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THERAPY PATTERN AND POTENTIAL FOR DRUG INTERACTIONS IN COPD PATIENTS AT THE S.K. LERIK REGIONAL HOSPITAL OF KUPANG CITY

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INTISARI

Penyakit Paru Obstruktif Kronis (PPOK) adalah penyakit respirasi yang ditandai dengan hambatan aliran udara yang persisten dan berhubungan dengan peningkatan respon inflamasi kronis oleh gas atau partikel iritan tertentu. Penatalaksanaan PPOK menggunakan kombinasi obat untuk mengatasi gejala penyakit tersebut, yang bervariasi tergantung kondisi pasien. Kombinasi obat-obatan ini berpotensi mengakibatkan terjadinya interaksi antar obat, salahh satu *Drug Related Problem* (DRP). DRP ini dapat berupa perubahan efek suatu obat akibat diberikan bersamaan dengan obat lain. Penelitian ini bertujuan untuk mendeskripsikan terapi farmakologi dan potensi interaksi obat pada terapi pasien PPOK di Rumah Sakit Umum Daerah S. K. Lerik Kupang. Penelitian ini merupakan penelitian non-eksperimental dan observasional dengan rancangan penelitian deskriptif menggunakan data retrospektif. Sampel pada penelitian ini adalah data rekam medik pasien PPOK yang dirawat inap di Rumah Sakit umum daerah S. K. Lerik Kupang dengan teknik pengambilan sampel dilakukan secara *total sampling*. Hasil penelitian menunjukkan bahwa penanganan terapi pasien PPOK di RSUD S.K. Lerik sebagian besar menggunakan kombinasi terapi kortikosteroid (metilprednisolon), bronkodilator (salbutamol), dan antibiotik (seftriakson). Potensi kejadian interaksi obat tertinggi adalah pada tingkat keparahan ringan, yaitu interaksi antara metilprednisolon dan salbutamol yang diberikan kepada semua pasien (12 pasien).
Kata Kunci: PPOK, kortikosteroid, salbutamol, antibiotik, interaksi obat

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a respiratory disease characterized by persistent airflow limitation and is associated with an increased chronic inflammatory response to certain irritants, gases, or particles. COPD management uses a combination of drugs to treat the disease's symptoms, which varies depending on the patient's condition. The combination of these drugs has the potential to cause drug interactions that result in Drug Related Problems (DRP). A DRP is defined as a change in the effect of a drug due to being given together with other drugs. This study aims to describe the pharmacological therapy given and the potential for drug interactions in COPD therapy at the S.K Lerik Regional General Hospital. This research is descriptive, non-experimental, and observational, using retrospective data. The sample in this study was the medical record data of COPD patients hospitalized at the S.K Lerik Regional General Hospital, with a total sampling technique. The study's results revealed that the COPD patients' treatment at the S.K Lerik Hospital mainly uses a combination of corticosteroid therapy (methylprednisolone), bronchodilators (salbutamol), and antibiotics (ceftriaxone). The highest potential for drug interactions was at the mild severity level with the interaction between methylprednisolone and salbutamol, which was given

to all patients (12 patients). Due to the high potential for drug interactions of these two drugs, further monitoring is needed in COPD patients to determine the manifestations of these drug interactions in clinical conditions

Keywords: *COPD, corticosteroid, salbutamol, antibiotic, drug interaction*

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is an avoidable and curable chronic respiratory disease distinguished by persistent and usually progressive airflow limitation. Exposure to certain irritant gasses or particles increases the chronic inflammatory response of the airways, resulting in COPD (Vogelmeier *et al.*, 2017). In 2019, COPD resulted in 3.23 million deaths worldwide, making this disease the third-highest cause of death (World Health Organization, 2023).

COPD develops slowly and manifests in symptoms such as difficulty breathing, coughing, and fatigue. These symptoms interfere with the patient's comfort and ability to take part in daily activities (World Health Organization, 2023). To treat this disease, COPD patients typically receive therapy to reduce or relieve their symptoms because this disease cannot be cured. However, the disease's development can be slowed down. Treatment of COPD symptoms generally uses two or more drugs or polypharmacy (Hanlon *et al.*, 2018). The drug classes that COPD patients receive include β2 agonists, anticholinergics, methylxanthines, corticosteroids, and phosphodiesterase-4 inhibitors. Furthermore, COPD patients who are hospitalized frequently have comorbidities. As a result, these patients would be administered a high number of drugs. This condition can increase the possibility of interactions between the drugs being used by the patients.

Research on drug-related problems (DRPs) categorization in COPD patients conducted by Li et al. (2019) showed that of the 393 patients sampled, 96.9% or around 381-393 patients received polypharmacy services with an average of 11 drugs per patient. Antibiotics, antihypertensives, bronchodilators, corticosteroids, and expectorants are the five most common medication classes for COPD. Proton pump inhibitors (PPIs; 10.2%), corticosteroids (19.8%), and antibiotics (36.7%) were the three most common drug classes that cause DRP (Li *et al.*, 2019). Sundh et al. (2017) discovered that the most used pharmacological therapy for COPD is a combination of LABA and inhaled corticosteroids (Sundh *et al.*, 2017). Another study by Price (2022) showed that the most frequently used therapy was a combination of corticosteroids and LABA and a combination of corticosteroids, LABA, and long-acting muscarinic antagonist (LAMA) (Price *et al.*, 2014).

As per data from the 2013 Basic Health Research (RisKesDas), the incidence of COPD patients in Indonesia is 3.7% of the total population, or approximately 9.2 million people. According to Aini and Dokhi (2019), Kalimantan and the Nusa Tenggara Islands have the highest prevalence of COPD in Indonesia (Aini & Dokhi, 2019). NTT province ranks first in the highest prevalence of COPD patients, with 10% (Badan Penelitian dan Pengembangan Kesehatan, 2013).

Despite the high prevalence of COPD patients, data on COPD therapy in NTT is still limited. Therefore, this study examines the pattern of COPD therapy used at S.K Lerik Hospital, one of the general government hospitals in Kupang City, as well as the potential for drug interactions that occur due to polypharmacy in the COPD therapy of patients with comorbidities. It differs from previous studies by Santoso and Azalea (2018) and Muriyanto *et al*. (2021), which discussed polypharmacy and the potential for drug interactions in outpatient therapies in healthcare facilities on Java Island (Santoso & Azalea, 2018; Muriyanto et al., 2022). The S.K Lerik Hospital was chosen because it is a type C government-owned public hospital in Kupang that provides services to all of Kupang's citizens.

Additionally, this hospital receives referrals from type D hospitals and public health centers (*puskesmas*) and has never researched the potential for drug interactions in COPD patients before

RESEARCH METHODS

This study used a total sampling method. The inclusion criteria were all medical records of patients diagnosed with COPD who received treatment at the Inpatient Installation of RSUD S.K. Lerik Kupang from January to December 2020. This research had ethical clearance approval from Islamic Hospital Sultan Agung Semarang (*Rumah Sakit Islam Sultan Agung Semarang*) with number of: 278/KEPK-RSISA/X/2023. The exclusion criteria were non-COPD patients and outpatient COPD patients. The data were processed using Microsoft Excel®, and potential drug interactions were identified using the drug interaction checker application on the Drugs.com website.

RESULTS AND DISCUSSION

According to this study's findings, in total, there were 12 (7 men, 5 women) COPD patients treated at S.K. Lerik Hospital in 2020, with patients over 65 years of age accounting for the greatest number of patients (seven), followed by patients aged 56-65 years (four) and 46-55 years (one) (see Figure 1).

COPD is more likely to be experienced by men over 60. COPD is an illness brought on by repeated exposure to hazardous particles and gas, resulting in the formation of chronic inflammation, which results in pathological changes and airway obstruction (Whetsel & Wietholter, 2016). This disease is chronic and progressive; thus, its manifestations usually require a long time of exposure to irritants (Bourdet & Williams, 2020). The main cause of the formation of COPD is chronic exposure to cigarette smoke and other smoke exposure, which eventually triggers persistent inflammation (Vogelmeier *et al.*, 2017). According to the Indonesian National Statistics Agency (2020), the percentage of smokers aged less than 18 years in Indonesia is 3.81%, with a percentage of 7.26% for men and 0.17% for women (Badan Pusat Statistik, 2020).

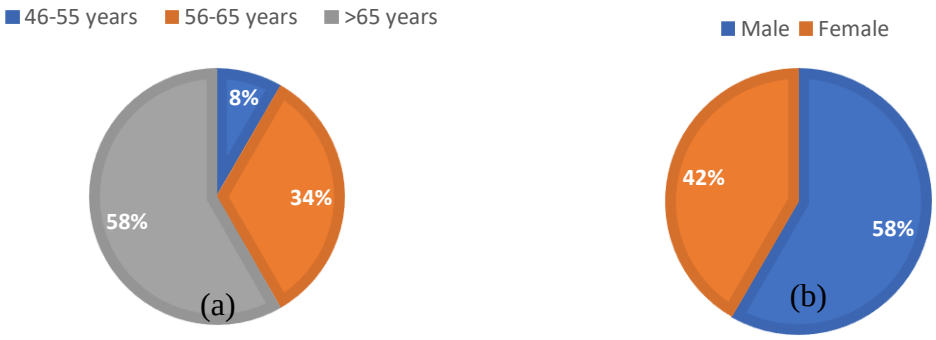

Figure 1. The percentage of COPD patients divided by (a) Age Group, (b) Sex.

According to Ntritsos (2018), the smoking rates for women are higher in developed countries than in developing countries. Consequently, the prevalence of female COPD patients is higher in these developed countries (Ntritsos *et al.*, 2018). Another study by Mutmainnah (2015) revealed that 80.28% of COPD patients were men, 64.78% were in the elderly group, and 61.97% were smokers or had a history of chronic smoking (Mutmainnah et al., 2015). A seven-year prospective study by Thomsen et al. (2013) also stated that 41% of COPD patients were former smokers, and 37% were active smokers (Thomsen *et al.*, 2013).

This study's results and the previous research aligns with Minister of Health Decree (Keputusan Menteri Kesehatan or KepMenKes) Number HK.01.07/Menkes/687/2019 concerning National Guidelines for Chronic Obstructive Pulmonary Disease Medical Management, which states that 37-38.2% of smokers are from the age group of 25-64 years and the prevalence of smoking is 16 times higher in men (65.9%) than women (4.2%). Of this percentage, around 15-20% of smokers will experience COPD. Another study by Kusumawardani et al. (2016) also proved that not only

active smokers are at risk of developing COPD, but passive smokers also have a higher risk of developing COPD than patients who are not passive smokers (3.7% versus 3.2%) (Kusumawardani et al., 2016).

In this study, 12 patients diagnosed with COPD received pharmacological therapy through corticosteroids, bronchodilators, and antibiotics (see Table I). All patients received a combination of corticosteroids, methylprednisolone, and bronchodilators to maintain their condition and treat COPD exacerbations. All patients received a β2- agonist bronchodilator, salbutamol, and inhalation therapy (nebulizer), and one patient received a salbutamol nebulizer combined with aminophylline. Based on KepMenKes Number HK.01.07/Menkes/687/2019, all COPD patients must receive a bronchodilator for inhalation.

Bronchodilators are the main therapy for treating COPD symptoms to improve patient's tolerance to activities and quality of life. The bronchodilator salbutamol is a short-acting β2 agonist, relaxing the muscles of the respiratory tract by stimulating the adenyl cyclase enzyme to increase the production of cyclic adenosine monophosphate (cAMP). Salbutamol is generally used for acute relief of symptoms and tends to be less expensive than long-acting β2 agonists, such as salmeterol. Meanwhile, aminophylline is an ethylenediamine salt of theophylline, a methylxanthine derivative compound, which works by inhibiting the phosphodiesterase enzyme so that intracellular cAMP levels remain high, causing the relaxation of the smooth muscles of the respiratory tract and resulting in bronchodilation (Whetsel & Wietholter, 2016). Theophylline also reduces the prevalence of acute exacerbations in COPD patients by providing better FEV1 (forced expiratory volume in the first second) value when combined with inhaled corticosteroids, compared to using corticosteroids alone. The use of theophylline has the potential to improve corticosteroid resistance in COPD patients (Barnes, 2013).

The corticosteroid given to COPD patients in this study was methylprednisolone. Due to its strong anti-inflammatory effect, methylprednisolone is a synthetic systemic corticosteroid used to treat COPD. Corticosteroids are given to COPD patients with a high risk of exacerbations and prophylaxis to prevent further exacerbation (Whetsel & Wietholter, 2016).

In addition, the COPD patients in this study received antibiotic therapy. Eight patients received intravenous ceftriaxone, three received ceftriaxone and oral azithromycin, and one received intravenous levofloxacin. In COPD therapy, antibiotics are administered to treat acute exacerbations and infections, especially acute bronchitis exacerbations, which account for one-third of the cases caused by bacterial infections (Reis *et al.*, 2018). The bacteria usually involved in acute exacerbations of COPD are Methicillin-resistant *Staphylococcus aureus* (also known as MRSA), *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (Whetsel & Wietholter, 2016). Research by Huckle et al. (2018) proved that azithromycin and erythromycin have the best therapeutic effect in treating acute exacerbations of COPD patients and provide better health conditions. Meanwhile, macrolide antibiotics show anti-inflammatory effects that are compatible with COPD conditions. Although it is beneficial in COPD therapy, treatment with this antibiotic requires special supervision because it can lead to antibiotic resistance if improperly used (Huckle et al., 2018).

In addition to being given therapy for COPD management, these patients also received other therapies due to their comorbid diseases (see Table II). The most widely used drug classes are gastrointestinal and cardiovascular drugs. Most COPD patients experience symptoms of gastrointestinal disorders, such as dyspepsia, gastroesophageal reflux disease, and cardiovascular disease. Chiu et al. (2022) stated that COPD patients are at high risk of experiencing gastrointestinal disorders (Chiu *et al.*, 2022). Research by Su et al. (2018) also showed that the administration of the proton pump inhibitor therapy in COPD patients with comorbid gastroesophageal reflux disease gave good results in the form of a reduced risk of acute exacerbations in patients. Apart from the gastrointestinal tract, COPD patients also experience many comorbid cardiovascular disorders. Most COPD patients have a history of smoking, which is a risk factor for cardiovascular disorders (Su *et al.*, 2018). Westerik et al. (2017) conducted a cohort study that showed that comorbidities increased

the risk of acute exacerbations in COPD patients, and the most commonly experienced comorbidities were hypertension and coronary heart disease (Westerik *et al.*, 2017).

Table I. Types of Treatment of COPD Patients at S. K. Lerik Regional General Hospital in 2020

Drug Groups	Drug Type	Total Use
Corticosteroid (intermediate-acting)	Methylprednisolone	12
Bronchodilator		
B2-agonist	Salbutamol nebulizer	12
Methylxanthine	Aminophylline	1
Antibiotic	Ceftriaxone	8
	Ceftriaxone + Azithromycin	3
	Levofloxacin	1

Other drug therapies given to COPD patients in this study were ondansetron, cetirizine, paracetamol, ambroxol, and codeine. Ondansetron was also administered to a patient to alleviate nausea and vomiting. Meanwhile, cetirizine, ambroxol, and codeine treat other COPD symptoms, such as chronic cough and increased sputum production (Yawn et al., 2021). Antitussives are not recommended for COPD patients because the cough response can provide a protective effect by increasing mucus clearance. However, opioids may benefit dyspnoea in patients with moderately severe conditions (Whetsel & Wietholter, 2016). Meanwhile, a meta-analysis study by Cazzola et al. (2017) proved that mucolytics have a beneficial effect on COPD patients because they can reduce the prevalence of exacerbations in patients (Cazzola *et al.*, 2017).

Table II. Therapies for Comorbid COPD Patients at RSUD S.K. Lerik in 2020

Drug Groups	Drug Type	Total Use
Cardiovascular		
Combination	Amlodipine + Candesartan	3
Single	Amlodipine	1
	Candesartan	1
Diuretic		
Loop diuretic	Furosemide	4
Gastrointestinal		
Proton pump inhibitor	Omeprazole	8
H2 receptor antagonist	Ranitidine	3
Antacids	Antacid	2
Antiemetic	Ondansetron	1
Antihistamine	Cetirizine	1
Analgesic – antipyretic	Paracetamol	1
Antitussive	Codeine	1
Mucolytic agent	Ambroxol	2

In this study, COPD patients received an average of 6-10 drugs per patient. This polypharmacy condition provides the potential for interactions to occur between drugs used by patients. The highest potential for drug interactions in this study was between methylprednisolone and salbutamol because all COPD patients used both drugs (Table III). Based on the *drug interaction checker* application on the *Drugs.com* website, the severity of the interaction between the two drugs is mild. Beta-2 adrenergic agonists can cause prolongation of the Q.T. interval and increase dose-related potassium loss. Theoretically, combining salbutamol with other agents that prolong the Q.T. interval may have additive effects, increasing the risk of ventricular arrhythmias (Drugs.com, 2021). Moreover, salbutamol has the potential side effect of increasing blood pressure, causing hypokalemia and hyperglycemia (Johnson et al., 2022). The potential for this effect can be increased by corticosteroids, such as methylprednisolone, which has side effects such as hypertension,

hyperglycemia, and arrhythmias (Ocejo & Correa, 2022). Despite being frequently used together in clinical practice, beta-2 adrenergic agonists and corticosteroids can have additive hypokalemic effects. The type of interaction for this effect is pharmacodynamic synergism. Therefore, the patient's serum potassium levels during therapy must be monitored, and the drugs must be administered through different dosage forms or routes. Patients in this study were given methylprednisolone orally, and salbutamol was given as a nebulizer (inhalation).

Table III. Distribution of potential drug interactions by severity in S.K. Lerik Hospital in 2020

Severity	Drug A	Drug B	The number of potential interaction events	Types of Interaction based on Mechanism
Major	Levofloxacin	Methylprednisolone	1	Unknown
Moderate	Aminophylline	Salbutamol	2	Pharmacodynamic (synergistic)
				Pharmacokinetic (excretion)
		Azithromycin	1	Pharmacokinetic (metabolism
	Azithromycin	Salbutamol	3	Pharmacodynamic (synergistic)
	Furosemide	Salbutamol	1	Pharmacodynamic (synergistic)
		Omeprazole	2	Pharmacodynamic (synergistic)
	Methylprednisolone	Aminophylline	1	Pharmacokinetic (metabolism)
				Pharmacodynamic (synergistic)
		Amlodipin	2	Pharmacodynamic (antagonistic)
		Candesartan	2	Pharmacodynamic (antagonistic)
		Furosemide	2	Pharmacodynamic (synergistic)
	Salbutamol	Ondansetron	2	Pharmacodynamic (synergistic)
Minor	Methylprednisolone	Salbutamol	12	Pharmacodynamic (synergistic)
	Ranitidine	Paracetamol	1	Pharmacodynamic (synergistic)
	Furosemide	Aminophylline	1	Unknown

There were 18 potential interaction events with moderate severity, with the highest potential being when combining azithromycin and salbutamol at three potential events (Table III). This combination increases the risk of cardiovascular events, such as irregular heart rhythms or arrhythmias, because the two drugs have the same side effect, prolonging the heart's Q.T. interval.Although these side effects are uncommon, patients with heart conditions, such as congenital long Q.T. syndrome, other heart diseases, cardiac conduction abnormalities, or electrolyte disturbances (e.g., potassium or magnesium deficiency caused by severe or prolonged diarrhea or vomiting), are more vulnerable. The risk of electrolyte disturbances such as hypokalemia can also increase because using salbutamol alone can cause hypokalemia. This risk can still occur even if salbutamol is inhaled directly into the lungs (*Drugs.com*). Because they have similar side effects, the type of potential interaction that can occur is a synergistic pharmacodynamics interaction.

For potential drug interactions with severe severity, there was only one potential event: the use of levofloxacin and methylprednisolone. Based on the drug interaction checker from the Drugs.com website, administering methylprednisolone and levofloxacin can increase the risk of tendinitis and tendon rupture (the mechanism is unknown). Although rare, the use of levofloxacin may cause tendinitis, and the side effect of long-term use of corticosteroids is also tendinitis. Therefore, the risk of tendinitis can increase when levofloxacin is combined with corticosteroids, such as methylprednisolone, especially in patients > 60 years old. From the potential side effects of the two drugs, it can be concluded that there is a potential for synergistic pharmacodynamic interactions because the use of both drugs can increase each drug's potential side effects. In minimizing the potential for drug interactions, clinical pharmacists can consider replacing or looking for other drug alternatives that do not cause interactions. Dosage adjustments, in this case, can also be taken into consideration.

The limitation of this study is that it used a retrospective approach from past data. Hence, direct monitoring for the drug interactions could not be performed. In addition, because this study used a retrospective method, there is a possibility of over-the-counter (OTC) or traditional herbal drug use that is not recorded in the medical record. Moreover, the number of study samples was small because only one year of medical record data from hospitalized COPD patients was used.

CONCLUSIONS

The treatment of COPD patients at RSUD S.K. Lerik mostly used a combination of corticosteroid therapy (methylprednisolone), bronchodilators (salbutamol), and antibiotics (ceftriaxone). Of the combination therapies received by patients, the highest potential for drug interactions was at the mild severity level, namely the interaction between methylprednisolone and salbutamol, which was given to all patients (12 patients).

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