MedMax Publishers

Journal of Psychiatry Research Review Article

Selective Serotonin Recaptation Inhibitors and COVID-19. Beware of "not see the Forest for the Trees"

Jose Luis Turabian

Specialist in Family and Community Medicine, Health Center Santa Maria de Benquerencia. Regional Health Service of Castilla la Mancha (SESCAM), Toledo, Spain

***Corresponding author**

Corresponding author: Jose Luis Turabian, Specialist in Family and Community Medicine, Health Center Santa Maria de Benquerencia Toledo, Spain. E-mail: jturabianf@hotmail.com.

Received: 29 October 2020; **Published**: 10 December 2020

Abstract

Selective serotonin recaptation inhibitors (SSRIs) have antiviral activity, especially modulating viral effects through their interaction with the Sigma-1 receptor, which is why they have been proposed as potential drugs in the treatment of COVID-19. In addition, they are drugs widely used at the community level. COVID-19 can present symptoms of anxiety and depression. Isolation measures for patients and contacts, as well as lockout measures in communities to limit the spread of infections, and limitations of social contacts in general, are sources of anxiety and depression that can present a significant frequency in the community. In this scenario, it is suggested to take advantage of the opportunity to carry out retrospective case – control studies and prospective clinical trials (in the presence of authorized medical conditions -anxiety and depression) designed to answer specific questions about biomedical results of repurposing SSRIs in early stages of COVID -19 in general medicine. But one should not lose sight of the very important limitations and risks of the use of these drugs, which limit these studies, such as the difficulties of diagnosis, the stigma of diagnosis, the uncertainty of their usefulness in mild situations, the pharmacological risks of treatment -adverse reactions and pharmacological interactions-, the difficulty of discontinuation, and the medicalization of society.

Keywords: SSRIs, Depression, Cytokines, COVID-19, SARS-CoV-2, Inflammation

Introduction

Since December 2019 the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identified as the cause of the 2019 coronavirus disease (COVID-19), has spread throughout the world. To date, in the treatment of seriously ill patients, remdesivir (with some doubts) and dexamethasone remain the only pharmacological option that has been shown to have a positive effect on the course of the disease [1-3]. But current treatment recommendations are described according to the severity of the disease. Thus, for COVID-19 patients who are not hospitalized or who are hospitalized but not receiving supplemental oxygen, no particular antiviral or immunomodulatory treatment is recommended, and it is not recommend the use of dexamethasone; for patients hospitalized on oxygen (but without the need for a high-flow device or mechanical ventilation), remdesivir alone or with dexamethasone is recommended [4, 5].

In short, these only two drugs are not applicable to mild or moderate patients at the level of general medicine, whose treatment could prevent their evolution to more severe situations. Consequently, other substances that are ideally effective in initially milder phases of COVID-19 are urgently being sought. However, the problem is that new drugs must go through several stages of clinical trials before being approved for use in patients, which is a time-consuming process. Because time is short, another approach can be chosen: repurposing drugs. In this sense, known drugs have been mapped against all the possible mechanisms in which SARS-CoV-2 operates to cause complications, and an extensive list of existing drugs that could play a role has been reported as potentially useful for the treatment of COVID-19 [6-10]. Some of them have already been studied in some depth and many others are under study or clinical trials are being designed to assess whether they are effective SARS-CoV-2 inhibitors [11].

Today, with the focus on vaccines, research on the most promising existing drugs to treat SARS-CoV-2 is being neglected. Therefore, in addition to vaccine studies, we should focus on testing repurposind drugs. These studies can be rapidly implemented for the benefit of millions of people around the world, with the goal of preventing serious disease and death (12). On the other hand, general practitioners (GPs) have been overlooked in this pandemic, with very few registered studies of primary care COVID-19 treatments, despite the need for early disease research [13].

One set of the drugs that has been reported that can be reused to combat COVID-19 is group of selective serotonin reuptake inhibitors (SSRIs). This group of antidepressant drugs, commonly used in primary care, may be a surprising source of immunomodulation due to binding to the sigma-1 receptor that closes the inflammatory cascade of the endoplasmic reticulum in cells [14]. An important feature of the pathophysiology of COVID-19 is the activation of immune cells, with the consequent massive production and release of inflammatory mediators that can cause impairment of various organ functions. In general,

both stressors and depression are associated with decreased activities of cytotoxic T cells and natural killer (NK) cells that affect processes such as immune surveillance of tumors, fighting infections [15].

Furthermore, stress and depression are associated with SARS-CoV-2 infection and thus lead to a weakening of the immune response of patients and more severe respiratory symptoms or even death [16]. Thus, Selective serotonin recaptation inhibitors (SSRIs) have a potential antiviral effect, a modulating effect on respiratory symptoms, antioxidant properties and immunoregulatory effects, in addition to their main action as antidepressants; And furthermore, its low cost could add a benefit to COVID-19 patients [16].

In this scenario, this article aims to summarize, conceptualize and reflect on the pros and cons of the possible role of SSRIs as potentially useful drugs for the treatment of COVID-19 of mild severity and at the primary care level.

Methods

For the literature review, a pragmatic approach was used that was based on a non-systematic or opportunistic search for information, considering the bibliographic references of selected articles, reviews of books related to the topic and searches on the Internet based on published studies in English and Spanish on COVID-19 treatment. The comments in this article should be considered as a personal point of view, based on the author's experience and the review cited above.

Discussion

Anxiety / depression in relation to COVID-19 and treatment with antidepressants

COVID-19 can affect people both physically and mentally. Stress, anxiety, and depression are associated with COVID-19 infection and fear of the pandemic. People with COVID-19 may experience a new onset or exacerbation of psychiatric manifestations in response to communication of the diagnosis, the need for forced isolation, the presence of highly distressing medical symptoms, and the potential risk of death. Furthermore, intensive care support and experimental medical treatments with psychiatric side effects may be an additional risk factor for the appearance of psychiatric symptoms [17-19].

The associated stress, anxiety and depression had shown to be responsible for a part in the pathogenesis of COVID-19. Stress is defined as the process by which environmental requirements transform the organism's adaptability, leading to psychological and biological changes. Clinical evidences have proved an association between specific mood disorders, caused by sustained or chronic stress and the immune dysregulation. Immune dysregulation is a consequence of elevation of cortisol, the stress hormone, and reduction of serotonin. This hormonal dysregulation might promote the initiation and progression of the infection. In addition, stressful conditions associated with infection had shown to cause an elevation in the levels of the inflammatory mediator interleukin-6 (IL-6) that causes a decrease in the number and activity of cytotoxic T-cells and NK cells. Moreover, the resulted depression due to prolonged stress was found to be associated with higher levels of serum IL-6 and tumor necrosis factor-alpha (TNF-α) catecholamines, inhibitory T cells and histamine [19-27]. Consequently, for these reasons, people with COVID-19 or with new or decompensated mental disorders during the pandemic, may require treatment with SSRIs.

Role of serotonin

Serotonin (5-hydroxytryptamine, 5-HT) in addition to its classic function as a neurotransmitter regulating mood, behaviors and psychological state (the decrease in its levels is one of the main causes of symptoms similar to those of depression), has immunomodulatory properties, increasing immune function, as well as adaptive and innate immunity, by central and peripheral mechanisms [28-32]. Much research has concluded that elevated serotonin levels play a critical role in immunity against viral and bacterial infections [31, 33, 34]. In general, antidepressants have been found to increase the immune system response by inhibiting pro-inflammatory factors, particularly C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and IL-6 [35].

SSRIs: effects on the immune system

SSRIs are used as antidepressants and anxiolytics by manipulating serotonin within the brain. SSRIs increase serotonin by preventing its reuptake in the presynaptic cell and then increasing the level of serotonin within the synaptic cleft to bind to the postsynaptic receptor. SSRIs have shown an effective role in relieving the symptoms of stress and anxiety, enhancing the role of immunity in coping with infections by inhibiting pro-inflammatory factors, in particular CRP, TNF-α, IL-1β and IL-6. SSRI has been shown to prevent the elevation of cytokine levels that causes depression. Therefore, SSRI can help control the symptoms of COVID-19 patients due to its potent anti-inflammatory activity, to hinder the cytokine release syndrome that is responsible for aggravating the progression of the disease and the consequent increased TNFα. This effect is due to binding to the sigma-1 receptor in immune cells. SSRIs may even have an effective role for lung disease; because of a significant increase in oxygen saturation was observed [35-44]. Many investigations have reported the high therapeutic efficacy of SSRIs by reversing oxidative damage through protective enhancement of antioxidant status after stress-induced decline [42, 45, 46].

Antiviral Effects of SSRIs

SSRIs have antiviral effects through potentiation of certain antivirals, downregulation of HIV receptors and coreceptors, decreased Ebola virus activity, and reduced Coxsackievirus B4 viral replication by using them together with antiviral [47-50].

SSRIs May Be Helpful in Early Stages of COVID-19

The symptoms of COVID-19 have been shown to range from mild or asymptomatic to severe. Most of the infected patients show mild to moderate respiratory problems and recover without vigorous treatment interventions. The severity of COVID-19 is highly dependent on immunity and the release of inflammatory mediators [51]. Critically ill patients show symptoms of mild or severe cytokine storms due to the overactivity of the immune system, being the main cause of death due to pulmonary fibrosis. This cytokine storm releases different inflammatory mediators, mainly IL-6. Cytokines metabolize tryptophan leading to depression due to reduced serotonin production; in this way, a relationship is established between depression and susceptibility to infection, decreasing T cells and the immune system [16, 18, 44]. In these circumstances, scientists believe that this makes SSRIs suitable for early treatment of infected patients who are at increased risk of severe disease.

Fluoxetine

Fluoxetine significantly reduces cytokine release. But, in addition, fluoxetine has been reported to inhibit SARS-CoV-2 already at very low concentrations. However, it appears that it is

not the serotonin reuptake mechanism that is responsible for this effect. This is supported by the fact that other drugs in the SSRI group, such as paroxetine and escitalopram, do not inhibit the replication of SARS-CoV-2. On the other hand, fluoxetine has a specific effect on SARS-CoV-2 viruses, no effect being observed on other viruses such as rabies virus, human respiratory syncytial virus, human herpes virus 8 or herpes simplex virus type 1 [11, 52, 53].

Sertraline

Sertraline is a member of the SSRIs with a favorable therapeutic option for COVID-19 patients, including elderly patients or those with underlying cardiovascular disorders, because it has a broad therapeutic index and minimal anticholinergic activity. Sertraline decrease and regulating anti-inflammatory effects of pro-inflammatory cytokines; Also, it increase the activity of antibiotics against some bacterial strains. In addition, their antiviral efficacy has been reported [54-58].

Fluvoxamine

Fluvoxamine is an antidepressant that can prevent overreactions of the immune system (cytokine storms) by binding to the sigma-1 receptor. In the laboratory, fluvoxamine reduced the damaging effects of the inflammatory response during sepsis and protected mice from lethal septic shock. Current results suggest that fluvoxamine may mitigate the risk of hospitalization and death from COVID-19 [12, 59-62].

The Sigma-1 receptor (Sig-1R)

Sig-1R resides specifically in the endoplasmic reticulum membrane associated with mitochondria. It can interact with ion channels and other receptors. Sig-1R is particularly concentrated in certain regions of the central nervous system. It has been implicated in various phenomena, including cardiovascular function, schizophrenia, clinical depression, addiction to methamphetamine or cocaine, cancer, amnesia, pain, depression, Alzheimer's disease, stroke, neuroprotection of the retina, and HIV infection. Sig-1R is believed to be a pluripotent modulator with multiple resulting functional manifestations in living systems. Sig-1R mediates the signalling of a variety of drugs, and it is suggested that it modulates cytokines. It is believed that Sig-1R could be acting in the release of Ca ++ and in the inhibition of voltage-gated K + channels. Sig-1R plays a role in modulating cathepsin B levels in HIV-1 infected macrophages. Likewise, it mediates the first steps of viral RNA replication; The initial steps of HCV infection have been reported to be regulated by Sig-1R. Presumably, Sig-1R could play a role in the infectivity of SARS-CoV-2 [63-69].

Risks and doubts regarding SSRIs

SSRIs are one of the most important classes of drugs for treating depression and other mental health problems. Antidepressant use is rapidly increasing worldwide, and up to 8% to 10% of adults in the United States take one or more antidepressants; However controversy regarding the efficacy, acceptability, and safety profile of antidepressant medications has gradually increased. These medications are associated with a wide range of safety problems. In people with COVID-19, their use can be particularly challenging. Psychotropic medications can interact with medical treatments for COVID-19, and some of their adverse effects can worsen the course and outcome of the underlying medical condition [70, 71].

One problem is its prescription without a recorded psychiatric diagnosis, which has increased substantially over the past decade [72]. In addition, there are a number of risks, dangers, and obstacles to the use of antidepressants, and to the recognition, diagnosis, and treatment of depression and anxiety disorders at the general medical level. One of the particular risks is the development of Torsades de Pointes, which are often due to additive risk factors including a history of arrhythmia or heart conditions, electrolyte abnormalities and drug interactions (DDI), and QT lengthening that can be aggravated in the simultaneous administration of hydroxychloroquine and azitromicina. The addition of hydroxychloroquine to fluoxetine produces additive effects on potassium channels (pharmacodynamic DDI); Fluoxetine, in turn, is a potent CYP2D6 inhibitor. The use of SSRIs to prevent or treat COVID-19 infections without considering DDIs or the risk of arrhythmias is of concern [73].

Another practical problem is the difficulty of diagnosis, as anxiety / depression is not a dichotomous health problem (yes / no), but rather moves on a continuum [74]. Furthermore, using instruments to obtain a quantitative depression score is not beneficial for GPs. [75]. Even more, psychiatric diagnosis can disempower people rather than help them [76]. There is insufficient understanding of the natural history of anxiety and depression, with difficulty in discontinuing antidepressants, but with an apparently chronic nature of depressive and anxiety disorders [77,78]. The overmedicalization of mild symptoms is also well documented, determined in part by determined by the design and operation of the health system that results in the medicalization of mild distress, while severe mental illness remains untreated [79]).

Likewise, there are doubts about its usefulness; A meta-analyzes of Food and Drug Administration trials suggest that antidepressants are only marginally efficacious compared to placebos and document profound publication bias that inflates their apparent efficacy [80]. Evidence shows that only one in nine people benefit from antidepressants - the remaining eight are unnecessarily at risk of adverse drug effects. Mood disturbances often reflect real life circumstances. Many depressive presentations respond to judicious "watchful waiting." Most cases of depression, even severe or persistent, are successfully treated with psychosocial interventions, which are preferred by patients, beneficial for self-esteem and social functioning [81].

Finally, some preliminary and incomplete data suggests the lack of utility in real practice of the use of psychotropic drugs in COVID-19. In this sense, it has been reported that psychiatric illness is associated with increased medical morbidity and higher mortality in CIVID-19 [82]. Although psychiatric the treatments have not been reported, so data are lacking, it can be assumed that SSRIs are among the most used drugs, and thus, it seems to suggest, by common sense, that their positive effect was little or did not exist.

Conclusions

All drugs that facilitate serotonin transmission can also attenuate the cytokine storm associated with COVID-19. Since SSRIs are widely used (in their authorized indications; and within the framework of difficulties, doubts, risks and barriers that exist for general medicine), it is suggested that retrospective case-control studies be carried out, where the response of different endpoints in patients with COVID-19 exposed and not exposed to SSRIs, be evaluated. These results could be the indication of conducting clinical trials that confirm or reject the hypothesis of its usefulness in the treatment of COVID-19. But, knowing all the details around SSRIs and COVID-19, one could ask: Why not use SSRIs in COVID-19, without previous clinical trials, based on the inevitability of depression associated with the release

cytokines? And in late cases of COVID-19 to prevent depression symptoms associated with the release of cytokines? Why not prescribe SSRIs at the beginning of the disease before the onset of complications? But, watch out for "not see the forest for the trees"! This expression is often used to highlight that you may be unable to get a general understanding of a situation because you are too preoccupied with details. SSRIs as other drugs postulated as potential prophylactic and treatment interventions for COVID-19, based on pharmacological hypotheses and laboratory studies, should not be used in patients with COVID-19 until there are clinical trials that support that use and such drugs have proper authorization. And its use in depression / anxiety associated with COVID-19, has even greater risks and problems, than its use in non-COVID-19 patients with anxiety / depression. It is needed to waiting for evaluations and sees the long-term perspective before making the suggestion for its use.

References

1. NIH (2020) NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19. NIH.
2. Spinner CD, Gottlieb RL, Criner GJ, José Ramón Arribas López MD; Anna Maria Cattelan, MD, et al. (2020) Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 324: 1048-1057.
3. Scudder L (2020) Drug Treatment for COVID-19: A Quick Summary for PCPs. Medscape;
4. NIH (2020) Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. COVID-19 Treatment
5. NIH (2020) What's New in the Guidelines. Last Updated: October 9, 2020. COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/whats-new/
6. Stokowski L (2020) Could These Old Drugs Help Fight COVID and Save Lives? Medscape; Sep 08. https://www.medscape.com/viewarticle/937021?nlid=137264_4663&src=WNL_mdplsnews_200911_mscpedit_fmed&uac=327178AR&spon=34&impID=2559953&faf=1#vp_1
7. Gordon DE, Jang GM, Bouhaddou M, et al. (2020) A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 583: 459-68.
8. Institut Pasteur (2020) Revealing how SARS-CoV-2 hijacks human cells; points to drugs with potential to fight COVID-19 and a drug that aids its infectious growth. https://www.pasteur.fr/en/research-journal/press-documents/revealing-how-sars-cov-2-hijacks-human-cells-points-drugs-potential-fight-covid-19-and-drug-aids-its
9. Brooks M (2020) Six Potential Treatments for COVID-19 Identified. Medscape; Sep 04. https://www.medscape.com/viewarticle/936912?nlid=137238_430&src=WNL_mdplsfeat_200908_mscpedit_fmed&uac=327178AR&spon=34&impID=2555102&faf=1#vp_1
10. Smith E, Davis-Gardner ME, Garcia-Ordonez RD, et al. (2020) High-Throughput Screening for Drugs That Inhibit Papain-Like Protease in SARS-CoV-2. SLAS DISCOVERY: Advancing the Science of Drug Discovery. October. https://journals.sagepub.com/doi/10.1177/2472555220963667
11. Antidepressant inhibits coronavirus. A standard drug for the treatment of depression might also be effective against Covid-19, a new study by Würzburg scientists shows which has been published on a preprint server. Healthcare-in-Europe. Com; 18.06.2020. https://healthcare-in-europe.com/en/news/antidepressant-inhibits-coronavirus.html#
12. PRNewswire (2020) Fluvoxamine Data Unveiled as Promising Early Treatment in Patients with Mild COVID-19. COVID-19 Early Treatment Fund Urging Businesses, Government and Americans to Provide More Funding to Clinical Trials of Repurposed Drugs. COVID-19 Early Treatment Fund; Oct 06. https://www.prnewswire.com/news-releases/fluvoxamine-data-unveiled-as-promising-early-treatment-in-patients-with-mild-covid-19-301146870.html
13. Coombes R (2020) Covid-19: This time it's personal for Gps. BMJ; 371:m3898. https://www.bmj.com/content/371/bmj.m3898?utm_source=etoc&utm_medium=email&utm_campaign=tbmj&utm_content=weekly&utm_term=20201009
14. Shaffer L (2020) 15 drugs being tested to treat COVID-19 and how they would work. Nature Medicine; 15 MAY. doi: 10.1038/d41591-020-00019-9. https://www.nature.com/articles/d41591-020-00019-9
15. Cao X (2020) COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol; 20(5): 269-70. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7143200/
16. Hamed MGM, Hagag RS (2020) The possible immunoregulatory and anti-inflammatory effects of selective serotonin reuptake inhibitors in coronavirus disease patients. Med Hypotheses 144: 110140.
17. Mathers M (2020) Coronavirus outbreak creating extra stress and anxiety for people with mental health problems, warns charity. Independent; 13 March. https://www.independent.co.uk/life-style/health-and-families/coronavirus-stress-mental-health-problems-anxiety-covid-19-a9401061.html.
18. Wang C, Pan R, Wan X, et al. (2020) Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res; 17: 1729.
19. Salleh MR (2008) Life event, stress and illness. MJMS; 15:9.
20. Jones KA, Thomsen C (2013) The role of the innate immune system in psychiatric disorders. Mol Cell Neurosci; 53:52-62.
21. Spiegel D, Giese-Davis J (2003) Depression and cancer: mechanisms and disease progression. World J Biol Psychia; 54: 269-282.
22. Rot M, Mathew SJ, Charney DS (2009) Neurobiological mechanisms in major depressive disorder. CMAJ.1 80:305–13.
23. Godbout JP, Glaser R (2006) Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. J Neuroimmune Pharmacol; 1: 421–427.
24. Reiche EMV, Nunes SOV, Morimoto HK (2004) Stress, depression, the immune system, and cancer. Lancet Oncol; 5: 617-625.
25. Zorrilla EP, Luborsky L, McKay JR, et al. (2001) The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav Immun;15: 199-226.
26. Qin C, Zhou L, Hu Z, et al. (2020) Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis;ciaa 248.
27. Guo YR, Cao QD, Hong ZS, et al. (2020) The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res; 7:11.
28. Costa LHA, Santos BM, Branco LGS (2020) Can selective serotonin reuptake inhibitors have a neuroprotective effect during COVID-19? European Journal of Pharmacology 889: 173629.
29. Kubera M, Maes M, Kenis G, Kim YK, Lason W (2005) Effects of serotonin and serotonergic agonists and antagonists on the production of tumor necrosis factor alpha and interleukin-6. Psychiatry Res; 134:251–8.
30. Wan M, Ding L, Wang D, Han J, Gao P (2020) Serotonin:

A Potent Immune Cell Modulator in Autoimmune Diseases. Front Immunol; 11: 186.
31. Schuff-Werner P, Splettstoesser W (1999) Antioxidative properties of serotonin and the bactericidal function of polymorphonuclear phagocytes. Adv Exp Med Biol; 467: 321-5.
32. Mössner R, Lesch K-PJB (1998) behavior, and immunity. Role of serotonin in the immune system and in neuroimmune interactions. Brain Behav Immun 12: 249-271.
33. Dursun SM, Reveley MA (1995) Serotonin hypothesis of psychiatric disorders during HIV infection. Med Hypotheses 44:263-267.
34. Bliznakov E (1980) Serotonin and its precursors as modulators of the immunological responsiveness in mice. J Med 11: 81-105.
35. Eyre HA, Lavretsky H, Kartika J, Qassim A, Baune BT (2016) Modulatory Effects of Antidepressant Classes on the Innate and Adaptive Immune System in Depression. Pharmacopsychiatry 49: 85–96.
36. Leonard B (1995) SSRI differentiation: pharmacology and pharmacokinetics. Hum Psychopharmacol 3: S149-S158.
37. Wilson D.R., Warise L (2008) Cytokines and their role in depression. Perspect Psychiatr Care 44:285-289.
38. Hannestad J, DellaGioia N, Ortiz N, Pittman B, Bhagwagar ZJB (2011) Citalopram reduces endotoxin-induced fatigue. Brain Behav Immun; 25: 256-259.
39. Sukoff Rizzo SJ, Neal SJ, Hughes ZA, et al. (2012) Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes. Transl Psychiatry; 2(12):e199.
40. Wang L, Wang R, Liu L, Qiao D, Baldwin DS, Hou R (2019) Effects of SSRIs on peripheral inflammatory markers in patients with major depressive disorder: A systematic review and meta-analysis. Brain Behav Immun; 79: 24-38.
41. Roumestan C, Michel A, Bichon F, et al. (2007) Anti-inflammatory properties of desipramine and fluoxetine. Respir Res 8: 35.
42. Perna G, Cogo R, Bellodi L (2004) Selective serotonin re-uptake inhibitors beyond psychiatry: Are they useful in the treatment of severe, chronic, obstructive pulmonary disease? Depress Anxiety 20: 203-204.
43. Sacre S, Medghalchi M, Gregory B, Brennan F, Williams R (2010) Fluoxetine and citalopram exhibit potent antiinflammatory activity in human and murine models of rheumatoid arthritis and inhibit toll-like receptors. Arthritis Rheum 62: 683-93.
44. Hamed MGM (2020) Why is SSRI not used for prevention and treatment in patients with coronavirus? Researchgate. Discussion.
45. Zafir A, Banu N (2007) Antioxidant potential of fluoxetine in comparison to Curcuma longa in restraint-stressed rats. Eur J Pharmacol 572: 23-31.
46. Ahmadimanesh, M., Abbaszadegan, M. R., Morshedi Rad, D., Moallem, S. A., Mohammadpour, A. H., e al. (2019). Effects of selective serotonin reuptake inhibitors on DNA damage in patients with depression. Journal of Psychopharmacology. 33: 1364-1376.
47. Sharma G, Champalal Sharma D, Hwei Fen L, et al. (2013) Reduction of influenza virus-induced lung inflammation and mortality in animals treated with a phosophodisestrase-4 inhibitor and a selective serotonin reuptake inhibitor. Emerg Microbes Infect 2:e54.
48. Greeson JM, Gettes DR, Spitsin S, et al. (2016) The Selective Serotonin Reuptake Inhibitor Citalopram Decreases Human Immunodeficiency Virus Receptor and Coreceptor Expression in Immune Cells. Biol Psychiatry; 80: 33-39.
49. Johansen LM, DeWald LE, Shoemaker CJ, et al. (2015) A screen of approved drugs and molecular probes identifies therapeutics with anti-Ebola virus activity. Sci Transl Med; 7: 290ra89.
50. Alidjinou EK, Sané F, Bertin A, Caloone D, Hober D (2015) Persistent infection of human pancreatic cells with Coxsackievirus B4 is cured by fluoxetine. Antiviral Res 116: 51-54.
51. Ruan Q, Yang K, Wang W, Jiang L, Song J (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan. China. Intensive Care Med 46: 846–868.
52. Zimniak M, Kirschner l, Hilpert H, Seibel J, Bodem J (2020) The serotonin reuptake inhibitor Fluoxetine inhibits SARS-CoV-2. BioRxiv; 2020.06.14.150490. https://doi.org/10.1101/2020.06.14.150490
53. Pharma News (2020) Antidepressant fluoxetine (Prozac) suppresses replication of SARS-CoV-2. ChemDiv;
54. Murdoch D, McTavish D (1992) Sertraline. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depression and obsessive-compulsive disorder. Drugs 44: 604-624.
55. Tynan RJ, Weidenhofer J, Hinwood M, Cairns MJ, Day TA, et al. (2012) A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. Brain Behav Immun; 26: 469-479.
56. Lu Y, Xu X, Jiang T, et al. (2019) Sertraline ameliorates inflammation in CUMS mice and inhibits TNF-α-induced inflammation in microglia cells. Int Immunopharmacol; 67: 119-128.
57. Ayaz M, Subhan F, Ahmed J, et al. (2015) Sertraline enhances the activity of antimicrobial agents against pathogens of clinical relevance. J Biol Res (Thessalon) 22: 4.
58. Kouznetsova J, Sun W, Martínez-Romero C, et al. (2014) Identification of 53 compounds that block Ebola virus-like particle entry via a repurposing screen of approved drugs. Emerg Microbes Infect 3: e84.
59. Clinical Trials (2020) US researchers evaluate antidepressant fluvoxamine for Covid-19. May 13th. https://www.clinicaltrialsarena.com/news/us-fluvoxamine-covid-19-trial/#:~:text=Researchers%20from%20the%20Washington%20University,for%20patients%20with%20Covid%2D19.
60. Keyser Z (2020) Scientists test antidepressants for treatment of COVID-19. Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), is for the treatment of obsessive compulsive disorder and depression, among other disorders. The Jerusalem Post; MAY 13. https://www.jpost.com/international/uva-study-leads-wu-to-test-antidepressants-as-possible-covid-19-treatment-627835
61. Dryden J (2020) Study to evaluate antidepressant as potential COVID-19 treatment. Drug fluvoxamine may help prevent life-threatening 'cytokine storm'. Washington University School of Medicine in St. Louis; April 13. https://medicine.wustl.edu/news/study-to-evaluate-antidepressant-as-potential-covid-19-treatment/
62. Huwiler S (2020) University research sparks clinical trial to test antidepressant that could treat COVID-19. University neuroscientists learn that antidepressant Fluvoxamine may minimize immune system damage from COVID-19. The Cavalier Daily; June 5. https://www.cavalierdaily.com/article/2020/06/university-research-sparks-clinical-trial-to-test-antidepressant-that-could-treat-covid-19]
63. Su TP, Su TC, Nakamura Y, Tsai SY (2016) The Sigma-1 Receptor as a Pluripotent Modulator in Living Systems. Trends Pharmacol Sci 37: 262-278.

64. Su TP, Su TC, Nakamura Y, Tsai SY (2016) The Sigma-1 Receptor as a Pluripotent Modulator in Living Systems. Trends Pharmacol Sci 37: 262-278.
65. Maurice T, Su TP (2009) The pharmacology of sigma-1 receptors. Pharmacol Ther; 124(2):195-206.
66. López OV, Gorantla S, Segarra AC, et al. (2019) Sigma-1 Receptor Antagonist (BD1047) Decreases Cathepsin B Secretion in HIV-Infected Macrophages Exposed to Cocaine. J Neuroimmune Pharmacol 14: 226-240.
67. Friesland M, Mingorance L, Chung J, Chisari FV, Gastaminza P (2013) Sigma-1 receptor regulates early steps of viral RNA replication at the onset of hepatitis C virus infection. J Virol 87: 6377-6390.
68. Zhu LX, Sharma S, Gardner B, et al. (2003) IL-10 Mediates Sigma1 Receptor-Dependent Suppression of Antitumor Immunity. J Immunol; 70: 3585-3591.
69. Yesilkaya UH, Balcioglu YH, Sahin S (2020) Reissuing the sigma receptors for SARS-CoV-2. J Clin Neurosci.
70. Ostuzzi G, Papola D, Gastaldon C, et al. (2020) Safety of psychotropic medications in people with COVID-19: evidence review and practical recommendations.BMC Med; 18(215).
71. Barclay L (2019) Are Safety of Antidepressants Validated? Medscape Education Clinical Briefs.
72. Mojtabai R, Olfson M (2011) Proportion Of Antidepressants Prescribed Without A Psychiatric Diagnosis Is Growing. Health Aff (Millwood) 30.
73. de Leon J, Schoretsanitis G (2020) Rapid Response: Hydroxychloroquine and chloroquine may not be free of important risks in the treatment and prevention of COVID-19 infections. BMJ; 368: m1071.
74. Perez Franco B, Turabian JL (2006) [Is the orthodox approach to depression valid in primary care?].[Article in Spanish]. Aten Primaria; 37: 37-39.
75. Pettersson A, Björkelund C, Petersson E-L (2014) To score or not to score: a qualitative study on GPs views on the use of instruments for depression. Fam Pract 31: 215-221.
76. Callard F, Bracken P, David AS, Sartorius N (2013) Has psychiatric diagnosis labelled rather than enabled patients? BMJ; 347:f4312.
77. van Rijswijk E, van Hout H, van de Lisdonk E, Zitman F, van Weel C (2009) Barriers in recognising, diagnosing and managing depressive and anxiety disorders as experienced by Family Physicians; a focus group study. BMC Fam Pract; 10: 52.
78. Scholten W, Batelaan N, Van Balkom A (2020). Barriers to discontinuing antidepressants in patients with depressive and anxiety disorders: a review of the literature and clinical recommendations. Therapeutic Advances in Psychopharmacology.
79. Doblytė S (2020). Under- or Overtreatment of Mental Distress? Practices, Consequences, and Resistance in the Field of Mental Health Care. Qual Health Res. 531
80. Pigott HE, Leventhal AM, Alter GS, Boren JJ (2010) Efficacy and Effectiveness of Antidepressants: Current Status of Research. Psychoteraphy and Psychosomatics. Psychother Psychosom;79: 267-279
81. Braillon A, Lexchin J, Blumsohn A, Hengartner MP (2019) The "pharmaceuticalisation" of life. BMJ 365: l1972.
82. Li L, Li F, Fortunati F, Krystal JH (2020) Association of a Prior Psychiatric Diagnosis With Mortality Among Hospitalized Patients With Coronavirus Disease 2019 (COVID-19) Infection. JAMA Netw Open 3: e2023282.

Citation: Jose Luis Turabian (2020) ZSelective Serotonin Recaptation Inhibitors and COVID-19. Beware of "not see the Forest for the Trees". *J Psy Res.*