

Drug safety of frequently used drugs and substances for self-medication in COVID-19

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Abstract: During the COVID-19 pandemic, the behavior of self-medication has increased. The dissemination of misleading information regarding the efficacy of certain drugs or substances for the prevention and treatment of COVID-19 has been the major contributing factor for this phenomenon. Alongside with the increase in self-medication behavior, the inherent risks to this act such as drug–drug interactions, adverse events, drug toxicity, and masking of symptoms have also increased. Self-medication in the context of COVID-19 has led to drug misuse leading in some cases to the development of fatal adverse drug reactions. It is important that during this ongoing pandemic drugs with potential clinical efficacy against COVID-19 are adequately analyzed regarding their efficacy, safety, and monitoring. The aim of this review is to describe the available evidence regarding the efficacy, safety, and monitoring of the drugs and substances that have been shown to be frequently used for self-medication in patients with COVID-19 (hydroxychloroquine, non-steroidal anti-inflammatory drugs, ivermectin, azithromycin, vitamins, aspirin, and chlorine dioxide) to adequately characterize their risks, safe use, monitoring strategies, and to reinforce the concept that these substances should not be used for self-medication and require a medical prescription.

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Plain Language Summary

Drug safety of frequently used drugs and substances for self-medication in COVID-19

Dissemination of information about potential COVID-19 treatments has led individuals to self-medicate and expose themselves to risks such as drug–drug interactions, side effects, antibiotic resistance, and misdiagnosis. There is a need to review the medical literature to evaluate the safety and efficacy of the drugs and substances commonly used by the population for the treatment and prevention of SARS CoV-2 infection. In this review, we included drugs that are frequently used for self-medication and commonly advertised such as ivermectin, hydroxychloroquine, chlorine dioxide, azithromycin, and non-steroidal anti-inflammatory drugs, among others. A brief introduction of the drug and its mechanism of action, followed by a summary of the efficacy in COVID-19 and safety, will be described for each drug in order to promote their responsible use.

Keywords: aspirin, azithromycin, COVID-19, hydroxychloroquine, ivermectin, SARS CoV-2, self-medication

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Introduction

The COVID-19 pandemic has promoted irresponsible self-medication due to individual fear of

contracting the virus, limited access to healthcare services, and the massive release of misleading information. Self-medication is a form of self-care

that, when practiced responsibly, can help reduce the burden on the health care system and alleviate patient symptomatology. The World Health Organization (WHO) defines responsible self-medication as the practice in which individuals treat their symptoms of illness with medicines that are approved and available without prescription, with drugs of proven safety, quality, and efficacy and for their indicated condition.¹ However, self-medication in the context of the COVID-19 pandemic cannot meet these criteria because the drugs and compounds recommended for the treatment of COVID-19 to date have no proven efficacy for this disease.

At the onset of the pandemic, many drugs with *in vitro* and *in vivo* activity against SARS CoV-2 (severe acute respiratory syndrome coronavirus 2) were hypothesized to have clinical efficacy in COVID-19.²⁻⁴ As an example, hydroxychloroquine and chloroquine can have potentially life-threatening side effects if they are not carefully dosed and monitored. They were initially authorized and recommended by the FDA (Food and Drug Administration) and other regulatory agencies and guidelines^{5,6} for its use in hospitalized patients with COVID-19 because of encouraging evidence of *in vitro* and small uncontrolled studies.^{7,8} However, misleading information about their efficacy led people to self-medicate with such drugs exposing them to rare but potentially fatal harms such as ventricular arrhythmias, hepatic failure, and serious and cutaneous adverse reactions (Drug Rash with Eosinophilia and Systemic Symptoms, Steven-Johnson syndrome).⁹⁻¹¹ Nevertheless, in light of serious cardiovascular adverse effects (QT prolongation, *torsades de pointes*, sudden death)^{9,12} and lack of efficacy in large randomized clinical trials such as the RECOVERY¹³ and Solidarity trial,¹⁴ the authorization was revoked.

Self-medication is a public health problem because it has potential risks such as adverse drug reactions (ADRs), drug–drug interactions (DDIs), antibiotic resistance, drug toxicity, incorrect choice of medication, and masking of symptoms, of which some may have lethal complications as discussed above. The prevalence of self-medication for COVID-19 prevention and management was found to be 33.9% in hospitalized adults with COVID-19 and <4–88% in the general population.¹⁵ The reasons for self-medication in patients with COVID-19 were also analyzed.

The main reasons for self-medication were emergency illness, delays in receiving hospital services, distance to the health care facility, and proximity to the pharmacy, and the most commonly used drugs were vitamin C or multivitamins and anti-malarials, obtained mainly from pharmacies.¹⁶ On the contrary, Quispe-Cañari *et al.*¹⁷ found in a cross-sectional multicenter study that the main drugs used for self-medication in COVID-19 were acetaminophen, ibuprofen, azithromycin, penicillin, antiretrovirals, and hydroxychloroquine for a variety of symptoms including fever, fatigue, cough, sneezing, muscle pain, nasal congestion, sore throat, headache, and breathing difficulty.

Furthermore, there is evidence suggesting that the COVID-19 pandemic has increased the reporting of ADRs associated with self-medication. For instance, Gras *et al.* compared the reporting of ADRs related to self-medication in a French Pharmacovigilance database in 2020 to the previous year, where they found that 3.7% of the reported ADRs were linked to self-medication compared with 1.6% in 2019. Demonstrating a higher proportion of medication errors in the COVID-19 period.¹⁸ In addition, several studies have demonstrated a high prevalence of self-medication during the pandemic; Acharya *et al.* found a prevalence of 50.4% of self-medication among medical students and staff of a tertiary care center. From these patients 50% purchased the drugs or substances directly from the pharmacy, and the most frequently used compounds were paracetamol, vitamin C, zinc, multivitamins, vitamin D, azithromycin, cough syrup, and ibuprofen.¹⁹ Several other questionnaire-based studies have similar results when considering the most frequently used drugs for self-medication in COVID-19; these being analgesics, anti-inflammatories, antibiotics (azithromycin), ivermectin, chloroquine, and vitamins.²⁰⁻²²

However, other substances such as chlorine dioxide became popular during the COVID-19 pandemic especially in Latin America.²³ At the beginning of the pandemic, chlorine dioxide, a disinfectant used to treat residual waters, was advertised as a ‘miracle cure’ for COVID-19 and was even approved in some countries for the treatment and prevention of COVID-19.²⁴ However, exposure at high doses of this substance has been linked to thyroid suppression, DNA damage, and neurotoxicity. Soriano-Moreno

et al. conducted a cross-sectional study to evaluate the prevalence and the factors associated with chlorine dioxide consumption. Of 3610 adult Peruvian participants, they found a prevalence of 8% and 16% for the prevention and treatment of COVID-19, respectively, indicating that chlorine dioxide is a substance being used for self-medication in COVID-19.²⁵

A recent systematic review regarding self-medication practices to prevent or manage COVID-19 found that the most frequently used medications were antibiotics, chloroquine or hydroxychloroquine, vitamins or supplements, ivermectin, and ibuprofen.¹⁵ However, other drugs such as aspirin were also reported by high-quality studies.²⁶ Based on the studies mentioned previously, the aim of this review is to describe the available evidence regarding the efficacy, safety, and monitoring of the drugs and substances that have been shown to be frequently used for self-medication in patients with COVID-19 [hydroxychloroquine, non-steroidal anti-inflammatory drugs (NSAIDs), ivermectin, azithromycin, vitamins, chlorine dioxide, aspirin] to adequately characterize their risks, safe use, monitoring strategies, and to reinforce the concept that these substances should not be used for self-medication and require a medical prescription.

Drug used for self-medication in COVID-19

Hydroxychloroquine

Hydroxychloroquine is a chemically synthesized disease-modifying drug that belongs to the 4-aminoquinolines drug class and is currently used for the treatment of several autoimmune diseases;²⁷ most importantly systemic lupus erythematosus (SLE) where it has shown to be more effective.²⁸ It has been linked with antimalarial, anti-inflammatory, anti-infectious, and immunomodulatory effects. The majority of hydroxychloroquine mechanisms of actions are attributed to its properties as a weak base and as a highly lipophilic compound, which allows it to enter lysosomes, endosomes, and autophagosomes increasing their pH and thereby interfering with vesicular enzyme function (conversion of heme to hemozoin in the malaria parasite, interference with antigen processing and presentation, inhibiting virus-cell membrane fusion).²⁹ The increased pH caused by hydroxychloroquine in the endosome containing MHCII (major histocompatibility complex II)

prevents the clipping of the invariant chain and thus the formation of the MHCII/peptide complex (usually only with low-affinity antigens such as self-antigens)²⁷ ultimately leading to interference of cytokine release, B cell activation, and induction of apoptosis of autoreactive T-cells. Recently, inhibition of toll-like receptor signaling has also been attributed to hydroxychloroquine. Given its anti-inflammatory and potential antiviral properties, it was a rational compound to be evaluated against SARS CoV-2. *In vitro* studies showed that chloroquine and hydroxychloroquine could inhibit the entry of SARS CoV-2 into the cell.³⁰

Efficacy in COVID-19. Due to *in vitro* evidence of hydroxychloroquine and chloroquine antiviral activity against SARS CoV-2,^{7,8} several clinical trials on their use in COVID-19 have emerged, albeit with contradictory results.^{31–35} A recent meta-analysis reviewed only blinded, placebo-controlled RCTs (randomized controlled trials) to evaluate the efficacy and safety of hydroxychloroquine as prophylaxis and treatment for COVID-19.³⁶ Hydroxychloroquine as pre- and post-exposure prophylaxis showed no decrease in the risk of SARS CoV-2 infection, as treatment of non-hospitalized patients it showed no decrease in the risk of hospitalization or death, and individually the results showed no clinical benefit. Regarding hydroxychloroquine for the treatment of hospitalized patients with COVID-19, they found no difference in the duration of hospital stay, no decreased risk for mechanical ventilation between patients treated with hydroxychloroquine *versus* placebo.³⁶ Furthermore, a meta-analysis of RCTs evaluating the effect of azithromycin and hydroxychloroquine in the treatment of hospitalized patients with COVID-19 found that azithromycin with or without hydroxychloroquine had no effect on mortality or on the requirement for mechanical ventilation.³⁷

Safety and monitoring. Hydroxychloroquine is generally safe; however, it is a substrate for CYP2C8, CYP3A4/5, and CYP2D6;³⁸ therefore, it is susceptible to many pharmacokinetic interactions of which some have clinically significant DDIs. Gastrointestinal adverse reactions such as nausea, vomiting, abdominal pain, and diarrhea are the main ADRs associated with hydroxychloroquine; therefore, it is recommended to be taken with meals. Rare cases of elevated liver function tests (LFT) and fulminant liver failure have been

reported.³⁹ Cardiotoxicity occurs after chronic exposure to hydroxychloroquine as a result of interference with lysosomal function that leads to the accumulation of glycogen and phospholipids. However, acute conduction abnormalities have also been described, as hydroxychloroquine blocks the I_{kr} (rapid component of the delayed rectifier potassium current) on the cardiac action potential through inhibition of the Kv 11.1 potassium channel leading to *torsades de pointes*.⁴⁰ This was a major problem at the beginning of the pandemic because many drugs with QT interval prolongation potential were used concomitantly.^{41–43} On the contrary, hydroxychloroquine-induced lysosomal dysfunction also leads to the accumulation of lipofuscin, which is toxic to the photoreceptors and the retinal epithelial cells, seen in hydroxychloroquine-induced ocular toxicity.²⁷

Extrapolated information of hydroxychloroquine management in SLE is mentioned regarding monitoring during chronic treatment. It is important to consider that a daily dose of hydroxychloroquine of >5 mg/kg (real weight); chronic kidney disease stage 3, 4, or 5; cumulative dose of >600 – 1000 ; and adjuvant tamoxifen therapy are risk factors for ocular toxicity and must be taken into account.⁴⁴ A basic ophthalmological check-up should be obtained within the first 6 months of treatment. In case of chronic kidney disease with glomerular filtration rate <30 ml/min, dose must be adjusted to a maximum of 3 mg/kg. Regarding myopathies or cardiomyopathies, creatinine kinase and lactate dehydrogenase should be measured before starting the treatment and every 3–6 months.⁴⁴ Muscle strength and tendon reflexes surveillance should also be monitored. Monitoring for acute treatment with hydroxychloroquine should involve assessing the risk factors for QT interval prolongation such as electrolyte abnormalities, renal failure, structural heart disease, and concomitant use of other drugs with known risk of QT prolongation.⁴⁰

Ivermectin

Ivermectin is a drug used for its antiparasitic activities in daily clinical practice. During the pandemic, it showed inhibitory properties on SARS CoV-2 replication as well as with other viruses.⁴⁵ The proposed mechanism of action is the binding and destabilizing of the importin (IMP) α/β 1-heterodimer, thereby preventing

IMP α/β 1 from binding to the viral protein and preventing it from entering the nucleus.² This could increase viral clearance and thus decrease the likelihood of developing the infectious process.⁴⁶ It has been one of the most mentioned drugs during the pandemic due to its antiviral potential, with multiple results in elaborated studies that tend to be with small populations and in non-standardized schemes for the management of such condition.⁴⁷

Efficacy in COVID-19. Cruciani *et al.* published in their meta-analysis that there were no differences in mortality between ivermectin treatment arm and the control groups (low level of certainty). In patients with severe baseline diseases (3 reports, 304 patients), the use of ivermectin significantly decreased mortality compared with controls. Regarding disease progression [to severe pneumonia, admission to intensive care unit (ICU), and mechanical ventilation], the results were the same. The evidence is limited and approximately 36% of the studies had a high probability of performance bias.⁴⁸ A systematic review of the literature reported that ivermectin may have an impact on decreasing mortality and viral clearance. However, the therapeutic regimens varied in different studies and with important limitations from the methodological design.⁴⁹

A Cochrane review assessed the efficacy and safety of ivermectin compared with standard of care, placebo, or any other proven intervention for people with COVID-19 receiving inpatient or outpatient treatment and for the prevention of infection with SARS CoV-2. The authors concluded that they were uncertain about the efficacy and safety of ivermectin used to treat or prevent COVID-19 based on the available evidence.⁵⁰ Some experimental studies in murine models record that eventually the mixture between remdesivir and ivermectin could have a synergistic effect in the management of patients with SARS CoV-2 infection.⁵¹ Still, we hope to see some results from a meta-analysis studying the impact of ivermectin in the population.^{52,53}

Safety and monitoring. Pedrozo *et al.* analyzed in a small group, the characteristics of self-medication in healthcare workers diagnosed with COVID-19. When analyzing the group that took ivermectin, they found that there were no statistically significant differences in clinical severity;

however, abdominal pain, diarrhea, and taste alterations were more frequent in those who received multiple doses of this drug.⁵⁴

In the study conducted by Popp *et al.*,⁵⁰ the record on the presence of adverse reactions at 10, 14, and 28 days was not conclusive. Mohan *et al.*,⁵⁵ in their study, recorded a frequency of abdominal pain of 11.2%; they did not detect serious adverse events with doses of 12 and 24 mg of ivermectin. Cruciani *et al.*,⁴⁸ in his meta-analysis, describe an estimated frequency between 1% and 2%.

When using ivermectin, it is recommended to monitor skin reactions, as well as vertigo, ataxia, confusion, tachycardia, orthostatic hypotension, and increased transaminases.⁵⁶

The FDA and other institutions in charge of drug surveillance currently recommend not using the drug for this indication until conclusive studies are available to support this recommendation.⁵⁷

Azithromycin

Macrolides are bacteriostatic agents, derived from *Streptomyces erythreus*. Azithromycin is a semi-synthetic derivative of erythromycin, the first macrolide. It acts through reversible binding to the 50s subunit of the bacterial ribosome interfering with the translocation of the tRNA molecules on the ribosome from the acceptor site to the peptidyl site, resulting in impaired protein synthesis.

Efficacy in COVID-19. Its antibacterial role supported its use in COVID-19 infection; however, studies have failed to show effectiveness, at least in monotherapy.^{58–60} Alveolar damage due to SARS CoV-2 infection results in higher risk of bacterial co-infection; in such cases, there are international guidelines (The National Institute for Health and Care Excellence, American Thoracic Society and Infectious Diseases Society of America) that recommend the use of antibiotics considering the microbiological and clinical evidence to guide the appropriate therapy.⁶¹ The usage of antibiotics such as azithromycin is not advised unless there is evidence of bacterial pneumonia.⁶²

Aside from its antibacterial activity, azithromycin has an immunomodulatory effect. *In vitro* studies

have shown how azithromycin regulates many inflammatory pathways including ERK 1/2 (extracellular signal-regulated kinase) and NF-κB (nuclear factor kappa light chain enhancer of activated B cells) signaling proteins involved in cytokine production, one of the identified factors attributed to COVID-19 mortality. To date, there is no evidence of antiviral activity against SARS CoV-2 unlike other viruses like Ebola or Zika. Since the beginning of the pandemic, some studies reported a significant decrease in viral load with a short course of treatment (3–6 days) with azithromycin 500 mg per day on the first day and 250 mg per day plus hydroxychloroquine.^{63,64} However, they had randomization issues, short samples, along with methodological pitfalls that could bias the results. A systematic review even found an increase of 7% in mortality in patients receiving both drugs in non-randomized studies.⁶⁵ Despite all the biological effects associated with azithromycin, studies had failed to show effectiveness alone or together with antimalarials in reducing the need for oxygen therapy, ICU management, length of stay, or mortality associated with COVID-19.^{66,67}

Safety and monitoring. One of the main concerns is the risk of QTc interval prolongation defined in most trials as significant when >500 ms or an increase of more than 60 ms from the baseline. Since the onset of the pandemic, reports of cardiovascular adverse effects including QTc prolongation and ventricular arrhythmias have increased, even in indications other than COVID-19¹² leading to a revoke of FDA emergency authorization for the use of drugs such as hydroxychloroquine and azithromycin in COVID-19 treatment.⁶⁸ Studies show that there is a significant increased risk for QTc prolongation in combination with hydroxychloroquine within the first 4 days of treatment, in comparison with monotherapy, with substantial decrease in QTc after stopping the medication.^{42,67} Furthermore, the risk of fatal cardiac outcomes (TdP, ventricular tachycardia, ventricular fibrillation, or cardiac arrest) is associated with azithromycin plus hydroxychloroquine with up to 12.27% increase in average risk of severe arrhythmia; however, the population with coronary artery disease and congestive heart failure are at higher risk.⁶⁷ A retrospective study found a TdP risk of 0.4% in 251 patients with COVID-19, much higher than other well-known QTc prolonging drugs that have a risk of 0.1% such as

sotalol.⁴² There is heterogeneity in the baseline characteristics of the selected patients and not all risk factors that predispose to a QTc prolongation were taken into account in the analysis of all studies (sex, chronic diseases, age, electrolytic alterations, genetic factor), in that way, the risk in certain populations is still unknown, for example, younger patients may be at a lower risk, due to low prevalence of structural heart disease compared with older populations. On the contrary, azithromycin alone has not shown any considerable risk for these complications, remarking the importance of drug interactions in measuring the overall risk of QTc prolongation.⁶⁹⁻⁷¹ In light of this evidence, it is advisable to maintain close electrocardiographic monitoring, when azithromycin is used in combination with hydroxychloroquine or other QT prolonging drugs. It should be taken into consideration that it is more difficult to assess QTc prolongation in cases where prolongation of QRS is also an issue; as in the case of antimalarials, in these cases certain groups have opted to measure the JTc interval measuring from the J point at the beginning of the ST segment to the end of the T wave, correlating a measure of 410 ms with 500 ms of the QT interval.⁴²

Other adverse effects related to azithromycin therapy include gastrointestinal distress, hepatotoxicity, and hypersensitivity reactions, but none of these have been relevant in COVID-19 treatment.⁶⁷

Non-steroidal anti-inflammatory drugs

NSAIDs are widely used around the world for musculoskeletal inflammatory conditions as well as for the management of nociceptive pain and sometimes as an antipyretic. The mechanism of action is through inhibition of cyclooxygenase (COX) 1 and 2, also known as prostaglandin endoperoxide synthetase, its selectivity on the enzyme isoform is given mainly by its chemical structure. As a result, the production of prostaglandins and thromboxane A₂ from the synthesis of arachidonic acid is decreased.⁷²

Prostaglandins synthesis has been related to the proinflammatory activity of SARS CoV-2, as well as its entry into the host and its respective replication. Several investigators have reported the interaction of prostaglandin receptors, such as EP₄ (prostaglandin E₂ receptor 4), associated with

cell surface binding to immunoglobulins. At the same time, SARS CoV-2 infection has shown a significant increase in the synthesis and expression of COX-1 and COX-2 as well as up-regulation of PGE₂ production in mononuclear cells. On the contrary, an effect on the innate immune response has been observed.⁷²

Efficacy in COVID-19. The debate on whether NSAIDs (especially ibuprofen) increased susceptibility to acquire SARS CoV-2 infection was discussed since the onset of the pandemic. Some data revealed that there was up-regulation of ACE2 (angiotensin-converting enzyme) receptors as well as masking of symptoms such as fever. However, multiple regulatory bodies did not make recommendations in this regard due to lack of conclusive evidence.⁷³

Lund *et al.* conducted a population-based cohort study analyzing the impact of NSAIDs use in SARS CoV-2-positive patients. In matched analyses, treatment with NSAIDs was not associated with mortality, risk of ICU hospitalization, mechanical ventilation, or renal replacement therapy.⁷⁴ Some of the limitations of the study could be related to the use of NSAIDs to treat early symptoms of SARS CoV-2 disease, as well as the lack of knowledge about the prescribed therapeutic regimen and adherence to it.⁷⁴ Several meta-analyses have shown that using NSAIDs, including ibuprofen, does not increase the risk of serious complications such as severe acute respiratory distress syndrome (ARDS), hospitalization, ICU admission, and death, in patients both confirmed and suspected of SARS CoV-2 infection.^{75,76}

Safety and monitoring. In a retrospective observational cohort study, the use of NSAIDs has been associated with an increased risk for the development of acute kidney injury in patients with COVID-19.⁷⁷ However, it is important to analyze that several of them also received multiple antibiotic drugs such as vancomycin, piperacillin/tazobactam, and aminoglycosides with a significant risk of associated nephrotoxicity.⁷⁷

The risk of gastrointestinal injury is associated with the mechanism of action of NSAIDs, and in general, higher doses are associated with this outcome.⁷⁸ Even with selective COX-2 inhibitors, gastrointestinal injury has also been described.

For treating COVID-19, this might not be a major drawback since the expected duration of treatment will not exceed a few days to weeks. However, patients with significant cardiovascular comorbidities (e.g. obesity, uncontrolled diabetes, coronary artery disease, or ischemic stroke) might not be ideal candidates for using this agent.⁷⁹

For the prescription of NSAIDs in general, recommendations extrapolated from conventional scenarios are made. Monitor the patient's dose and comorbidities (e.g. obesity, uncontrolled diabetes mellitus, cardiovascular disease), as well as serum creatinine, urea nitrogen, blood count, and transaminases (occasionally elevated in patients with SARS CoV-2 infection). It is also suggested not to maintain prolonged periods.⁷⁸

Acetylsalicylic acid

As with NSAIDs, the use of acetylsalicylic acid (ASA) has been widely debated, in principle because of the risk of coagulopathy due to endothelial dysfunction and microvascular thrombosis that may occur in people with SARS CoV-2 infection.⁸⁰ ASA is associated with a reduction in atherosclerotic cardiovascular disease (ASCVD) when used for primary prevention; however, it is unlikely to be clinically significant given the increase in bleeding. More importantly, the effect of aspirin's treatment effect does not increase as ASCVD risk increases, as many hypothesize.^{81,82}

Efficacy in COVID-19. There are multiple studies with variable results to confirm whether the use of ASA is associated with an impact on morbidity and mortality in patients with COVID-19;⁸³ however, population size, patient admission characteristics during health care, and the use of other medications may eventually be limiting to the studies.⁷²

Kow and Hassan published a meta-analysis in which they reported reduced risk of severe COVID-19 with aspirin use relative to no treatment (pooled odds ratio=0.50; 95% confidence interval=0.32–0.77).⁸⁴ Likewise, in the meta-analysis by Ritika and Anoop, the odds ratio was found to be 0.70 [0.63, 0.77] indicating a lower probability of death in COVID-19 patients in the

aspirin group compared with non-aspirin group. However, no effect 0.00 [–0.04, 0.04] was observed after the exclusion of outliers.⁸⁵

On the contrary, Sahai *et al.*⁸⁶ performed a descriptive analysis in which they reported that the use of low doses of ASA had no significant impact on mortality *versus* those not taking this drug (13.3%–15.3%, $p=0.53$); however, using the composite thrombotic endpoint of MI (myocardial infarction), VTE (venous thromboembolisms), and thrombotic stroke, aspirin was associated with more thrombotic events (9.3% aspirin *versus* 2.8% non-aspirin; $p=0.005$).⁷⁴

Although multiple studies consider that there is no significant impact on mortality, the evidence remains variable⁸⁷ and it is important to continue evaluating the impact of this type of drug on COVID-19 outcomes.

Safety and monitoring. Although there are not many studies that have analyzed the safety of ASA in patients with SARS CoV-2, it is important to remember that this condition usually presents not only with thrombotic events but also with bleeding and thrombocytopenia, so the risk of bleeding should be taken into account. Likewise, in patients who present with cardiovascular thrombotic events and require both anticoagulation and antiplatelet therapy, ASA should be used with caution.^{74,76}

Vitamins (ascorbic acid)

Vitamin C has been proposed for the treatment of respiratory infections since it was isolated in the 1930s⁸⁸ and, for this reason, it has also been one of the most commonly used drugs during the pandemic. Recent studies suggest that ascorbic acid may attenuate pathological responses in the septic microvasculature. Some studies have shown that ascorbic acid infusion improved capillary blood flow and micro and arteriolar responsiveness to vasoconstrictors in septic animals.^{89,90}

It is a hydrophilic substance that limits its passage through simple diffusion. Absorption, distribution, and elimination are handled by the sodium-dependent vitamin C transporter (SVCT) family of proteins that cotransports sodium ions and ascorbate (ASC).⁹¹

Because of its antioxidant, immunomodulatory, and secondary anti-inflammatory mechanism, it could become a pharmacological strategy to treat patients with SARS CoV-2 infection.⁴⁵

Efficacy in COVID-19. There are few clinical trials that have studied the impact of ascorbic acid on mortality in patients with SARS CoV-2 infection. And those that have been performed have multiple limitations as well as small study populations.^{92,93}

Tomasa-Irriguible and Bielsa-Berrocal have recorded that the most critical patients admitted to the ICU had low or undetectable serum vitamin C levels. However, due to their limitations, they suggest further studies to confirm this finding in this condition.⁹⁴ Some studies conducted in China and Finland have suggested that the use of high doses of vitamin C could reduce the duration of respiratory symptoms such as cough, fatigue, and shortness of breath, as well as increase the PaO₂/FiO₂ ratio.^{95,96}

Thomas *et al.*⁹⁷ conducted an open-label randomized factorial trial using vitamin C; however, the study was terminated for lack of benefits after the interim analysis.

Now, there are still protocols under development analyzing the outcomes with ascorbic acid and vitamin D supplementation.^{98,99}

Safety and monitoring. Among the adverse effects recorded with high doses of ascorbic acid are acute tubular injury and oxalate nephropathy, so it would be pertinent to monitor in patients with associated renal disease or with multiple risk factors associated with renal injury.⁹⁵

Likewise, in patients with a history of glucose-6-phosphate dehydrogenase deficiency, a risk of hemolysis has been reported.¹⁰⁰

Chlorine dioxide and chlorine derivatives

Chlorine dioxide (ClO₂) and other chlorine derivatives are used as disinfecting agents in many scenarios due to their strong oxidant properties. ClO₂ usually derives from sodium chlorite mixed with a solution of water and other acids.¹⁰¹ The inactivation and denaturing of many proteins results in damage of organic compounds,

including virus inactivation. ClO₂ has been demonstrated to inactivate bacterial viruses through interaction with viral capsid proteins without significant damage to RNA material. Since then, it has been hypothesized that ClO₂ interacts with amino acid residues, mainly cysteine, tyrosine, tryptophan, histidine, hydroxyproline, and proline in a slower rate.¹⁰² For example, antimicrobial activity against influenza virus was related with denaturing of a hemagglutinin through a tryptophan residue, interfering with its receptor-binding capacity.¹⁰³ SARS CoV-2 contains a similar protein with 54 tyrosine, 12 tryptophan, and 40 cysteine residues.¹⁰⁴

To be effective, ClO₂ must be used in aqueous solution, so using moisturized gas can also inactivate environmental particles of viruses. There are disinfection methods that used sprayed ClO₂ solutions to achieve faster dispersion without reaching limit values, 0.1 ppm TWA and 0.3 ppm STEL.¹⁰⁵

Evidence in COVID-19. The presence of SARS CoV-2 in the mouth and upper and lower respiratory tract leads to the biological plausibility that disinfection of the nasal and oral cavity through direct application of ClO₂ could decrease the viral load. Its disinfecting properties lead to widespread advertisements of ClO₂ containing products to prevent and treat COVID-19 when administered by oral or parenteral route. A Cochrane review of antimicrobial mouthwashes and nasal sprays administered to patients with suspected or confirmed COVID-19 infection found a lack of clinical evidence for the efficacy of these approaches, lacking serious academic research regarding these products, with no information on changes in COVID-19 viral load in patients, the incidence of COVID-19-positive test or infection, or adverse effects, such as anosmia changes in the local microbiome in the oral cavity, nasal cavity, or pharynx.¹⁰⁶

Human alveoli can be affected by the oxidizing properties of ClO₂; in sufficient amount ClO₂ can decrease glutathione and other antioxidants by interacting directly with epithelial cells, leading to lung injury when environmental permitted limit values are surpassed. The FDA has received reports of ventricular arrhythmia, methemoglobinemia, hemolytic anemia associated with

liver dysfunction, and diarrhea when oral products are ingested.¹⁰⁵

Safety and monitoring. To date, The Pan American Health Organization (PAHO) does not recommend the use of chlorine dioxide or sodium chlorite by oral or parenteral route in patients with suspected or diagnosed with COVID-19.¹⁰⁷ Currently, there is no ongoing relevant study, likely due to no biological plausibility or preliminary clinical evidence to support its effectiveness in prevention or treatment and the risk of potential severe adverse effects.

Conclusion

In conclusion, self-medication is a natural behavior in response to a complex situation such as the COVID-19 pandemic. However, self-medication has associated risk factors to develop ADRs and DDIs and therefore healthcare professionals must recognize and approach this practice to assure the correct use of drugs. Most of the drugs used in self-medication for COVID-19 have poor evidence, and the available studies have important limitations. Self-medication was driven by the massive dissemination of misleading information at the onset of the pandemic, accompanied by the emergency authorization of regulatory agencies. The media should take responsibility for the information they give about therapeutics and they should support responsible self-medication and the rational use of medicines. There is a need to educate the general population about the advertised drugs and substances for the prevention and treatment of COVID-19 to avoid the risks of self-medication.

Author contributions

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