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editorial

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Prevention of COVID-19 by drug repurposing: rationale from drugs prescribed for mental disorders

At present, no treatments or vaccines are available to treat or prevent the coronavirus SARS-Cov-2 infection. As drug development is time-consuming and costly, there is an urgent need to find a rationale for repurposing clinically approved compounds that could rapidly enter clinical trials. To guide the selection of molecules for the prevention of SARS-Cov-2 infection, we believe that there is great potential in exploring drugs prescribed for mental

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disorders. Indeed, these past few weeks, an intriguing relationship appeared between SARS-CoV-2 infection and psychiatric disorders. Patients with mental disorders were intuitively thought to be at increased risk of becoming infected: non-compliance to protective measures, delayed access to health services due to social discrimination, confined conditions in psychiatric units favoring dissemination of infections, and a high prevalence of high risk co-morbidities (diabetes, cardio-vascular disorders, obesity). Alarmed by these high risk situations, psychiatric departments in France created specialized COVID-19 units dedicated to psychiatric patients. Very much to our surprise, these units remained nearly empty during the lock-down period since only a small proportion of psychiatric patients were found to have COVID-19, suggesting that these patients, under treatment surveillance, may be at reduced risk of SARS-CoV-2 infection. This raised a compelling question: do the pharmacological treatment of these patients play a role in the observed protective effect?

In order to rationalize our observations, we first identified the most commonly used drugs for in and out-patients (*i.e.,* consumption of all the drugs in the Psychiatric department of Henri Mondor Hospital, Creteil, France from 2019 to April 2020). We ended up with a list of 18 drugs (Table 1). We then mined the literature to find information about possible, at least *in vitro*, antiviral activity of these 18 compounds. We also compared these 18 drugs with published molecules known to have *in vitro* antiviral activities [1,2] using various chemoinformatics strategies (*e.g.*, computation of molecular descriptors and compounds clustering carried out on about 300 molecules with *in vitro* antiviral activities on various viruses including SARS-CoV-2). The reasoning here is that if a molecule X belonging to our list of 18 most commonly prescribed drugs is not documented to have *in vitro* antiviral activity but can be chemically grouped (*e.g.*, presence of identical substructures) with a molecule with known *in vitro* antiviral activity, it is highly likely that molecule X will also have antiviral

TABLE 1

Eighteen commonly prescribed psychotropic drugs (in- and out-patient treatment programs)

Commonly prescribed psychotropic drugs in our department

Name (consumption rank)	Class	cLogP	Number of basic N / pKa of the most basic group	CAD(yes or no)	PLD (yes or no experimental or predicted)	Examples of published *in vitro* antiviral activity
Alimemazine (13)	anxiolytic	4.2	1 / 9.42	y	y (predicted)	not known but chemically similar to Promethazine or Chlorpromazine, known to have antiviral activity against MERS and SARS or Ebola
Amisulpride (16)	anti-psychotic	0.9	1 / 7.05	n	y	not known
Aripiprazole (8)	anti-psychotic	4.4	1 / 7.46	y	y	Ebola virus
Cetirizine (14)	anti-histamine anxiolytic	2.1	1 / 7.42	y	n (predicted)	HRV
Citalopram (18)	anti-depressant	2.8	1 / 9.78	y	y	HIV
Clozapine (2)	anti-psychotic	3.2	1 / 7.35	y	y	Inhibition of Epstein-Barr Virus Lytic Reactivation HIV
Cyamemazine (10)	anti-psychotic	4.0	1 / 9.42	y	y (predicted)	not known but chemically similar to Promethazine or Chlorpromazine, known to have antiviral activity against MERS and SARS or Ebola
Diazepam (7)	anti-depressant	2.9	0 / 2.92	n	n	not known
Escitalopram (17)	anti-depressant	2.7	1 / 9.78	y	y (predicted)	not known but chemically similar to Citalopram or Chlorphenoxamine, a molecule known to act on MERS and SARS
Hydroxyzine (12)	anti-histamine anti-depressant	3.0	1 / 7.77	y	y	Selective inhibition of hepatitis C virus infection MERS
Lithium (4)	mood-stabilizing	NA	0 / NA	n	n	Antiviral effect of lithium chloride on mammalian orthoreoviruses
Lorazepam (3)	anxiolytic	2.9	0 / NA	n	n	not known
Melatonin (9)	anti-depressant	1.5	0 / NA	n	y	Possible roles in bacterial and viral infections
Nicotine (1)		1.2	1 / 8.6	partial	y (predicted)	Inhibits the production of pro-inflammatory cytokines in mice infected with cox-sackievirus B3
Quetiapine (11)	anti-psychotic	2.7	1 / 7.06	y	y	not known but chemically similar to Clozapine mentioned above
Sertraline (15)	anti-depressant	4.2	1 / 9.85	y	y	Ebola virus, Zika Virus, HIV H
Valproate (5)	anti-depressant	2.2	0 / NA	n	n	HSV
Zopiclone (6)	sedative	0.71	1 / 6.89	n	y (predicted)	not known

activity (*i.e.*, the so-called similarity principle in medicinal chemistry).

Among the 18 most commonly prescribed psychotropic drugs, ten have documented *in vitro* antiviral activities, while four of the eight remaining compounds were found structurally very similar to compounds with known *in vitro* antiviral activity (Table 1) using various clustering approaches. For example, no publications about antiviral activity were found for Alimemazine and Cyamemazine but these molecules are very similar to Promethazine which acts on Ebola and MERS [3] and Chlorpromazine which acts on MERS and SARS [4]. We also observed that 14 of the 18 most prescribed psychotropic drugs are cationic amphiphilic drugs (CADs) which are known to perturb intracellular trafficking (Table 1). CADs are characterized by hydrophobic-aromatic ring systems and a side chain that carries one (or more) ionizable amine functional group. To define the CAD nature of our 18 compounds, we computed pKa and log P values as reported earlier [5] with the ChemAxon chemistry toolkit (https://chemaxon.com/). Further, CADs often induce phospholipidosis (drug-induced phospholipidosis or PLD) *in vitro* [6] and hundreds of drugs have already been tested *in vitro* or the property can be predicted *in silico* [7]. The four molecules that are not CADs or PLP inducers are Lithium (not an organic molecule), Diazepam, Lorazepam and Valproate. In addition, Nicotine which is largely prescribed to psychiatric patients to help them quit smoking, could be considered as a partial CAD and is predicted to be a PLD. This compound may not modulate intracellular trafficking but could act via binding to specific receptors such as the acetylcholine receptor (nAChR) and possibly regulate the angiotensin converting enzyme 2 (ACE2) receptor [8].

Drugs against SARS-CoV-2 could operate at different stages of the virus lifecycle. Yet, to protect the population, acting on the virus entry phases through drug repurposing represent an attractive solution. Different strategies can be envisioned, from specific inhibition of some proteases and receptors, to mechanisms such as endocytosis. Overall, our analysis suggests that the most commonly prescribed psychotropic drugs, including some antihistamine agents used as anxiolytics, possess *in vitro* antiviral activity (Table 1). The vast majority of these drugs are CAD and/or PLD compounds. If we take the example of the highly debated anti-malarial Chloroquine and Hydroxychloroquine that have *in vitro* antiviral activity, these compounds are also CAD and PLD compounds (they display two ionizable amine groups while most often, psychotropic drugs contain only one ionizable amine group). These two anti-malarial drugs are lysosomotropic agent that accumulates in acidic organelles such as endosomes and lysosomes and neutralizes their pH thereby inhibiting the activity of some proteases such as Cathepsins required for effective viral infection (NB: they also have other functions as most medicinal drugs). Another example is Chlorpromazine, related to the commonly prescribed Alimemazine or Cyamemazine (Table 1). Chlorpromazine is a CAD and PLD agent and is known to inhibit cell-cell fusion and disrupt clathrin-mediated endocytosis [9]. In addition, several of the above mentioned commonly used psychotropic drugs may also act by interacting with some specific receptors. For instance, a number of psychoactive drugs (antipsychotics, antidepressants, anticonvulsants) and psychostimulants, all belonging to a variety of structural, pharmacological and therapeutic classes, can bind to sigma-1 receptors, and induce numerous molecular events [10].

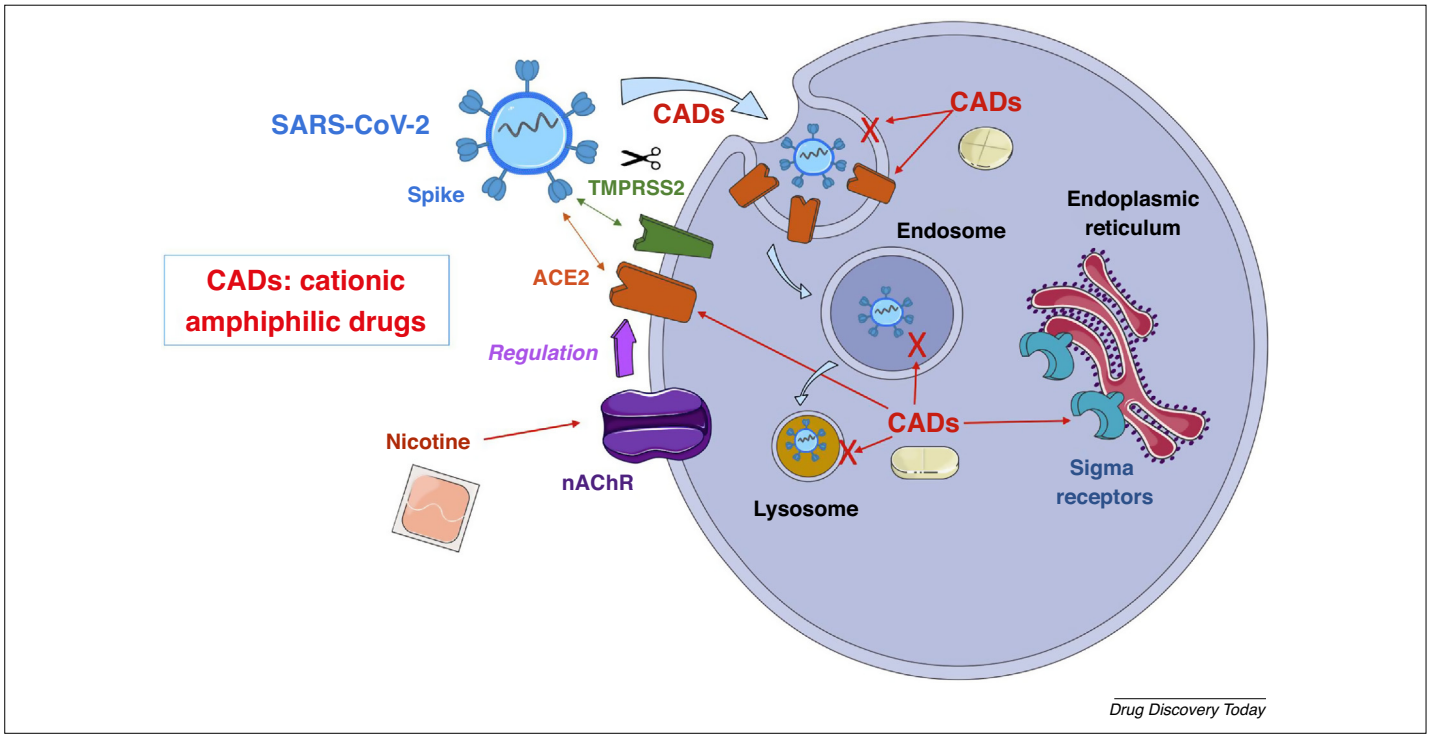

FIGURE 1

Potential effects of psychotropic drugs on SARS-CoV-2.

This very simplified cartoon highlights SARS-CoV-2 cell entry. Angiotensin-converting enzyme 2 receptor (ACE2), Acetylcholine receptor (nAChR), Transmembrane surface serine protease (TMPRSS2). Some graphical elements were taken from the free medical art collection distributed by the Servier laboratory.

In summary, we propose that some of the drugs commonly prescribed to psychiatric patients could protect them from SARS-CoV-2 infection via the modulation of the endo-lysosomal pathway, membrane fusion and yet to be characterized interactions with specific receptors (e.g., nAChR, ACE2 and Sigma receptors, Fig. 1). Based upon the above analysis, we suggest that one of these CAD molecules or a combination could be used as preventive treatment against SARS-CoV-2 infection, especially drugs with reduced adverse effects (*e.g.*, low dosage nicotine patch associated with an antihistamine agent). Further studies are currently ongoing in our groups to identify and test the above mentioned molecules *in vitro* and in clinical settings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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