



Open Trial of the Addition of Divalproex Sodium for Improving the Symptoms of Batak and Non-Batak Males with Schizophrenia in North Sumatra, Indonesia

Novi Prasanty^{1,2,*}, Elmeida Effendy², Mustafa Mahmud Amin², Muhammad Joesoef Simbolon^{1,2}, Vita Camellia¹ and Muhammad Surya Husada¹

¹Department of Psychiatry, Faculty of Medicine, University of Sumatera Utara, Medan, Indonesia

²Department of Psychiatry, Faculty of Medicine, Islamic University of Sumatera Utara, Medan, Indonesia

*Corresponding author: Jl, Pintu Air IV Gg, Kolam Jaka, No.5 LK. X., 20142 Medan, Indonesia. Tel/Fax: +62-8116178330, Email: noviprasanty86@gmail.com

Received 2018 March 29; Revised 2019 March 09; Accepted 2019 May 10.

Abstract

Background: Ethnicity is one of many intrinsic factors influencing the drug response and its severity in patients with schizophrenia. In North Sumatra, Indonesia, information is very limited on the effect of divalproex sodium in Batak and non-Batak tribes.

Objectives: The study aimed to investigate differences in positive and negative syndrome scale (PANSS) scores between Batak and non-Batak males with schizophrenia receiving risperidone treatment alone or in combination with divalproex sodium.

Methods: This open trial experimental study was conducted on 60 Batak and non-Batak male subjects with schizophrenia. The doses of divalproex sodium and risperidone were 1500 mg and 6 mg, respectively. The sample was obtained from Prof. Dr. M. Ildrem Psychiatric Hospital, North Sumatra, Indonesia, in a span of six months from September 2017 to February 2018. The mini international statistical classification of diseases-10 (Mini ICD-10) structured interviews were used for diagnosis.

Results: There were no differences between the Batak and Non-Batak groups in the PANSS positive subscale score ($P = 0.766$), PANSS negative subscale score ($P = 0.789$), and PANSS total score ($P = 0.673$) in six weeks of observation.

Conclusions: There were no significant differences in the PANSS scores between males with schizophrenia from Batak and non-Batak tribes who received risperidone monotherapy or combined with divalproex sodium.

Keywords: Schizophrenia, Divalproex Sodium, Risperidone, Tribes

1. Background

Schizophrenia is a chronic mental disorder that includes a group of heterogeneous symptoms and cognitive disorders. Based on evidence from epidemiologic data, imaging and post-mortem analyses, A hypothesis on the development of nerves and dopamine which has transformed into two main theories of schizophrenia is obtained. Other hypotheses emphasize the effect of genetic and environmental factors during the early stage of life and the lack of brain development with negative effects on mental health in adulthood. Schizophrenia is generally marked by psychopathologic damage involving cognitive, emotional, perceptual, and behavioral aspects. The damage which manifests in patients and influences epidemiology is usually severe and long-lasting. Schizophrenia is a common psychotic disorder with the early-onset of age of 18 years old. It is a chronic disease that disturbs patients and their families and brings a big impact on the social and

economic status of patients. For male patients, the attack peaks at the age of 10 - 25 years. About 90% of patients under treatment are at the age of 15 - 55 years (1-5).

The treatment of schizophrenia patients is suboptimal where chronic recurrence might happen and side effects of therapy are concerning. Monoamine, especially dopamine, has been the focal point in pathophysiology research of schizophrenia for several years. Evidence suggests abnormalities in neurotransmitter systems, including gamma aminobutyric acid ergic (GABAergic) system (5).

Antipsychotics are the gold standard for the treatment of patients with schizophrenia. However, not all patients respond well to antipsychotic monotherapy. A recent pharmacoepidemiologic study evaluated the psychotropics prescription and found the substantial effect of mood stabilizers as adjunctives. About 15% to 50% of patients in various countries show improvements over time

by adding mood stabilizers on antipsychotic drug Divalproex sodium is a mood stabilizer that has been used with antipsychotics as an adjunct therapy. The dosage and duration of adding this medication should be adjusted (6).

The variability in medication response depends on extrinsic factors, such as food and additional prescription, and intrinsic factors, such as gender, ethnicity, age, weight, liver and kidney function, and genetic differences in enzymes metabolizing or carrying the drug. Genetic variety can affect metabolizing enzymes. Several polymorphisms can influence the selectivity of substrate or inducibility of drug metabolic pathway. Genetics is a factor affecting drug effects by changing pharmacokinetic or pharmacodynamic properties. Besides, environmental and cultural factors related to diet, climate, and habits, psychosocial factors, and beliefs towards ethnic groups will influence medicine absorption. The difference in distribution, bio-transformation, excretion, and receptor interaction will influence the effectiveness or obedience towards the discipline in medicinal therapy (7-9).

In general, ethnic groups of the Indonesian population are determined to follow a paternalistic line (father/male), for example, the Batak and Javanese tribes. In this case, Batak tribe men will give offspring who are also Batak. The Batak tribe is one of the Indonesian ethnic groups located in North Sumatra. The Batak name is a collective theme to identify several ethnic groups who live and come from Tapanuli and East Sumatra. Not only the Batak tribe but also some other tribes such as Java, Malay, and Minang are the inhabitants of the Sumatra region, especially North Sumatra (10).

With the effect of ethnic factors on the variability and absorption process of the drug, this study tried to provide an overview of the differences between Batak and non-Batak tribes towards the addition of divalproex sodium as one of the additional therapies to one of the typical antipsychotics, namely risperidone, to reduce symptoms in the treatment of schizophrenia.

2. Objectives

This study aimed to determine the differences in positive and negative syndrome scale (PANSS) scores between Batak and non-Batak males with schizophrenia receiving risperidone treatment alone or combined with divalproex sodium.

3. Materials and Methods

3.1. Research Design

The study was designed as an open trial experimental study. The sample was selected from among patients re-

ferring for treatment and hospitalization to the Psychiatric Hospital of Prof. Dr. M. Ildrem Medan. Based on the inclusion and exclusion criteria (11), 60 schizophrenic male patients from Batak and non-Batak tribes were recruited, consisting of 30 subjects (15 Batak and 15 non-Batak) who received risperidone therapy with the addition of divalproex sodium and 30 subjects (15 Batak and 15 non-Batak) who only received risperidone. The number of patients in the sample was determined based on the formula of the sample size for the calculation of the numerical scale in unpaired groups in accordance with previous studies in Indonesia (12). Sampling was conducted at the Mental Hospital of Prof. Dr. M. Ildrem Medan, North Sumatra, Indonesia. The survey lasted six months from September 2017 to February 2018. The study obtained an ethical code (507/KEPK FK USU-RSUP HAM/2017) from the Ethics Committee of the Faculty of Medicine, University of Sumatera Utara, Indonesia, based on the Nuremberg Code and Helsinki Declaration.

3.2. Research Subjects

The subjects were diagnosed using the diagnostic criteria and Mini ICD structured interviews (10). The inclusion criteria included an age of 20 - 45 years, a disease history of over two years, the PANSS total score of 80 - 150 (acute phase of treatment) (13), body weight of < 65 kg to match the groups for body mass index (BMI) to be within the normal range, normal liver physiological function, and willingness to participate as a respondent in interviews. The dose of divalproex sodium was 1500 mg, adjusted to the dose of divalproex sodium ranging from 10 to 30 mg/kg to get the optimum dose and minimize the possible side effects during treatment with divalproex sodium (14). The exclusion criteria included PANSS excited component (PANSS-EC) of > 20, a history of chronic medical disease, and a history of substance use (except for caffeine and nicotine).

3.3. Research Procedure

Before the intervention, every research unit was assessed for the PANSS score, weight, and height (for BMI). Divalproex sodium extended release (ER) was administered once a day at night. It was titrated from 500 mg/day on day 1 and increased gradually to 1500 mg/day on day 7. The intake continued to week 6. Risperidone was given twice a day until the dose 6 mg on day 7. If there were treatment side effects, the patient would be excluded from research (on treatment analysis study) and administered with trihexyphenidyl at the dose of 5 - 15 mg/day; then, the doses of divalproex sodium and risperidone were lowered and the patient was replaced by a new patient to meet the sample size. Observations were made in week 3 and week 6.

3.4. Statistic Data Analysis

Once collected, the data were processed step by step as follows: (1) editing, a step to investigate data completeness from the interview, (2) Coding, as an approach to classify answers based on their types, (3) tabulation, as an activity of inputting research data to a table based on observed variables, and (4) data analysis that was done by SPSS 21. The research data for each group were analyzed using the general linear model to analyze the data from more than one measurement. To compare Batak and non-Batak tribes, the independent *t*-test was performed (15).

4. Results

Table 1 shows the characteristics of study subjects in the Batak and non-Batak tribes. There was no significant difference between the ethnic groups in terms of patients' characteristics and PANSS scores at baseline. Therefore, the groups were homogeneous before the intervention.

Table 2 shows the difference in the PANSS positive subscale scores between the groups receiving risperidone monotherapy or combined with divalproex sodium. In the Batak tribe, there was a significant improvement in the PANSS positive score from the beginning of the study (week 0) to the end of the study (week 6) between those receiving additional divalproex sodium therapy (15.400 ± 1.352) and those who only received risperidone therapy (19.733 ± 1.486), ($P = 0.000$ and $P < 0.001$, respectively). The same results were found for the non-Batak ethnic group, that is the group receiving additional divalproex sodium showed more improvement at the end of the study (14.820 ± 1.355) than those who only received risperidone therapy (18.933 ± 1.458) ($P = 0.000$ and $P < 0.001$, respectively). However, the differences between the two Batak and non-Batak tribes were not significant in the improvement of the PANSS positive subscale scores for each therapy at the end of the study at week 6 ($P = 0.766$ and $P > 0.05$, respectively).

Table 3 shows that in the Batak tribe, there was a significant difference in the improvement of the PANSS negative subscale scores from the beginning of the study (week 0) to the end of the study (week 6) between those receiving additional divalproex sodium therapy (8.867 ± 1.060) and those who only received risperidone therapy (12.200 ± 2.932) ($P < 0.001$). For the non-Batak ethnic group, there was a significant difference at the end of week 6 between patients that received additional divalproex sodium (8.867 ± 1.060) and those who only received risperidone therapy (12.200 ± 2.932), ($P = 0.000$ and $P < 0.001$, respectively). There were no significant differences in the improvement of the PANSS negative subscale scores for each therapy at

the end of the study (week 6) between the Batak and non-Batak tribes ($P = 0.789$ and $P > 0.05$, respectively).

As shown in Table 4 for the Batak group, the difference was significant in the improvement of the PANSS total score from the beginning of the study (week 0) to the end of the study (week 6) between patients receiving additional divalproex sodium therapy (46.067 ± 2.404) and those who only received risperidone therapy (55.200 ± 1.740) ($P = 0.000$ and $P < 0.001$, respectively). For the non-Batak ethnic group, there was a significant difference at the end of week 6 between patients received additional divalproex sodium (45.201 ± 2.186) and those who only received risperidone therapy (54.600 ± 1.156) ($P = 0.000$ and $P < 0.001$, respectively). There were no significant differences in the improvement of the PANSS total scores for each therapy at the end of the study (week 6) between the Batak and non-Batak tribes ($p = 0.673$ and $P > 0.05$, respectively).

Based on Table 5, there were no significant differences in side effects in each group between patients receiving additional divalproex sodium or risperidone monotherapy ($P > 0.05$).

5. Discussion

This is the first study conducted in Indonesia and North Sumatra (one of the provinces of Indonesia) to investigate differences in drug response and symptom severity measured through PANSS scores in two different tribes, i.e. the Batak and non-Batak tribes. The Batak tribe is the dominant tribe among other tribes in North Sumatra based on data from the Central Bureau of Statistics in North Sumatra (16). Therefore, this study tried to explore different drug responses as a function of different characteristics possessed by each ethnic group, including Batak and non-Batak as the main ethnic groups in North Sumatra.

Based on Tables 2 - 4, this study showed the benefits of adding divalproex sodium to the treatment of schizophrenia to reduce symptoms, especially positive symptoms, measured by the PANSS in Batak and non-Batak tribes for six weeks. This can be related to dopamine hyperactivity that is considered as one of the main reasons for positive symptoms in schizophrenia. It is known that GABAergic drugs such as valproate are potent for the treatment of schizophrenia because they have a working principle that decreases dopamine regulation. Adequate loss of glutamate function in GABA interneurons containing parvalbumin in the hippocampus can cause hyperactive glutamate output from glutamate neurons projected by this circuit to mesolimbic dopamine. In other words, if the NMDA (N-Methyl-D-Aspartate) receptor in the hippocampal ventricular GABA interneuron is hypoactive, the glutamatergic pathway to the nucleus accumbens will be too

Table 1. The Distribution of Subjects Based on Their Characteristics

Characteristics	Batak			Non-Batak			Batak-Non-Batak
	Risperidone ± Divalproex Sodium	Risperidone	P Value	Risperidone ± Divalproex Sodium	Risperidone	P Value	P Value
Marital status			1.000 ^a			0.605 ^a	0.347 ^a
Married	5 (33.333)	5 (33.333)		5 (33.333)	6 (40.000)		
Single	10 (66.667)	10 (66.667)		10 (66.667)	9 (60.000)		
Occupation			0.706 ^a			0.605 ^b	0.720 ^b
Working	5 (33.333)	4 (26.667)		6 (40.000)	5 (33.333)		
Not working	10 (66.667)	11 (73.333)		9 (60.000)	10 (66.667)		
Education			1.000 ^a			1.000 ^a	1.000 ^a
SD or SMP	8 (53.333)	8 (53.333)		6 (40.000)	6 (40.000)		
SMA or higher education	7 (46.667)	7 (46.667)		9 (60.000)	9 (60.000)		
Age	28.73 (4.56)	29.38 (4.56)	0.640 ^c	30.13 (4.76)	31.07 (4.87)	0.940 ^c	0.426 ^c
Duration of illness	5.13 (2.47)	5.38 (2.58)	0.781 ^d	5.03 (2.37)	4.58 (2.36)	1.481 ^d	0.534 ^d
BMI	22.02 (1.55)	22.70 (1.91)	0.144 ^c	22.20 (1.65)	22.60 (1.81)	0.230 ^d	0.675 ^c
PANSS positive score, week 0	32.400 ± 2.444	32.933 ± 2.219	0.573 ^d	31.930 ± 2.434	31.543 ± 2.201	0.457 ^d	0.587 ^d
PANSS negative score, week 0	24.000 ± 3.873	22.667 ± 2.289	0.261 ^d	23.532 ± 3.643	21.964 ± 2.369	0.381 ^d	0.643 ^d
PANSS, total score, week 0	94.400 ± 3.661	93.067 ± 3.195	0.297 ^d	93.700 ± 3.661	92.567 ± 3.605	0.210 ^d	0.857 ^d

Abbreviations: SD, elementary school; SMP, junior high school; SMA, senior high school.

^aChi-square test.

^bFisher test.

^cMan Whitney U test, P < 0.05.

^dIndependent t-test.

Table 2. The Difference in the PANSS Positive Subscale Scores Between Batak and Non-Batak Males with Schizophrenia Receiving Risperidone Monotherapy or Combined with Sodium Divalproex

PANSS Positive Score	Batak			Non-Batak			Batak-Non-Batak
	Risperidone ± Divalproex Sodium	Risperidone	P Value	Risperidone ± Divalproex Sodium	Risperidone	P Value	P Value
Week 0	32.400 ± 2.444	32.933 ± 2.219	0.000 ^a	31.930 ± 2.434	31.543 ± 2.201	0.000 ^a	0.766
Week 3	21.933 ± 2.154	25.200 ± 1.014		20.733 ± 2.138	24.420 ± 1.514		
Week 6	15.400 ± 1.352	19.733 ± 1.486		14.820 ± 1.355	18.933 ± 1.458		

^aGeneral linear model, P < 0.05.

Table 3. The Difference in the PANSS Negative Subscale Scores Between Batak and Non-Batak Males with Schizophrenia Receiving Risperidone Monotherapy or Combined with Sodium Divalproex

PANSS Negative Score	Batak			Non-Batak			Batak-Non-Batak
	Risperidone ± Divalproex Sodium	Risperidone	P Value	Risperidone ± Divalproex Sodium	Risperidone	P Value	P Value
Week 0	24.000 ± 3.873	22.667 ± 2.289	0.000 ^a	23.532 ± 3.643	21.964 ± 2.369	0.000 ^a	0.789
Week 3	11.600 ± 1.502	14.867 ± 1.600		11.350 ± 1.502	13.987 ± 1.930		
Week 6	8.867 ± 1.060	12.200 ± 2.932		8.867 ± 1.060	12.200 ± 2.932		

^aGeneral linear model, P < 0.05.

active, which stimulates GABAergic neurons projected to the globus pallidus to disrupt the ventral tegmental area (VTA), which in turn inhibits the GABA release from globus

pallidus to VTA. This will lead to the disinhibition of the dopamine pathway in the mesolimbic area and thus the excessive release of dopamine in the nucleus accumbens.

Table 4. The Difference in the PANSS Total Score Between Batak and Non-Batak Males with Schizophrenia Receiving Risperidone Monotherapy or Combined with Sodium Divalproex

PANSS Total Score	Batak			Non-Batak			Batak-Non-Batak	
	Risperidone ± Divalproex Sodium	Risperidone	P Value	Risperidone ± Divalproex Sodium	Risperidone	P Value	P Value	
Week 0	94.400 ± 3.661	93.067 ± 3.195	0.000 ^a	93.700 ± 3.661	92.567 ± 3.605	0.000 ^a	0.673	
Week 3	60.000 ± 2.330	69.267 ± 1.335		59.800 ± 2.070	68.674 ± 1.935			
Week 6	46.067 ± 2.404	55.200 ± 1.740		45.201 ± 2.186	54.600 ± 1.156			

^aGeneral linear model, P < 0.05.

Table 5. The Frequency of Adverse Effects in the Study Groups^a

Adverse Effect	Batak			Non-Batak		
	Risperidone-Divalproex Sodium	Risperidone	P Value	Risperidone-Divalproex Sodium	Risperidone	P Value
Weight gain	3	2	1.000	2	1	1.000
liver function enhancement	1	1	1.000	2	1	1.000
Gastrointestinal effect	5	2	0.400	5	3	0.660
Extrapyramidal syndrome (tremor)	2	1	1.000	1	1	1.000

^aFisher test P < 0.05.

In addition, glutamate and GABA, through local and integrative circuit control and feedback, regulate cortical and subcortical activation and can be associated with the expression of psychotic symptoms, mood deficiency, cognitive function, and attention and social interaction (17-19).

In addition to affecting the metabolism of coadministered antipsychotics, valproate can modify clinical symptoms in schizophrenia through epigenetic modification. Recent research in schizophrenia shows the deficit of GABAergic neurotransmission Functions detected in schizophrenic patients are related to the downregulation of several GABAergic genes, including glutamate acid decarboxylase 67 (GAD67) and reelin. This downregulation can be a pathogenetic mechanism that underlies complex symptomatology in schizophrenia. This includes positive, negative, and cognitive symptoms.

Therefore, in terms of pharmacological intervention that normalizes GABAergic neurotransmission (such as adjunctive valproate) appears as a new target in strategies for treating schizophrenia. This is while antipsychotic drugs currently in use are not designed to target GABAergic transmission (4, 20-22).

Several previous studies, such as those conducted by Abad N et al. (23), Citrome et al., (24) and Casey et al. (25), have shown many effects for adding divalproex sodium to several types of antipsychotics such as risperidone, olanzapine, and haloperidol for schizophrenia treatment. This strategy is also beneficial for changes in the PANSS score,

hostility PANSS, in terms of both positive symptoms, agitation and aggression, and negative symptoms. Although the method is different in each study, the objective is the same, which is benefiting from adding divalproex sodium for the treatment of schizophrenia. The duration of adding divalproex sodium for schizophrenia treatment is also different. Some research has argued that treatment was only seen as significant from the beginning of the administration to the second, third, and fourth weeks, while there are also studies reporting the benefits until the 12th week with no significant change thereafter (23-28). Other studies showed no significant improvement at the end of the study and more benefits were seen at the beginning of the addition of divalproex sodium especially for the improvement of positive symptoms when compared to those who were not treated with Divalproex sodium (29).

Valproate was also reported to be useful for patients with treatment-resistant and chronic schizophrenia. In addition, the combination of divalproex sodium with antipsychotics can accelerate the treatment period compared to monotherapy with antipsychotics (30, 31). This is in line with this study showing that divalproex sodium addition was effective from week 3 to week 6 of the study. This could be the basis for seeing the benefits of divalproex sodium addition for the treatment of schizophrenia.

A similar study was carried out by Tarigan and Syamsir in North Sumatra with 92 people with schizophrenia who were divided into two groups. By looking at the BPRS

scores for weeks 1 and 9 after the use of haloperidol antipsychotics and the addition of divalproex sodium, the difference between the scores was significant at $P = 0.001$ (32). The difference of the study was only in use of the combination of a first-generation antipsychotic (haloperidol) with divalproex sodium regardless of differences in tribes of North Sumatra. However, in this study, the effects of the addition of divalproex sodium on the treatment of schizophrenia were compared between Batak and non-Batak people. This is based on that the Batak tribe is famous for its openness, spontaneity, and aggressiveness both physically and verbally, rudeness, and stubbornness. Moreover, the Batak people often choose to express their anger. The Batak people who prioritize self-esteem tend to focus on themselves, their families, or relatives around them. If there are strangers who interfere or do bad things, the Batak people will tend to directly attack with emotion. This makes the Batak tribe possess weak emotional regulation. This is while non-Batak tribes are not too expressive and are able to control their anger with better emotion regulation. This affects the way of socialization of the Batak tribe to be less adaptive, which results in their poor regulatory ability compared to non-Batak tribes (33-35).

A recent review of drug metabolism shows that one of the most important sources of variability in drug response is genetic variability in drug metabolic enzymes. Differences between ethnic groups in the metabolizing enzymes have the potential to cause variability in dose choice. Cytochrome or cytochromes P450 (CYP) is the main source of variability in pharmacokinetics and drug response. The expression of each CYP is influenced by a combination of mechanisms and unique factors including genetic polymorphism, induction by xenobiotics, regulation by cytokines, hormones, illness duration, sex, and age. Gene allele polymorphism is very dependent on ethnicity and leads to different pharmacogenetic phenotypes (7-9).

No significant differences were seen in symptom reduction between people with schizophrenia from the Batak and non-Batak tribes as measured by the PANSS, which can be due to various factors derived from extrinsic factors such as the environment (diet, climate, alcohol, drugs, and pollutants) although they were not explored further in this study. These factors can surely lead to variations in the broad drug response in individuals and even wide variations in individual groups. Cultural or psychosocial factors such as ethnic groups, attitudes, and beliefs may influence the effectiveness or adherence to a drug therapy discipline. It is known in cultural psychiatry that cultural interactions and psychiatric disorders have roles to play in differences in symptoms, diagnosis, and variations in dose response to psychotropics among different ethnic groups. Further research related to gene polymor-

phisms and socio-cultural influences may be fruitful in the future to see drug responses in certain ethnic groups (9).

The metabolic effects of the combination of valproate with typical and atypical antipsychotics include weight gain, sedating effects, and the increasing liver enzymes and gastrointestinal side effects. In this study, the side effects of divalproex sodium such as weight gain and gastrointestinal and liver dysfunction were not measured. Some medical interaction has been reported between valproate and antipsychotics, but there is much evidence showing that valproate might increase the effect of atypical antipsychotics in treating schizophrenia (36-38).

5.1. Drop Out

During the study, three participants, including one from the Batak group and two from the non-Batak group, experienced drug side-reactions, i.e., extrapyramidal syndrome, in the form of continuous tremors; therefore, trihexyphenidyl was given with doses ranging from 2 to 15 mg in the second week, the patients were excluded from the study, and replaced by new participants to fulfill the number of research units.

5.2. Limitations

This was an open trial study. The study did not see when and for how long the patients did not receive treatment for the first time and when they first received treatment. The history of hospitalization in patients was also not taken into account in this study. Grouping of Batak and non-Batak tribes was not done more specifically, as, in North Sumatra, there are various types of Batak tribes, including the Karo Batak, Toba Batak, Simalungun Batak, Mandailing Batak, Pakpak Batak, and Angkola Batak. The same condition was indicated with non-Batak tribes in North Sumatra, including Java, Malay, Nias, Minang, Aceh, and China. The intrinsic factors related to gene examination and extrinsic factors related to psychosocial, metabolic, and drug response were also not explored further in each ethnic group.

5.3. Conclusions

The addition of divalproex sodium to schizophrenia therapy could decrease PANSS scores, especially positive symptoms scores. There were no significant differences between the two Batak and non-Batak ethnic groups in the decrease of symptom severity measured by PANSS in each treatment group. However, significant differences were seen between people receiving risperidone combined with divalproex sodium and those who only received risperidone therapy in the decreased PANSS scores in both Batak and non-Batak groups from the beginning of the treatment (week 0) until the end of the intervention (week 6).

Acknowledgments

The author would like to express gratitude to the director of Prof. Dr. M. Ildrem Medan Psychiatric Hospital for providing the opportunity to perform the study. The author's gratitude also goes to the Ethics Committee of the Faculty of Medicine of the University of Sumatera Utara.

Footnotes

Authors' Contribution: Novi Prasanty, Elmeida Effendy, Mustafa Mahmud Amin were involved in the research. Novi Prasanty, Elmeida Effendy, Mustafa Mahmud Amin, Muhammad Joesoef Simbolon, Vita Camellia, Muhammad Surya Husada were involved for drafting and analyzing research data.

Clinical Trial Registration Code: Clinical Trial Registration Code: ISRCTN16522451 (Acquired from ISRCTN Registry, BMC)

Declaration of Interest: All authors declare no conflicts of interest.

Ethical Considerations: The study followed the current ethical considerations based on the nuremberg code and Helsinki Declaration and received an ethics code with the number of 507/KEPK FK USU-RSUP HAM/2017.

Financial Disclosure: No financial interest is reported.

Funding/Support: No financial or material support was received.

References

- Prasanty N, Amin MM, Effendy E, Simbolon J. Low vitamin D serum level increases severity symptoms in schizophrenic patients measured by positive and negative symptoms scale (PANSS) in batak tribe Sumatera Utara, Medan-Indonesia. *Bali Medical Journal*. 2018;7(1):249. doi: [10.15562/bmj.v7i1.921](https://doi.org/10.15562/bmj.v7i1.921).
- Diaz-Caneja CM, Pina-Camacho L, Rodriguez-Quiroga A, Fraguas D, Parellada M, Arango C. Predictors of outcome in early-onset psychosis: A systematic review. *NPJ Schizophr*. 2015;1:14005. doi: [10.1038/npjschz.2014.5](https://doi.org/10.1038/npjschz.2014.5). [PubMed: [27336027](https://pubmed.ncbi.nlm.nih.gov/27336027/)]. [PubMed Central: [PMC4849440](https://pubmed.ncbi.nlm.nih.gov/PMC4849440/)].
- Sadock BJ, Sadock VA, Ruiz P. Schizophrenia. *Kaplan and Sadock's Synopsis of psychiatry behavioral sciences/clinical psychiatry*. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2015. p. 649-701.
- Tseng PT, Chen YW, Chung W, Tu KY, Wang HY, Wu CK, et al. Significant effect of valproate augmentation therapy in patients with schizophrenia: A meta-analysis study. *Medicine (Baltimore)*. 2016;95(4). e2475. doi: [10.1097/MD.0000000000002475](https://doi.org/10.1097/MD.0000000000002475). [PubMed: [26825886](https://pubmed.ncbi.nlm.nih.gov/26825886/)]. [PubMed Central: [PMC5291556](https://pubmed.ncbi.nlm.nih.gov/PMC5291556/)].
- Casey DE, Daniel DG, Tamminga C, Kane JM, Tran-Johnson T, Wozniak P, et al. Divalproex ER combined with olanzapine or risperidone for treatment of acute exacerbations of schizophrenia. *Neuropsychopharmacology*. 2009;34(5):1330-8. doi: [10.1038/npp.2008.209](https://doi.org/10.1038/npp.2008.209). [PubMed: [19052541](https://pubmed.ncbi.nlm.nih.gov/19052541/)].
- Horowitz E, Bergman LC, Ashkenazy C, Moscona-Hurvitz I, Grinvald-Fogel H, Magnezi R. Off-label use of sodium valproate for schizophrenia. *PLoS One*. 2014;9(3). e92573. doi: [10.1371/journal.pone.0092573](https://doi.org/10.1371/journal.pone.0092573). [PubMed: [24664210](https://pubmed.ncbi.nlm.nih.gov/24664210/)]. [PubMed Central: [PMC3963914](https://pubmed.ncbi.nlm.nih.gov/PMC3963914/)].
- Burroughs VJ, Maxey RW, Levy RA. Racial and ethnic differences in response to medicines: Towards individualized pharmaceutical treatment. *J Natl Med Assoc*. 2002;94(10 Suppl):1-26. [PubMed: [12401060](https://pubmed.ncbi.nlm.nih.gov/12401060/)]. [PubMed Central: [PMC2594139](https://pubmed.ncbi.nlm.nih.gov/PMC2594139/)].
- Yasuda SU, Zhang L, Huang SM. The role of ethnicity in variability in response to drugs: Focus on clinical pharmacology studies. *Clin Pharmacol Ther*. 2008;84(3):417-23. doi: [10.1038/clpt.2008.141](https://doi.org/10.1038/clpt.2008.141). [PubMed: [18615002](https://pubmed.ncbi.nlm.nih.gov/18615002/)].
- Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther*. 2013;138(1):103-41. doi: [10.1016/j.pharmthera.2012.12.007](https://doi.org/10.1016/j.pharmthera.2012.12.007). [PubMed: [23333322](https://pubmed.ncbi.nlm.nih.gov/23333322/)].
- Heriawan R. *Kewarganegaraan, suku bangsa, agama, dan bahasa sehari-hari penduduk Indonesia*. Jakarta: Badan Pusat Statistik; 2011. p. 1-13.
- Sastroasmoro S, Ismail S. *Dasar-dasar metodologi penelitian klinis*. Third ed. Jakarta: Sagung Seto; 2008.
- Dahlan MS. *Besar Sampel dalam penelitian kedokteran dan kesehatan*. Third ed. Jakarta: Salemba Medika; 2013.
- Opler LA, Opler MG, Malaspina D. Reducing guess work in schizophrenia treatment, panss can target gauge therapy predict outcomes. *Curr Psychiatr*. 2006;5(9):76-84.
- Stahl SM. *Essential psychopharmacology prescriber's guide*. New York: Cambridge University Press; 2015. p. 711-7.
- Dahlan MS. *Statistik untuk kedokteran dan Kesehatan: Deskriptif, bivariat dan multivariat, dilengkapi dengan menggunakan SPSS*. Third ed. Jakarta: Sagung Seto; 2015.
- Rajamarpondang GD. *Dahlilan na tolu dan prinsip dasar nilai budaya batak*. 1 ed. Medan: Deposit daerah Sumatera Utara; 2010.
- Glick ID, Bosch J, Casey DE. A double-blind randomized trial of mood stabilizer augmentation using lamotrigine and valproate for patients with schizophrenia who are stabilized and partially responsive. *J Clin Psychopharmacol*. 2009;29(3):267-71. doi: [10.1097/JCP.0b013e3181a443d0](https://doi.org/10.1097/JCP.0b013e3181a443d0). [PubMed: [19440081](https://pubmed.ncbi.nlm.nih.gov/19440081/)].
- Ayano G. Bipolar disorders and valproate: Pharmacokinetics, pharmacodynamics, therapeutic effects and indications of valproate: Review of articles. *Bipolar Disord*. 2016;2(2):1-5. doi: [10.4172/2472-1077.1000109](https://doi.org/10.4172/2472-1077.1000109).
- Suzuki T, Uchida H, Takeuchi H, Nakajima S, Nomura K, Tanabe A, et al. Augmentation of atypical antipsychotics with valproic acid. An open-label study for most difficult patients with schizophrenia. *Hum Psychopharmacol*. 2009;24(8):628-38. doi: [10.1002/hup.1073](https://doi.org/10.1002/hup.1073). [PubMed: [19946935](https://pubmed.ncbi.nlm.nih.gov/19946935/)].
- Guidotti A, Dong E, Kundakovic M, Satta R, Grayson DR, Costa E. Characterization of the action of antipsychotic subtypes on valproate-induced chromatin remodeling. *Trends Pharmacol Sci*. 2009;30(2):55-60. doi: [10.1016/j.tips.2008.10.010](https://doi.org/10.1016/j.tips.2008.10.010). [PubMed: [19110320](https://pubmed.ncbi.nlm.nih.gov/19110320/)].
- Dong E, Chen Y, Gavin DP, Grayson DR, Guidotti A. Valproate induces DNA demethylation in nuclear extracts from adult mouse brain. *Epigenetics*. 2010;5(8):730-5. doi: [10.4161/epi.5.8.13053](https://doi.org/10.4161/epi.5.8.13053). [PubMed: [20716949](https://pubmed.ncbi.nlm.nih.gov/20716949/)].
- Christian Machado Ximenes J, Crisóstomo Lima Verde E, da Graça Naffah-Mazzacoratti M, Socorro de Barros Viana G. Valproic acid, a drug with multiple molecular targets related to its potential neuroprotective action. *Neurosci Med*. 2012;3(1):107-23. doi: [10.4236/nm.2012.31016](https://doi.org/10.4236/nm.2012.31016).
- Abad N MH, Ghaffarian Shirazi HR, Mohammadi A, Kashkouli Behroozi M, Hosseini Mehrian Z, N. Sodium valproate as an adjunctive to trifluoperazine in the treatment of schizophrenia. *J Am Sci*. 2013;9(10s):60-2.
- Citrome L, Casey DE, Daniel DG, Wozniak P, Kochan LD, Tracy KA. Adjunctive divalproex and hostility among patients with schizophrenia receiving olanzapine or risperidone. *Psychiatr Serv*. 2004;55(3):290-4. doi: [10.1176/appi.ps.55.3.290](https://doi.org/10.1176/appi.ps.55.3.290). [PubMed: [15001730](https://pubmed.ncbi.nlm.nih.gov/15001730/)].

25. Casey DE, Daniel DG, Wassef AA, Tracy KA, Wozniak P, Sommerville KW. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. *Neuropsychopharmacology*. 2003;**28**(1):182-92. doi: [10.1038/sj.npp.1300023](https://doi.org/10.1038/sj.npp.1300023). [PubMed: [12496955](https://pubmed.ncbi.nlm.nih.gov/12496955/)].
26. Sim K, Yong KH, Chan YH, Tor PC, Xiang YT, Wang CY, et al. Adjunctive mood stabilizer treatment for hospitalized schizophrenia patients: Asia psychotropic prescription study (2001-2008). *Int J Neuropsychopharmacol*. 2011;**14**(9):1157-64. doi: [10.1017/S1461145711000563](https://doi.org/10.1017/S1461145711000563). [PubMed: [21557883](https://pubmed.ncbi.nlm.nih.gov/21557883/)].
27. Sajatovic M, Coconcea N, Ignacio RV, Blow FC, Hays RW, Cassidy KA, et al. Adjunct extended-release valproate semisodium in late life schizophrenia. *Int J Geriatr Psychiatry*. 2008;**23**(2):142-7. doi: [10.1002/gps.1854](https://doi.org/10.1002/gps.1854). [PubMed: [17582828](https://pubmed.ncbi.nlm.nih.gov/17582828/)].
28. Omranifard V, Amel AK, Amanat S. Sodium valproate as adjunctive drug in treatment of schizophrenia. *Iran J Psychiatry Behav Sci*. 2007;**1**(1):12-5.
29. Basan A, Kissling W, Leucht S. Valproate as an adjunct to antipsychotics for schizophrenia: A systematic review of randomized trials. *Schizophr Res*. 2004;**70**(1):33-7. doi: [10.1016/j.schres.2004.01.016](https://doi.org/10.1016/j.schres.2004.01.016). [PubMed: [15246461](https://pubmed.ncbi.nlm.nih.gov/15246461/)].
30. Kelly DL, Conley RR, Feldman S, Yu Y, McMahon RP, Richardson CM. Adjunct divalproex or lithium to clozapine in treatment-resistant schizophrenia. *Psychiatr Q*. 2006;**77**(1):81-95. doi: [10.1007/s11126-006-7963-9](https://doi.org/10.1007/s11126-006-7963-9). [PubMed: [16397757](https://pubmed.ncbi.nlm.nih.gov/16397757/)].
31. Gobbi G, Gaudreau PO, Leblanc N. Efficacy of topiramate, valproate, and their combination on aggression/agitation behavior in patients with psychosis. *J Clin Psychopharmacol*. 2006;**26**(5):467-73. doi: [10.1097/01.jcp.0000237945.35022.45](https://doi.org/10.1097/01.jcp.0000237945.35022.45). [PubMed: [16974186](https://pubmed.ncbi.nlm.nih.gov/16974186/)].
32. Tarigan RW, Syamsir BS. Perbedaan efektifitas haloperidol tunggal dan haloperidol dengan sodium divalproex terhadap keparahan pasien skizofrenia paranoid. Program magister kedokteran klinik ppsds-i ilmu kedokteran jiwa. University Sumatera Utara; 2009.
33. Suciati R, Agung IM. Perbedaan ekspresi emosi pada orang Batak, Jawa, Melayu dan Minangkabau. *J Psikologi*. 2017;**12**(2):99-108. doi: [10.24014/jp.v12i2.3236](https://doi.org/10.24014/jp.v12i2.3236).
34. Yolanda WG, Wismanto YB. Perbedaan regulasi emosi dan jenis kelamin pada Mahasiswa yang bersuku Batak dan Jawa. *Psikodimensia*. 2017;**16**(1):72-80. doi: [10.24167/psiko.v16i1.948](https://doi.org/10.24167/psiko.v16i1.948).
35. Kurniawan AP, Hasanat NU. Perbedaan ekspresi emosi pada beberapa tingkat generasi suku jawa di yogyakarta. *Psychol J Fac Psychol Gadjah Mada Univ*. 2004;**34**(1):1-17. doi: [10.22146/jpsi.7086](https://doi.org/10.22146/jpsi.7086).
36. Citrome L, Shope CB, Nolan KA, Czobor P, Volavka J. Risperidone alone versus risperidone plus valproate in the treatment of patients with schizophrenia and hostility. *Int Clin Psychopharmacol*. 2007;**22**(6):356-62. doi: [10.1097/YIC.0b013e3281c61baf](https://doi.org/10.1097/YIC.0b013e3281c61baf). [PubMed: [17917554](https://pubmed.ncbi.nlm.nih.gov/17917554/)].
37. Vincenzi B, Greene CM, Ulloa M, Parnarouskis L, Jackson JW, Henderson DC. Lithium or valproate adjunctive therapy to second-generation antipsychotics and metabolic variables in patients with schizophrenia or schizoaffective disorder. *J Psychiatr Pract*. 2016;**22**(3):175-82. doi: [10.1097/PRA.0000000000000149](https://doi.org/10.1097/PRA.0000000000000149). [PubMed: [27123797](https://pubmed.ncbi.nlm.nih.gov/27123797/)]. [PubMed Central: [PMC5331927](https://pubmed.ncbi.nlm.nih.gov/PMC5331927/)].
38. Winter HR, DeVane CL, Figueroa C, Ennis DJ, Hamer-Maansson JE, Davis PC, et al. Open-label steady-state pharmacokinetic drug interaction study on co-administered quetiapine fumarate and divalproex sodium in patients with schizophrenia, schizoaffective disorder, or bipolar disorder. *Hum Psychopharmacol*. 2007;**22**(7):469-76. doi: [10.1002/hup.869](https://doi.org/10.1002/hup.869). [PubMed: [17729385](https://pubmed.ncbi.nlm.nih.gov/17729385/)].