To the Editor

We read the study by Hoertel et al. [1] with great interest. The authors used a Cox’s regression model to evaluate the impact of individuals treated with antidepressants on the outcome following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Of the 7230 patients hospitalized following SARS-CoV-2 infection, 4.8% were treated with antidepressants within the first 48 h of admission. The analysis suggests a 27–57% risk reduction (HR, 0.56; 95% CI, 0.43–0.73, \( p < 0.001 \)) of intubation or COVID-19 related death in antidepressant-treated subjects. Although the study’s retrospective nature does not allow for establishing a causal link that will require a randomized controlled trial, this is an important observational study, which illustrates the possibility that antidepressants might have properties that protect against the action of SARS-CoV-2 virus.

There is growing evidence for substantial neurological and psychiatric morbidity following COVID-19 infection, with the greatest risk in patients who had severe COVID-19 [2]. It is of interest that psychotropic compounds commonly used to treat mental disorders exercise a putative preventive effect against the most catastrophic outcomes related to SARS-CoV-2 infection. In complementarity with Hoertel’s explanation, we carried out a literature search of PubMed, Google Scholar, and Scopus by using the name of each drug commonly used in mental health or the class of psychotropic drugs as keywords combined with ‘antiviral’ or ‘SARS’ or ‘COVID-19’. The aim was to identify psychotropic compounds, the level of supporting preclinical or clinical evidence for anti SARS-CoV-2 action, and the putative mechanisms of action. Table 1 reports the emerging evidence for different psychotropics for their anti-SARS CoV-2 action. While the current evidence supports a potential anti SARS-CoV-2 role for several antidepressants including the antipsychotic chlorpromazine, the mood stabilizer lithium, and the anti-dementia drug memantine, the level and strength of evidence remain diverse. The evidence for mood stabilizers, chlorpromazine, and memantine is more speculative at this moment than that for certain antidepressants with substantial clinical, observational, and preclinical data.

The literature reports an in vitro action of antidepressants against the activity of acid sphingomyelinase [3, 4]. There is also recent observational evidence to support the potential usefulness of functional inhibitors of acid sphingomyelinase, including antidepressants and antipsychotics, among patients hospitalized for severe COVID-19 [5]. In addition, a possible mechanism of action of psychotropic drugs is related to virus cell entry via clathrin-mediated endocytosis. Another potential action of psychotropic drugs is modifying the balance between pro and anti-inflammatory cytokines, which could protect against the most deleterious consequences of an indiscriminate immunological response [6]. One of the advantages of psychotropic drugs is the efficient crossing of the blood-brain barrier and the affinity for synaptic receptors, most of which trigger functions that could interact with the immune system at different levels [6]. Tolerance and safety are vital parameters for drug repurposing to treat or prevent infections with SARS COV-2. Psychotropic medications are widely used in clinical practice with well-known safety and tolerability parameters. Antidepressants, compared to antipsychotics or mood stabilizers, have a favorable safety profile [4] and are better tolerated in older individuals.

In conclusion, the realization that psychotropic compounds have potentially significant antiviral properties in the context of SARS-CoV-2 can improve our understanding of these molecules [7], and also offers a new opportunity for repurposing their role in our pharmacological armamentarium if antiviral characteristics are better characterized in controlled studies. It is premature to launch a meta-analysis or a systematic review because of the number and...
| Psychotropic agent and number of published articles | Type of study and references | Antiviral mechanism of action |
|--------------------------------------------------|------------------------------|------------------------------|
| **Antidepressants (14 articles):**                | Randomized controlled clinical trial: | - Fluvoxamine: Sigma-1 receptor (S1R) agonist. The S1R is an endoplasmic reticulum chaperone protein with various cellular functions, including regulation of cytokine production through its interaction with the endoplasmic reticulum stress sensor inositol requiring enzyme 1α (IRE1α) (Lenze et al., 2020; Seftel et al., 2021). |
| Randomized controlled clinical trials: 1         | 1- Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients with Symptomatic COVID-19: A Randomized Clinical Trial. JAMA. 2020;324:2292–2300. (N= 80 receiving fluvoxamine). | |
| Non-randomized or Non-controlled clinical trials: 1 | Non-randomized clinical trial: 1- Seftel D, Boulware DR. Prospective Cohort of Fluvoxamine for Early Treatment of Coronavirus Disease 19. Open Forum Infect. Dis. 2021;8:ofab050. (N=65 receiving Fluvoxamine) |
| Observational studies: 3                         | Observational study: 1- Hoertel N, Sánchez-Rico M, Vernet R, Beeker N, Jannot A-S, Neuraz A, et al. Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: results from an observational study. Mol Psychiatry. 2021;4:1–14. (N=345 receiving antidepressants) |
| Preclinical studies: 8                          | Preclinical studies: 1- Dyall J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, et al. Repurposing of Clinically Developed Drugs for Treatment of Middle East Respiratory Syndrome Coronavirus Infection. Antimicrob Agents Chemother (Bethesda). 2014;58:4885–4893. |
| Opinions: 1                                      | 2- Shen L, Niu J, Wang C, Huang B, Wang W, Zhu N, et al. High-Throughput Screening and Identification of Potent Broad-Spectrum Inhibitors of Coronaviruses. J Virol. 2019;93 e00023-e00019. |
|                                                  | 3- Günther S, Reineke PYA, Fernández-García Y, Lieske J, Lane TJ, Ginn HM, et al. X-ray screening identifies active site and allosteric inhibitors of SARS-CoV-2 main protease. Science. 2021;abf7945. |
|                                                  | 4- Zimniaik M, Kirschner L, Hilpert H, Geiger N, Danov O, Oberwinkler H, et al. The serotonin reuptake inhibitor Fluoxetine inhibits SARS-CoV-2 in human lung tissue. Sci. Rep. 2021;11:5890. |
|                                                  | 5- Dechaumes A, Nekoua MP, Belouzard S, Sane F, Engelmann I, Dubuisson J, et al. Fluoxetine Can Inhibit SARS-CoV-2 In Vitro. Microorganisms. 2021;9:339. |
|                                                  | 6- Schloer S, Brunotte L, Mecate-Zambrano A, Zheng S, Tang J, Ludwig S, et al. Drug synergy of combinatory treatment with remdesivir and the repurposed drugs fluoxetine and Itraconazole effectively impairs SARS-CoV-2 infection in vitro. Br J Pharmacol. 2021;178:2339–2350. |
|                                                  | 7- Schloer S, Brunotte L, Goretzko J, Mecate-Zambrano A, Korthals N, Gerke V, et al. Targeting the endolysosomal host-SARS-CoV-2 interface by clinically licensed functional inhibitors of acid sphingomyelinase (FIASMA) including the antidepressant fluoxetine. Emerg Microbes Infect. 2020;9:2245–2255. |
|                                                  | 8- Carpinteiro A, Edwards MJ, Hoffmann M, Kochs G, Gripp B, Weigang S, et al. Pharmacological Inhibition of Acid Sphingomyelinase Prevents Uptake of SARS-CoV-2 by Epithelial Cells. Cell Rep Med. 2020;1:100142 |
### Table 1 continued

| Psychotropic agent and number of published articles | Type of study and references | Antiviral mechanism of action |
|----------------------------------------------------|-----------------------------|------------------------------|
| **Opinion:** | 1- Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV. Fluvoxamine: A Review of Its Mechanism of Action and Its Role in COVID-19. Front Pharmacol. 2021;12:652688. | -Inhibitor of viral Ribonucleic acid (RNA) polymerase, probably related to blockade of co-factor phosphorylation through inhibition of Glycogen synthase kinase-3β (GSK-3β) (Santos et al., 2021; Bou Khalil, 2020; Nowak & Walkowiak, 2020; Rajkumar, 2020). |
| **Mood stabilizer: Lithium (11 articles):** | 2- Suwanwongse K, Shabarek N. Lithium Toxicity in Two Coronavirus Disease 2019 (COVID-19) Patients. Cureus. 2020;12:e3834. (N=2 receiving lithium) | -Inhibition of nuclear factor kappa light-chain-enhancer of activated B cells (NF-κB) (Rajkumar, 2020). |
| Randomized controlled clinical trials: 0 | **Preclinical study:** | 1- Nielsen RE, Rybakowski J, Sani G, et al. Lithium Chloride Combination with Rapamycin for the Treatment of COVID-19 Pneumonia. Med Hypotheses. 2020;142:109822. | -Reduction in cyclooxygenase-2 expression (Murru et al., 2020; Rajkumar, 2020; Spuch et al., 2020). |
| Non-randomized or Non-controlled clinical trials: 0 | Observational studies: | 1- Ly K, Thibault J, Roberge D, et al. Lithium reduces the concentration of the anti-inflammatory cytokine IL-10 in mice, increases the concentration of the anti-inflammatory cytokine IL-10 and decreases that of pro-inflammatory cytokines IL-6 and tumor necrosis factor alpha (TNF-α) after administration of endotoxin (Nobile et al., 2020). | -Dopamine antagonism enhances blood prolactin levels. Prolactin plays a significant role in adaptive immunity, both humoral (mediated primarily by B cells and helper T cells) and cellular (mediated primarily by T lymphocytes), through endocrine, paracrine, and autocrine mechanisms. Prolactin exhibits immunosuppressive response in relatively higher doses under certain conditions (Sen, 2020). |
| Observational studies: 2 | Preclinical studies: | 1- Chen CZ, Shinn P, Itkin Z, Eastman RT, Bostwick R, Rasmussen L, et al. Drug Repurposing Screen for Compounds Inhibiting the Cytopathic Effect of SARS-CoV-2. Front Pharmacol. 2021;11:592737. | -Antiviral activity of the phenothiazines might be the inhibition of the SARS-CoV main protease (Chen et al., 2021). |
| Preclinical studies: 1 | | 1- Wang Y, Wang Z, et al. Effect of Lithium on Prolactin Levels. Drug Discov Today. 2020;18:535 (N=6 receiving lithium) | -Protection of host cells from apoptosis triggered by viral infection (Rajkumar, 2020). |
| Opinions: 12 | | 1- Hong Y, Liu J, et al. Lithium Chloride Treatment for COVID-19 Pneumonia: A Non-Randomized Clinical Trial. J Med Virol. 2020;92:e9228. (N=6 receiving lithium) | |
| **Antipsychotic: Chlorpromazine (Phenothiazine) (16 articles):** | 2- Villouteix BO, Beaune PH, Tamouza R, Krishnamoorthy R, Leboyer M. Prevention of COVID-19 by drug repurposing: rationale from drugs prescribed for mental disorders. Drug Discov Today. 2020;16:10035–10040. | |
| Randomized controlled clinical trials: 0 | Preclinical studies: | 1- Wang Y, Wang Z, et al. Effect of Lithium on Prolactin Levels. Drug Discov Today. 2020;18:535 (N=6 receiving lithium) | |
| Non-randomized or Non-controlled clinical trials: 0 | Observational studies: | 1- Ly K, Thibault J, Roberge D, et al. Lithium reduces the concentration of the anti-inflammatory cytokine IL-10 in mice, increases the concentration of the anti-inflammatory cytokine IL-10 and decreases that of pro-inflammatory cytokines IL-6 and tumor necrosis factor alpha (TNF-α) after administration of endotoxin (Nobile et al., 2020). | |
| Observational studies: 1 | Preclinical studies: | 1- Chen CZ, Shinn P, Itkin Z, Eastman RT, Bostwick R, Rasmussen L, et al. Drug Repurposing Screen for Compounds Inhibiting the Cytopathic Effect of SARS-CoV-2. Front Pharmacol. 2021;11:592737. | |
| Preclinical studies: 3 | | 1- Wang Y, Wang Z, et al. Effect of Lithium on Prolactin Levels. Drug Discov Today. 2020;18:535 (N=6 receiving lithium) | |
| Opinions: 12 | | 1- Hong Y, Liu J, et al. Lithium Chloride Treatment for COVID-19 Pneumonia: A Non-Randomized Clinical Trial. J Med Virol. 2020;92:e9228. (N=6 receiving lithium) | |
Table 1 continued

| Psychotropic agent and number of published articles | Type of study and references | Antiviral mechanism of action |
|----------------------------------------------------|-----------------------------|------------------------------|
| and Autophagy Process as a Novel Therapeutic Strategy in COVID-19. Int J Biol Sci. 2020;16:1724–1731. | **Observational study:** | - Antagonism of α7 nicotinic acetylcholine receptors (α7nAChR) and N-methyl-D-aspartate (NMDA) receptors may decrease angiotensin-converting enzyme 2 (ACE2) receptor expression and reduce oxidative stress and inflammation, hence potentially reducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virulence (Hasanagic & Serdarevic, 2020). |
| 2- Nobille B, Durand M, Courtet P, Van de Perre P, Nagot N, Molés JP, et al. Could the antipsychotic chlorpromazine be a potential treatment for SARS-CoV-2? Schizophr Res. 2020;223:373–375. | 1- Rejdak K, Grieb P. Adamantanes might be protective from COVID-19 in patients with neurological diseases: multiple sclerosis, parkinsonism and cognitive impairment. Mult Scler Relat Disord. 2020;42:102163. (N=7 receiving memantine) | - Potent protective effect against lesions induced by 6-hydroxydopamine (6-OHDA) in dopaminergic pheochromocytoma (PC12) cells related to reversing nerve growth factor IB (NGFIB) upregulation. NGFIB activates the nuclear factor-xB (NF-xB) signaling pathway, potentiates the induction of pro-inflammatory gene expression, and enhances mouse resistance to lipopolysaccharide (LPS)-induced sepsis (Brenner-SR, 2020). |
| 3- Sen A. Repurposing prolactin as a promising immunomodulator for the treatment of COVID-19: Are common Anti-antiemetics the wonder drug to fight coronavirus? Med Hypotheses. 2020;144:110208. | 2- Park MH, Kwon DY. A retrospective review of memantine use and COVID-19-associated mortality from a national database [letter]. J Med Virol. 2020. e-pub ahead of print. 14 July 2020; https://doi.org/10.1007/jmv.26266. | - Pharmacological inhibition of ionotropic NMDA glutamate receptors suppresses neurological symptoms of disease and reduces the expression of pro-inflammatory cytokines in the rat brain (Jiménez-Jiménez et al., 2020). |
| 4- Al-Horani RA, Kar S, Aliter KF. Potential Anti-COVID-19 Therapeutics that Block the Early Stage of the Viral Life Cycle: Structures, Mechanisms, and Clinical Trials. Int J Mol Sci. 2020;21:5224. | 3- Brenner SR. The potential of memantine and related adamantanes such as amantadine, to reduce the neurotoxic effects of COVID-19, including ARDS and to reduce viral replication through lysosomal effects [letter]. J Med Virol. 2020;92:2341–2342. | - Antagonism of α7 nicotinic acetylcholine receptors (α7nAChR) and N-methyl-D-aspartate (NMDA) receptors may decrease angiotensin-converting enzyme 2 (ACE2) receptor expression and reduce oxidative stress and inflammation, hence potentially reducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virulence (Hasanagic & Serdarevic, 2020). |
| 5- Chugh H, Awasthi A, Agarwal Y, Gaur RK, Dhawan G, Chandra R. A comprehensive review on potential therapeutics interventions for COVID-19. Eur J Pharmacol. 2021;890:173741. | 4- Cimolai N. Potentially repurposing adamantanes for COVID-19 pandemic and the Potential Role of Phenothiazines: A Call for Research Studies [letter]. J Clin Psychopharmacol. 2020;40:641–642. | - Potent protective effect against lesions induced by 6-hydroxydopamine (6-OHDA) in dopaminergic pheochromocytoma (PC12) cells related to reversing nerve growth factor IB (NGFIB) upregulation. NGFIB activates the nuclear factor-xB (NF-xB) signaling pathway, potentiates the induction of pro-inflammatory gene expression, and enhances mouse resistance to lipopolysaccharide (LPS)-induced sepsis (Brenner-SR, 2020). |
| 6- Stip E, Rizvi TA, Mustafa F, Javaid S, Aburuz S, Ahmed NN, et al. The Large Action of Chlorpromazine: Translational and Transdisciplinary Considerations in the Face of COVID19. Front Pharmacol. 2020;11:577678. | 5- Chugh H, Awasthi A, Agarwal Y, Gaur RK, Dhawan G, Chandra R. A comprehensive review on potential therapeutics interventions for COVID-19. Eur J Pharmacol. 2021;890:173741. | - Antagonism of α7 nicotinic acetylcholine receptors (α7nAChR) and N-methyl-D-aspartate (NMDA) receptors may decrease angiotensin-converting enzyme 2 (ACE2) receptor expression and reduce oxidative stress and inflammation, hence potentially reducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virulence (Hasanagic & Serdarevic, 2020). |
| 7- Muric NN, Arsenijevic NN, Borovcanin MM. Chlorpromazine as a Potential Antipsychotic Choice in COVID-19 Treatment. Front Psychiatry. 2020;11:612347. | 6- Stip E, Rizvi TA, Mustafa F, Javaid S, Aburuz S, Ahmed NN, et al. The Large Action of Chlorpromazine: Translational and Transdisciplinary Considerations in the Face of COVID19. Front Pharmacol. 2020;11:577678. | - Potent protective effect against lesions induced by 6-hydroxydopamine (6-OHDA) in dopaminergic pheochromocytoma (PC12) cells related to reversing nerve growth factor IB (NGFIB) upregulation. NGFIB activates the nuclear factor-xB (NF-xB) signaling pathway, potentiates the induction of pro-inflammatory gene expression, and enhances mouse resistance to lipopolysaccharide (LPS)-induced sepsis (Brenner-SR, 2020). |
| 8- Sathyamoorthy N, Chintamaneni PK, Chinni S. Chlorpromazine as a Potential Antipsychotic Choice in COVID-19 Treatment. Front Psychiatry. 2020;11:612347. | 7- Muric NN, Arsenijevic NN, Borovcanin MM. Chlorpromazine as a Potential Antipsychotic Choice in COVID-19 Treatment. Front Psychiatry. 2020;11:612347. | - Antagonism of α7 nicotinic acetylcholine receptors (α7nAChR) and N-methyl-D-aspartate (NMDA) receptors may decrease angiotensin-converting enzyme 2 (ACE2) receptor expression and reduce oxidative stress and inflammation, hence potentially reducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virulence (Hasanagic & Serdarevic, 2020). |
| 9- Stip E. Psychiatry and COVID-19: The Role of Chlorpromazine [letter]. Can J Psychiatry. 2020;65, 39–740. | 8- Sathyamoorthy N, Chintamaneni PK, Chinni S. Chlorpromazine as a Potential Antipsychotic Choice in COVID-19 Treatment. Front Psychiatry. 2020;11:612347. | - Potent protective effect against lesions induced by 6-hydroxydopamine (6-OHDA) in dopaminergic pheochromocytoma (PC12) cells related to reversing nerve growth factor IB (NGFIB) upregulation. NGFIB activates the nuclear factor-xB (NF-xB) signaling pathway, potentiates the induction of pro-inflammatory gene expression, and enhances mouse resistance to lipopolysaccharide (LPS)-induced sepsis (Brenner-SR, 2020). |
| 10- Ruiz de Pellón Santamaria Á. Psychosis Treatment During COVID-19 Pandemic and the Potential Role of Phenothiazines: A Call for Research Studies [letter]. J Clin Psychopharmacol. 2020;40:641–642. | 9- Stip E. Psychiatry and COVID-19: The Role of Chlorpromazine [letter]. Can J Psychiatry. 2020;65, 39–740. | - Antagonism of α7 nicotinic acetylcholine receptors (α7nAChR) and N-methyl-D-aspartate (NMDA) receptors may decrease angiotensin-converting enzyme 2 (ACE2) receptor expression and reduce oxidative stress and inflammation, hence potentially reducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virulence (Hasanagic & Serdarevic, 2020). |
| 11- Schmidt U, Rein T. Novel treatment targets for COVID-19: Contribution from molecular psychiatry [letter]. World J Biol Psychiatry. 2020;21:572–575. | 10- Ruiz de Pellón Santamaria Á. Psychosis Treatment During COVID-19 Pandemic and the Potential Role of Phenothiazines: A Call for Research Studies [letter]. J Clin Psychopharmacol. 2020;40:641–642. | - Potent protective effect against lesions induced by 6-hydroxydopamine (6-OHDA) in dopaminergic pheochromocytoma (PC12) cells related to reversing nerve growth factor IB (NGFIB) upregulation. NGFIB activates the nuclear factor-xB (NF-xB) signaling pathway, potentiates the induction of pro-inflammatory gene expression, and enhances mouse resistance to lipopolysaccharide (LPS)-induced sepsis (Brenner-SR, 2020). |
| 12- Javelot H, Weiner L, Petignet J, Meyer G, Briet J, El-Hage W, et al. Psychoactive compounds as multifactorial protection factors against COVID-19 [letter]. Ir J Med Sci. e-pub ahead of print. 18 August 2020; https://doi.org/10.1007/s11845-020-02346-9. | 11- Schmidt U, Rein T. Novel treatment targets for COVID-19: Contribution from molecular psychiatry [letter]. World J Biol Psychiatry. 2020;21:572–575. | - Antagonism of α7 nicotinic acetylcholine receptors (α7nAChR) and N-methyl-D-aspartate (NMDA) receptors may decrease angiotensin-converting enzyme 2 (ACE2) receptor expression and reduce oxidative stress and inflammation, hence potentially reducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virulence (Hasanagic & Serdarevic, 2020). |

**Anti-dementia: Memantine (9 articles):**
Randomized controlled clinical trials: 0
Non-randomized or Non-controlled clinical trials: 0
Observational studies: 1
Preclinical studies: 0
Opinions: 8
heterogeneity of clinical studies completed or underway. However, the diversity of the antiviral mechanisms of psychotropic drugs deserves to be studied in a translational way.

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AUTHOR CONTRIBUTIONS
ES designed and directed the project, developed the theory, and finalized the manuscript. All other authors contributed by reviewing the literature in their respective areas, writing and improving different portions of the manuscript, and approved the submitted version.

COMPETING INTERESTS
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ADDITIONAL INFORMATION
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