Prevalence of anxiety and depression and its comorbidities in patients with chronic kidney disease on hemodialysis and peritoneal dialysis

Authors
Camila Edith Stachera Stasiak[1]
Kalyl Singh Bazan[1]
Renata Stoeberl Kuss[2]
Adriana Fatima Menegat Schuinski[1]
Gilberto Baroni[1]

[1] State University of Ponta Grossa.
[2] Santa Casa de Misericordia Hospital of Ponta Grossa.

ABSTRACT

Introduction: Patients with chronic kidney disease (CKD) who perform renal replacement therapy (RRT) are subject to a higher prevalence of mood disorders. **Objective:** The aim of this study is to compare the prevalence of anxiety and depression in patients on hemodialysis (HD) and peritoneal dialysis (PD), taking into account comorbidities that may contribute to this. **Methods:** The study was done in Ponta Grossa with CKD patients, using Beck Depression and Anxiety Inventory (BDI and BAI) and the Hospital Anxiety and Depression Scale (HADS). **Results:** We studied 155 patients, 128 in the HD group and 27 in PD. In the first, depression was found in 22.6% of patients in the BDI and 9.3% in HADS, and anxiety 25.7% in the BAI and 11.7% in the HADS. In the PD group, 29.6% of patients had depression in the BDI and 14.8% in HADS, and anxiety 11.1% in the BAI and none in HADS. **Conclusion:** The hemodialysis or peritoneal dialysis did not influence the prevalence of anxiety and depression in patients with CKD.

Keywords: anxiety; depression; hemodialysis units, hospital; peritoneal dialysis; renal dialysis; renal insufficiency, chronic.

INTRODUCTION

Chronic kidney disease (CKD) is considered a public health problem worldwide. It is defined by kidney tissue injury (with or without a decrease in glomerular filtration rate) and/or a decrease in kidney function over a period of three or more months. When the glomerular filtration rate (GFR) is below 15 ml/min/1.73 m^2, the patient is in the terminal stage or dialysis, requiring renal replacement therapy (RRT), dialysis or transplant as alternative treatments.[1] According to the Brazilian Dialysis Census performed in 2010, the number of patients on dialysis has increased gradually from 42,695 in 2000 to 92,091 in 2010.[2] The estimated number of patients who started treatment in 2010 was 18,972. Of these, 90.6% were receiving hemodialysis (HD) and 9.4% were on peritoneal dialysis (PD).

Patients submitted to RRT are subject to reduced quality of life compared to the general population and a have higher prevalence of mood disorders.

Submitted on: 01/20/2013.
Approved on: 03/05/2014.

Correspondence to:
Gilberto Baroni.
State University of Ponta Grossa.
Santa Casa de Misericordia Hospital of Ponta Grossa.
Av. Dr. Francisco Burzio, nº 774, Centro. Ponta Grossa, PR, Brasil.
CEP: 84010-200.
E-mail: gbaroni@superig.com.br

DOI: 10.5935/0101-2800.20140047

The relationship between quality of life is inversely proportional to the prevalence of anxiety and depression, according to Muñoz.[3] This condition may represent an increase in morbidity and mortality in dialysis patients, as well as compromising treatment compliance and downgrading their immune and nutritional status, both because of symptoms of depression or anxiety as per associated symptoms - such as loss of concentration, loss of motivation, sleep disorders, fatigue, depressed mood and difficulty understanding information.[4,5]

Several questionnaires have been developed to assess anxiety and depression symptoms. Among them, some of the most used are Beck's Depression and Anxiety Inventories; and the Hospital Anxiety and Depression Scale (HADS), both validated, including patients with CKD.[6] The Beck Depression Inventory (BDI) was developed by Aaron T. Beck, and is performed to detect depressive symptoms and their intensity in patients aged over 13 years. The scale consists of 21 items, and the intensity of each one varies according to the degree of symptom severity, being rated from 0 to 3 (0 corresponds to mild or no symptoms; 3 corresponds to severe symptoms).[7] The final score interpretation is given as follows: absence of depression between 0-13; mild depression between 14-19; moderate between 20-28; and severe depression between 29-63. BDI is simple to use; it can be used for various types of populations and its items correspond to the DSM-IV; therefore, it can be used both in research and in the clinical setting. Some limitations include the possible overlap between depression symptoms and other medical conditions, and the care that must be taken in performing diagnosis based only on questionaries.[8]

The Beck Anxiety Inventory (BAI) was developed to measure anxiety in adult patients. It can be used in different populations and is easy to deploy and interpret. Some limitations to its use are the lack of studies on the influence of other comorbidities, and patients with panic disorder also score high on the BAI. Thus, with the BDI, BAI has 21 items that assess symptom intensity from 0 (absent) to 3 (severe symptoms; almost unbearable).[9,10] A score of 0-7 indicates minimum level of anxiety; 8-15 mild anxiety, 16-25 moderate and 26-63 severe anxiety.

The Hospital Anxiety and Depression Scale (HADS) was developed to identify potential new cases of anxiety and depression in adults. HADS differs from other scales because it contains items that address symptoms of anxiety and depression associated with physical illness (such as weight loss, insomnia, fatigue, headache and dizziness) to prevent interference from somatic disorders in scale scoring.[11] It contains 14 items related to emotional and cognitive aspects of depression and anxiety, with seven items for each subscale. Each item is graded 0 to 3, indicating symptom intensity or frequency. The total score ranges from 0-42, and 0-21 for each subscale. The higher the score, the more severe the symptoms; 0-7 indicates the absence of significant symptoms; mild symptoms between 8-10; 11-15 and 16-21 for moderate and severe symptoms, respectively.

Although quality of life is affected both in HD and in PD, studies indicate that there are differences between them.[12-14] HD patients have higher rates of depression compared to patients on PD, because the patient has to stay continuously connected to the machine during hemodialysis, restricting their daily activities and independence. In addition, suicide rates are higher among hemodialysis patients. PD patients have more autonomy, flexibility and control with fewer restrictions in their diet and social lives, which contributes to a better quality of life.

There are few studies comparing the prevalence of mood disorders among patients on HD and PD, associated to the comorbidities presented by them. The aim of this study is to compare the prevalence of anxiety and depression in two distinct groups: patients submitted to HD and PD, taking into account the presence of *diabetes mellitus*, CKD cause, dialysis time, prior transplant or not, registration into the transplantation queue, amaurosis, prior amputations and the use of beta-blockers and antidepressants.

Methods

This study was observational cross-sectional, held at the Renal Replacement Therapy unit of the Santa Casa de Misericordia hospital in Ponta Grossa, PR - Brazil, with all patients with CKD undergoing treatment at the time of the study. The project was approved by the Research Ethics Committee (COEP) from the State University of Ponta Grossa (UEPG) under number 05107812.5.0000.0105 and the Research Evaluation Committee (COAP) from the Santa Casa de Misericordia hospital of Ponta Grossa.

155 patients were interviewed, 128 in the group of patients on hemodialysis and 27 on the peritoneal dialysis group. The researchers interviewed patients after signing the Consent Form, using the Beck Depression and Anxiety Inventory and the Hospital Scale of Anxiety and Depression. The questionnaires were used with all patients orally. Exclusion criteria were: known psychiatric disorders except for depression and anxiety, and refusal to participate.

Statistical analysis was carried out by comparing the mean scores between patients on hemodialysis and peritoneal dialysis using the Student's *t*-test, because all distributions were normal, and the chi-square test. Furthermore, multiple regressions were performed with each of the scores for anxiety and depression (BDI, BAI, HADS-Depression and HADS-Anxiety) and their correlation with the type of dialysis, age, gender, *diabetes mellitus*, duration of RRT, registration in the transplantation queue, use of antidepressants and beta-blockers. Results with *p*-value less than 0.05 (5%) were considered significant.

Results

155 patients were studied, 128 in the group of patients on HD and 27 on PD. In the HD group, the mean age was 54.96 ± 12.76 years; 70 (54.7%) were men; 37 (28.9%) had *diabetes mellitus*; 8 (6.3%) patients had undergone prior kidney transplantation and 47 (36.7%) were in the queue to receive transplants. No patient had previous amputations and 1 (0.8%) had amaurosis. With respect to medication, 6 (4.8%) patients used antidepressants and 15 (11.8%) were under beta-blockers. The median time to initiation of treatment with HD was 5.02 ± 3.86 years and the most prevalent cause of CKD was hypertension, in 52 (40.6%) patients. Depression of any intensity was found in 29 (22.6%) patients in the BDI and 12 (9.3%) in the HADS. Anxiety of any intensity was found in 33 (25.7%) patients in the BAI and 15 (11.7%) in the HADS.

In the PD group, the mean age was 56.48 ± 14.18 years; 12 (44.4%) patients were men, 13 (48.2%) had *diabetes mellitus*, 3 (11.1%) had undergone prior kidney transplantation and 8 (29.6%) were in the transplant queue. No patient had previous amputations or blindness and no patient used antidepressants or beta-blockers. The median time to treatment onset with peritoneal dialysis was 4.56 ± 2.65 years and the most prevalent cause of CKD was *diabetes mellitus* in 11 (40.7%) patients; followed by hypertension in 10 (37%) patients. Patient characteristics are summarized on Table 1. Depression of any intensity was found in 8 (29.6%) patients according to the BDI and in 4 (14.8%) in the HADS. Anxiety of any intensity was found in 3 (11.1%) patients in the BAI and none when the HADS was used. The prevalence of anxiety and depression is summarized on Table 2, and the mean scores of the questionnaires are summarized on Table 3.

The data that showed statistical significance with anxiety, in both questionnaires, were its negative correlation with age and, with the BAI it was the positive correlation with the use of antidepressants. As far as depression is concerned, the presence of *diabetes mellitus* had a positive correlation in both the BDI and the HADS, and the use of beta-blockers had negative correlation with the BDI. Gender, type of dialysis, RRT duration time and enrollment in the kidney transplantation queue showed no statistically significant relationship with anxiety or depression. The correlation coefficients between the risk factors evaluated and the scores of BDI, BAI and HADS are depicted on Table 4.

Discussion

The prevalence of depression in patients with CKD, according to the BDI, was similar to that found in the literature, about 20%-25%.[15-17]

Table 1 Baseline characteristics of the patients assessed

	Hemodialysis n = 128	Peritoneal dialysis n = 27	*p**
Age (mean value in years/standard deviation)	54.96 (12.76)	56.48 (14.18)	0.51
Gender			
Male	70 (54.69%)	12 (44.44%)	
Female	58 (45.31%)	15 (55.56%)	0.44
Diabetes mellitus	37 (28.91%)	13 (48.15%)	0.08
RRT duration (years)	5.02 (3.86)	4.56 (2.65)	0.57
Prior transplant	8 (6.25%)	3 (11.11%)	0.63
Transplant queue	47 (36.72%)	8 (29.63%)	0.63
CKD cause			
High Blood Pressure	52 (40.63%)	10 (37.04%)	
Diabetes mellitus	32 (25%)	11 (40.74%)	
Glomerulonefrites	16 (12.50%)	3 (11.11%)	
Other	28 (21.87%)	3 (11.11%)	0.26
Amputations	0 (0%)	0 (0%)	1
Amaurosis	1 (0.78%)	0 (0%)	0.38
Medications			
Antidepressants	6 (4.76%)	0	0.59
Beta-blockers	15 (11.81%)	0	0.07

* Mean (standard deviation); Student *t*-test; Chi-square test.

Table 2 Depression and anxiety prevalence in patients under hemodialysis and peritoneal dialysis

	Hemodialysis n = 128	Peritoneal dialysis n = 27	*p**
BAI	33 (25.7%)	3 (11.1%)	0.16
HADS-Anxiety	15 (11.7%)	0	0.13
BDI	29 (22.6%)	8 (29.6%)	0.60
HADS-Depression	12 (9.3%)	4 (14.8%)	0.61

* Chi-square test.

Table 3 BAI, BDI and HADS score mean values in patients under hemodialysis and peritoneal dialysis*

	Hemodialysis n = 128	Peritoneal dialysis n = 27	*p***
BAI	11.04 (8.55)	8.66 (5.93)	0.08
HADS-Anxiety	4.24 (4.21)	3.14 (3.44)	0.21
BDI	13.22 (8.58)	13.25 (9.10)	0.98
HADS-Depression	5.25 (4.26)	4.70 (5.22)	0.20

* Mean (PD); Student *t*-test ** Correlation (r) between the: Beck-A and HS-A: 0.71 ($p < 0.0001$) scales; Beck-D and HS-D: 0.75 ($p < 0.0001$) scales.

However, according to the HADS, results showed conflicting data with those in the literature - with lower prevalence of both anxiety and depression. The items evaluated for each questionnaire are distinct, and the BDI assesses a wider variety of symptoms, including symptoms related to physical illness, such as weight loss, insomnia and fatigue. HADS can be used as a screening test, but the diagnosis should be made based on clinical criteria, according to the DSM-IV TR, for the institution of effective treatment and improved quality of life for the patient.[18]

The type of dialysis performed did not influence the prevalence of anxiety and depression in CKD patients, diverging from

Table 4 Correlation coefficient between the risk factors assessed and the BECK and HADS scores

	BDI*		HADS-Depression**		BAI***		HADS-Anxiety****	
	r	*p*	r	*p*	r	*p*	r	*p*
Age	0.02	1	0.10	1	0.19	0.02	0.16	0.03
Male gender	0.01	0.9	0.002	1	0.17	0.10	0.15	0.09
Diabetes mellitus	0.22	0.004	0.19	0.01	0.01	0.29	0.06	0.73
RRT duration	0.05	0.15	0.04	0.2	0.03	0.63	0.10	0.33
Peritoneal dialysis	0.04	0.87	0.01	0.44	0.10	0.26	0.10	0.20
Transplant queue	0.11	0.15	0.11	0.28	0.05	0.80	0.07	1
Beta-blocker use	0.21	0.03	0.12	0.33	0.01	0.62	0.11	0.07
Antidepressant use	0.09	0.18	0.11	0.12	0.28	0.003	0.15	0.23

* $p = 0.01$; $R^2 = 0.12$ ** $p = 0.06$; $R^2 = 0.08$ *** $p = 0.007$; $R^2 = 0.12$ **** $p = 0.03$; $R^2 = 0.10$; multiple regression.

the current literature.[12-14,19] Both according to the mean value and by multiple regression analysis, the difference in prevalence between HD and PD was not significant. Depression levels found were higher in PD patients, while anxiety levels were higher in HD patients, but without statistical significance. Higher levels of anxiety in patients who received HD can be explained because they need to stay connected to the machine for several hours a week, restricting their independence and autonomy. Moreover, they are subjected to the stress of hospital visits every two or three days, transportation to the hospital, having to share time with other patients, restricted diet and inability to make long trips. These factors could contribute to a higher prevalence of depression in these patients, but our study showed no such result.

Patient age was negatively correlated with anxiety scores, suggesting that older patients have a lower prevalence of anxiety. Studies show that the older the patient, the higher the prevalence of somatic symptoms, decreased quality of life, restrictions in social life and higher depression rates.[19,20] Corroborating this study, Bayat *et al.*[21] found no correlation between depression and patient age, as well as gender. However, Theofilou[19] showed that women have poorer mental health, with a higher prevalence of somatic symptoms and social dysfunction relative to men among HD patients, and higher rates of anxiety among PD patients. Their study suggests that men and women may differ in specific aspects of the questionnaires, such as suicidal ideal for instance, which could explain the difference between the scores found in different types of questionnaires that assess various clinical aspects of the same disease. In our study, patient gender had no significant correlation with the prevalence of anxiety or depression.

Diabetes mellitus was positively correlated with BDI and HADS depression scales. Other studies have found similar results, suggesting that diabetes may be a risk factor for higher depression scores.[15-17] Depression is associated with hyperglycemia and an increased risk for complications from diabetes, which may explain this finding.[22] This relationship is very important, and many patients with CKD suffer from diabetes.

RRT duration had no significant correlation with anxiety or depression. Cukor *et al.*[23] suggest that depression and anxiety run different courses in HD patients. Patients who remained depressed after 16 months of follow-up showed a decrease in quality of life and higher levels of depression. These patients fell into three patterns of disease: some patients had not been diagnosed with depression and had mild symptoms after follow-up; other patients had intermittent symptoms of depression and showed moderate levels in the second stage, and the third group remained with severe symptoms of depression. Anxiety does not follow this pattern, with no significant differences among patients with chronic intermittent anxiety or chronic depression after follow-up. However; the prevalence of anxiety associated with depression was higher after 16

months of follow up. A limitation of our study is to have the patient follow-up to diagnose possible progression or remissions in symptoms of anxiety and depression over time. Ginieri-Coccossis *et al.*[13] found a reduction of mental health, social relationships and quality of life in patients undergoing HD for more than four years, but this relationship was not present in PD patients.

Interesting findings were related to the medication studied. Beta-blocker use was negatively correlated with the BDI, suggesting that it would have a protective effect against depression. Beta-blockers, especially the fat-soluble ones, have been associated with depression since the late 60's.[24] Lipid solubility determines the degree of beta-blocker penetration on the blood-brain barrier, leading to possible side effects on the central nervous system such as depression, lethargy, nightmares and confusion. Propranolol is very soluble, whereas metoprolol has moderate lipid solubility. Water-soluble drugs, such as atenolol, have a longer half-life and cause fewer CNS side effects.[25] Furthermore, pindolol has been used as an antidepressant enhancer with primary action on serotonergic receptors, but the studies are inconclusive.[26] A limitation of our study was the non-selection of the type of beta-blocker used, making it impossible to have a more thorough analysis on which specific drug could have a protective effect on depression.

The use of antidepressants was positively correlated with the BAI, suggesting that patients who use antidepressants have a higher prevalence of anxiety, or that its use can increase anxiety. Anxiety disorders are responsive to various types of antidepressants, especially selective serotonin reuptake inhibitors and reuptake inhibitors of serotonin and norepinephrine, including being recommended their continued long-term use in patients who responded to medical therapy in an acute fashion.[27] However, even with first-line drugs, only one third of patients have remission of their anxiety.[28,29] The present study did not assess the type of antidepressant used, use onset and whether the patient had therapeutic response, which may contribute to the result that patients who use antidepressants have shown a higher prevalence of anxiety.

In addition to the aforementioned limitations, we can also add the small number of patients responding to the questionnaires, because the study was performed in a RRT unit only, with a limited number of patients. More studies are needed to correlate the probable risk factors for the development of anxiety and depression in patients with CKD under different forms of RRT.

Conclusion

Depression and anxiety disorders are highly prevalent mood disorders among patients undergoing RRT, so they should be properly diagnosed and treated, to improve the quality of life of patients with CKD. We found no statistically significant difference between the dialysis modalities performed (HD or SD). Age, *diabetes mellitus* and the use of antidepressants or beta-blockers appear to influence the prevalence of anxiety and depression.

References

1. Bastos MG, Bregman R, Kirsztajn GM. Doença Renal Crônica: Frequente e Grave, mas também prevenível e tratável. Rev Assoc Med Bras 2010;56:248-53. DOI: http://dx.doi.org/10.1590/S0104-42302010000200028
2. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Santos DR. Relatório do censo brasileiro de diálise de 2010. J Bras Nefrol 2011;33:442-47. DOI: http://dx.doi.org/10.1590/S0101-28002011000400009
3. Muñoz SR, Oto RA, Barrio AR, Fernández M. Evolución de la calidad de vida en pacientes en hemodiálisis: estudio prospectivo a un año. Rev Soc Esp Enferm Nefrol 2006;9:55-8.
4. Barros BP, Nishiura JL, Heiberg IP, Kirsztajn GM. Ansiedade, depressão e qualidade de vida em pacientes com glomerulonefrite familiar ou doença renal policística autossômica dominante. J Bras Nefrol 2011;33:120-8. DOI: http://dx.doi.org/10.1590/S0101-28002011000200002
5. Pallant JF, Bailey CM. Assessment of the structure of the Hospital Anxiety and Depression Scale in musculoskeletal patients. Health Qual Life Outcomes 2005;3:82. DOI: http://dx.doi.org/10.1186/1477-7525-3-82
6. Loosman WL, Siegert CE, Korzec A, Honig A. Validity of the Hospital Anxiety and Depression Scale and the Beck Depression Inventory for use in end-stage renal disease patients. Br J Clin Psychol 2010;49:507-16. DOI: http://dx.doi.org/10.1348/014466509X477827
7. Beck AT, Steer RA, Brown GK. Beck depression inventory: second edition manual. San Antonio: The Psychological Corporation; 1996.
8. Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). Arthritis Care Res (Hoboken) 2011;63:S454-66. DOI: http://dx.doi.org/10.1002/acr.20556
9. Beck AT, Steer RA. Manual for the Beck Anxiety Inventory. San Antonio: The Psychological Corporation;1990.

10. Muntingh AD, van der Feltz-Cornelis CM, van Marwijk HW, Spinhoven P, Penninx BW, van Balkom AJ. Is the Beck Anxiety Inventory a good tool to assess the severity of anxiety? A primary care study in the Netherlands Study of Depression and Anxiety (NESDA). BMC Fam Pract 2011;12:66. DOI: http://dx.doi.org/10.1186/1471-2296-12-66
11. Marcolino JAM, Mathias LAST, Piccinini-Filho L, Guaratini AA, Suzuki FM, Alli LAC. Escala hospitalar de ansiedade e depressão: estudo de validade de critério e da confiabilidade com pacientes no pré-operatório. Rev Bras Anestesiol 2007;57:52-62. DOI: http://dx.doi.org/10.1590/S0034-70942007000100006
12. Wu AW, Fink NE, Marsh-Manzi JV, Meyer KB, Finkelstein FO, Chapman MM, et al. Changes in quality of life during hemodialysis and peritoneal dialysis treatment: generic and disease specific measures. J Am Soc Nephrol 2004;15:743-53. DOI: http://dx.doi.org/10.1097/01.ASN.0000113315.81448.CA
13. Ginieri-Coccossis M, Theofilou P, Synodinou C, Tomaras V, Soldatos C. Quality of life, mental health and health beliefs in haemodialysis and peritoneal dialysis patients: investigating differences in early and later years of current treatment. BMC Nephrol 2008;9:14. DOI: http://dx.doi.org/10.1186/1471-2369-9-14
14. Varela L, Vàzquez MI, Bolaños L, Alonso R. Predictores psicológicos de la calidad de vida relacionada con la salud en pacientes en tratamiento de diálisis peritoneal. Nefrología (Madr.) 2011;31:97-106.
15. Finkelstein FO, Wuerth D, Finkelstein SH. An approach to addressing depression in patients with chronic kidney disease. Blood Purif 2010;29:121-4. DOI: http://dx.doi.org/10.1159/000245637
16. Hedayati SS, Yalamanchili V, Finkelstein FO. A practical approach to the treatment of depression in patients with chronic kidney disease and end-stage renal disease. Kidney Int 2012;81:247-55. PMID: 22012131 DOI: http://dx.doi.org/10.1038/ki.2011.358
17. Hedayati SS, Minhajuddin AT, Toto RD, Morris DW, Rush AJ. Prevalence of major depressive episode in CKD. Am J Kidney Dis 2009;54:424-32. PMID: 19493599 DOI: http://dx.doi.org/10.1053/j.ajkd.2009.03.017
18. Cukor D, Coplan J, Brown C, Friedman S, Newville H, Safier M, et al. Anxiety disorders in adults treated by hemodialysis: a single-center study. Am J Kidney Dis 2008;52:128-36. PMID: 18440682 DOI: http://dx.doi.org/10.1053/j.ajkd.2008.02.300
19. Theofilou P. Depression and anxiety in patients with chronic renal failure: the effect of sociodemographic characteristics. Int J Nephrol 2011;2011:514070. PMID: 21716702
20. Bossola M, Ciciarelli C, Di Stasio E, Conte GL, Vulpio C, Luciani G, et al. Correlates of symptoms of depression and anxiety in chronic hemodialysis patients. Gen Hosp Psychiatry 2010;32:125-31. DOI: http://dx.doi.org/10.1016/j.genhosppsych.2009.10.009
21. Bayat N, Alishiri GH, Salimzadeh A, Izadi M, Saleh DK, Lankarani MM, et al. Symptoms of anxiety and depression: A comparison among patients with different chronic conditions. J Res Med Sci 2011;16:1441-7.
22. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24:1069-78. DOI: http://dx.doi.org/10.2337/diacare.24.6.1069
23. Cukor D, Coplan J, Brown C, Peterson RA, Kimmel PL. Course of depression and anxiety diagnosis in patients treated with hemodialysis: a 16-month follow-up. Clin J Am Soc Nephrol 2008;3:1752-8. DOI: http://dx.doi.org/10.2215/CJN.01120308
24. Pinho MX, Makdisse MP, de Carvalho MJC, de Carvalho ACC. Betabloqueadores e depressão: há evidências para essa associação? Rev Soc Cardiol Estado de São Paulo 2003;13:27-35.
25. Bortolotto LA, Consolim-Colombo FM. Betabloqueadores adrenérgicos. Rev Bras Hipertens 2009;16:215-20.
26. Santos MA, Hara C, Stumpf BLP, Rocha FL. Depressão resistente a tratamento: uma revisão das estratégias farmacológicas de potencialização de antidepressivos. J Bras Psiquiatr 2006;55:232-42. DOI: http://dx.doi.org/10.1590/S0047-20852006000300010
27. Donovan MR, Glue P, Kolluri S, Emir B. Comparative efficacy of antidepressants in preventing relapse in anxiety disorders - a meta-analysis. J Affect Disord 2010;123:9-16. DOI: http://dx.doi.org/10.1016/j.jad.2009.06.021
28. Huh J, Goebert D, Takeshita J, Lu BY, Kang M. Treatment of generalized anxiety disorder: a comprehensive review of the literature for psychopharmacologic alternatives to newer antidepressants and benzodiazepines. Prim Care Companion CNS Disord 2011;13. DOI: http://dx.doi.org/10.4088/PCC.08r00709
29. Karaiskos D, Pappa D, Tzavellas E, Siarkos K, Katirtzoglou E, Papadimitriou GN, et al. Pregabalin augmentation of antidepressants in older patients with comorbid depression and generalized anxiety disorder-an open-label study. Int J Geriatr Psychiatry 2013;28:100-5. DOI: http://dx.doi.org/10.1002/gps.3800