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COMMENTARY

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Repurposing functional inhibitors of acid sphingomyelinase (fiasmas): an opportunity against SARS-CoV-2 infection?

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Abstract

What is known and objective: Infection by SARS-CoV-2, the virus responsible of COVID-19, is associated with limited treatment options. The purpose of this study was to evaluate the rationale for repurposing functional inhibitors of acid sphingomyelinase (FIASMAs), several of which are approved medicines, for the treatment of SAR-CoV-2 infections.

Comment: We propose and discuss the FIASMAs' lysosomotropism as a possible explanation for their observed in vitro activities against viruses, and more specifically against infections caused by coronaviruses such as SARS-CoV-2. Successful in vitro-to-in vivo translation of FIASMAs requires that their pharmacokinetics (dosing regimen and drug-drug interactions) are matched with viral kinetics.

What is new and conclusion: Drug repurposing to ensure rapid patient access to effective treatment has garnered much attention in this era of the COVID-19 pandemic. The observed lysosomotropic activity of small-molecule FIASMA compounds suggests that their repurposing as potential drugs against SARS-CoV-2 is promising.

KEYWORDS
ABCB1 transporter, acid sphingomyelinase, antiviral activity, functional inhibitors of acid sphingomyelinase, in vitro and in silico, repurposing, SARS-CoV-2

1 | WHAT IS KNOWN AND OBJECTIVE

The SARS-CoV-2 outbreak poses major therapeutic problems, and there is an urgent need for a specific antiviral agent to treat this infection, thus decreasing viral shedding and subsequent transmission. Although numerous clinical trials are in progress and patients at different disease severity stages have been targeted, the vast majority of these trials are for treatment purposes and not preventive purposes (1,628 trials versus 289 trials, cf Living mapping and living systematic review of COVID-19 studies at https://covid-nma.com/dataviz; 28 October 2020). Initial trials in the search for an effective therapeutic yielded disappointing results (1,2) and the strategy of repurposing marketed drugs offers new opportunities. (3) The so-called "drug repurposing" strategy actually includes several different methodological approaches, and to date, the most successful examples of drug repurposing have not involved a systematic approach but rather serendipity.(3) In the repositioning strategy the first step, that is the identification of the candidate molecule (s) for a given indication is critical. The approaches that address this step are either experimental and/or computational.(3) Among the potential approaches, exciting new opportunities are afforded by the use of new data sources—including clinical data repositories.

Numerous organic molecules, including currently marketed drugs, have the potential to functionally inhibit, in a reversible and additive manner, the activity of acid sphingomyelinase (ASM) which is a lysosomal glycoprotein involved in a wide range of disorders (4) including virus infections. These molecules identified by the

acronym FIASMA (ie functional inhibitors of acid sphingomyelinase) have the potential to disrupt the entry of viruses into cells. The purpose of this study was to provide a rationale for repurposing of FIASMAs (functional inhibitors of ASM) for the prophylactic and/or therapeutic treatment of SARS-CoV-2 infections through a literature search in PubMed and the medRxiv.org preprint server for Health Sciences.

2 | COMMENT

2.1 | FIASMA's (see Supplement material for a list of FIASMAs)

Acid sphingomyelinase (ASM) is a lysosomal glycoprotein anchored to the inner lysosomal membrane. Under specific stimuli, ASM is translocated to the external leaflet of the cell membrane under specific stimuli where it catalyses the hydrolysis of sphingomyelin into ceramide and phosphorylcholine. Sphingomyelin is the most abundant sphingolipid component of the mammalian plasma membrane where it is associated with cholesterol in lipid rafts. ASM inhibitors work either by direct inhibition or by functional inhibition (FIASMA). Functional inhibitors of ASM (FIASMAs) are cationic amphiphilic molecules; they are relatively heterogeneous in terms of chemical structure but have several shared characteristics. In general, FIASMAs are polycyclic molecules, with at least one basic nitrogen atom (pKa >4 which corresponds to a partially protonated functional group at acidic pH), showing moderate to high lipophilicity (log p > 3).(5)

The internal wall of lysosomes is negatively charged due to the abundant presence of phospholipids. Several positively charged proteins form electrostatic interactions with the internal wall of the lysosome, and this protects them from lysosomal degradation. ASM is attached to the lysosomal membrane through this mechanism. FIASMAs are integrated into the lysosomal membrane through their lipophilic components, presenting their positively charged component to the lysosomal lumen. FIASMA activity results in the detachment of the ASM from the lysosomal membrane and its subsequent proteolytic degradation in the lysosomal lumen. Hence, ASM-activating stimuli cannot effect the translocation of ASM to the external leaflet of the cell membrane, resulting in the perturbation of the activities downstream of this signalling cascade, including lipid raft formation (Figure 1).

However, residual ASM activity is necessary for cell viability. There are significant differences in the intra-lysosomal capture speed depending on lipophilicity (logP) and degree of ionization (pKa) (from minutes to hours in cell culture systems). Indeed, desipramine, fluoxetine, maprotiline, paroxetine and protriptyline have rapid lysosomal capture (<30 min) with moderate lysosomal accumulation (lysosome/extracellular concentration ratio <100:1).(6) Drugs with significant FIASMA activities (residual activity <50% at a concentration of 10 μM) have been previously characterized (6-8) and are listed in a table as Supplementary material.

2.2 | FIASMA's and coronaviruses

In general, viruses exploit the cellular mechanisms of endocytosis to penetrate the cytosol. However, several different mechanisms of internalization may be involved, including clathrin-mediated endocytosis, macropinocytosis, caveolar/lipid raft-mediated endocytosis, or one of several incompletely characterized clathrin-independent and caveolin/lipid raft-independent mechanisms.(9) During infection with Coronoviridae, lipid raft-mediated endocytosis (10) and the clathrin-mediated pathway (11) have both been demonstrated to play a role in internalization, resulting in the identification of these processes as potential targets for drugs acting at the internalization step (ie fusion and entry). However, the targeting of the late compartments of the endocytic pathway after the delivery of the SARS-CoV genome to the cytoplasm is also a viable approach for the disruption of replication, as shown with the FIASMA amiodarone.(12) Indeed, various approaches targeting SARS-CoV-2 should be considered, with those targeting the virus directly likely to be the most effective.(13) However, the approaches targeting the biology of the host cells have the advantage that they are less influenced by genetic variations (which are less frequent in host cells than in viruses). As they are lysosomotropic drugs with specific activities, attention should be focused on FIASMA interference with lipid raft-mediated endocytosis following ASM inhibition (and in some cases, FIASMA interference with other steps in the endocytic pathways.

Three broad categories of experiments have been used to explore the efficacy of FIASMAs in coronarovirus diseases: *in silico* studies (bacterial sequencing techniques, molecular modelling, whole cell simulations, etc.); and *in vitro* studies and *in vivo* studies (animal studies and clinical trials retrospective or prospective). In almost all studies, the status of the FIASMAs was not known by the authors. In the first set of studies,(11,12,14-18) the antiviral activity of FIASMAs against the SARS-CoV and MERS-CoV viruses was explored. In the second set of studies, different drugs were tested against the SARS-CoV-2 using *in silico* (19-29) and *in vitro* studies.(30-40) These are listed in Table 1. *In vivo* studies have been performed using either human cells infected with SARS-CoV-2 or as part of clinical studies. In a recent study using human cells, amitriptyline, desipramine, escitalopram, fluoxetine, imipramine, maprotiline, and sertraline demonstrated almost complete *ex vivo* inhibition of the infection of human epithelial cells (and other different human cell lines) by SARS-CoV-2 and pp-VSV-SARS-CoV-2 spike particles.(41)

Several retrospective studies in humans have suggested a better prognosis for COVID-19 patients receiving either psychotropic drugs (chlorpromazine or fluoxetine) or amlodipine. In addition, a lower prevalence of COVID-19 infections in psychiatric patients (4%) than in healthcare professionals (14%) has been reported. From these observations, suggestions of the prophylactic effect of psychoactive compounds against Sars-CoV-2 have emerged,(42-44) and a clinical trial (ie The ReCoVery study) is ongoing. Although the antiviral activity of chlorpromazine involves the inhibition of clathrin-mediated endocytosis, its FIASMA status was not mentioned.

Several other studies have identified a potential role for known FIASMAs in the treatment of COVID-19. A recently submitted study (45) explored the association between antidepressant use and the risk of intubation or death in inpatients with COVID-19. A significant association was observed between the use of any antidepressant and a reduced risk of intubation or death. When specific antidepressant use was considered, significant associations were found for escitalopram, fluoxetine and venlafaxine. Interestingly, fluoxetine is a known FIASMA. A recent retrospective study (46) on 65 inpatients who tested positive for SARS-CoV-2 and were treated or not treated with calcium channel blockers (CCB, ie nifepidine or amlodipine as FIASMA) for hypertension found that patients treated with CCB were significantly more likely to survive than those not treated with CCB (50% survival in the CCB group versus 14.6% survival in the no-CCB group). This result was confirmed in a submitted study (39) which reported that COVID-19 patients with hypertension treated with amlodipine (N = 44) for hypertension had significantly reduced mortality (3/44; 6.8%) than COVID-19 patients (N = 46) treated with other medications for hypertension (mortality: 12/46; 26%). Finally, a study (47) reporting double-blind randomized, fully remote clinical trials of fluvoxamine versus placebo found that outpatients with symptomatic COVID-19 who had been treated with fluvoxamine had a lower likelihood of clinical deterioration over 15 days than patients treated with placebo.

In total, 32 FIASMAs have been identified through *in silico*, *in vitro* or *in vivo* studies as potential antiviral drug candidates against SARS-CoV, MERS-CoV or SARS-CoV-2. Of these, six show activity against all three coronaviruses (chlorpromazine, clomipramine, emetine, fluphenazine, loperamide and promethazine, see Table 1). Considering the results of recent *in vivo* studies, four FIASMAs (amlodipine, amitriptyline and fluoxetine or fluvoxamine) merit particular interest; and their activities should be explored in future prospective studies.

It should be noted that our understanding of SARS-CoV-2 cell penetration is limited. Apart from caveolar/lipid raft-mediated endocytosis, clathrin-mediated endocytosis and micropinocytosis are potentially involved in cell entry and may themselves be modulated by FIASMAs, including chlorpromazine, sertraline and promethazine (inhibitors of clathrin-mediated endocytosis), and imipramine (an inhibitor of micropinocytosis)(48) Furthermore, the endocytic mechanisms exploited by coronaviruses may vary according to the level in the respiratory tract. Nasal epithelial cells express a wide variety of endocytic markers, whereas pneumocytes have a more restricted pattern of expression, with micropinocytosis as the predominant endocytic pathway.(48) The identification of type II alveolar pneumocytes as preferential targets of SARS-CoV-2 may explain the late alveolar damage observed in some patients.

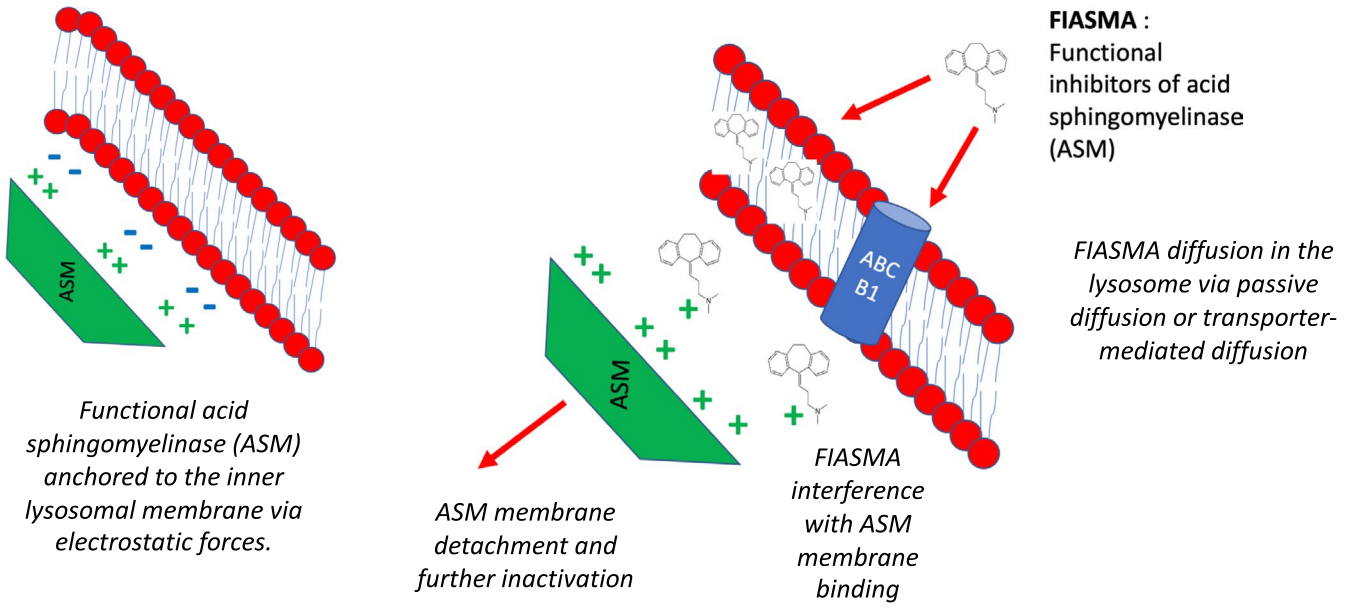

FIGURE 1 Mechanisms of action of functional inhibitors of acid sphingomyelinase (ASM). Left: ASM is anchored to the inner leaflet of the lysosomal membrane by electrostatic forces so that the enzyme is protected from proteolytic degradation. Specific stimuli allow the translocation of ASM from the inner lysosome to the external leaflet of the cell where ASM catalyses the hydrolysis of sphingomyelin into ceramide and phosphorylcholine. Sphingomyelin is the most abundant sphingolipid component of the mammalian plasma membrane where it is associated with cholesterol to form lipid rafts. Right: FIASMA are cationic drugs with lipophilic properties that diffuse in the lysosome by passive diffusion and potentially via an additional mechanism using ABCB1 transporter located on the lysosomal membrane. These drugs become protonated in the intra-lysosomal acidic environment and increase the intra-lysosomal pH so that ASM is detached from the inner leaflet of the lysosomal membrane and is further degraded by proteolysis. ASM translocation is no longer effective and the formation of lipid rafts is altered. Hence, different mechanisms of internalization used by viruses (ie fusion and entry) to penetrate in the cytosol of cells are altered.

2.3 | In vitro-to-in vivo translation

Solid evidence of antiviral activity based on *in vitro* and on pre-clinical studies is a prerequisite for further studies in humans. However, the *in vivo* translation of antiviral activity requires that the drugs have a suitable profile of drug exposure (concentration and duration) at the site(s) of action. Hence, drug pharmacokinetics and drug regimens are essential parameters for a successful translation.

FIASMA are lipophilic, basic, amine drugs and as such have a very high volume of distribution. Indeed, amitriptyline and of chlorpromazine have steady state volume of distribution (Vdss) values of is 14.4 L per kg (49) and 8.9 L per kg.(50) Lipophilic drugs are highly metabolized with a significant first-pass effect. The systemic clearance of amitriptyline and chlorpromazine is quite high (0.9 L/min and 1.3 L/min), and they have a low and variable oral bioavailability, ranging from 4% to 38% for chlorpromazine (50) and from 33 to 62% for amitriptyline.(49) Despite the fact that they have a high volume of distribution, the apparent elimination half-life values are not too excessively long (approx. 11 h and 18.5 h for amitriptyline and chlorpromazine), largely because of their high clearance.

TABLE 1 Functional inhibitors of acid sphingomyelinase with activity against SARS-CoV, MERS-CoV and SARS-CoV-2 on *in silico*, or *in vitro* and in *ex vivo* models. nteraction with P-gp (substrate and/or inhibition) was retrieved from Metrabase a public cheminformatics and bioinformatics database for transporter data analysis (http://www-metrabase.ch.cam.ac.uk).

FIASMA	SARS-CoV		MERS-CoV		SARS-CoV−2		P-gp substrate	P-gp inhibitor
Amiodarone	□■	(12,20)			□□■	(20,25,40)	o	+
Amitriptyline					□□□❖	(24,26,27,41)	+	+
Amlodipine					□□■■■	(27,28,37-39)	o	+
Astemizole	■	(16)	■■	(16,18)			+	+
Benztropine	■	(16)	■	(16)			o	o
Bepridil					□■	(26,35)	+	+
Carvedilol					□	(21)	o	+
Cepharanthine					□■	(29,30)	+	+
Chlorpromazine	■■■	(11,16,17)	■■	(16,18)	□□■	(28,29,34)	+	+
Clemastine					□□	(19,29)	-	o
Clofazimine					■■	(23,38)	o	+
Clomipramine	■	(16)	■■	(16,18)	■	(34)	+	+
Cloperastine					□□	(19,29)	o	o
Desipramine					❖	(41)	+ / -	+
Emetine	■	(16)	■	(16)	□□■■■■	(22,29,31-34)	+	+
Fluoxetine					■■❖	(36,40,41)	+	+
Fluphenazine	■	(16)	■■	(16,18)	■	(34)	o	+
Imipramine					□■❖	(26,40,41)	+	+
Loperamide	■	(17)	■	(17)	■	(30)	+	+
Maprotiline					❖	(41)	-	+
Melatonine					□□	(21,28)	o	o
Paroxetine					□	(21)	+	+
Pimozide					■	(35)	+	+
Promazine	□■†	(14,15)					-	+
Promethazine	■	(16)	■■	(16,18)	■	(34)	-	+
Quinacrine					□	(21)	o	o
Sertraline					■❖	(38,41)	+	+
Tamoxifene	■	(16)	■■	(16,18)			-	+
Trifluoperazine					■	(38)	+	+
Triflupromazine	■	(16)	■■	(16,18)			+	+
Trimipramine					□	(26)	-	+
Thioridazine					■	(38)	+	o

Note: In bold: drugs active against the 3 coronaviruses.

in silico (□), in vitro (■), ex vivo (❖) and negative result (†).

P-gp interaction: no information (o), positive information (+), negative information (-).

However, reaching a steady state to obtain a maximal effect would require a delay (approximately seven-times the half-life) that may prove unsuitable in an epidemic context, either for prevention or for curative use. Alternatively, a loading dose may be used to reach the steady state more rapidly, provided the tolerance profile is not a limiting factor. Furthermore, as illustrated for these two prototypic drugs, oral bioavailability is a factor of inter-individual variability that needs to be considered.

Other variability factors that may impact dosing, including renal and hepatic impairment and drug-drug interactions with concomitant medications, should also be considered especially because these drug candidates are lipophilic drugs usually with significant first-pass effect. In particular, attention should be paid to FIASMAs interacting with P-gp, either as substrate and/or as inhibitor (Table 1). P-gp is present in the lysosomal membrane (51) and P-gp substrates may have a higher lysosomal distribution than drugs only subject to passive diffusion.(52) Hence, co-administration of a strong P-gp inhibitor (eg clarithromycin, itraconazole, verapamil and some HIV protease inhibitors) with FIASMAs may decrease their lysosomal accumulation. Such features should be considered as part of a drug combination therapy in the management of SARS-CoV-2 infection.

Before prophylactic use in individual contact patients, knowledge of the pharmacokinetics in different sub-populations (including paediatrics and geriatrics) should be estimated. In addition to drug pharmacokinetics, viral kinetics must be considered to optimize dosing regimens, especially considering the limited window in which antiviral therapy can be initiated in a curative setting. Viral kinetics (ie time to peak viral load and duration of viral shedding) vary among viruses and are not yet well defined for SARS-CoV-2. These aforementioned elements are mandatory to define the initiation and of duration of any antiviral treatment.(53) Thus, precise details of drug pharmacokinetics and viral kinetics have to be known beforehand to ensure successful treatment.

2.4 | Framework of future investigations

First, retrospective investigations on confirmed COVID-19 studies should be conducted to explore the prevalence and the potential effects of FIASMAs. Indeed, it would be worthwhile to investigate whether patients infected with the SARS-CoV-2 virus who have been exposed to FIASMA's demonstrate a more favourable evolution of the disease. Data available in the clinical hospital data warehouses may help test this assumption and to identify marketed drugs that could be repurposed. For example, in the Erasme hospital from Brussels, 370 (27%) of the 1373 cases of hospital admission for COVID-19 (March to October 2020) were prescribed at least one FIASMA. In the Rennes University Hospital, 8.5% of patients admitted for COVID-19 (55 on 642 until May 5, 2020) were treated with FIASMAs. Second, pharmaco-epidemiological studies be performed to explore whether the chronic prescription of particular FIASMAs in the general population is associated with a low prevalence of the severe symptoms of the COVID-19 infection. Third, known FIASMAs should be tested *in vitro* to explore their activity against SARS-CoV-2. Fourth, FIASMAs with either a protective effect in the general population or a significant activity *in vitro* should be tested in vivo using a notably randomized double-blinded study against a placebo.

3 | WHAT IS NEW AND CONCLUSION

The drug repurposing approach has garnered significant attention in the COVID-19 pandemic era, providing some hope of an effective treatment in the near future. Current knowledge suggests that FIASMAs should be investigated for repurposing as potential drugs against SARS-COV-2. These are small molecules showing lysosomotropism with clinically approved indications in various diseases. We strongly suggest exploring the possible protective effects of the FIASMAs in subjects treated chronically for various diseases. Furthermore, FIASMAs showing positive in those studies should be tested in off-label therapy using notably large-sized, randomized and double-blinded controlled clinical trials.

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CONFLICT OF INTEREST

All the authors (PLC and GL) disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

AUTHOR CONTRIBUTIONS

All authors performed the literature search and wrote the manuscript.

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REFERENCES

1. Cao B. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. *N Engl J Med*. 2020;382:1787-1799.
2. Baden LR, Rubin EJ. Covid-19.the search for effective therapy. *N Engl J Med*. 2020;382:1851-1852.
3. Pushpakom S, et al. Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov*. 2019;18:41-58.
4. Beckmann N. Inhibition of acid sphingomyelinase by tricyclic antidepressants and analogons. *Front Physiol*. 2014;5:331.
5. Kornhuber J. Functional Inhibitors of Acid Sphingomyelinase (FIASMAs): a novel pharmacological group of drugs with broad clinical applications. *Cell Physiol Biochem*. 2010;26:9-20.
6. Kornhuber J, et al. Identification of new functional inhibitors of acid sphingomyelinase using a structure-property-activity relation model. *J Med Chem*. 2008;51:219-237.
7. Kornhuber J, et al. 2013. Functional Inhibitors of Acid Sphingomyelinase (FIASMAs). Gulbins E, Petrache I (Eds). *Sphingolipids: Basic Science and Drug Development*. Springer-Verlag Wien. https://doi.org/10.1007/978-3-7091-1368-4.

8. Hoehn R, et al. (2016) Melatonin acts as an antidepressant by inhibition of the Acid Sphingomyelinase/Ceramide system. *Neurosignals*. 2016;24(1):48-58.
9. Mercer J, et al. Virus entry by endocytosis. *Annu Rev Biochem*. 2010;79:803-833.
10. Choi KS, et al. Murine coronavirus requires lipid rafts for virus entry and cell-cell fusion but not for virus release. *J. Virol*. 2005;79:9862-9871.
11. Inoue Y, et al. Clathrin-dependent entry of severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted. *J Virol*. 2007;81:8722-8729.
12. Stadler K, et al. Amiodarone alters late endosomes and inhibits SARS coronavirus infection at a post-endosomal level. *Am J Respir Cell Mol Biol*. 2008;39:142-149. https://doi.org/10.1165/rcmb.2007-0217OC
13. Li H, et al. Updated approaches against SARS-CoV-2. *Antimicrob Agents Chemother*. 2020;64:e00483-e520. https://doi.org/10.1128/AAC.00483-20
14. Zhang XW, Yap YL. Old drugs as lead compounds for a new disease? Binding analysis of SARS coronavirus main proteinase with HIV, psychotic and parasite drugs. *Bioorg Med Chem*. 2004;12:2517-2521. https://doi.org/10.1016/j.bmc.2004.03.035
15. Barnard DL, et al. Is the anti-psychotic, 10-(3-(dimethylamino)propyl)phenothiazine (promazine), a potential drug with which to treat SARS infections? Lack of efficacy of promazine on SARS-CoV replication in a mouse model. *Antiviral Res*. 2008;79:105-113. https://doi.org/10.1016/j
16. Dyall J, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. *Antimicrob Agents Chemother*. 2014;58:4885-4893.
17. de Wilde AH, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother*. 2014;58:4875-4884.
18. Liu Q, et al. Testing of Middle East respiratory syndrome coronavirus replication inhibitors for the ability to block viral entry. *Antimicrob Agents Chemother*. 2015;59:742-744. https://doi.org/10.1128/AAC.03977-14
19. Gordon DE, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature*. 2020;583(7816):459-468. https://doi.org/10.1038/s41586-020-2286-9
20. Cava C, et al. In Silico discovery of candidate drugs against Covid-19. *Viruses*. 2020;12:404. https://doi.org/10.3390/v12040404
21. Zhou Y, et al. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov*. 2020;16(6):14. https://doi.org/10.1038/s41421-020-0153-3
22. Das S, et al. An investigation into the identification of potential inhibitors of SARS-CoV-2 main protease using molecular docking study. *J Biomol Struct Dyn*. 2020;2020(13):1-11. https://doi.org/10.1080/07391102.2020.1763201
23. Ke YY, et al. Artificial intelligence approach fighting COVID-19 with repurposing drugs. *Biomed J*. 2020;43(4):355-362. https://doi.org/10.1016/j.bj.2020.05.001
24. Arya R, et al. Potential inhibitors against papain-like protease of novel coronavirus (SARS-CoV-2) from FDA approved drugs. *ChemRxiv*; 2020. https://doi.org/10.26434/chemrxiv.11860011.v2
25. Mirabelli C, et al. Morphological cell profiling of SARS-CoV-2 infection identifies drug repurposing candidates for COVID-19. version 2. *bioRxiv*. 2020;10:117184. https://doi.org/10.1101/2020.05.27.117184
26. Sencanski M, Perovic V, Pajovic SB, Adzic M, Paessler S, Glisic S. Drug Repurposing for Candidate SARS-CoV-2 Main Protease Inhibitors by a Novel In Silico Method. *Molecules*. 2020;25(17):3830. https://doi.org/10.3390/molecules25173830
27. Dayer MR. Old drugs for newly emerging viral disease, COVID-19: Bioinformatic Prospective. *arXiv*. 2020. arxiv.org
28. Hsieh K, Wang Y, Chen L, Zhao Z, Savitz S Drug repurposing for COVID-19 using graph neural network with genetic, mechanistic, and epidemiological validation. *arXiv*. 2020. arxiv.org
29. Sauvat A, Ciccosanti F, Colavita F, et al. On-target versus off-target effects of drugs inhibiting the replication of SARS-CoV-2. *Cell Death Dis*. 2020;11(8):656. https://doi.org/10.1038/s41419-020-02842-x
30. Jeon S, et al. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. *Antimicrob Agents Chemother*. 2020;64(7):1–9. https://doi.org/10.1128/AAC.00819-20
31. Choy KT, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res*. 2020;178:104786. https://doi.org/10.1016/j
32. Ianevski A, et al. Potential antiviral options against SARS-CoV-2 infection. *Viruses*. 2020;12:E642. https://doi.org/10.3390/v12060642
33. Yang CW, et al. Repurposing old drugs as antiviral agents for coronaviruses. *Biomed J*. 2020;43(4):368-374. https://doi.org/10.1016/j.bj.2020.05.003
34. Weston S, et al. FDA approved drugs with broad anti-coronaviral activity inhibit SARS-CoV-2 in vitro. 2020. https://doi.org/10.1101/2020.03.25.008482
35. Vatansever EC, et al. Targeting the SARS-CoV-2 Main Protease to Repurpose Drugs for COVID-19. *bioRxiv*. https://doi.org/10.1101/2020.05.23.112235.
36. Zimniak M, Kirschner L, Hilpert H, Seibel J, Bodem J. The serotonin reuptake inhibitor Fluoxetine inhibits SARS-CoV-2.*Biorxiv*, 2020. biorxiv.org
37. Straus MR, Bidon M, Tang T, Whittaker G. Daniel S.FDA approved calcium channel blockers inhibit SARS-CoV-2 infectivity in epithelial lung cells. *bioRxiv*. 2020. biorxiv.org
38. Xiao X, Wang C, Chang D, Wang Y, Dong X, Jiao T Identification of potent and safe antiviral therapeutic candidates against SARS-CoV-2. *bioRxiv*. 2020. biorxiv.org
39. Zhang L, Sun Y, Zeng HL, Peng Y, Jiang X, Shang WJ. Calcium channel blocker amlodipine besylate is associated with reduced case fatality rate of COVID-19 patients with hypertension. *medRxiv*. 2020. medrxiv.org
40. Schloer S, Brunotte L, Goretzko J, 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(1):2245-2255. https://doi.org/10.1080/22221751.2020.1829082
41. Carpinteiro A, et al. Pharmacological inhibition of acid sphingomyelinase prevents uptake of SARS-CoV-2 by epithelial cells. *Cell Reports Medicine*. 2020;1(8):100142.
42. Plaze M, et al. Repurposing chlorpromazine to treat COVID-19: the reCoVery study]. *Encephale*. 2020;46(3):169-172. https://doi.org/10.1016/j.encep.2020.05.006
43. Javelot H, et al. Towards a pharmacochemical hypothesis of the prophylaxis of SARS-CoV-2 by psychoactive substances. *Med Hypotheses*. 2020;144:110025.
44. Villoutreix BO, et al. Prevention of COVID-19 by drug repurposing: rationale from drugs prescribed for mental disorders. *Drug Discov Today*. 2020;25(8):1287-1290. https://doi.org/10.1016/j.drudis.2020.06.022
45. Hoertel N, et al. Association between SSRI Antidepressant Use and reduced risk of intubation or death in hospitalized patients with coronavirus disease 2019: a multicenter retrospective observational study. *medRxiv* 2020. https://doi.org/10.1101/2020.07.09.20143339
46. Solaimanzadeh I. Nifedipine and Amlodipine are associated with improved mortality and decreased risk for intubation and mechanical ventilation in elderly patients hospitalized for COVID-19. *Cureus*. 2020;12(5):e8069.

47. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs Placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. 2020;324(22):2292-2300. https://doi.org/10.1001/jama.2020.22760
48. Glebov OO. Understanding SARS-CoV-2 endocytosis for COVID-19 drug repurposing. *FEBS J*. 2020;287(17):3664-3671. https://doi.org/10.1111/febs.15369
49. Schulz P, et al. Amitriptyline disposition in young and elderly normal men. *Clin Pharmacol Ther*. 1983;33(3):360-366.
50. Yeung PK. Pharmacokinetics of chlorpromazine and key metabolites. *Eur J Clin Pharmacol*. 1993;45(6):563-569.
51. Yamagishi T, et al. P-glycoprotein mediates drug resistance via a novel mechanism involving lysosomal sequestration. *J Biol Chem*. 2013;288:31761-31771. https://doi.org/10.1074/jbc.M113.514091
52. Scherrmann JM. Intracellular ABCB1 as a Possible Mechanism to Explain the Synergistic Effect of Hydroxychloroquine-Azithromycin Combination in COVID-19 Therapy. *AAPS J*. 2020;22(4):86. https://doi.org/10.1208/s12248-020-00465-w
53. Smith PF, et al. Dosing will be a key success factor in repurposing antivirals for COVID-19. *Br J Clin Pharmacol*. 2020;1–4. https://doi.org/10.1111/bcp.14314

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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