

ANALYSIS OF THE USE OF DRUG CATEGORY OFF LABEL IN HOSPITAL PATIENTS AT HOSPITAL

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ABSTRACT

The increasing use of off-label category drugs is the reason clinicians use these drugs because the clinical response has not had a significant impact on treatment as well as various reasons for specific therapeutic purposes. While adverse events and adverse reactions to drugs from off-label category drugs tend to continue to increase, so we need continuous and continuous data and study of therapies about the use of off-label category drugs. The purpose of this study was to analyze the characteristics of usage patterns and reasons for administering off-label categories of drugs to inpatients in hospitals. This research was conducted at the hospital. Dr. Wahidin Sudiro Husodo Makassar. Research uses data in the form of inpatient prescriptions in the internal medicine, children's and obgin's sections with a prescription number of 150 sheets. The results showed that the indication of disease using off-label category drugs was not dominated by one particular disease but rather based on the needs and conditions of the disease and the drug availability of the off label drug. The pattern of treatment using off-label categories of drugs given orally is the most dominant given by the clinician. The type of drug that is commonly used in the off-label category is not dominated by certain classifications, but drugs with indicated anti-pain are the choices for the type of drug used. The reason the clinician decides to use off-label category drugs is because the on-label category drugs have not been able to contribute to healing the diagnosis of the disease while some drugs based on experience for drugs that have not been approved can provide a significant healing process.

Keywords; off-label category drug analysis

INTRODUCTION

Off-label drug use is the use of drugs outside the indications approved by the authorized agency. The use of off-label category drugs for therapeutic purposes must require a process of proving efficacy and risk of side effects so that when the drug is used for certain therapeutic purposes the drug is safe. While on-label category drugs are drugs that have a marketing authorization issued by BPOM or the Ministry of Health, on-label category drugs by the authorities can guarantee that drugs have been tested for safety, efficacy and quality so that risks can be overcome or minimized. The use of off-label category drugs can cause side effects and risks that may outweigh potential benefits. Ethical and legal issues relating to the promotion of commercial use of off-label drugs have also increased due to very fast information and in-depth technological studies on the use of off-label categories of drugs. Use outside the label has not been formally evaluated, and the evidence provided for one clinical situation may not apply to another person. The use of off-label drugs, cannot be categorized as the use of drugs that violate the law or legal ethics, but can be categorized as use that is risky because it can cause adverse effects up to 23%.^{3, 5, 15} The publication of Adriana 2017 research results in Brazil with prospective methods shows that 157 newborns and 1187 prescriptions analyzed found that there were 56.0% of drugs in the off-label category and 7.2% of the illegal category recipes.¹ Documents released by the European survey agency EMEA in 2004 reported that there were

serious adverse events for patients using off-label categories.⁸ The increasing use of off-label category drugs is the reason clinicians use these drugs because the clinical response has not had a significant impact on treatment as well as various reasons for specific therapeutic purposes. While adverse events and adverse reactions to drugs from off-label category drugs tend to continue to increase, so we need continuous and continuous data and study of therapies about the use of off-label category drugs. The use of off-label categories of drugs is often beneficial and provides new breakthroughs in treating certain cases of disease. It may be that clinical evidence of its efficacy already exists, but approval has not been requested from the competent authorities for various reasons. But it should also be noted that because this drug is used outside the indications written on the drug label, so if the drug has an undesirable effect, various reports of unwanted events give caution in using off-label category drugs.

MATERIAL AND METHOD

This research will be carried out at Wahidin Sudiro Husodo Hospital Makassar in April - November 2018. This type of research is quantitative research with a cross-sectional study design. This study uses a survey method that is collecting prescription drugs that are categorized as off-label drugs in several departments in hospitals and then analyzing the relationship between variables. The population in this study was prescribing hospital doctors for inpatients and doctors who wrote prescription drugs

off-label categories. The sample size in this study used parameter estimation with data on the proportion of 150 prescription drugs for the off-label category. The sampling technique in this study was conducted by random sampling, which is choosing a prescription drug category off-label. Data processing and analysis techniques in this study use multivariate analysis methods that can be used to confirm whether the measurement analysis was built in accordance with what was hypothesized.

RESULT

This study is an observational study related to the use of off label categories for inpatients in hospitals. Wahidin Sudiro Husodo Hospital Makassar. Research results show that the use of off-label categories of drugs provides benefits to the development of therapy but on the other hand the threat of side effects and regulation of marketing authorization have not been obtained from the authorities. The results of the study related to the use of off label category drugs in patients receiving treatment at the Hospital Wahidin Sudiro Husodo Makassar

Table 1. Use of off-label categories of drugs related to dosage, route of administration and indications of drugs that affect the treatment process.

No.	Drugs	Dosage	Administration route	Indication
1	Metronidazole tab 500mg	10 tablets made to powder	Smear on the wound surface	Wound care
2	Metronidazole tab 500mg	10 tablets were crushed and dispersed in gentamicin ointment	Smear on the wound surface	Wound care
3	Metronidazole tab 500mg	10 tablets were crushed and dispersed in fucidic acid ointment	Smear on the wound surface	Wound care
4	Metronidazole 500 mg/100 ml	100 ml wash the wound	Intravena	Wash the wound
5	Aspar insulin	10 unit	Intravena	Hipercalemia
6	Metformin 500 mg tab	500 mg/8 hours	Oral	Polycystic ovarium syndrome (PCOS)
7	Sucralfate susp 100 ml	100 ml wash the wound	Oral	Wash digestive wounds
8	Captopril tab	6,25 mg/8 hours	Oral	Anti remodeling
9	Chloroquine tab	200 mg/24 hours 250 mg/days (3,5-4 mg/kg body weight /days)	Oral	Systemic Lupus Erythematosus (SLE)
10	Laxative syrup	60 ml	Rectal/clisma	Anal cleansing
11	Misoprostol tab	40 ug/dosage	Pervaginal	Labor Stimulating
12	Carbamazepine tab	100 mg	Oral	Mood stabilizer
13	Gabapentin tab	300 mg	Oral	Neuropathy therapy
14	Risperidone tab	0,25 mg/12 hours	Oral	Overcoming hyperactivity disorders
15	Codein Paracetamol	20 mg 500 mg/made to powder	Oral	Cancer pain
16	Amitriptyline 6,25 mg Paracetamol 500 mg Diazepam 1 mg Coffein 20 mg	Made to powder	Oral	Overcome pain

17	Cyproheptadine tab	4 mg/8 hours	Oral	Increased appetite
18	Zinkid tablet	50 mg	Oral	Wilson diseases
19	Domperidon tab	10 mg	Oral	Breast milk stimulation

Table 1 shows that the majority of off-label category drugs are used in oral form or the same as the drug administration approved by the authorities (BPOM/on label) but with different indications and characteristics of the disease. The category of off label drugs is drugs outside the indications listed on the label and not yet or outside approval by the authorized body or institution such as the BPOM or the FDA (Food Drug Administration). Reasons for

using off label categories are lack of clinical response to previous treatment, intolerance or contraindications to alternatives or reasons such as the availability of approved drugs as indicated or patients with alternative treatments for clinical or logistical reasons. Factors of pharmacokinetic data, pharmacodynamics and drug side effects, which have not been optimal are other reasons for the use of off label categories of drugs.

Table 2. The classification of pharmacotherapy and the reason doctors give prescriptions for the use of off-label categories of drugs

No.	Drugs	Pharmacotherapy Classification	Indications off label	Reason doctors give off label category drugs
1	Metronidazole tab 500mg	Anaerobic/antibacterials	Antiinfection / Wound care	Accelerate wound drying
2	Metronidazole tab 500mg	Anaerobic/antibacterials	Wound care	Accelerate wound drying
3	Metronidazole tab 500mg	Anaerobic/antibacterials	Wound care	Accelerate wound drying
4	Metronidazole tab 500 mg/100 ml	Accelerate wound drying	Wound care	Clean the wound so as to avoid infection
5	Aspar insulin	Antidiabetic	Hyperkalemia	Provided to patients who experience hyperkalemia in diabetic kidney disorders while in hospital
6	Metformin 500 mg tab	Antidiabetic	Polycystic ovarium syndrome	Given to patients who have PCOS (Polycystic Ovary Syndrome) due to hormonal imbalance and increased hormone and ovulation disorders
7	Sucralfate susp 100 ml	Gastrointestinal disorders (ulcer drugs and inflammation of the stomach)	Washing digestive wounds, the digestive tract used orally especially to treat active duodenal ulcers. Sucralfate is a cytoprotective agent	Preventing the occurrence of stress ulcers in patients with gastroesophageal reflux disease (GERD)
8	Captopril tab	Antihypertensive	Anti remodeling	Reducing the risk of heart failure by preventing remodeling in the left ventricle of the heart (restoring the function / model of the left ventricle of the heart)

9	Chloroquine tab	Antimalarials	SLE (Systemic Lupus Erythematosus)	stabilization of the lysosomal membrane thereby inhibiting the release of lysosomal enzymes, binding to DNA, disrupting DNA antibody attacks, decreasing prostaglandin and leukotriene production, decreasing T cell activity, and releasing IL-1 and tumor necrosing factor α (TNF- α). The aim is to improve the regression of erythema of skin lesions
10	Laxative syrup	Laxative	Clisma/levament	Rectal cleansing for colonoscopy preparation
11	Misoprostol	Gastrointestinal disorders (gastric ulcer prevention drugs classified as prostaglandin E1 synthesis)	Labor Stimulating	Shorter induction, progress delivery is faster
12	Carbamazepine	Overcoming seizures in epilepsy	Mood stabilizer	Improve the stability of the behavioral conditions
13	Gabapentin	Anti convulsions	Neuropathy therapy	Treatment in patients with impaired nerve function (tingling), feel punctured or painful
14	Risperidone	Medication to overcome psychiatric disorders (antipsychotics)	Overcoming hyperactivity disorders	Overcome behavioral disorders or hyperactivity and overcome anxiety
15	Codein Paracetamol	Treatment of cough and fever	Treatment of cancer pain	The two drugs are different classes and mechanisms, but the combination of the two drugs can increase pain reduction significantly for cancer patients
16	Amitriptyline 6,25 mg Paracetamol 500 mg Diazepam 1 mg Coffein 20 mg	Analgetics	Neuropathy	Treatment of neuropathy (cramps)
17	Cyproheptadine	Antihistamin	Increased appetite	Increase appetite
18	Zinkid tab	Treatment for diarrhea	Wilson diseases	Maintain copper levels in the body, after spending excess copper in the body and prevent interference due to excess copper

19	Domperidon tab	Treatment and prevention of vomiting	Streamlining breast milk	Stimulates the hormone prolactin so that it increases milk production
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Table 2 shows that pharmacotherapy of drugs used for off-label category drugs shows that doctors use or administer off-label category drugs. The table shows that the pharmacotherapy of the drug category is off label and the reason the doctor gives

the drug indicates that desired therapy with different goals. The lack of clinical response and the use of active compounds from these drugs is a significant reason for the use of off label category drugs

DISCUSSION

Treatment patterns, off-label category drugs used in hospital hospitals. Dr. Wahidin Sudiro Husodo Makassar, is something that cannot be avoided because the clinical response has not shown changes and the potential of active compounds of the drug that can be used for different therapies so that it is possible to be used, then other factors using off label categories are due to drug supply for use as a treatment is not available.

Metronidazole is an antimicrobial class of nitroimidazole derivatives used to treat infections caused by protozoan microorganisms and anaerobic bacteria. The mechanism of action of Antibacterials in preventing the spread of infectious agents or killing infectious agents so they do not spread. Its mechanism of action is that it inhibits nucleic acid synthesis by damaging DNA. Table 1 shows that metonidazole is used as an off label drug for wound healing. The reason it is used for the treatment and healing of wounds, methodidazole is given in powder and ointment mixed with gentamicin ointment and fucid acid ointment. The combination of these drugs is in the form of ointments that can facilitate penetration into the wound site. Tablet administration that should be administered orally is given in the form of topical and a dose of 10 tablets crushed with 5000 mg active substance dispersed into gentamicin ointment or fucid acid ointment. The mechanism of action of metronidazole ointment for the purpose of wound care or wound drying is the reduction of inflammation or lesions and erythema perilesi⁷.

A form of the type of fast-acting insulin hormone, insulin works by reducing blood sugar levels. Aspart insulin is used to treat type 1 (insulin-dependent) diabetes in adults and children who are at least 2 years old. The drug is used as an off label drug for patients with hyperkalemia, which is the accumulation of potassium in the blood. The mechanism of action of the drug is to push and move potassium into the cell and stimulate absorption by the cell membrane.

Metformin is one of the biguanid antidiabetic groups with the aim of controlling high blood sugar, usually used by people with type 2 diabetes. Metmorphine works by helping to restore the body's proper response to naturally produced insulin. For women

who experience hormonal disorders that cause polycystic ovary syndrome (PCOS / PCOS) are metabolic disorders associated with irregular menstrual cycles, hormonal imbalances, and insulin resistance problems. Insulin resistance is a condition where the body's cells stop reacting to normal insulin levels, the condition is found in women suffering from PCOS and ovulation problems. Metformin as an off label category drug is used to overcome insulin resistance by regulating reproductive hormones and restoring ovulation and helping to ovulate. The use of metformin can make the menstrual cycle more orderly and the process of ovulation can be controlled.

Sucralfate syrup is an indigestion drug to treat and prevent gastric ulcer and duodenal ulcer. This drug works by forming a layer on the wound and protect it from stomach acid which can slow healing. The use of Sukralfat for the off label category is washing wounds in patients who have duodenal ulcers

Captopril is a drug to treat high blood pressure (hypertension) which is included in the ACE inhibitors class. This drug works by inhibiting the angiotensin-converting enzyme which then decreases the amount of angiotensin II (a hormone that causes blood vessel constriction and increases blood pressure). The use of captoril for the off label category is as an antiremodeling, a condition where there is a decrease in the function of the heart pump so that the heart undergoes cell remodeling through a variety of complex biochemical mechanisms and ultimately decreases heart function, this is due to myocardial infarction conditions, chronic hypertension, and cardiomyopathy⁶.

Chloroquine is a drug used to prevent and treat malaria, or treat infectious diseases caused by mosquitoes infected with parasites. Chloroquine works in the erythrocyte phase and is not effective in the hepatic phase. The use of Chloroquine for the off label category is as a treatment for Systemic Lupus Erythematosus (SLE), stabilization of the lysosome membrane thereby inhibiting the release of lysosomal enzymes, binding to DNA, disrupting DNA antibody attacks, decreasing prostaglandin and leukotriene production, decreasing T cell activity, and releasing IL-1 and tumor necrosing factor α (TNF- α). The aim is to improve the regression of erythema of skin lesions.

Laxatives (Phenolphthalein, Liquid paraffin, Glycerin) action by stimulating peristalsis in the large intestine and inhibiting the absorption of excess water from feces and smoothing out the feces. The use of laxatives for the off label category is as clisma or lavement for sufferers to be colonoscopy.

Misoprostol is a gastrointestinal drug used to prevent and treat peptic ulcers, prevent ulcers in the small intestine. Misoprostol works to reduce acid levels in the stomach, and increase levels of mucus and bicarbonate in the stomach. The use of misoprostol for the off label category is. Misoprostol has been extensively studied in reproductive health, and is widely recommended for the treatment of missed and incomplete miscarriages, abortion induction, and cervical preparation before uterine instrumentation, labor induction and prophylaxis of postpartum hemorrhage and treatment. The use of misoprostol for off-label indications is to induce labor. Misoprostol is a prostaglandin class that works to ripen the cervix and is given intravaginally. Carbamazepine is a drug used to prevent and control seizures or convulsions. These drugs are included in the class of anticonvulsant drugs or antiepileptic drugs. Carbamazepine drug is a drug used to treat epilepsy and neuropathy patients. Carbamazepine also treats certain mental or mood conditions such as bipolar disorder.

Gabapentin is an anticonvulsant drug that functions to treat seizures, works by affecting the nervous system, clinicians give gabapentin with a diagnosis of anti-convulsions or antiepilepsy.

The interaction of gabapentin and morphine can increase gabapentin levels in blood plasma. Whereas with antacids can reduce the absorption of gabapentin by the digestive tract. This drug should be stored at room temperature, away from direct light and places that have moisture.

Gabapentin given for neuropathy or pain therapy in the off label category is given an initial dose: 300 mg orally on the first day, 300 mg orally twice a day on the second day, then 300 mg orally 3 times a day on the third day. Gabapentin as an off-label category is also mostly used to help treat patients who experience nerve dysfunction (tingling), feel punctured or pain medication or pain as a substitute for opioid therapy. Likewise, the administration of drugs with the composition of Amitriptylin 6.25 mg, Paracetamol 500 mg, Diazepam 1 mg, Coffein 20 mg and the composition of Codein, Paracetamol as an off label category for pain therapy

Risperidone for the on label category is used as a drug to treat psychiatric disorders (antipsychotics) such as schizophrenia or bipolar disorder. Risperidone can increase blood sugar, even if the patient does not have diabetes, so people with mental disorders are more at risk of developing diabetes. The initial dose is 2 mg per day, which can be increased to 4 mg per day on the second day. Medication can be given once a day or divided into

two consumption schedules. The treatment dose is 4-6 mg per day. The maximum dose is 16 mg per day.

Although the use of risperidone as an off label category for hyperactivity therapy is still low and the evidence base is still small, the choice of this drug by clinicians is used for that therapy.

Cyproheptadin is the most commonly used by people for appetite enhancement and usually the drug is combined with dexamethasone. Ciproheptadine is an allergy medicine that belongs to an antihistamine group that works to inhibit the release of histamine (H1) as a trigger for allergies. Ciproheptadine is used for the off label category as a drug of choice for appetite enhancer, although it has not been scientifically proven.

CONCLUSION

Based on the results of research and analysis of the Discussion of the Use of Off Label Categories of Medicines for Inpatients in Hospitals, this study can be concluded as follows:

1. Indications of diseases using off-label categories of drugs are not dominated by one particular disease but rather based on the needs and conditions of the disease and the drugs available off-label drugs
2. The pattern of treatment using off-label categories of drugs is given orally most doniman given by clinicians
3. The type of drug that is commonly used in the off-label category is not dominated by certain classifications, but drugs with indicated anti-pain are the choice for the type of drug used
4. The reason the clinician decides to use off-label category drugs is because the on-label category drugs have not been able to contribute to healing the diagnosis of the disease while some drugs based on experience for drugs that have not been approved can provide a significant healing process.

ACKNOWLEDGEMENT

Socialization related to the safety of off-label category drug use. In-depth studies are needed related to the use of off-label category drugs before deciding on the use of these drugs both in clinical and economic aspects of the patient. Likewise, the management of off-label category drugs requires handling which illustrates that the use of the drug is appropriate for use from the pharmacokinetic, pharmacodynamic, biopharmaceutical aspects of the drug

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