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Drugs Interaction in Clinical Management for (Generalized Anxiety Disorders) Inpatients: A Retrospective Study

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Abstract*−GAD (Generalized anxiety disorder) or Comprehensive Anxiety Disorder is a feeling of severe anxiety that is persistent, accompanied by somatic symptoms that cause social function and work function disorders. GAD patients often get more than two types of drugs thereby increasing the likelihood of drug interactions. The mechanism of drug interactions is divided into pharmacokinetics and pharmacodynamics. This study was aimed to investigate the potential for drug interactions and management of drug interaction events so it was able to minimize the incidence of drug interaction in GAD patients in YANKESWA Banyumas Regional Hospital by providing rational therapy. The method of this research was a retrospective observational study. Data were analyzed descriptively using Stockley's Drug Interaction, Drug Interaction Facts and www.drugs.com database. The results revealed that of 47 GAD patients, there were 89.36% incidence of drug interactions, with pharmacodynamic interactions dominating 68.57% compared to pharmacokinetics 31.42%. The most common interaction is the interaction between sertraline and alprazolam.

Keywords: GAD, drug interaction

I. INTRODUCTION

GAD (Generalized anxiety disorder) or Comprehensive Anxiety Disorder is a feeling of severe anxiety, persistent, accompanied by somatic symptoms that cause impaired social function and work function (Locke, et al., 2015).

Riskesdas data in 2013 showed the prevalence of mental emotional disorders as indicated by symptoms of depression and anxiety for the age of 15 years and overreaching around 14 million people or 6% of the total population of Indonesia. While the prevalence of severe mental disorders, such as schizophrenia up to 400,000 people or 1.7 per thousand populations. According to WHO data (2016), there were around 35 million people affected by depression, 60 million people affected by bipolar, 21 million people affected by schizophrenia, and around 47.5 million affected by dementia.

The common symptoms often found in GAD are: anxiety or feelings of tension, fatigue, concentration difficulty, irritability, muscle tension, sleep disturbance, which usually lasts for 6 months. GAD can also occur with physical symptoms such as: tachycardia, tremors, palpitations, sweating, and gastrointestinal disorders. According to Ikawati (2013) anxiety disorders associated with abnormalities in some parts of the brain and impaired function of several neurotransmitters, such as : norepinephrine (NE), GABA (Gamma Amino Butyric Acid), and serotonin (5 -HT), amygdala structure which is a temporal lobe in the brain plays an important role in stimulating and responding to anxiety symptoms. Locus Ceruleus (LC) located in the bone marrow is the main part of the brain that contains NE with a wider distribution area of the brain that is responsible for anxious responses (such as: vagus, hypothalamus, lateral and paraventricular).

Some drugs interact together with their mechanism. A vast number of drugs interact, not with a single mechanism, but often with two or more mechanisms that work together. To make it easier, the mechanism of drug interaction can be divided into pharmacokinetics and pharmacodynamics (Baxter, 2008).

With this research, it is expected to provide benefits to the community, especially for the GAD (Generalized Anxiety Disorder) patients who want to recover to undergo the treatment according to doctor's recommendations, and can provide information related to the potential drug interactions, severity and management of drug interaction events. So that this study is able to minimize the incidence of drug interaction in GAD patients in Banyumas Regional Hospital by providing rational therapy.

II. METHOD

This study design was a descriptive study with a quantitative approach to a particular population or sample. The source of this research data was obtained from the retrospective data collection from the YANKESWA Medical Record of Banyumas Regional Hospital. This research was conducted in June-July 2019. Before the data collection, we established the inclusion and exclusion criteria. Inclusion criteria are criteria or characteristics that need to be fulfilled by each member of the population that can be taken as a sample while exclusion criteria are characteristics of a population member that cannot be taken as a sample (Notoatmodjo, 2012).

III. RESULTS AND DISCUSSION

Management of GAD in outpatient were carried out through the Integrated YANKESWA Outpatient Clinic in Banyumas Regional Hospital with pharmacotherapy and non-pharmacotherapy. The study was conducted in June-July 2019 retrospectively with the total sampling method and took data from the Patient Medical Record from January 2017 to December 2018 with a total sample of 72 samples and those who met the inclusion criteria were 47 Medical Records data.

A. *Drug Interactions*

Interaction data obtain by observation from the high incidence of drug interactions, this needs a concern from a pharmacist. Drug interactions in the clinical data collected using Stockley's Drug Interaction, Drug Interaction Facts, www.drug.com data base and Medscape Drug Interactions Checker. Based on the results of observations on therapies received by 47 GAD patients, 42 patients have the potential for drug interactions. Medication interactions that can be observed in this study are potential drug interactions that are drug interactions with drugs that might be able to deal with the problem after consuming them. Identified drug interactions are as many as 35 combinations. In the potential for drug interactions in the literature, there are two components according to the level of severity and the mechanism of drug interactions. The results in this research can be said as the latest data for the potential of drug interactions in GAD patients in Banyumas Regional Hospital.

TABLE 1. POTENTIAL DRUG INTERACTIONS IN GAD PATIENTS BASED ON THE NUMBER OF MEDICAL RECORDS WHICH INTERACT

Incidence of Interaction	Number of Medical Record	Percentage (%)
There are interaction	42	89,36
No interaction	5	10,64
Total	47	100

From the data in table 1, it can be seen that the percentage of the number of medical records interaction was 42 medical records (89.36%) and 5 medical records (10.64%) did not experience drug interactions.

B. *Types of Drug Interaction*

TABLE 2. TYPES OF DRUG INTERACTIONS THAT OCCUR IN GAD PATIENTS

No	Drug Interaction			Number	Percentage (%)
1	Sertraline	X	Alprazolam	7	20,00
2	Aspirin	X	Omeprazole	1	2,85
3	Omeprazole	X	Cyanocobalamin	1	2,85
4	Fluoxetine	X	Alprazolam	6	17,14
5	Fluoxetine	X	Clobazam	1	2,85
6	Sertraline	X	Clobazam	5	14,28
7	Fluoxetine	X	Alprazolam	1	2,85
8	Chlorpromazine	X	Trihexilfenidil	2	5,71
9	Chlorpromazine	X	Clobazam	1	2,85
10	Amitriptilin	X	Clobazam	1	2,85
11	Trihexilfenidil	X	Clobazam	1	2,85
12	Lorazepam	X	Amitritilin	4	11,42
13	Lorazepam	X	Sertralin	2	5,71
14	Trihexilfenidil	X	Risperidone	2	5,71
15	Amitriptilin	X	Alprazolam	6	17,14
16	Methylprednisolone	X	Natriumdiclofenac	1	2,85
17	Methylprednisolone	X	Valsartan	1	2,85
18	NatriumDiclofenac	X	Valsartan	1	2,85
19	Trifluoperazin	X	Trihexifenidil	1	2,85
20	Chlorpromazine	X	Sertralin	1	2,85
21	Sertralin	X	Trihexifenidil	1	2,85
22	Chlorpromazine	X	Trifluoperazin	1	2,85
23	Sertraline	X	Trifluoperazin	1	2,85
24	Furosemide	X	Alprazolam	1	2,85
25	Alprazolam	X	Nitroglycerin	1	2,85
26	Furosemide	X	Bisoprolol	1	2,85
27	Alprazolam	X	Bisoprolol	1	2,85
28	Sertraline	X	Clopidogrel	1	2,85
29	Alprazolam	X	Carbamazepine	1	2,85
30	Amitriptilin	X	Fluoxetine	1	2,85
31	Risperidone	X	Carbamazepine	1	2,85
32	Clozapine	X	Risperidone	1	2,85
33	Clozapine	X	Fluocetine	1	2,85
34	Sertralin	X	Clozapine	3	8,57
35	Amitriptilin	X	Sertraline	1	2,85
Total				**35**	**100**

From the data in Table 2, it was shown that the result of 57 drug interactions that have been identified, there are 3 types of the largest drug interactions, namely drug interactions between sertraline and alprazolam, 7 cases of drug interactions (20.00%); fluoxetine and alprazolam with Amitriptyline and alprazolam with 6 cases of drug interactions (17.14%); sertraline and clobazam with 5 cases of drug interactions (14.2%).

One of the therapies used for GAD patients is benzodiazepines. Based on the data in the table, it was found that benzodiazepine drug that was often used was alprazolam. Alprazolam works on the receptor complex of GABAA-benzodiazepines. Chemical systems and GABA receptors produce alprazolam inhibitors or calming effects on the central nervous system. Benzodiazepines, especially alprazolam, cause marked suppression of the hypothalamic-pituitary-adrenal axis. The therapeutic abilities of alprazolam resemble other benzodiazepines, including anxiolytic, anticonvulsants, muscle relaxants, hypnotics, and amnestic. Alprazolam is effectively used in the treatment of panic disorders and agoraphobia and appears to be more selective in these conditions than other benzodiazepine drugs. Alprazolam is a drug that has received approval from the FDA for use in short-term (up to 8 weeks) panic disorder therapy, with or without agoraphobia (Fahrul, 2012).

Sertraline and fluoxetine drugs are drugs with the same class, i.e. SSRIs (serotonin 5-HT reuptake inhibitors). The mechanism of SSRIs in reducing depressive symptoms by selectively inhibiting 5HT reuptake. The difference between sertraline and fluoxetine based on antidepressant classification, pharmacology and pharmacokinetics is that in the blockade of serotonin reuptake, similar to norepinephrine but in dopamine, sertraline is stronger than fluoxetine. Bioavailability of sertraline oral > 44%, fluoxetine 80%, drug binding of sertraline and fluoxetine are the same as much as 95%, sertraline half-life is faster than fluoxetine. The half-life of sertraline is 26 hours and fluoxetine 24-27 hours (Prasetyaningrum and Advistasari, 2016).

C. *Interaction Category Based on Severity*

TABLE 3. PERCENTAGE OF DRUG INTERACTION CATEGORIES IN GAD

Severity	Number of Interaction Category	Percentage (%)
Major	3	8.57
Moderate	28	80.00
Minor	4	11.42
Total	35	100

From the data in Table 3, the percentage of interaction groups based on the severity shows for the major groups, 3 drug interaction events (8.57%), minor 4 drug interaction events (11.42%) and moderate 28 drug interaction events (80. 00%). Most drug interactions in this study were in the moderate category. Moderate interactions are clinically significant, usually avoiding combinations of drugs taken together and using them

only in special circumstances. From this severity it can be concluded that the use of drug combination in inpatient GAD in Banyumas Regional Hospital needs to be considered again, because the moderate severity indicates that the drug has the potential to endanger the patient and several types of intervention / monitoring must be carried out (Barliana et al., 2013).

D. Interaction Category Based on Interaction Mechanism

TABLE 4. PERCENTAGE OF DRUG INTERACTION CATEGORIES IN GAD PATIENTS BASED ON INTERACTION MECHANISMS

Interaction Mechanism	Number of Interaction Category	Percentage (%)
Pharmacokinetic	11	31.42
Pharmacodynamic	24	68.57
Total	35	100

From the data Table 4, it was seen that the percentage of drug interactions with pharmacodynamic mechanism was the highest with 24 types (68.57%) compared to drug interactions with pharmacokinetics mechanism with 11 types (31.42%). Drug interactions based on pharmacokinetic mechanism are the interactions that occur when one drug changes the absorption, distribution, metabolism and excretion of another drug. Pharmacodynamic interactions have been increased with receptors and have resulted in changes in the effect of one drug, which has a synergistic effect if the effect strengthens or antagonists if the effect is reduced (Tatro, 2009).

From the description above, it can be concluded that almost all of the GAD inpatients at Banyumas Regional Hospital are likely to experience drug interactions and the most common type of interaction is pharmacodynamic interaction. It is known that the drug treatment in pharmacokinetics is the most frequent occurrence of sertraline and alprazolam with a total of 7 drug interactions. The use of sertraline and alprazolam simultaneously concomitantly absorbs vitamin B12. Ranitidine is a H2 receptor antagonist that interferes with the absorption of vitamin B12 by digestion, a process that depends on the presence of stomach and pepsin. Clinical studies have shown that vitamin B12 absorption can occur during treatment with this agent (ranitidine) (Drugs.com, 2019; Tatro, 2009).

The mechanism of pharmacodynamics is known to be the most common drug interactions between fluoxetine and alprazolam with Amitriptyline and alprazolam as many as 6 drug interaction events. Consumption of fluoxetine along with alprazolam decrease antihypertensive effect from several calcium channel inhibitors.

This mechanism is related to the change in blood vessel tone, which depends on the prostacycline, prostanoid, and other mediators of vasodilator. When an aspirin drug is added, the patient's regimen that has been using amlodipine causes an increase in blood pressure (Drugs.com, 2019). In addition the use of Amitriptyline and alprazolam simultaneously.

IV. CONCLUSION

The results of the study showed that 47 GAD patients occurs 42 (89.36%) drug interactions, with pharmacodynamic interactions more than 68.57% compared to pharmacokinetics 31.42%. The most common interactions are interactions between sertraline and alprazolam.

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