) of the United States, the combination of opioids with medications that suppress the central nervous system (CNS) can result in severe side effects, such as slowed or labored breathing and even death. If feasible, it is advised not to combine codeine and cetirizine due to probable drug interactions. These medications should only be used together if other treatment alternatives are insufficient[24].

The most frequent occurrence of Ceftriaxone-Furosemide is often observed at a moderate severity level. Both medications exhibit drug interaction processes. Specifically, furosemide can potentially enhance the nephrotoxic effect of cephalosporins, such as ceftriaxone. The probable interaction is due to the combined nephrotoxic effects. It is recommended to closely monitor renal function when administering furosemide and ceftriaxone[24].

The Probable of Drug-Food Interaction

The probable drug-food interactions in patients with chronic renal disease were 47.06% (24 patients). Total 21 various types of probable drug-food interactions with 116 cases. Each patient has the probable drug-food interaction from 1 to 2. There exists a notable correlation between the prescribed drug number and the number of drug-food interactions that pose a risk to the patient[28,29]. Most of the patients received more than five drugs in this current study.

The current study analyzed probable drug-food interactions based on severity. Most probable drug-food interactions in patients with chronic renal disease are of moderate severity. However, there are probable

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drug-food interactions at severe severity, including Domperidone/grapefruit juice and Clopidogrel/grapefruit juice (Table 3). Based on research by Koni et al. (2022) explained that most drugs interact with grapefruit[30].

Based on the management of potential drug-food interactions, the most common is need to avoid using drugs with food. The drugs that have the most probable drug-food interaction in patients with chronic renal disease include lansoprazole, atorvastatin and diltiazem (Table 4). Previous research showed varying results, indicating that the medications with the highest degree of interaction with food include omeprazole and aspirin[31].

The food items or nutrients that have the potential to interact with drugs in the current research are grapefruit juice, caffeine, fiber, foods rich in pectin, and soybean (Table 4). The study conducted by Kose et al. (2021) demonstrated comparable findings, indicating that grapefruit and high-fiber diets frequently exhibit potential medication interactions[31]. The current study explored nutritionist records relating to the dietary regimens of individuals with chronic renal disease and revealed that the majority patients followed dietary plan such as low sodium, low sugar, or low protein. It is necessary to conduct screenings to identify foods that may have interactions with drugs being taken by patients. Pharmacists can collaborate with nutritionists at health facilities to accomplish this task.

The medicines that have the highest probability of interacting with food are lansoprazole and atorvastatin (Table 4). First, the analysis of the current study indicates that lansoprazole has the potential to interact with food. Extended therapy (lasting ≥2 years) can result in impaired absorption of dietary vitamin B12 and the consequent shortage of vitamin B12[24]. Lansoprazole belongs to the class of drugs known as proton pump inhibitors. Swarnakari et al. (2022) research indicates that prolonged and excessive usage of proton pump inhibitors can lead to a deficit in vitamin B12 32. Unlike the research conducted by Alifiar (2016), this study indicates that meals can decrease the bioavailability of lansoprazole by 70%, thus diminishing its effectiveness[33]. Lansoprazole absorption may be hindered by the presence of meals[33]. A study conducted by Abdollahi et al. (2018) reveals that omeprazole, a type of proton pump inhibitor, can potentially interact with food in hospitalized patients. Omeprazole inhibits vitamin B12 absorption. Administration avoid consuming meals high in vitamin B12 before or during the administration of the medication[27].

Second, the analysis of the current study indicates that atorvastatin has the potential to interact with grapefruit juice. Consuming grapefruit juice can elevate atorvastatin levels in the bloodstream. The primary cause of this interaction is attributed mainly to certain components found in grapefruit juice that have the ability to hinder the activity of CYP3A4 24. The findings of this investigation are comparable to the outcomes of Koni et al. (2022) 29. The interaction between atorvastatin and grapefruit juice is classified as moderate. Therefore, it is necessary to refrain from consuming big amounts of grapefruit juice[24].

Considering potential drug-food interactions is crucial for enhancing treatment efficacy. Pharmacists and clinical personnel should prioritize monitoring commonly prescribed medications that have the potential to interact with food[14]. Several suggestions exist for managing potential drug-food interactions (Table 4). Furthermore, to mitigate drug-related issues, it is crucial to provide the patient with education regarding the interactions between drugs and food[34].

These findings emphasize the crucial role of pharmacist and healthcare workers in avoiding and managing drug-drug interactions and drug-food interactions. Researchers should consider examining potential drug-drug interactions and potential drug-food interactions in various disorders utilizing alternative screening tools for interactions. Conducting research on factors associated to potential drug-drug interactions and potential drug-food interactions is crucial as well.

Conclusion

The most probable drug-drug interaction based on severity and management was Ceftriaxone-Furosemide (moderate), which required medication monitoring in patients hospitalized with chronic renal disease. Furthermore, the most probable drug-food interaction based was lansoprazole-food contains vitamin B12 and the need to avoid consuming meals high in vitamin B12.

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Conflict of Interest

None declared.

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Table 1. Socio-demographics of patient with hypertension

The Probable of Drug-Drug Interaction		Frequency (%)
Prescribed drug number	2-4	6 (11.76%)
	≥5	45 (88.24%)
Number of drug-drug interaction	1-6	30 (85.71%)
	≥7	5 (14.29%)
Severity	Minor	10 (16.67%)
	Moderate	42 (70%)
	Major	8 (13.33%)
Management	There is no need to take any action	11 (18.33%)
	Medication monitoring	37 (61.67%)
	Modification of the medication is recommended	11 (18.33%)
	Avoiding drug combinations is recommended	1 (1.67%)

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Table 2. The Probable of Drug-Drug Interaction Based on Severity and Management

The Probable of Drug-Drug Interaction	Frequency	Management
Minor (top 5)		
Domperidone-Ciprofloxacin	7	There is no need to take any action
Ferrous sulphate-Calcium Polystyrene Sulphonate	3	There is no need to take any action
Ferrous sulphate -Lansoprazole	3	There is no need to take any action
Ondansetron-Metronidazole	3	There is no need to take any action
Paracetamol-Ondansetron	2	There is no need to take any action
Moderate (top 5)		
Ceftriaxone-Furosemide	13	Medication monitoring
Candesartan-Furosemide	12	Medication monitoring
Dutasteride-Sucralfate	10	Modification of the medication is recommended
Domperidone- Chlorpheniramine maleate	7	Medication monitoring
Sodium Chloride- Chlorpheniramine maleate	7	Avoiding drug combinations is recommended
Major (top 5)		
Codeine-Cetirizine	12	Modification of the medication is recommended
Ciprofloxacin- Sucralfate	10	Modification of the medication is recommended
Codeine-Braxidin® (clidinium-chlordi-azepoxide)	3	Modification of the medication is recommended
Phenytoin-Dexamethasone	2	Modification of the medication is recommended
Ceftriaxone-Calcium Gluconate	1	Modification of the medication is recommended

Table 3. Assessment of Probable Drug-Food Interaction Based on Severity

Severity	The Probable of Drug-Food Interaction	Effect
Minor	Ciprofloxacin/caffeine	Ciprofloxacin may increase the serum concentration of Caffeine and Caffeine Containing Products[24]
	Diltiazem/grapefruit juice	Grapefruit Juice can enhance the levels of Diltiazem in the bloodstream[24]
	Digoxin/fiber	Pectin may decrease the serum concentration of Cardiac Glycosides[24]
	Levothyroxine/grapefruit juice	Grapefruit Juice can reduce the levels of Levothyroxine in the bloodstream[24]
	Atorvastatin/grapefruit juice	Consuming grapefruit juice can elevate atorvastatin levels in the bloodstream[24]
	Simvastatin/grapefruit juice	Grapefruit Juice may increase the serum concentration of Simvastatin [24]
Moderate	Levothyroxine/caffeine	Levothyroxine may enhance the adverse/ toxic effect of sympathomimetics (caffeine). Specifically, the risk of coronary insufficiency may be increased in patients with coronary artery disease[24]
	Levothyroxine/soybean product	Soybean may diminish the therapeutic effect of Thyroid Products[24]
	Digoxin/food high in pectin	Pectin may decrease the serum concentration of Cardiac Glycosides[24]
Major	Domperidone/grapefruit juice	Grapefruit juice may increase the serum concentration of Domperidone[24]
	Clopidogrel/grapefruit juice	Grapefruit Juice may decrease serum concentrations of the active metabolite of Clopidogrel[24]

Table 4. The Probable of Drug-Food Interaction Based on Management

Management	Drug Class	The Probable of Drug-Food Interaction		Frequency
		Drug	Food / Nutrient	
There is no need to take any action	Antihypertensive	Diltiazem	Grapefruit juice	9
Total				**9**
Administer without regard to food	5 Alpha-Reductase Inhibitor	Dutasteride	Food general but not interact significantly	5
	Antibiotic	Cefixime	Food general	5
	Antihypertensive	Spironolactone	Food general	3
	Analgesic Combination	Paracetamol-Tramadol	Food general	2
		Levofloxacin	Food general	2
	Decongestant	Pseudoephedrine	Food general	2
	Gastrointestinal drug	Ondansetron	Food general	5
	Histamine H1 Antagonist	Cetirizine	Food general	3
Total				**27**
Medication monitoring	Antibiotic	Ciprofloxacin	Caffeine	8
	Gastrointestinal drug	Lansoprazole	Vitamin B12	20
Total				**28**
Take with food	Antiplatelet	Aspirin	Food general	3
	Antibiotic	Metronidazole	Food general	4
	Calcium salts	Calcium carbonate	Food general	4
Total				**11**
Administer 30 minutes before food	Thyroid Product	Levothyroxine Sodium	Soybean, grapefruit juice, caffeine	5
Total				**5**
Administer 30 minutes after food	Alpha 1 Blocker	Tamsulosin	Food general	5
Total				**5**
Avoid concurrent administration with food	Antiplatelet	Clopidogrel	Grapefruit juice	8
	Antiarrhythmic agent	Digoxin	Fiber or food high in pectin	2
	Gastrointestinal drug	Domperidone	Grapefruit juice	6
	HMG-CoA Reductase Inhibitor	Atorvastatin	Grapefruit juice	11
		Simvastatin	Grapefruit juice	4
Total				**31**

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5,6-, 8,9-, 11,12- and 14,15-Epoxyeicosatrienoic Acids (EETs) Induce Peripheral Receptor-Dependent Antinociception in PGE2-Induced Hyperalgesia in Mice

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Abstract

Epoxyeicosatrienoic acids (EETs) are cytochrome P450-epoxygenase-derived metabolites of arachidonic acid that act as endogenous signaling molecules in multiple biological systems, including their controversial effects on pain, including reports of the central analgesic effect and its action in inducing pain. The aim of this study was to verify the peripheral antinociceptive effect of EETs and the effect of the selective EET receptor antagonist, 14,15-EEZE, on this antinociception. The nociceptive threshold was determined by paw pressure withdrawal, and hyperalgesia was induced by intraplantar injection of PGE2 to evaluate the effect of EETs administration. EETs (5,6-, 8,9-, 11,12-, and 14,15-EET) were administered intraplantarly to male mice (n = 5). To examine the mechanism of action, a non-selective EET receptor antagonist (14,15-EEZE) was administered peripherally. Intraplantar injections of 5,6-, 8,9-, and 11,12-EET (32, 64, and 128 ng) or 14,15-EET (128, 256 and 512 ng), five minutes before the third hour after PGE2 injection induced a dose-dependent antinociceptive response. EETs showed peak action five minutes after injection, and this effect decreased concomitantly with a reduction in the nociceptive effect of PGE2 until approximately 100 min after injection (270 min after PGE2 injection). The maximum dose of each EET completely reversed the hyperalgesia induced by PGE2. The antinociceptive effect of EETs was confined to the paw that received the injection, indicating a localized effect. Intraplantar injection of the EET antagonist, 14,15-EEZE, reversed in a dose-dependent manner (32-512 ng/paw) the peripheral antinociception induced by 5,6-, 8,9-, 11,12-, and 14,15-EET. Our results provide evidence that EETs induce a peripheral antinociceptive effect and that the mechanism of action involves EET receptor activation.

Keywords: antinociception, EET, epoxyeicosatrienoic acids.

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Introduction

Epoxyeicosatrienoic acids (EETs) are metabolites of arachidonic acid produced by cytochrome P450 epoxygenases and are metabolized in the body through a variety of pathways, the most important being the soluble epoxide hydrolase pathway[1-2]. EETs are important signaling molecules that mediate and regulate a series of events, such as inflammation[3], cancer[4], angiogenesis[5] and cardiovascular diseases[6].

Among the various biological actions of EETs, the literature presents controversial results in the field of pain. Some studies have demonstrated that EETs are analgesics, which a reduction in lipopolysaccharide-induced thermal hyperalgesia was observed[7]. Terashvili et al. (2008) observed that 14,15-EET, but not other EETs, produced antinociception when injected into the periaqueductal gray matter, indicating a central analgesic effect of EETs[8]. In contrast, it was shown that 8,9-EET has a nociceptive effect in a zymosan-induced inflammatory model[9]. Furthermore, it has been shown that 5,6-EET causes central mechanical hypersensitivity[10]

Various bioactive lipid mediators regulate nociceptive pain and inflammation in peripheral tissues by interacting with receptor systems on primary sensory neurons and neighboring host-defense cells, such as macrophages, mast cells and keratinocytes[11].
EETs are important signaling molecules for mediating and regulating a range of local events, such as inflammation[3] and angiogenesis[5]. Soluble epoxide hydrolases inhibitors delivered through the transdermal route attenuated thermal hyperalgesia and mechanical allodynia in rats treated with LPS[7], indirectly indicating a peripheral effect for EETs. In light of these observation, this study aims to verify the peripheral effect of EETs on PGE2-hyperalgesia nociception and the involvement of their receptors, seeking to broaden the knowledge about these.

Methods

Animals

The experiments were performed on 30-40 g (10-12 weeks) male Swiss mice (CEBIO-ICB/UFMG, Belo Horizonte, Brazil). The calculated sample size was n=4/group, 216 in total. The animals were maintained in a temperature-controlled room on an automatic 12-hour light/dark cycle, with free access to food and water. All tests were carried out during the light phase and animals were randomly selected. The animal experimental protocols were approved by the UFMG Ethics Committee on the Use of Animals (protocol 75/2017) and all animal care are in accordance with the recommendations for the evaluation of experimental pain in animals[12].

Measurement of Nociceptive Threshold

Hyperalgesia was induced by subcutaneous injection of PGE2 (2 µg/paw) into the mice's plantar surface hind paw. The mechanical nociceptive threshold was assessed by measuring the response to a paw pressure test, and adapted to mice[13]. An algesimeter (Ugo-Basile, Italy), which consisted of a cone-shaped paw-presser with a rounded tip, was used to apply linearly increasing pressure to the hind paw. The weight in grams required to elicit a nociceptive response to paw withdrawal was defined as the nociceptive threshold. A cut-off value of 160 g was used to prevent possible damage to the paws. The nociceptive threshold was measured in the hind paw and determined as the average of three consecutive trials recorded before (baseline nociceptive threshold) and at different time points after the PGE2 and EETs injections. The results are expressed in grams. To minimize stress, the mice were habituated to the apparatus two days prior to the experiments.

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Drugs

5,6-, 8,9-, 11,12-, and 14-15 epoxyeicosatrienoic acid (Cayman Chemical, USA) were diluted in ethanol 6.4% in saline. 14,15-Epoxyeicosa-5(Z)-enoic acid (Cayman Chemical, USA) was diluted in ethanol 6.4% in saline. Prostaglandin E2 (Sigma, USA), the hyperalgesic agent, was diluted in ethanol 10% in saline. All the drugs were subcutaneously injected into the plantar surface of the right paw in a volume of 20 µL per paw.

Experimental Protocol

In all experiments, the baseline nociceptive threshold of each animal was measured before the injection of any substance. To evaluate the temporal development of the dose-response curve of each EET, these drugs were injected 5 min prior to the peak of action of PGE2-induced hyperalgesia (180 min). Nociceptive threshold measurements were performed at different time points from 180 to 300 min after the first injection. To determine whether each EET acted only peripherally, PGE2 was injected into both hind paws. The highest dose of each EET was administered only to the right paw, while the contralateral paw received the vehicle (ethanol in saline). Nociceptive threshold measurements were taken in both hind paws to exclude systemic effects. For these experiments and the EETs antagonist protocol, the nociceptive threshold was measured before any injection (zero time) and 180 min after PGE2 injection (peak action). The difference between these values was expressed as the Δ of the nociceptive threshold. The protocols follow previous experiments and studies already published by our research group[14].

Statistical Analysis

Results are presented as the mean ± standard error of the mean (S.E.M.). Statistical analysis was carried out using Graph Prism 8.0.2 software and the data were analyzed by analysis of variance (ANOVA) followed by Bonferroni test. Statistically significance was set at $p<0.05$.

Results and Discussion

Antinociception of EETs on PGE2-induced Nociception in the Paw of Mice and Exclusion of the Systemic Effect

Injection of 2 µg PGE2 into the plantar hind paw skin caused nociceptive threshold (NT) to decrease significantly at all timepoints across a 4-h period (Figs 2,3,4 and 5, solid red circle), which had a peak effect at three hours where NT decreased to maximal of baseline. Vehicle-treated control (black solid circle) showed no significant changes in NT over the same 4-h testing period, comparing to basal measurement.

To evaluate the potential peripheral antinociceptive effects induced by different EETs, dose-response curves were used over time against hyperalgesia induced by PGE2. Intraplantar injection of 5,6-, 8,9-, and 11,12-EET (32, 64, and 128 ng) or 14,15-EET (128, 256, and 512 ng), five minutes before the third hour after PGE2 injection (peak action of this substance), induced a dose-dependent antinociceptive response (Figs 2,3,4 and 5). All evaluated EETs showed a similar response profile, although 14,15-EET, despite having the same efficacy, was less potent than the others EETs. EETs showed peak action five minutes after injection, and this effect decreased, concomitantly with a reduction in the nociceptive effect of PGE2 until approximately 100 min after injection (270 min after PGE2 injection). The maximum dose of each EET completely reversed the hyperalgesia induced by PGE2. We tested for potential analgesic effects of EETs in the absence of inflammatory pain, and the same maximal doses of them did not significantly change NT (not shown).

Among the different substances that can induce hyperalgesia, in this study, PGE2 was used, whose nociceptive effect is related to the ability of this substance to decrease the activation threshold of nociceptive primary afferent neurons due to an increase in neuronal excitability[15]

The pronociceptive PGE2 effect is thought to be caused by activation of Gs protein-coupled EP2 and EP4 receptors in nociceptive neurons and involves cAMP synthesis[16]. Mechanistically, cAMP-dependent pathways phosphorylate neuronal voltage-gated sodium channels (NaV) necessary for action potential generation[17]. Sensitization of nociceptors induced by PGE2 does not depend on the participation of cells or intermediate mediators, and nociceptors are directly activated in vitro by high concentrations of PGE2[18]. Therefore, using a pain model induced by PGE2 eliminates the possibility that the effect of the studied substance is the result of blocking in the release or action of mediators involved in the inflammatory process[19].

To exclude possible systemic effects, PGE2 was administered at time zero in both hind paws, and each EET at its highest dose was injected only in the right hind paw five minutes before the third hour after PGE2 injection. Measurements of the nociceptive threshold of both hind paws were taken immediately before and three hours after the intraplantar injection of PGE2, and the difference between the means of the measurements was calculated (Δ of the nociceptive threshold). At their highest doses, 5,6-, 8,9-, 11,12- and 14,15-EET, induced an effect restricted to the treated paw without changing the PGE2-induced hyperalgesia in the contralateral paw, indicating that these doses of EET are only locally effective (Insert Figs 2, 3, 4, 5).

In the present study, the hyperalgesic agent PGE2 was used as an experimental model to verify whether EETs have peripheral antinociceptive effects. Our results demonstrated that 5,6-, 8,9-, 11,12- or 14,15-EET, when injected into the mouse paw, induced peripheral antinociception against PGE2 hyperalgesia which was restricted to the treated paw and did not alter the hyperalgesia induced by PGE2 in the contralateral paw, indicating that the maximum doses of EET used were only effective locally. These data are in agreement with those of previous studies showing that topical administration of a mixture of EETs reduced thermal hyperalgesia in a pain model induced by the injection of lipopolysaccharide (LPS) in the rats' paw[7]. Furthermore, it has been shown that intracerebroventricular injection of 14,15-EET also induces antinociception[8]. Similarly, it was demonstrated that intraplantar injection of 5,6-EET induces mechanical, but not thermal, nociception, and this event is dependent on transient receptor potential ankyrin 1 (TRPA1).10 In contrast, 8,9-EET induces mechanical, but not thermal, hyperalgesia[9].

Effect of 14,15-EEZE on EETs-induced Antinociception

Intraplantar injection of the EET antagonist, 14,15-EEZE, reversed in a dose-dependent manner the peripheral antinociception induced by 5,6-, 8,9-, 11,12- and 14,15-EET (Fig. 6). When administered alone using the same protocol, the highest dose of the antagonist did not change the response to PGE2 or the vehicle (Fig. 6E).

EETs are responsible for diverse biochemical and functional responses; therefore, it is believed that more than one mechanism or signal transduction pathway is responsible for all their actions. Some functional effects of EETs, such as their ability to regulate gene

expression, suggest an intracellular action of these substances[20,21]. However, other studies indicate that EETs act via membrane-binding sites or receptors.22-24 Studies suggest that EET actions are partly, mediated by signaling from G protein-coupled receptors (GPCRs). Therefore, possible candidate GPCRs for EET receptors were selected, and it was observed that EETs, as well as other free fatty acids, bind with low affinity to GPR40 and GPR132 receptors in hematopoietic and vascular endothelium cells[25,26]. The authors report that these GPCRs are related with increase of intracellular calcium concentration and also with ERK phosphorylation. However, despite an intense search for the molecular mechanisms underlying the biological actions of EETs, these are still not fully understood, and the identity of EET receptor remains unknown. Later, binding study provided a potential mechanism of action for this analgesia by determining that EETs bind the peripheral benzodiazepine receptor also known as the translocator protein (TSPO)[27].

The literature has already identified the structural requirements for the biological activity induced by EETs, making it possible to characterize specific antagonists of these substances[28]. Among the non-selective pharmacological antagonists of EETs, 14,15-EEZE, has been shown to inhibit vascular relaxation induced by 5,6-, 8,9-, 11,12- and 14,15-EET in bovine coronary arteries[29]. Furthermore, the same antagonist reduced the protective action of exogenous and endogenous EETs in dog hearts, and inhibited cell motility in prostate carcinoma induced by 11,12-EET[30].

Antagonists are important pharmacological tools for identifying the biological actions of substances that are objects of study. Therefore, we used the EETs antagonist 14,15-EEZE to demonstrate the peripheral antinociceptive effects of these substances on PGE2-induced hyperalgesia. This antagonist reversed the peripheral antinociceptive effects of EETs, confirming that these substances induce antinociception via receptor activation.

Conclusion

Our results provide evidence that EETs induce a peripheral antinociceptive effect in PGE2-induced pain model. Studies found in the literature have reported isolated effects of EETs related to central analgesia8 and even pain9,10, in addition to indirect evidence for the inhibition of their synthesis7. While these assays in mice have limitations in their predictive capacities, they do show a robust and reproducible antihyperalgesic response, opening up possibilities for investigating this class of substance with perspectives for its therapeutic application. The use of the AX antagonist suggests the participation of specific receptors in the peripheral antinociceptive action of the EETs evaluated.

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Conflict of Interest

None declared.

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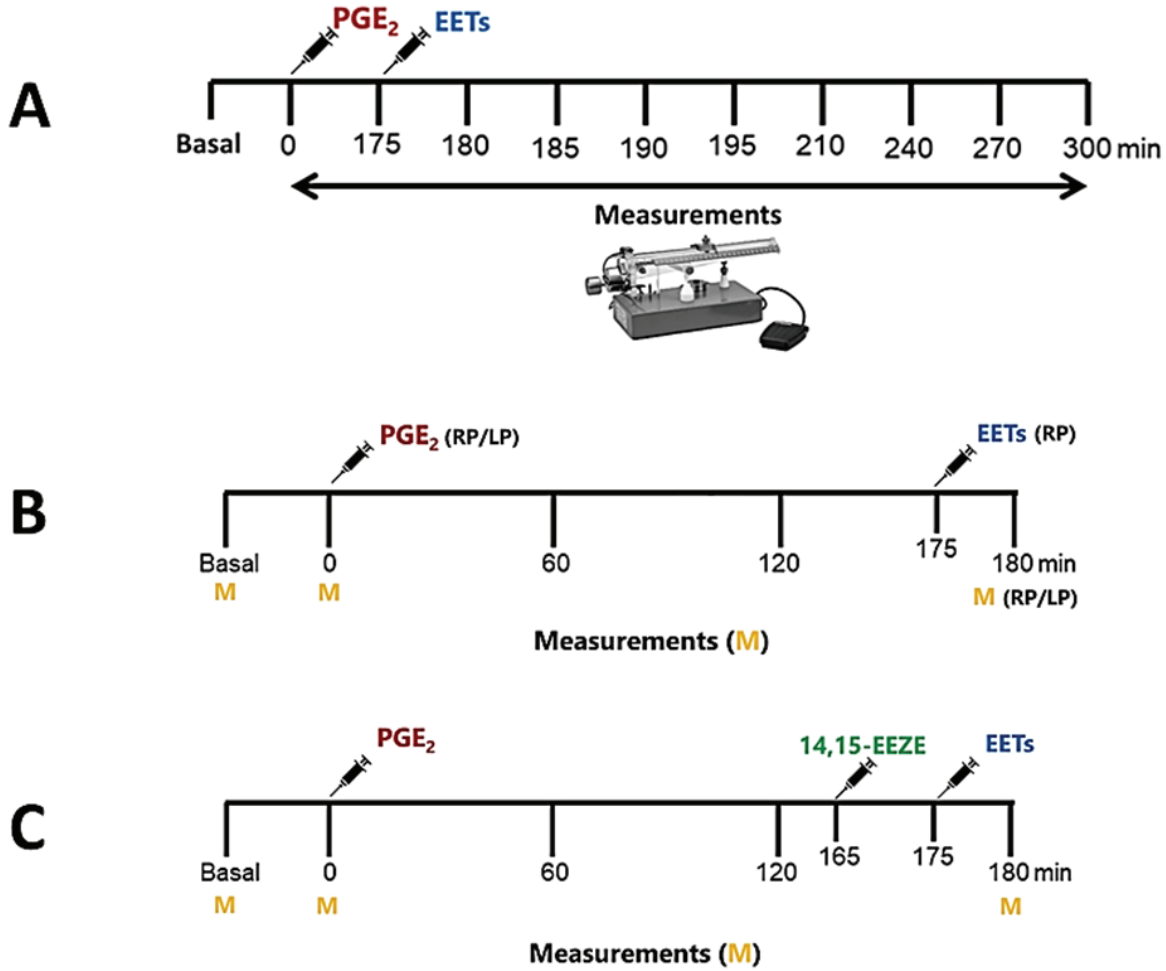

Figure 1. (A) Experimental protocol for the temporal evaluation of the antinociceptive effect of EETs. (B) Exclusion of the Systemic antinociceptive effect of EETs. PGE2 was administered at 0 min in the right (RP) and left (LP) hind legs of the animals, while EETs, at their maximum doses, were administered after 175 min only in the RP and its vehicle in the LP. Measurements of the nociceptive threshold of both paws were made before and after 180 min of PGE2 injection (time at which the maximum effect is observed). (C) Effect of EET receptor antagonist (14,15-EEZE) on EETs-induced Antinociception. In the experiments evaluating EETs receptors involved in antinociception induced by EETs, the Δ of the nociceptive threshold was used, which refers to the difference between the nociceptive threshold obtained at the beginning of the experiment before any injection (baseline value) and the threshold measured after 180 min PGE2, Prostaglandin E2; EETs, Epoxyeicosatrienoic acids.

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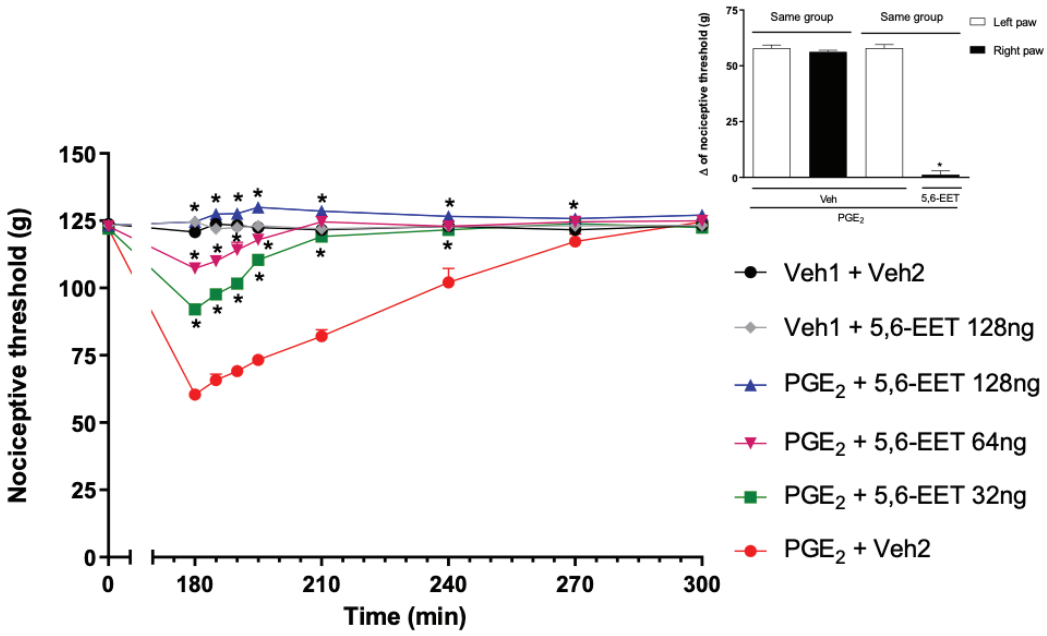

Figure 2. Antinociceptive effect of intraplantar injection of 5,6-EET in PGE2-induced hyperalgesia. The graph shows the time course of the peripheral antinociceptive effect of different doses of 5,6-EET, and the insert shows the exclusion of systemic antinociceptive effect of 5,6-EET (128 ng) in hyperalgesic paws; $F(3, 12) = 383.9$. Data are presented as mean ± SEM (n = 4). * indicates a significant difference compared with PGE2 + Veh ($P<0.05$), ANOVA with Bonferroni post-test. Veh= Vehicle. Veh1 = ethanol 10%, Veh2 = methyl acetate 6.4%. $F(5, 18) = 253.2$. PGE2= Prostaglandin E2; EETs= Epoxyeicosatrienoic acids.

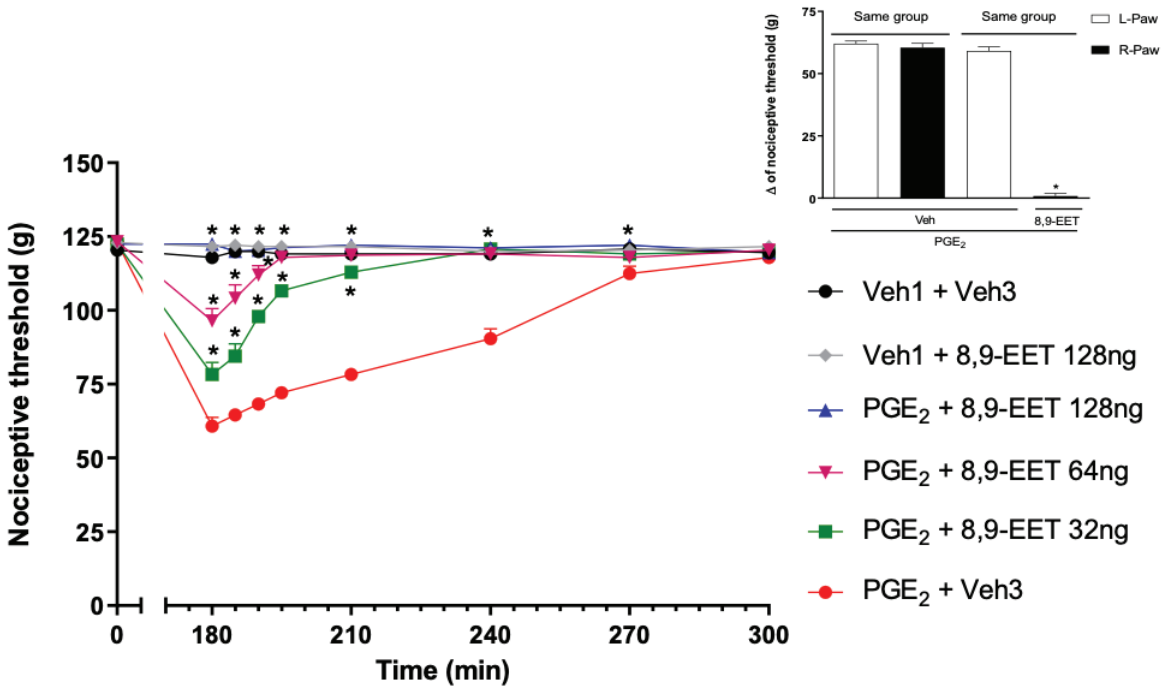

Figure 3. Antinociceptive effect of intraplantar injection of 8,9-EET in PGE2-induced hyperalgesia. The graph shows the time course of the peripheral antinociceptive effect of different doses of 8,9-EET, and the insert shows the exclusion of systemic antinociceptive effect of 8,9-EET (128 ng) in hyperalgesic paws; $F(3, 12) = 462.4$. Data are presented as mean ± SEM (n = 4). * indicates a significant difference compared with PGE2 + Veh ($P<0.05$), ANOVA with Bonferroni post-test. Veh1 = ethanol 10%, Veh2 = ethanol 6.4%. $F(5, 18) = 117.6$.

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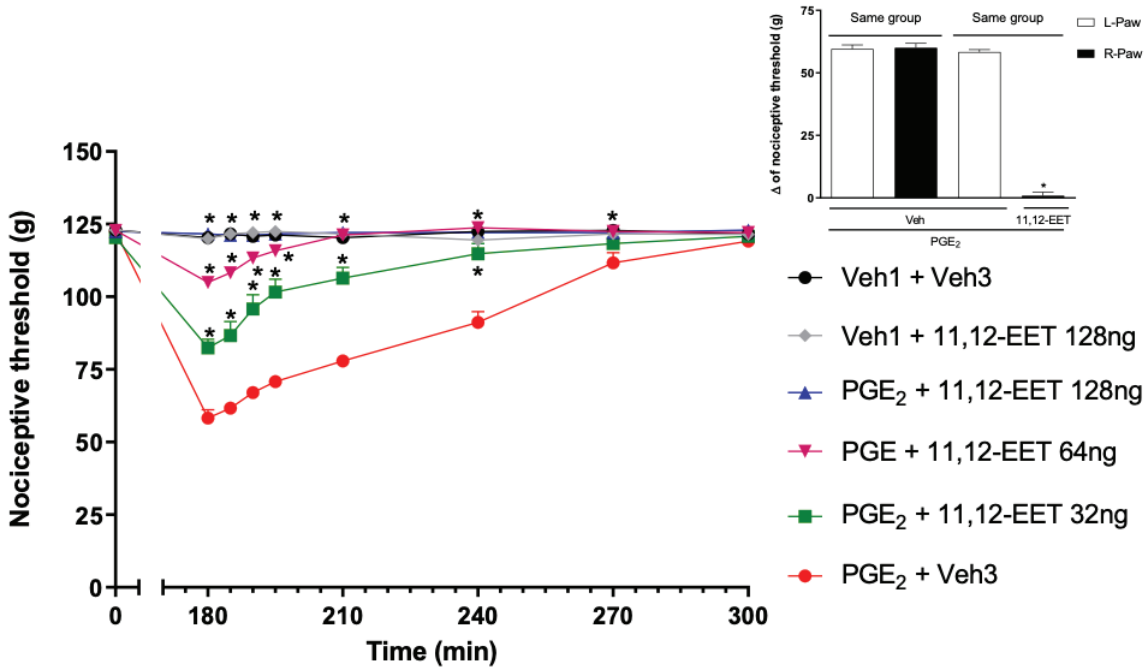

Figure 4. Antinociceptive effect of intraplantar injection of 11,12-EET in PGE2-induced hyperalgesia. The graph shows the time course of the peripheral antinociceptive effect of different doses of 11,12-EET, and the insert shows the exclusion of systemic antinociceptive effect of 11,12-EET (128 ng) in hyperalgesic paws; F(3, 12) = 395.7. Data are presented as mean ± SEM (n = 4). * indicates a significant difference compared with PGE2 + Veh ($P<0.05$), ANOVA with Bonferroni post-test. Veh1 = ethanol 10%, Veh2 = ethanol 6.4%. F(5, 18) = 113.2.

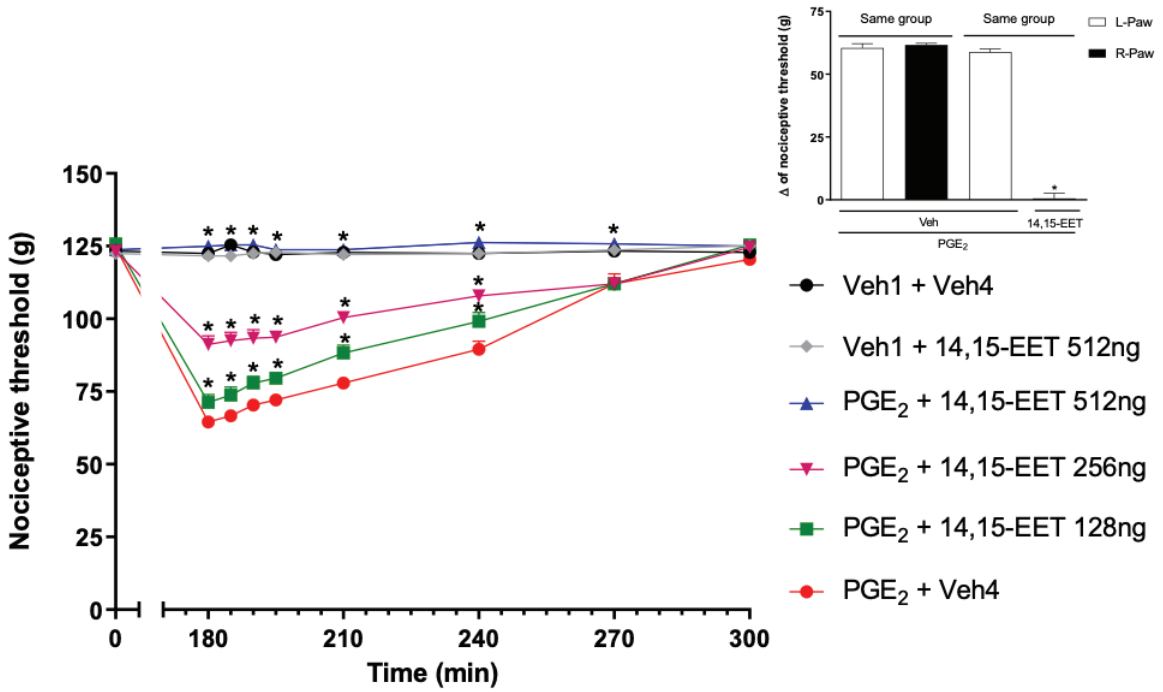

Figure 5. Antinociceptive effect of intraplantar injection of 14,15-EET in PGE2-induced hyperalgesia. The graph shows the time course of the peripheral antinociceptive effect of different doses of 14,15-EET, and the insert shows the exclusion of systemic antinociceptive effect of 14,15-EET (512 ng) in hyperalgesic paws; $F(3, 12) = 392.3$. Data are presented as mean ± SEM (n = 4). * indicates a significant difference compared with PGE2 + Veh ($P<0.05$), ANOVA with Bonferroni post-test. Veh1 = ethanol 10%, Veh2 = ethanol 25.6%. $F(5, 18) = 178.4$.

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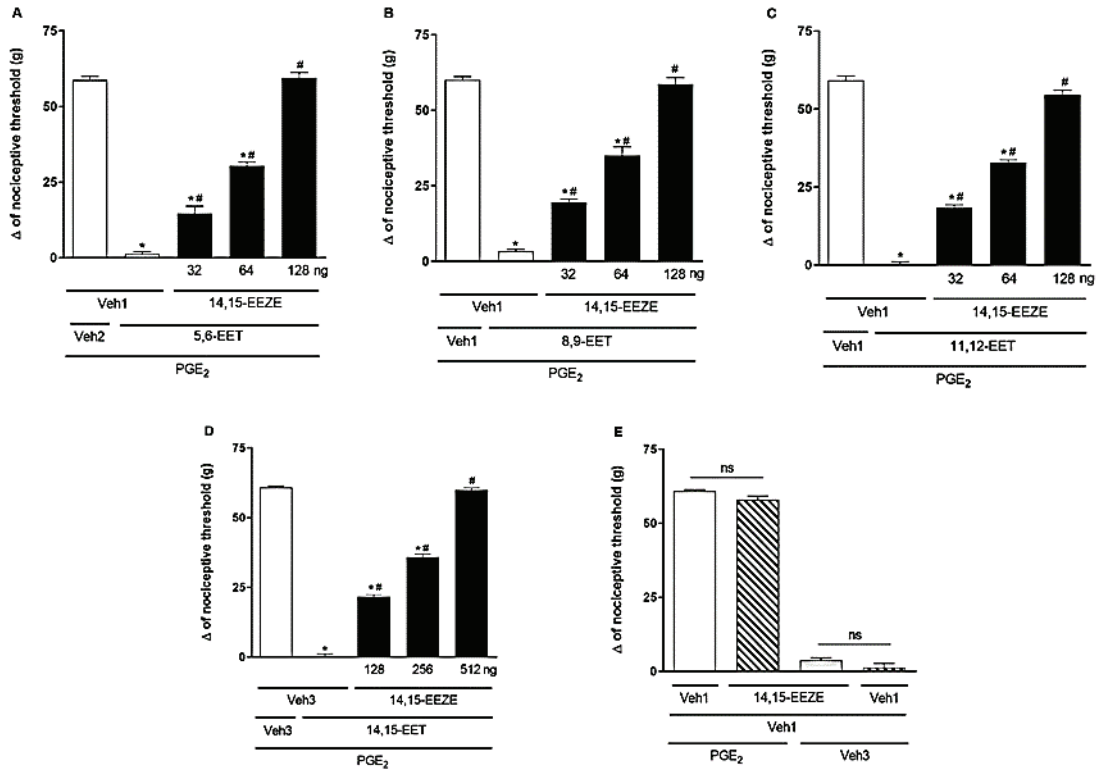

Figure 6. Effect of the pretreatment with EETs receptor antagonist on the EETs-induced peripheral antinociception against the hyperalgesia induced by PGE2. 14,15 EEZE (32, 64, 128, 256 and 512 ng/paw) was injected into the right hind paw 10 min prior to the intraplantar injection of (A) 5,6-, (B) 8,9-, (C) 11,12-, (D) 14,15-EET (128, 128, 128 and 512 ng/paw, respectively) and (E) Vehicle. EETs were given 175 min after the local injection of prostaglandin E2 (PGE2; 2 µg/paw). Measurements were made at 180 min. Each column represents the mean ± SEM (n=4). Veh1 = ethanol 6.4%, Veh2 = methyl acetate 6.4%, and Veh3 = ethanol 10%. * $p<0.05$ compared to the PGE2 + Veh + Veh and # $p<0.05$ compared to the PGE2 + Veh1 + EET; one-way ANOVA followed by the Bonferroni test. (A) $F(4, 15) = 275.7$; (B) $F(4, 15) = 189.1$; (C) $F(4, 15) = 455.3$, (D) $F(4, 15) = 997.4$, (E) $F(3, 12) = 965.5$.

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The Health Profile of Students and Teachers in Madrasah Al Ihsan, Kecamatan Ciparay, Kabupaten Bandung

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Abstract

The prevalence of diabetes mellitus and hypertension in Indonesia is increasing both in low- and high-income communities. Therefore, health awareness should be started from a younger age for the prospective future generation. This study, included in a community engagement activity, aims to assess the health profile, in terms of blood pressure (BP) and total cholesterol, of the students (by cross-sectional method) and teachers (by cohort method) of a private madrasah in the rural area of Kecamatan Ciparay, Kabupaten Bandung, West Java. 54 students and 10 teachers participated in this study. Results revealed that the students' average systolic and diastolic BP were 120.23 mmHg and 78.67 mmHg, respectively. The average systolic BP of the teachers in August 2021, January 2022, and August 2022 was 136.8 mmHg, 128.1 mmHg, and 131.9 mmHg, respectively. The average diastolic BP of the teachers in August 2021, January 2022, and August 2022 were 91.6 mmHg, 87.3 mmHg, and 87.1 mmHg, respectively. Moreover, the average cholesterol levels of the students (148.38 mg/dL) and the teachers (190.81 mg/dL) were categorized as normal. Taken together, the health profile of the students and the teachers in Madrasah Al Ihsan is within the normal range. This activity gets positive support from the school and needs sustainability.

Keywords: blood pressure; blood glucose; cholesterol; diastole; hypertension; systole

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Introduction

Metabolic disorders occur when there is a malfunction in the metabolism process, which eventually causes an alteration in the body's homeostasis. Metabolic disorders are (1) glucose homeostasis dysfunction or diabetes mellitus; (2) insulin resistance; (3) hypertension; (4) dyslipidemia; and (6) microalbuminuria (urea albumin excretion rate >20 mg/min or albumin/creatinine ratio >30 mg/g). The relationship between metabolic diseases and cardiovascular disorders (CVD) is prominent[1]. Metabolic disorders affect various systems in the body. Insulin resistance leads to damage to blood vessels, which eventually causes endothelial dysfunction, vascular resistance, hypertension, and vessel wall inflammation[2]. According to the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Hypertension Guidelines, hypertension is defined if systolic blood pressure (BP) of > 130 mmHg or diastolic BP of >80 mmHg. First-line therapy is lifestyle modification[3,4].

Hypercholesterolemia is defined as an elevation of plasma cholesterol levels (> 200 mg/dL) with normal plasma triglycerides, an LDL cholesterol >190 mg/dL, or >160 mg/dL with one major risk factor, or >130 mg/dL with two cardiovascular risk factors. The important risk factors include age (male >45 years, female >55 years), hypertension, diabetes mellitus, smoking, and low HDL cholesterol5. Hypertension has been known as the silent killer. This disease has been a global burden for decades due to its high mortality rates. Moreover, the prevalence of hypertension is increasing in both low- and high-income communities in Indonesia. Approximately 200,000 patients with hypertension in Kabupaten Bandung were recorded in 2019[6].

Madrasah Al-Ihsan is located in Kecamatan Ciparay, Kabupaten Bandung. This school has been accredited B with 24 teachers and proper classrooms to facilitate 219 students. Based on the information provided by the headmistress, this madrasah is a non-profit school that does not take any fees from the students. The students mostly come from lower-income parents, e.g., who worked as pedicab drivers or agricultural laborers, in the surrounding area.

Our concern is that health awareness should be started at a younger age for the future generation. Therefore, this study, included in a community engagement activity, aims to assess the health profile, in terms of blood pressure (BP) and total cholesterol, of the students (by cross-sectional method) and teachers (by cohort method) of Madrasah Al Ihsan, a private madrasah in the rural area of Kecamatan Ciparay, Kabupaten Bandung, West Java. The community engagement activity in Madrasah Al Ihsan is routinely carried out every semester, started in 2021, and has been continuing to present.

Methods

Participants

This study was conducted with a total of 64 participants. The participants for the cross-sectional study were students of grades XI and XII (n = 54; aged 16-19 years), and the participants for the cohort study were teachers (n = 10; aged 23-60 years). The participants were asked to assemble in a large classroom and were briefed about the procedure of the health examination.

Health examination

Before the health examination, the participants were interviewed about their illness history, eating habits, and smoking habits. They were asked to fill out a registration form and put their signatures on it (Figure 1).

The participants were given health cards with

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their names on them and examined their BP using a digital sphygmomanometer. The BP of the participants was measured by following a standard procedure, e.g., the participants were asked to sit for several minutes, and the measurement was done on the upper part of the left arm positioned near the heart[7,8]. The BP measurement was repeated twice. Eventually, the participants were examined for their blood cholesterol levels using disposable lancets and Autocheck GCU (glucose, cholesterol, and uric acid) devices. After the examination, the participants were encouraged to ask anything related to their health status and medication and were given suggestions about a healthy lifestyle.

Results and Discussion

The cross-sectional study included a community engagement activity at Madrasah Al Ihsan, Kecamatan Ciparay, Kabupaten Bandung Barat, which was attended by students of grades XI and XII (n = 54; aged 16-19 years; male 25 and female 29) and teachers (n = 10). During physical observation, all the students were confirmed healthy, with an average body weight of 51.22 kg. There was no student with obesity, although 3 students (2 females and 1 male) showed a body weight of more than 65 kg with proportional heights. One student was extremely thin, with a body weight of less than 40 kg. Two male students were smokers, smoking 2-3 cigarettes per day.

The BP measurement of the students revealed an average systolic and diastolic BP of 120.23 mmHg and 78.67 mmHg, respectively. Of those, five students showed high systolic BP, and 14 students had high diastolic BP (Table 1). Students with high systolic BP did not always show high diastole, and vice versa. Fifteen students were categorized as hypertensive by referring to the 2017 ACC/AHA Hypertension Guidelines (depicted as a darker shade of cells in Table 1).

The BP measurements of the teachers were carried out in three periods: August 2021, January 2022, and August 2022. The average systolic BP of the teachers in August 2021, January 2022, and August 2022 was 136.8 mmHg, 128.1 mmHg, and 131.9 mmHg, respectively. The average diastolic BP of the teachers in August 2021, January 2022, and August 2022 were 91.6 mmHg, 87.3 mmHg, and 87.1 mmHg, respectively (Table 2).

The blood cholesterol assay of the students revealed a normal range (average 144.29 mg/dL); however, one female student was categorized as having hypercholesterolemia with a blood cholesterol level of 202 mg/dL, although her body weight was only 39 kg and she had a normotensive BP (Table 1). Additional data on the blood glucose of the students indicated an average value of 90.20 mg/dL (Table 1); however, one male student with a body weight of 60 kg showed a blood glucose level of 142 mg/dL.

The blood cholesterol assay of the teachers resulted in an average of 190.81 mg/dL, which is categorized as normal, although three teachers had shown high cholesterol levels (Table 2). It is well known that teenagers and young adults have the tendency to consume unhealthy foods, particularly those containing fats, salts, and sugars. A study in the US reported that young adults, aged 12 to 19 years, showed a prevalence of 14% for prehypertension/hypertension, 22% for borderline-high/high LDL cholesterol, 6% for low HDL cholesterol (<35 mg/dL), and 15% for prediabetes/diabetes. It was reported that 80% of CVD can be prevented through diet and lifestyle, and young adolescents are ideal targets for prevention programs because they are in the process of establishing lifestyle habits. Unhealthy diets and a lack

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of vegetables and fruits contributed to weight gain and dyslipidemia in this age period [9].

A cross-sectional study that assessed coronary heart disease risk in students of the University of New Hampshire aged 18–24 years (n = 1701) resulted in an alarmingly high prevalence of abnormal risk factor profiles, with high rates of overweight, elevated LDL cholesterol, and increased systolic and diastolic BP[10]. More interestingly, a previous study on 166 students of the Arabian Gulf University, Kingdom of Bahrain, aged 16-30 years reported that only 15.6% of students indicated hypercholesterolemia and male students have the tendency to show higher total cholesterol levels than females. Another study on 180 students of Baylor University who implemented a sedentary lifestyle proved that male students displayed a high risk of dyslipidemia compared to female students[11].

Chinese students aged 15-26 years (n = 3484) indicated normal blood glucose levels (65-110 mg/dL); nevertheless, male Chinese students had higher cholesterol levels[12]. A recent study in 2020 published as a thesis at J. William Fulbright College of Arts and Sciences, The University of Arkansas, subjected to 27 students aged 19-27 years, reported a positive correlation between the duration of sleep and LDL levels of the students (each additional sleep time correlated to the increase of LDL 14.3 mg/dL)[13].

Similar studies on the cholesterol levels and BP of teachers have also been conducted elsewhere 14,15. A cross-sectional study of teachers at SMA Fons Vitae I Jakarta (n = 52) found that 36 teachers (69.23%) had normal blood cholesterol levels and 20 teachers (38.46%) had pre-hypertension status 14. Another study reported the nutritional behavior, lipid profile, and fasting blood glucose of teachers at SMP Negeri Makassar[15].

Interestingly, although there are various ethnic groups in Asia, a study reported that generally, the levels of serum lipids correlate with age 16. A cross-sectional study (n = 46239) on the plasma cholesterol and LDL levels in adult Chinese was also reported as alarmingly high 17,18. Age was positively correlated with total cholesterol, triglyceride, and LDL-cholesterol levels in men ≤40 and between 40 and 60 years old and women ≤40 and between 60 to 70 years old. The trends in HDL-C levels with age were relatively irregular, although HDL-C levels in women were higher than in men[18].

It was confirmed that routine physical activity can improve lipid status in elderly patients with dyslipidemia[19,20]. Nonetheless, although it is notable that routine physical activity can benefit health by increasing the body's antioxidant defenses, it should be noted that heavy physical activity may raise the production of reactive oxygen species and result in cell injury [21,22]. Moreover, oxidative stress may influence gastrointestinal motility in obese patients[23]. Currently, oxidative stress can be predicted by measuring trans-4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA) levels in the blood by employing immunohistochemical and ELISA methods[24].

The health profile, in terms of BP and cholesterol levels, of the students and the teachers in Madrasah Al Ihsan, Kecamatan Ciparay, Kabupaten Bandung revealed a good result. However, due to the limited number of participants and different students during each semester of study, the health profile cannot be assessed thoroughly. This activity is routinely carried out every semester, started in 2021, and has been continuing to present.

Conclusion

The cross-sectional study included in a community engagement activity carried out

at Madrasah Al Ihsan, Kecamatan Ciparay, Kabupaten Bandung, revealed that the student's average systolic and diastolic BP were 120.23 mmHg and 78.67 mmHg, respectively. The average systolic BP of the teachers in August 2021, January 2022, and August 2022 was 136.8 mmHg, 128.1 mmHg, and 131.9 mmHg, respectively. The average diastolic BP of the teachers in August 2021, January 2022, and August 2022 were 91.6 mmHg, 87.3 mmHg, and 87.1 mmHg, respectively. Moreover, the average cholesterol levels of the students (148.38 mg/dL) and the teachers (190.81 mg/dL) were categorized as normal. Taken together, the health profile of the students and the teachers in Madrasah Al Ihsan is within the normal range.

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Conflict of Interest

None declared.

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Table 1. Health profile of the students

Age	Gender	Systolic BP (mmHg)	Diastolic BP (mmHg)	Blood glucose (mg/dL)	Blood cholesterol (mg/dL)	Body weight (kg)
16	F	146.5	106.5	86	144	50
16	F	123.5	82	85	142	56
16	M	118.5	80	95	131	54
17	M	128.5	94.5	107	160	60
17	M	115	76	142	150	60
17	M	101.5	65	101	158	51
17	F	118	73.5	111	153	55
17	F	105	65	90	150	48
17	F	135	83	81	152	54
17	F	124.5	78	121	145	43
17	M	106.5	70	94	156	53
17	M	117.5	66	109	140	51
17	M	107.5	64	80	144	48
17	F	127	91	76	141	73
17	F	110	75	82	130	38
17	F	125	75	72	142	56
17	F	101	63	76	142	55
17	F	107	77.5	82	138	40
17	M	97	65	60	131	45
17	M	108	60.5	72	141	48
17	F	113	76.5	74	181	48
17	F	100.5	70.5	99	151	41
17	F	169	122	74	181	69
17	M	115	74.5	118	135	49
17	F	111	71	85	149	43
17	M	136.5	75	105	151	58
17	M	171	122	81	140	54
17	M	129	89	105	119	50

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17	M	122.5	65.5	132	129	54
17	M	115	68	97	119	48
17	F	113	75	66	142	49
17	F	116.5	71.5	97	156	42
17	M	126.5	87.5	90	124	62
17	F	123.5	79	95	202	39
18	F	111.5	78	99	180	51
18	M	126.5	83	90	136	54
18	F	103.5	66	102	140	58
18	M	116	74.5	79	140	49
18	F	117	78	77	80	52
18	M	128.5	74.5	69	143	70
18	M	117.5	78	82	165	52
18	M	103	69	54	121	48
18	M	121	81	104	131	48
18	F	115	77.5	69	130	44
18	F	161	110	86	138	45
18	M	145	81	98	154	56
18	M	130.5	73	87	157	63
18	F	126	81.5	97	150	55
18	F	110	81	83	177	41
18	F	106	77.5	82	140	40
18	F	126.5	79	132	132	60
18	M	115	82	78	114	50
19	F	124	93.5	86	142	44
19	F	104.5	72.5	77	153	42

The darker shaded cells indicate a higher or lower value than normal.

Table 2. Health profiles of the teachers

Age	Sex	Systolic BP (mmHg)			Diastolic BP (mmHg)			Blood cholesterol (mg/dL)
		Aug-21	Jan-22	Aug-22	Aug-21	Jan-22	Aug-22	
23	F	122	95	103	83	67	84	196
37	F	116	110	117	80	75	80	188
37	M	150	138	136	107	100	89	233
41	F	111	100	108	80	65	59	239
42	M	127	135	143	75	95	93	197
50	F	120	115	120	85	83	83	206
52	F	130	135	128	95	93	92	169
54	M	128	128	129	88	90	79	178
60	F	192	185	185	125	125	125	195
60	F	172	140	150	98	80	87	193

The darker shaded cells indicate a higher or lower value than normal.

Figure 1. The participants were interviewed about their illness history, eating, and smoking habits while they were filling out the registration forms.

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The Rise of Artificial Intelligence in Pharmacy: Transforming Medication Management and Patient Care

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Abstract

Artificial intelligence (AI) is rapidly transforming healthcare, with significant implications for pharmacy practice. This review explores the diverse applications of AI in pharmacy, emphasizing its potential to revolutionize medication management, patient care, public health, disease management, and pharmacy workflow efficiency. AI algorithms can analyze a vast amount of patient data, allowing pharmacists to identify potential drug interactions, evaluate medication safety and effectiveness, and offer personalized treatment suggestions. In the realm of public health, AI supports disease management through epidemiological monitoring and targeted interventions. Additionally, AI-driven robotic dispensing systems and automated inventory management enhance pharmacy workflow efficiency by streamlining operations and optimizing resource allocation. Telepharmacy, further augmented by AI, is revolutionizing remote healthcare by improving accessibility, efficiency, and patient outcomes. Despite these advancements, challenges such as data privacy and potential bias in AI algorithms persist. However, the potential of AI in pharmacy is undeniable. By addressing these challenges and fostering collaboration among pharmacists, AI developers, and regulatory bodies, the future of pharmacy is poised to deliver personalized care, improved patient outcomes, and enhanced public health. This integration of AI into pharmacy practice represents a significant step toward a more effective and patient-centered approach to healthcare.

Keywords: Artificial intelligence (AI), pharmacy practice, healthcare

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Introduction

Artificial Intelligence (AI) is a field within computer science where we develop problem-solving techniques through symbolic programming. Over time, it has developed into a comprehensive science of problem-solving with extensive applications in fields such as engineering, business, and healthcare. With AI, fueled by advancements in machine learning and data analytics, we are entering another new age of automation, efficiency improvements and intelligent decision-making[1].

In recent years, AI has already shown tremendous potential in revolutionizing healthcare in ways no one could have predicted; some of which are medical record keeping, treatment preparation and system auditing. The main goal of the application fields in health is to identify whether there are links between patient outcomes and different prevention or therapy approaches. This technological advancement has led to enhanced diagnostic accuracy, more efficient workflows for healthcare providers, and significantly improved patient outcomes[2].

As compared to people, AI can accomplish some activities faster and more accurately. Pharmacists can use AI and machine learning to analyze large amounts of patient information including, but by no means limited to medical history records, lab results and even their medication profile. AI refers to intelligence that is provided so that results of clinical trials can be better in a significant manner. This allows them to determine whether a drug has potential interactions, evaluate the safety and efficacy of a medication, and deliver tailor-made recommendations on patients. The potential of AI in pharmacy practice is vast, and applications cover an array of medication management, inventory control, and patient education opportunities[3].

Significant potential is seen in AI application across many frontiers of pharmaceutical practice. In the same way, even though there is much promise in its use of AI technology, to develop it fully will still require filling research gaps. The most crucial element is comprehending the influence of AI services on financial and clinical results and fully implementing them within current pharmaceutical systems[4]. This review delves into the exciting world of AI applications in pharmacy practice. We will explore the current landscape and needs as well as outline some promising future directions for AI in this field, while also analyzing gaps in research.

Methods

To determine the scope of this narrative review, we searched PubMed, Google Scholar, and Scopus for relevant articles. We employed various search terms to locate relevant articles. which included “Artificial intelligence,” “Pharmacy practice”, “Medication Management”, “Patient Care”, “Public Health and Disease Management”, “Pharmacy Workflow and Efficiency”, and “Telepharmacy”. We reviewed the reference lists of relevant articles to identify other potentially significant papers on the subject. The journals were screened with inclusion criteria of articles related to AI in pharmacy and published in 2014-2024, as well as exclusion criteria of repository and review articles.

Results and Discussion

Medication Management and Patient Care

Pharmacists have the opportunity to utilize AI algorithms to analyze a patient’s medical history, current prescriptions and the extent of allergic reactions. This significantly reduces medication errors, improves patient safety, and prevents adverse outcomes. For instance, pharmaceutical order reviews can be

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optimized using machine learning algorithms to identify inappropriate prescriptions that require reevaluation by clinical pharmacists[5]. AI's ability to detect deviations early allows for quick intervention, reducing adverse reactions and enhancing patient safety through comprehensive medication management[4].

While pharmacist-led interventions are effective in improving medication adherence, they often involve complex processes. AI technology offers a promising solution by addressing multiple barriers to adherence[6]. AI can track patient habits, refill patterns, and medication history to identify factors leading to non-adherence, ultimately improving adherence rates and treatment outcomes[7]. Furthermore, AI is transforming pharmacy operations by automating routine tasks, allowing pharmacists to focus more on patient care. The Robotic Dispensing System in Community Pharmacies, for example, automates the selection, packaging, and labeling of medicine, enhancing accuracy and speed while freeing up pharmacists to provide direct patient care. These AI-driven advancements are poised to revolutionize pharmacy practice, promoting medication adherence, improving patient safety, and streamlining workflows for better health outcomes[8].

Another example is IBM Watson, a powerful computer that uses AI and advanced analytics to answer questions. Watson for Oncology is designed to help doctors make better decisions in cancer treatment by analyzing a patient's medical data and offering care options based on an extensive and growing network of experts. Watson draws from over 200 textbooks, 12 million text pages, and 290 medical periodicals, as well as literature and findings, giving it access to a vast reservoir of knowledge[1].

Public Health and Disease Management

AI algorithms can analyze patient data in real time as well as pharmacy dispensing records to identify patterns and likely infectious disease outbreaks. For instance, the BlueDot AI system effectively tracks outbreaks based on travel patterns and medication purchases. This continuous surveillance allows public health systems to intervene early, reducing disease spread and protecting lives[9].

Historical analysis of social media activity regarding epidemics followed by highly accurate prediction of epidemic location and timing are made possible by AI. Consider a future where AI notifies pharmacists about potential outbreaks in their locality so they could immediately advise patients, liaise with other healthcare officers from the local department of health among others. This collaboration between AI and pharmacists enhances their ability to uncover hidden trends and improve medical care[3].

Beyond that, AI can help pharmacists in addressing issues of health inequities by looking up such data as zip codes, demographics, and medical histories. By pinpointing areas with significant socioeconomic differences, AI can recommend targeted interventions. For example, AI could identify regions with high diabetes rates, leading to educational programs, free drug distribution, or improved access to care[10].

Pharmacy Workflow and Efficiency

Computerized Prescriber Order Entry (CPOE) is a system that provides a digital platform for doctors to enter and send medical orders, including those for medications, laboratory tests, admissions, radiology, and procedures, instead of using manual methods. This reduces errors from illegible handwriting and transcription mistakes. CPOE systems

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manage medication histories and electronically transmit orders to pharmacists, enhancing patient safety[11].

AI-powered robotic systems can greatly automate repetitive tasks like inventory management or medication dispensing activities. By analyzing historical data, AI can predict medication demand and optimize stock levels, helping avoid stockouts and allowing pharmacists to focus on critical tasks[6]. Pharmacist can optimize their inventory management by using artificial intelligence in analyzing historical sales data, patient demographics and seasonal trends to predict future drug demand with higher accuracy. It ensures that pharmacies have enough stock on hand to meet patient needs while minimizing the risk of expired medications. This automation streamlines pharmacy operations, reduces errors, and frees up pharmacists to focus on patient care[12].

Telepharmacy

Telepharmacy is an innovative approach that utilizes telecommunication and technology to provide remote pharmacy services, meeting the increasing demand for accessibility, convenience, and cost-effectiveness in healthcare. The integration of artificial intelligence into these systems has the potential to significantly elevate the quality of telepharmacy services, offering improved patient outcomes, especially in underserved and rural communities[13]. For instance, chatbots with natural language understanding can speed up the process of gathering patient history by asking questions and offering prompts tailored to the patient's answers. These chatbots can also identify potential diagnoses, such as adverse drug events, and record them for future reference[14].

Integrating ChatGPT into telepharmacy services offers considerable potential. ChatGPT exhibits the capability to simulate the role of a telepharmacist effectively, maintaining a professional persona while handling patient inquiries. It follows commands accurately, understands complex case details, and offers precise, mostly accurate answers to medication-related questions. Additionally, it delivers responses that are consistently clear, concise, and sufficiently comprehensive, enhancing its usefulness in virtual healthcare settings where precision and clarity are vital[15]. The summary of findings is shown in Table 1.

Challenges and Limitations

Despite numerous benefits of AI to pharmacy practice, it has some difficulties and limitations. It is crucial for these concerns to be addressed in order to ensure ethical and responsible AI implementation in pharmacy. AI algorithms rely on huge chunks of patient data. This sensitive information must always be secured through privacy and security measures at the pharmacies that handle it. Besides, regulatory frameworks cannot keep pace with the rapid development of AI technologies. Efficacious, safe and ethical use of AI in healthcare requires clear and consistent regulations. Proper regulatory frameworks must be established through collaboration between regulatory bodies, healthcare providers, and AI developers for use of AI in pharmacy[29].

Data collection biases used in training AI models have the potential to generate biased outcomes. For instance, minorities may be underrepresented by datasets created with racial bias in dataset creation, therefore, lower prediction error rate than expected may occur. If there is an underlying bias and inequality within the healthcare system, even when the AI systems are trained with correct and representative data problems can arise[30].

The next hurdle is AI development that follows data acquisition. Overfitting occurs when

the AI system learns irrelevant relationships between patient variables and outcomes. This problem arises when there are too many variables compared to the outcomes, leading to inaccurate predictions due to the use of inappropriate algorithm features. Algorithms like classification and clustering might demonstrate high accuracy with limited data, but this performance may not be reliable in real-world situations. Furthermore, one of the most difficult challenges in medical data processing is the need to combine text, numerical, image, and video data into a single algorithm[31].

Although a few barriers were noted, pharmacists showed a positive attitude toward working with AI. These emphasize the importance of creating learning programs that will enhance pharmacists' knowledge about artificial intelligence while also providing enough financial support in order to overcome the challenge of high operational costs for implementing this into practice. Technical assistance can help pharmacists get over not having sufficient AI software and technology. By doing this, community pharmacies can have better integration of AI technology hence enhancing patient care and health outcomes[32].

Conclusion

Artificial intelligence's positive influence on the pharmacy sector holds great promise for patients and pharmacists. AI tools empowered by AI can allow personalized care plans, increase or improve patients' adherence to medications and give pharmacists more time for improving patient consultations. As AI becomes more collaborative with pharmacists, it will be possible to create a better performing medical system that is more centered around the patient. However, this future needs to be approached cautiously if at all. Issues of data privacy and security issues, possibilities of biased algorithms in AI as well as dealing with legislations have to be dealt with first. There should be open channels of communication between the pharmacists, developers of this technology and regulatory bodies involved. The use of Artificial Intelligence within Pharmacy can only be ethical if carried out collectively yet effectively while prioritizing the welfare of patients in all instances.

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Conflict of Interest

None declared.

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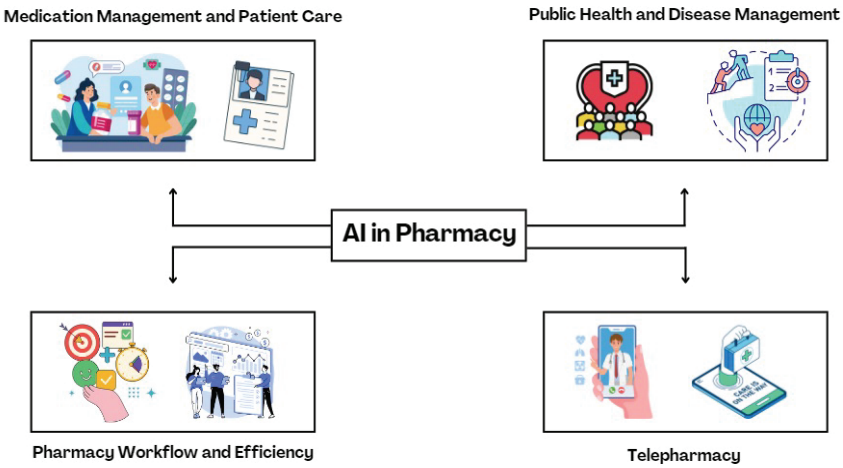

Figure 1. The Role of AI in Modern Pharmacy

Table 1. Study Characteristics and Main Findings of Implementation of AI Applications in Pharmacy Practices

Author, year	Country	Study design	Type of AI	Objectives and Main findings
Takase et al, 2022[8]	Japan	Experimental and statistical analysis	Robotic dispensing systems	This study aims to evaluate the impact of robotic dispensing systems and collaborative work with pharmacy support staff on medication dispensing. The overall rate of prevented dispensing errors significantly dropped from 0.204% to 0.044%. Likewise, the rate of unprevented dispensing errors saw a marked reduction from 0.015% to 0.002%. Errors related to incorrect drug strength and wrong medications, which pose serious health risks, were almost entirely eliminated. Moreover, the median dispensing time per prescription for pharmacists was significantly reduced, from one minute to just 23 seconds.

Blasiak et al, 2022[16]	Singapore	Prospective feasibility trial	CURATE.AI, an AI-driven platform that leverages a patient's own prospectively or longitudinally collected data to dynamically determine their optimal personalized dosing.	The objective of this study is to evaluate the feasibility of conducting prospective trials for CURATE.AI, aid in hypothesis formulation, identify potential risk factors, and support the design of these trials. On average, the prescribed dose was reduced by 20% (±13.8%) compared to the projected standard of care (SOC) dose. Among the nine patients involved, the average number of completed cycles was 3.9 (±2.2 cycles), with the longest duration being 8 cycles. Out of 40 total dosing decisions, CURATE.AI recommendations were considered in 27 cases, with 26 of those being accepted for prescription.
Momattin, et Al, 2021[17]	Saudi Arabia	Data collection	Robotic Pharmacy	This study is designed to improve efficiency, reduce medication dispensing errors, enhance patient satisfaction, and allow pharmacists more time for direct patient consultations. The average wait time decreased by 53%, patient satisfaction with pharmacy wait time increased by 20%, and overall satisfaction with pharmacy services rose by 22%. Additionally, pharmacist productivity increased by 33%. The dispensing process was error-free.

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Rodriguez-Gonzalez et al, 2019[18]	Spain	A prospective before-and-after design using disguised observation.	Robotic dispensing system	This study explores the frequency of medication dispensing errors before and after introducing a robotic original pack dispensing system in an outpatient hospital pharmacy, along with its effects on stock management quality and staff satisfaction. The medication dispensing error rate decreased from 1.31% (43 errors out of 3,284 prescriptions) to 0.63% (19 errors out of 3,004 prescriptions), leading to a relative risk reduction RRR) of 51.7%. When excluding errors from residual manual dispensing, the error rate further dropped to 0.12% (3 out of 2,496), with an RRR of 90.8%. The daily median time spent by staff on stock management was reduced by 59.3%, from 96 minutes to 39 minutes.
Thapen, 2016[19]	United Kingdom	Retrospecti-ve design	DEFENDER, a software system for outbreak detection and forecasting.	This study aims to develop and evaluate a data-driven system for early detection and forecasting of epidemics. The DEFENDER system demonstrated significant potential for early detection and forecasting of epidemics. Using symptoms along with previous case data improved the accuracy of our predictions by 37% compared to a model that only used previous case data.
Rolland et al, 2020[20]	United States and France	Retrospecti-ve design	ProMED-mail, a global online disease reporting system	This study is designed to assess the effectiveness of ProMED-mail in detecting public health emergencies of international concern. Of the undiagnosed disease events described in ProMED-mail, 6.5% (24 out of 371) were reported in the Disease Outbreak News. The median delay between the first ProMED-mail notification and the corresponding Disease Outbreak News publication was 18.5 days, with a range from -1 to 254 days.

Surya et al, 2020[21]	Global	Predictive modeling and data-driven analysis study	Bluedot, AI model that provides intelligence on infectious diseases	The objective of this study is to predict humans by spotting infectious disease outbreaks. On December 31, 2019, the Canadian health monitoring company BlueDot issued an early alert about the COVID-19 outbreak in China and its potential global spread—nine days before the World Health Organization made its public announcement. BlueDot also leveraged global air travel data to predict the cities and countries most at risk. The first locations affected by the virus were among the top 11 countries identified by BlueDot.
Puca et al, 2020[22]	Global	Descriptive epidemiolo-gical study	EpiWATCH, intelligence surveillance tool	This study aims to identify information about the number of confirmed/probable/suspected mumps cases and also the date, country, and location of outbreaks. EpiWATCH recorded 65 mumps outbreaks worldwide and detected reported mumps cases within days of news outlets releasing the information, much faster than the months it usually takes for validated sources to publish such data. EpiWATCH identified mumps outbreak data that had not been previously detected by the WHO or CDC.

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Jungreith-mayr et al, 2021[11]	Germany	Comparati-ve study	Computerized physician order entry (CPOE) system	The purpose of this study is to explore the specific impact of implementing a CPOE system in general wards of a large tertiary care hospital on the quality of prescription documentation. The overall mean prescription F-score, which measures adherence to 20 criteria, rose significantly from 57.4% ± 12.0% (based on 1,850 prescriptions) before the system was implemented to 89.8% ± 7.2% (based on 1,592 prescriptions) after im-plementation.
Segal et al, 2019[23]	Israel	Prospective study	Machine-learning based clinical decision support system	This study is designed to evaluate the accuracy, effectiveness, and practical value of medication error warnings produced by a new system that uses abnormal data detection methods. The system had a low alert burden, with warnings issued for only 0.4% of all medication orders. Of these alerts, 60% were triggered after the medication had already been administered. The alerts were found to be 85% accurate and 80% helpful, with 43% of them resulting in changes to subsequent medical orders.
Laustalot et al, 2019[24]	France	Prospective observation-nal study	Computerized physician order entry (CPOE) system	The objective of this study is to evaluate the clinical interventions made by pharmacists, particularly the acceptance of these interventions, issues related to CPOE, and their potential impact on patient safety. CPOE-related errors accounted for 14.7% of the total errors, a significant improvement compared to the 49% reported a decade earlier.

Bu et al, 2022[25]	China	Perspective based on a case study	AI-based medication consultation	The objective of this study is to establish an internet hospital pharmacy service model based on AI and to offer new insights into pharmacy services in internet hospitals during the COVID-19 pandemic. A total of 426 medication consultations were provided, with 48.83% occurring outside of regular working hours. Consequently, an AI-based medication consultation service was proposed for times when pharmacists were unavailable.
Roy et al, 2023[26]	USA	Pilot investigation using data from two Phase II clinical trials	AiCure, a computer vision-assisted mobile application, to monitor medication adherence in patients.	The purpose of this study is to enhance patient retention and the quality of clinical trial data. In one of the trials, 43% of participants were found to be less than 80% compliant with their medication regimen. The model successfully identified high-risk patients with low adherence, with the 14-day monitoring period model offering the most accurate predictions and a lower false omission rate.
Jennifer et al, 2023[27]	USA	Comparati-ve evaluation study	Chatbot focused on medication guidance	This study aims to evaluate the clinical completeness, accuracy, usefulness, and safety of responses provided by a chatbot and a medication database to common inpatient medication-use queries. The medication database answered 194 (97%) of the questions, with 88% being clinically correct, 76% sufficiently complete, 83% safe, and 81% useful compared to pharmacists' responses. In contrast, the chatbot responded to 160 (80%) of the questions, with 85% deemed clinically correct, 65% sufficiently complete, 71% safe, and 68% useful.

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Daniel et al, 202228	France	Proof-of-concept study	Chatbot using IBM's Watson API combined with a custom dictionary.	The objective of this study is to develop and implement an artificial intelligence (AI) chatbot to provide answers to questions from hospital caregivers about drugs and pharmacy organization. The chatbot received good evaluation scores, which are speed: 8.2 out of 10, usability: 8.1 out of 10, and appearance: 7.5 out of 10. Seven key themes were identified, including queries about opening hours and specific prescriptions. 70% of testers were generally satisfied with the chatbot.