Reflections on the Special Experiment in General Medicine of the Non-Specific Antiviral Drug, and Authorized as Antitussive, Cloperastine. Talking Advantage of the Opportunity to Study its Effects on Coronavirus Disease 2019 (Covid-19)

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ABSTRACT
Cloperastine represents a special case on the list of drug repurposing potentially useful for treating COVID-19 in the early stages of the disease at the community or general practice level. Cloperastine is an antitussive drug marketed worldwide and especially by countries in North America, Europe, Japan, Brazil, Russia, India, China, South Africa, and Australia. The most common symptom of COVID-19 is cough. Therefore cloperastine already has the indication for its use in COVID-19. This supposes a comparative advantage over the rest of potentially useful reusable drugs for COVID-19, which may be indicated in comorbidities of the patient with COVID-19, but are not indicated for COVID-19 itself. Cloperastine is also a non-specific antiviral drug and has an action on the Sigma-1 receptor, which specifically resides in the endoplasmic reticulum membrane-associated with mitochondria. In addition, cloperastine is a type 1 sodium-dependent glucose cotransporter inhibitor, blocking glucose uptake in lung cells. A proposal is made to study the hypothesis of the potential effect of cloperastine in COVID-19, to assess the outcome of exposure to this drug (duration of symptoms, severity, hospitalization, viral load, etc.), in retrospective case-control studies and prospectively -and this possibility is a distinctive case of cloperastine compared to the rest of potentially useful drugs in the treatment of COVID-19-, through clinical trials, taking advantage of the special experiment of its authorized prescription from of the approved indication of cloperastine in the treatment of cough.

Key words: COVID-19; SARS-CoV-2; Antiviral Drugs; Sigma-1 receptors; Biomedical Research; COVID-19 drug treatment; General Practice.

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Introduction
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing of coronavirus disease 2019 (COVID-19), which emerged in the human population at the end of 2019, had already reached pandemic proportions in March 2020.1,2 To date, COVID-19 has caused more than 34 million cases and 1 million deaths worldwide.3 Therapeutic options and vaccines for COVID-19 are desperately needed to respond to
their ongoing. Finding effective treatments and vaccines will transform the impact of the COVID-19 pandemic on lives and economies around the world. However, regarding vaccines, there can be a long way to go to find an effective vaccine. Among other uncertainties, the effect of mutations on protein expression and the antigenicity required to elicit an antibody response (or to interact with passive antibodies) is unclear. For a decade, attempts to develop vaccines against Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome have been unsuccessful. Furthermore, COVID-19 disproportionately affects older age groups, where immune senescence leads to poorer-quality immune responses. Additionally, infections with other coronaviruses and challenges with experimental vaccines have resulted only in short-term protective immunity.4

On the other hand, the most useful public health approaches for slow transmission are social and behavioral in nature.5 Control measures, based on isolation, contact tracing and quarantine, can lessen and delay the burden of the ongoing epidemic, but these measures are associated with profound social and economic disturbances; furthermore, these interventions may be inadequate to control local outbreaks, even when perfect isolation is assumed. The effect of infectivity before the onset of symptoms, combined with the presence of asymptomatic infected patients further complicates the use of contact tracing. In short, useful drugs are needed. Therefore, research aimed at the identification of new drugs and drug reformulations suitable for therapeutic and prophylactic use (drug repurposing) for different drugs with antiviral action through different mechanisms, remains fully justified.6

Therefore, it is clear that tools -drugs- are needed to keep people alive, improve symptoms and reduce the duration and severity of the disease. It is in this context where it would be very useful to find an antiviral drug that acts early, so that transmission can be reduced and contribute to the control of outbreaks.7

Drugs that can be used as an early treatment at the general medicine (GM) level are of particular interest. Early treatment, if successful, would allow us to avoid the serious complications seen in COVID-19. The two promising categories of drugs targeting COVID-19 viral infection and immunopathology are classic antivirals and immunomodulators. While treatment for COVID-19 outside of the hospital setting is currently limited to supportive therapy, more than 1,000 clinical trials are underway looking at a variety of drug treatments.7,8 The drugs -remdesivir and dexamethasone- of which the first useful results are known to refer to hospitalized and seriously ill patients.8-10

But, none of these interventions is applicable at the onset of the disease or at the community level in GM. This line of investigation has been overlooked. It should be borne in mind that all severe and critical COVID-19 patients were previously mild or moderate COVID-19 patients or uninfected people. In addition to the benefits of early treatment, the preferable or ideal option would be to do it with an existing drug (drug repurposing): this method would be the fastest and most cost-effective clinical way to mitigate the impact of COVID-19. That means reducing hospitalizations, which can reduce mortality, but it can also mean reducing viral load, and that can have a profound impact on transmission within communities.7
Consequently, existing drugs are being sought that could play a role in mitigating COVID-19 or slowing its transmission. Drug repurposing is "a kind of fruit within the reach of clinical doctors." In this way, outcomes data could be obtained quickly to help prioritize the drugs that could be tested in larger confirmatory studies.\textsuperscript{7,11-13} To date, there is no specific medicine recommended to prevent or treat the new coronavirus, at least at the level of GM, however, those infected with the virus should receive appropriate care to relieve and treat symptoms.\textsuperscript{14}

More than seventy drugs are being studied for their possible application in the COVID-19 pandemic. Of these, some are drugs that are already being used for various indications, and others are experimental pharmaceuticals. 26 of the 29 genes of the SARS-CoV-2 have been studied in detail. At least 332 proteins in human cells become targeted by the coronavirus.\textsuperscript{15} Some viral proteins target a single human cell protein; other proteins in the virus appear to interact with dozens of cellular proteins. The mechanism, barely deciphered, is of extraordinary complexity. Pharmacological research investigates drugs (already marketed or substances with pharmaceutical potential) that block the human proteins that the virus needs to first penetrate, and then replicate, in the cell. Some specific treatments are under investigation, and will be tested through clinical trials. Among the drugs that are already being used for various indications and that could be repurposing drugs, is the antihistamine cloperastine, which is a special case, as in addition to its possible antiviral effect, it is indicated as a non-opioid antitussive, and it can be used early and at the level of general medicine.\textsuperscript{16} In this scenario, this article aims to reflect on this case or special experiment of the potentially useful drug in COVID-19, cloperastine, as drug repurposing, and as early treatment at the level of GM, thus taking advantages of the natural experiments that exist in its prescription authorized as antitussive in COVID-19.

**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 Internet based on published studies 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**

Effective therapies are urgently needed for the SARS-CoV-2 pandemic. But, the investigation of therapies against COVID-19 accumulates failures, being the only two acceptable drugs, with mixed results, so far remdesivir and dexamethasone. In general it can be said that both antiviral drugs and immunomodulators might have their place in the management of COVID-19. Unfortunately, no drugs have been approved yet to treat infections with human coronaviruses. As it will take years to develop new therapies for SARS-CoV-2, the current focus is on the repurposing of drugs that have been approved or are in development for other conditions.\textsuperscript{17} Thus, the ongoing COVID-19 pandemic has forced the clinical and scientific community to try drug repurposing of existing antiviral or immunomodulators agents as a quick option against SARS-CoV-2.\textsuperscript{13}
The community level (out-of-hospital) represents metaphorically "a Petri dish" where results of thousands of natural experiments are being produced against potentially useful drugs in COVID-19 that are waiting to be observed, and that behind some of them may be the discovery of a wonder drug. Meticulous community studies, at the general medicine level, should be done with each of the natural experiments that are taking place. In some of them, the "zone of antagonism" may appear, as it occurred in serial experiments in the laboratory on the search for antibiotics, and the tell-tale clear zone or "zone of antagonism may be visible at an unexpected moment in a Petri dish, where one microbe battled against an enemy for space or food." The richness of these experiments is that they are already underway, and their results can be quickly evaluated through retrospective studies, so that, like a gardener spotting a sturdy shoot, valuable results can be observed which would deserve to be verified with clinical trials.18

Likewise, a number of approved and common drugs have been reported for other diseases or symptoms: 1) azithromycin and doxycycline (for various infections), 2) alaph1 antagonists (for arterial hypertension and benign prostatic hypertrophy), 3) tocilizumab (in the treatment of various types of arthritis), 4) statins (for dyslipidemia), 5) selective serotonin reuptake inhibitors, as fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine, etc. (for depression / anxiety), 6) antipsychotic, 7) progesterone, 8) vitamin D or calcifediol (25OHD), 9) vitamin C, 10) colchicine (for rheumatological and cardiac conditions), 11) Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 (AT1) receptor antagonists (for hypertension and heart failure), 12) ivermectine (as treatment and control of several tropical diseases, 13) with beta-blockers such as propranolol, nebivolol, carvedilol, atenolol, etc. (for heart problems and high blood pressure), 14) and antihistamines such as clemastine and cloperastine (for cough of various causes).21

Using different methods, all known drugs have been mapped against all the possible mechanisms in which SARS-CoV-2 operates to cause complications.7,15,19,20 And a number of these have been reported to be promising compounds for clinical trials against COVID-19: Some drugs can fight COVID-19, while others promote infectivity. Among them are camostat, a transmembrane serine protease inhibitor licensed for use in Japan to treat pancreatitis and esophagitis, the antiandrogen bicalutamide, zotatofine, and ternatine-4 / plitidepsin, niclosamide, favipiravir, leeronlimab, interferon beta, interferon lambda, and other monoclonal antibodies, and a metabolite of the antiviral drug remdesivir.7,15,20

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A number of these drugs modulate proteins within the cell known as the Sigma-1 (Sig-1R) and Sigma2 (Sig-2R) receptors, show promise for clinical trials against COVID-19, including fluvoxamine, a commonly prescribed drug for depression, and which is a regulator of serotonin, but also activates the Sig-1R, progesterone, hydroxychloroquine; the antipsychotic drugs haloperidol and cloperazine; siramesin, an antidepressant and anxiolytic drug; and the antihistamines clemastine and cloperastine. That is, among this group of drugs, is cloperastine.15, 20, 21

The Cloperastine Special Experiment: an Advantageous Opportunity

Cloperastine represents a special case on the list of reusable drugs potentially useful for
treating COVID-19 in the early stages of the disease. It is an antitussive drug available in many countries such as Japan, Hong Kong, and some European countries, such as Spain; it was first introduced in 1972 in Japan and then in Italy in 1981. Cloperastine is marketed worldwide and especially by countries in North America, Europe, Japan, Brazil, Russia, India, China, South Africa and Australia. In Spain, where it is available, it can be obtained without a prescription (it is not funded by the Public Health System), and it is prescribed and used frequently. And even clinical guidelines usually recommend it for the treatment of dry cough.

On the other hand, coughing is the most common symptom of COVID-19 (84%). And therefore cloperastine already has the indication for its use in COVID-19. This supposes a comparative advantage over the rest of potentially useful repurposing drugs for COVID-19, which may be indicated in comorbidities of the patient with COVID-19, but are not fully indicated (authorized) for COVID-19 itself.

**COVID-19 as an endothelial disease**

COVID-19 can be conceptualized as an endothelial disease with respect to its complications. This unifying hypothesis can help understand the complex pathophysiology of this current plague and can also help inform our therapeutic approaches to combat the consequences of SARS-CoV-2 infection. Recent studies suggest that pulmonary complications are the result of a disturbance of the blood vessels. The interior of the blood vessels is lined by a single layer of endothelial cells. Research carried out in recent decades has revealed its role in a multitude of functions, among which the control of arterial tone, fibrinolysis and vascular growth stand out. As if that were not enough, under physiological conditions the endothelium prevents inflammation and formation of blood clots. In COVID-19, endothelial cells alter the integrity of the vascular barrier. This would lead to tissue edema (accumulation of fluid in the lungs), inflammation of the endothelium (endothelitis), activation of the coagulation pathways, and uncontrolled infiltration of inflammatory cells. Although it is still too early to have a definitive answer, everything indicates that treatments that prevent endothelial damage could be beneficial for COVID-19 patients. Here, Sig-1R, that is located in the endoplasmic reticulum, plays a modulator role.

**Action of Cloperastine as a Potential Drug in COVID-19**

Cloperastine or cloperastine, also known as cloperastine hydrochloride and cloperastinephendizoate (or hibenzoate), is an antitussive and antihistamine. Cloperastine was first studied at the University of Tokyo and was introduced in Japan in the 70s of the last century. It is a derivative of diphenhydramine. Scientists found that this substance had a more effective effect than codeine, which has been used for years to treat coughs.

A cluster of SARS-CoV-2 antivirals with characteristics of lysosomotropic agents, meaning that they are lipophilic weak bases capable of penetrating into cells, has been identified. These agents include cloperastine, which are likely to inhibit SARS-CoV-2 replication by non-specific (off-target) effects, meaning that they probably do not act on their "official" pharmacological targets, but rather interfere with viral replication through...
non-specific effects on acidophilic organelles including autophagosomes, endosomes, and lysosomes. In conclusion, in a tentative classification of SARS-CoV-2 antivirals into specific (on-target) versus non-specific (off-target) agents based on their physicochemical characteristics, cloperastine would be among the non-specific (off-target) antivirals.\(^{43}\)

Cloperastine has an action on Sig-1R, which specifically resides in the endoplasmic reticulum membrane associated with mitochondria (an interface between endoplasmic reticulum and mitochondria). In addition to being able to translocate to the plasma membrane to interact with ion channels and other receptors, Sig-1R also occurs in the nuclear envelope, where it recruits chromatin remodeling factors to affect gene transcription. Sig-1Rs have also been reported to interact with other membranous or soluble proteins at other loci, including the cytosol.\(^{44}\)

The Sig-1R is a transmembrane protein expressed in many different tissue types. It is particularly concentrated in certain regions of the central nervous system. It has been implicated in several 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 thought to be a pluripotent modulator with multiple resulting functional manifestations in living systems.\(^{44,45}\)

Much is known about the binding affinity of hundreds of synthetic compounds to the Sig-1R, although its mechanisms of action with respect to other biochemical agents are not well established. It is thought that the 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 macrophages derived from HIV-1 infected monocytes exposed to cocaine in vitro and in vivo (46). Nonopioid Sig-1R, as a cellular factor, mediates the early steps of viral RNA replication. In general, the initial steps of HCV infection have been reported to be regulated by Sig-1R.\(^{47}\)

The Sig-1R is unique endoplasmic reticulum protein that mediates signaling of a variety of drugs, and it is suggested that there is a Sig-1R-dependent modulation of cytokines.\(^{48}\) Receptor binding is one of the main determinants of tissue tropism for coronaviruses and appears to be an important mediator of the pathophysiology of COVID-19. The SARS-CoV-2 spike protein plays the most important roles in viral binding, fusion, and entry, and serves as a target for the development of antibodies, entry inhibitors, and vaccines. It has been hypothesized about the possible participation of a wide range of receptors in the entry of SARS-CoV-2 cells. A foregoing line of evidence supports the hermeneutical notion that the SARS-CoV-2 might enter the cell via angiotensin-converting enzyme-2 receptors. Presumably, Sig-1R and Sig-2R might play a role in the infectivity of SARS-CoV-2. Previous research has suggested that pharmacological manipulation of both Sig-1R and Sig-2R activity might provide antiviral activity, particularly for RNA viruses including hepatitis C virus (HCV) and human immunodeficiency viruses (HIV). These findings indicate that sigma receptors may also be involved in the cellular transmission of SARS-CoV-2, which has a genomic structure similar to that of HCV and HIV.\(^{49}\)
Furthermore, cloperastine has another effect; it is actually a type 1 sodium-dependent glucose cotransporter (SGLT1) inhibitor. It blocks glucose uptake in lung cells (27, 50). Selective analogs of the natural glycoside floridzin are marketed drugs that reduce hyperglycemia in diabetes by inhibiting the active sodium-glucose cotransporter SGLT2 in the kidneys. Additionally, intestinal SGLT1 is now recognized as a target for glycemic control. Among the new SGLT1 inhibitors beyond the glycoside chemical space is cloperastine.\textsuperscript{50}

Epithelial glucose transport is performed by Na+ -glucose transporters SGLT1 and SGLT2. In the intestine, glucose uptake in the diet is mediated for the most part by SGLT1, and humans with mutations in the SGLT1 gene show glucose / galactose malabsorption. In the kidney, both SGLT1 and SGLT2 transporters are expressed, and recent studies have identified that SGLT2 mediates up to 97% of glucose reabsorption.\textsuperscript{51} The study of primary human lung cells that were infected in the laboratory with SARS-CoV-2 showed how the cells began to accumulate large amounts of lipid droplets. After infection, lung proteins decrease the ability of lung cells to burn carbohydrates and fatty acids. Lung cells are not designed to retain fat, which could explain some of the severe damage to the lungs of COVID-19 patients. The virus is dependent on glucose absorption, cholesterol production, and fatty acid oxidation.\textsuperscript{27}

Outcomes of cloperastine on COVID-19
Researchers have reported a 20% or 30% reduction in the virus, in the laboratory, what is only a modest reduction (27), and cloperastine has only been tested against the virus in laboratory experiments (15, 20). But, considering that cloperastine is a drug that is in many medicine cabinets in the homes of ordinary people, and that it could improve COVID-19, more research is needed on it.

Regular use of cloperastine: the natural experiment in Spain (and in other countries like Japan or Italy)
Cloperastine is a cough suppressant and antihistamine; it’s already the right indication in COVID-19. This fact makes it more interesting in relation to its possible efficacy against COVID-19. Furthermore, it’s readily available in many countries, even though it’s mainly sold in Japan and European countries, especially Spain. On the other hand, Spain or Italy was some of the countries where the first wave of COVID-19 was most intense, from March to May 2020. Spain, likewise, is being the country with the highest infection rates in Europe from July to September 2020, in the second wave (at the time of writing this article), and it is one of the countries with the most deaths from COVID-19 by the number of inhabitants (Peru, Belgium, the United Kingdom, and Spain, are the countries with the most deaths with coronavirus by the number of inhabitants: Peru leads the ranking with 87 deaths per 100,000 inhabitants, while Spain registers 61; In addition, Spain had the second-highest mortality rate in the worst of the pandemic).\textsuperscript{52}

The coincidence of these facts means an opportunity for the clinical-epidemiological study, by offering a special natural experiment, where cloperastine is being used as an antitussive, and probably frequently in the dry cough of an upper respiratory vial in all types of patients, including COVID-19. This situation would allow, with some ease, the performance of retrospective case-control
studies\textsuperscript{53} (which may be common to all drugs repurposing with a potential effect on COVID-19), but also prospective studies, using the drug in its approved indication, as an antitussive in COVID-19, which is a special case of this drug.

Randomized clinical trials remain the best available method for understanding the causal relationship between an intervention and subsequent evolution at the population level for most diseases, but in the absence of data from randomized trials, there is an obligation to rely on observational studies.\textsuperscript{54} However, with cloperastine, it would be possible to carry out clinical trials without violating any ethical norm, and with adequate sample sizes.\textsuperscript{55} and in the application of these treatments in the clinical practice of GM as well as early in the evolution of COVID-19.

Conclusion
The proposal is made to study the hypothesis of the potential effect of cloperastine in COVID-19, a drug used as an antitussive and that has potential actions as a nonspecific antiviral, taking advantage of the natural experiment of its high prescription in some places, to assess both retrospectively the effect of exposure to that drug and the results of the disease (duration of symptoms, severity, hospitalization, viral load, etc.), as prospectively - and this possibility is a distinctive case of cloperastine compared to the other drugs potentially useful in the treatment of COVID-19, based on clinical trials, from the approved indication of cloperastine in the treatment of cough.

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