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Increasing Knowledge, Attitude, and Practice in using Traditional Medicines through Pharmacist's Education and Mentoring in Mojokerto

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ABSTRACT

Background: The use of traditional medicines globally continues to increase and must be balanced with increased knowledge, attitudes, and practice in using traditional medicines through pharmacist education and mentoring.

Objectives: This research aims to determine the description of the use of traditional medicine, the level of knowledge, attitudes, and practice of the community in using it, and the influence of pharmacist education and mentoring on it.

Methods: This research design was quasi-experimental with a pre-test and post-test control group with 406 community research subjects. It involved 14 pharmacists in providing education and mentoring through WhatsApp group media by providing material according to the modules prepared. The instrument used a questionnaire developed from previous research and tested for validity and reliability. Data collection was carried out prospectively by the participant-self, and analyzed using the Wilcoxon Signed Ranks Test.

Results: This study's total number of respondents was 406, divided into 203 as the intervention group and 203 as the control group. The description of the respondent's KAP level before the intervention is in the medium category and after the intervention is in the high category based on the Wilcoxon Signed Ranks Test results at a 95% confidence level (α=0.05) in the intervention group.

Conclusion: The use of traditional medicines in the phytopharmaca class is 3%, standardized herbal medicines are 35%, and jamu is 62%. The level of knowledge, attitudes, and practice of the community in using traditional medicine in Mojokerto Regency is, on average, in the medium category. This research also shows the influence of pharmacist education and mentoring on increasing knowledge, attitudes, and practice scores from medium to high.

Keywords: attitude; education; knowledge; practice; traditional medicine

INTRODUCTION

Traditional medicine has a long history and has been widely used for health maintenance, prevention, and treatment of disease even before modern medicines like today were discovered. Views on traditional medicines and complementary products globally have experienced a consistent increase. In the WHO Global Report on Traditional and Complementary Medicine, 88% of WHO member countries acknowledged the existence of the use of traditional medicine and complementary products.[1] The level of acceptance of the use of herbal medicine as an alternative treatment in general is high (58%).[2] Reports on the result of national basic health research show that the household population that uses traditional health services is more likely to use ready-made products by

48%.[3] The prevalence of traditional medicines and complementary products in Indonesia is high. One in four respondents (24.4%) uses traditional health services or medicine. [4]

Pratiwi et al.'s research shows that public knowledge about herbal medicine products containing hazardous chemicals that can harm health still needs to be higher.[5] Only 17.6% of respondents knew about hazardous chemicals in herbal medicine products but needed help recognizing the characteristics of herbal medicine that contained dangerous chemicals, and only 8.8% of respondents knew how to choose safe traditional medicine.[5] Research on knowledge, attitudes, and utilization of traditional medicine has been carried out in communities in Debre Tabor Town, Amhara Regional State, North Central Ethiopia, with the results that the community has good knowledge about traditional medicine. However, their attitudes and practices are poor even though traditional medicine is acceptable, easy to access, and affordable.[6] Cross-sectional research among communities in Merawi Town, Northwest Ethiopia, shows that community knowledge about traditional medicine is classified as good, and the prevalence and acceptance of traditional medicine are also high.[7]

Apart from assessing the level of knowledge, attitudes, and practices (KAP) of the community towards traditional medicines, this research will also provide interventions in the form of pharmacists' education and mentoring to increase KAP in the use of traditional medicines. Increasing public knowledge and awareness as part of the drug and food control system, including traditional medicine, is very important because the community or consumers determine whether to buy and use traditional medicine products.[8] Apart from that, the increasing use of traditional medicine in society has several problems, including hoaxes circulating in society regarding traditional medicine, especially during the Covid-19 pandemic, hazardous chemicals that are deliberately mixed in traditional medicine products, which can endanger health and traditional medicine without a distribution permit which is still found based on surveillance carried out by the National Agency Drug and Food Control in 2020 and 2021.[9]

Although the use of technology to obtain various information, including regarding traditional medicine, can be easily obtained, the knowledge and use of traditional medicine still need to be evenly distributed. It is still necessary to convey information directly to the public to avoid errors in obtaining information[5]. The research was conducted at Mojokerto Regency pharmacies to know the description of the use of traditional jamu, standardized herbal medicines, and phytopharmaca, assess the level of KAP of using traditional medicines, and know the effect of providing pharmacists's education and mentoring on KAP of traditional medicine among communities.

METHODS

Research Design

The research used quasi-experimental research with pre-test and post-test design using a control group by measuring KAP using traditional medicine. The research was conducted from April to July 2022 among community users of pharmaceutical services at Mojokerto Regency pharmacies.

Population and sample

The population in this study was people in Mojokerto Regency. The number of respondents in this study was calculated based on the prevalence of traditional medicine use of 48%. Z = 1.94 is a table value with a confidence level of 95% with e (margin of error) 5%. Using the formula $n = Z^2P (1-P)/e^2$, the minimum sample size is 376. The number of respondents involved in this research was 406. Sampling was carried out at simple random. The inclusion criteria for respondents in this study are people living in Mojokerto Regency who use pharmaceutical services at pharmacies, adults aged 18 years and over who can read, write, and communicate well, who use or not use traditional medicines and in the future, it is possible to use traditional medicines and those who willing to contribute to this research by filling out informed consent. The exclusion criteria in this study were people who decided not to use traditional medicine currently and in the future, pharmacists, and pharmacist assistants. This research also involved pharmacists as providers of education and mentoring with the criteria of being the pharmacist in charge of the pharmacy as well as the owner of the pharmacy facility, providing traditional medicine information products and services.

Control and Intervention Groups

In this study, there were control and intervention groups, the respondents have a chance to choose where they are belong to which group. The intervention group received pharmacist education and mentoring. The intervention was carried out for one month using learning media and discussions via WhatsApp group. In this

stage, it is hoped that respondents will actively participate in all the material and discussions provided. The material provided by the pharmacist is from the module that has been prepared. Material consist the definition of traditional medicines, classification of traditional medicines, dosage forms of traditional medicines, identification of traditional medicines through labels, distribution permits for traditional medicines, awareness of the existence of counterfeit traditional medicines and without distribution permits, how to choose and use traditional medicines, awareness of the presence of hazardous chemicals in traditional medicine and side effects, an application to see the guarantee of the safety of traditional medicine and awareness of hoax traditional medicine information on the internet media.

Instruments and data collection

The instrument used is a questionnaire developed from previous research.[5,10,11] The questionnaire developed consists of 28 question items which are divided into three domains namely the knowledge domain consists of 15 Question items that have answer options "True," "False," and "Do not know," the attitude domain consists of 7 statements with 5 point Likert scale response options starting from "Strongly Disagree" to "Strongly Agree," the practice domain consists of 6 statements with a 5-point Likert scale response option ranging from always, often, sometimes, rarely to never. Apart from that, this questionnaire also has an initial section which concerns data on the sociodemographic characteristics of the respondents. Validity and reliability tests were carried out by distributing questionnaires to 30 respondents outside the research respondents. The results of the validity test in the KAP domains show that each question/statement is valid, with corrected item-total correlation > r table, namely 0.361 with a confidence level of 95%, and reliability test results for the KAP domains obtained a Cronbach's alpha value > 0.6. Data collection was carried out prospectively, starting with all respondents filling out a questionnaire (pre-test). In the intervention group, they participated in pharmacist education and mentoring. After that, respondents filled out the final questionnaire (post-test).

Data analysis

The intervention and control groups assessment was the community's KAP level in using traditional medicine. Determining the level of KAP is divided into three categories: the excellent/high category, the medium/fair category, and the poor/low category. How to determine the categorization using the guidelines contained in Table I.[12]

Descriptive statistical analysis was carried out to describe the use of traditional medicine and the level of KAP, and the Wilcoxon Signed Ranks Test statistical test was used to see differences in the level of KAP in each group using SPSS for Windows Version 25.

RESULTS AND DISCUSSIONS

This study's total number of respondents was 406, divided into 203 as the intervention group and 203 as the control group. The sociodemographic characteristics of the respondents can be seen in Table II. Based on this table shows that the respondents in this study were spread across the age range of fewer than 25 years as much as 29.6%, 26 - 44 years, as much as 30%, 35 - 44 years, as much as 25.4%, 45 – 54 years as much as 11.3% and over 55 years as much as 3.7%. The educational level of respondents in this study varied from the lowest elementary school/equivalent to the highest with postgraduate education. Most of the respondents in this study (51.5%) had completed senior high school/equivalent education. Most respondents work in the private sector (64.3%), with the highest income level being less than 3 million rupiah per month (62.6%). People's KAP towards an object is influenced by factors including education, age, and occupation/income level.[13–15]

Traditional medicinal products in Indonesia circulating in pharmacies are classified into jamu, standardized herbal medicine, and phytopharmaca [16] From observing data in pharmacies in this study, the use of traditional Indonesian medicines based on their classification can be seen in Figure 1. Only 3% of phytopharmaca products, 35% of standardized herbal medicine products, and 62% of jamu are used by the community in Mojokerto Regency. The most widely used phytopharmaca are preparations with indications to restore the immune system, while standardized herbal medicines and jamu are preparations for symptoms of colds. The use of phytopharmaca still needs to be improved. The limitations in the use of phytopharmaca are in line with research conducted by Sari Dewi et al., which produced data on the use of phytopharmaceuticals of 4.17%, much more than standard herbal medicinal products of 43.45% and herbal medicines of 52.38%.[17] The limited use of phytopharmaca by the community is caused by several factors, including the fact that the number of phytopharmaca products registered at National Agency Drug and Food Control is much smaller, only 25 items,

Table I. Details of KAP Assessment Levels (Azwar, 2012)

	Knowledge	Attitude	Practice
Number of questions	15	7	6
Minimum score/percentage	0 / 0%	7 / 20%	6 / 20%
Maximum score/percentage	15 / 100%	35 / 100%	30 / 100%
Low category (%)	< 33,3	< 46,7	< 46,7
Medium category (%)	33,3 – 66,7	46,7 – 66,7	46,7 – 66,7
High category (%)	>66,7	73,3	73,3

compared to standardized herbal medicine and jamu.[18,19] Phytopharmaca in Indonesia must prove their safety and efficacy through clinical trials on humans, which requires high costs and a long time. This is a factor in the slow pace of phytopharmaca in Indonesia.[20] Research and development of phytopharmaca are still quite popular, but there are obstacles to standardizing natural ingredients and limited research funds. [21]

The community's level of KAP in using traditional medicines on the market was assessed by filling out validated questionnaires. The respondents' KAP levels are shown in Figure 2. Description of the level of community knowledge in using traditional medicines in pharmacies in Mojokerto Regency: Most respondents (48.8%) have a medium level of knowledge, 42.6% have a high level of knowledge, and a small portion (8.6%) have a low level of knowledge. The results of this research are in line with research conducted by Zulkarni et al., which concluded that the majority (65%) of the people of Sapiran Village, Aur Birugo Tigo Baleh District, Bukittingi City, have a sufficient level of knowledge about traditional medicine.[22] An illustration of the level of attitude of respondents regarding the use of traditional medicine in pharmacies in Mojokerto Regency: 38.4% of respondents had a good attitude, 58.4% had a moderate attitude, and only 3.2% of respondents had a bad attitude toward the use of traditional medicine. Most respondents (59.9%) have good practices in using traditional medicine. As many as 29.8% had moderate practice, and 10.3% had poor practice regarding traditional medicine. The level of community KAP towards an object related to health, including the use of traditional medicine, can increase or decrease their health status. A low KAP level tends to reduce health status, and conversely, a high KAP level can improve health status.[23] Research conducted by Yanti et al., also shows that good knowledge, positive attitudes, and good behavior can also overcome health problems related to preventing disease transmission during the COVID-19 pandemic in Indonesia.[24] High public awareness of choosing traditional medicinal products that meet the requirements for safety, quality, and efficacy is one of the factors in avoiding material loss or even the threat of danger to life due to the continued circulation of traditional medicines that contain hazardous chemicals[25]. Good practice in choosing traditional medicine or herbal supplements based on the Guidelines for the Use of Herbs and Health Supplements in Facing COVID-19 19, issued by the National Agency Drug and Food Control, is to apply the "Cek KLIK" principle. The principle of "Cek KLIK" is to check the packaging, label, distribution permit, and product expiration before using it.[26]

Increased KAP before and after being given pharmacist education and mentoring can be seen in Table III, IV, and V. Based on the data, intervention in the form of pharmacist education and mentoring influenced increasing KAP of using traditional medicine from the medium category to the high category in the intervention group (significance Value (2-tailed) < 0.05) and there was no increase in the control group. One of the responsibilities of a community pharmacist is to provide the best information about the use of traditional medicines, provide information on potential side effects, drug interactions, and the risk of harm from using traditional medicines, provide professional services about the use of traditional medicines in self-medication services for OTC medicines. This shows that pharmacists are professionals and experts in traditional medicine.[27,28]

Providing education and mentoring to respondents is supported by facilities and infrastructure such as learning modules and pictures in booklets to facilitate respondents' understanding. These infrastructure facilities are a fact that can be linked to increased KAP in the use of traditional medicine. Research in Saudi Arabia regarding the effectiveness of using booklets as an educational medium by providing Patient Discharge Information booklets to patients who have undergone cesarean section and the results of the research show an increase in KAP of experimental participants regarding diagnosis, medical procedures, treatment, lifestyle, eating patterns, and psychological health. In contrast, the control group in this study showed a decrease in KAP in control participants from pre-test to post-test scores regarding medical procedures, medication, signs and symptoms of awareness, lifestyle, eating patterns, and psychological health[29]. Other research shows that the use of illustrated pocketbooks has been proven to increase the knowledge of patients and supervisors about taking medication from pulmonary tuberculosis patients in the Jember area, Indonesia[30]. Another study aimed to

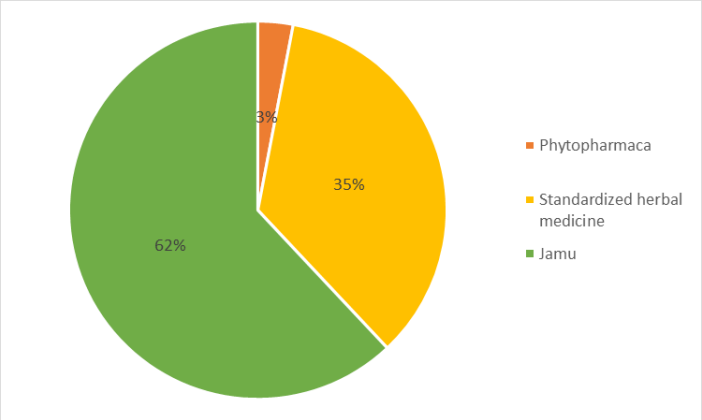

Figure 1. Use of Traditional Medicine Based on Classification

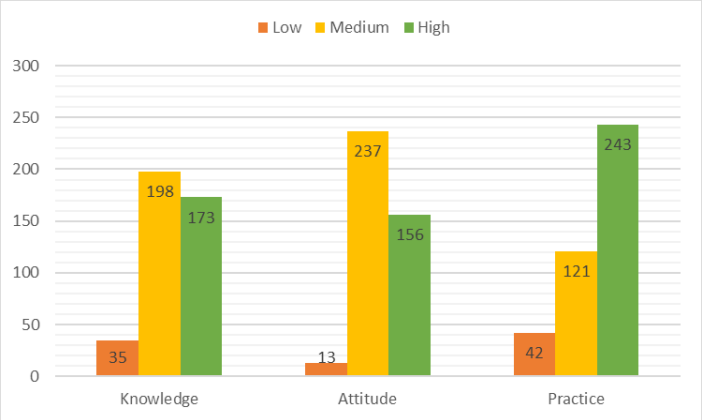

Figure 2. Categories of Level of KAP

Table II. Sociodemographic characteristics of respondents (n=406)

Sociodemographic characteristics		Number of persons (%)
Age of respondent (years)	< 25	120 (29,6)
	26 – 34	122 (30,0)
	35 – 44	103 (25,4)
	45 – 54	46 (11,3)
	> 55	15 (3,7)
Education of respondent	Elementary School/Equivalent	11 (2,7)
	Junior High School/ Equivalent	23 (5,7)
	Senior High School/ Equivalent	209 (51,5)
	Diploma	52 (12,8)
	Bachelor	101 (24,9)
	Postgraduate	10 (2,5)
Occupation of respondent	Government employee	26 (6,4)
	Private sector	261 (64,3)
	Self-employed	59 (14,5)
	Retired	2 (0,5)
	Unemployed / Housewife	58 (14,3)
Monthly income (million rupiah)	< 3	254 (62,6)
	3 – 5	126 (31,0)
	6 – 10	21 (5,2)
	>10	5 (1,2)

Table III. Pre-test and Post-test Knowledge of Control and Intervention Groups

Knowledge Variable	Control Groups		Intervention Groups	
	Pre-test	Post-test	Pre-test	Post-test
Average score	8,81	8,87	8,58	11,86
Standard deviation	3,128	3,154	2,981	2,528
Average score percentage	58,73	59,13	57,20	79,07
Level	Sedang	Sedang	Sedang	Tinggi
significance value (p)	0,741		0,000	

Table IV. Pre-test and Post-test Attitudes of Control and Intervention Groups

Attitude Variable	Control Groups		Intervention Groups	
	Pre-test	Post-test	Pre-test	Post-test
Average score	24,50	24,26	24,44	26,89
Standard deviation	3,781	4,119	3,674	3,267
Average score percentage	70,00	69,31	69,83	76,83
Level	Sedang	Sedang	Sedang	Tinggi
significance value (p)	0,205		0,000	

Table V. Pre-test and Post-test Practice Control and Intervention Groups

Practice Variable	Control Groups		Intervention Groups	
	Pre-test	Post-test	Pre-test	Post-test
Average score	21,21	21,45	21,50	25,51
Standard deviation	4,975	4,378	4,783	3,421
Average score percentage	70,70	71,50	71,67	85,03
Level	Sedang	Sedang	Sedang	Tinggi
significance value (p)	0,172		0,000	

measure the effectiveness of knowledge, attitude, and practice (KAP)-based rehabilitation education in KAP patients with intervertebral disc herniation, resulting in an increase in KAP after being given health education, thereby encouraging good rehabilitation behavior and changing KAP patients.[31]

According to Alonzo, and Khoso et al., there are four dimensions of health behavior.[32] The first is preventive health behavior, preventing health problems and distancing oneself from health hazards. This action includes selecting and using traditional medicines whose safety and efficacy have been proven empirically and scientifically. The second dimension of health behavior is detective health behavior. In this dimension, the act of obtaining traditional medicine products through official places, one of which is a pharmacy, and carrying out the "Cek KLIK" action before deciding to use traditional medicines circulating on the market. The principle of "Cek KLIK" is checking packaging, labels, distribution permits, and expiration. The distribution permit approval as a guarantee of safety and efficacy can be done via the "BPOM Mobile" application. The third dimension of health behavior is health promotion. This dimension is almost the same as the first dimension. However, it is aimed more at improving the health status of individuals using traditional medicinal products to maintain health or improve the body's immune system. Finally, the fourth is Health Protector. By increasing KAP in using traditional medicines, it is hoped that individuals in the community can protect themselves and their families from health problems related to traditional medicines containing hazardous chemicals, traditional medicines without distribution permit approval, or other problems.

The results of the research can provide an evaluation of the vital role of pharmacists in providing education and mentoring to the community in using traditional medicines on the market so that they can increase KAP regarding traditional medicines and improve people's behavior in using traditional medicines to meet the requirements of safety, quality, and efficacy in efforts to improve the level of public health. Community pharmacists have essential responsibilities, one of which is providing the best information about the use of traditional medicines, providing information on potential side effects, drug interactions, and the risk of harm from using traditional medicines, providing professional services about the use of traditional medicines in self-medication services for OTC medicines.[27,28] The limitations of this research are not analyzing the relationship

between sociodemographic and KAP of using traditional medicines, using the module as an educational guide but not examining how the module influences increasing KAP of using traditional medicines as well as educational and mentoring methods via WhatsApp group media cannot ensure that all respondents actively follow all the material provided in education and mentoring.

CONCLUSION

Communities in Mojokerto Regency use 3% of the phytopharmaca, 35% of standardized herbal medicines, and 62% of jamu. The level of knowledge, attitudes, and practices of the community in using traditional medicine in Mojokerto Regency is, on average, in the medium category. This research also shows that there is an influence of pharmacist education and mentoring on increasing knowledge, attitude, and practice scores from the medium to high category in the intervention group.

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STATEMENT OF ETHICS

This research has undergone ethics testing at Dr. Moewardi Hospital Surakarta with number 952/X/HREC/2021.

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Ethylene Glycol Toxicity and Its Therapy Management: A Literature Review

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ABSTRACT

Background: Ethylene glycol (EG) is an antifreeze substance commonly used as an additive for syrup preparations. One of the detrimental effects caused by EG toxicity is acute renal failure (ARF) and death, assuming therapy and management are delayed. Presently, there are limited studies on toxicity of EG and therapy. Therefore, this study aimed to provide an overview of EG toxicity levels, clinical manifestations, arising reactions, and therapy management methods.

Objectives: A narrative review design was employed with data collected from PubMed and Google Scholar. The strategy used keywords such as “ethylene glycol toxicity” and "acute renal" with the assistance of Boolean operators including AND and OR.

Methods: The result showed that the minimum EG level for toxicity was at 22 mg/dL, followed by metabolic acidosis with an increased anion gap (>10mmol/L). Based on case reports from one experimental study, the clinical manifestations of patients experiencing EG poisoning included decreased consciousness, tachycardia, and coma, with ARF occurring after 24-72 hours.

Results: Write study findings in this section.

Conclusion: EG poisoning could cause kidney damage in the form of ARF and lead to death, assuming therapy was delayed. Presently, the most effective therapy for EG poisoning was fomepizole.

Keywords: ethylene glycol, renal failure, therapy, toxicity

INTRODUCTION

The hazards associated with Ethylene Glycol (EG) is widely discussed among stakeholders, including the public, healthcare professionals, pharmaceutical industries, and the Indonesian government.[1] In addition, it is extensively used as radiator fluids and brake oil.[2] World Health Organization (WHO) had officially reported cases of EG poisoning in Gambia, particularly affecting children who experienced toxic effects such as Acute Renal Failure (ARF), leading to death. According to a report dated October 5, 2022, WHO confirmed the deaths of 66 children in Gambia due to the use of contaminated syrup preparations.[3] After analysis, it was discovered that the cause of death, resulting in ARF, was contamination with EG and Diethylene Glycol (DEG) detected in the syrup preparations. The local Drug Regulatory Authority identified 4 syrup preparations suspected of being contaminated with EG and DEG.[3] Based on this case report, pediatric patients suffering from ARF had a history of using syrup preparations containing EG or DEG. Currently, there is no reported evidence ARF related to EG, leading to the need for comprehensive studies on EG.

In theory, EG is not recommended for human consumption due to toxic properties, sweet taste, and antifreeze characteristics. This chemical compound is often used as an additive in household fluids.[4] Syrup preparations suspected to contain EG or DEG may originate from common additives such as propylene, polyethylene glycol, sorbitol, and glycerine or glycerol.[6]

The relationship between EG and ARF can be anticipated based on toxicity mechanism. Preliminary studies stated that direct quantitative testing was the most accurate method for detecting EG poisoning. Due to limited resources and technology, conducting a comprehensive toxicity examination in clinical laboratories.[5] is impractical. In addition, the literature on EG toxicity remains limited. This present literature review addresses

scientific inquiries regarding EG toxicity levels, mechanisms, associated effects, and therapeutic management methods.

METHODS

Study design

This study adopted a narrative review method.

Search strategy

Literature was searched from PubMed and Google Scholar using keywords such as EG toxicity and acute renal, with Boolean operators, namely AND and OR. The focus is on studies related to EG toxicity.

Eligibility criteria

The inclusion criteria comprised case studies, pharmacological tests, or observational investigations addressing scientific inquiries about EG toxicity levels, mechanisms, clinical symptoms or manifestations, and therapeutic management methods. However, the exclusion criteria included duplicate articles, non-case reports, and experimental studies. The search was not constrained by publication year due to the scarcity of relevant studies meeting these criteria. The selection process included adhering to specific inclusion criteria and mapping studies by sorting and interpreting qualitative and quantitative data while categorizing materials based on issues and titles.

Data Extraction

Data was extracted from eligible studies, comprising information such as authorship, study type (observational or experimental), and objectives. The main aim of this scientific study is to provide a comprehensive overview of EG toxicity, clinical conditions, and appropriate therapeutic management methods.

Data Analysis

The results from the narrative synthesis are shown in Figure 1, providing an overview of the included studies.

RESULTS AND DISCUSSION

EG affects individuals differently, potentially leading to central nervous system depression, cardiorespiratory instability, and renal failure, all of which can be fatal without proper management.[4-6] EG poisoning can result in severe consequences such as metabolic disturbances, morbidity, or death, particularly when diagnosis is delayed. In general, patients require hospitalization and prolonged intensive therapy.[7,8]

EG metabolites, including metabolic disturbances and acidosis characterized by an increased anion gap, induce toxic effects. The formation and deposition of Calcium Oxalate Crystals (COC) causes tubular necrosis, resulting in ARF.[9] Emergency conditions such as ARF typically occur in 24 to 72 hours after EG ingestion. Surviving patients may experience the following symptoms: pelvic pain, haematuria, proteinuria, and oliguria. Recovery usually occurs in several weeks.[10] as observed in reported cases of EG poisoning in children from Gambia.

Toxicity mechanism of EG includes the binding of ionized calcium (iCa) with oxalic acid, resulting in the formation of COC stored in various organs, causing damage to body parts.[11] While the severity of acidosis is closely associated with EG toxicity, it remains unclear whether there is an additive correlation between low iCa levels, the severity of poisoning, and the development of complications such as ARF and death. A previous study reported no correlation between iCa and patients' blood pH. There is no relationship between iCa and subsequent consequences such as organ damage, morbidity, and mortality.[12]

EG Toxicity Levels

When EG levels exceed a certain threshold value, it induces harmful effects. Literature reviews from 2004 onwards have documented EG toxicity levels ranging from 22 to 706 mg/dL, as shown in Table I. The tolerance level or safe threshold for EG in syrup preparations was established at 0.5 mg/kgBW per day.[13] The lowest EG level causing toxic effects is reportedly 22 mg/dL.[14] Meanwhile, another source stated that toxic dose of EG was 0.1 ml/kg (with solution purity of 95%) or 1 to 2 ml/kg (~1500 mg/kg), with severe toxicity occurring at levels >0.5 g/L.[6]

Based on the 4 referenced case studies, EG levels in the blood and anion gap are the main parameters to assess the severity of EG toxicity. Toxic EG level, estimated at approximately 1 L/kg, equals twice EG distribution

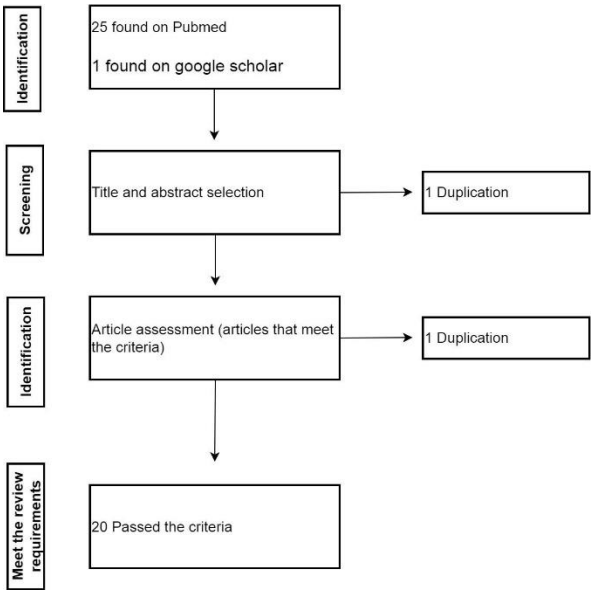

Figure 1. Flow diagram and narrative review

Table I. EG Toxicity Levels Based on Literature Review

No.	Authors (Year)	Study Method/Subject	EG levels and anion gap in cases
1	Rosen (2021)	Case report of a 52-year-old female patient.	EG level in blood: 22 mg/dL Anion gap: >43 mmol/L
2	Ahmad (2021)	Case presentation of a 50-year-old female patient.	EG level in blood: 64 mg/L Anion gap: 21 mmol/L
3	Cox and Phillips (2004)	Case report of a 16 and 59-year-old boy and woman, respectively.	EG level in blood Case 1: 163 mg/dL Case 2: 511 mg/dL Anion gap Case 1: 35 mmol/L Case 2: 32 mmol/L
4	Velez (2007)	Case report of a 33-year-old man.	EG level in blood: 706 mg/dL Anion gap: 10 mmol/L

volume, ranging from 0.5 to 0.8 L/kg. The anion gap measurements ranged from 10 to 43 mmol/L in these cases. Although the normal anion gap ranges from 12 to 16 mmol/L, instances of EG toxicity with an anion gap of 10 mmol/L have been observed. This implied that high EG levels or anion gap exceeding the normal limit served as parameters for EG toxicity requiring therapeutic intervention.

The American Clinical Toxicology Practice Guidelines state that the threshold for EG level causing toxic effects is 20 mg/dL, or it can also be measured in osmol units at 10 mOsm/L.[15] These levels are usually determined after confirming EG poisoning in the patient.[15,16] The extent of EG consumption directly influences the observed toxicity levels.[17] Furthermore, the time since ingestion, specific EG formulations, and individual patient factors such as body distribution and metabolism can also affect EG level examinations.

Mechanism of EG Toxicity

The literature review stated that EG do not directly cause toxicity, rather the metabolites induce fatal effects ranging from ARF to death.[9] EG metabolism mainly occurs in the liver, where alcohol dehydrogenase (ADH) converts it to glycolaldehyde. Subsequently, aldehyde dehydrogenase (ALDH) transforms glycolaldehyde into glycolate. The glycolate is further converted into glyoxylic acid, which, is metabolized by lactate dehydrogenase (LDH-5) into oxalate, the main compound responsible for EG toxicity.[14,9]

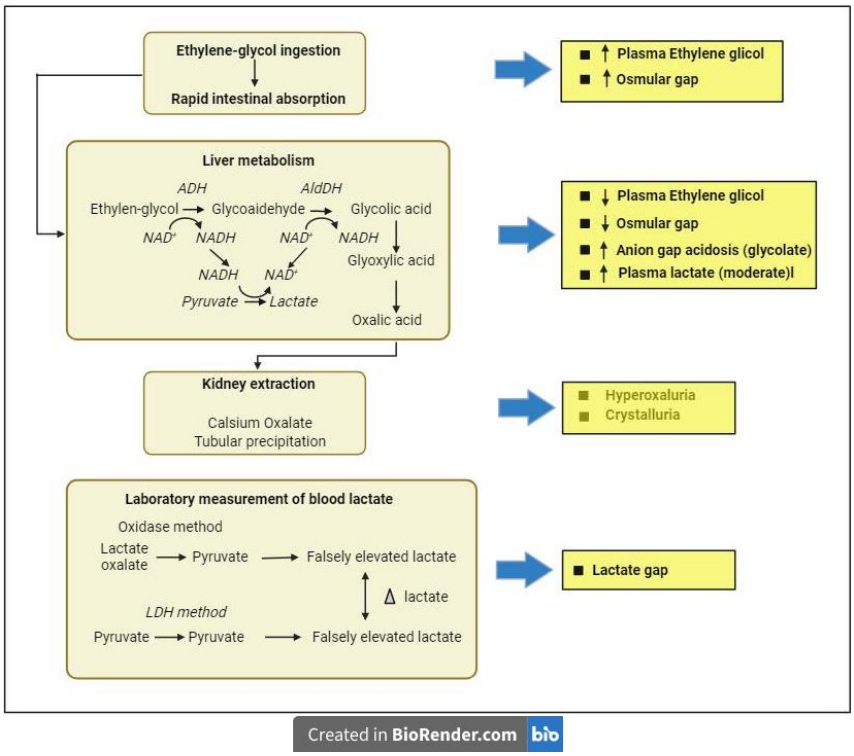

Figure 2. Mechanism of EG Toxicity

EG is rapidly absorbed in the digestive system and is further subjected to liver metabolism through ALDH, producing glycolic acid. This process affects the anion gap due to the presence of the glycolate anion, thereby reducing NAD+ to NADH. Furthermore, NADH is re-oxidized to NAD+, generating lactic acid.[6,15] ADH metabolizes EG absorbed by the digestive system into 4 toxic substances, namely glycoaldehyde, glycolate, glyoxylate, and oxalate.[18,8] Finally, EG metabolism in the liver produces oxalic acid, which contributes to the formation of COC in the kidneys.[12] These COC deposits tend to affect various systems, as follows:

Digestive system

EG causes gastric irritation due to calcium oxalate deposition on the intestinal mucosa.[15]

Central nervous system

EG induces central nervous system depression, which can increase from unresponsive sleep to coma.[15,10]

Renal system

EG metabolites contribute to reversible renal failure, characterized by oliguria or even anuria. The deposition of COC in the proximal tubular epithelium causes renal failure.[15,10] This phenomenon has also been observed in cattle, where kidney surgery showed crystal deposits.[19]

Cardiovascular system

The autopsy results showed the presence of calcium oxalate deposits in the heart.[15,10]

Clinical Manifestations of EG Toxicity

EG can lead to various symptoms and prognoses, as shown in Table II. Literature searches showed significant blood chemistry results in EG-poisoned patients, namely (1) heightened blood potassium, (2) decreased blood CO_2, (3) increased creatinine levels, elevated anion gap, and (4) acidic pH (<7.3). Patients may also show symptoms such as decreased consciousness level, metabolic acidosis, and tachycardia. Laboratory tests often show increased serum osmolality, acidic arterial pH (<7.3), anion gap >17, and bicarbonate value <20.

EG affects the central nervous system, and this is detected by the following symptoms, namely confusion, ataxia, hallucinations, slurred speech, and coma. The most severe effects occurred 6 to 12 hours after EG

Table II. Symptoms and Prognoses of EG Poisoning Based on Literature Review

Authors	Symptoms	Prognoses
Song (2017)	Reduced consciousness, pulse and respiratory rates of 98 beats and 30 breaths per minute, respectively, proteinuria, microscopic hematuria. Tachycardia with a heart rate of 134 beats per minute.	The patient experienced a fainting episode, and ARF improved after 23 days.
Silva (2018)	Feeling drowsy, headache, unconsciousness, heart rate 100 beats per minute, blood pressure 130/70 mmHg, reduced urine output, pH 7.08, lactate level 13.9 mmol/L.	The patient gradually improved after 4 days of therapy with normal creatinine levels.
Velez (2007)	Depression and anxiety, blood pressure 132/87 mmHg, heart and respiratory rates 95 beats, and 18 breaths per minute, respectively, oxygen level 96%, still responsive.	The patient did not experience ARF and was discharged on day 4.
Cox (2004) Case I	Reduced consciousness, agonal breathing, heart rate 114 beats per minute, blood pressure 146/76 mmHg, tachycardic heart.	The patient improved.
Case II	Drowsy, responsive to stimuli, heart rate 87 beats per minute, blood pressure 127/88 mmHg, respiratory rate 24 breaths per minute.	
Scaalley (2002)	Decreased consciousness, but still responsive to stimuli, heart and respiratory rates 116 beats, and 28 breaths per minute, blood pressure 158/80 mmHg, oxygen level 99%.	N/A
Rosen (2021)	Decreased consciousness, unresponsive to stimuli. Bradycardia and cessation of pulse, CPR was performed, followed by renal function replacement (CRRT). Severe liver shock, renal failure, and respiratory injury.	The patient was discharged after therapy for 85 days.

poisoning.[8] Preliminary studies also stated that calves exposed to EG poisoning showed central nervous system disturbances such as stereotyped behavior, depression, paralysis, and seizures. Chemical laboratory tests commonly detected signs of azotemia or kidney function decline, observed through microscopic evidence of tubular necrosis.[19] Another study focused on the brain stated that EG poisoning caused bilateral symmetric hyperintensity in the basal ganglia, thalamus, and brainstem.[20]

Management of EG Toxicity

Based on the literature review, the recommended initial therapy for EG toxicity included the administration of fomepizole and sodium bicarbonate, as shown in Table III. This method was designed to address the mechanism of toxicity and prognoses resulting from the rapid absorption of EG in the digestive tract. Peak EG levels were observed in the first 1 to 4 hours after ingestion, leading to the onset of ARF in 24 to 72 hours.

Several studies stated the critical need for rapid-action therapy through intravenous injection in cases of EG toxicity. Therapy protocols commonly included administering antidotes to expedite elimination as well as bicarbonate therapy aimed at normalizing pH and anion gap levels. Patients with severe toxicity are diagnosed with significant EG and lactate levels or anion gap values.

Fomepizole is the main antidote therapy for EG poisoning, and it functions by inhibiting ADH enzymes secreted in the liver during EG metabolism. The inhibition of EG metabolism prevents the formation of toxic metabolites. Fomepizole antidote therapy should start when EG levels exceed 20 to 25 mg/dL or metabolic acidosis is present (plasma bicarbonate <15 mmol/L). The initial dose of fomepizole is 15 mg/kgBW, followed by maintenance therapy of 10 mg/kgBW every 12 hours for a minimum of 4 times for patients without hemodialysis or every 6 hours for those with hemodialysis until normal pH is reached.[6] According to EG toxicity management guidelines, when the standard therapy fails, fomepizole may be continued at 15 mg/kg every 12 hours until acidosis is resolved, symptoms disappear, and EG levels are normalized.[21] Additional therapy includes intravenous thiamine and pyridoxine 100 mg and 50 mg every 12 hours and 6 hours. In cases where fomepizole is unavailable, ethanol may be administered to prevent EG metabolism into oxalic acid.[6] However, due to the significant side effects of ethanol, it should be considered as a last resort in therapy.

Table III. Management of EG Toxicity Based on Literature Review

Authors	Management	Therapy	Prognoses
Song (2017)	Fluid replacement (NaCl)	Sodium bicarbonate, thiamine (initial therapy). Fomepizole was administered at 15 mg/kg i.v, then 10 mg/kg, 4 doses every 12 hours.	The condition of the patient deteriorated, and this eventually led to a coma.
	Renal replacement therapy (RRT)		The patient still experienced ARF.
	Hemodialysis		On day 23, the patient started to improve and was discharged.
Moore (2008)	Fluid replacement		The patient returned to normal after 36 hours of management.
	Hemodialysis Respiratory assistance		
Velez (2007)	Hemodialysis	Given fomepizole at 15 mg/kg i.v. after 4 hours of EG ingestion. Continued with 10 mg/kg, for a total of 8 doses every 12 hours (4 doses at 15 mg/kg, and 10 mg/kg).	The patient did not experience ARF and was discharged on day 4.
Cox (2004) Case I		Administered 80g of activated charcoal sodium bicarbonate i.v. and 800 mg of fomepizole i.v.	The patient improved.
	Hemodialysis for 6 hours	Fomepizole was administered at 15 mg/kg i.v, then 10 mg/kg every 12 hour interval for 4 doses during dialysis. For 2 days, thiamine 100 mg i.v, and pyridoxine 100 mg and 50 mg, respectively i.v every 6 hours.	
Case II	Administration of NaCl fluid	Sodium bicarbonate i.v.	
		Fomepizole was administered at 15 mg/kg i.v, then 10 mg/kg every 12 hour interval for 4 doses during dialysis.	
	Hemodialysis for 6 hours	Thiamine and pyridoxine 100 mg and 50 mg i.v every 12 hours, and 6 hours.	The patient improved on day 8 and was discharged.
Scalley (2002)	In the first hour, administration of activated charcoal	Fomepizole for standard therapy: First dose at 15 mg/kg, administered every 6 hour Subsequent doses 10 mg/kg every 12 hour interval for 4 doses.	
Rosen (2021)	Clinical suspicion of alcohol poisoning, the patient received resuscitation fluid	Start with administration of sodium bicarbonate, fomepizole, thiamine, and pyridoxine.	
	Hemodialysis		

because EG entering the bloodstream with hepatic metabolism into oxalic acid. The metabolism of oxalic acid in the liver then led to the formation of COC in the kidneys, contributing to ARF. Increased oxalic acid levels trigger metabolic acidosis in patients, leading to compensatory respiratory alkalosis characterized by hyperventilation and tachycardia, which progresses to decreased consciousness. Acidic pH and an increased anion gap are important parameters for initial management, including using sodium bicarbonate, an alkaline solution. Additionally, patients diagnosed or identified with severe EG poisoning require fluid replacement and hemodialysis. Renal replacement therapy (RRT) may be recommended when patients with more severe conditions fail to respond to standard therapy.

CONCLUSION

In conclusion, EG metabolites caused toxic effects and symptoms, including disturbances in the central nervous system, metabolic acidosis, anion gap, and COC formation. Based on the literature review, the minimum EG level that caused toxic symptoms was 22 mg/dL with an anion gap value > 10 mmol/L. EG poisoning could lead to kidney damage (ARF) and eventually death, assuming not promptly and correctly treated. The most effective management of EG poisoning was fomepizole antidote therapy, which could be combined with palliative measures such as sodium bicarbonate, normal saline, and hemodialysis adjusted to the existing clinical manifestations.

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CONFLICT OF INTEREST

We don’t have conflicts of interest or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interests and expert testimony or patent licensing arrangements), or non-financial interests such as personal or professional relationships, affiliations, knowledge or beliefs in the subject matter or materials discussed in this manuscript

STATEMENT OF ETHICS

None

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Analysis of Clinical Outcomes Based on Demographic Characteristics of Patients with Type 2 Diabetes Mellitus

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ABSTRACT
Background: Diabetes is one of the top 10 causes of death worldwide. Many factors increase the risk of mortality and morbidity in patients with diabetes such as age, sex, BMI, educational attainment, and marital status.
Objectives: The study aimed to analyze clinical outcomes based on patient demographics.
Methods: This method was cross-sectional and was conducted at Antapani Medika Clinic, Bandung. Inclusion criteria for this study were diabetic patients who had complete medical records, and who were receiving oral antidiabetic therapy for at least 6 months. Exclusion criteria for study were patients with diabetes who were on insulin therapy, patients with tuberculosis, and pregnant and lactating women. Data on demographic characteristics were analyzed descriptively. Chi-square and likelihood ratio tests were used to analyze differences in clinical outcomes based on therapy achievement on patient demographics.
Results: The results showed that HbA1c target levels were achieved by patients who were 65 years of age or older (68%), had a BMI in non-obese category (80.8%), had diabetes for six years or more (80.8%), were married (62.9%), attended college (68.4%), exercised 3 to 6 times per week (64.9%), did not smoke (61.9%), and had no comorbidities (65.3%). This study concludes that there is an association between BMI and duration of diabetes and achievement HbA1c target ($p<0.05$).
Conclusion: The clinical implications of this study are as a guide for health workers in Indonesia in management of diabetes so that they can provide services to patients according to the medical needs of patients.
Keywords: Clinical Outcome; Diabetes; HbA1c; Patient demographic

INTRODUCTION

Diabetes mellitus (DM) is a serious condition that occurs when blood glucose levels rise above normal levels due to the body's inability to produce enough insulin and is a global health threat.[1,2] Diabetes is one of the top 10 causes of death worldwide.[3] According to the International Diabetes Federation (IDF), the number of patients with DM will reach 643 million in 2030 and 783 million in 2045, and more than 6.7 million people between the ages of 20 and 79 years will suffer from type 2 DM. The World Health Organization (WHO) predicts that the rate of type 2 DM in Indonesia will increase to 21.3 million by 2030, and Indonesia will occupy the second position of country with the highest diabetes rate in Southeast Asia.[4] Data from the Basic Health Survey (RISKESDAS) explained the increase in DM to 8.5% in 2018, and one of the factors causing the increase in DM prevalence is obesity. The increase in central obesity increased from 25.6% to 31% in DM patients, while body weight increased from 11.5% to 13.6% in DM patients.[5]

Diabetes Mellitus (DM) can cause complications such as macrovascular disease (heart, brain, or vascular disease) and microvascular disease (eye and kidney disease), nervous system disease, or neuropathy (motor, sensory, or autonomic neuropathy).[1] In addition, diabetes increases the risk of Coronary Artery Disease (CAD)

and stroke by a factor of 2-4 times.[6] Therefore, lowering HbA1c levels is one of the main goals of therapy to prevent complications of DM.[1]

Obesity impairs insulin secretion and pancreatic beta-cell function, leading to hyperglycemia. Patients who are obese have a 14% increased risk of DM. Obesity is a risk factor for cardiovascular disease, including hyperlipidemia, hypertension, insulin resistance, endothelial dysfunction, and inflammation.[7] Research shows that diabetes is associated with metabolic risk factors such as increased BMI and lifestyle factors such as poor diet, smoking habit, and physical inactivity. An increase in BMI is associated with a 30.8% increase in mortality in patients with diabetes.[3]

In addition to obesity, another factor that contributes to the high prevalence of DM is ethnicity or culture, such as unhealthy lifestyle habits. These risk factors cause the development of DM to become increasingly worse because of the relationship with increased blood pressure, dyslipidemia, smoking habit, and obesity. The age factor influences the prevalence of DM, where with increasing age, changes occur in the anatomy and physiology of the body, resulting in a decreased life expectancy in DM patients.[7] This study is supported by a study conducted by Munganyinka et al., which explained that women are more likely to be diagnosed with diabetes. In addition, in several countries, the prevalence of diabetes increases with age, especially in patients over the age of 65 years.[8]

Another demographic factor that is responsible for the high prevalence of DM is educational attainment. Educational attainment is related to the ability to make lifestyle choices. Patients with low educational attainment tend to have unhealthy lifestyles, obesity, and increased alcohol consumption, which lead to worsening of DM. As with educational attainment, employment status influences the development of DM. Patients with a status of not having a job may have an increased risk of unhealthy lifestyles, such as lack of exercise, increased alcohol consumption and smoking, and cause worsening of the clinical outcome of DM.[7] In line with this study, the results of the study by Park et al., which examined the relationship between physical activity and the risk of atrial fibrillation in diabetes patients, explained that the group of diabetes patients who regularly did physical activity (exercise) had a low risk of Atrial Fibrillation (AF) (HR 0.91, 95%CI 0.89 – 0.94).[9]

Control of Glycemic Variability (GV) is one of the factors that have been proven to affect the psychological state of patients and quality of life of patients. So increasing GV will improve the quality of life of diabetes patients, which will ultimately affect clinical outcomes.[10] Uncontrolled clinical outcomes have an economic impact as indicated by hospital costs, especially for patients over 65 years of age, by 26% from 2012 to 2017.[11] Antapani Medika Clinic in Bandung was selected for this study because it is one of the teaching clinics in Bandung. Antapani Medika Clinic Bandung has a vision statement which is to become the leading and best family health service center of choice in West Java Province, and a mission statement which is to improve the level of public health by providing quality services at affordable costs and having professional human resources who continuously develop their competencies. Pharmaceutical services are an inseparable part of realizing this vision and mission, and outcome evaluation for diabetes patients had never been conducted at Antapani Medika Clinic in Bandung. In addition, this study provides a demographic overview in the form of age, sex, body mass index, duration of diabetes, marital status, educational attainment, exercise frequency, smoking status, and comorbidities, which can indirectly make a difference in the clinical outcome targets to be achieved. This study is expected to contribute to to science in general by providing an overview of patient demographics that influence clinical outcomes in patients with diabetes. It suggests that patient demographics should be considered in the delivery of therapy to improve outcomes. Based on the above explanation, this study aimed to analyze clinical outcomes based on demographics in type 2 diabetes patients.

METHODS

Study design and ethical approval

This study is a cross-sectional observational study with a total of 69 participants. This study was conducted at the outpatient department of Medika Antapani Clinic in Bandung from April to May 2019. Ethical approval to conduct this study was obtained from the Ethics Committee of CUCMS (Cyberjaya University College of Medical Sciences), with reference number CUCMS/CRERC/AL-ER(06/2019).

Population and samples

The sample size was calculated using the Lameshow formula with a precision level of 0.05 (5%)[12], where n is the minimum sample size required, Z is the standard value of 1.96 at the 95% confidence level, p is the population estimate (418,000 ≈ 0.04), q is 1-p (0.96), and e is the sampling error (standard value 5% or 0.05). The

number of diabetes patients in Indonesia was 10,300,000 and the number of diabetes patients in West Java was 418,000 patients, so $p = 418{,}000/10{,}300{,}000 = 0.04$ and $n = \frac{1.96^2 \times 0.04 \times 0.96}{0.05^2} = 60$. The minimum sample size in this study was 60 participants, and participants in this study were increased by 15% of the minimum number of participants to account for incomplete medical record data (69 participants). Inclusion criteria for this study were patients diagnosed with diabetes, both male and female, patients with complete medical records, and patients receiving oral antidiabetic therapy for at least 6 months. The exclusion criteria for this study were patients with diabetes who were on insulin therapy, patients with TBC, and women who were pregnant and lactating.

Study instruments

The data was collected using medical records, and who were receiving oral antidiabetic therapy for at least 6 months at the outpatient department of Medika Antapani Clinic in Bandung.

Data collection and analysis

Data collection was based on the inclusion and exclusion criteria data. Patient demographics such as age, sex, body mass index (BMI), comorbidities, educational attainment, occupation, smoking habits, marital status, and baseline HbA1c from the patient's medical record were recorded. Data were analyzed using statistical test software. The clinical outcome was categorized as achieved if the HbA1c for 6 months achieved a decrease of <7% and as not achieved if the HbA1c level for 6 months did not decrease and was ≥7%. Data on demographic characteristics were analyzed descriptively. Differences in clinical outcomes based on patient demographics were analyzed using the chi-squared and likelihood ratio tests.

RESULTS AND DISCUSSION

Patient Characteristics

Based on the data in Table I, most patients with diabetes in this study were female (71%) and less than 65 years of age (63.8%). Based on a study by Ciarambino et al., it is clear that hormones have a major impact on metabolism and inflammatory responses in women. Women have poorer metabolic control and therefore have a higher risk of developing diabetes.[13]

In line with this study, a study by Celik et al., also explained that diabetes risk factors are increasing in young women around the world because of unhealthy lifestyles, resulting in increased body weight and obesity compared to men.[14] The Korean Diabetes Association stated that the prevalence of diabetes in adults aged 30 years or older doubled from 2.23 million in 2006 to 4.94 million in 2018. The study explained that in the case of diabetes, blood glucose control is more difficult to achieve in the younger age group because of environmental factors such as smoking habits, alcohol preferences, lack of physical activity, obesity, sleep disorders, and poor dietary habits.[15] According to Palungan et al., the high incidence of diabetes in adolescents and young adults is due to puberty, insulin resistance, and deterioration of beta cell function.[16,17] Similar to this study, they explained that in adolescents and young adults, increased consumption of calorie-dense foods, and sugary drinks and decreased physical activity lead to an increased risk of diabetes.[18] The study by Kim et al., also explained that in 2014, 4.8 million people aged 30 years or older in Korea had diabetes.[19]

In this study, the highest duration of diabetes was less than 6 years (62.3%), and most patients were obese (62.3%). Obesity increases the risk of developing diabetes because obesity is an important factor in insulin resistance. In addition, duration and obesity are also associated with the risk of developing cardiovascular complications in diabetes.[20,21] This is consistent with studies explaining that the duration of diabetes is associated with progressive impairment of insulin secretion over time due to failure of beta-cell function.[22]

The predominant educational attainment among the participants in this study was high school (47.8%), with the predominant marital status was married (89.9%). Educational attainment is associated with improved biomedical and psychosocial outcomes in patients with diabetes and obesity. Patients with a high educational attainment can make decisions, self-manage disease symptoms, and in the future may help prevent complications and increase patient compliance.[23] Meanwhile, marital status is associated with a significant increase in body weight, thereby increasing the risk of diabetes.[24]

The frequency of exercise in this study was dominated by 3 to 6 times per week (53.6%), with most participants not having a smoking habit (91.3%). Physical activity has been associated with metabolic syndrome.[25] In contrast to this study, a study by Veridiana et al., showed that the prevalence of diabetes was highest in those

Table I. Data on Demographic Characteristics of Patients with Type 2 DM

Characteristics	Number of Patients (n=69) (%)
Age	
< 65 years old	44 (63.8)
≥ 65 years old	25 (36.2)
Sex	
Woman	49 (71)
Man	20 (29)
Body Mass Index (BMI)	
Obesity	43 (62.3)
Non-obesity	26 (37.7)
Duration of Diabetes	
< 6 Years	43 (62.3)
≥ 6 Years	26 (37.7)
Marital Status	
Married	62 (89.9)
Unmarried	7 (10.1)
Educational Attainment	
Elementary and middle school	17 (24.6)
High school	33 (47.8)
College	19 (27.6)
Frequency of *exercise*	
Once every 1–2 weeks	32 (46.4)
3–6 times per week	37 (53.6)
Smoking Status	
Smoker	6 (8.7)
Non-smoker	63 (91.3)
Comorbidities	
With comorbidities	20 (29)
Without comorbidities	49 (71)

with light physical activity (3.1%) and low in those with heavy physical activity (0.9%), indicating a relationship between physical activity and the incidence of diabetes.[26] Meanwhile, smoking is associated with the influence of nicotine, which affects the body's metabolism, insulin sensitivity, and pancreatic beta-cell function.[27] A meta-analysis of research explained that environments with cigarette smoke cause fatal and serious diseases and significantly increase the risk of diabetes.[19,28,29] The majority of patients in this study had no comorbidities (71%). This contrasts with the study conducted by Jelinek et al., which explained that the prevalence of diabetes increases in patients with comorbidities such as dyslipidemia and hypertension. In addition, comorbidities of diabetes are associated with risk factors for kidney disease, hypertension, and dyslipidemia.[30]

Analysis of Clinical Outcomes Based on Patient Demographic Characteristics

Table II shows the demographic characteristics of patients and clinical outcomes on HbA1c levels. The results obtained statistically show that there was a significant difference between demographic characteristics (body mass index and duration of diabetes) and clinical outcomes ($p<0.05$). This explained that there was a relationship between BMI and duration of diabetes on achieving the HbA1c target. Similar to this study, the study by Harahap et al., explained that there was a significant relationship between body mass index and the outcome of blood glucose levels ($p=0.000$). It is explained that a BMI in the "obese" category causes changes in the body's metabolism and an increase in blood glucose levels due to high body fat, so that the formation of blood glucose continues continuously and causes adipose tissue to release fat molecules into the blood, which will affect the cell's response to insulin.[31] Weight loss improves outcomes in patients with diabetes. Patients with a BMI of <24, 24-28, and ≥28 kg/m2 can achieve controlled clinical outcomes of HbA1c (HbA1c < 7%) of 35.7%, 39.1%, and 33.7%.[32] An increase in BMI of 1 kg/m2 can increase the risk of uncontrolled blood glucose by 11%.[33] This indicates that the management of overweight and obesity is important in achieving HbA1c targets.[34] Similar to

Table II. Differences in clinical outcomes by patient demographic characteristics

Variable	HbA1c Level (n=69)		P-Value
	Achieved (%)	Not Achieved (%)	
Age			
< 65 years old	27(61,4)	17(38.6)	0,581[a]
≥ 65 years old	17(68)	8(32)	
Sex			
Female	28(57,1)	21(42,9)	0,073[a]
Male	16(80)	4(20)	
Body Mass Index (BMI)	23(53,5)	20(46.5)	0,045*[a]
Obesity			
Non-obesity	21(80,8)	5(19.2)	
Duration of Diabetes			
< 6 Years	23(53,5)	20(46.5)	0,022*[a]
≥ 6 Years	21(80,8)	5(19.2)	
Marital Status			
Married	39(62,9)	23(37.1)	0,656[a]
Unmarried	5(71,4)	2(28.6)	
Educational Attainment			
Elementary and middle school	9(52,9)	8(47.1)	0,635[b]
High school	20(60,6)	13(39.4)	
College	13(68,4)	6(31,6)	
Frequency of *exercise*			
Once every 1–2 weeks	20(62,5)	12(37,5)	0,839[a]
3–6 times a week	24(64,9)	13(35,1)	
Smoking Status			
Smoker	5(83,3)	1(16,7)	0,297[a]
Non-smoker	39(61,9)	24(38,1)	
Comorbidities			
With comorbidities	12(60)	8(40)	0,677[a]
Without comorbidities	32(65,3)	17(34,7)	

this study, other studies explained that the duration of diabetes affects blood glucose control, as indicated by patients with diabetes duration of ≥5 years having an average HbA1c level of between 6.5% and 7.9% and a lower risk of death compared to those with a shorter duration of diabetes (<5 years). This study explained that the longer the duration of diabetes with good blood glucose control, the lower the risk of death.[35]

Table II shows that the proportion of participants under 65 years of age who achieved HbA1c target was 61.4%, while the proportion of participants 65 years of age or older who achieved HbA1c target was 68%. This explained that patients who are less than or equal to 65 years of age, exercised regularly, and had healthy lifestyle habits such as not smoking were able to achieve optimal therapy. In contrast to this study, the study by Shamshirgaran et al., showed that the groups of those aged 49 years or older, 50 to 59 years, and 60 years or older were not able to achieve target blood glucose (OR = 0.49 95% CI: 0.28–0.86 and OR = 0.44 95% CI: 0.24–0.80).[36] This was due to the influence of income level, disease duration, hypercholesterolemia, high LDL levels, and hypertension.[36] Another study also showed that patients with diabetes aged < 60 years and ≥ 60 years did not achieve blood glucose targets with average HbA1c levels of 8.6% ± 2.1% and 8.0%±1.6% with OR HbA1c > 7.0% because of obesity, dyslipidemia, smoking, long illness, and kidney disease.[37]

The achievement of HbA1c target in women was 57.1% and in men was 80%, as both women and men had the habit of physical activity 3 to 6 times a week. In line with this study, a study explained that there were no differences in the achievement of blood glucose control between men and women and there was a decrease in HbA1c levels in both men and women. This was because both men and women can self-manage healthy lifestyle habits and improve quality of life to control blood glucose levels.[38,39]

Achievement of HbA1c target was 62.9% in participants with "married" marital status. According to one study, marital status is associated with better adherence among patients who have a partner with diabetes.[40]

The results of the study of Kposowa et al., explained that married men have social support from their partners and they have a better quality of life so that clinical outcomes are achieved.[41] Achievement of HbA1c target was 60.6% among participants with a high school education and 68.4% among those with a college education. Educational attainment influences the improvement of glycemic control in patients with diabetes. The study results explain that the level of education can increase patients' knowledge about the disease, so patients pay more attention to their habits and blood glucose control can reach targets.[42] Among participants who exercised 3 to 6 times per week, 64.9% achieved their HbA1c target. Physical activity has been a recommendation for diabetes management. Physical activity has benefits that improve glycemic control and glycemic variables and reduce insulin resistance. Low levels of physical activity may increase the risk of cardiovascular disease in patients with diabetes.[43] Physical activity 3 times a week for 60 minutes for 2 months significantly reduces blood glucose and HbA1c levels.[44]

The patients who participated in this study were mostly non-smokers. The non-smoking rate was 61.9%. Consistent with this study, the results of the study by Sia et al., explained that there was a significant difference in reducing HbA1c levels in smoking and non-smoking patients by 0.30%. In addition, patients who smoked had higher HbA1c levels than non-smokers (6.65% vs 6.44%, $p < 0.001$).[45] The patients in this study were dominated by those without comorbidities, with an HbA1c target achievement of 65.3%. The factor that caused the absence of comorbidities to influence clinical outcomes in this study was that monotherapy is effective in reducing HbA1c levels in patients. In addition, patients also had the habit of not smoking and regularly engaging in physical activity to achieve therapy targets. In line with this study, the results of another study explained that 78% of diabetes patients with chronic kidney disease (CKD) (OR: 1.78, 95% CI: 1.55-2.05) had uncontrolled blood glucose levels that were higher than patients without CKD.[46]

CONCLUSION

There was an association between BMI and duration of diabetes and achievement of HbA1c target ($p<0.05$).

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STATEMENT OF ETHICS

Ethical approval to conduct this study was obtained from the Ethics Committee of CUCMS (Cyberjaya University College of Medical Sciences), with reference number CUCMS/CRERC/AL-ER(06/2019).

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Analysis of Drug Management at Tegal City Pharmaceutical Installation

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ABSTRACT

Background: Medicine is one of the most essential elements in health service efforts. Good drug management will affect the availability of drugs and improve the degree of health in the community.

Objectives: This study aims to determine the effectiveness and efficiency of drug management at the Tegal City Pharmaceutical Installation in 2021 related to compliance with the Indonesian Ministry of Health and WHO indicators.

Methods: This research is descriptive research with a quantitative approach. Data was taken retrospectively through document tracing and supplemented with qualitative data through interviews to deepen findings in the field. Data obtained and the results of interviews with the Head of Installation and pharmaceutical personnel, totaling five respondents, will then be compared with standard indicators from the Indonesian Ministry of Health and WHO. Data analysis in this study used indicators of selection, procurement, distribution, and use of drugs. The values of the indicators that have been obtained are subsequently compared with the existing standard values.

Results: The results of drug management research at the Tegal City Pharmaceutical Installation are at the selection stage of proposing drugs to Fornas. The procurement stage of drug suitability with Fornas is 96.4%, the fund allocation percentage is 92%, and the planning accuracy is 95.7%. The distribution stage of the level of drug availability 12-18 is 13.92 months, the accuracy of the number of distributions to the Puskesmas is 100%, the percentage of drugs experiencing empty stock, dead stock, and overstock is 0%, the percentage of damaged and expired drugs is 0%. The use stage of drug items per prescription is 3.5 drug items, the percentage of antibiotic use in non-specific patients is 30.7%, the percentage of non-pneumonia Acute Respiratory Infections (ARI) antibiotic use is 34.2%, and myalgia injection use is 0%.

Conclusion: The conclusion of drug management at the selection, procurement, distribution, and use stages in 2021 carried out at the Tegal City Pharmaceutical Installation has yet to follow standards. Of the 14 indicators studied, only 8 follow the standard, and 6 other indicators still need compliance to evaluation.

Keywords: City Pharmaceutical Installation; Drug management cycle; Indicators.

INTRODUCTION

Medicine is a basic human need that is irreplaceable in health services that are useful for saving lives and improving the quality of health. Access to medicines, especially essential medicines, is one of the human rights under one of the objectives of the 2006 National Drug Policy (KONAS), namely ensuring the availability, equity and affordability of drugs, especially essential medicines, so that people obtain medicines when needed at the right place and time.[1] The availability of medications for health services is greatly influenced by drug accessibility.

Based on the strategy plan of the Republic of Indonesia 2019-2024, there was an increase in the availability of drugs and vaccines in 2019 by 94.22% from 79.38% in 2015. However, the availability of drugs still cannot be evenly distributed in each province. This difference illustrates that drug logistics management still needs to be improved.[2]

One of the events that has a significant impact on the current availability of drugs is the outbreak of the COVID-19 pandemic. Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a new type of coronavirus that has never been identified in humans.[3] Judging from the spread of COVID-19, which has almost reached all provinces in Indonesia with an increasing number of cases or deaths, nearly all sectors are affected by this outbreak. As activities in various regions are restricted, the sustainability of the pharmaceutical supply chain becomes an issue. If this outbreak continues, the supply of medicines and pharmaceutical raw materials may decline, leading to a large-scale supply shortage.[4]

Research on drug management analysis at the Tegal City Pharmaceutical Installation has never been carried out before, so in the process of drug management, it is possible for non-compliance with standards. Drug management in pharmaceutical installations in other districts/cities has been carried out by Gurning et al, Boku et al, Aisah et al, and Abadi, Suryagama, Nugroho, and Budiarso.[5,6,7,8,9,10,11] The difference between this study and previous drug management studies is in the research variables. The variables of this study include the stages of selection, procurement, distribution, and use. This study aims to determine whether drug management at the Tegal City Pharmaceutical Installation is in accordance with the standards set by the Indonesian Ministry of Health and WHO and determine what factors influence drug management.[1213]

METHODS

Study design

This research is descriptive research with a quantitative approach. Data was taken retrospectively through document tracing and supplemented with qualitative data through interviews to deepen findings in the field and comprehensively understand the phenomenon studied by comparing standards from the Indonesian Ministry of Health and WHO.

Population and samples

The research subjects as informants were 5 respondents: the Head of the Tegal City Pharmaceutical Installation and four officers related to the drug management process. The samples used in this study are all drug reporting indicators of Puskesmas and COVID-19 drugs related to drug procurement indicators.

Study instruments

The data collection instrument used by the study used indicator sheets and checklists of drug management based on the Ministry of Health of the Republic of Indonesia in 2010, pharmaceutical management training materials in district/city pharmaceutical installations and rational drug use according to WHO.

Data collection

The primary data source used in the selection stage research is proposing drugs to Fornas. Procurement is the conformity of items with the national formulary, the allocation of procurement funds, and the planning accuracy. Distribution is the level of drug availability, the accuracy of the amount of distribution to Puskesmas, empty stock items, fewer stock items (1 to <12 months), safe stock (12-18 months), excessive stock items (>18 months), non-prescription drugs (>3 months), expired drug values, and damaged drug values. Use is the use of rational drugs consisting of drug items per prescription, the use of antibiotics in non-specific diarrhoea patients and non-pneumonia ARI, and the use of myalgia injections. Secondary data is obtained by observing documents consisting of annual drug planning and usage reports, financial department budget reports, drug procurement reports, purchase books, damaged/expired drug reports, order letters, and pharmaceutical installation profiles. Support management consists of organizational structure, the person in charge, the amount of human resources, and administrative means.

Data Analysis

Analysis of this research data is obtained from the results of interviews and documentation by organizing data into categories, describing it into units, synthesizing, arranging it into patterns, and sorting out which ones

are important. It will be learned and then concluded so that they are understood by themselves and others. Data analysis in this study used indicators of selection, procurement, distribution, and use of drugs. The values of the indicators that have been obtained are subsequently compared with the existing standard values.

RESULTS AND DISCUSSION

Selection

The indicator used is proposing to Fornas. The goal is to avoid drugs that have no therapeutic value, reduce the number of types of drugs, and increase drug efficiency. Offering drugs to Fornas is the process of submitting drug standards by the Puskesmas, which will be used at the Puskesmas itself. Submissions are made for drugs listed in Fornas, where the submission process will be reviewed by the PI (Pharmaceutical Installation) of Tegal City and the selection of drugs on the E-Catalogue. Indicators can be seen in Table I.

Procurement

Item conformity to Fornas

This indicator aims to determine the level of drug suitability following the National Formulary in Tegal City Pharmacy Installation. The calculation is done by dividing the drug items following Fornas by the drug items available at the Pharmaceutical Installation multiplied by 100%. Based on data collected from the drug inventory report 2021 in Tegal City Pharmacy Installation, the indicator drug items available at the Pharmaceutical Installation are compared to the National Formulary. The calculation value with the indicator of the suitability of available drug items with Fornas is 96.7%, while according to the indicator from the Ministry of Health, it is 100% (Table II). These results can conclude that drug planning has yet to follow standards. Research from Lutsina & Lette explains that drug selection in Puskesmas must refer to Fornas related to meeting drug needs at Puskesmas.[14] In contrast to the results of Anggriani research, which demonstrated that the suitability of drugs with Fornas is as much as 77.01%, this is due to the lack of accuracy and consideration in the selection of drug items at the Puskesmas.[15] Based on interviews conducted, indicator drug items that are not available at the Tegal City Pharmaceutical Installation, namely dihydroartemisin + paperquin and primaquin drug items, include drugs for malaria. Based on the interview results, the cause of the absence of malaria drugs is that Tegal City is not an endemic area, and malaria cases in the Tegal City area have not been found. Therefore, planning for malaria drugs is abolished.

Percentage of Drug Procurement Fund Allocation

Percentage indicator of drug procurement fund allocation to compare the total funds of Tegal City Pharmacy Installation with drug procurement funds. The total budget funds for Tegal City Pharmacy Installation in 2021 are IDR 1,113,192,364, where the entire budget becomes the budget allocation. Based on these data, it is known that the total funds in Tegal City Pharmacy Installation with drug procurement funds at pharmaceutical installations. The allocation of funds shows that the budget for drug procurement is 92% of the total budget for pharmaceutical installations outside the medical device budget (Table II). Total drug procurement funds are available funds allocated for drug procurement. The percentage value of drug procurement shows that the need for procurement fund allocation has not met existing standards, according to the Indonesian Ministry of Health, ideally 100%. This result is in line with research by Ta'au, where it was found that the allocation of funds obtained was 96.49%; this shows a non-conformity with the Indonesian Ministry of Health 2010 standards. The reason for the discrepancy in the allocation of funds that occurs is due to changes in disease patterns that have an impact on adjustments to the budget of funds obtained from the government.[16] Research by Carinah received budget results in 2021 at UPTD Farmasi Subang Regency, which still do not meet the standards; this happened because of several budget refocusing related to the COVID-19 pandemic.[17] Research conducted by Ariyani said the same thing; the previously planned budget was finally refocused and reallocated by the government, which caused the budget from the centre to eventually have to be cut so that it had an impact on the ratio of financial independence.[18]

Based on interviews that have been conducted, this is about the percentage of drug procurement fund allocation that has not been following the indicators of the Indonesian Ministry of Health because several drugs are not recorded due to vacancies in distributors due to the high demand for a drug during the COVID-19 pandemic, for example for dexamethasone, vitamin C, and vitamin D drugs. The discrepancy in the allocation of funds obtained is due to the budget used adjusted to the budget received from the government. In addition, during the pandemic, several budgets were cut, which also had an impact on the allocation of funds.

Table I. Selection Indicator

Indicator	Result	Standard
Proposing Drugs to Fornas	Yes	Yes

Table II. Procurement Indicators

Indicators	Results	Standard
Item Conformity to Fornas	96.4%	100%
Percentage of Drug Procurement Fund Allocation	92.0%	100%
Percentage of COVID-19 Drug Fund Allocation	99.9%	100%
Accuracy of Drug Planning	95.7%	100%

In the allocation of funds for COVID-19 drugs, parties from Tegal City Pharmacy Installation also purchase drugs outside the grant from the centre; this is done to prevent shortages of drugs provided by the central government. The percentage of accuracy of planning funds with procurement realization showed a result of 99.9%. The results of the planning accuracy indicator are less than the standard set by the Indonesian Ministry of Health, which is 100%. Based on the interview results, this is due to the difference in prices at the time of independent calculation and the price determined by the distributor.

Accuracy of Drug Planning

The percentage of suitability of procurement planning funds showed a yield of 95.7%. The total procurement fund in question is a fund that is only for the procurement of drugs, while the total drug use fund is the funds obtained from the results of drug use in one year. The planning accuracy indicator gets results that are less than the standard set by the Indonesian Ministry of Health, which is 100% (Table II); this can be caused by changes in prescribing patterns and disease patterns influenced by the COVID-19 pandemic. This result is not much different from research from Sariah in 2021 also explained that the accuracy of planning at the Banjarmasin City Pharmaceutical Installation also got a percentage of 68% due to the number of disease cases decreasing or the prescribing doctor moving tasks so that the drugs planned and available at the Puskesmas were rarely prescribed or not prescribed anymore.[19] This is also in line with the results of the interviews conducted, namely the inaccuracy of planning that occurs caused by several things including recipe writing patterns, as well as changes in disease patterns due to the COVID-19 pandemic.

Distribution

Drug Availability

This indicator determines the adequacy of drugs in Tegal City Pharmacy Installation that is sustainable for community services. Medicines provided for health services in the city must follow needs, which means that the number of drugs available at the City Pharmacy Installation must be equal to the stock time of arrival of drugs. The percentage value in the calculation of drug availability indicators at the Tegal City Pharmacy Installation in 2021 shows that the level of drug availability is 13.92 months, whereas the standard value is 12-18 months, which means that the majority of drugs are still in the safe category. Based on the Indonesian Ministry of Health standards, if the value of the calculation of drug availability is <12 months, the availability value is included in the understock category, and if the value of drug availability is >18 months, it is included in the overstock category. The names of drug items that experience an availability level of <12 months are amoxicillin 125/5ml, amoxicillin 500mg, magnesium sulfate 40%, methylergomethrin 0.125, anti-tuberculosis drug category 1, and paracetamol 500mg, this is due to the planning that is not following the method of consumption so that if there is a change in disease patterns and prescribing will affect the planning which results in drug availability will be hampered. Based on the value of the availability of drug categories in Tegal City Pharmacy Installation, it is known that the COVID-19 pandemic did not significantly impact the availability of drugs in Tegal City Pharmacy Installation in 2021.

Research from Amiruddin & Septarani A, entitled Study on Drug Availability at Meo-Meo Health Center in Baubau City stated that the availability of drugs at Meo-Meo Health Center was not following standards, which was due to non-fulfilment of drugs submitted by Usage Report and Drug Request Sheet (LPLPO) by UPTD Pharmaceutical Installation. The lack of availability of drugs at the Puskesmas creates a shortage of drugs that

can harm the Puskesmas because many prescriptions are not served, so patients leave the Puskesmas, which can reduce visits and income of the Puskesmas.[20]

Based on the interviews conducted, factors that affect the results of the level of drug availability, namely the number of drugs in a year, the average monthly use of drugs, and drug waiting time. With these factors, it can be known that the stock of drugs in a year is in the safe category, but if there is a shortage of some drugs or if the drugs needed by the Puskesmas experience a shortage, the Puskesmas will share drugs with Puskesmas that have more stock. Drug planning is usually carried out for 18 months, and the procurement time until the drug arrives at Tegal City Pharmacy Installation is approximately 6 months. The receiving committee carries out the process of receiving and inspecting goods that come, whose duty is to match the name and quantity of drugs, batch number, expiration time, manufacturer and distribution permit number.

Accuracy of Distribution Amount to Puskesmas

The percentage in calculating the accuracy indicator of drug distribution in Tegal City Pharmacy Installation in 2021 is 100%; this follows the standard of the Indonesian Ministry of Health, which is 100% (Table III). A total of eight Puskesmas in the working area of Tegal City are all served according to request, in contrast to the research conducted by Salmah, which obtained a drug distribution accuracy value of 61.5% at the Jambi City Health Center. This problem occurs because in making requests in each distribution period, the Puskesmas drug manager does not take into account the optimum stock, meaning that the drug manager does not take into account the waiting time and drug vacancy time, which can result in the availability of drugs in the Puskesmas, some are excessive, and some are lacking.[21]

Based on the interview results, the Tegal City Pharmaceutical Installation distribution system distributes Puskesmas every year at the beginning of the month. The distribution flow at the Pharmaceutical Installation is that the drug manager from the Puskesmas will make and send LPLPO to the Pharmaceutical Installation. Then, the Pharmaceutical Installation will screen the request. If the request meets the criteria, the requested drug will be prepared and distributed to the Puskesmas. As for COVID-19, drugs are distributed to health services in need, such as hospitals and health centres, and for self-isolation treatment.

Percentage of Drugs Experiencing Empty Stock

The purpose of this indicator is to assess the level of drugs that experience empty stocks. The calculation of the percentage indicator of drugs experiencing empty stock in Tegal City Pharmacy Installation in 2021 with a value of 0%. Therefore, it can be concluded that the percentage indicator of drug vacancies has met the standards according to the Indonesian Ministry of Health of 0% (table III), which means that there are no drug stocks that experience vacancies. Based on the results of an interview with the person in charge of Tegal City Pharmacy Installation, it was determined that this is because City Pharmacy Installation always compiles and analyzes the pharmaceutical needs of Puskesmas in its work area; adjusts to the available budget and takes into account the time of drug vacancies, buffer stock, and avoids excess stock. This is in line with the research of Rintanantasari, which results in drugs experiencing an empty stock of 0% at the Puskesmas Tulungagung Regency and Kupang City, which means it follows the standard. All drug needs at the Puskesmas have been met according to the amount and type of drugs required.[22] Although there are drug items that have various dosages, the Puskesmas still provides the medicine items so that drug vacancies can be avoided.

Percentage of Drugs Experiencing Dead Stock

A high percentage of drugs experiencing dead stock indicates that drug turnover is not good and causes inventory to accumulate in warehouses. Based on data on the list of dead drugs in Tegal City Pharmacy Installation in 2021, the calculation of the percentage indicator of drugs experiencing dead stock in Tegal City Pharmacy Installation in 2021 gets a result of 0% (Table III). It can be concluded that the percentage indicator of drugs experiencing empty stock has met the standards used. This is different from Khairani research, which stated that dead stock in two health centres in the Magelang region had values of 40% and 20%. This was due to factors such as changes in prescribing patterns, expiration dates that were too short, and not following requests with drug receipts from UPTD Pharmaceutical Installations.[23]

Percentage of Drugs Overstocked

The purpose of this indicator is to assess the level of drugs that are experiencing excess stock. Based on data on the list of empty drugs in Tegal City Pharmacy Installation in 2021, the percentage of drugs overstocked in Tegal City Pharmacy Installation in 2021 is 0% (Table III). This figure complies with the Indonesian Ministry of

Health standards. This study is different from the Rintanantasari study, which found that the drug experienced excess stock at the Tulungagung and Kupang Health Centers by 38.23% and 39.56%, respectively; this was due to planning that exceeded use, changes in disease patterns from the previous year.[22]

Percentage of Damaged or Expired Drugs

The purpose of calculating the percentage of damaged and expired drugs is to determine the amount of City Pharmacy Installation losses due to too many damaged and expired drugs. Defective and expired drugs are calculated using a list of defective and expired drugs in one year that reflects the distribution system and planning system inaccuracies and deficiencies, as well as regular observation of the quality of drug storage. Based on the data collected in Tegal City Pharmacy Installation, the percentage value in the calculation of percentage indicators and the value of expired drugs in Tegal City Pharmacy Installation gives a value of 0%. These results follow the standards provided by the Indonesian Ministry of Health, namely 0% (Table III); this shows the appropriateness of planning and observation in storing and distributing appropriate drugs to obtain ideal results; this is in line with the research of Rintanantasari, which got 0% results of expired and damaged drugs in the Tulungagung and Kupang health centres.[22] The results differ from the Cholilah study; there are still expired drugs at the Tegal City health centre due to the close expiration time received by the Puskesmas.[24]

Use

Drug Items Per Prescription

The drug item per prescription indicator provides an overview of the number of drug items prescribed on each prescription sheet. This data can also illustrate the rationality of drug use, especially the occurrence of polypharmacy prescribing. Polypharmacy is the excessive use of drugs in one prescription that does not follow the diagnosis and health condition of patients in health services, in this case, Puskesmas. Based on data collected at Tegal City Pharmacy Installation, the calculation results show that the average use of medicinal items per prescription in the Pharmacy Installation working area health centre in Tegal City is 3.5 drug items. Based on the standards set by WHO, the estimated value of the average number of drug items per prescription sheet is 1.8-2.2 drug items (Table IV). This value is a standard used to minimize the occurrence of polypharmacy. One of the causes of polypharmacy is the condition of patients who have chronic diseases or complications from a disease, so doctors prescribe more than one drug to treat this problem. Polypharmacy can result in an increased risk of drug side effects or ADR (Adverse Drug Reaction), drug interactions, drug waste, and improved patient medical costs. Based on the interviews conducted with the Head of the Tegal City Pharmacy Installation, the average prescription value of 3.5 was also due to the average patient in the Tegal City community health centre suffering from more than one disease.

Research conducted by Dewi at the Kuta District Health Center in 2017 showed that the average number of medicinal items per prescription sheet was 2.9.[25] Furthermore, research conducted by Ihsan in all Kendari City health centres in 2016 showed that the average number of medicinal items per prescription sheet was 3.23.[26] The results of these two studies show that the average value of drug items per prescription sheet exceeds the estimated value from WHO. The reason for this is also because the patients who seek treatment are mostly older adults who suffer from more than one disease.

Percentage of Antibiotic Use in Non-Specific Diarrhea Patients

The percentage of antibiotic use in non-specific diarrhoea patients in the Tegal City Pharmacy Installation working area health centres is used to monitor the use of antibiotics. Such usage in these cases is categorized as irrational drug use, which can cause serious events like resistance to the use of antibiotics. The calculation result of the percentage of antibiotic use in non-specific diarrhoea patients in the pharmacy installation working area health centre in Tegal City was 30.7%; not meeting WHO standards, namely <8% (Table IV). Based on information from the results of interviews that have been conducted, antibiotics are generally not needed for non-specific diarrhoea because most of the causes of non-specific diarrhoea are foods that stimulate the digestive tract or foods that are contaminated with toxins that trigger digestive disorders, which do not require antibiotics. However, there are a small number of cases (10–20%) where non-specific diarrhoea is caused by food contaminated by pathogenic bacteria such as *V. cholera*, *Shigella*, enterotoxigenic *E. coli*, *Salmonella* and *Campylobacter* due to unhygienic processing. Patients will experience symptoms in the form of pain and even cramps in the stomach. In cases like this, antibiotics are given.

The results obtained at Tegal City Pharmacy Installation differed from those of Sari, where the use of antibiotics in non-specific diarrhoea patients at community health centres in the Pasuruan Regency area obtained

Table III. Distribution Indicators

Indicators	Results	Standard
Drug Availability	13.92 Month	12-18 Month
Accuracy of Distribution Amount to Puskesmas	100%	100%
Percentage of Drugs Experiencing Empty Stock	0%	0%
Percentage of Drugs Experiencing Dead Stock	0%	0%
Percentage of Drugs Overstocked	0%	0%
Percentage of Damaged or Expired Drugs	0%	0%

Table IV. Use Indicators

Indicators	Results	Standard
Drug Items Per Prescription	3.5 items	1-2.2 item
Percentage of Antibiotic Use in Non-Specific Diarrhea	30.70%	<8%
Percentage of Non-Pneumonia ARI Antibiotic Use	34.2%	<20%
Percentage of Myalgia Injection Use	0%	<1%

a value of 7.59%.[27] This result is very good because it meets the existing standards, namely <8%.[13] he use of antibiotics in cases of non-specific diarrhoea should not be necessary because most of them are caused by viral infections, food and/or lactose intolerance. The primary therapy is the provision of sufficient rehydration fluids and electrolyte supplements, as well as the administration of absorbents to reduce the frequency of defecation. Antibiotics are only given when diarrhoea is accompanied by fever and slimy and bloody stools, and a bacterial culture test has been carried out to determine the cause of the diarrhea.[28]

Percentage of Non-Pneumonia ARI Antibiotic Use

Acute Respiratory Infections (ARI) are infections caused by viruses or bacteria in the respiratory tract, so not all of them are treated with antibiotics. The calculation result of the percentage of use of non-pneumonia ARI antibiotics in Pharmacy Installation working area health centres in Tegal City was 30.7%. This result is not in accordance with WHO standards, which specify a threshold of <20% (Table IV). Based on the results of interviews conducted, this is because the prescriber is giving medicine that is not actually needed for the disease in question, in this case, giving antibiotics for non-pneumonic ARI, which is generally caused by viruses. Anita et al research obtained results that were more than the specified indicator, namely 63.826%. Anita explained that this was caused by a lack of public knowledge about antibiotics, which was a risk factor for increasing levels of bacterial resistance to antibiotics.[29]

Percentage of Myalgia Injection Use

Indicators for using injections for myalgia influence the level of rationality for using injection drugs. Therefore, the use of myalgia injections must be monitored and evaluated. The percentage value of injection use in myalgia cases in the Pharmacy Installation working area health centre in Tegal City was 0%, which means that the indicator for rational drug use is in accordance with the standard, namely <1% (Table IV). This result is different from research by Indiarto, which explained that the use of injection treatment for myalgia in Madura, East Java, was 1.42%; this is because the public perception that injection preparations are more effective than oral preparations influences doctors to prescribe medication in injection form.[30,28]

Management Support

The indicators used to support management are the pharmacy installation organizational structure, the person in charge of the pharmacy installation, the number of human resources, the availability of operational costs, and the availability of administrative facilities (Table V).

Organizational structure

Regency/city regional services may form Regional Service Technical Implementation Units (UPT) to carry out operational technical activities or certain supporting technical activities within an agency. The formation of a regional service UPT is determined by a regent or mayor regulation after written consultation with the Minister of Home Affairs. The organizational structure of the Tegal City Pharmacy Installation has the form of a Health

Table V. Management Support Indicators

Indicators	Results	Standard
Organizational structure	UPTD	UPTD
Person in Charge of Pharmacy Installation	Apothecary	Ners
Number of Human Resources	≥7 Person	7 Person
Operating Costs	Available	Available
Administrative Facilities	Available	Available

Service Technical Implementation Unit (UPTD) (Table V); this is in accordance with the standard targets set by the Indonesian Ministry of Health, where it is hoped that every pharmacy installation will have the form of a UPTD. Based on the results of interviews with the Tegal City Pharmacy Installation, the organizational structure at the Tegal City Pharmacy Installation is in the form of a UPTD, which was previously still part of the Pharmacy Section of the Tegal City Health Service. In contrast to Purwanto research, the Bantul District Pharmacy Installation is a work unit under the Food and Beverage Pharmacy Section.[31]

Person in Charge of Pharmacy Installation

An apothecary must carry out activities in planning and evaluating drug needs. In this case, the person responsible for Tegal City Pharmacy Installation is the apothecary. Based on interviews conducted at the Tegal City Pharmacy Installation, there is an apothecary but not the Head of the Tegal City Pharmacy Installation, and this is different from Boku research, which found that the person in charge of City Pharmacy Installation was an apothecary.[6] This is due to in Tegal City Pharmacy Installation the appointment of section heads by local government policy.

Number of Human Resources

Human resources run the drug management system. The standard number of human resources set by the Indonesian Ministry of Health is ≥ 7 people. Based on the research results, it was found that the number of human resources at Tegal City Pharmacy Installation was 7 people; this is in accordance with the established standards. In contrast to Ingrid research, the human resources at City Pharmacy Installation Southeast Minahasa only had 5 people consisting of 2 apothecaries and 3 TTKs; this influenced the results of drug planning.[32]

Operating costs

Operational costs are needed to carry out the drug management process. The standards set by the Indonesian Ministry of Health for each City Pharmacy Installation are available. The research results obtained from Tegal City Pharmacy Installation were the availability of funds for transportation when distributing medicines to health centres and spending on office stationery. This research is in line with Susanti, who obtained the results that operational funds are needed to carry out the drug management process.[33]

Administrative Facilities

The Indonesian Ministry of Health standards regarding administrative facilities that City Pharmacy Installation should have include furniture, data processing (computer/laptop), printer, communication equipment, and information such as an internet network to support the drug management process. From the research results, data was obtained that in Tegal City Pharmacy Installation, there were administrative facilities available to support drug management. This research is in line with Susanti, who states that adequate administrative facilities and infrastructure are needed to achieve good availability in managing medicines and health supplies.[33]

CONCLUSION

The drug management cycle at the selection, procurement, distribution and use stages in 2021 carried out at the Tegal City Pharmacy Installation as a whole is not in accordance with standards. Of the 20 indicators studied, 12 indicators are in accordance with standards, and 8 other indicators are not yet in accordance. Factors that influence drug management in the Tegal City Pharmacy Installation include human resources, namely prescribers and supporting management, namely local government policy. It is necessary to evaluate the use of

antibiotics in patients with non-specific diarrhoea so that resistance does not occur because the numbers show values above the standard values.

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STATEMENT OF ETHICS

This research was approved with ethical clearance approval obtained from Dr. Moewardi Surakarta Hospital with number 1,151/IX/HREC/2022 on September 1, 2022. The study was conducted at the Tegal City Pharmaceutical Installation in 2022.

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Correlation Between Warfarin Levels in the Blood and the Value of Normal INR in Fibrillation Atrium Inpatients

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ABSTRACT

Background: Warfarin is an anticoagulant inhibitor of vitamin K that is effective in preventing systemic embolization in atrial fibrillation patients. Warfarin has a narrow therapeutic index, so it requires monitoring of rates to prevent the occurrence of toxic effects and to ensure the passage of INR values.

Objectives: The study aims to find out the correlation between warfarin levels and normal INR values.

Methods: Observational research method with the collection of retrospective data on the medical records of patients treated with atrial fibrillation at Prof. Dr. Margono Soekarjo Hospital, Purwokerto, in January 2019–December 2021. Warfarin levels were calculated pharmacokinetically using the steady-state concentration (Css) and plasma concentration (Cp) formulas. Data analysis is carried out using the Spearman test to determine the correlation between warfarin levels and normal INR values.

Results: The number of patients with normal INR values was less than the number of patients with abnormal INR values, namely 21 patients and 48 patients. The Spearman test results show a p-value of 0.31 (p>0.05), showing that the correlation between warfarin levels in the blood and the corresponding INR value is not significant (p> 0.05), and the R value in the Spearman test is 0.122, showing that the direction of the correlation is positive with very weak correlation strength.

Conclusion: The correlation between warfarin levels in the blood and the appropriate INR value is not significant (p>0.05), where the R value in the Spearman test shows R=0.122, meaning the direction of the correlation is positive with a very weak correlation strength.

Keywords: atrial fibrillation; INR; warfarin levels

INTRODUCTION

Atrial fibrillation is a heart rhythm disorder characterised by uncoordinated atrial contractions and rapid ventricular response.[1] A person is diagnosed with atrial fibrillation based on the results of an electrocardiogram (ECG) examination. ECG results showed inconsistent, unclear atrial activity (P waves), irregular RR intervals of 30 seconds, and a ventricular rate reaching 90–170 beats per second with an irregular pulse.[2] The prevalence of atrial fibrillation has increased by 33% in the last 20 years. It is known that the number of atrial fibrillation cases in the world in 2017 reached 37,534 million (4,977 cases per million population), and by 2050, it is predicted that this will increase by >60%.[3] The prevalence of atrial fibrillation increases with age. By the age of 80, atrial fibrillation incidence is driven by a lifetime risk of 22%.[4]

Anticoagulant medication is the first choice of treatment for stroke prevention for patients with atrial fibrillation because it is suspected of an increased risk of stroke and has been shown to be involved in 15% of stroke events. Vitamin K antagonists, such as warfarin, and new oral anticoagulants (NOACs), such as rivaroxaban and edoxaban, are examples of oral anticoagulants that can be used. The class of indirect thrombin inhibitors that includes heparin, fondaparinux, and enoxaparin also includes intravenous anticoagulants. Pharmacological rhythm control therapy can use antiarrhythmics such as propafenone and amiodarone. In the meantime,

combination medication, which includes beta-blockers, digoxin, diltiazem, and verapamil, can be prescribed to control heart rate.[2,5]

Patients with atrial fibrillation are able to prevent stroke or systemic embolization with warfarin.[6] Patients with atrial fibrillation can lower their risk of stroke by about 60% using warfarin. By preventing an increase in coagulation factors that are dependent on vitamin K, warfarin has anticoagulant effects. Warfarin's initial therapeutic effect starts with its suppression of factor II, also known as thrombin. The first line of treatment for atrial fibrillation in order to prevent stroke is warfarin. Because of its pharmacokinetic parameters, warfarin has a narrow therapeutic index. Therefore, levels need to be monitored frequently.[7] Therapeutic blood levels of warfarin are in the range of 1 to 4 mg/L.[8] Over-the-therapeutic levels of warfarin might increase the risk of bleeding events such as hematuria, melena, severe bruises, or low haemoglobin.[9] Monitoring drug levels in the blood in Indonesia cannot be done directly because the costs involved are relatively expensive. One way to monitor drug levels in the blood is to calculate drug levels pharmacokinetically using a formula based on the therapeutic dose given to the patient, so that an overview of drug levels in the blood can be obtained.[10] Warfarin levels are measured in the blood using the concentration steady-state (Css) formula for patients who have taken the drug for a minimum of four days and have amounted to steady state, and the plasma concentration (Cp) formula for patients who have taken the medication for one to three days but have not yet reached steady state.[11]

Therapeutic monitoring of anticoagulants in atrial fibrillation patients is measured by the prothrombin time parameter expressed by the International Normalized Ratio (INR).[7] Because one of the side effects of anticoagulant medicine is that blood clots easily, making it difficult to stop bleeding if it happens, an INR is a crucial part of anticoagulant therapy. INR provides an indicator to ensure that the anticoagulant impact is not significantly strong and to avoid these negative effects. When treating atrial fibrillation with warfarin, the ideal INR is 2.5, or between 2 and 3.[12] The research results of Furdiyanti et al. (2014) show that the maintenance dose of warfarin on days 15–30 is an average of 2.24 ± 0.77 mg/day, while the estimated average warfarin level is at steady state or on The 30th was 0.658 ± 0.315 mg/L, and 9 patients (10.47%) had values within the therapeutic range. The results of the INR examination showed that 54 patients (62.79%) did not reach the INR target, and 32 patients (37.21%) reached the INR target. The correlation between the estimated blood warfarin levels and the INR value is not significant with a value of $p = 0.180$ ($p > 0.05$), while the correlation coefficient value of 0.146 indicates a positive correlation direction with a very weak correlation strength.[8] This strengthens the concept of therapeutic drug monitoring. Prof. Dr. Margono Soekardjo Hospital, Purwokerto, has never conducted research on estimating warfarin levels in the blood, so it is necessary to determine the level of warfarin in the blood pharmacokinetically as well as analyze correlations between the level of warfarin in the blood and the observance of the normal INR value in patients with atrial fibrillation. Besides that, further precautions must be taken when using warfarin, a drug with a narrow therapeutic index. The purpose of this study was to determine the blood levels of warfarin using the pharmacokinetic formula and to observe a correlation between the blood levels of warfarin and the atrial fibrillation patients' getting a normal INR value.

METHODS

This study is a descriptive-analytic one that was conducted utilising medical record data from inpatients diagnosed with atrial fibrillation at Prof. Dr. Margono Soekarjo Hospital, Purwokerto, from January 2019 to December 2021. The test participants were not given medication or otherwise engaged in.

Study design

Observational research method with the collection of retrospective data on the medical records of patients treated with atrial fibrillation in the Prof. Dr. Margono Soekarjo Hospital, Purwokerto period of January 2019–December 2021.

Population and samples

All inpatient atrial fibrillation patients treated at Prof. Dr. Margono Soekarjo Hospital, Purwokerto, from January 2019 to December 2021 comprised the study's population. The total sampling method was used for collecting the data. The study sample included patient medical record data that fulfilled the inclusion criteria. The inclusion criteria in question are as follows: patients with complete medical records that include patient identity (age, gender, weight, and medical history), drug history (dose, interval within warfarin administrations, and length of warfarin administration), and objective data (INR) are those who are diagnosed with atrial

fibrillation and are being treated with oral warfarin therapy. The study excluded patients who died while taking warfarin and those who were pregnant.

Study instruments

The Case Report Form (CRF) is the tool utilized in this study. The patient's identity, including name, initials, medical record number, age, weight, warfarin dosage and interval, and INR value data, is included on the CRF.

Data collection

The total sampling method was used to collect research samples. The study was conducted in the medical records division of Prof. Dr. Margono Soekarjo Hospital, Purwokerto, from May 2022 to May 2023.

Data Analysis

Univariate Analysis

This analysis aims to describe the characteristics of each variable to be studied. The results of the analysis include age, gender, diagnosis, pattern of warfarin use, calculation of warfarin levels grouped based on levels that are suitable for therapy and levels that are not suitable for therapy based on calculations of drug levels in the blood after administration of warfarin, as well as INR values grouped based on normal INR values and abnormal INR values.

Bivariate Analysis

The association between two variables—the blood warfarin levels and the INR values of atrial fibrillation patients—was examined using bivariate analysis. The correlation between these two variables was determined using the Spearman's test. Although the Spearman statistic test is non-parametric, it is not required that the data follow a normal distribution. The correlation coefficient value indicates the strength of the correlation between warfarin levels and the accordance of the normal INR value, whereas the significance value in the Spearman test indicates if there is a correlation between the two variables.

Independent Variable

Blood warfarin levels were the study's independent variable. The average warfarin levels at steady state, minimum warfarin levels at steady state, maximum warfarin levels at steady state, and plasma levels that are still above steady state are all included in the pharmacokinetic formula used for estimating the blood levels of warfarin. Less than 1 mg/dL and more than 4 mg/dL are considered to be above the therapeutic range for warfarin levels. The therapeutic range is referred to as between 1-4 mg/dL. Patients who have taken warfarin for more than four days or who have reached steady state are able to determine the concentration steady-state (Css) formula: [11]

$$Cp = \frac{F \times D \times Ka}{Vd(Ka-K)}(e^{-k.t} - e^{-ka.t})$$

Note : *Cp = Drug levels in the blood* (mg/L); F = *Bioavailability fraction* (99%); D = *Warfarin dosage* (mg); τ = *Dose intervals* (hour); t = *Peak time* (hour); Vd = *Volume distribution* (Liter) (0.14 L/kg); K = *Elimination rate constant* (jam^{-1}); (K = $\frac{0.693}{\frac{t1}{2}elimination}$, $t^1/_2$ elimination = 40 hours); Ka = Absorption rate constant (jam^{-1}); (Ka = $\frac{0.693}{\frac{t1}{2}absorption}$, $t^1/_2$ absorption= 0,5 hour)

Through monitoring the patient's blood warfarin levels and using the Concentration Steady State (Css) and Plasma Concentration (Cp) formulas to estimate warfarin levels pharmacokinetically, the study was able to determine the patient's warfarin levels based on the dosage and interval of warfarin administration.[11]

The clearance calculation procedures involve multiplying a volume of distribution, which is determined by multiplying the body weight of each patient by a set value of 0.693 and dividing the result by the 40-hour half-life of warfarin. The concentration steady state average (C_{SS} ave) formula is then filled in with the estimated clearance value. In the meantime, the elimination rate (k), which is determined by dividing the constant value by the warfarin half-life, is used to estimate C_{SS}min and C_{SS}max. This results in an elimination rate value of 0.0173 hours per day. The 693 and dividing the result by the 40-hour half-life of warfarin. The consentration steady state minimum (C_{SS}min) and concentration steady state maximum (C_{SS}max) formulas are then filled in using the estimated elimination rate values. The Ka value (absorption rate constant) used for Cp calculations is obtained by dividing the constant value by the absorption half-life of warfarin, which produces a value of 1.386 hours.

When a fixed dose is administered at the same drug administration interval, the concentration steady state average represents the average drug concentration in plasma during the dosing period at steady state. In addition to the concentration steady state average, estimates for concentration steady state maximum and concentration steady state minimum are also obtained. The maximum and lowest drug concentrations in plasma at steady state that result from administering a set dose at the same dosing interval are known as C_{SS}max and C_{SS}min. Cp is the medication's plasma concentration. For patients whose warfarin usage has occurred for no fewer than four days, steady state warfarin levels (Css) are determined; for patients whose warfarin use has lasted for less than four days, Cp is utilised. The drug's elimination half-life should be taken into consideration while calculating dosage intervals.[11]

Dependent Variable

The accordance of the usual INR value is the research's dependent variable. When treating atrial fibrillation with warfarin, the preferred INR value is in the range of two and three.[12]

Eligibility criteria

The study sample included patient medical record data that fulfilled the inclusion criteria. The inclusion criteria in question are as follows: patients with complete medical records that include patient identity (age, gender, weight, and medical history), drug history (dose, interval within warfarin administrations, and length of warfarin administration), and objective data (INR) are those who are diagnosed with atrial fibrillation and are being treated with oral warfarin therapy. The study excluded patients who died while taking warfarin and those who were pregnant.

RESULTS AND DISCUSSION

The population of inpatient atrial fibrillation patients at Prof. Dr. Margono Soekarjo Hospital in the period January 2019–December 2021 was 697. Of the samples obtained, 63 patients met the inclusion criteria, and 10 patients met the exclusion criteria because they died while using warfarin. Of the 63 patients, there were 6 who used 2 different doses of warfarin, so the total number of cases calculated by pharmacokinetic blood levels of warfarin was 69.

Patient Characteristics

The characteristics of the 63 patients included in the inclusion criteria are presented in Table I. The results of the study show that the number of male patients is greater than that of female patients, namely 55.56% and 44.44%. The results of this study are in accordance with research by Chung, M.K., et al. (2020), which stated that the prevalence of atrial fibrillation in 1990–2010 was that men had a higher prevalence every year than women.[13] There are several things that influence the difference in the incidence of atrial fibrillation in men and women, such as anatomical factors in the form of the size of the left atrium and hormonal factors. Men have a larger atrium than women.[14] The left atrium plays a major role in cardiac physiology by collecting blood during systole and modulating left ventricular filling during diastole. Left ventricular diastolic dysfunction or mitral valve disease can cause pressure on the left atrium and volume overload, which, if maintained, can result in remodelling and enlargement of the left atrium. In this regard, left atrial enlargement is associated with a higher risk of atrial fibrillation (4–7) and cardiovascular events.[15] Sex hormones also influence the incidence of atrial fibrillation. The incidence of atrial fibrillation in premenopausal women is low but increases after menopause. This is due to post-menopausal hormonal changes, namely estrogen. With reduced oestrogen levels after menopause, blood pressure, cholesterol, metabolic syndrome, and BMI increase, which can develop into atrial fibrillation. In men over 80 years of age, reduced testosterone levels increase the risk of atrial fibrillation threefold.[16] Lifestyle factors can also influence the risk of atrial fibrillation, such as men having a higher prevalence of being overweight, smoking, and consuming alcohol compared to women. Smoking, alcohol consumption, and overweight/obesity showed moderate to strong associations with atrial fibrillation. The risk of atrial fibrillation differed substantially across the spectrum of health behaviours, with a 282% increased risk in people who smoked, drank more alcohol (14 units/week), and were obese compared with normal-weight nonsmokers with no or no alcohol consumption. Avoiding these three health behaviours could help prevent approximately 25% of all cases of atrial fibrillation in the population if a direct causal effect of these behaviours is assumed.[17]

The age characteristics of the patients in this study are categorised based on the World Health Organisation (2021), which states that the age categories of patients are divided into 3 categories: 0–18 years

Table I. Patient Characteristics

Patient Characteristics	Amount (n)	Percentage (%)
Gender		
Male	35	55.56
Female	28	44.44
Age (WHO, 2021)		
19-60 y.o (Adult)	31	49.2
>60 y.o (Elderly)	32	50.8
Primary Diagnosis		
Cardiovascular		
Atrium Fibrillation	36	57.14
Congestive Heart Failure	10	15.87
Stroke infarct	4	6.34
Premature Ventricular Contractions	2	3.17
Mitral Valve Insufficiency	2	3.17
Bronchopneumonia	2	3.17
Others	5	7.93
Non-Cardiovascular		
Pertrochanteric fracture	1	1.58
Leukemia	1	1.58
Secondary Diagnosis		
Cardiovascular		
Atrium Fibrillation	27	20.3
Congestive Heart Failure	22	16.54
Mitral stenosis	10	7.51
Pneumonia	10	7.51
Cardiomegaly	9	6.76
HHD	9	6.76
Premature ventricular contractions	7	5.26
Bronchopneumonia	5	3.75
Chronic cardiac ischemia	5	3.75
Mitral valve insufficiency	4	3
Others	25	18.79
Non-Cardiovascular		
Dyspepsia	10	12.5
Hypokalemia	9	11.25
Kidney failure	6	7.5
Hyperkalemia	6	7.5
Others	49	61.25

old is children, 19–60 years old is adults, and over 60 years old is elderly. Based on table I, the characteristics of patients in this study show that there are more elderly patients (> 60 years) than adult patients (19–60 years), namely 50.8% and 49.2%. These results are in accordance with research by Morseth, B., et al. (2021) showing that the incidence of atrial fibrillation increases with age.[18] The prevalence of atrial fibrillation increases exponentially at age 50 and increases rapidly after age 70.[19] When it comes to atrial fibrillation, a 40-year-old man has a 26% chance and a 22.7% risk of experiencing it when he is 80 years old, whereas a 40-year-old woman has a 23% danger and a 21.6% risk when she is 80 years old.[20] Patients who are older than those who are younger are more susceptible to warfarin. These multifactorial age-related alterations in drug response include reduced clearance, albumin binding, and renal excretion, all of which affect pharmacokinetics. Furthermore, through drug-drug and disease-drug interactions, older patients with more concomitant diseases and concurrent medication use may have complex impacts on the effects of warfarin.[21] Patients with structural heart disease, comorbidities, and cardiovascular risk factors are more likely to die from atrial fibrillation. Atrial fibrillation and comorbidities can often lead to heart disease. Hypertension (67–76%), heart failure (22–42%), diabetes (20–

24%), obesity (20–35%), chronic lung disease (10–18%), thyroid dysfunction (8–11%), kidney failure (11–22%), stroke/transient ischemic attack (9–16%), and neuropsychiatric disorders (19%) are among the most common comorbidities.[22] In this study, based on Table I, heart failure is the most common cardiovascular disease that accompanies the incidence of atrial fibrillation, both in primary diagnosis (15.87%) and secondary diagnosis (16.54%).

Heart failure occurs due to tachycardia, fibrosis, and irregular atrial contractions, which are the pathophysiological causes of atrial fibrillation. Diastolic dysfunction, or shortening the heart's relaxation period during diastole when the ventricles fill with blood, occurs when brought on by prolonged tachycardia. A rapid heartbeat shortens the time the ventricles can fill, disrupting ventricular relaxation and leading to heart failure. The ventricles may become rigid due to fibrosis, which makes it difficult for them to contract during diastole. It might also aggravate the symptoms of heart failure.[23] The incidence of atrial fibrillation in heart failure patients was 46.7%, significantly increasing the risk of acute heart failure hospitalisation[24]. Meanwhile, the most common non-cardiovascular disease that accompanies atrial fibrillation is dyspepsia (12.5%).

Usage Patterns for Oral Warfarin

Based on the results of this study, there were five dosage regimens given to inpatients diagnosed with atrial fibrillation. These doses are 1 mg, 2 mg, 3 mg, 5 mg, and 6 mg, given every 24 hours. Based on Table II, it is known that the warfarin dose of 2 mg every 24 hours is the dose most commonly used in atrial fibrillation patients, with a total of 62 patients (89.87%). The range of warfarin doses used in this study was around 1 mg–6 mg/day, so the warfarin dose used was lower than the dose recommended by PIONAS BPOM (2023), which states that usually the dose of warfarin is a continued support or maintenance dose in adults for atrial fibrillation patients. is 3 mg–9 mg/day, depending on prothrombin time. The usual induction dose of warfarin in adults with atrial fibrillation is 10 mg/day for 2 days, and higher doses are not recommended.[25] However, according to Effendi (2017), the principles of atrial fibrillation therapy are: antithrombotic for stroke prevention, heart rate control, heart rhythm control, and additional therapy. The warfarin dose used must be adjusted to the INR target of 2–3.[26] Following the start of treatment, the frequency of INR testing decreases when the INR response is monitored until an established dose-response correlation is maintained.[27] The amount of warfarin used must be suitable for the patient's condition; otherwise, bleeding events such as hematuria, melena, excessive bruising, or decreased haemoglobin will occur. In addition, taking a high dose of warfarin can result in bleeding or thrombosis.[9,28]

Many variables, including age, gender, comorbidities, nutritional state, concurrent use of drugs, compliance, and genetic polymorphisms, affect a patient's response to warfarin.[29,30] Numerous factors, including age, gender, comorbidities, nutritional condition, concurrent drug usage, compliance, and genetic polymorphisms, affect a patient's reaction to warfarin.[8] Age and genetic variants in VKORC1 and CYP2C9 affect the variability of INR values among Indonesians, while gender, body weight, and concurrent use of other medicines have little effect on INR values.[31] A number of variables, including failure with therapy, drug interactions (pharmaceutical or herbal), dietary or alcohol intake changes, comorbid or systemic disorders, or other unidentified causes, can affect INR values that fluctuate in individuals. Patient noncompliance is one of the variables that can alter the INR.[32]

Warfarin Levels in Blood Estimated Using Pharmacokinetics

Data used to calculate estimated levels include warfarin dose (mg), warfarin bioavailability (99%), patient body weight, volume of distribution (L), clearance value (L/hour), peak time (hours), and warfarin administration interval (hours). Data regarding warfarin dose (mg), patient weight (kg), and warfarin administration interval were obtained through patient medical record data at Prof. Dr. Margono Soekarjo Hospital, Purwokerto. Data regarding warfarin's bioavailability of 99%, distribution volume of 0.14 L/BW, and warfarin's half-life of 40 hours were obtained from the literature.[33] Patients may suffer toxic effects because the drug concentration is too high (exceeding C_{SS} max) or subtherapeutic effects because the drug concentration is too low (lower than C_{SS} min).[34]

This study's findings showed that 69 inpatient atrial fibrillation cases were treated with warfarin. Of the patients in this case, 4 (5.79%) had warfarin levels that were within the therapeutic limit, and 65 (94.21%) had levels that were below it. The findings of this investigation are consistent with a study conducted in 2020 by Rahmatini, R., et al., which showed that more patients had warfarin concentrations below 1 mg/L than patients with concentrations within the therapeutic range; especially, of a total of 45 patients, 23 patients (51%) had concentrations below 1 mg/L.[35] According to research from Furdiyanti, N.H., et al. (2014), of 86 patients, only

Table II. Warfarin Use Patterns in Inpatient Atrial Fibrillation Patients Based on Dosage at Prof. Dr. Margono Soekarjo Hospital, Purwokerto

Dosage warfarin	Number of Patients	(%)
1 mg/24 hours	2	2.9
2 mg/24 hours	62	89.87
3 mg/24 hours	3	4.35
5 mg/24 hours	1	1.44
6 mg/24 hours	1	1.44
Total	**69**	**100**

10.47% had warfarin levels in the therapeutic range on day 7, only 8.14% had levels in the therapeutic range on day 10, and only 10.47% had levels in the therapeutic range on day 30.[8] Table III shows the pharmacokinetic estimate of warfarin blood levels.

Variations in parameter values in pharmacokinetic calculation, such as volume of distribution (Vd) and clearance (Cl), caused variations in the drug levels in the blood of research respondents. The literature's volume of distribution and clearance values which are often Caucasian in race were collected from studies conducted with non-Indonesian populations.[36] Additionally, variations in the dosages administered, the use of additional medications, and individual variability may have contributed to variations in the drug levels in the blood of the study's participants. It's important to think about dosage settings and delivery frequency to ensure that blood medication levels stay within the therapeutic range. In general, a medicine won't have a therapeutic effect if its level is below the minimum effective concentration (MEC). On the other hand, signs of drug toxicity often manifest if the drug level in the blood surpasses the minimum toxic concentration (MTC). A number of combinations is another significant factor that might have an important effect on the medication levels in a treatment regimen.[37] The measurement of drug levels in the blood is significantly influenced because of individual variability, which includes factors such as body weight, drug dosage, age, gender, and polytherapy.[38]

Table III shows patients with steady-state warfarin levels (Css). Of the four patients who had warfarin levels within the therapeutic range, only two had normal INR values, namely patient no. 17 and patient no. 45, while patients no. 14 and 18 had warfarin levels within the therapeutic range, but based on examination of the INR values, these patients had INRs greater than 3. Based on medical records, patient number 14 experienced clinical improvement in the form of reduced shortness of breath and improvement in vital signs in the form of normal RR (respiratory rate) and pulse. Both patients did not experience symptoms of toxicity such as coughing up blood, nosebleeds, or bloody stools after 4 days of using oral warfarin. In addition, based on patient medical record data, patient No. 17 had warfarin levels in the therapeutic range and had a normal INR range, indicating that the patient had clinical improvement, namely reduced shortness of breath and abdominal pain and improvement in vital signs (normal pulse and respiratory rate). This can be caused because the onset of action of warfarin is usually 24 to 72 hours. The half-life of warfarin is generally 40 hours, so peak therapeutic effects can be seen 5 to 7 days after initiation.[39] Therefore, it can be stated that warfarin's therapeutic effects can endure in the body for a while, even if its levels are below what is suggested.

Besides that, a different administration dose is another factor that affects the impact of variable warfarin levels in the blood on the clinical improvement of the patient. The correlation between dosage and drug concentration in the blood is significant. Higher doses usually result in higher levels, while smaller amounts usually generate lower levels. It's important to think about dosage settings and delivery frequency to ensure that blood medication levels stay within the therapeutic range. In general, a drug can't have a therapeutic effect if its level is below the minimal effective concentration. However, signs of drug toxicity usually surface if the blood drug level is higher than the minimum toxic concentration.[10] The correlation between dosage and plasma, or drug concentration in the blood, serves as a foundation for drug therapy monitoring. Drug levels in the blood can be estimated, and this data can be used to adjust the dosage to get the right concentration and therapeutic effect.[40] According to the study's findings, participants' blood levels of warfarin vary even though they received the same dose of the drug. Age variants, drug interactions during therapy, hepatic and renal function problems, and comorbidities are among the reasons for this.[10,21,41]

Drug interactions also affect warfarin levels in the blood. The presence of combinations in a therapeutic regimen can significantly influence drug levels.[40] Protein-binding interactions are one of the pharmacokinetic mechanisms of drug interactions with warfarin. This interaction may cause warfarin to be eliminated from protein binding sites, increasing warfarin concentrations in free plasma and increasing the potential for warfarin

Table III. Estimation of steady-state Warfarin levels (C_{SS} ave, C_{SS} max, and C_{SS} min) in Atrial Fibrillation Patients at Prof. Dr. Margono Soekarjo Hospital, Purwokerto.

No	Warfarin dose (mg/day)	Vd (L)	Cl (L/hour)	Estimating levels (mg/L)			INR
				C_{ss} ave	C_{ss} max	C_{ss} min	
1	2	0.14	0.121	0.680	0.808	0.525	2.76
2	2	0.14	0.133	0.618	0.735	0.478	1.01
3	2	0.14	0.194	0.425	0.505	0.328	1.43
4	3	0.14	0.158	0.523	0.622	0.404	1.02
5	2	0.14	0.121	0.680	0.808	0.525	1.09
6	6	0.14	0.146	0.283	0.337	0.219	1.09
7	2	0.14	0.097	0.850	1.010	0.657	1.20
8	2	0.14	0.218	0.378	0.449	0.292	1.54
9	2	0.14	0.150	0.549	0.652	0.424	1.31
10	2	0.14	0.150	0.549	0.652	0.424	1.34
11	2	0.14	0.218	0.378	0.449	0.292	1.47
12	2	0.14	0.158	0.523	0.622	0.404	1.71
13	2	0.14	0.121	0.680	0.808	0.525	1.03
14	2	0.14	0.121	1.020*	1.212	0.788	5.04
15	2	0.14	0.158	0.523	0.622	0.404	6.18
16	2	0.14	0.170	0.486	0.577	0.375	1.92
17	2	0.14	0.146	1.417*	1.684	1.094	1.13
18	2	0.14	0.146	1.701*	2.020	1.313	6.00
19	2	0.14	0.121	0.680	0.808	0.525	1.64
20	2	0.14	0.146	0.567	0.673	0.438	1.21
21	1	0.14	0.133	0.309	0.367	0.239	4.2
22	2	0.14	0.146	0.567	0.673	0.438	1.19
23	2	0.14	0.116	0.709	0.842	0.547	3.15
24	2	0.14	0.116	0.709	0.842	0.547	1.99
25	2	0.14	0.121	0.680	0.808	0.525	1.36
26	3	0.14	0.194	0.638	0.758	0.492	1.24
27	2	0.14	0.158	0.523	0.622	0.404	3.60
28	2	0.14	0.114	0.724	0.860	0.559	3.37
29	2	0.14	0.211	0.391	0.464	0.302	1.01
30	2	0.14	0.124	0.667	0.792	0.515	1.49
31	2	0.14	0.114	0.724	0.860	0.559	1.07
32	2	0.14	0.146	0.567	0.673	0.438	3.48
33	2	0.14	0.121	0.680	0.808	0.525	1.98
34	2	0.14	0.177	0.466	0.554	0.360	1.23
35	2	0.14	0.121	0.680	0.808	0.525	1.08
36	2	0.14	0.097	0.850	1.010	0.657	0.91
37	2	0.14	0.121	0.680	0.808	0.525	1.36
38	2	0.14	0.201	0.410	0.487	0.316	1.01
39	2	0.14	0.143	0.577	0.685	0.445	1.77
40	2	0.14	0.121	0.680	0.808	0.525	4.92
41	2	0.14	0.170	0.486	0.577	0.375	1.92
42	2	0.14	0.182	0.454	0.539	0.350	1.64
43	2	0.14	0.090	0.919	1.092	0.710	1.26
44	2	0.14	0.107	0.773	0.918	0.597	0.92
45	3	0.14	0.116	1.063*	1.263	0.821	1.42
46	2	0.14	0.114	0.724	0.860	0.559	7.93
47	2	0.14	0.182	0.454	0.539	0.350	1.15
48	2	0.14	0.194	0.425	0.505	0.328	1.45
49	2	0.14	0.109	0.756	0.898	0.584	2.5

Table III. (Continued)

No	Warfarin dose (mg/day)	Vd (L)	Cl (L/hour)	Estimating levels (mg/L)			INR
				C_{ss} ave	C_{ss} max	C_{ss} min	
50	2	0.14	0.109	0.756	0.898	0.584	7.92
51	2	0.14	0.109	0.756	0.898	0.584	7.28
52	2	0.14	0.099	0.830	0.986	0.641	2.94
53	2	0.14	0.124	0.667	0.792	0.515	6.80
54	2	0.14	0.112	0.739	0.878	0.571	1.37
55	2	0.14	0.133	0.618	0.735	0.478	1.42
56	2	0.14	0.146	0.567	0.673	0.438	1.45
57	2	0.14	0.097	0.850	1.010	0.657	5.35
58	2	0.14	0.097	0.850	1.010	0.657	4.85
59	2	0.14	0.146	0.567	0.673	0.438	1.36
60	2	0.14	0.124	0.667	0.792	0.515	2.24
61	2	0.14	0.114	0.724	0.860	0.559	0.98
62	2	0.14	0.170	0.486	0.577	0.375	1.60
63	2	0.14	0.170	0.486	0.577	0.375	2.43
64	2	0.14	0.141	0.586	0.697	0.453	1.06
65	2	0.14	0.097	0.850	1.010	0.657	1.09
66	2	0.14	0.121	0.680	0.808	0.525	1.81
67	2	0.14	0.150	0.549	0.652	0.424	1.14
68	2	0.14	0.121	0.680	0.808	0.525	1.25
69	2	0.14	0.146	0.567	0.673	0.438	3.05

Note = *within the therapeutic range (1-4 mg/L)

toxic exposure.[41] Warfarin concentrations are influenced by liver and kidney function. Damage to the kidneys can change the responsiveness and bioavailability of drugs that are mostly metabolised by the liver, as well as decrease non-renal clearance. Warfarin dosages for patients with moderate to severe renal impairment should be lower than for those without mild renal impairment. Warfarin levels may increase as a result of reduced kidney function, increasing the risk of bleeding.[42] Furthermore, because the liver is the main pathway of warfarin treatment, abnormal liver function may increase warfarin levels, lower coagulation factors, and increase the risk of bleeding. Because the metabolism of warfarin depends on cytochrome P450 enzymes, people with liver diseases or disorders may have changes in the activity of these enzymes.[43]

When using warfarin anticoagulant therapy, the risk of adverse events can be prevented by monitoring therapeutic levels and monitoring INR. Individual patient factors such as compliance, dosage, and INR monitoring play an important role in the success of warfarin therapy in atrial fibrillation patients.[44] The purpose of monitoring INR readings in this study is to keep current with patients' warfarin drugs. An INR of two to three should be considered while treating bleeding in atrial fibrillation.[12] This range is used to lower the risk of systemic embolism and prevent venous thromboembolism in patients with valvular heart disease and atrial fibrillation.[45]

Correlation of Warfarin Levels with Corresponding Normal INR Values

The purpose of this study was to determine the normal INR value for patients with atrial fibrillation who were taken to Prof. Dr. Margono Soekarjo Hospital, Purwokerto, and the blood levels of warfarin. Spearman For the purpose of finding out if there was a correlation between the two variables, a test analysis occurred. Table IV shows the analysis results.

Based on these results, the number of patients who had normal INR values was smaller than the number of patients who had abnormal INR values, namely 21 patients and 48 patients. The results of the Spearman-test statistical analysis showed a p value of 0.31 ($p > 0.05$), meaning that the correlation between warfarin levels in the blood and the corresponding INR value was not significant. The same results were also shown in research by Furdiyanti, N.H., et al. (2014), showing the results of the Spearman correlative test between warfarin levels in the blood and the INR value, which showed a value of $p = 0.180$ ($p > 0.05$), meaning the correlation between warfarin levels in the blood and insignificant INR values[8]. Separate from that, research by

Table IV. Correlation of warfarin levels in patients who have normal INR values

Compatibility of INR Normal Values	Number of Patients	INR (Mean ± SD)	Warfarin levels (mg/L) (Mean ± SD)	*p value*	*R*
The normal INR value is appropriate.	21	(1.33±0.29)	(1.30±0.32)	0.31	0.122
The normal INR value is not appropriate.	48	(4.57±1.85)	(0.61±0.14)		
Total	**69**				

Suryoputri, M.W., et al. (2020) shows drug levels and clinical outcomes obtained in respondents who used monotherapy or polytherapy of valproic acid have no significant correlation ($p > 0.05$).[10]

The Spearman test result for this study's R value is R = 0.122, showing a positive correlation with a very weak correlation strength. This study correlates with that of Furdiyanti, N.H., et al. (2014), who found that the Spearman test correlation coefficient measured an r value of 0.146, indicating a very low, even positive correlation strength and direction.[8] Many variables, such as the amount of the warfarin dose, drug interactions, noncompliance, alcohol, smoking, and genetic factors, may contribute to the failure to achieve a normal INR.[42] In this study, 62 of the 69 patients who had atrial fibrillation received 2 mg of warfarin daily. The AHA/ACC Guideline to Warfarin Therapy (2014) states patients with atrial fibrillation using a dose of 5 mg/day will achieve an INR value > 2 in 5–6 days. Whereas the 5 mg dose had a mean time for achieving the target INR of 2.0–3.0 in a study by Agustini, T., T., et al. (2016), which was significantly different compared to the 2 mg dose and the 4mg dose.[44] However, warfarin dosing is highly individualised for each patient, and maintenance of warfarin dosing can be challenging due to variations in patient characteristics.[46] Drug and/or food interactions can also affect absorption and inhibit the anticoagulant effect of warfarin, requiring higher warfarin doses to achieve therapeutic INR. Factors in warfarin distribution can also influence INR values. Warfarin is highly bound to plasma proteins. Changes in protein levels or protein binding interactions can result in the displacement of warfarin from protein binding sites, increasing free warfarin plasma concentrations, and potentially affecting INR values.[42]

Numerous drugs and herbal products have the ability to either increase or decrease the effects of warfarin levels. According to data obtained from medical records, 52 out of 69 patients in this study used digoxin and warfarin, 21 out of 69 patients used bisoprolol and warfarin, and 13 out of 69 patients used aspirin and warfarin. Digoxin and aspirin use together may increase the risk of bleeding, so warfarin doses must be adjusted based on prothrombin time, or INR. Additionally, vitamin K-rich foods (broccoli, spinach, lettuce, mustard greens, and kale) may increase warfarin levels when combined with warfarin in the body, which decreases warfarin's effectiveness.[47] This risk may further increase with patient age and other diseases.[48] Additionally, other drugs, such as cimetidine, can increase INR by inhibiting the metabolism of R-warfarin. Concomitant use of warfarin with salicylates may cause an increased risk of bleeding because salicylates inhibit platelet aggregation, may cause gastric irritation, and result in increased free warfarin levels because salicylates have a higher affinity for protein binding sites. Phenytoin may cause an increase or decrease in INR. After the initiation of phenytoin, the INR may increase due to the displacement of warfarin from protein binding sites. Meanwhile, there are interactions between warfarin and herbal products. Green tea has been associated with inhibiting the effects of warfarin and decreasing INR due to its high amount of vitamin K.[49]

The amount of warfarin needed to achieve desired anticoagulation and the amount of treatment needed to reach target INR vary significantly among individuals. Clinical or lifestyle factors (e.g., patient age, weight, BMI, gender, smoking status, medical history, and current medications) as well as genetic factors have been shown to relate to some of these differences. The two most significant known genetic predictors of warfarin dosage are the VKORC1 and CYP2C9 genotypes. The enzyme vitamin K epoxide reductase, which has been encoded through the VKORC1 gene, triggers the rate-limiting step in vitamin K recycling, which is the reduction of vitamin K epoxide to vitamin K. Warfarin is another medication that affects this enzyme. Variations in VKORC1 genetics might enable patients to take warfarin at different dosages. Higher warfarin dosages are needed in individuals with elevated VKORC1 enzymes in order to achieve the target concentration. The liver's CYP2C9 enzyme has responsibility for taking down warfarin. In affecting the rate of warfarin metabolism, CYP2C9 variability might have an impact on the body's level of warfarin. This genetic variability may affect the amount of warfarin that needs to be given in order to achieve the necessary INR range.[50]

There might be other medications that can affect warfarin levels because the pharmacokinetic estimation of warfarin levels in this study didn't take into consideration other drug use in patients. It is crucial to take into

consideration other factors that could have an influence on the INR value if it is within the therapeutic range while the warfarin level in the blood remains below the target. Adjusting the warfarin dose is necessary if monitoring shows bleeding events in patients. The warfarin dose is required to be adjusted to enhance clinical outcomes and patient safety. In addition, the limited sample size in this study could have an influence on the correlation between patients' warfarin levels and appropriate INR values.

CONCLUSION

Based on the results of this study, it can be concluded that the correlation between warfarin levels in the blood and the appropriate INR value is not significant ($p > 0.05$), where the R value in the Spearman test shows $R = 0.122$, meaning the direction of the correlation is positive with a very weak correlation strength.

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STATEMENT OF ETHICS

This study complies with ethical guidelines and has been granted approval by Prof. Dr. Margono Soekarjo, Hospital, Purwokerto, Ethics Committee under reference number 420/04627, April 2022.

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Assessing Job Satisfaction of Community Pharmacists with The Warr-Cook-Wall Instrument in West Java

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ABSTRACT

Background: Improving the quality of public health cannot be separated from the role of pharmacists who are responsible for providing pharmaceutical services. Pharmacists' long working hours and great responsibility impact how satisfied they feel with their jobs.

Objectives: This study aims to determine the level of job satisfaction and identify the variables that affect community pharmacists' job satisfaction in West Java.

Methods: A cross-sectional study conducted in mid-December 2022 to mid-February 2023 with research subjects' community pharmacists working in pharmacies, primary health centers or clinics in the West Java region. A convenience sampling technique was used for selecting a community pharmacist. This study involved 145 community pharmacists and used a semi-structured questionnaire, Warr-Cook-Wall satisfaction scale and implemented the Likert scale to describe pharmacists' job satisfaction of community pharmacists in West Java. The analysis used is univariate analysis (descriptive and distribution analysis) and bivariate analysis (multiple regression linear analysis).

Results: Most community pharmacists in West Java are more satisfied with the variables in the intrinsic factor (3.0±0.66) than extrinsic factors (3.0±0.70). However, their satisfaction is still low on recognition (2.9±0.7) and income (2.7±0.8). Community pharmacists' job satisfaction is influenced by pharmacy ownership type (p=0.04) and working hour (p=0.05). The regression analysis indicates that working hour had negatively influenced job satisfaction.

Conclusion: Community pharmacists feel satisfied with their job, and their satisfaction level is affected by pharmacy working hours.

Keywords: Community pharmacist; Job Satisfaction; Warr-Cook-Wall Instrument.

INTRODUCTION

The age and life expectancy is one of the indicators used to estimate the average length of life of the population. [1,2] According to H.L. Blum, The community's health status may be impacted by the factors of the health services offered. [3] Therefore, the quality of public health can be improved by providing the best health services, especially in primary health facilities that are easily accessible to the community and are the first place to visit. Primary health facilities or the community sector, include pharmacies, health centers, and clinics. [4,5]

Improving the quality of public health cannot be separated from the role of pharmacists who are responsible for providing pharmaceutical services. Pharmacists must rationalise drug usage and provide patient counselling regarding the prescribed medications to increase patient outcomes. [6] Generally, from drug selection to delivery, pharmacists are responsible for every element of patient care. This is due to the transition in services from drug management to drug management and clinical pharmacy services to improve patients' quality of life. [7] Pharmacists' long working hours and excellent responsibility have an impact on how satisfied they feel with their jobs. [8]

Job satisfaction is a variable that indicates how someone feels about their work and can be achieved by meeting the expectations of each person who involved in the job. [8] Higher job satisfaction can help pharmacists perform better, such as making good patient interactions and patients who trust them to voice their concerns. Additionally, this affects pharmacists' commitment to the organization and may reduce their desire to leave their jobs. [6,8] Low job satisfaction among pharmacists can lead to issues with patient care, including incorrectly administration, a lack of counselling, the incidence of drug side effect, medication interactions, and even deadly issues including patient mortality. [9]

Throughout time, factors arising from individual human resources, environment and management can have different impacts on job satisfaction. [10] There have been many studies related to job satisfaction of community pharmacists conducted in many countries around the world. Previous research conducted in Lithuania, reported that factors that can reduce pharmacists' job satisfaction are workplace character, individual variation, repetitive work, heavy workload, work conflict, and inadequate salary. [6] In addition, research in Iraq reported that sociodemographic characteristics such as age and gender strongly influence job satisfaction, while years in practice, working patterns and working hours also influence but are not too high. [8] Research conducted in Indonesia shows that the factors that influence the job satisfaction of pharmacists in Pratama clinics in Pekanbaru City are job security (78.9%), treatment (78.8%), relationships with colleagues (78.0%), promotions and salaries (77.3%), and relationships with bosses (76.0%). [11]

In addition, many pharmacists in Indonesia work in primary health care facilities. Based on data from the Indonesian Health Profile and Health Workforce Ratio documents, the province with the most primary health care facilities (pharmacies, health centers and clinics) in Indonesia is West Java, followed by Central Java and East Java. [12,13] Of course, this is an important task for the Indonesian Pharmacists Association, especially for these three provinces, as a professional organization to always monitor and pay attention to the job satisfaction of community pharmacists which can affect pharmacist performance. However, at present, researchers have little information regarding the factors that influence the job satisfaction of community pharmacists in the three provinces, especially in West Java. Therefore, this study aims to determine the level of job satisfaction of community pharmacists in West Java and the factors that influence it.

METHODS

Study design

This research used a cross-sectional study design conducted on community pharmacists in West Java.

Population and samples

There are 18 districts and nine cities included in the West Java IAI PD area. The process of distributing and waiting for questionnaires to be filled in was carried out from mid-December 2022 to mid-February 2023. The research subjects used in this study were pharmacists working in the community sector (pharmacies, primary health care, and clinics) in West Java Province. The respondents were selected using convenience sampling based on their willingness to participate. The selection of study participants is selected based on the inclusion criteria, there are (1) pharmacists who work in the community (pharmacies, Primary health centers, or clinics), (2) Having worked for at least six months with the perception that the pharmacists were familiar and aware of the workplace policies, (3) Willing to fill out online questionnaire, but if the participants did not complete the questionnaire, will exclude from this study.

The total population of community pharmacists working in the community sector (pharmacies, primary health care, and clinics) is 3,475 pharmacists. [13] The calculation used 95% Confidence Interval (CI), and 10% sampling error, and we use the formula with total population known. [14]

$$\boldsymbol{n} = \frac{\boldsymbol{NZ}_{\left(\mathbf{1}-\frac{\boldsymbol{a}}{\mathbf{2}}\right)}^{\mathbf{2}}\boldsymbol{P}\,(\mathbf{1}-\boldsymbol{P})}{\boldsymbol{Nd}^{\mathbf{2}} + \boldsymbol{Z}_{\left(\mathbf{1}-\frac{\boldsymbol{a}}{\mathbf{2}}\right)}^{\mathbf{2}}\boldsymbol{P}\,(\mathbf{1}-\boldsymbol{P})}$$

n = number of sample, N = number of population, $Z_{(1-a/2)}$ = CI, P = Proportion of occurence, and d = sampling error. Therefore, the minimum sample obtained from the formula is 93.5 respondent, and round up to 100 respondent.

Study instruments

This study used a self-administered semi-structured questionnaire and validated questionnaire from previous study and was translated from English to Indonesian and back into English. [8,15] The validity test was carried out by testing construct validity and using the opinions of experts (judgment experts), in this study

assisted by a supervisor from the Faculty of Pharmacy UGM who has experience in social research. The instrument divided into three sections which aim to measure the research variables: (1) demography and job characteristics (age, gender, marriage status, education level, working location, the institution of work, distance to the workplace, time spent at the workplace, working experience, income, length of practice, job position, pharmacy ownership type, type of primary health center, type of pharmacy, working hour, average patient a day, average prescription a day, and other institutions), (2) pharmacist job satisfaction (modified Warr-Cook-Wall satisfaction scale), which was used to assess the level of job satisfaction; (3) examples of barriers affecting job satisfaction and pharmacist' opinions on future job options. [8,11,15–21]

The Warr-Cook-Wall questionnaire aims to measure job satisfaction that is divided into intrinsic and extrinsic factors. In this section, the tools consist of 19 questions from Warr-Cook-Wall instrument and the other study (recognition from other health workers, the amount of responsibility, the opportunity to use abilities, the amount of variety in a job, the freedom to choose the method of working, physical work conditions, fellow workers, boss, income, hours of work, the attention to the suggestion, and patient contact, Institutional support, skill and knowledge of non-pharmacists staff, facility, total staff, reward, and punishment). [8,15,19–21] Each parameter was scored using a four-point scale, namely, one means very dissatisfied, two means dissatisfied, three means satisfied, and four means very satisfied. To assess job satisfaction, the scores were categorised as very dissatisfied ($1.0 \leq x \leq 1.75$); dissatisfied ($1.75 \leq x \leq 2.5$); satisfied ($2.5 \leq x \leq 3.25$); and very satisfied ($3.25 \leq x \leq 4.0$). [22] The questionnaire was tested on 30 respondents to see whether the measurements used were reliable and free from errors. The Cronbach's alpha value in all questions is above 0.90. These results show that the instruments used have good reliability and can be used to support the research.

Data collection

Data were collected by distributing Google Form links to respondents who met the inclusion criteria. The researcher contacted the respondents personally on the WhatsApp application, and the researcher asked for help from the secretary of the management of each IAI Branch Management in West Java to spread the questionnaire link through the member group in each West Java IAI Branch Management.

Data Analysis

The analysis in this study used statistical analysis software, and the collected data was analyzed with descriptive analysis to represent the total number of respondents as a number (n), a percentage (%), and mean ± SD; and distribution analysis with Mann-Whitney test and the Kruskal-Wallis test. The multiple regression linear analysis is used to measure the correlation between the independent variable (demographics and job characteristics factors) and the dependent variable (job satisfaction) both partially (T-test statistics) and simultaneously (F-test statistics). The significant value for all tests is $p<0.05$. Before conducting the t-test and f-test, it would be better if the classical assumption test stage is carried out, which consists of (1) multicollinearity analysis; (2) heteroscedasticity analysis; and (3) autocorrelation test.

RESULTS AND DISCUSSION

This study aims to determine the job satisfaction level of community pharmacists in West Java and the factors that influence it. In this study, the variables used were demographics and job satisfaction as independent variables and job satisfaction as the dependent variable consisting of intrinsic factors and extrinsic factors.

Demography and Job Characteristics

A total of 145 pharmacists were willing to participate in the survey. The dominant age of participants was between 31 and 40 years with 76.6% being female. Of the 27 regions, where pharmacists work in each city or district in the West Java Branch of the Indonesian Pharmacists Association, was categorized into three regions, and the most filled by pharmacists in region 2 (46.9%). Demographic characteristics are presented in Table I.

Pharmacist Job Satisfaction

Intrinsic factor

The intrinsic factors consist of five variable that are answered based on the Likert scale by choosing between a score of 1-4 (very dissatisfied – satisfied). As shown in Table II of the 145 respondents, majority of pharmacists answered that they were satisfied with the five variables. The highest mean was obtained from the

Table I. Demographic characteristics of community pharmacists

Characteristics	Category	n	%
Age	≤25	13	9.0
	26-30	52	35.9
	31-40	57	39.3
	>40	23	15.9
Gender	Male	34	23.5
	Female	111	76.6
Marriage status	Married	35	24.1
	Single	110	75.9
Educational level	Bachelor	129	89.0
	Master degree	16	11.0
Working location	Region I	38	26.2
	Region II	68	46.9
	Region III	39	26.9
Institution of work	Primary health centers	32	22.1
	Pharmacy	88	60.7
	Clinic	25	17.2
The distance to workplace	≤ 10 Km	113	77.9
	11 - 20 Km	23	15.9
	> 20 Km	9	6.2
Time spent to the workplace	≤ 15 minutes	69	47.6
	16 - 30 minutes	49	33.8
	> 30 minutes	27	18.6
Work experience in other than community pharmacy	Yes	78	53.8
	No	67	46.2
Currently having other jobs besides being a community pharmacist	Yes	80	55.2
	No	65	44.8
Job position	Owner	14	9.7
	Pharmacist in charge	90	62.1
	Vice Pharmacist	9	6.2
	Civil Servant	18	12.4
	Non-Civil Servant	14	9.7
Income	≤ Rp. 2,000,000	11	7.6
	Rp. 2,100,000 – Rp. 3,000,000	59	40.7
	Rp. 3,100,000 – Rp. 4,000,000	30	20.7
	> Rp. 4,100,000	45	31.0
Length or practice	≤ 5 years	94	64.8
	> 5 years	51	35.2
Pharmacy ownership type	Chain pharmacy	63	71.6
	Independent pharmacy	25	28.4
Type of primary health centers	Outpatient	23	71.9
	Inpatient	9	28.1
Type of pharmacy	Retail Pharmacy	76	86.4
	Non-retail pharmacy	12	13.6
Working hour	≤ 7 hours	80	55.2
	≥ 7 hours	65	44.8
Average patient a day	≤ 75 patients	101	69.7
	76 - 150 patient	30	20.7
	> 150 patients	14	9.7
Average prescription a day	≤ 50 prescriptions	110	75.9
	51 - 100 prescription	24	16.6
	> 100 prescriptions	11	7.6

Table II. The overview of job satisfaction based on intrinsic factors (n=145)

No	Variables	Level of Satisfaction				Mean ± SD	Conclusion
		Very Dissatisfied n (%)	Dissatisfied n (%)	Satisfied n (%)	Very Satisfied n (%)		
1	The recognition from other health workers	4 (3)	30 (21)	84 (58)	27 (19)	2.9 ± 0.7	Satisfied
2	The amount of responsibility	3 (2)	23 (16)	88 (61)	31 (21)	3.0 ± 0.7	
3	Opportunity to use the abilities	2 (1)	16 (11)	88 (61)	39 (27)	3.1 ± 0.6	
4	The amount of variety in a job	1 (1)	22 (15)	95 (66)	27 (19)	3.0 ± 0.6	
5	The freedom to choose a method of working	2 (1)	15 (10)	85 (59)	43 (30)	3.2 ± 0.7	
	Overall job satisfaction for intrinsic factors					**3.04 ± 0.66**	

Description: 1.0 ≤ x ≤ 1.75 Very dissatisfied; 1.75 ≤ x ≤ 2.5 Dissatisfied; 2.5 ≤ x ≤ 3.25 Satisfied; 3.25 ≤ x ≤ 4.0 Very satisfied

freedom to choose a method of working variable (3.2 ± 0.7), and overall job satisfaction of intrinsic factors obtained satisfied with the value 3.04 ± 0.66.

Extrinsic factor

The extrinsic factors domain consists of 12 variables. As shown in Table III of the 145 respondents, most respondents answered that they were satisfied with all variables, with the most significant percentage being the tenth question, "Are you satisfied with the number of patients you serve while working?" with 97 respondents (67%) answering satisfied. The highest mean was obtained from institutional support (IAI and Health Department) (3.2 ± 0.6), and overall job satisfaction of extrinsic factors obtained satisfied with the value 3.0 ± 07.

The results obtained from this study indicate that pharmacists working in the community sector (pharmacies, primary health centers, and clinics) in West Java are satisfied with their work which is in line with the results reported by research in developing countries conducted on community pharmacists in Iraq and Malaysia. [8,23] This value of job satisfaction can be explained by the assessment results from the Warr-Cook-Wall questionnaire, which show that community pharmacists in West Java are more satisfied with intrinsic factors, with the highest satisfaction being 'the freedom to choose their method of working' and the lowest satisfaction being recognition. In addition, on extrinsic factors, community pharmacists have the highest satisfaction with institutional support and the lowest satisfaction with income. Several studies that have been conducted have aligned results on factors that get low job satisfaction scores, name recognition, and income. [17,24,25]

Recognition is an important variable that affects job satisfaction, especially from the community. Looking back at Maslow's theory of job satisfaction, each individual has a level of job satisfaction (need hierarchy theory) divided into five levels. It is not easy to get the highest satisfaction value on the recognition item because it is at the fourth level, which the individual will only obtain if he or she has passed the previous levels of satisfaction, namely psychological, security, and social. [21,26] In this study, the reason the recognition variable is included in the important variables is that currently, not many people have noticed the presence of pharmacists, which may be due to pharmacists not having enough time to provide counseling or other interactions. In addition, pharmacists have other responsibilities as drug supply managers with monthly reporting to the Health Office and the Food and Drug Administration, which can reduce interaction time with patients. [17] From several studies that have been conducted, the income variable is indeed a variable that has a lower satisfaction value than other variables. Likewise, in this study, although the mean value obtained is still in the satisfied range, it is at the bottom of the rankings, indicating that many community pharmacists in West Java are not satisfied with their income. Pharmacists' dissatisfaction with the amount of salary they earn or the imbalance between income and costs, can reduce work motivation which has an impact on decreasing the level of job satisfaction of pharmacists, which is a common reason for employee retention. In work, income is an element that significantly contributes to job

Table III. The overview of job satisfaction based on extrinsic factors (n=145)

No	Variables	Level of Satisfaction				Mean ± SD	Conclusion
		Very Dissatisfied n (%)	Dissatisfied n (%)	Satisfied n (%)	Very Satisfied n (%)		
1	The physical work conditions	1 (1)	26 (18)	72 (50)	46 (32)	3.1 ± 0.7	
2	Fellow workers	2 (1)	12 (8)	82 (57)	49 (34)	3.2 ± 0.7	
3	Boss	3 (2)	29 (20)	68 (47)	45 (31)	3.1 ± 0.8	
4	Total staff	12 (8)	32 (22)	70 (48)	31 (21)	2.8 ± 0.9	
5	Skills and knowledge of non-pharmacist staff	1 (1)	22 (15)	89 (61)	33 (23)	3.1 ± 0.6	
6	Reward and punishment in job	11 (8)	34 (23)	73 (50)	27 (19)	2.8 ± 0.8	
7	Income	10 (7)	48 (33)	67 (46)	20 (14)	2.7 ± 0.8	Satisfied
8	Hours of work	2 (1)	14 (10)	96 (66)	33 (23)	3.1 ± 0.6	
9	Attention is given to your suggestions/public respect	3 (2)	24 (17)	86 (59)	32 (22)	3.0 ± 0.7	
10	Patient contact	2 (1)	21 (14)	97 (67)	25 (17)	3.0 ± 0.6	
11	Facility	5 (3)	28 (19)	87 (60)	25 (17)	2.9 ± 0.6	
12	Institutional support (IAI and Health Department)	2 (1)	12 (8)	92 (63)	39 (27)	3.2 ± 0.6	
	Overall job satisfaction for extrinsic factors					**3.0 ± 0.70**	

Description: 1.0 ≤ x ≤ 1.75 Very dissatisfied; 1.75 ≤ x ≤ 2.5 Dissatisfied; 2.5 ≤ x ≤ 3.25 Satisfied; 3.25 ≤ x ≤ 4.0 Very satisfied

satisfaction and is the most common reason for employee retention. [27,28] In addition, it is also essential to look at Herzberg's Two Factor Theory which explains intrinsic factors as motivational factors and extrinsic factors as hygiene factors that can affect job satisfaction. Achievement and recognition variables are included in the motivational factor, which, if fulfilled, will prevent employees from feeling less support. It has an impact on employee performance. One of the hygiene factors is salary. This variable has an important role that must be fulfilled in order to prevent employee dissatisfaction. [29,30]

The Differences between Independent and Dependent Variables

Table IV showed that the mean value of pharmacists' job satisfaction was more significant in the range of age between 31-40 (3.1±0.4; p>0.05); female pharmacists' (3.0±0.5; p>0.05); pharmacists' work in clinic (3.1±0.4; p>0.05); pharmacists with the income between Rp 2,100,000 – Rp 3,000,000 (3.1±0.5 p>0.05); pharmacists' who worked > 5 years (3.0±0.5; p>0.05). The other differences found in the working hours variable with the highest mean value is less than seven hours (3.1±0.5; p<0.05); and work in independent pharmacy (3.1±0.3; p<0.05).

Interestingly, the differences in job satisfaction based on the average number of patients per day served by pharmacists (76 - 150 patients) have the highest job satisfaction compared to others (3.1±0.5; p>0.05) and based on the average prescriptions per day by pharmacists' (51-100 perceptions) have the highest job satisfaction compared to others (3.1±0.5; p>0.05).

In this study, job satisfaction scores were significantly influenced by pharmacy ownership type, with pharmacists working in independent pharmacies having high satisfaction scores against pharmacists working in chain pharmacies. Pharmacists' dissatisfaction with chain pharmacies is due to higher workload and stress than independent pharmacies. [31,32] In line with the research on job satisfaction of community pharmacists in Malaysia, which shows that pharmacists working with independent community types (mean = 131.91) have higher job satisfaction than chains (mean = 146.64), franchises (mean = 151.91) and supermarkets (mean = 156.50), with a significance value of more than 0.05 (p = 0.492) which means that the type of pharmacy community does not

Table IV. The differences between independent and dependent variables

Characteristics	Category	Mean ± SD	p-value
Age	≤25	3,0±0.5	
	26-30	3.0±0.5	0.60
	31-40	3.1±0.4	
	>40	2.9±0.5	
Gender	Male	3.0±0.4	0.69
	Female	3.0±0.5	
Marriage status	Married	3.0±0.5	0.40
	Single	3.0±0.5	
Educational level	Bachelor degree	3.0±0.5	0.56
	Master degree	3.1±0.5	
Working Location	Region I	3.0±0.4	
	Region II	3.0±0.5	0.55
	Region III	3.0±0.5	
Institution of work	Primary health centers	3.0±0.6	
	Pharmacy	3.0±0.5	0.92
	Clinic	3.1±0.4	
Distance to workplace (Km)	≤ 10	3.0±0.5	
	11 - 20	3.0±0.5	0.91
	> 20	3,0±0.5	
Time to workplace (minutes)	≤ 15	3.0±0.5	
	16 - 30	3.1±0.5	0.74
	> 30	2.9±0.2	
Work experience elsewhere than in community pharmacy	Yes	3.0±0.5	0.76
	No	3.0±0.5	
Other current institution other than community pharmacy	Yes	3.0±0.5	0.10
	No	3.1±0.5	
Job position	Owner	3.2±0.4	
	Pharmacist in charge	3.0±0.4	
	Vice pharmacist	2.6±0.4	0.06
	Civil servant	3.1±0.5	
	Non-civil servant	3.0±0.7	
Income	≤ Rp. 2,000,000	2.9±0.5	
	Rp. 2,100,000 – Rp. 3,000,000	3.1±0.5	0.42
	Rp. 3,100,000 – Rp. 4,000,000	3.0±0.5	
	> Rp. 4,100,000	3.0±0.5	
Length of practice	≤ 5 years	3.0±0.5	0.38
	> 5 years	3.0±0.5	
Pharmacy ownership type	Chain pharmacy	2.9±0.5	0.04
	Independent pharmacy	3.1±0.3	
Primary health centers type	Outpatient	3.0±0.4	0.77
	Inpatient	3.0±0.4	
Type of pharmacy	Non-retail pharmacy	3.0±0.4	0.69
	Retail pharmacy	3.0±0.5	
Working hours	≤ 7 hours	3.1±0.5	0.05
	≥ 7 hours	2.9±0.5	
Average patient a day	≤ 75 patients	3.0±0.5	
	76 - 150 patient	3.1±0.5	0.85
	> 150 patients	2.9±0.5	
Average prescription a day	≤ 50 prescriptions	3.0±0.5	
	51 - 100 prescription	3.1±0.5	0.56
	> 100 prescriptions	2.9±0.4	

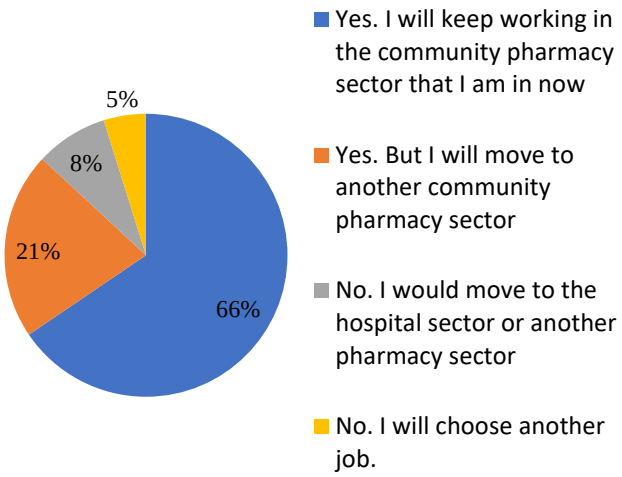

Figure 1. Overview of Pharmacists' Opinions on the Choice of Pharmacist Profession in the Future

differ significantly on job satisfaction. [33] Research in China revealed that the recruitment standards set for chain pharmacists are higher and stricter than for independent pharmacists, with a more systematic training system for accepted pharmacists. [34] In addition, pharmacist job satisfaction research in Virginia and the US also reported that pharmacists practicing in independent community pharmacies had higher job satisfaction than chain community pharmacies. After investigation, it was found that the dissatisfaction felt by pharmacists working in chain pharmacies was due to higher workload and stress than in independent pharmacies, which resulted in a high intention of pharmacists to leave the job because they felt that the perceived work stress would have an impact on the pharmacist's mental and physical health and relationship with family or close people. [31,32] In addition, working hours also influenced job satisfaction scores, with pharmacists working less than seven hours having higher satisfaction scores than pharmacists working more than seven hours. This indicates that long work duration will increase the workload, and pharmacists must work more effectively. [35] This study reported that pharmacists with working hours of more than seven hours had lower satisfaction. This may be due to high working hours indicating more contact with patients, which may lead to fatigue and decreased work productivity. [8,36]

The Correlation between Job Satisfaction and Demography and Job Characteristics

Nineteen variables of pharmacist demography and job characteristics (age, gender, marriage status, education level, working location, the institution of work, distance to the workplace, time spent at the workplace, working experience, income, length of practice, job position, pharmacy ownership type, type of primary health centers, type of pharmacy, working hour, average patient a day, average prescription a day, and other institutions) were use to assess the multiple regression and the effect of independent variable to the job satisfaction as dependent. Variable through t-analysis and f-analysis. The independent variable does not significantly affect on job satisfaction simultaneously, with the working hour having a partially significant effect on the job satisfaction than the other variables ($p<0.05$), but has a negative value that indicates that the working hour variable is inversely proportional to job satisfaction. The model of this multiple linear regression indicates that just 44.5% of total job satisfaction can be explained by the independent variables (R adjusted square = 0.445). Whereas the others are influenced by another factor outside the variables of this study (100% - 44.5% = 55.5%).

In the regression model, hypothesis testing using multiple linear regression analysis shows that there is no significant relationship between job satisfaction and demographic and job characteristics of community pharmacists in West Java. This is because the significance value of the F-test> 0.05 which indicates that demographic variables and job characteristics do not simultaneously affect job satisfaction. Then the results of the t-test on 19 variables show that only one variable has a significance value <0.05, indicating that only one of the 19 variables has a partial effect on job satisfaction, namely working hours. Similar to previous research, which reports that the working hours variable is one of the demographic characteristics that can affect job satisfaction.

[8] However, in this study, the value of working hours correlated negatively with job satisfaction. Working hours can have a positive impact if given flexibly, making employees more comfortable so that they have a strong commitment to work and are motivated to provide optimal performance to create more benefits for their work. [37]

Overview of Pharmacists' Opinions on the Choice of Pharmacist Profession in the Future

The results of this study in the Figure 1 showed that most community pharmacists in West Java choose to continue working in their current community sector (66%). While the other community pharmacists in West Java choose will move to another community pharmacy sector (21%), move to the hospital or another pharmacy sector (8%), and will choose another job (5%).

In this study, most community pharmacists continued working in the community pharmacy sector. Likewise, previous research reported the same thing. [8] So even though several things cause dissatisfaction in pharmacists, if pharmacists are interested in working in this community pharmacy sector, pharmacists will still provide optimal performance. However, it would be better if the workplace agency pays more attention and re-evaluates pharmacists' job satisfaction to provide comfort for pharmacists and increase profits in the workplace. Pharmacists are also expected to express more input or criticism to the relevant agencies if they feel that something is not appropriate in the workplace, so that pharmacists, institutions, and the Indonesian Pharmacists Association as an organization profession can work together to create satisfaction at work.

This study has some limitations. First, this study was conducted online and had obstacles in reaching a much larger community pharmacist, so there is a high possibility that there are community pharmacist work areas that are not represented in this study. Second limitation, this study describes job satisfaction in general, so there may be differences in job satisfaction scores at each work institution (pharmacies, health centers, and clinics). The last is the data were collected through an online questionnaire, so it is possible that random questionnaires were filled in due to time or other thoughts from respondents that were outside the researcher's intention. For further study, it is necessary to conduct research on the job satisfaction of community pharmacists by adding certain variables according to the conditions of pharmacists in the region or by conducting direct interviews with pharmacists to obtain more detailed analysis results.

CONCLUSION

Community pharmacists in West Java are more satisfied with the variables in the intrinsic factor (3.04±0.66) than extrinsic factors (3.0±0.7). However, their satisfaction is still low on the recognition and income. Factors affecting the job satisfaction of community pharmacists in West Java are working hours.

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STATEMENT OF ETHICS

The study was conducted after obtaining ethical approval from the Ethics Commission of the Faculty of Medicine, Public Health and Nursing (FKKMK) UGM with the number KE/FK/1690/EC/2022.

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Level of Self-Directed Learning Readiness (SDLR) in Online Learning among Pharmacy Students in Indonesia

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ABSTRACT

Background: Health science development is currently rapidly changing due to the Covid-19. Changes have taken place not only in terms of scientific development but also in terms of learning methods. Almost all learning methods have shifted into online learning, requiring students to be more active.

Objectives: This study aims to determine the level of SDLR among pharmacy students in Indonesia, especially during the pandemic.

Methods: The sampling was conducted using an proportional sampling technique based on the distribution of Pharmacy Schools (PTF) in all the provinces in Indonesia. The level of readiness of these pharmacy students was measured using a questionnaire that consisted of four domains. The questions were scored according to the characteristics of the questions (negative or positive).

Results: The results of this study showed that 1884 respondents participated in this study. The basic characteristics showed that 89.1% participants were private pharmacy schools and 84.4% of them were female respondents. The mean of each domain of SDLR for self-management, the desire to learn, the emotional competency, and the responsible decision-making was 3.24 ± 2.65, 3.37 ± 2.09, 3.04 ± 1 87, 3.16 ± 2.16, respectively. Based on gender, the difference of mean in sub domain was p=0.000 (need for learning), p=0.002 (hope for outcome), and p=0.000 (identifying problem).

Conclusion: In conclusion, the Self-Directed Learning Readiness (SDLR) among pharmacy students in Indonesia is quite high during the pandemic with a score above 3 (scale 1-4).

Keywords: online learning; pharmacy students; self-directed learning readiness (SDLR)

INTRODUCTION

Health science is currently rapidly developing, especially during a pandemic, where all the learning methods have shifted into distance learning 1. In addition to affecting learning methods, the rapid developments of sciences have also required students to be more active in both learning and seeking additional information to supplement what they have learned in higher education 2. Self-Directed Learning Readiness (SDLR) is a process where individuals will take the initiative, with or without the help of others, to identify learning needs, formulate learning objectives, identify learning resources both from humans and from other materials, to select and implement learning strategies as well as to evaluate learning outcomes3. SDLR (Self-Directed Learning Readiness) is one of the factors that determine students' success in the learning process4. The level of SDLR among health science students is affected by individual attitudes, self-discipline, learning abilities, and desire to learn. Some of these abilities will support the adaptability and long-life learning of health workers in the world of work5.

One study of Self-Directed Learning Readiness (SDLR) was conducted in India on medical students showed that it is necessary to revise the curriculum to cover learning methods that will improve students' SDLR6. A previous study on pharmacy students was conducted at the University of Maryland, it was focused on the

students' readiness to face laboratory practice. The results showed that 44% of students had a quite high level of readiness before conducting the laboratory practice as indicated by the students' activity of making study groups and writing reports. The research also showed that readiness to learn was also influenced by an individual's study habits7. The development of pharmaceutical science requires pharmacy students to be faster in accessing the latest evidence, especially concerning cases that occur in the field. In addition, competencies is also inherent in all health students. With the existence of SDLR, students will have the ability as lifelong learners, and this is a part of andragogy8. Another study in Malaysia regarding the readiness of students to participate in e-learning in Southeast Asia showed that most students were ready to participate in e-learning provided by their respective universities9.

In Indonesia, there are many studies about SDLR during pandemic. One of them is study that conducted in faculty of medicine in Sam Ratulangi University. It is showed that total of 109 students (69.87%) had high SDLR score, 44 students (28.2%) had moderate score, and three students (1.92%) had low score10. Another study about SDLR in Yogyakarta showed that a very weak negative relationship between learners' resilience and their grades11. This study aimed to determine the level of SDLR among pharmacy students in Indonesia, especially during the pandemic, in which most of the learning methods are online based.

METHODS

Study design

This study was cross-sectional research.

Population and samples

Based on Higher Education database from the Ministry of Education, Culture, and Research of Indonesia until August 2020, there were 258 pharmacy schools in Indonesia (public and private schools). The sampling was conducted using an area sampling technique based on the distribution of pharmacy schools in all the provinces in Indonesia. The inclusion criteria were pharmacy schools in Indonesia that had students until the fourth year grade, and willing to take part in this research. Pharmacy school with less than 100 students was excluded based on the consideration that the students were not evenly distributed in all semesters. After excluding pharmacy school based on the number of students, 149 pharmacy school were included. There were a total number of 81000 students at 149 pharmacy school and by using the Slovin formula, the minimum sample size was 1100.

Study instruments

The level of readiness of the pharmacy students was measured using a questionnaire that consisted of four domains, consisted self-management, desire to learn, emotional competency, and responsible decision making. This questionnaire used a Likert scale of 1-4 as well as negative and positive statements (1: strongly disagree, 2: disagree, 3: agree, and 4: strongly agree). The questions were scored according to the characteristics of the questions (negative or positive). The questionnaire was developed by adopting the previous studies1,5,6. The questions of the domains are listed in Table I.

Data collection

A proportional sampling technique was used based on the distribution of pharmacy school in each province. The total 1184 respondents participated in this study.

Data Analysis

The data were analyzed descriptively to describe the level of readiness of pharmacy students in online learning. The relationship between the respondent characteristics and SDLR scores was analyzed using the Student-T test and Linear Regression. The validation and reliability of the questionnaire were tested using the Cronbach alpha value and the r-value of Pearson correlation analysis (n=300). The Cronbach alpha obtained for the Self-management, Desire to learn, Emotional Competencies, and Responsible decision-making domains were 0.743, 0.626, 0.684, 0.834, respectively. Each of which met the reliability criteria (>0.6). The r count obtained for each item in the questionnaire was greater than the r table, thus meeting the validity criteria.

RESULTS AND DISCUSSION

A total of 1884 respondents who spread throughout Indonesia participated in this study. Table II shows the characteristics of the respondents in which 89.1% went to private pharmacy schools, with 84.4% of them

Table I. Questions in the self-management domain

Domain	Indicator (Subdomain)	Code
Self-Management	Time management skill	TMS
	Social networking	SN
	Environment support	ES
	Moral and ethical	ME
	Communication manner	CM
	Ability	A
Desire to Learn	Covering passion	CP
	Enthusiasm for learning	EL
	The need for learning	NL
	Hope the outcomes of learning	HOL
	The ideals to be achieved	IA
Emotional Competencies	Regulation	R
	Collaboration	C
	Connection	C
Responsible Decision Making	Critical Thinking	CT
	Identifying problems	IP
	Analyzing situations	AS
	Evaluation and reflection	ER
	Skills/performance	S/P
	Knowledge	K

Table II. Respondents' Characteristics

Characteristics	n= 1884 (%)	Mean (SD)
Types of Schools		
State Schools	206 (10.9)	
Private Schools	1678 (89.1)	
Gender		
Female	1590 (84.4)	
Male	294(15.6)	
Age		20.28 (2.63)
SDLR Domains (mean and SD using Likert 1-4 scale)		
Self-management		3.24 (2.65)
Desire to learn		3.37 (2.09)
Emotional competency		3.04 (1.87)
Responsible decision making		3.16 (2.16)

were female students. The mean age was 20.2 years. This characteristic was similar with previous studies, where the proportion of female students was more dominant than male students and most of them aged 20-25 years[6,8,9]

The four domains in the questionnaire obtained scores greater than 3, with the lowest score being the desire to learn domain. The results of this study are in line with those of a previous study, that pharmacy students had a high level of SDLR in different situations[8]. Nonetheless, the results of research on SDLR were different in terms of the readiness of pharmacy students to conduct laboratory practicum. There were more students with a low level of SDLR although the difference was not significant.

Table III presents the scores for each question in each subdomain. In the self-management domain, the lowest scores were found in environmental support. A previous study revealed that good time management skills affect the success of the learning process. Time management is a part of self-management, in which students are required to have the ability to manage their personal needs based on abilities and priorities. In addition, time limitation requires students to be able to improve their learning performance[12]. Based on the study in Kupang, it is showed that the use of the social interaction tool was positively associated with students' academic success, the perceived ease of using the social presence tool was negatively associated with students' success. Students are reliant on themselves in the online learning environment, and they may have a better chance of academic

Table III. Distribution of mean of Subdomain in Self-directed Learning Readiness

Domain	Subdomain	Mean (SD) (n=1884)
Self-Management	Time management skill	2.97 (0.37)
	Social networking	3.21 (0.38)
	Environment support	2.88 (0.58)
	Moral and ethical	3.07 (0.63)
	Communication manner	2.94 (0.46)
	Ability	3.16 (0.44)
Desire to Learn	Covering passion	2.74 (0.56)

success[13]. Another study demonstrated that SDLR is influenced by environmental elements such as the teacher-student connection, the facilitation process, and the availability of learning resources, as well as motivational factors such as academic performance, interest in topics, and the fulfillment of self-expectations[14].

Based on the desire to learn domain, enthusiasm for learning obtain the lowest score. Meanwhile, in the emotional competence and responsible decision-making domains, critical thinking and analyzing situation ability had the lowest scores. Support for learning readiness during the pandemic is very crucial to conduct distance learning. The presence of facilities such as mobile phones, laptops or computers, and the internet is the key to properly conduct learning processes. As has been known, not all regions in Indonesia have equally good access to the internet, preventing the learning process to run well. In addition to facility support, supports for the learning process in the form of clear learning objectives, appropriate assessments, workloads given by lecturers, and good teaching methods are also important in conducting distance education[15].

The desire to learn domain determines a student's ability as a lifelong learner[5]. Pharmacy students should have the ability as lifelong learners regarding the rapid changes in health science[8,16]. Therefore, the low score for the enthusiasm for learning subdomain should be a concern for both lecturers and the management degree program. It is necessary to further explore the factors that potentially lower enthusiasm for learning. Heavy workloads, uninteresting learning models, and complicated assessment methods may affect the enthusiasm for learning.

Table IV shows significant differences in the scores of certain domains based on the types of schools. The scores for the emotional competence domain and several sub-domains on private pharmacy schools were higher than those of state pharmacy schools. The presence of differences in the domain and subdomain scores based on the types of pharmacy schools indicated the desire of pharmacy students to achieve better results. This study was the first study that showed the differences between public and private pharmacy schools. Various things can lead to the differences in the scores of the domains and subdomains of SDLR, including the level of stress due to adapting to the distance learning process, the pandemic conditions that require everyone to stay at home to maintain health which then restricts social life, as well as increased tasks with a certain time limit, thus causing students to lack time to live a healthy life, rest and work out[16]. The types of schools also determine the quality of the human resources. Lecturers' readiness in facilitating distance education should pay attention to not only the materials to be delivered to students, but also the condition of the students who will have to understand the materials and complete various assignments at the same time. Therefore, there were various factors caused by the types of schools that led to the differences in the results, in addition to differences in the number of students in public and private schools. There was one study of which the result is in line with this study, especially in terms of the time management section. Private schools obtained higher scores significantly for time management than public school [12].

Table V presents significant differences in the subdomain scores based on gender, where the score for the need for learning and hope for outcome subdomains among female students was higher than that among male students. The result is also in line with previous research on the students of health study programs in which the SDLR scores of female students were better than male students[17]. In addition, according to the situation in each country, female students usually have more social responsibilities than male students, so they are used to identifying problems and learning new things to find solutions to these problems[12].

The results of the linear regression analysis between the respondents' age and the domain scores showed a significant relationship in the subdomains of social networking and skill performance with p values of 0.04 and 0.01. A previous study conducted on the students of the health study program also showed similar results, where senior students had better SDLR scores than junior students. This study also showed that the demographic characteristics of the students such as gender, previous educational background, and personal characteristics

Table IV. Differences between domain and subdomain scores based on the types of pharmacy institutions status

Domain	Public school of pharmacy (mean, SD)	Private school of pharmacy (mean, SD)	P-value
Emotional competencies	2.75 (0.34)	3.05 (1.97)	0.029*
Subdomain	PTN (mean, SD)	PTS (mean, SD)	P-value
Time management	2.85 (0.40)	2.98 (0.36)	0.000*
Social networking	3.13 (0.35)	3.22 (0.39)	0.002*
Moral Ethic	2.89 (0.85)	3.09 (0.63)	0.000*
Communication manner	2.86 (0.37)	2.95 (0.46)	0.006*
Covering passion	2.46 (0.57)	2.77 (0.55)	0.000*
Enthusiasm of learning	2.44 (0.65)	2.65 (0.63)	0.000*
Ideals to be achieved	3.40 (0.37)	3.49 (0.34)	0.003*
Self-regulated	2.60 (0.47)	2.85 (0.44)	0.000*
connection	2.71 (0.44)	2.83 (0.45)	0.000*
Critical thinking	2.52 (0.48)	2.78 (0.44)	0.000*
Identifying problem	2.88 (0.41)	3.00 (0.35)	0.000*
Situation analysis	2.88 (0.41)	2.97 (0.39)	0.002*
Evaluation and reflection	2.61 (0.54)	2.81 (0.48)	0.000*
Skill performance	3.09 (0.42)	3.18 (0.410)	0.002*

Table V. Differences in subdomain significance based on gender

Subdomain	Male (mean, SD)	Female (mean, SD)	*p* value
Need for learning	3.19 (0.50)	3.31 (0.46)	0.000
Hope for outcome	3.56 (0.43)	3.65 (0.40)	0.002
Problem identification	3.03 (0.40)	2.98 (0.34)	0.000

greatly affected the SDLR level of the students in the first year. This should be of concern for both lecturers who teach in the first year and academic supervisors, to be able to implement various learning strategies and methods.

Table VI presents the total score per domain both at the national level and based on the types of pharmacy school. It can be concluded that the scores for the domains of SDLR among the students at private pharmacy school of were higher than those at the national level. This is possible because private schools had a higher proportion of students.

Figure 1 shows the proportion of the students of which the SDLR scores were above the national average. It was only in terms of the desire to learn domain that the students of private pharmacy schools had a better proportion than public pharmacy school. Although the students from private schools had better scores in terms of the domain and subdomain scores than the students from public schools, public schools had a higher number of students whose scores were above the national average. This indicates that the students from public schools made better efforts for SDLR. These efforts can be made by the students in terms of the adaptation process and by the educational institutions in terms of improving facilities and infrastructure. In addition, public schools may have previously applied distance learning, encouraging students to have better readiness to participate in the distance learning process during the pandemic.

Several factors that can determine the level of SDLR among students in the health sector in Indonesia, based on a previous study are curriculum, lecturer experiences, student background, and cultural factors in a country. Improvements to the curriculum and the ability of lecturers to change the student-based learning process will improve SDLR. In the context of learning during the pandemic, it is not only changing the learning method from face-to-face meetings to online learning but also maintain the concept of student-based learning. In some situations, a particular study program that has always become a favorite study program over generations and lecturer experiences determine the success of the study, which certainly will affect the SDLR of students[16]. A previous study on medical students at several public universities also showed that the proportion of students with a high SDLR was 44-62%[16].

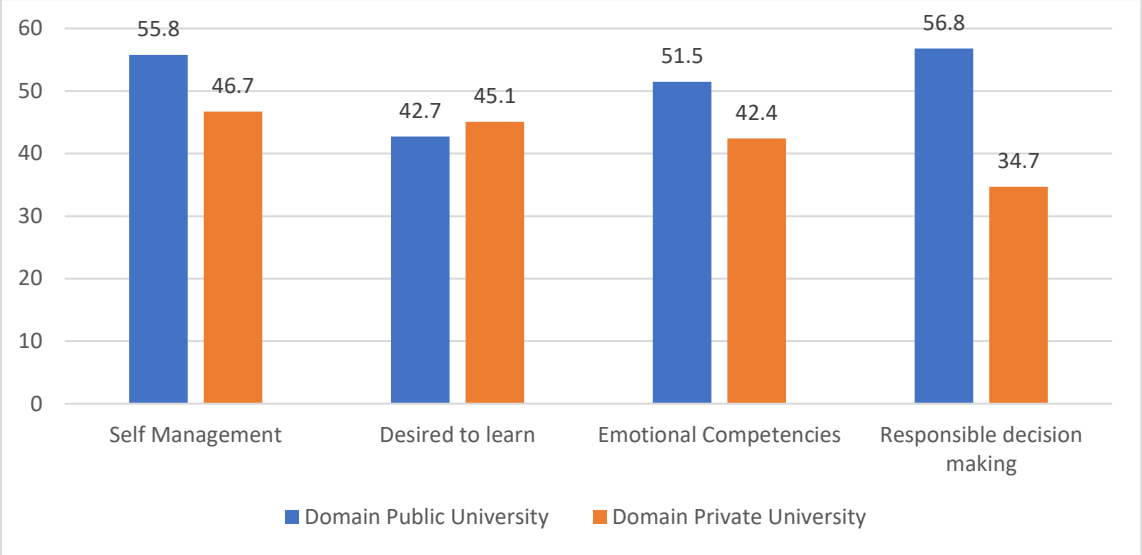

Figure 1. The proportion of SDLR Scores of Each Domain on National SDLR Scores

Table VI. SDLR domain scores at the national level and based on the types of schools of pharmacy

Domain	National Mean (SD)	Public University Mean (SD)	Private University Mean (SD)
Self-Management	36.44 (3.40)	35.60 (3.38)	36.54 (3.39)
Desire to learn	28.92 (2.67)	28.00 (2.57)	29.04 (2.67)
Emotional Competencies	25.83 (2.87)	24.74 (3.09)	25.96 (2.82)
Responsible decision making	29.96 (3.13)	28.88 (3.06)	30.09 (3.11)

This study had a strength, i.e. a national survey was conducted, allowing the results of the study to descriptively represent pharmacy students in Indonesia. In addition, the questionnaire used in this study was adopted from various previous studies on the students from the health study program of which the validity and reliability had been tested. However, this study also had a limitation, i.e. the number of private schools involved was higher than the number of public schools, possibly affecting the results of the statistical analysis.

CONCLUSION

In general, the pharmacy students in Indonesia have a quite high level of SDLR during the pandemic with a score greater than 3 (scale 1-4). It is necessary to conduct future studies regarding some domains with a quite low level of SDLR. Future research needs to explore the factors of the low level by considering both student readiness and the facilities and infrastructure of educational institutions.

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STATEMENT OF ETHICS

This research was conducted with ethical approval from Ahmad Dahlan University No. EC:012010054.

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The Influence of Pharmaceutical Companies Marketing Activities on Physicians' Prescribing: Literature Review

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ABSTRACT

Background: Pharmaceutical companies through marketing strategies introduce the products to the user. Physicians are the target of prescription drug marketing. For a long time, pharmaceutical companies have done many marketing activities. They are spend a big portion for the marketing activities. The aims of that activities, to influence physicians' prescribing.

Objectives: This article aimed to examine the influence of marketing activities from pharmaceutical companies on physicians' prescribing in various countries.

Methods: Scopus is used as a database to collect articles with keywords named "pharmaceutical marketing" and prescribing. Inclusion criteria are original articles, published in 2018-2023, in English, open access. In the end, eight articles were reviewed in this study.

Results: The result of this study shows pharmaceutical companies apply a marketing mix strategy to promote their product. This strategy consists of four elements product, price, place, and promotion. All of the element influences physicians' prescribing, generally. Promotion startegies such as medical representative visits and gifts are the most influential strategies for physicians' prescribing. The influence can't be generalized because it also depends on the socioeconomic state of the country, culture, work location or environment, practice experience,geography, and ethical issues.

Conclusion: Promotion strategy is the most influential for prescribing than product, place, and price but the influence based oh the physicians' characteristics. So, pharmaceuitcal compines must indentify their user to decide a appropriate strategy.

Keywords: marketing mix; medical representative; pharmaceutical marketing; physicians' prescribing; promotion

INTRODUCTION

A company will try to maintain and even improve its competitive advantages, including pharmaceutical companies. Competitive advantages are companies' assets to win the market competition[1]. Generally, pharmaceutical companies have two types of products namely over-the-counter (OTC) products and ethical/prescription products. Prescription products are a big contributor to pharmaceutical companies' income. Division prescription pharmaceuticals of Kalbe Farma contribute 21,3% of total net sales in 2022[2]. Kalbe's prescription pharmaceuticals consist of unbranded generics, branded generics, and licensed products. Their contribution to prescriptions net sales are27%, 50%, and 23% respectively. Kimia Farma Corporate also shows the same condition, prescription drugs contribute 45,61% of their total net sales[3].

Pharmaceutical companies spend a big portion of their asset on marketing activities. Pharmaceutical companies spend one-third of their revenue on marketing, which is twice that spent on research and development[4]. Kalbe Farma's selling expenses in 2022 are around 5,749 billion in rupiah, an increase of 3,6%

from 2021[2]. This is many times over than expenses for research and development only 292 billion in rupiah. The same condition is seen in Kimia Farma Corporate, with operating expenses for promotion around 18,92% and 3,54% for research and development[3].Nine of 10 big pharmaceutical companies in the world spent more on marketing than research and development[5].

There are 232 pharmaceutical manufacturers in Columbia, the largest expenditure for advertising is around 75%, and the smallest for detailing expenses is 8,5%[6]. Detailing expenses are payment for marketing and promotional activities such as sales representative operations. Other marketing activities include giving gifts to individual recipients. District of Columbia reported a total of gift expenses is $19.7 million for cash, food, or in-kind consideration. The target of these expenses are physicians, nurses, dentists, medical staff, and pharmacists[6]. In 2016, pharmaceutical companies in the United States invested 13.5 USD to free samples for physicians[7]. Anthony A. Barrueta at Kaiser Permanente website reported in 2016 pharmaceutical industry spent $13.5 billion on free samples[8].

All of the marketing activities especially prescription drugs make physicians the main target because the use of the product is based on physicians' prescribing. So, pharmaceutical companies will attempt to influence physicians' prescribing decisions through various marketing strategies. Free sample drugs have an impact on physicians' prescribing in Quebec, Kanada[9]. Also in Pakistan, gifts from pharmaceutical companies create interest in physicians' prescribing[10]. This kind of condition has been going on for a long time in various countries. This article will resume some research from various countries around 2018-2023. Previous literature studies conducted by Murshid *et al* reviewed 40 studies published from 2000 to 2016[11]. They investigated the influence of medical representatives and other promotional tools on prescribing behavior. So, this research will give an idea of the marketing strategies that have influenced physicians' prescribing in various conditions for at last 5 years. The results can be a consideration for pharmaceutical companies to arrange effective and efficient marketing strategies.

METHODS

Study design

This is research with a literature study design.

Search strategy

The article-collecting process focused only on Scopus. This database is used because Scopus is the biggest article source, a good reputation and credibility. The article which Scopus indexed is acknowledged good quality article internationally. The keywords to search the articles are "pharmaceutical marketing" and "prescribing" within the article title, abstract, and results.

Eligibility criteria

The inclusion criteria are an original article, publication in English, an open-access article, and an article published in 2018-2023. That period was chosen because we want to know the up-to-date pharmaceutical marketing' trend last 5 years. Articles that don't meet these criteria will be excluded.

Data Extraction

One hundred twenty articles were found based on keywords. The first selection is based on the published date, 88 articles were published before 2018 so they are deleted. After that, 32 articles were selected by looking at the type of article and the language, 25 articles met the criteria, namely original articles in English. Next, based on accessibility, only 14 open-access articles for this review. The last is an assessment of the articles regarding the suitability of the title to the content and research objectives, only 8 articles met the criteria.

Data Analysis

Figure 1

RESULT AND DISCUSSIONS

From this review know that there are various strategies for pharmaceutical companies to market their products. This strategy is used to influence the physicians' prescribing behavior. The strategies used by various pharmaceutical companies around the world such as Jordania[12], the United States[13], Ethiopia[14], Lebanon[15], India[16,17], Australia[18], and Belgium[19]. Mix marketing strategy is the most strategy used by pharmaceutical

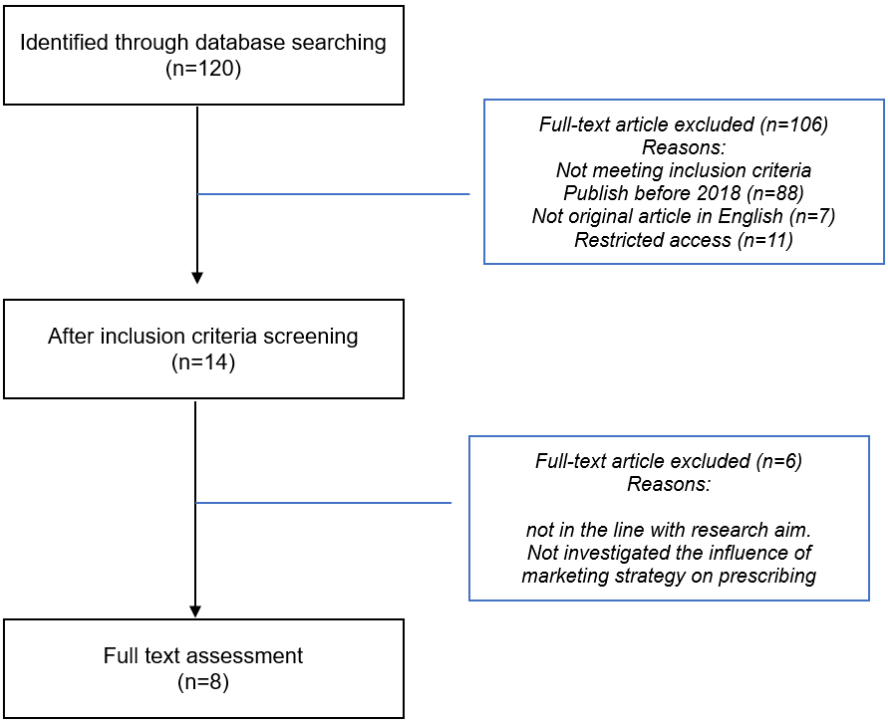

Figure 1. The study flow chart of articles is included in this review.

companies. Pharmaceutical companies apply all of the marketing mix elements or only one of them such as promotion. Table I.

Al Tabbah *et al*[12] and Hailu *et al*[14]assess the influence of marketing mix strategies on Jordanian[12] and Dessie[14], Ethiopia physicians' prescribing. Their quantitative study shows the same results that marketing mix influences physicians' prescribing, generally. All elements of the marketing mix namely product, price, place, and promotion have an influent on physicians prescribing in the different portions. Price is the most influential strategy in Jordanian physicians and promotion strategy has the lowest impact. Meanwhile, in Dessie promotion strategy is the most influential in their physicians' prescribing followed by product, price, and place strategy respectively.

Other articles in this review focus on promotion strategy in physician prescribing. Eisenberg *et al*[13], in the United States, assess the influent of pharmaceutical promotion activities like medical representative visits and giving a gift and/or meals to the physicians prescribing opioids. These activities show that they have an impact on opioid prescribing. The result is increasing opioid prescribing and opioid overdose cases in the US. So, The United States government made some policies, one of them being a restriction on gifts and meals for physicians and medical representatives' access to the health centers. This policy has a good impact on opioid prescribing, medical representative visit restrictions reduce 4,7 percent of days for all types of opioids prescribed (4.87 percent on generic opioids and 11 percent on brand-name opioids marketed. Khazzaka[15]through quantitative research wants to know correlated promotion tools from pharmaceutical companies and Lebanese physicians prescribing. The results show that being visited by medical representatives is the most important promotion tool that influences Lebanese physicians' prescribing, followed by free drug samples, supporting continued medical education (CME). These results are in line with Vandenplas *et al* research[19], Belgium physicians are also influenced by medical representative visits for their prescribing especially on biological products with new mechanisms of action. The phenomenon is also seen in India, Sharma *et al*[17], results of their research show that medical representative visits influence the physicians' prescribing.

Krunal *et al*[16] conducted further research about medical representatives in India. They are focused on medical representative qualities. A medical representative with good qualities has a high impact on physicians' prescribing. Based on this research, a good medical representative has a good skill in detailing for describing the product and building good communication and interaction with the physicians. Next, the medical representative

Table I. Characteristics of the included article in this review

No	Author	Date	Place	Research Method	Participant	Marketing Strategies	Main Found
1	Al Tabbah *et al*[20]	2022	Jordan	Cross-sectional, quantitative	315 physicians (general practitioners and specialists, private and public sector)	Marketing mix (product, price, place, and promotion)	Marketing mix has a moderate to high influence on Jordan physicians' prescribing. Pricing strategy has the greatest impact on prescribing.
2	Eisenberg *et*[13]	2020	United State	Retrospective, quantitative	Physicians who prescribed medications covered by Medicare Part D (85 US Academic Medical Center)	Promotion strategy (medical representative visit and gift)	Restriction of medical representative visits and gifts reduces the volume of opioid prescriptions.
3	Hailu *et al*[14]	2021	Dessie, Ethiopia	Mix Method	136 physicians (quantitative), 14 specialist physicians (qualitative)	Marketing mix (product, price, place, and promotion)	All of the elements in the marketing mix influence Dessies' physician prescribing. Promotion strategy has the greatest influence on prescribing.
4	Khazzaka*et al*[15]	2019	Lebanon	Cross-sectional, quantitative	282 physicians who practice in urban and rural regions of Lebanon	MRs' visits, Sales calls, Free drug samples, Brochures, Gifts (medical equipment), Low-cost gifts, Sponsorship for personal tours or conferences, Direct mail, Journal Subscription, Participating in CME	The most important promotion tools that influent prescribing behavior are medical representatives visiting followed by free drug samples, the company's participation in CME, and sponsors for personal tours or traveling.
5	Krunal *et al*[16]	2021	Gujarat, India	Cross-sectional, quantitative	122 physicians (general practitioners and specialists)	Medical Representative	A medical representative with good skill in detailing, scientific knowledge, and a good personality influences physicians' prescribing.
6	Parker *et al*[18]	2020	Australia	Qualitative	28 members of NSW DTCs	Promotion	free samples, lunches, financial links, fund trials, and routine visiting hospitals' staff influence drug list decisions.

Table I. (Continues)

No	Author	Date	Place	Research Method	Participant	Marketing Strategies	Main Found
7	Sharma *et al*[17]	2021	Maharashtra, India	Cross-sectional, quantitative	100 clinicians in a teaching hospital	drug promotional literature (medical representatives, advertisements in journals, brochures, and direct mailing)	Brochures are the most useful for clinicians followed by medical representatives.
8	Vandenplas *et al*[19]	2022	Belgia	Qualitative	19 specialist physicians	Marketing mix (product, price, place, promotion)	All of the marketing mix elements influence physicians' prescribing.

must have a good personality and good skill of grooming. The last, medical representative must have good knowledge, not only about their products but also the scientific ones.

All of the research above shows that pharmaceutical marketing influences physicians' prescribing. Parker *et al*[18] through their research in New South Wales, Australia complements these findings. They involved all members of the drug and therapeutics committee (DTC) consisting of physicians, pharmacists, and nurses. The results show that pharmacists and nurses also be the target of pharmaceutical marketing strategy especially in the process of inputting the product to the hospital drug list.

Pharmaceutical companies invest their asset in a large portion for marketing strategies. From the action, pharmaceutical companies want to make their product known and superior in the eyes of physicians. That is the purpose of marketing strategy[12,13]. Marketing mix is a general strategy to market products or services[1]. The marketing mix consists of four elements product, price, place, and promotion. They are linked to each other[21]. Pharmaceutical companies combine all of them to influence physicians' prescribing behavior[12,14].

Price

Physicians in Jordania[12] and Dessie[14]are influenced by pricing strategy. The price of the drug will impact on medication cost that the patient must pay. That has a high impact on medication adherence[12]. So, when choosing the product, physicians consider the product's price that is suitable for patients' wealth. This is correlated with the economic static of the country, The World Bank classified Jordania as a lower-middle-income country and Ethiopia as a lower-income country. Different results show in Belgium[19], a country with better economic status, the cost of the products has a limited effect on physicians' prescribing.

Product

Effective and safety are criteria of the good quality of pharmaceutical products. Products with good quality increase customer satisfaction and loyalty to repeat use of the products[22–24]. Related to a product strategy, senior physicians with long-time experience in practice are more influenced. They have many experiences in handling patients with various cases and conditions. They have more experience with the products and the alternatives in their practice. They have a strong basis for drug choice[12].Not only related to practice experiences but product strategy is also related to the type of health centers. Physicians in the private sector are more influenced by product strategy because they are allowed to mention the name/brand of the products in their prescribing[12]. So, product strategies such as creating an easy-to-remember product name can influence physicians' prescribing. In different conditions seen in Indonesia, the quality of the product does not influence physicians' loyalty to prescribing. In line with Chang *et al*[25] found that product quality does not directly influence customer loyalty but indirectly through customer satisfaction.

Place

Place strategy is known as a distribution strategy. Jordanian physicians mostly agree that this strategy influences their prescription[12]. Distribution strategy related to product availability, availability of local agents representing the principal company, and fast delivery. Physicians will prescribe the product which is ready in pharmacy installation[12,14]. Physicians in Dessie, in the private sector, emphasized that improving companies' supply chains made their work easier. Meanwhile, in Dessie's public sector, found that agents in the city made physicians easy to prescribe the products.

Promotion

There are many activities related to promotion strategy. Research in Saudi Arabia involving 250 physicians found 99,5% of them agree that they are exposed to pharmaceutical promotion at least once time[26]. Promotion strategy has the most influence on physicians' prescribing followed by product, place, and price[12]. Khazzaka[15] investigated some promotional tools from pharmaceutical companies especially medical representative visits, free drug samples, brochures, gifts (medical equipment, low-cost gifts, sponsorship for personal tours, direct email, journal subscriptions, and participating in CME. Parker mentioned that pharmaceutical companies will influence members of DTC with various activities to submit the product to the hospital drugs list[18]. The activities include medical representative visits, fund trials of new medicines, and providing lunches for staff in hospital meetings. All of the articles in this research have the same found that medical representatives as a part of the promotion strategy have an impact on physicians' prescribing behavior. Medical representatives are spearheads of pharmaceutical companies because one of their jobs is visiting physicians to describe the product and build a good relationship with the physicians[27]. Physicians who practice in Yaman said that medical representative visits

are something normal[28]. Ali *et al* capture that in Jordania-Iraq, face-to-face meetings between medical representatives and physicians an important and influence physicians' prescribing[29]. The face-to-face meetings will increase physicians' belief in the medical representatives, the information, and the products.

Al-Areefi through qualitative research identifies physicians' reasons for accepting or rejecting medical representative visits[28]. There are some reasons for accepting medical representative visits. First, physicians presume medical representatives are a source of drug information[28]. When visiting physicians, medical representatives describe and present the product offered, the information about the indications, side effects, and contraindications, and compare their product with the competitor. This is in line with other research that medical representatives are a source of drug information for physicians, especially new drugs[19,30]. Information from medical representatives is useful for physicians because they don't have much time to search for new drugs and medication information[17,28,31,32]. Second, moral considerations such as friendship and the idea of helping each other are the physicians' reasons for accepting medical representative visits[28]. The last reason is medical representatives' visits give them financial benefits[28].

Gifts from pharmaceutical companies influence United States physicians to prescribe opiod[13]. Providing a meal for lunch or dinner also has an impact on physicians' prescribing[14,18]. The other researcher also captures the same found that free drug samples, gifts (medical equipment), and sponsorship for personal tours or conferences have an impact on prescribing[15,33]. This acceptance is based on some reason[33]. First, common sense for something free, the uncomfortable to refuse, and the physicians said that the gift from pharmaceutical companies helps them to remember the drug/product because 74,7% of gifts are accompanied by the name of the companies and product also their logo[33]. The same condition is also found in Indonesia, the physicians' loyalty to prescribe a product is influenced by gifts received from pharmaceutical companies[31]. Wood *et al*[34] found that Columbia physician prescribing was also influenced by gift-giving from the pharmaceutical company. Gift-giving correlates with an increasing number of prescriptions, the number of drugs on prescription for patients, the cost that patients must pay, and increasing prescriptions for branded drugs. Otherwise, found in Russia[35] and Iraq[36] that gift-giving from pharmaceutical companies doesn't influence significantly physicians' loyalty to prescribe the product.

Not often do the physicians reject medical representative visits. There are physicians' reasons to reject the visits[28]. First, etic consideration. Second, a conflict between physicians and pharmaceutical companies related to the previous commercial commitment. Third, the medical representative came at the wrong time, disrupting the physicians' practice hours. Last, low-quality of medical representatives. Related quality of medical representatives, Krunal *et al*[16] investigated the medical representative quality in physicians' eyes. The results show medical representatives who have good skills in detailing, dressing neat and professionally when visiting physicians, and also have a good knowledge of the product and scientific evidence correlated with physicians' prescribing in India. As mentioned above, medical representatives as an information source for physicians must provide accurate and credible information. Sharma *et al*[17] found that the accuracy of the claims by pharmaceutical companies was between 50%-75% and mostly supported by poor evidence. This was found not only in medical representatives but also in the leaflets or brochures.

CONCLUSION

Pharmaceutical companies through marketing strategies to physicians introduce their prescription products. The marketing mix is used to influence physicians' prescribing behavior. Promotion strategy has the most influence on physicians' prescribing than product, price, and place strategies. Medical representatives and gifts as a part of the promotion strategy are impactful on physicians' prescribing. The influence of marketing strategy on physicians' prescribing depends on various backgrounds like socioeconomic status, work environment, practice experience, and ethical issues. Therefore, pharmaceutical companies must identify their physicians' characteristics to decide the appropriate strategy. Pharmaceutical companies must have good-quality medical representatives. Periodic training can be carried out to maintain and improve the quality of medical representatives.

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STATEMENT OF ETHICS

This article was written in accordance with the code of ethics and not published or under review in other journals.

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