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Research Article

The Analysis of Health Professionals' Knowledge and Attitudes Related to the Implementation of Pharmacovigilance in Pharmaceutical Service Facilities

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ABSTRACT

In 2024, the Indonesia Food and Drug Authority received 13,238 reports of adverse events (AEs), with around 3,773 reports in May alone. A lack of understanding of the urgency of pharmacovigilance results in a small number of reports compared to the population. This potentially poses unidentified safety risks, reduces quality of life and increases the cost of therapy. This research aims to describe and provide information related to the knowledge and attitudes of healthcare professionals in responding to safety information or AEs, as well as explain the types of drugs and side effects seen by healthcare professionals. This is a non-experimental prospective study and uses a descriptive-analytic research design. The data were taken from August to October 2024, by using a structured questionnaire. The respondents of this study are healthcare professionals, who are 72% females and 28% males. Almost 54% have received and found AEs. The most frequently reported AEs were related to Antibiotics, Analgesics, Anticonvulsants, Anti-Tuberculosis, and Bronchodilators. Based on Pearson Correlation Analysis, there was a moderately significant relationship between knowledge and attitudes (p<0.05). It can be concluded that the number of AEs reported will be increased if there is an increase in healthcare professional knowledge continuously

INTRODUCTION

The aims of drug therapy to cure and prevent the disease are just like double-edged swords, which are able to cure a disease in optimal ways, while they can also induce adverse events (AEs). The AEs that might happen are often because of drug interaction, medication error, inappropriate dose or as a result of a comorbid condition of the patient's disease.

The Thalidomide tragedy that happened in the early 1960s was the turning point of drug safety awareness. The drug got an approval from the Authority but then induced an AE of phocomelia in a newborn baby. Learning from the tragedy, patient safety should be an important point in the health care service and closely related to drug safety. Accordingly, health professionals are expected to be more aware about the occurrence of AEs during the therapy and report them to the Authority.

Based on Indonesian Food and Drug Authority in 2022, the number of AEs received was not more that 10,000 reports yearly. The reporting numbers are fairly low (BPOM, 2022). In May 2024, the reports were below 10,000 reports or only approximately 3,773 reports (BPOM, 2024). One factor to consider is that the lack of understanding about the urgency of pharmacovigilance leads to the minimum number of reports when compared to the large number of people in the population. This disparage could potentially induce the unidentified safety risk, decreasing the quality of life and also increasing the cost of therapy.

Based on that background, it is necessary to conduct this study on the relationship between the level of knowledge and attitude of the Health

Professionals for implementing pharmacovigilance in their healthcare facilities. The aims of this study are to describe and give the information related to the health professionals' knowledge and attitude on how to respond to the safety information or AEs from their patients and to describe the type of medicines involving AEs received by the health professionals.

METHODS

This non-experimental study was conducted by collecting data prospectively using a descriptive-analytic design study. The primary data were taken from a structured questionnaire. Before subjects completed the questionnaire, they were informed about the concerns of the study and the importance of their data privacy. In order to minimize the possibility of bias, the questionnaires were disseminated to health professionals within the period September to October 2024, through an online communication platform that was accessible and reachable by the researchers. Moreover, there was an interview process involving calling the respondents in random order.

The number of samples included was based on the Lemeshow equation, in which the total population is unknown (Sugiono, 2016). The population involved in this study are all health professionals who work at health facilities and also at pharmaceutical industries.

$$n = \frac{Z^2P + (1-p)}{d^2}$$

Remarks:
n = number of samples
z = normal value/standard (1.96)
p = maximal of estimation (50% or 0.5)
d = alpha (level of mistake) which usually uses 1% or 0.01%, 5% or 0.05%, and 10% or 0.1% (it depends on the researcher)

Before distributing the questionnaire to the respondents, it was validated. The validity of the questionnaire is based on the *r* score, which *r* count > *r* table. The *r* scores of the questionnaire for variables knowledge are 0.689; 0.598; 0.776; 0.746; 0.776; 0.767; 0.810; 0.761; 0.789, and for variables attitude result are 0.722; 0.529; 0.641; 0.522; 0.631; 0.818. Based on that results, it shows that the questionnaire is valid (*r* table = 0.361). Meanwhile, the reliability test which is based on Cronbach's alpha score is 0.876 > 0.6, and it is considered reliable.

Ethical Clearance

This research has received ethical permission from the Health Research Ethics Committee of Harapan Bangsa University, Purwokerto, with number B.LPPM-UHB/929/09/2024 on September 20, 2024 and valid until September 20, 2025.

RESULTS AND DISCUSSION

The Characteristics of Respondents

The number of respondents in this study was 100 respondents. The detailed description of the respondents is explained in Table 1. This study has more female respondents (72%) than male ones (28%). This number is not aligned with the data from the Indonesian Health Ministry in 2022. The Indonesia health profile in 2022 mentions that the number of female and male populations in Indonesia is almost equal. It is about 137,890,954 males and 136,968,140 females (Kemenkes RI, 2023). Based on Smith's (2008, as quoted from Jackson, Ervin, Gardner & Schmidt, 2001; Kendall, 1999; Lucas & Smith, 2004; Morahan-Martin, 1998; Ogen and Chung, 2003; O'Brien, 1999; Tannen, 1991; Travers, 2003; Turkle, 1995), the differences on how females and males use cyberspace may exacerbate the effects of differences in how females and males engage in social transactions, resulting in disparities in online survey response rates. According to some academics, females are more likely to engage in online activity characterized by communication and information exchange. In contrast, males are more likely to engage in online activity characterized by information searching.

Based on the Employment Data for 2024, the 3 (three) large working group population range of Indonesian citizens aged from 35 – 39 years old (16,602,867 persons), 30 – 34 years old (16,555,574 persons), and 40 – 44 years old (16,292,858 persons) (BPS, 2024). The working age ranges between 20 and 40 years, and this age is considered very productive. It is because if the age is below 20 years, most of them do not have enough mature skills and are still in their education period. Meanwhile, at the above 40 years, their abilities begin to decline (Yasin and Priyono, 2016).

Based on Indonesia regulation concerning the implementation of pharmacovigilance, it regulates the implementation of pharmacovigilance activities in pharmaceutical industries. However, there is one part in the

regulation that mentions about how the pharmacovigilance process is in the healthcare facility. Due to that regulation, this study involved all health professionals, both in healthcare facilities and pharmaceutical companies. By the end of the study, the result shows that the percentage of pharmacists as respondents is higher than other healthcare professionals, about 76%. This is due to the fact that the pharmacist's scope of work is wider than other healthcare professionals and is always related to the administration process of medication. The pharmacist may work in any of the following 6 (six) fields: pharmacy, *Puskesmas,* clinic, hospital, pharmaceutical industry, and drug distributor.

In this study, pharmacists who actively report AEs are clinical pharmacists in the hospital. Hence, there are some barriers for the implementation process of pharmacovigilance in the hospital, based on the interview process: (1) Most of the healthcare facilities do not have a dedicated person to coordinate the pharmacovigilance report, (2) There is no adequate information on how to process the adverse event report, (3) less concern about the importance of the report, and (4) The process of adverse event reporting is complicated,

Table 1. The description of the social demography of the respondents

Characteristic	Frequency (N)	Percentage (%)
Sex		
Male	28	28.0
Female	72	72.0
Age (Years)		
17-25	1	1.0
26-35	34	34.0
36-45	55	55.0
46-55	10	10.0
Education Background		
Doctor	1	1.0
Magister	33	33.0
Dentist	1	1.0
Pharmacist	44	44.0
Midwife	1	1.0
General Practitioner	4	4.0
Specialist Physician	3	3.0
Nurse	1	1.0
Bachelor	4	4.0
Nurse Vocation	8	8.0
Profession Background		
Pharmacist	76	76.0
Pharmacist assistants	1	1.0
Midwife	1	1.0
Dentist	2	2.0
Specialist Physician	3	3.0
General Practitioner	5	5.0
Nurses	12	12.0
Workplace		
Pharmacy	27	27.0
Pharmaceutical Industry	7	7.0
Private Clinics	7	7.0
Puskesmas	17	17.0
Hospital	42	42.0
Work Experience (years)		
> 10	47	47.0
1 - 5	32	32.0
5 - 10	21	21.0

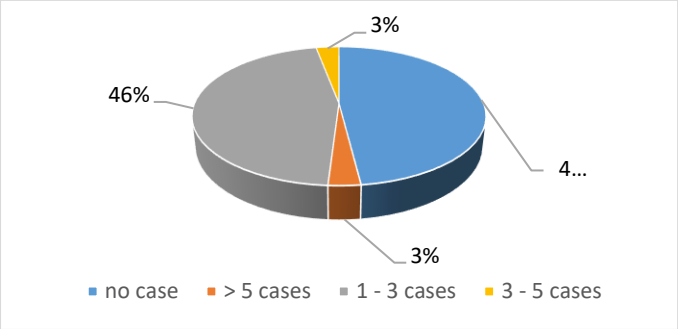

Figure 1. The number of adverse events that were received.

Table 2. The characteristics of knowledge and attitude of the healthcare professionals related to the implementation of Pharmacovigilance

Variable	Category	Number	Percentage (%)
Knowledge	Good	93	93
	Fair	7	7
Attitude	Good	64	64
	Fair	34	34
	Poor	2	2

dilemmatic, and there are difficulties in getting the updated information about the follow up and investigation results of the adverse event. These findings are similar to Hussain *et al.* (2022) research, which mentioned their study in Pakistan identified the healthcare professionals who had poor knowledge about pharmacovigilance and adverse drug reaction reporting also identified a lack of awareness about pharmacovigilance guidelines and the absence of a pharmacovigilance center to be the barriers to Adverse Drug Reaction reporting.

The Knowledge and Attitude

From a total of 100 respondents, about 48%, have not received and reported any AE cases. However, 3% of respondents have received and reported more than 5 (five) AEs (Figure 1). The drugs and the AEs received during their professional practice are described in Table 2. The most common drug classes reported to cause AEs are antibiotics, analgesics, antituberculosis, anticonvulsants, and bronchodilators.

The healthcare professional's knowledge and attitude were measured using a structured questionnaire. The structured questionnaire has two parts: the first part is to measure knowledge, and the second part is to measure attitude. Each part has 9 (nine) questions for the first part and 6 (six) questions for the second part. A description of the knowledge results is explained in Table 2.

The result of the Pearson Correlation Analysis was 0.001. This result shows that there is a significant correlation between their knowledge and attitudes even though the correlation is small (p<0.05). According to recent research, knowledge is a conscious effort to investigate, discover and improve one's understanding from various sources and knowledge is the most important domain for creating individual action (Sabiti *et al.,* 2023).

A significant increase in intention to report adverse drug reactions (ADRs) will be achieved if there is increased knowledge about reporting ADRs and positive attitudes. The results of this research are in accordance with the research results of Eff *et al.* (2024), which was conducted on 130 nurses at Hospital X Bekasi. According to the study's findings, pharmacovigilance and ADR knowledge have a significant impact on how well it is implemented to meet patient safety objectives (F computed is larger than F table / 64.5 > 2.67; (R^2) = 0.667). Enhancing patient safety culture is significantly impacted by pharmacovigilance expertise (p-value = 0.000). Additionally, pharmacovigilance expertise is thought to have a 60.9% impact on patient safety culture (Eff *et al.,* 2024).

A significant increase in intention to report ADRs will be achieved if there is increased knowledge about reporting ADRs and positive attitudes. The level of knowledge of health workers can be increased through education/training related to pharmacovigilance. This intervention has been

proven to be effective as shown in a cross-sectional study among 115 doctors and nurses of a tertiary care teaching hospital in India. After the educational intervention, both physicians' ($Z = -5.344$, $p < 0.001$) and nurses' ($Z = -8.808$, $p < 0.001$) participant scores significantly improved. Both doctors and nurses believed that the biggest obstacle to reporting ADRs was a lack of awareness or understanding. An educational intervention is expected to increase healthcare workers' reporting by improving their understanding of pharmacovigilance (Shenoy *et al.,* 2023).

The Adverse Events of the Drug Reported

Based on respondents' answers, there were 5 (five) main drug categories reported/known during their professional practice: antibiotics, analgesics, antituberculosis, anticonvulsants, and bronchodilators. Table 3 explains the drug names and ADRs in detail.

Antibiotics

The main AEs reported while using antibiotics are allergic reactions and skin rash. The skin reaction is the most prevalent side effect of administering beta-lactam antibiotics such as amoxicillin. Type I reactions are rapid hypersensitivity reactions generated by the synthesis of antibody-reactive chemicals on cell surfaces, which results in degranulation and the release of mediator cells. Immunoglobulin E (IgE) mediates type I responses. Mature B cells develop into plasma cells and generate IgE. Mast cells and basophils have the high-affinity IgE (FcεR1) receptors that bind IgE.

Table 3. The Generic Drug Name and The Adverse Events

Drug Name	Adverse Events
Antibiotics (n=10)	
Amoxicillin	Allergic Reaction
Cefadroxil	Steven Johnson syndrome
Cefotaxime	Skin Rash
	Rash
Ciprofloxacin	Rash and Pruritus
Levofloxacin	Bradycardia and Dyspnea
	Angioedema
	Hypertransaminasemia
Metronidazole	Nausea and Vomiting
Sulfa	Allergic Reaction
Analgesic (n = 8)	
Acetaminophen	Allergic Reaction
	Allergic Reaction
	Steven Johnson syndrome
Aspirin	Bleeding
Ketorolac	Skin Rash, Nausea
	GI Bleeding
Mefenamic Acid	Allergic Reaction
	Angioedema
Antituberculosis (N=4)	
Rifampicin	Hypertransaminasemia (kids)
Rifampicin, Isoniazid, Pyrazinamide, Ethambutol	Skin Rash with Erythema and Fever
	Skin Rash
	Allergic Reaction
Anticonvulsant (n = 3)	
Carbamazepine	Steven Johnson syndrome
	Steven Johnson syndrome
Pregabalin	Dizziness
Bronchodilator (N=3)	
Salbutamol	Palpitations, Tachycardia
	Palpitations
Terbutaline (and Glyceryl Guaiacolate)	Periorbital edema

When an allergen crosses an IgE-bound receptor, hypersensitivity reactions occur (Syamsudin, 2011). Steven Johnson Syndrome(SJS)/Toxic Epidermal Necrolysis (TEN) is an uncommon hypersensitivity reaction that occurs in approximately 6 cases per million people per year. The SJS is a type IVc reaction in which the responses are mediated by cytotoxic CD8+ T lymphocytes that promote apoptosis or necrosis of the keratinocyte (Maker *et al.,* 2019).

Based on VigiAccess (WHO, 2024), there have been 216,778 Adverse Drug Reactions (ADRs) related to levofloxacin. The ADRs were related to cardiovascular (4%; 13,218 Adverse Drug Reactions (ADR)), respiratory (6%; 19,736 ADRs), and hepatobiliary disorder (1%; 4,030 ADRs). For other antibiotic drugs, there have been around 7% or 15,988 ADR cases of immune system disorders when using amoxicillin, 34% or 2,440 ADR cases of skin and subcutaneous tissue disorders when using cefadroxil, and a similar number of skin and subcutaneous tissue disorders ADR cases when using Cefotaxime (33%; 25,566 ADRs).

The antibiotics that have induced skin reaction ADRs are Sulfa and Ciprofloxacin. The information from VigiAccess shows that 27% (66,638 cases) of Ciprofloxacin and 40% (89,071 cases) of Sulpha reported potential ADRs of the skin and subcutaneous tissue disorders ADRs. Related to another antibiotic of Metronidazole, the VigiAccess data informed that about 25% (37,099 cases) of ADRs is related to gastrointestinal disorders.

Analgesic

When acute moderate-to-severe pain occurs, ketorolac, a nonsteroidal anti-inflammatory drug, can be used. This drug is frequently used to treat pain following surgery. Multiple-dose formulations of ketorolac include oral, nasal spray, intravenous, and intramuscular. This drug is frequently used to treat pain following surgery. Cyclooxygenases (COX), which transform arachidonic acid into prostacyclin, thromboxane, and prostaglandins, are inhibited by ketorolac. Inhibition of these chemicals reduces inflammation, fever, and pain. Ketorolac's mechanism of action is not only by inhibition of cyclooxygenase-1 but also cyclooxygenase-2.

Like other non-steroid anti-inflammatory drugs (NSAIDs), peptic ulcers and intestinal or stomach perforations can be brought on by ketorolac. These side effects usually cause symptoms such as nausea, vomiting, and abdominal pain. One of the health workers in this study reported that a patient experienced nausea after being given ketorolac. These data are similar to the most commonly reported potential side effects of ketorolac in VigiAccess, which include gastrointestinal disorders (21%; 12045 ADRs), where ADR reports of nausea rank highest with a number of reports of 6920 ADRs worldwide. Another report in this study stated that the patient experienced gastrointestinal bleeding after receiving a ketorolac injection. In VigiAccess, gastrointestinal hemorrhage is the fourth most common symptom of gastrointestinal disorders with a total of 658 ADRs (WHO, 2024).

According to Campobasso *et al.,* (2008), people who have NSAID allergies or bad reactions should not take ketorolac. A case series reported by Yogi *et al.,* (2023) showed that anaphylactic responses to ketorolac manifest as allergic rashes, swelling, hypotension, and breathing difficulties. Anaphylactic responses from ketorolac are uncommon, but it can happen to people who have never had a medication allergy before. These allergic reactions also happened to one of the patient in this study, who experienced a skin rash. According to VigiAccess, skin and subcutaneous tissue disorders are the second potential side effect of ketorolac with a total of 11,717 reports (20%) worldwide, of which 3,380 reported skin rash symptoms.

Aspirin is an NSAID analgesic agent. It works by reducing prostaglandin in the body which causes pain, fever, and inflammation. Low doses of aspirin are used to treat or prevent heart attacks, and strokes with a mechanism as an antiplatelet. However, aspirin is linked to a higher risk of serious gastrointestinal bleeding. According to a meta-analysis by McQuaid and Laine (2006) people who frequently use aspirin have a roughly two-fold increased risk of gastrointestinal bleeding when compared to those who take a placebo. The result is similar to a prospective study of 87,680 women enrolled in the Nurses' Health Study in 1990 who provided biennial data on aspirin use. According to the study's findings, frequent aspirin use is linked to gastrointestinal bleeding. Dosage seems to have a stronger correlation with risk than aspirin use length (Huang *et al.,* 2011).

Our research found that one patient reported experiencing an ADR in the form of bleeding. It is unclear whether the bleeding is in the digestive tract or where. VigiAccess data informed that the most common reported

potential side effects of aspirin are skin and subcutaneous tissue disorders (27%; 749 ADRs); gastrointestinal disorders (23%; 658 ADRs); general disorders and administration site conditions (10%; 286 ADRs). The highest reported form of ADRs in the event of gastrointestinal disorders is melena (86 ADRs), which is a sign of bleeding in the upper gastrointestinal tract, which is consistent with our study. Emphasizing the use of the lowest effective dose for both short-term and long-term users is one way to reduce the negative effects of aspirin therapy. Additionally, we are aware that patients with hemophilia, a recent history of stomach or intestinal bleeding, or an NSAID allergy should not take aspirin.

Another NSAID that has also been reported to cause adverse events is mefenamic acid. The events were related to allergic reactions and angioedema. NSAID-exacerbated respiratory disease (NERD), NSAID-induced urticaria/angioedema (NIUA), and NSAID-exacerbated cutaneous disease (NECD) are the three most common clinical phenotypes of NSAID hypersensitivity reactions caused by non-immunological processes (Yeung *et al.,* 2020). Based on VigiAccess, there are 24,109 reports with mefenamic acid ingredients. There are about 2,325 of 13,345 ADRs related to Angioedema and about 1,064 ADRs (3%) related to immune system disorders.

Antituberculosis

First-line anti-tubercular (Anti-TB) therapy are rifampicin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E), and streptomycin (S) can induce various AEs. Based on the study by Shi *et al.,* (2024), among 1430 patients undergoing antituberculosis (anti-TB) therapy, 440 (30.77%) reported at least one ADR caused by anti-TB medications. The most prevalent ADR was hyperuricemia, followed by hepatic function test abnormalities, liver injury, and gastrointestinal symptoms. In this study also informed that the main treatment regimens associated with those adverse events are HRE (32.33%, 205/634), HREZ (29.34%, 186/634), HRZS (14.98%, 95/634), HRZ (12.46%, 79/634), HE (2.05%, 13/634), HRES (1.89%, 12/634), HEZ (1.89%, 12/634), RZ (0.95%, 6/634), and HR (0.79%, 5/634).

Another AE that also happens during antituberculosis therapy is cutaneous ADRs. It can range from mild pruritus to life-threatening toxic epidermal necrolysis (TEN). In this study, the reactions reported by respondents to the authority are skin rash and erythema. Almost 80% of ADRs are caused by predictable, nonimmunologic effects of drugs and the rest are caused by unpredictable effects that may or may not be immune-mediated. Immune-mediated reactions account for 5–10% of all drug reactions. The commonest implicated drug was ethambutol (E) 18 (45%), pyrazinamide (Z) 8 (20%), isoniazid (H) 7 (17.5%), rifampicin (R) 6 (15%), streptomycin (S) 3 (7.5%), and levoflo xacin 2 (5%) patients (Sharma *et al.,* 2020).

Based on the VigiAccess, there are 17% (17,346 ADRs) reported potential cases of hepatobiliary disorder (e.g. Hypertransaminasemia), 20% (20,738 ADRs) of skin and subcutaneous tissue disorder (e.g. rash and erythema), 10% (10, 587 ADRs) of general disorders and administration site conditions (e.g. Pyrexia, chills), and 1% (1,403 ADRs) of Immune system disorder (e.g. Allergic Reaction). Regarding the AEs of skin and subcutaneous tissue disorders that appear like skin rash and erythema, 19% (17,061 of 65,310 ADRs) might happen while using the Isoniazid, 18% (13,802 of 57,481 ADRs) in Pyrazinamide and 20% (12,642 of 45,617 ADRs) of Ethambutol (WHO, 2024).

Other AEs that may occur during using antituberculosis are related to immune disorders and general disorders and administration site conditions. For the immune disorder, each antituberculosis product has the same potentiate to induce the AEs, about 1% for each product. In addition, about 7% (701 of 65,310 ADRs) of Pyrazinamide and the same number also happens while using Ethambutol 7% (5,544 of 45,617 ADRs) (VigiAccess, 2024).

Anticonvulsant

Pregabalin (PGB) is a more recent gabapentinoid, often known as an antiepileptic drug (AED), that has many structural similarities with gabapentin (GBP). In the USA and Europe, PGB was authorized for the treatment of neuropathic pain (NeP) in 2004 (Oteri *et al.,* 2010). Since then, PGB has been given further indications for several NeP conditions. PGB is widely used for the primary management of neuropathic pain disorders, such as postherpetic neuralgia, diabetic peripheral neuropathy, fibromyalgia, low back pain with radiculopathy, and central pain brought on by spinal cord damage. Additionally, PGB has been linked to treating generalized anxiety disorder.

According to VigiAccess, the most commonly reported potential side effects of PGB are general disorders and administration site conditions (21%; 68,219 ADRs), nervous system disorders (18%; 58,546 ADRs), and psychiatric

disorders (9%; 29,711 ADRS). In the nervous system disorders category, the three highest reported side effects were dizziness (17,692 ADRs), somnolence (11,235 ADRs), and headache (5,472 ADRs) (WHO, 2024).

Dizziness and somnolence are the most frequent AEs observed in PGB trials, occurring in at least 10% of any age or dosage group. 31% of patients treated with PGB experience dizziness, compared to 9% of patients getting a placebo. Headaches are a very common side effect (possibly experienced by more than 1 in 10 patients) (Pfizer, 2005). With higher PGB dosages, the frequency of these most prevalent adverse effects rises. It is unlikely, nonetheless, that the dose given to elderly people has anything to do with this dose-related impact.

When PGB is started, these AEs frequently happen, and they usually resolve after PGB is discontinued. Nine to fourteen percent of individuals getting PGB and four to seven percent of patients receiving a placebo in clinical trials looking at DPN or PHN stopped their therapy early because of dizziness (3–4%) and somnolence (2–3%). Therefore, the findings from this study are in accordance with the reference, that health workers found undesirable events in the form of headaches after patients used PGB. If the patient experiences an AE, PGB cannot be stopped immediately but must be done gradually over a period of at least 1 week, to avoid drug withdrawal syndrome.

Carbamazepine is an anticonvulsant that has a main mechanism of blocking presynaptic voltage-gated sodium channels. It is thought that blocking sodium channels prevents synaptic glutamate and perhaps other neurotransmitters from being released (Spiller, 2005). The FDA has approved carbamazepine for the treatment of acute manic and mixed episodes in bipolar I disorder, trigeminal neuralgia, and epilepsy. Furthermore, carbamazepine shares structural similarities with the cyclic antidepressant imipramine and may alter cardiac sodium channels in cases of severe overdose.

According to VigiAccess, the most commonly reported side effects of carbamazepine are skin and subcutaneous tissue disorders (21%; 28,583 ADRs) with the three highest clinical manifestations being rash (7,601 ADRs), Steven-Johnson syndrome (3,986 ADRs), and pruritus (3,709 ADRs). The next highest side effects from VigiAccess are nervous system disorders (15%; 20,505 ADRs), and general disorders and administration site conditions (12%; 16,394 ADRs). Data from VigiAccess are very consistent with the results of this study, in which two health workers reported the incidence of Stevens-Johnson syndrome (SJS) due to carbamazepine (WHO, 2024). Dermatological reactions such as SJS, toxic epidermal necrolysis, maculopapular eruptions, and drug reactions with eosinophilia and systemic symptoms (DRESS syndrome) are considerably more common, according to retrospective research (Dean, 2015).

SJS are skin conditions thought to follow the pattern of a type IV hypersensitivity mechanism, which can be brought on by the administration of various medications or infectious agents as part of the spectrum of severe cutaneous adverse reactions (SCARs). The most commonly implicated medications include oxicam, allopurinol, nonsteroidal anti-inflammatory medicines, sulfa pharmaceuticals, and antiepileptics (lamotrigine, carbamazepine, phenytoin, and phenobarbital).

In carbamazepine-induced SJS cases, certain HLA alleles have a substantial correlation with drug-induced SJS/TEN. According to a meta-analysis of 11 investigations involving 343 cases of SJS/TEN brought on by carbamazepine, the genes HLB-B*4001, HLB*4601, and HLB*5801 were powerful protective factors.

Among Asians, HLA-B· 1502 is the most important factor associated with carbamazepine-induced SJS. Before prescribing carbamazepine, genetic screening for HLA-B∗1502 can be done, particularly in Southeast Asia where this allele is quite prevalent (Nasir *et al.,* 2017). Testing for the HLA-B*1502 gene is recommended for patients with Han Chinese heritage. HLA*3101 is another crucial allele to take into account when using this drug. European, Japanese, and Korean ancestry all carry this gene (Ferrell and McLeod, 2008).

Bronchodilator

Salbutamol, a short-acting β2-agonist (SABA), is frequently used as part of routine asthma treatment. Its strong smooth muscle relaxant characteristics, which enable the suppression of bronchial smooth muscle contraction and subsequent bronchodilation, are the basis of salbutamol's therapeutic efficacy. According to the 2024 GINA guideline, SABA is used in STEP 1 of asthma management, as an alternative controller and reliever in adults and adolescents over 12 years. The use of SABA must always be combined with ICS (Inhaled corticosteroid), because SABA only handles the symptom rather than the illness (Anonym, 2024).

Increased airway hyperresponsiveness (AHR), increased airway inflammation, decreased bronchodilator efficacy, elevated allergic response, and elevated eosinophils are all linked to regular SABA use, even for a period of one to two weeks. Moreover, excessive SABA use can raise mortality and exacerbations (Quint *et al.,* 2022). Consequently, salbutamol alone is not recommended. After two hours, the maximal plasma salbutamol concentration is seen, indicating that oral treatment is quickly and effectively absorbed. However, the medicine only has 50% bioavailability due to the first-pass impact, which is linked to both significant hepatic and pre-systemic metabolism in the intestinal mucosa (Skoner, 2000).

Other characteristics of salbutamol include its effects on the heart, uterus, metabolism, and nervous system. Therefore, it is possible that salbutamol can cause side effects on the cardiovascular. In particular, salbutamol may cause tachycardia and peripheral cardiac vasodilation-induced reflex. Salbutamol increased heart rates in asthmatic patients by 23% when inhaled and 28% when taken orally (Winter *et al.,* 1984). In a study including healthy participants, nebulized or intravenous salbutamol caused a dose-related rise in systolic blood pressure and heart rate (Corea *et al.,* 1984). Salbutamol administration raised resting heart rate (baseline HR and PEF increased from 71±8 to 80±11 bpm (p<0.05) and 454.0±64.5 to 475.3±71.4 L/min (p<0.05), respectively), according to a randomized, double-blind, placebo-controlled crossover study conducted in 15 healthy adults. It has no effect on blood pressure, heart rate, or perceived exertion during exercise or recuperation, though. Throughout every protocol phase, the variables HR, BP, and Borg were comparable between interventions (p>0.05) (Feitoza *et al.,* 2017).

According to VigiAccess, the most common reported potential side effects of salbutamol are injury, poisoning and procedural complications (21%; 42,457 ADRs), general disorders and administration site conditions (18%; 36,227 ADRs), and respiratory, thoracic and mediastinal disorders (13%; 26,785 ADRs). Potential side effects in the cardiac disorders category rank fourth (6%; 11,353 ADRs) reported to VigiAccess, with the first to third ranks being tachycardia (4,073 ADRs), palpitations (3,880 ADRs), and cardiac flutter (743 ADRs). Data from VigiAccess are very consistent with the results of this study, in which two health workers reported the incidence of palpitations and tachycardia due to salbutamol (WHO, 2024). Therefore, some experts and researchers said that patients with asthma who also have cardiovascular conditions (such as hypertension, cardiac arrhythmias, or coronary insufficiency) should use this SABA with caution because they are more likely to experience serious cardiac side effects (Price and Clissold, 1989).

Terbutaline functions similarly to albuterol and salbutamol. Terbutaline is a relatively selective β2-agonist. In Indonesia, terbutaline can be administered orally, nebulized, subcutaneously, and intravenously. There are also oral preparations in combination with guaifenesin. At comparable dosages, the adverse reaction profile of terbutaline and salbutamol is similar.

According to VigiAccess (WHO, 2024), the most commonly reported potential side effects of terbutaline are nervous system disorders (20%; 3,089 ADRs); cardiac disorders (18%; 2,767 ADRs); general disorders, and administration site conditions (12%; 1,808 ADRs). Potential side effects in the eye disorders category only reported 1% (145 ADRs), with the first to third ranks are periorbital edema (29 ADRs), visual impairment (23 ADRs), and eyelid edema (22 ADRs). Data from VigiAccess is very consistent with the results of this study, which is one health worker reported the incidence of periorbital edema due to terbutaline.

CONCLUSIONS

The follow-up action and reporting process of the adverse events that have been received by the healthcare professional is one of the attitudes that correlate with the level of knowledge. In addition, there also needs to be continuous knowledge about the importance of reporting adverse events. Based on the response, almost 54% had reported and found an adverse event. The number of cases is various, starting from 1 to 5 cases. The most drug categories reported are antibiotics, analgesics, anticonvulsants, anti-tuberculosis, and bronchodilators.

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CONFLICT OF INTEREST

There is no conflict of interest.

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