# Living in Urban Areas, Low Education, Cognitive Function, and Medication Adherence Are Factors Related to Major Depression among Epilepsy Patients in Manado, Indonesia

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## Abstract

**Purpose:** The aim of this study was to identify factors related to major depression among epilepsy patients in city of Manado.

**Methods:** This was a cross-sectional study conducted in Neurology Clinic and appropriate bivariate analysis was used to test the relationship between sociodemographic and clinical variables with major depression.

**Findings:** Living in urban areas, low education, low cognitive function, and low medication adherence are factors related to major depression. The relationship between medication adherence and depression is found in previous studies but the other significant factors in this study are not.

**Conclusion:** Our region has some particular factors related to major depression among epilepsy patients. These findings considered in designing local treatment strategy and health policy.

***Keyword:*** *Epilepsy, major depression, Manado-Indonesia, related factors.*

## Introduction

Depression is one of the comorbid symptoms that often occur in patients with epilepsy. Depression is a neuropsychiatric complication that often occurs in patients with chronic epilepsy. The prevalence rates reported more than 30% in the population with epilepsy, and between 20% - 55% in epilepsy centers.[1] However, until now there are no available data regarding these cases in Manado the capital city of North Sulawesi.

Depression problems in epilepsy can be influenced by sociodemographic factors and clinical factors. This prompted the writer to conduct a study on the role of sociodemographic and clinical factors in epilepsy patients with depression in the neurology outpatient clinic from general hospital of Prof. Dr. R. D. Kandou Manado.

### Purpose

The purpose of this research is to know and analyze depressive disorders in epilepsy, the prevalence of depressive disorders in people with epilepsy, the differences in sociodemographic and clinical characteristics between epilepsy patients who suffer from depression and those who do not experience them, and to know the association between both sociodemographic and clinical factors and epilepsy with depression

## Method

This was a cross-sectional study. The sample population were the epilepsy patient at general hospital of Prof. Dr. R. D. Kandou Manado period December 2018 to February 2019. The research data collection in this study used a cross-sectional method. Recruitment of 107 research subjects, who met the inclusion criteria

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took part in the study, who can speak Indonesian, aged 18-65 years, get antiepileptic drug therapy, willingness to participate.

Examination of epilepsy patients, who are outpatient at the neurology clinic is carried out with anamnesis, physical examination, neurological examination, investigation, and MMSE. If it meets the inclusion criteria, a depressive disorder (NDDI-E) will be examined. Data on sociodemographic factors and data on clinical factors were also recorded on the research form.

The distribution of sociodemographic factors and clinical variables is presented in the tabulation form according to the type of variable. Numerical scale variables are presented as the median and interquartile range (IQR) because the "Shapiro Wilk" test shows that all distribution is abnormal. Categorical scale variables are shown in total N and proportions. Differences in sociodemographic and clinical characteristics according to depression status (major vs no depression) were tested with the "Mann-Whitney U" test for numerically classified variables, and chi-square test for categorical variables. Logistic regression models for binary outcomes were used to quantify the relationship of depression status and independent variables both at the bivariate level (univariable regression) and multivariate. All variables released from the univariate regression results were included in the variable selection for multivariate modeling. The regression modeling results were reported as Odds Ratios (OR), lower and upper limits of the 95% confidence interval, CI, and p values. The research data management was mostly taking place in R 3.5.2 statistical software application, which was also the main tool of statistical analysis.

## Result

There were 107 subjects recruited in this study with half of the subject is female patients and the mean of age 29,42 years. More than half of the subjects live in a rural area. Senior high school graduates found in 77% subject. Unmarried subjects found in 63%. Most of the subject (74%) is Minahasa ethnic. Epilepsy onset during childhood are 37%, adolescents are 37%, and the rest is adult. Subjects with monotherapy found in 72%, mainly with phenytoin (52%), carbamazepine (11%), and valproate (7%). Median duration of taking antiepileptic medication is 2.0 (1.0-9.5) years. Median of MMSE is 28.0 (27.0-29.0). Highly medication compliance found in 73% subjects. Sociodemographic factor that influences major depression is subjects living in urban (p=0,039) and who are not reached senior high school (p=0.002). The clinical factor is MMSE (p=0,001) and low medication compliance (p=0,026).

The selection of the final model for multivariate analysis was assisted by the "*forward selection*" facility in application R. Overall residence, education, AED therapy, administration of folic acid, MMSE value, type of epilepsy, and MMAS-8 categories were selected as independent variables of multivariable regression. However, the results are quite consistent with the findings of the univariable level. The magnitude of the relationship between major depression and place of residence, the level of education (especially elementary-junior high school vs. high school) in this multivariable regression appeared smaller than the univariable results.

## Discussion

The prevalence of depressive disorders in patients with epilepsy in the neurology department at 69% for a period of 3 months of data collection using NDDI-E. This study included 10 subjects (9.35%) who had the desire to suicide.

The total sample of this study was also the majority unmarried because it belongs to the age group of 18-25 years. Comparison of the percentage between the number of men and women married to major depression (16% vs. 22%), while the percentage between the number of unmarried men and women with major depression was equally large with both of them in 31%. During this study, it has been found that the increase of mayor depression by unmarried patients are mostly because of the condition of the patients, that they cannot share their depression to someone.

The research in 74 subjects who experienced major depressive disorders were 39 people women and 35 people men (p=0.846). But from the results of statistical calculations, there was no significant difference between sex differences towards major depression (p=0.846). It was suspected that there were hormonal differences, the effects of childbirth, differences in psychosocial stressors between men and women.[2]

Many of the subjects with focal epilepsy experienced major depression and most of all with temporal lobe epilepsy (65%). This is consistent with Sheline's literature study report that depression in patients with temporal and frontal lobe epilepsy has a higher likelihood of depression. Hippocampal atrophy is a characteristic of mesial temporal lobe epilepsy, which is commonly found in people with depression with epilepsy.[3]

The variables that are most associated with the occurrence of major depression, were places of living between city or village, and education as the sociodemographic factors and MMSE values and medication compliance as the clinical factors. People with epilepsy, who live in urban/urban areas, have more major depression, possibly because medication adherence was low[4] due to more daily activities, stress levels was also higher when living in cities than in villages. Subjects in this study who experienced major depression were found at the level of education who graduated from elementary school to junior high school. The patient will cause frequent feelings of unconfident and have limited knowledge, because of the low level of education. This limited knowledge will be impacting that they do not know the importance of compliance with taking medication.

Focal epilepsy mostly uses AED treatment with carbamazepine and phenytoin, but carbamazepine is an AED often causes Steven Johnson syndrome and HLA-B*1502 examination, which as a genetic marker in Steven Johnson syndrome due to carbamazepine is not yet known by the general public in Indonesia. While phenytoin is more often used because of its smaller incidence, it causes Steven Johnson syndrome smaller than carbamazepine, and phenytoin is included in drugs that are included in the Indonesia government insurance. The most widely used AED of polytherapy is a combination of phenytoin and clobazam because the AED is included in the government insurance, all subjects in this study were the government insurance participants. It's just that the use of AED levetiracetam in the subjects of this study has little effect on major depression because the samples are very limited or few so that they cannot provide a statistically significant correlation. Harsono's study found depression was one of the side effects of using AED phenytoin[5] pregabalin, levetiracetam. Felbamate is also a depressogenic drug. The drug lamotrigine also has an effect on mood.[6] Phenobarbital and Phenytoin reduce free tryptophan plasma levels, while carbamazepine increases free tryptophan plasma levels, free tryptophan plasma influences serotonin replacement.[7] From an analysis of the relationship between AED therapy and the risk of major depression, the use of polytherapy or combination AED is statistically significantly associated with the occurrence of major depression.

The subjects who received low dose of folic acid were found to have major depression. Alpert and Froscher's study showed a resemble result that epilepsy patients who were given very low concentrations of folic acid generally showed higher depression than those who were given normal levels of folic acid concentration. Low levels of folic acid 5-methyltetreahydrofolate derivatives are associated with depression severity.[8,9] According to Setiawan, the need for folic acid needed is 0.5-1 mg daily orally.[10]

MMSE has a role to determine the decline in cognitive function that is often found in epilepsy, which depends on several factors including etiology, seizure type, certain epilepsy syndrome, location of the lesion or seizure focus, frequency and duration of seizures, age at onset, other psychiatric disorders such as anxiety and depression, and anti-epileptic drugs taken by them.[11] Higher depression scores are associated with lower cognitive function. Every decrease in 1 score point from the MMSE value will have a higher risk of causing depression.

The subjects who had low medication adherence were found to experience major depression, and according to multivariate analysis of low compliance to drink the medication (MMAS-8: 0-5) with a value of $p = 0.026$, which lead to a significant relationship with the occurrence of depression on the patient. This is in accordance with "Gidal and Garrett's" research regarding medication adherence is one of the factors that can still be improved, found that low drug compliance will cause uncontrolled epilepsy seizures. This continuous uncontrolled seizure will cause major depression.[6,12]

The subjects of this study were obtained during uncontrolled seizure frequency with major depression as much as 53%. Based on the Indonesia government insurance rules, epilepsy patients with controlled

seizures will be treated more in hospital type B or C, whereas the referral system is the patient epilepsy that was found to have major depression with uncontrolled seizures became more prevalent in this study sample.

The weakness of this study is that folic acid levels were not examined because epilepsy patients who were given very low concentrations of folic acid generally showed high depression, and limited use of AED types. Clobazam given can be a confounder between Clobazam which causes depression or indeed there have been symptoms of depression before then given Clobazam. The study also did not have data on the history of status epilepticus that might have been experienced by the study subjects.

The weaknesses of this study are that the low concentrations of folic acid, clobazam masked the research result, and no status of epilepticus history on the patients. The folic acid levels were not examined because epilepsy patients who were given very low concentrations of folic acid generally showed high depression and limited usage of AED types, because AED. Clobazam that given to the patients can be the trigger to causes depression or the depression already happened before the given Clobazam. The research also did not have the historical data of status epilepticus, which has been through by the study subjects.

## Conclusion

Epilepsy patients with major depression have different sociodemographic and clinical characteristics compared with epilepsy patients who do not experience depression. The sociodemographic factors associated with epilepsy sufferers with depression are epilepsy onset and education, while the clinical factors are AED, MMSE and medication adherence.

**Conflict of Interest :** There is no any conflict of interest within this study and publication

**Ethical Clearance :** This study has obtained the ethical approval of the research from the Health Research Ethics Committee of general hospital Prof. Dr. R.D. Kandou, Manado, with the registration number of 172 / EC-KEPK / IX / 2018.

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