CORRESPONDENCE

Diversity of mechanism of action of psychotropic drugs in their anti-COVID-19 properties

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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

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Table 1. Psychotropic drugs and their putative anti-COVID-19 properties.

Psychotropic agent and number of published articles	Type of study and references	Antiviral mechanism of action
Antidepressants (14 articles): Randomized controlled clinical trials: 1 Non-randomized or Non-controlled clinical trials: 1 Observational studies: 3 Preclinical studies: 8 Opinions: 1	**Randomized controlled clinical trial:** 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 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 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) 2- Hoertel N, Sánchez-Rico M, Gulbins E, Kornhuber J, Carpinteiro A, Lenze EJ, et al. Association between FIASMAs and Reduced Risk of Intubation or Death in Individuals Hospitalized for Severe COVID-19: an observational multicenter study. Clin Pharm Therap. 2021;cpt.2317. (N=277 receiving a functional inhibitor of acid sphingomyelinase with 158 receiving antidepressants) 3- Diez-Quevedo C, Iglesias-González M, Giralt-López M, Rangil T, Sanagustin D, Moreira M, et al. Mental disorders, psychopharmacological treatments, and mortality in 2150 COVID-19 Spanish inpatients. Acta Psychiatr Scand. 2021 Jun;143(6):526–534. (N=1011 receiving a psychotropic medication with 481 receiving antidepressants) **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. 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, Reinke 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:eabf7945. 4- Zimniak 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	-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). -Clomipramine: Active against Middle East respiratory syndrome coronavirus (>50% inhibition) with no or low cytotoxicity (<30% toxicity) (Dyall et al., 2014). -Desipramine: Active against Coronaviruses (CoVs) genetically engineered human CoV strain (HCoV-OC43) (Shen et al., 2019). -Quipazine maleate - Inhibits viral replication through activity against the SARS-CoV-2 main protease (Mpro), which is essential for viral replication (Günther et al., 2021).

Table 1 continued

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	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.	
Mood stabilizer: Lithium (11 articles): Randomized controlled clinical trials: 0 Non-randomized or Non-controlled clinical trials: 0 Observational studies: 2 Preclinical studies: 1 Opinions: 8	**Observational studies:** 1- Spuch C, López-García M, Rivera-Baltanás T, RodríguesAmorím D, Olivares JM. Does Lithium Deserve a Place in the Treatment Against COVID-19? A Preliminary Observational Study in Six Patients, Case Report. Front Pharmacol. 2020;11 (N=6 receiving lithium) 2- Suwanwongse K, Shabarek N. Lithium Toxicity in Two Coronavirus Disease 2019 (COVID-19) Patients. Cureus. 2020;12:e8384. (N=2 receiving lithium) **Preclinical study:** 1- Viel T, Chinta S, Rane A, Chamoli M, Buck H, Andersen J. Microdose lithium reduces cellular senescence in human astrocytes - a potential pharmacotherapy for COVID-19? Aging. 2020;12:10035–10040. **Opinions:** 1- Gómez-Bernal G. Lithium for the 2019 novel coronavirus. Med Hypotheses. 2020;142:109822. 2- Villoutreix 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; 25:1287–1290. 3- Ishii N, Terao T, Hirakawa H. Association between trace levels of lithium in drinking water and COVID-19associated mortality [letter]. Bipolar Disord. 2021;23:100. 4- Santos LFT, Silva NL, Fidalgo TM. A tale of (glycogen synthase kinase) three: Lithium, the kidney and coronavirus disease 19 [letter]. Bipolar Disord. 2021;23:99. 5- Bou Khalil R. Lithium chloride combination with rapamycin for the treatment of COVID-19 pneumonia. Med Hypotheses. 2020;142:109798. 6- Murru A, Manchia M, Hajek T, Nielsen RE, Rybakowski JK, Sani G, et al. Lithium's antiviral effects: a potential drug for CoViD-19 disease? Int J Bipolar Disord. 2020;8:21. 7- Nowak JK, Walkowiak J. Lithium and coronaviral infections. A scoping review. F1000Res. 2020;9:93. 8- Rajkumar RP. Lithium as a candidate treatment for COVID19: Promises and pitfalls. Drug Dev Res. 2020; 81:782–785.	-Inhibition 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). -Protection of host cells from apoptosis triggered by viral infection (Rajkumar, 2020). -Inhibition of nuclear factor kappa light-chain-enhancer of activated B cells (NF-κB) (Rajkumar, 2020). -Inhibition of Interleukin 6 (IL-6) induced activation of Signal transducer and activator of transcription 3 (STAT3), perhaps mediated through inhibition of GSK-3β (Rajkumar, 2020). -Inhibition of Interleukin 1 beta (IL1β) production. (Murru et al., 2020; Rajkumar, 2020; Spuch et al., 2020). -Reduction in cyclooxygenase-2 expression (Murru et al., 2020; Rajkumar, 2020; Spuch et al., 2020).
Antipsychotic: Chlorpromazine (Phenothiazine) (16 articles): Randomized controlled clinical trials: 0 Non-randomized or Non-controlled clinical trials: 0 Observational studies: 1 Preclinical studies: 3 Opinions: 12	**Observational study:** 1- Hoertel N, Sánchez-Rico M, Vernet R, Jannot A-S, Neuraz A, Blanco C, et al. Observational Study of Chlorpromazine in Hospitalized Patients with COVID-19. Clin Drug Investig. 2021;41:221–233. (N=55 receiving chlorpromazine) **Preclinical studies:** 1- Weston S, Coleman CM, Haupt R, Logue J, Matthews K, Li Y, et al. Broad Anti-coronavirus Activity of Food and Drug Administration-Approved Drugs against SARS-CoV-2 In Vitro and SARS-CoV In Vivo. J Virol. 2020;94:e01218–220. 2- 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. 3- Dittmar M, Lee JS, Whig K, Segrist E, Li M, Kamalia B, et al. Drug repurposing screens reveal cell-type-specific entry pathways and FDA-approved drugs active against SARS-Cov-2. Cell Reports. 2021;35:108959. **Opinions:** 1- Yang N, Shen H-M. Targeting the Endocytic Pathway	-Inhibitor of clathrin-mediated endocytosis may have an impact on cells of the immune system (Sathyamoorthy et al., 2020). -In mice, increases the concentration of the anti-inflammatory cytokines Interleukin 10 (IL-10) and decreases that of pro-the inflammatory cytokines IL-6 and tumor necrosis factor alpha (TNFα) 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). -Antiviral activity of the phenothiazines might be the inhibition of the SARS-CoV main protease (Chen et al., 2021). -Blockage of cell entry pathways used by SARS-CoV-2 (Dittmar et al., 2021).

Table 1 continued

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	and Autophagy Process as a Novel Therapeutic Strategy in COVID-19. Int J Biol Sci. 2020;16:1724–1731. 2- Nobile B, Durand M, Courtet P, Van de Perre P, Nagot N, Molès JP, et al. Could the antipsychotic chlorpromazine be a potential treatment for SARS-CoV-2? Schizophr Res. 2020;223:373–375. 3- Sen A. Repurposing prolactin as a promising immunomodulator for the treatment of COVID-19: Are common Antiemetics the wonder drug to fight coronavirus? Med Hypotheses. 2020;144:110208. 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. 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. 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. 7- Muric NN, Arsenijevic NN, Borovcanin MM. Chlorpromazine as a Potential Antipsychotic Choice in COVID-19 Treatment. Front Psychiatry. 2020;11:612347. 8- Sathyamoorthy N, Chintamaneni PK, Chinni S. Plausible role of combination of Chlorpromazine hydrochloride and Teicoplanin against COVID-19 [letter]. Med Hypotheses. 2020;144:110011. 9- Stip E. Psychiatry and COVID-19: The Role of Chlorpromazine [letter]. Can J Psychiatry. 2020;65, 39–740. 10- Ruiz de Pellón Santamaría 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. 11- Schmidt U, Rein T. Novel treatment targets for COVID-19: Contribution from molecular psychiatry [letter]. World J Biol Psychiatry. 2020;21:572–575. 12- Javelot H, Weiner L, Petrignet 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.	
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	**Observational study:** 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) **Opinions:** 1- Hasanagic S, Serdarevic F. Potential role of memantine in the prevention and treatment of COVID-19: its antagonism of nicotinic acetylcholine receptors and beyond [letter]. Eur Respir J. 2020;56:2001610. 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/10.1002/jmv.26266. 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. 4- Cimolai N. Potentially repurposing adamantanes for COVID-19 [letter]. J Med Virol. 2020;92:531–532. 5- Tipton PW, Wszolek ZK. What can Parkinson's disease teach us about COVID-19? [letter]. Neurol Neurochir Pol. 2020;54:204–206.	-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 (SARSCoV-2) virulence (Hasanagic & Serdarevic, 2020). -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-κB (NF-κB) signaling pathway, potentiates the induction of pro-inflammatory gene expression, and enhances mouse resistance to lipopolysaccharide (LPS)-induced sepsis by inhibiting NF-κB activity, suppressing aberrant cytokine production (Jiménez-Jiménez et al., 2020). -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).

Table 1 continued

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	6 -Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JAG. Anti-Inflammatory Effects of Amantadine and Memantine: Possible Therapeutics for the Treatment of Covid-19? J Pers Med. 2020;10:217. 7 -Cortes Borra A. Adamantanes for the Prevention of COVID19: A Review of Case Reports. J Pharmaceu Pharmacol. 2020;8:3. 8 - Tomar PPS, Arkin IT. SARS-CoV-2 E protein is a potential ion channel that can be inhibited by Gliclazide and Memantine. Biochem Biophys Res Commun. 2020;530:10–14.	

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.

Emmanuel Stip[1,2], Danilo Arnone[1,3], Karim Abdel Aziz[1] and Syed Fahad Javaid[1]✉

[1]Department of Psychiatry and Behavioral Sciences, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates. [2]Department of Psychiatry, University of Montréal, Montréal, Canada. [3]King's College London, Institute of Psychiatry, Psychology, Neuroscience, Department of Psychological Medicine, Centre for Affective Disorders, London, United Kingdom.
✉email: sjavaid@uaeu.ac.ae

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2. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021;8:416–427.
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6. Baumeister D, Ciufolini S, Mondelli V. Effects of psychotropic drugs on inflammation: consequence or mediator of therapeutic effects in psychiatric treatment? Psychopharmacol (Berl). 2016;233:1575–1589.
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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

DA has received travel grants from Jansen-Cilag and Servier and sponsorship from Lundbeck. The other authors report no conflict of interest.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to S.F.J.

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