ARTÍCULO DE REVISIÓN

Gac Méd Caracas 2022;130(1):135-141
DOI: 10.47307/GMC.2022.130.1.15

No depression for my old heart, before and after the event

Sin depresión para mi viejo corazón, antes y después del evento

Michele de Lima[1], Luis Fernando Escobar Guzman[2], Cristian Andres Escobar Guzman[3], José Ramon Lanz-Luces[4], José Daniel Lanz-Souquett[5]

SUMMARY

Background*: Depression and cardiovascular diseases (CVD) are highly prevalent in the elderly. Depression could be a CVD risk factor as well as an ailment sequela.* **Objective***: To review diagnostical, pathophysiological, and therapeutic factors involved in depression-cardiovascular diseases.* **Methods***: The research was carried out using the keywords of a 10-years range of published studies in Portuguese, English, and Spanish from Scielo and PubMed databases. Inclusion criteria: In vitro studies, cohort studies, case-control, and clinical trials. Studies out of time range, mean age <60 years, other psychiatric diseases were excluded.* **Results***: Depression and CVD in the elderly are a growing problem. Heterogeneous diagnostic scales is often observed in trials. A multidisciplinary approach is needed for better treatment in this population attached by several comorbidities.* **Conclusion***: Depression is a risk factor for the development of CVD and can determine prognosis in the elderly.*

Keywords*: Depression, cardiovascular disease, elderly, risk factor, prognosis.*

RESUMEN

Antecedentes*: La depresión y las enfermedades cardiovasculares (ECV) son muy prevalentes en los ancianos. La depresión podría ser un factor de riesgo de ECV, así como una secuela.* **Objetivo***: Revisar los factores diagnósticos, fisiopatológicos y terapéuticos involucrados en la relación depresión-ECV.* **Métodos***: La investigación se llevó a cabo utilizando las palabras clave de un rango de 10 años, de estudios publicados en portugués, inglés y español de las bases de datos Scielo y PubMed. Criterios de inclusión: estudios in vitro, estudios de cohortes, casos y controles y ensayos clínicos. Estudios fuera de rango, edad <60 años, o aquellas que evaluaran simultáneamente otras enfermedades psiquiátricas fueron excluidos.* **Resultados***: La depresión y las ECV en los ancianos es un problema creciente. Se observan escalas de*

DOI: https://doi.org/10.47307/GMC.2022.130.1.15

ORCID: 0000-0003-4553-4877[1]
ORCID: 0000-0003-0515-4108[2]
ORCID: 0000-0001-8737-0319[3]
ORCID: 0000-0003-2252-2435[4]
ORCID: 0000-0001-8232-0339[5]

[1]Nurse specialized in psychiatry and mental health. Universidade Nove de Julho (UNINOVE)- Rua Vergueiro, 235/249 – Liberdade, 01525-000 São Paulo, SP- Brasil.

[2]PhD in cardiology. Hospital Beneficência Portuguesa de São Paulo (BP) - Rua Maestro Cardim, N⁰ 769, Bela Vista. 01323-001 - São Paulo - SP, Brasil

[3]Physician. Universidade de São Paulo (USP). Av. Dr. Arnaldo, 455 - Cerqueira César 01246903 –

[4]PhD in cardiology. Hospital Beneficência Portuguesa de São Paulo (BP) - Rua Maestro Cardim, N⁰ 769, Bela Vista. 01323-001 - São Paulo - SP, Brasil

[5]Medical student. Laboratorio Clínico Lanz Av. Edif. Anexo Centro Médico, PB, Local Nº. 4, Las Avenidas, 6201, Maturin - Monagas, Venezuela

Corresponding author: Michele de Lima.
Rua Castro Alves 318, apartamento 64, bairro Aclimação; São Paulo- SP, Brasil.
CEP: 01532000 E-mail: micheli_limalopes@hotmail.com

Recibido: 29 de septiembre 2021
Aceptado: 20 de febrero 2022

diagnóstico heterogéneas en los ensayos clínicos. Es necesario un abordaje multidisciplinario para un mejor tratamiento en esta población con varias comorbilidades. **Conclusión***: La depresión es un factor de riesgo para el desarrollo de ECV y afecta el pronóstico en el anciano.*

Palabras clave: *Depresión, enfermedad cardiovascular, anciano, facto de riesgo, pronóstico.*

INTRODUCTION

Depression is a high-prevalent disorder in the elderly, a phenomenon that has grown from 5 % - 10 % in the early 2000s (1) up to 52.6 %-62.8 %, in recent times, depending on the screening method used (2).

In the elderly, depression diagnosis and treatment are demanding, mainly because of preexisting pathologies. Those maladies can act as aggravating/overlapping factors (3) affecting depression perception depending on the patient's level of education (4). Several scales are diagnostic tools, and the Yesavage-EDG Geriatric Depression Scale is the only one created specifically for the elderly. It consists of thirty questions that avoid the scope of somatic complaints developed in the last week. There is a short version format with 15 questions to simplify and is more suitable for patients with cognitive disorders and has a 60 %-100 % sensitivity and specificity between 64 %-81 % (5). However, most of the literature relating to depression and cardiovascular diseases (CVD) uses the Patient Health Questionary (PHQ-2 and PHQ-9) (6,7). In addition, for clinical assessment and diagnosis in outgoing patients, the Hamilton Rating Scale for depression and the Self-Rating Depression Scale are also used (8). Some others use the Center for Epidemiological Studies Depression Scales (CES-D) (9,10).

Besides depression and with high regularity but under other conditions, CVD are the leading causes of death in women and men. They account for about 20 % of all deaths in individuals over 60 years (11,12).

Furthermore, after an ischemic event (common threshold in CVD), depression in most cases is present and can influence outcomes. A meta-analysis revealed that depression after myocardial infarction (MI) had 1.76-fold increased mortality for all causes, even adjusting for other cardiac risk factors (13). In this scenario, especially in the elderly, recent worldwide data from the PURE study (14), which comprised 21 countries, also showed that patients with CVD and depression had a higher risk of new cardiovascular events. In parallel, the ELSA-Brasil Baseline Data suggested that depressive symptoms (mild to moderated) are associated with coronary atherosclerosis (mostly calcium content), after adjusting age and gender, persisting in older patients (15).

Thereby, this work aims to analyze relevant pathophysiological, clinical, and therapeutic aspects of depression as a risk factor for cardiovascular diseases in the elderly.

MATERIAL AND METHOD

The review was carried out through searching articles indexed in the Scielo and PubMed databases. Studies addressing depression as a risk factor for CVD, infarction, and stroke in the elderly using the keywords, published between 2010 and 2020 in Portuguese, English, and Spanish, were included. We only considered studies with prospective and cross-sectional designs. Publications with a small sample size (less than 100), studies that identified depression from antidepressant treatment, self-reported depression treatment, single-item measures, or studies that mislabeled nonspecific screening indices of probable psychiatric caseness as measures for depression, or those that simultaneously assessed anxiety were excluded. Thus, we worked with 25 scientific articles (Figure 1).

Depression as a predisposing factor for CVD

Individuals who suffer from early depression have higher morbidity and mortality from CVD when compared to those without the disorder, regardless of traditional risk factors (16). Likewise, depression is associated with adverse cardiac outcomes in healthy people and individuals with previous CVD (17).

There is evidence that insomnia and reduced sleep quality play important roles in the etiology

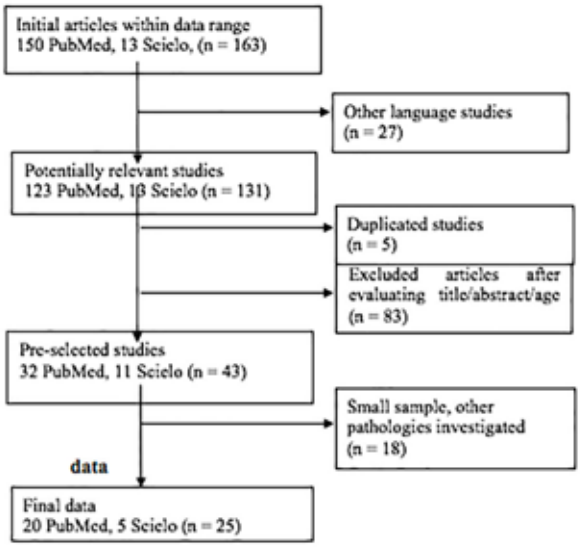

Figure 1. Working flowchart.

of hypertension in middle-aged individuals suffering from depression (18). However, in a large community-based study with 9294 patients over 65 years, depressive individuals had lower blood pressure values than non-depressive ones, independently from medication use and cardiovascular events history, using the CES-D (Center for Epidemiological Scale Depression) (19).

A high prevalence of depression has also been observed in individuals with coronary artery disease (CAD) (20). This condition is also strongly associated with unhealthy behaviors, especially sedentary lifestyle, smoking, excessive alcohol intake, and poor adherence to drug treatment (21).

Behavioral interventions, considered a short-term approach for depression, can include assistance in applying sleep hygiene practices and modifying maladaptive sleep habits (22) and as a result, could influence those unhealthy behaviors CAD-related.

Another fundamental aspect to consider is drugs treatment's influence. As an example, we stressed tricyclic antidepressants. These drugs increase cardiovascular risk because of their cardiotoxic properties even at therapeutic levels (influencing blood pressure, heart rate, and myocardial electrical impulse). For example, nortriptyline, desipramine, and amitriptyline can cause orthostatic hypotension (23), which is a great concern, especially in the elderly. Otherwise, drugs such as beta-blockers, methyldopa, and reserpine (antihypertensive) can exacerbate and even cause depression (24).

Pathophysiology

Depression is also associated with interestingly subtle pathophysiological changes, such as inflammation, altered platelet function, endothelial dysfunction, hypercortisolism, and reduced heart rate variability (HRV) (Figure 2).

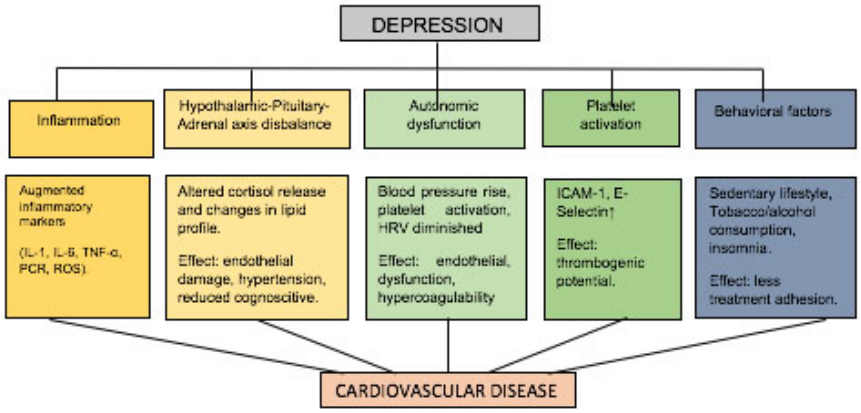

Figure 2. Mechanism proposal for depression leading to cardiovascular disease. IL-1: Interleukin 1, IL-6: Interleukin 6, TNF-α, Tumor necrosis factor alfa, ROS: reactive oxygen species, sICAM-1: soluble intercellular adhesion molecule.

Inflammation

Depressed patients express higher levels of interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), interferon-alpha (IFN-alpha), C-reactive protein (CRP), and its receptors in peripheral blood and cerebrospinal fluid (25). Evidence suggests that reduced dopaminergic function in these individuals may mediate the relationship between the observed inflammation with increasing age, causing neuroinflammation through the recruitment of activated immune cells to the brain.

Once in the central nervous system (CNS), cytokines reduce dopamine transmission, limiting the availability of tetrahydrobiopterin (BH4) and decreasing dopamine synthesis. Slowed cognition and motor functioning may lead to depression by increasing stress, impairing functioning, and ultimately decreasing activity levels and relate to a decrease in dopamine levels (26). There is data showing a direct association between depression and C-reactive protein concentrations in patients who suffered MI, in men (hazard ratio [HR] = 1.96, 95 % confidence interval [CI] = 1.24–3.09, p = 0.004), with little evidence in women (p = 0.85) (27).

Platelet activation and endothelial dysfunction

Platelets play an important role in homeostasis and the development of atherosclerosis, thrombosis, and vascular events through their interaction with subendothelial components and other coagulation factors. Experimentally, depression-like symptoms were observed in mice, and associated with suppression of endothelial dilation, despite the maintenance of NO and COX-2 dependent pathways in the mesenteric arteries (28). Clinically, in The Maastricht Study, endothelial dysfunction biomarkers (sICAM-1, sE-Selectin) were associated with depressive disorder, regardless of other risk factors (29).

In moderate depression, some authors have found increased platelet aggregation and inflammatory markers (TNF-α, IL-6, CRP) in patients with the acute coronary syndrome (ACS) (30). In patients with major depression (PHP-9 scores ≥10), Ormonde do Carmo et al. (31) suggested that there is an alteration in the intra-platelet signaling pathway of L-arginine-NO-cGMP. Plasma levels of platelet factor IV and beta thromboglobulin, markers of platelet activation, are also higher in this pathology (32).

Autonomic regulations alterations

Patients with depression and stable CAD had significantly less HRV than their counterparts (33) as well after a MI (34). In a prospective study, patients with depression had significantly less HRV than non-depressed cardiac patients. From the Heart and Soul Study, with a mean age population above 60 years, Gehi et al. (35) did not find a specific association of depression and HRV in patients with stable heart disease. Nonetheless, de Jonge et al. (36) found a differential association with two symptom dimensions from the patient health questionary (PHQ-9) and HRV in the same population.

Consequently, there is a need to surpass difficulties distinguishing depression from CAD symptoms. Though, while many patients with cardiovascular disease will exhibit mild symptoms difficult to be separate from the grief response of a significant illness, others will experience moderate to severe depression (22).

Hypothalamic-Pituitary-Adrenal axis activation

In depression, failure of counter-regulatory mechanisms generates sustained hyperactivity of the Hypothalamic-Pituitary-Adrenal [HPA] and Sympathetic-Adrenal [SA] systems. In the Dutch Famine Birth Cohort Study, after a five-year follow-up of 725 patients, it was found that the release of cortisol chronically alters the lipids metabolism, leading to metabolic syndrome and perpetuating the pro-inflammatory state, in addition to generating endothelial damage, hypertension, and reduced cognitive ability (37).

Oxidative stress, mitochondria

Oxidative stress occurs when levels of oxidants and reactive oxygen species (ROS) exceed the body's ability to neutralize them, emerging as a possible contributor to aging. There is a decrease in antioxidant levels associated with increased free radicals and levels of the product

of oxidative damage in depressed patients compared to control subjects, negatively affecting the mitochondrial DNA, resulting in mutations that compromise the mitochondrial synthesis of proteins, oxidative capacity, and adenosine triphosphate synthesis (38).

Depression treatment in the elderly

The objective of treating depression in the elderly is to reduce the disease-associated psychological distress, the risk of suicide, improve the patient's general condition, and ensure a better quality of life. Treatment strategies involve psychotherapy, mainly through cognitive-behavioral therapy (CBT), psychopharmacological intervention, and if necessary, electroconvulsive therapy. Initially, it is a must to identify the factors triggering the emergence of depressive events, or even aggravating an existing depression (38).

CBT, preferably with professionals specializing in the elderly, compared with conventional pharmacological treatment, has shown outstanding efficacy in identifying triggering factors and in treating depressed elderly patients (39). To promote behavioral activation in cognitive restructuring and preventing relapses, helps to a stable and lasting change in lifestyle, more compatible with the self-care necessary in chronic diseases management like depression (40).

The psychopharmacological treatment of depression in the elderly depends essentially on the patient's tolerability profile concerning drugs. Selective serotonin reuptake inhibitors are the first choice, especially escitalopram and sertraline. Among the drugs in this category, these two have been the most studied in the elderly population. In general, tricyclic antidepressants are not the first choice for elderly patients due to adverse effects, particularly anticholinergics (41).

When it is necessary to prescribe this class of medication, nortriptyline is recommended, starting with low doses, and cautiously increasing it. It is a need to consider the prescription drugs adverse effects, the risk of drug interactions, and the presence of several diseases that commonly affect the elderly. We do not recommend medications that produce or potentiate anticholinergic effects, postural hypotension, disorders of the cardiac conduction system, and delirium. The association of psychopharmacological treatment with psychotherapy has shown favorable results when the patient is at imminent risk of suicide (42).

Final considerations

Depression is not only a significant and independent risk factor for cardiovascular disease development, but also can be a result of cardiovascular ailment. CBT treatment, in addition to pharmacological, must consider the elderly's unique nutritional characteristics. More research is required to produce adequate actions for improving knowledge about the association, prevention, and control of both pathologies.

REFERENCES

1. Blazer DG. Depression in late life: Review and commentary. J Gerontol Biol Sci Med Sci. 2003;58(3):M249-265.
2. Matias AG, Fonsêca Mde A, Gomes Mde L, Matos MA. Indicators of depression in elderly and different screening methods. Einstein (Sao Paulo). 2016;14(1):6-11.
3. Mitchell PB, Harvey SB. Depression, and the older medical patient - when and how to intervene. Maturitas. 2014;79(2):153-159.
4. Gonzalez ACT, Ignácio ZM, Jornada LK, Réus GZ, Abelaira HM, dos Santos MAB, et al. Depressive disorders and comorbidities among the elderly: A population-based study. Rev Bras Geriatr Gerontol. 2016;19(1):95-103.
5. Brown EL, Raue P, Halpert KD, Adams S, Titler MG. Detection of depression in older adults with dementia. J Gerontol Nurs. 2009;35(2):11-15.
6. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-613.
7. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care. 2003;41(11):1284-1292.
8. Tarolla E, Biondi M, Fabi E, Ga'viano I, Gigantesco A, Tarsitani L, et al. Measuring depression with questions about well-being: A study on psychiatric outpatients. Riv Psichiatr. 2012;47(4):304-308.
9. Hertzog C, Van Alstine J, Usala PD, Hultsch

DF, Dixon RA. Measuremen properties of the Center for Epidemiological Studies Depression Scale (CES-D) in older populations. Psychol Assessment. 1990;2:64-72.

10. Beekman AT, Deeg DJ, van Tilburg T, Smit JH, Hooijer C, van Tilburg W. Major and minor depression in later life: A study of prevalence and risk factors. J Affect Disord. 1995; 36:65-75.
11. Mansur AP, Favarato D. Mortalidade por doenças cardiovasculares no Brasil e na região metropolitana de São Paulo: Atualização 2011. Arq Bras Cardiol. 2012;99(2):755-761.
12. Mansur AP, Favarato D. Tendências da Taxa de Mortalidade por Doenças Cardiovasculares no Brasil, 1980-2012. Arq Bras Cardiol. 2016;107(1):20-25.
13. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med. 2004;66(6):802-813.
14. Rajan S, McKee M, Rangarajan S, Bangdiwala S, Rosengren A, Gupta R, et al; Prospective Urban Rural Epidemiology (PURE) Study Investigators. Association of symptoms of depression with cardiovascular disease and mortality in low-, Middle-, and High-Income Countries. JAMA Psychiatry. 2020;77(10):1052-1063.
15. Santos IS, Bitencourt MS, Rocco PT, Pereira AC, Brunoni AR, Goultard AC, et al. Relation of Anxiety and Depressive Symptoms to Coronary Artery Calcium. ELSA-Brasil Baseline Data. Am J Cardiol. 2016;149(16):570-577.
16. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression, and cardiovascular disease: A clinical review. Eur Heart J. 2012;35(21):1365-1372.
17. Quintella RR. Questões acerca do diagnóstico da depressão e sua relação com o campo medico e científico. Psicologia Argumento. 2010;28(60):83-95.
18. Quintana JF. A relação entre hipertensão com outros fatores de risco para doenças cardiovasculares e tratamento pela psicoterapia cognitivo comportamental. Rev SBPH. 2011;14(1):03-17.
19. Lenoir H, Lacombe JM, Dufouil C, Ducimetière P, Hanon O, Ritchie K, et al. J Hypertens. Relationship between blood pressure and depression in the elderly. The Three-City Study. 2008;26(9):1765-1772.
20. Serrano CV, Setani KT, Sakamoto E, Andrei AM, Fraguas R. Association between depression and development coronary artery disease: pathophysiologic and diagnostic implications. Vasc Health Risk Manag. 2011:7:159-164.
21. Schenker Y, Stewart A, Na B, Whooley M. Depressive symptoms and perceived doctor-patient communication in the heart and soul study. J Gen Inter Med. 2009;24(5):550-556.
22. Doering LV, Chen B, McGuire A, Bodan RC, Irwin MR. Persistent depressive symptoms and pain after cardiac surgery. Psychosom Med. 2014;76(6):437-444.
23. Teply RM, Packard KA, White ND, Hilleman DE, DiNicolantonio JJ. Treatment of Depression in Patients with Concomitant Cardiac Disease. Prog Cardiovasc Dis. 2016;58(5):514-528.
24. Nóbrega OT, Oliveira MGK. A terapia medicamentosa no idoso: cuidados na medicação. Ciênc Saúde Coletiva. 2005;10(2):309-313.
25. Shao M, Lin X, Jiang D, Tian H, Xu Y, Wang L, et al. Depression and cardiovascular disease: Shared molecular mechanisms and clinical implications. Psychiat Res. 2020;21(285):112802.
26. Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological aging and the future of geriatric psychiatry. J Gerontol a Bio Sci. 2017;72(3):343-352.
27. Frasure-Smith N, Lesperance F, Irwin MR, Sauve C, Lesperance J, Theroux P. Depression, C-reactive protein, and two-year major adverse cardiac events in men after acute coronary syndromes. Biol Psychiatry. 2007;62(4):302-308.
28. Bouzinova EV, Norregaard R, Boedtkjer DM, Razgovorova IA, Moeller AM, Kudryavtseva O, et al. Association between endothelial dysfunction and depression-like symptoms in chronic mild stress model of depression. Psychosom Med. 2014;76(4):268-276.
29. Van Dooren FE, Schram MT, Schalkwijk CG, Stehouwer CD, Henry RM, Dagnelie PC, et al. Associations of low-grade inflammation and endothelial dysfunction with depression – The Maastricht Study. Brain Behav Immun. 2016;56:390-396.
30. Williams MS, Rogers HL, Wang NY, Ziegelstein RC. Do platelet-derived microparticles play a role in depression, inflammation, and acute coronary syndrome? Psychosomatics. 2014;55(3):252-260.
31. Ormonde do Carmo MB, Mendes-Ribeiro AC, Matsuura C, Pinto VL, Mury WV, Pinto NO, et al. Major depression induces oxidative stress and platelet hyperaggregability. J Psychiatr Res. 2015;61;19-24.
32. Laghrissi-Thode F, Wagner WR, Pollock BG, Johnson PC, Finkel MS. Elevated platelet factor 4 and beta-thromboglobulin plasma levels in depressed patients with ischemic heart disease. Biol Psychiatry. 1997;42(4):290-295.
33. Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, et al. Depression, heart rate variability, and acute myocardial infarction. Circulation. 2001;104(17):2024-2028.
34. Carney RM, Blumenthal JA, Freedland KE, Stein PK, Howells WB, Berkman LF, et al. Low heart rate variability and the effect of depression on post-

myocardial infarction mortality. Arch Intern Med. 2005;165(13):1486-1491.

35. Gehi A, Mangano D, Pipkin S, Browner WS, Whooley MA. Depression and heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. Arch Gen Psychi. 2005;62(6):661-666.
36. de Jonge P, Mangano D, Whooley MA. Differential association of cognitive and somatic depressive symptoms with heart rate variability in patients with stable coronary heart disease: Findings from the Heart and Soul Study. Psychosom Med. 2007;69(8):735-739.
37. de Rooij SR. Blunted cardiovascular and cortisol reactivity to acute psychological stress: a summary of results from the Dutch Famine Birth Cohort Study. Int J Psychophysiol. 2013;90(1):21-27.
38. Liu T, Zhong S, Liao X, Chen J, He T, Lai S, et al. A meta-analysis of oxidative stress markers in depression. PLoS One. 2015;10(10):e0138904.
39. Beutler LE, Scogin F, Kirkish P, Schretlen D, Corbishley A, Hamblin D, et al. Group cognitive therapy and alprazolam in the treatment of depression in older adults. J Consult and Clin Psychol. 1987;55(4):550-556.
40. Powell VB, Abreu N, Oliveira IR, Sudak D. Cognitive-behavioral therapy for depression. Braz J Psiquiatriy. 2008;30(2):S73-80.
41. Mottram PG, Wilson K, Strobl JJ. Antidepressants for depressed elderly. Cochrane Database of Syst Rev. 2006;25(1);CD003491.
42. Scalco MZ. Depression treatment of elderly patients using tricyclics, MAOI, SSRI, and other antidepressants. Braz J Psychiatry. 2002;24(1):55-63.