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Depression Associated With Sleeping Disorders Amid Stage 5 Chronic Kidney Disease Patients

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ABSTRACT

Introduction: In Stage 5 Chronic Kidney Disease patients on hemodialysis (CKD 5D patients), the prevalence of sleeping problems is high, ranging between 70 and 80%. Our health staff became aware that a significant number of patients complained about sleeping problems. **Objective:** The aim of this trial was evaluate the sleeping quality among CKD 5D patients as well as the possible clinical correlations. Participants and Methods: a single-center, cross-sectional, prospective clinical trial was designed with 103 CKD 5D patients. **Methods:** One hundred CKD 5D patients were asked about their quality of sleeping, answering the PSQI question. Patient who got score from 0 to 4 was considered with Good quality of Sleeping and therefore were allocated into the group G. Patients who scored 5 or above were considered with Sleeping Problem and therefore were allocated into the Group SP. Patient's medicine history was also recorded and the association between medicine and quality of life was investigated. **Results:** Our findings show high prevalence of sleep disorders among CKD 5D patients. Antidepressants showed a significant association with sleep disorders. **Conclusions:** our study suggests that CKD at stage 5 has a close relationship with sleep problems and also that CKD 5D patients on antidepressant treatment can have sleeping problem.

Keywords: Depression, Sleeping, Hemodialysis, Chronic Kidney Disease.

Introduction

Sleeping is a reversible and transitory status of behavior in which there is a switching off perception and irresponsivity to environment (Carskadon MA, Dement W., 2005). This condition is a result of a series of neurobiological processes that are necessary for all species in order to keep cognitive and physical health ("American Academy of Sleep Medicine Task Force", 1999).

Regulation of energetic balance, memory consolidation, body temperature control and hormone production related to hydro-electrolyte balance are some of the roles played by sleeping (Souza *et al*, 2007).

In CKD 5D patients on hemodialysis, the hydro-electrolytes balance is compromised and sleeping problems can worsen it (Daugirdas JT, Blake PG, 2007). Sleeping problems can also compromise work performance, social and familiar relationships. As consequence, the impact of sleeping problems in the life quality is huge, requiring treatment (Reimer MA, Flemons WW, 2003; Beaton *et al*, 2000). The prevalence of sleeping problems amid these patients is high, ranging between 70 and 80% (Lara *et al*, 2008). So there is reason to delve into the sleeping quality amid CKD 5D patients.

Among some tools used to evaluate sleep quality, the *Pittsburgh Sleep Quality Index (PSQI)* (Buysse *et al*, 1989) is regarded relevant and therefore is widely used for evaluating the nature and magnitude of sleeping problems. PSQI was validated to the Brazilian scenario by Bertolazi (2008); Sperber AD, 2004). Created in 1989 by Buysse, PSQI evaluates 7 components related to sleeping quality (subjective quality, latency, efficiency, duration, disturbances, use of medicines and daytime dysfunction).

In our dialysis center, during its clinical activities, our health staff became aware that a significant number of patients complained about sleeping problems. For this reason, we decided to evaluate sleeping quality of our CKD 5D patients.

Objective

The aim of this trial was evaluate the sleeping quality among chronic kidney disease patients at stage 5 (CKD 5D patients) undergoing hemodialysis as well as the possible clinical correlations.

Participants and Methods

Study Classification: a single-center, cross-sectional, prospective clinical trial was designed with approval given by the Ethics Committee of the University of Sao Paulo, Sao Paulo, Brazil. *Study Time*: the clinical trial was carried out from May 2014 to June 2014. *Study Site*: the clinical trial was performed at the RenalClass, a dialysis center situated in Sao Paulo City, Sao Paulo State, Brazil. One hundred fifty patients were enrolled in chronic hemodialysis program at that time. *Sample Size*: 103 patients were selected for this study.

Participant Selection - Inclusion criteria: Both male and female chronic kidney disease patients at stage 5 (CKD 5D patients) undergoing chronic hemodialysis aged from 18 years old were included. All patients were voluntary participants with the study only starting after approval of signed Informed Consent by the independent ethics committee of the University of Sao Paulo. *Exclusion criteria*: patients who did not consent to participate in this study; patients aged below 18 years old; pregnant women; oncologic patients; patients diagnosed with hypothyroidism; patients with cognitive deficit or mental illness; patients recently discharged from hospitals.

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Hemodialysis Parameters: the high-efficiency hemodialysis session was carried out during a period of 4 hours, three times a week, using polysulfone dialyser (F10), blood flow of 350 mL/min and dialysate flow of 500 mL/min. All patients had Kt/V within the parameters established by the guidelines (KDOQI, *Kidney Disease Outcomes Quality Initiative*). During the study, there were no alterations in the dialysis prescription (dialyzer, hemodialysis time and frequency of sessions, solution composition, hemodialysis machine, day period and other parameters).

Study Design: Patient characteristics recorded in the study include: sex, age, time enrolled on hemodialysis program and current medications. The clinical trial protocol was started with medical visits. During these visits, they were asked about their quality of sleeping, answering the PSQI questions. This is a multi-scale index composed by 19 questions that evaluate 7 components of Sleeping (Subjective Quality; Latency, Duration; Habitual Efficiency; Alterations or Disturbances; Use of Medicines and Daytime Dysfunction) - Figure 1. Each component can be scored from 0 to 3 points.

The criterion for determining whether a patient had a good sleeping quality (Group G) or not (Group PS) is described as follows: Patient who got score from 0 to 4 was considered with Good quality of Sleeping and therefore were allocated into the group G. Patients who scored 5 or above were considered with Sleeping Problem and therefore were allocated into the Group SP.

Statistical Analysis

The statistical analyses were performed with the *Statistical Product and Service Solutions* (SPSS) for Windows version 13.0 (IBM, The United States of America). *Descriptive Analysis*: The data were summarized using appropriate descriptive statistics for each type of variable. Frequency and percentages were determined for category variables (gender). The number of valid occurrences (n), mean, median, standard deviation, minimum value, and maximum value were determined for continuous variables. *Comparative Analysis*: The comparison between categorical variables (gender, categories of TPHD) per group (G and SlP) was performed using Chi-square Test. T-student Tests were used for the comparative analyses between the, Kt/V, BMI, Hemoglobin and Phosphorous, and Fisher's Test was used for comparison of categories of age per group (G or SP). A p-value < 0.05 is considered statistically significant (Confidence Interval - CI equals to 95%).

Results

Of total of 103 patients who commenced this clinical trial, 69 patients (66.99%) were identified with Sleeping Disorder, being allocated into the Group SpD (Sleeping Disorder) while 34 patients (33.01%) referred a good quality of sleeping, being allocated into the Group G (Good Quality of Sleeping). Patient characteristics are shown in Table I.

The comparison of Quality of Sleeping per gender shows that 27.3% of good quality of sleeping among females (n=12) and 37.3% among males (n=22). Therefore, no significant differences were identified in quality of sleeping per gender - (p-value =0.391; Table 1). In addition, considering the proportion of sleeping quality within the gender group (male or female) and admitting a null hypothesis equals to 0.5, we identified a significant difference in sleeping quality among females (p-value = 0.004) but not among males (p-value = 0.3239).

Considering the categorical variable age, the comparison of sleeping quality shows that 8 patients (25%) had a good quality of sleeping among patients under 60 and 26 patients (36.6%) had a good quality of sleeping among patients above or equal to 60. Considering only the proportion inside the group Age under 60, we identified a significant difference in the quality of sleeping (p value). However, considering the group above 60, there was no difference on the quality of sleeping (p-value).

The analysis of categorical variable BMI and Quality of Sleeping shows that 68.8% of patients who had BMI below 25 kg/m^2 (aged under 60) also complaint about Sleeping Disorder while 83.3% of the patients who had BMI above 25 kg/m^2 complained about Sleeping Disorder. Among patients above 60, 57.7% of patients who had BMI above 28 kg/m^2 complaint about Sleeping Disorder while 78.9% of patients who had BMI above 28 kg/m^2 complained about Sleeping Disorder. No significant differences were observed when categorical BMI was compared to Sleeping Quality (p-value > 0.05).

The comparison between dialysis adequacy (Kt/V) and Sleeping quality shows that a mean Kt/V equals to 1.22 (0.21) among patients with good quality of sleeping while patients with sleeping disorder had a mean Kt/V equals to 1.29 (0.23). No significant difference was identified between the groups (p-value = 0.159).

When the categorical variable TPHD was compared to quality of sleeping, we identified that 71% of patients who had less than a year on hemodialysis program also had sleeping disorder while 61.5% of patients on hemodialysis for a period equal or more than a year had sleeping disorder. Statistically, this is not significant (p-value= 0.444).

Considering the hemoglobin levels (≤12 or > 12), we verified that 67.6% of patients with hemoglobin level ? 12 were also diagnosed with sleeping disorder while 65.5% of patients with hemoglobin above 12 were diagnosed with sleeping disorder. No significant differences were observed as to quality of sleeping (p-value=1.000).

We compared the categorical variable Phosphorous (<5.5 and ≥ 5.5) and quality of sleeping. We observed that 60.9% of patients with phosphorous level below 5.5 had sleeping disorder while 71.9% of patients with phosphorous level ≥5.5 had sleeping disorder. No significant differences were identified between the groups (p-value = 0.329).

Finally, we compared 4 groups of medicines used by the patients and the quality of sleeping. Only one group of medicine (Group 1) shows strong correlation with sleeping disorder (antidepressant drugs) - p-value = 0.029. For the rest of groups, **antihypertensives**, anti-dyslipidemia and all drugs), we did not verify correlation (p-value > 0.05). Table 2 shows the results of the comparison between quality of sleeping per group of Drug and Figure 2 illustrates this correlation between Sleeping quality and Group 1.

Discussion

This trial provides relevant findings about the quality of sleeping, an essential aspect of quality of life among CKD 5D patients.

First of all, it is important to emphasize the patient characteristics and hemodialysis parameters. CKD 5D patients sample was considered homogeneous. The number of men (*n*=59) was slightly bigger than women (*n*=44). The number of patients aged above 60 years (*n*=71) was bigger than the number of patients aged below 60 years (*n*=32).

Beside our sample shows that the number of men is quite bigger than women, the sleeping problem is highly prevalent in both genders. In Brazil, a higher number of men among CKD 5D patient is common because men are used to searching for healthcare outpatients facilities lately than women. Therefore, the number of men on hemodialysis is typically higher than women ("The Brazilian Society of Nephrology," 2013). On the other hand, we show an important finding: a high prevalence of sleeping problem (66.99%).

As to BMI, the majority of patients (n=68) had BMI considered adequate (below 25 or below 28 kg/m^2). We analyzed BMI because occurrence of overweight/obesity is correlated to sleeping apnea (Wall *et al*, 2012). When we associated BMI and quality of sleeping, we did not identify any statistical significance (p-value > 0.05). However, this value indicated a trend to BMI is correlated to quality of sleeping. We are analyzing a larger number of CKD 5D patients in order to verify if there is correlation between BMI and quality of sleeping.

A large number of patients aged from 60 years were identified. Our results evidence a predominance of elderly and show concordance with many authors as observed by Bornivelli *et al,* (2008). Although these authors analyzed a smaller group, they identified a mean age near 60 years. They reiterated that sleep disorders are common in hemodialysis patients (Bornivelli *et al*, 2008).

We also identified another important finding. There was a predominance of patients on hemodialysis program time under than 12 months (*n*=62) and 39 patients on hemodialysis period equal or above 12 months. Most of the patients (*n*=68) had sleeping problems. This result suggests that the sleeping problems start earlier than we suspected and therefore there is no significant difference between the groups. We suggest that sleeping problems start at the early phases of chronic kidney disease because chronic diseases can be related to alterations of melatonin levels. Some data can corroborate this hypothesis. According to Campino and colleagues, melatonin also decreases the cortisol response to ACTH in humans, suggesting that the adjunctive use of melatonin in CKD 5D may have an impact on the cortisol/DHEA-S ratio. As consequence, we hypothetize the quality of sleeping could be affected by cortisol levels (Campino *et al*, 2008). This hypothesis is just being tested in our dialysis Centre and associated laboratory (Neuropharmacology Laboratory, Institute of Biomedical Sciences, University of Sao Paulo).

We also verified that 74 patients showed hemoglobin level below 12 g/L. We considered the analysis of hemoglobin and quality of sleeping extremely important because hypoxemia is correlated to a decrease of quality of sleeping. Poor oxygenation derived from low levels of hemoglobin can also lead to nocturnal hypoxemia and sleeping apnea. Considering the phosphorous control, 57 patients showed phosphorous level above or equal 5.5. This analysis is relevant due to the fact that levels of phosphorous are correlated to patient's treatment compliance. Then, phosphorous levels can be used as tracer for treatment compliance, if indirectly tested. Generally, patients whose phosphorous level is below 5.5 also have high level of treatment compliance as well as self-care.

Although our sample evidences no statistical difference between BMI and quality of sleeping, between hemoglobin and quality of sleeping as well as Phosphorous levels and quality of sleeping, we show a predominance of patients with anemia and poor control of phosphorous. Anemia and poor control of phosphorous are typical complications amid CKD 5D patients (Daugirdas JT, Blake PG, 2011).

As to hemodialysis parameters, all patients were on high-efficiency hemodialysis, carried out in 4-hour sessions, three times a week, using polysulfone dialyzer F10, 350 mL/min blood flow, and 500 ml/min dialysate flow. The mean Kt/V was similar between the two groups. This indicates a similar hemodialysis between the groups and also suggests that hemodialysis adequacy is not related to quality of sleeping. This result seems to be a new finding and excludes the influence of quality of dialysis on sleeping.

When we compared the quality of sleeping and the class of drug used by the patients, we identified that only drugs of group 1 (antidepressants) were correlated to quality of sleeping (p-value < 0.05). At this point, it is imperative to mention two factors related to this finding. The first one is that the major of patients were diagnosed with depression and restless legs. A feature of this disorder is the occurrence of sleeping disorder. Depression per se can lead to sleeping disorders (http://sleepfoundation.org/sleep-disorders-problems/depression-and-sleep). For this reason, sleeping problems can be identified in CKD 5D patients with uncontrolled depression or restless legs.

The relationship between depression and sleeping/vigil phase is driven by the relationship between two molecules: serotonin and melatonin (Hickman *et al*, 1999; Kamal *et al*, 2015). Melatonin synthesis. Melatonin is synthesized from serotonin through two enzymatic steps. First, serotonin is acetylated by NAT to yield N-acetylserotonin (NAS). The second step is the methylation from (*S*)-adenosylmethionine to the 5-hydroxyl group of *N*-acetylserotonin via the enzyme HIOMT. The rhythms of melatonin and serotonin have opposite phase during subjective night and day (Hickman *et al*, 1999).

The second factor is that these patients were on antidepressant treatment. According to Lexicomp's monographs, antidepressant drugs can lead to a high prevalence of sleeping problems (www.lexi.com/online). Most of these drugs are associated to a high level of sleeping problems (above 10% of patients who use these drugs). Therefore, even among patients with controlled depression or restless legs, sleeping problems can be verified as a result

of adverse drug reaction. In this way, sleeping problems can persist after the beginning of treatment for depression.

In addition, it is desirable to mention that melatonin and serotonin receptors are physically bounded (Kamal *et al*, 2015) and, therefore, alterations in melatonin levels can be related to sleeping problem and depression. We are still investigating the mechanism associated to these phenomena.

In conclusion, our study suggests that CKD at stage 5 has a close relationship with sleep problems and also that CKD 5D patients on antidepressant treatment can have sleeping problem. More investigations are needed in order to clarify the relationship between CKD at stage 5 and sleeping problem, and, depression and CKD at stage 5.

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Appendix

Figures

Figure 1: The Pittsburgh Sleeping Quality Index Form

Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

1. During the past month, when have you usually gone to bed?_____
2. During the past month, how long (in minutes) has it taken you to fall asleep each night?_____
3. During the past month, when have you usually gotten up in the morning?_____
4. During the past month, how many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed)_____

5. During the past month, how often have you had trouble sleeping because you...	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep? (prescribed or "over the counter")				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				
	No bed partner or room mate	Partner/room mate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or roommate?				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
If you have a roommate or bed partner, ask him/her how often in the past month you have had:				
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep, please describe:				

Scoring the PSQI

The order of the PSQI items has been modified from the original order in order to fit the first 9 items (which are the only items that contribute to the total score) on a single page. Item 10, which is the second page of the scale, does not contribute to the PSQI score.

In scoring the PSQI, seven component scores are derived, each 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0 to 21). Higher scores indicate worse sleep quality.

Component 1: Subjective sleep quality---question 9

Response to Q9	Component 1 score
Very good	0
Fairly good	1
Fairly bad	2
Very bad	3

Component 1 score:_____

Component 2: Sleep latency---question 2 and 5a

Response to Q2	Component 2/Q2 subscore
≤15 minutes	0
16-30 minutes	1
31-60 minutes	2
>60 minutes	3

Response to Q5a	Component 2/Q5a subscore
Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Sum of Q2 and Q5a subscores	Component 2 score
0	0
1-2	1
3-4	2
5-6	3

Component 2 score:_____

Component 3: Sleep duration---question 4

Response to Q4	Component 3 score
7 hours	0
6-7 hours	1
5-6 hours	2
5 hours	3

Component 3 score_____

Component 4: Sleep efficiency---question 1, 3, and 4

Sleep efficiency= (# hours slept/# hours in bed) X 100%
hours slept-question 4
hours in bed-calculated from responses to questions 1 and 3

Sleep efficiency	Component 4 score
>85%	0
75-84%	1
65-74%	2
<65%	3

Component 4 score:_____

Component 5: Sleep disturbance-question 5b-5j

Questions 5b to 5 j should be scored as follows:

Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Sum of 5b to 5j scores	Component 5 score
0	0
1-9	1
10-18	2
19-27	3

Component 5 score:_____

Component 6: Use of sleep medication-question 6

Response to Q6	Component 6 score
Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Component 6 score:_____

Component 7: Daytime dysfunction-question 7-8

Response to Q7	Component 7/Q7 subscore
Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Response to Q8	Component 7/Q8 subscore
No problem at all	0
Only a very slight problem	1
Somewhat of a problem	2
A very big problem	3

Sum of Q7 and Q8 subscores	Component 7 score
0	0
1-2	1
3-4	2
5-6	3

Component 7 score_____

Global PSQI Score: Sum of seven component scores:_____

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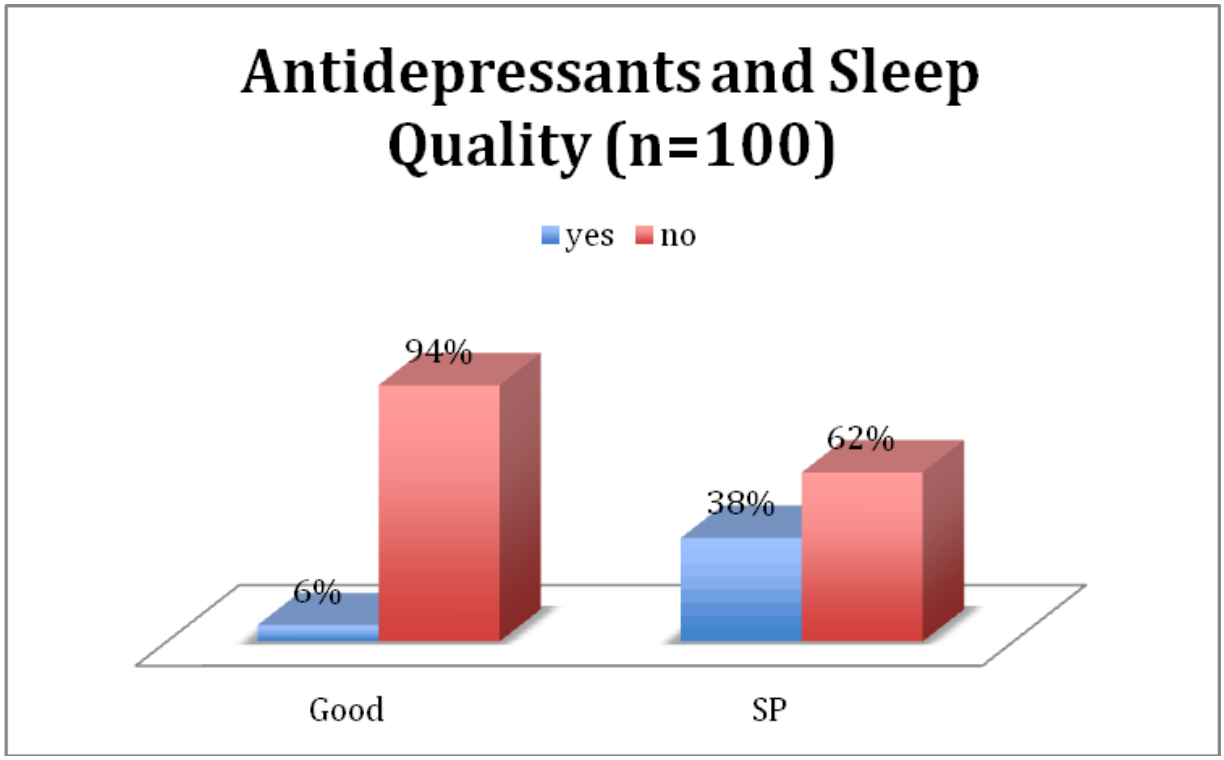
Figure 2: Antidepressants and Sleep Quality



*Chi-Square Test (p-value 0.029). CI - Confidence Interval: 95%. Good - group of patients with good quality of sleep. SP - group of patients diagnosed with Sleep Problem. Yes - patients on antidepressant treatment. No - patients not on antidepressant treatment

TABLES

Table 1: Patient Characteristics.

Patient Characteristics				
Characteristic	**Good**	**SP**	**All (*n*=103)**	**p-value**
Sex - Female (%)	12 (27,3)	32 (72,7)	44 (100)	0,391*
Sex - Male (%)	22 (37,3)	37 (62,7)	59 (100)	
Age - below 60 years	8 (25)	24 (75)	32 (100)	0,350*
Age - above or equal to 60 years	26 (36,6)	45 (63,4)	71 (100)	
BMI- age below 60				
< 25 kg/m²	5 (31,3)	11 (68,8)	16 (100)	0,685**
> or equal to25 kg/m²	3 (18,8)	13 (81,3)	16 (100)	
BMI- age above or equal 60 years				
< 28 kg/m²	22 (42,3)	30 (57,7)	52 (100)	0,171*
> or equal 28 kg/m²	4 (21,1)	15 (78,9)	19 (100)	
Kt/V - Me (SD)	1,22 (0,21)	1,29 (0,23)	1,27 (0,23)	0,159#
TPHD < 1 year	18 (29)	44 (71)	62 (100)	0,444*
TPHD > or equal to 1 year	15 (38,5)	24 (61,5)	39 (100)	
Hemoglobin				
≤ 12	24 (32,4)	50 (67,6)	74 (100)	1,000*
> 12	10 (34,5)	19 (65,5)	29 (100)	
Phosphorous				
< 5,5	18 (39,1)	28 (60,9)	46 (100)	0,329*
≥ 5,5	16 (28,1)	41 (71,9)	57 (100)	

*Chi-Square Test; ** T-student Test. ***Fisher's Test. CI - Confidence Interval: 95%. Level of Significance: p-value <0.05. TPHD: Time in Program of hemodialysis; Sex, Male or Female; Age, in years. Me: mean; SD: standard deviation; BMI: Body Mass Index, in kg/m².

Table II: Quality of Sleep per Group of Drug.

Quality of Sleeping per Group of Drugs			
Group of Medicine	Quality of Sleeping		
Group 1 (antidepressants)	**Good**	**SP**	**p-value**
No	33(37.9%)	54 (62.1%)	0.029*
Yes	1 (6.3%)	15 (93.7%)	
Group 2 (anti-hypertensives)			
No	7 (22,6)	24 (77,4)	0.212*
Yes	27 (37,5)	45 (62,5)	
Group 3 (anti-dyslipidemia)			
No	11 (27,5)	29 (72,5)	0.464*
Yes	23 (36,5)	40 (63,5)	
Group 4 (all drugs)			
No	5 (50)	5 (50)	0.292**
Yes	29 (31,2)	64 (68,8)	

*Chi-Square Test; **Fisher's Test. CI - Confidence Interval: 95%. Level of Significance: p-value <0.05. Good - group of patients with good quality of sleep. SP - group of patients diagnosed with sleep problem.