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## Overview of prolactin levels in patients with schizophrenia during antipsychotic therapy at HB. Saanin Mental Hospital Padang, Indonesia



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### ABSTRACT

**Background:** Schizophrenia, which affects about 0.85% of people worldwide, is the most common illness among psychotic disorders. Antipsychotic drugs have been a mainstay of schizophrenia treatment. Antipsychotics are now the most typical factor causing increased prolactin levels (hyperprolactinemia). This research aimed to determine the overview of prolactin levels in patients with schizophrenia that receive antipsychotic therapy at HB. Saanin Mental Hospital Padang.

**Methods:** This descriptive research included 50 patients with schizophrenia at HB. Saanin Mental Hospital Padang in July-December 2020. It was conducted using the ELISA test method to analyze prolactin levels. Data were analyzed using SPSS version 20.0 for Windows.

**Results:** From a total sample of 50 patients, the research subject characteristics were as follows, the mean age of the research subjects was 39.48±12.53 years old, most were male (68.0%), and the most used antipsychotics given were second-generation antipsychotics (Atypical) (64%). The prolactin level among the research subjects was 30.20 ng/mL (CI 95% 25.18-36.31). It indicates that the average prolactin level in the research subjects is higher than the normal prolactin level, which is 5-25 ng/mL. The research results showed that females have a significant higher average prolactin level than males ( $p < 0.05$ ). However, the use of typical, atypical, and combination antipsychotics do not show significant differences between groups ( $p > 0.05$ ).

**Conclusion:** Patients with schizophrenia at HB. Saanin Mental Hospital Padang, who became the research respondents and consumed antipsychotics, has higher prolactin levels than average.

**Keywords:** Antipsychotics, Prolactin, Schizophrenia, Therapy.

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### INTRODUCTION

Schizophrenia is the most important and prevalent disorder in psychotic disorders. The schizophrenic disorder is defined by fundamental and distinctive cognitive and perceptual abnormalities and inappropriate or dulled effects.<sup>1</sup> Although conscious awareness and intellectual abilities are retained, particular cognitive deficiencies may develop later.<sup>2</sup>

Schizophrenia affects around 0.85% of the world's population. It is prevalent in all societies and geographical regions. Schizophrenia has long been acknowledged as the most severe and incapacitating mental illness.<sup>3</sup> The financial expenses of this condition are substantial in the United States, projected to exceed \$40 billion yearly. Nevertheless, the indirect expenses borne by patients and their families are priceless. Schizophrenia

affects a considerable proportion of the population in every country. Males are 15 to 25 years old, while women are 25 to 35. The onset of schizophrenia before the age of 10 years or after 50 years is sporadic.<sup>4</sup>

Antipsychotic medications have been a cornerstone of treatment for schizophrenia and other psychotic illnesses for over 50 years. All currently available antipsychotic medications can modify dopamine levels.<sup>5</sup> Antipsychotic actions are thought to be mediated by dopaminergic neurons in the mesolimbic pathway. Although dopamine D2 receptors are not exclusive to mesolimbic structures, population structures and receptors are exclusively connected with the symptoms and functional difficulties associated with psychotic illnesses.<sup>6</sup> Schizophrenia is a severe form of psychotic disorder and tends to be chronic. Although schizophrenia is a single disease, it may be a group of

conditions consisting of various etiologies and covering multiple clinical features, responses to treatment, and course of illness.<sup>7</sup> The prevalence of schizophrenia between men and women is the same but differs in the onset of the first attack.<sup>1</sup>

Schizophrenia is found in all walks of life and geographic areas, both men and women. A systematic study stated that the estimated median prevalence of schizophrenia is 4.6 per 1000 people, with the lifetime risk of developing schizophrenia being around 0.3% - 0.7%. Schizophrenia in women becomes more different because women have their dynamics. Women as individuals have careers and jobs; on the other hand, women are wives and mothers to their children, and no less important because women have specific hormonal rhythms.<sup>1-3</sup>

Gender differences in schizophrenia can be studied in various aspects, including

pharmacological management. Women can have a 1.5-1.7 times greater risk of experiencing side effects than men. One of the side effects of antipsychotics that have become the main focus of attention in women is endocrine disorders that cause amenorrhea, galactorrhea, and weight gain. Menstruation has an essential role in women's lives, and the abnormalities that occur will affect fertility and quality of life and become new distress for women. Amenorrhea and weight gain can affect more than 50% of treatment adherence in female patients receiving antipsychotics. Thus, it is essential to pay attention to complaints of amenorrhea as a side effect of antipsychotics in the management of schizophrenia in women.<sup>8,9</sup>

Antipsychotics are drugs that treat psychotic symptoms, including schizophrenia. They can also improve mood and reduce excessive anxiety and sleeping disturbances. These drugs have two typical and atypical groups, but the latter is more commonly used.<sup>10</sup> Although antipsychotics are classified into typical antipsychotics and atypical antipsychotics, both have the same pharmacological activity to block dopamine receptors D2.<sup>11</sup> Typical antipsychotics effectively treat positive symptoms. In contrast, atypical antipsychotics effectively treat negative symptoms, known to have a lower risk of extrapyramidal side effects than typical antipsychotics.<sup>12,13</sup>

Antipsychotics become the most common cause of elevated prolactin levels (hyperprolactinemia). Several conventional antipsychotics have been found to regulate prolactin secretion, but most atypical antipsychotics do not. According to previous research, typical antipsychotics are still widely used.<sup>14</sup> Prolactin (PRL) is a hormone produced in the anterior pituitary gland, and its secretion is regulated by the prolactin inhibitory factor (PIF) in the hypothalamus. The main physiological inhibiting factor of prolactin is dopamine; therefore, drugs that block dopamine receptors can cause hyperprolactinemia. On the other hand, prolactin release is regulated by a prolactin-releasing factor (PRL), which is physiologically not known to be secreted through the hypothalamus. Numerous additional chemicals, including

thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide (VIP), oxytocin, and galanin, can function as PRL, while gamma-aminobutyric acid (GABA) can function as PIF.<sup>15</sup>

The average amount of prolactin is expressed differently in different laboratories. However, the highest limit for serum prolactin concentrations in men is defined at 20 ng/ml and for women who are not pregnant or breastfeeding at 24–25 ng/ml.<sup>16,17</sup> Thus, hyperprolactinemia is typically defined as a level greater than 20 ng/ml in men and 25 ng/ml in women. Hyperprolactinemia (HPRL) is a PRL level higher than normal as a consequence of laboratory evaluation.<sup>18</sup> However, when physiologic HPRL develops in contexts other than pregnancy and lactation, prolactin levels are pathologically defined as being over the normal range.<sup>19</sup>

HPRL is a release that occurs due to pituitary lesions or hypothalamic structural abnormalities and is a significant cause of reproductive failure in both sexes. Menstrual abnormalities can arise in women due to a lack of luteal phase during regular menstruation, irregular or infrequent periods (oligomenorrhea), or amenorrhea.<sup>20</sup> Galactorrhea may also occur independently or in conjunction with other menstrual problems. Hyperprolactinemia typically results in a loss of libido and erectile dysfunction in males due to testosterone shortage.<sup>18,19</sup>

According to research by Putri VR et al., the most common side effects of hyperprolactinemia in female subjects are changes in the menstrual cycle (65%). In contrast, most male subjects have erectile dysfunction (32%).<sup>20</sup> In addition, the other side effects are sexual dysfunction (19%), gynecomastia (16%), and galactorrhea (4%). Increasing prolactin levels cause all these diseases by 59%. According to research by Putri et al., the prevalence of sexual dysfunction in schizophrenic patients was 59.3% for males and 49.1% for females.<sup>21</sup>

From the background above and the problem of increasing prolactin levels (hyperprolactinemia), which impacts the morbidity of schizophrenic patients and the use of antipsychotic drugs, the researchers aimed to obtain an overview of prolactin levels in patients with schizophrenia who

received antipsychotic drug therapy in HB. Saanin Mental Hospital Padang.

## METHODS

This descriptive research included 50 patients with schizophrenia at HB. Saanin Mental Hospital Padang was conducted in July-December 2020. This research was carried out after obtaining ethical approval from the ethics committee of the Medical Faculty, Universitas Baiturrahmah, through honest clearance letter No. 065/ETIK-FKUNBRAH/03/08/2020.

### Data Collection

As many as 50 subjects met the inclusion criteria, namely patients who were diagnosed with schizophrenia based on DSM IV and received outpatient therapy at HB. Saanin Mental Hospital, Padang, received antipsychotic treatment for at least three months, cooperative, and agreed to participate in the research by signing the informed consent, were included in this research. Pregnant, breastfeeding individuals or unable to cooperate well were excluded from participation.

### Sample Collection

#### Prolactin Level Examination

Blood was taken from the median cubital vein as much as 3 ml, stored in a vacutainer gel separator tube, and then processed into serum and stored at -20°C in the Biomedical Laboratory, Medical Faculty, Universitas Baiturrahmah. The storing processes were carried out until all samples were collected. The evaluation of prolactin levels was done using the immunoenzymatic colorimetric method to quantitatively determine prolactin levels in serum.<sup>22</sup> This research used a kit from Diameter, and the inspection procedures followed the manufacturer's guidelines.

The procedures carried out were preparing the calibrator, followed by the preparations of wash solution and the serum sample previously stored at -20°C. As much as 50 µL of each standard, control, and selection were inserted into the corresponding wells using a micropipette. Each well received up to 100 L conjugate enzyme and was vigorously agitated for 10 seconds. The solution was then incubated at room temperature for 1 hour (22 – 28°C). The wells were rinsed

three times with distilled water (300 L each well). After a 5-second shake, 100 µL of substrate solution was added to each well and re-incubated at room temperature for 15 minutes. The enzymatic reaction was stopped in each well by adding 100 L of stop solution. Each well's absorbance (OD) was determined using a microtiter plate reader at 45010 nm. It is advised that the wells be read within ten minutes of the stop solution being added.

### Statistical Analysis

Data on gender and the Antipsychotic category, which are categorical, were presented in proportions and percentages. In contrast, the data on prolactin levels and age, which are numerical, were introduced in the forms of mean and standard deviation after being tested formerly using the normality test with  $p > 0.05$  using the Shapiro Wilk test if not normally distributed, the data transformation was done at log 10. Then the normality test was re-performed, and the results were presented in the geometric mean.<sup>23</sup>

A comparison of prolactin levels between men and women groups was conducted using an unpaired T-test. A one-way ANOVA was used to compare prolactin levels between typical, atypical, and combination groups. All data is analyzed using the SPSS version 20.0 or Windows.

## RESULTS

Research results using a sample of 50 people from data on schizophrenic patients receiving antipsychotic therapy at HB. Saanin Padang in 2019. The research results of the research subjects' characteristics are presented in Table 1. Based on Table 1, most research subjects were male (34 people, or 68%), the mean age of the research subjects was 39.48, and most of the antipsychotic therapy given was atypical antipsychotics (64.0%).

The research results of the overview of the average prolactin level based on the age of schizophrenic patients receiving antipsychotic therapy at HB. Saanin Mental Hospital, Padang, is presented in Table 2.

Based on Table 2, the prolactin level among the research subjects was 30.20 ng/mL. It indicates that the average prolactin

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**Table 1. Characteristics of Research Subjects.**

Subject Characteristics	n	%
Gender		
Male	34	68.0
Female	16	32.0
Age (Mean±SD)	39.48±12.53	
Antipsychotic		
Typical	4	8.0
Atypical	32	64.0
Combination	14	28.0
Amount	50	100.0

**Table 2. Average Prolactin Levels in Research Subjects.**

Variable	Geometric mean (ng/mL)	95% CI
Prolactin Level (ng/mL)	30.20	25.18-36.31

\*CI: Confidence Interval

**Table 3. Comparison of Prolactin levels between male and female subjects.**

Variables	n	Average (95%CI) <sup>a</sup> (ng/mL)	p <sup>b</sup>	Average comparison (95CI%) (ng/mL)
Male	34	26.75 (21.87 -32.36)	0.047*	0.68 (0.47-0.99)
Female	16	39.32 (28.18- 54.95)		

<sup>a</sup>geometric mean; <sup>b</sup>Unpaired T test; \*Statistically significant if p-value less than 0.05.

**Table 4. Comparison of Prolactin levels between groups of antipsychotic users.**

Variables	Group	n	Average (95 CI%) (ng/mL)	P
Antipsychotic	Typical	4	34.67 (9.33-125.89)	0.443
	Atypical	32	32.36 (25.12- 41.69)	
	Combination	14	24.55 (19.05-33.13)	

\*Statistically significant if p-value less than 0.05.

level in the research subjects is higher than the intermediate prolactin level, which is 5-25 ng/mL.

The research results of the average prolactin level based on the gender of schizophrenic patients receiving antipsychotic therapy at HB. Saanin Mental Hospital Padang is shown in Table 3. Based on Table 3, females have a higher average prolactin level (39.32 ng/mL) than males. These data show the mean prolactin level in females is significantly different compared to males ( $p=0.047$ ) (Table 3).

The research results of the overview of the average prolactin level based on antipsychotics of schizophrenic patients at HB. Saanin Mental Hospital Padang is listed in Table 4. Based on Table 4, the use of typical, atypical, and combination antipsychotics does not show significant differences between groups ( $p>0.05$ )

(Table 4). Based on Table 4, the use of typical, atypical, and combination antipsychotics does not show significant differences between groups ( $p>0.05$ ).

## DISCUSSION

In this research, the mean age of the subjects was  $39.48 \pm 12.53$  years. The results follow research that the average age of Schizophrenia patients is 34.39 years.<sup>3</sup> In a study by Bali Provincial Mental Hospital, patients seeking treatment at the Bali Provincial Hospital in 2013-2018 were mainly between 25-44 years or the adult age group.<sup>4,13</sup> Thus, there are similarities in the age range of the incidence of schizophrenia, which is in the adult age range.

One type of functional psychosis mental disorder is schizophrenia. Schizophrenia manifests positive and negative

symptoms, including disorganized speech, delusions, hallucinations, and cognitive and perceptual impairments. Avolition (decreased interest and drive), reduced desire to speak, poor communication content, flat affect, and disruption of personal connections are all negative indicators.<sup>24,25</sup>

Sex differences in schizophrenia can be studied in various aspects such as diagnosis, onset, a subtype of the disorder and symptoms, the risk of psychotic occurrence throughout the life cycle, genetic factors, pre and perinatal and hereditary factors, morbidities, causes, and effects of differential onset at different ages comparison of behavioral disorders caused by sex-specific disorders with infections caused by disease the course of the disease and its consequences brain development, structure, and function and management and care.<sup>26</sup>

Prolactin plays a variety of roles in men and women. Physical exertion, pharmaceutical use, pituitary adenoma, and kidney disease can all affect grades. Hormones are crucial for preparing breast tissue in women for breastfeeding following pregnancy. Males have significantly lower amounts than females.<sup>27</sup> The average PRL level in a nonpregnant woman is between 2 and 29 ng/mL, while 10 and 209 ng/mL in a pregnant woman. The typical amount in men is between 2 and 18 ng/mL. Amenorrhea, galactorrhea, diminished libido, and erectile dysfunction are all adverse outcomes of elevated PRL levels. One possible link between hyperprolactinemia and antipsychotic medication is osteoporosis, which can result in fracture.<sup>28</sup>

The standard therapy for people with schizophrenia is antipsychotics. Antipsychotics are divided into two broad groups: Typical Antipsychotics (dopamine receptor antagonists), examples of drugs such as Haloperidol, Chlorpromazine, Perphenazine, Trifluoperazine, Fluphenazine, Thioridazine, and Pimozide. And Atypical Antipsychotics (serotonin dopamine antagonists) are examples of drugs such as Clozapine, Olanzapine, Risperidone, Aripiprazole, Zotepine, Quetiapine, and Sulpiride.<sup>29,30</sup>

Antipsychotics exert their effects via four distinct pathways: the mesolimbic,

the mesocortical, the nigrostriatal, and the tuberoinfundibular—the tuberoinfundibular pathway connects the hypothalamus to the anterior pituitary gland. The potential of antipsychotics to block dopamine D2 receptors in the tuberoinfundibular path may lead to hyperprolactinemia. Every individual who takes antipsychotics that work by inhibiting dopamine as an inhibitor of prolactin secretion is at risk of developing hyperprolactinemia. Specific populations at high risk for hyperprolactinemia are children, young adults, premenopausal women, and women in the perinatal period.<sup>31</sup>

First-generation antipsychotics were generally associated with a higher risk of elevated prolactin levels than second-generation antipsychotics, except for risperidone and paliperidone. Second-generation antipsychotics such as olanzapine, quetiapine, ziprasidone, and aripiprazole have little effect on prolactin levels.<sup>32</sup> Elevated prolactin levels may occur within hours of starting therapy. Significant hyperprolactinemia can occur within 14 days and peak after 1-2 months of antipsychotic use. Some studies suggest tolerance can occur over time, where prolactin levels decrease after four months of antipsychotic use. A survey with risperidone found that after five years of service, the average prolactin level remained one-third of the prolactin level in the first year but was still higher than healthy controls without antipsychotics. A study states that clinical symptoms are significantly seen at prolactin levels ranging from 600-1200 mU/L (30-60ng/mL) or higher. There is also a mention that amenorrhea often occurs when prolactin levels are more than 60-100 ng/mL.<sup>33</sup>

Based on previous research, it was found that the research subjects were male, 71.3%, compared to 28.7% female. This is because the male sex usually has a very high aggressiveness, so it is difficult to handle if only treated at home. In contrast, the family can take the hostility of women with schizophrenia. In addition, women have the hormone estrogen, which acts as an antidopaminergic. It inhibits the release of dopamine in the nucleus accumbens.<sup>34</sup>

The female hormone oxytocin can also reduce the symptoms of psychosis

by inhibiting mesolimbic dopamine and improving thought patterns and social perception. Schizophrenia in men usually occurs between 15 and 25 years, while in women between 25 and 35 years. The percentage results are based on age in male patients who suffer more from schizophrenia, namely patients in adult patients aged 26 to 35 years, with a percentage of 24.5% and at least at the age of > 66 years, namely 2.12%. Meanwhile, female patients who suffer more from schizophrenia are aged 36 to 45 years, with 11.7%. This is because the onset of schizophrenia is usually in the early days of adulthood and late adulthood and rarely occurs before adolescence or after 40 years of age. This range is a productive age filled with many stress-triggering factors and has a significant burden of responsibility.<sup>35</sup>

Based on Table 3, females have a higher average prolactin level (39.32 ng/mL) than males. These data show the mean prolactin level in females is significantly different compared to males. The standard requirement for the diagnosis of schizophrenia is that there must be at least one of the above symptoms that are very clear (and usually two or more of the symptoms are less acute or less pronounced) of the symptoms belonging to one of the symptom groups (a) to (d) above, or at least two symptoms from groups (e) to (h) that must have been present for one month or more.

There is compelling evidence that gender affects clinical characteristics and schizophrenia. On average, women have a milder course of the condition than males; women develop the disease at a later age. Men experience fewer and shorter acute psychotic episodes, have fewer negative symptoms, have greater premorbid performance, and have a better reaction to antipsychotic medication than women. However, the evidence for gender variations in neurocognitive impairments and responsiveness to antipsychotic treatment is ambiguous. Numerous neuropsychological investigations have discovered that men are more easily distracted than women.<sup>34,36</sup>

Women should receive longer dose intervals than men to minimize the resultant negative effects. Throughout adulthood, women have menstrual periods

and use numerous contraceptive tablets. How much is known about the interactions between hormones and antipsychotic medications? In women, dosage should be adjusted throughout menstruation, pregnancy, postpartum, and menopause. Women treated for schizophrenia are more likely than men to take various other medications in addition to antipsychotic medications. In other words, there is a larger likelihood of drug interactions, which could result in a decrease or increase in serum antipsychotic levels.<sup>14,18</sup>

In schizophrenic patients, gender differences affect drug response in the following ways: a) Women experience delayed diagnosis, b) Males experience more deficit symptoms, c) Men are more likely to smoke and abuse substances, and d) Women have comorbid problems (mood disorders, sleep disorders, pain conditions, allergies, endocrine disorders, eating disorders, personality disorders, and psychophysiological disorders), necessitating the use of multiple concurrent medications.<sup>8</sup>

Men and women demonstrated disparities in all variables, possibly due to the impact of sex-specific hormones or differing sex roles. Numerous trials have established that women are more prone to hyperprolactinemia than men. Prolactin concentrations may increase to tenfold normal levels during antipsychotic treatment, according to a review of the literature. As a result, up to 78 percent of female patients in some trials have suffered amenorrhea with or without galactorrhea.<sup>36</sup>

Antipsychotic medications are the most often reported cause of hyperprolactinemia in patients with severe mental illnesses; the degree of prolactin elevation varies amongst medicines. Patients should be questioned about any symptoms they may be experiencing due to increased prolactin. Prolactin increase may cause menstrual abnormalities, galactorrhea in women, sexual dysfunction, and depression in the short term. Long-term concerns include a decrease in bone mineral density greater than expected with normal aging, which may result in osteoporosis.<sup>2,6</sup>

Based on Table 4, the use of typical, atypical, and combination antipsychotics does not show significant differences

between groups. Prolactin release can influence various circumstances, including gender, sexual activity, childbearing, stress, smoking, and drug use. Dopamine inhibits the hypothalamic-pituitary circuit's prolactin synthesis and can be enhanced by inhibiting type 2 (D2) dopamine receptors. The majority of currently available antipsychotic medications can increase prolactin production. This rise is connected with several adverse effects, including decreased libido and erectile dysfunction in males, galactorrhea and amenorrhea in women, hastened osteoporosis in women, weight gain, and an increased risk of cancer, particularly breast cancer in women. Antipsychotic drugs differ in their tendency to cause hyperprolactinemia. Second-generation antipsychotics tend to induce sustained hyperprolactinemia except for risperidone and amisulpride. Several mechanisms have been proposed to explain the propensity of different antipsychotics to cause hyperprolactinemia: a) D2 receptor-binding affinity, b) Can penetrate the blood-brain barrier (Blood-Brain Barrier), and c) the primary mechanism is modulated by monoamines other than dopamine.<sup>5,6,8</sup>

Age can be a factor in the onset of schizophrenia. Adults have a 1.8 times higher risk of suffering from schizophrenia because they have had many experiences dealing with life stressors. The characteristics of support sources and the ability to solve problems (coping) are also life stressors that can affect the age of schizophrenic patients. Coping is a tactic or thought and behavior to control situations beyond someone's strength or reduce negative emotions and conflicts caused by stress. Stress is a psychological response to internal or external factors that affect mental and physical conditions, feelings, attitudes, and quality of life.<sup>37</sup>

Based on research obtained from 50 patients with schizophrenia, males were twice as many as females. This research results follow Shakeri J et al. research that 193 of 280 respondents with schizophrenia are male.<sup>17</sup> This study also follows the meta-analysis research by Balijepalli C et al. The data from 46 studies revealed that schizophrenia patients were primarily male (60.09%). It is known that males are

more affected by schizophrenia because males are the basis of a household, so they experience more life problems. It is difficult to accept life conditions. In contrast, women have twice lowered the risk of suffering from schizophrenia because there is protection from estrogen, which acts as an antidopaminergic or blocks dopamine in the nucleus accumbens.<sup>32</sup>

Based on this research, the use of antipsychotic therapy in schizophrenic patients at the HB. Saanin Mental Hospital Padang was atypical, primarily antipsychotics, for as many as 32 people (64%). Administration of second-generation antipsychotics in schizophrenic patients can act as partial agonists at 5-HT<sub>1A</sub> receptors, which synergize with 5-HT<sub>2A</sub> receptor antagonists, can reduce positive and negative symptoms of schizophrenia, and better treat resistant patients. Moreover, these second-generation drugs have a lower risk of extrapyramidal symptoms than dopamine receptor antagonists. Antipsychotics of the second generation may increase extracellular 5-HT levels or act as direct agonists of 5-HT receptors, causing PRL secretion and inhibiting 5-HT synthesis or transmission, resulting in PRL release. Through a complicated action on the hypothalamus and pituitary, 5-HT stimulates PRL production. The dorsal raphe nucleus cells were the genesis of the serotonergic pathways that regulate PRL secretion. They terminated in the hypothalamic paraventricular nucleus, where they exerted their effects via 5-HT<sub>1A</sub> and 5-HT<sub>2A/C</sub> (5-HT<sub>2A/CR</sub>) receptors.<sup>2,8,10,12</sup>

The paraventricular nucleus is composed of cells that generate oxytocin and vasoactive intestinal peptide, both of which are classified as PRFs. Oxytocin cells project to the pituitary's posterior lobe, and oxytocin reaches the anterior pituitary via portal veins and systemic circulation, where it stimulates lactotrophs via their oxytocin receptors, resulting in the production of PRL. Vasoactive intestinal peptide cells project to the anterior pituitary, where they link to lactotroph cell membrane receptors, promoting PRL secretion. Additionally, the pituitary can create the vasoactive intestinal peptide, increasing PRL release via autocrine and

paracrine processes.<sup>8,12</sup>

In this research, the average prolactin level of all research subjects was 30.20 ng/mL. This value is higher than the 5-25 ng/mL average prolactin value. This research also found a significant difference in prolactin levels in the female group compared to the male group. This research follows previous research by Charan A et al. that females have higher prolactin levels than males.<sup>14</sup> The other studies that are in line with this research are researched by Alosaimi FD et al., in terms of gender, women (42.9 ± 61.3) have higher prolactin levels than men (24.4 ± 18.6), and research from Redman B et al., that from a total of 227 patients, there were 129 women had higher prolactin level than men.<sup>14,38</sup>

Increased prolactin levels (hyperprolactinemia) in women can be due to various physiological variables that affect prolactin levels, such as circadian rhythm, menstrual cycle phase, stress, eating habits, sleep, and sexual activity.<sup>30</sup> Serum PRL also varies circadian (up to fourfold), with the highest amounts occurring during sleep and peaking at 30 ng/ml between 4 and 6 a.m. Seasonal variations in PRL levels are also possible (higher in spring and summer). Additionally, it was discovered that PRL levels vary dramatically during the menstrual cycle. Compared to the follicular and luteal phases, the highest levels were during the menstrual cycle's middle phase (especially the second half). PRL levels also rise following exercise, eating, sexual activity, minor surgical operations, general anesthesia, myocardial infarction, epileptic episodes, and other acute stressors.<sup>39</sup>

There were no statistically significant differences in prolactin levels between groups of antipsychotic users in this study, either typical, atypical, or combination. However, it is known that the average of all three groups exceeds the normal prolactin level, and the average prolactin level of subjects with typical antipsychotics tends to be higher than the other groups. The research results follow previous studies. Research from Alosaimi FD et al. stated that the highest incidence of hyperprolactinemia (> 60%) was observed in patients taking lithium, clonazepam, risperidone, fluphenazine, paliperidone,

or haloperidol.<sup>18</sup> Other studies are also consistent with this research. Research from Tost M et al. that was examined in Indonesia found the effect of hyperprolactinemia that caused sexual dysfunction was the highest in respondents who used typical antipsychotic drugs, as much as 83.3%.<sup>24</sup>

Several processes underline it: histamine receptor antagonists, D2 dopamine receptor antagonists, cholinergic receptor antagonists, alpha-adrenergic receptor antagonists, and dopamine receptor antagonists. Dopamine is the primary hypothalamic PIF, inhibiting PRL secretion tonically primarily via the tuberoinfundibular dopaminergic pathway and the tuberohypophysial tract. The tuberoinfundibular dopaminergic system, composed of a group of dopaminergic neurons located in the hypothalamic arcuate nucleus, is critical for controlling human PRL release. Dopaminergic neurons in the perivascular area release dopamine.<sup>8,40</sup> Dopamine is then delivered to the anterior lobe of the pituitary via lengthy portal arteries. Another inhibitory dopamine channel, the tuberohypophysial tract, originates in the arcuate nucleus and projects to the intermediate and posterior pituitaries, where dopamine is released into the circulation and is transported to lactotroph cells by short portal capillaries. Dopamine attaches to the lactotroph cell membrane's dopamine D2 receptor. Stimulation of the D2 dopamine receptor decreases PRL gene transcription, synthesis, release, and lactotroph proliferation. Inhibition of the D2 receptor in lactotroph cells results in hyperprolactinemia due to the lack of dopamine as a prolactin release inhibitor in the anterior pituitary gland. As a result, standard antipsychotic medications significantly boost prolactin levels.<sup>12,41</sup>

## CONCLUSION

Based on the results of data analysis, it can be concluded that most of the schizophrenic patients at RSJ HB. Saanin Padang, who are research respondents, have an age range of 20-60 years, are male, and consume atypical antipsychotics. The average prolactin level was higher than usual based on age, sex, and antipsychotics.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

## ETHICAL CONSIDERATIONS

This study was approved by the Institutional Review Board of Baiturrahmah Padang, Indonesia.

## FUNDING

None.

## AUTHOR CONTRIBUTIONS

D.H. and B.E.S. equally contributed to this study. D.H. conceptualized the study. B.E.S. carried out the investigation. D.H. and M.A. reviewed and edited the manuscript. D.A. and D.H. performed visualization and designed the methodology. D.H., B.E.S, D.A., and M.A. validated the results. All authors have read and agreed to the published version of the manuscript.

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