# Evidence Search Service Results of your search request

## Ivermectin as a therapy for Covid-19

**ID of request:** 26884  
**Date of request:** 30th December, 2020  
**Date of completion:** 6th January, 2021

If you would like to request any articles or any further help, please contact:  Igor Brbre at [igor.brbre@nhs.net](mailto:igor.brbre@nhs.net)

Please acknowledge this work in any resulting paper or presentation as: Evidence search: Ivermectin as a therapy for Covid-19. Igor Brbre. ( 6th January, 2021). BRIGHTON, UK: Brighton and Sussex Library and Knowledge Service.

**Sources searched**  
EMBASE (13)  
Europe PMC (15)  
Google (Advanced) (3)  
MEDLINE (18)  
UpToDate (1)

**Date range used** (5 years, 10 years): 2019-onwards   
**Limits used** (gender, article/study type, etc.): none   
**Search terms and notes** (full search strategy for database searches below):

Relevant natural language and controlled vocabulary terms were selected and combined. Thesaurus terms were adapted for different databases. Medline and Embase searched on OVID. Results were revieweved for relevance and de-duplicated in EndNote. Full search strategy below.

Pre-prints search in Europe PMC:

(("COVID-19" or COVID19 or 2019nCoV or "Corona Virus" or Coronavirus or "CoV 2" or CoV2 or COVID or nCoV or SARS2 or SARSCoV or "SARS-CoV") AND "ivermectin") AND (SRC:PPR)

First 100 most relevant results reviewed

For more information about the resources please go to: <https://www.bsuh.nhs.uk/library/>.

## Summary of Results

From the NEJM Journal Watch blog post:

"The clinical trials data for ivermectin look stronger than they ever did for hydroxychloroquine, but we're not quite yet at the “practice changing” level. Results from at least 5 randomized clinical trials are expected soon that might further inform the decision. NIH treatment guidelines [still recommend against the use of ivermectin for treatment of COVID-19,](https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/ivermectin/) a recommendation I support pending further data — we shouldn't have to wait long."

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### [E. Search History](#SearchHistory)

## A. Synopses or Summaries

#### UpToDate

**Coronavirus disease 2019 (COVID-19): Management in hospitalized adults** (2020)

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=5ef74b351e7aef6b97d1b5f36e4f40e9)

Ivermectin has also been proposed as a potential therapy based on in vitro activity against SARS-CoV-2, but the drug levels used in vitro far exceed those achieved in vivo with safe drug doses [129]. In a retrospective review of 280 patients hospitalized with COVID-19, receipt of ivermectin was associated with a lower mortality rate; however, patients who received ivermectin were also more likely to receive corticosteroids, highlighting the potential for confounders to impact the findings of nonrandomized studies [130]. Various clinical trials of ivermectin are underway, but the only results available thus far are from low-quality unpublished trials. As with other interventions that are not supported by high-quality data, we do not use ivermectin outside of clinical trials.

## B. Systematic Reviews

#### Canadian Society for Pharmaceutical Sciences

**Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis** (2020)

Padhy Biswa Mohan, Mohanty Rashmi Ranjan, Das Smita, Meher Bikash Ranjan

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=91e4e0a1d841d533c3faf4fe606f1242)

The current management of COVID-19 is mostly limited to general supportive care and symptomatic treatment. Ivermectin is a broad-spectrum anti-parasitic drug used widely for the treatment of onchocerciasis and lymphatic filariasis. Apart from its anti-parasitic effect it also exhibits antiviral activity against a number of viruses both in vitro and in vivo. Hence, we conducted this systematic review and meta-analysis to assess the currently available data on the therapeutic potential of ivermectin for the treatment of COVID-19 as add on therapy. A total of 629 patients were included in the 4 studies and all were COVID-19 RT-PCR positive. Among them, 397 patients received ivermectin along with usual therapy. The random effect model showed the overall pooled OR to be 0.53 (95%CI: 0.29 to0.96) for the primary outcome (all-cause mortality) which was statistically significant (P=0.04). Similarly, the random effect model revealed that adding ivermectin led to significant clinical improvement compared to usual therapy (OR=1.98, 95% CI: 1.11 to 3.53, P=0.02). However, this should be inferred cautiously as the quality of evidence is very low. Currently, many clinical trials are on-going, and definitive evidence for repurposing this drug for COVID-19 patients will emerge only in the future.

#### European Journal of Clinical Investigation

**Efficacy of various treatment modalities for nCOV-2019: A systematic review and meta-analysis** (2020)

Misra S., Nath M., Hadda V., Vibha D.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=b2260cbd48f30873e9315a6dbf4886c0)

Background: Several therapeutic agents have been investigated for treatment of novel coronavirus 2019 (nCOV-2019). We conducted a systematic review and meta-analysis to assess the efficacy of various treatment modalities in nCOV-2019 patients. Method(s): A literature search was conducted before 29 June 2020 in PubMed, Google Scholar and Cochrane library databases. A fixed-effect model was applied if I2 < 50%, else results were combined using random-effect model. Risk ratio (RR) or standardized mean difference (SMD) along with 95% confidence interval (95% CI) was used to pool the results. Between-study heterogeneity was explored using influence and sensitivity analyses, and publication bias was assessed using funnel plots. Entire statistical analysis was conducted in R version 3.6.2. Result(s): Fifty studies involving 15 in vitro and 35 clinical studies including 9170 nCOV-2019 patients were included. Lopinavir-ritonavir was significantly associated with shorter mean time to clinical recovery (SMD -0.32; 95% CI -0.57 to -0.06), remdesivir was significantly associated with better overall clinical recovery (RR 1.17; 95% CI 1.07 to 1.29), and tocilizumab was associated with less all-cause mortality (RR 0.38; 95% CI 0.16 to 0.93). Hydroxychloroquine was associated with longer time to clinical recovery and less overall clinical recovery. It additionally had higher all-cause mortality and more total adverse events. Conclusion(s): Our meta-analysis suggests that except in vitro studies, no treatment has shown overall favourable outcomes in nCOV-2019 patients. Lopinavir-ritonavir, remdesivir and tocilizumab may have some benefits, while hydroxychloroquine administration may cause harm in nCOV-2019 patients. Results from upcoming large clinical trials may further clarify role of these drugs.Copyright © 2020 Stichting European Society for Clinical Investigation Journal Foundation

#### PLoS medicine

**Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis** (2020)

Kim Min Seo, An Min Ho, Kim Won Jun, Hwang Tae-Ho

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=c52637af448a00d693ad617181bed5a0)

BACKGROUND: Numerous clinical trials and observational studies have investigated various pharmacological agents as potential treatment for Coronavirus Disease 2019 (COVID-19), but the results are heterogeneous and sometimes even contradictory to one another, making it difficult for clinicians to determine which treatments are truly effective., METHODS AND FINDINGS: We carried out a systematic review and network meta-analysis (NMA) to systematically evaluate the comparative efficacy and safety of pharmacological interventions and the level of evidence behind each treatment regimen in different clinical settings. Both published and unpublished randomized controlled trials (RCTs) and confounding-adjusted observational studies which met our predefined eligibility criteria were collected. We included studies investigating the effect of pharmacological management of patients hospitalized for COVID-19 management. Mild patients who do not require hospitalization or have self-limiting disease courses were not eligible for our NMA. A total of 110 studies (40 RCTs and 70 observational studies) were included. PubMed, Google Scholar, MEDLINE, the Cochrane Library, medRxiv, SSRN, WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov were searched from the beginning of 2020 to August 24, 2020. Studies from Asia (41 countries, 37.2%), Europe (28 countries, 25.4%), North America (24 countries, 21.8%), South America (5 countries, 4.5%), and Middle East (6 countries, 5.4%), and additional 6 multinational studies (5.4%) were included in our analyses. The outcomes of interest were mortality, progression to severe disease (severe pneumonia, admission to intensive care unit (ICU), and/or mechanical ventilation), viral clearance rate, QT prolongation, fatal cardiac complications, and noncardiac serious adverse events. Based on RCTs, the risk of progression to severe course and mortality was significantly reduced with corticosteroids (odds ratio (OR) 0.23, 95% confidence interval (CI) 0.06 to 0.86, p = 0.032, and OR 0.78, 95% CI 0.66 to 0.91, p = 0.002, respectively) and remdesivir (OR 0.29, 95% CI 0.17 to 0.50, p < 0.001, and OR 0.62, 95% CI 0.39 to 0.98, p = 0.041, respectively) compared to standard care for moderate to severe COVID-19 patients in non-ICU; corticosteroids were also shown to reduce mortality rate (OR 0.54, 95% CI 0.40 to 0.73, p < 0.001) for critically ill patients in ICU. In analyses including observational studies, interferon-alpha (OR 0.05, 95% CI 0.01 to 0.39, p = 0.004), itolizumab (OR 0.10, 95% CI 0.01 to 0.92, p = 0.042), sofosbuvir plus daclatasvir (OR 0.26, 95% CI 0.07 to 0.88, p = 0.030), anakinra (OR 0.30, 95% CI 0.11 to 0.82, p = 0.019), tocilizumab (OR 0.43, 95% CI 0.30 to 0.60, p < 0.001), and convalescent plasma (OR 0.48, 95% CI 0.24 to 0.96, p = 0.038) were associated with reduced mortality rate in non-ICU setting, while high-dose intravenous immunoglobulin (IVIG) (OR 0.13, 95% CI 0.03 to 0.49, p = 0.003), ivermectin (OR 0.15, 95% CI 0.04 to 0.57, p = 0.005), and tocilizumab (OR 0.62, 95% CI 0.42 to 0.90, p = 0.012) were associated with reduced mortality rate in critically ill patients. Convalescent plasma was the only treatment option that was associated with improved viral clearance rate at 2 weeks compared to standard care (OR 11.39, 95% CI 3.91 to 33.18, p < 0.001). The combination of hydroxychloroquine and azithromycin was shown to be associated with increased QT prolongation incidence (OR 2.01, 95% CI 1.26 to 3.20, p = 0.003) and fatal cardiac complications in cardiac-impaired populations (OR 2.23, 95% CI 1.24 to 4.00, p = 0.007). No drug was significantly associated with increased noncardiac serious adverse events compared to standard care. The quality of evidence of collective outcomes were estimated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. The major limitation of the present study is the overall low level of evidence that reduces the certainty of recommendations. Besides, the risk of bias (RoB) measured by RoB2 and ROBINS I framework for individual studies was generally low to moderate. The outcomes deducted from observational studies could not infer causality and can only imply associations. The study protocol is publicly available on PROSPERO (CRD42020186527)., CONCLUSIONS: In this NMA, we found that anti-inflammatory agents (corticosteroids, tocilizumab, anakinra, and IVIG), convalescent plasma, and remdesivir were associated with improved outcomes of hospitalized COVID-19 patients. Hydroxychloroquine did not provide clinical benefits while posing cardiac safety risks when combined with azithromycin, especially in the vulnerable population. Only 29% of current evidence on pharmacological management of COVID-19 is supported by moderate or high certainty and can be translated to practice and policy; the remaining 71% are of low or very low certainty and warrant further studies to establish firm conclusions.

#### The Journal of antibiotics

**Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen** (2020)

Heidary Fatemeh, Gharebaghi Reza

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=4099dd16212b60b2807a83df7f6aa37b)

Ivermectin proposes many potentials effects to treat a range of diseases, with its antimicrobial, antiviral, and anti-cancer properties as a wonder drug. It is highly effective against many microorganisms including some viruses. In this comprehensive systematic review, antiviral effects of ivermectin are summarized including in vitro and in vivo studies over the past 50 years. Several studies reported antiviral effects of ivermectin on RNA viruses such as Zika, dengue, yellow fever, West Nile, Hendra, Newcastle, Venezuelan equine encephalitis, chikungunya, Semliki Forest, Sindbis, Avian influenza A, Porcine Reproductive and Respiratory Syndrome, Human immunodeficiency virus type 1, and severe acute respiratory syndrome coronavirus 2. Furthermore, there are some studies showing antiviral effects of ivermectin against DNA viruses such as Equine herpes type 1, BK polyomavirus, pseudorabies, porcine circovirus 2, and bovine herpesvirus 1. Ivermectin plays a role in several biological mechanisms, therefore it could serve as a potential candidate in the treatment of a wide range of viruses including COVID-19 as well as other types of positive-sense single-stranded RNA viruses. In vivo studies of animal models revealed a broad range of antiviral effects of ivermectin, however, clinical trials are necessary to appraise the potential efficacy of ivermectin in clinical setting.

#### medRxiv

**THE THERAPEUTIC POTENTIAL OF IVERMECTIN FOR COVID-19: A SYSTEMATIC REVIEW OF MECHANISMS AND EVIDENCE** (2020)

Kalfas Stefanie, Visvanathan Kumar, Chan Kim, Drago John

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=66ab3a23700def060958955c928c7814)

Results Search keywords-“COVID-19 (and synonyms) AND ivermectin”-generated 86 articles on PubMed, 48 on medRvix and 37 on clinicaltrials.gov at the time of writing. Twelve of these were listed as completed clinical trials and of these, 8 were included as investigators had released results. Positive mortality benefit, reduced time to clinical recovery, reduced incidence of disease progression and decreased duration of hospital admission were reported in patients across all stages of clinical severity. Limitations Due to the time-critical nature of the COVID-19 pandemic our review included preprint data, which must be interpreted with caution while it awaits peer review.

## C. Institutional Publications

#### CovidAnalysis

**Overview of all covid-19 ivermectin studies** (2021)

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=22bf65697aaf71d6747b926808d58b61)

Also by the same authors: Ivermectin is effective for COVID-19: meta analysis of 28 studies https://ivmmeta.com/

#### NEJM Journal Watch

**Ivermectin for COVID-19 — Breakthrough Treatment or Hydroxychloroquine Redux?** (2021)

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=b8275d8eba24f99354d7b327c1fd6769)

The clinical trials data for ivermectin look stronger than they ever did for hydroxychloroquine, but we’re not quite yet at the “practice changing” level. Results from at least 5 randomized clinical trials are expected soon that might further inform the decision. NIH treatment guidelines still recommend against use of ivermectin for treatment of COVID-19, a recommendation I support pending further data — we shouldn’t have to wait long.

#### Swiss Policy Research

**Covid-19: WHO-sponsored preliminary review indicates Ivermectin effectiveness** (2020)

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=6508b5187b623e900b22aa235268c4b2)

## D. Original Research

1. **A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness**  
   Ahmed Sabeena International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2020;:No page numbers.

Ivermectin, an FDA-approved anti-parasitic agent, was found in vitro to inhibit SARS-CoV-2 replication. To determine the rapidity of viral clearance and safety of ivermectin among adult SARS-CoV-2 patients we conducted a randomized, double-blind, placebo-controlled trial of oral ivermectin alone (12 mg once daily for 5 days) or in combination with doxycycline (12 mg ivermectin single dose and 200 mg stat doxycycline day-1 followed by 100 mg 12hrly for next 4 days) compared with placebo among 72 hospitalized patients in Dhaka, Bangladesh. Clinical symptoms of fever, cough and sore throat were comparable among the three treatment arms. Virological clearance was earlier in the 5-day ivermectin treatment arm versus the placebo group (9.7 days vs. 12.7 days; P = 0.02); but not with the ivermectin + doxycycline arm (11.5 days; P = 0.27). There were no severe adverse drug events recorded in the study. A 5-day course of ivermectin was found to be safe and effective in treating mild COVID-19 adult patients. Larger trials will be needed to confirm these preliminary findings. Copyright © 2020. Published by Elsevier Ltd.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=5737736cfd9ed0834512946aabe4b237)

1. **A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients**  
   Chowdhury Abu Taiub Mohammed Mohiuddin 2020;:No page numbers.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=443562b4a04d2712973aeff3881fe5ec)

1. **Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19: A Pilot Randomised, Controlled, Open Label, Multicentre Trial**  
   Krolewiecki Alejandro 2020;:No page numbers.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=f9eb0f98cda022f94acf3795dfe3a3cf)

1. **Antiviral treatment of covid-19**  
   Simsek Yavuz S. Turkish Journal of Medical Sciences 2020;50:611-619.

Currently, there is not any specific effective antiviral treatment for COVID-19. Although most of the COVID-19 patients have mild or moderate courses, up to 5%-10% can have severe, potentially life threatening course, there is an urgent need for effective drugs. Optimized supportive care remains the mainstay of therapy. There have been more than 300 clinical trials going on, various antiviral and immunomodulating agents are in various stages of evaluation for COVID-19 in those trials and some of them will be published in the next couple of months. Despite the urgent need to find an effective antiviral treatment for COVID-19 through randomized controlled studies, certain agents are being used all over the world based on either in-vitro or extrapolated evidence or observational studies. The most frequently used agents both in Turkey and all over the world including chloroquine, hydroxychloroquine, lopinavir/ ritonavir, favipiravir and remdesivir will be reviewed here.Nitazoxanide and ivermectin were also included in this review as they have recently been reported to have an activity against SARS-CoV-2 in vitro and are licensed for the treatment of some other human infections.Copyright © TUBITAK.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=01c80f9a9b37e54cb20aeb8d163231f8)

1. **Binding Mechanism and Structural Insights into the Identified Protein Target of Covid-19 with In-Vitro Effective Drug Ivermectin**  
   Sen Gupta Parth Sarthi 2020;:No page numbers.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=dbd8f69f4b0dbec05e3b78cb16a8514a)

1. **Clinically approved antiviral drug in an orally administrable nanoparticle for COVID-19**  
   Dhar S. ACS Pharmacology and Translational Science 2020;:No page numbers.

There is urgent therapeutic need for COVID-19, a disease for which there are currently no widely effective approved treatments and the emergency use authorized drugs do not result in significant and widespread patient improvement. The food and drug administration-approved drug ivermectin has long been shown to be both antihelmintic agent and a potent inhibitor of viruses such as Yellow Fever Virus. In this study, we highlight the potential of ivermectin packaged in an orally administrable nanoparticle that could serve as a vehicle to deliver a more potent therapeutic antiviral dose and demonstrate its efficacy to decrease expression of viral spike protein and its receptor angiotensin-converting enzyme 2 (ACE2), both of which are keys to lowering disease transmission rates. We also report that the targeted nanoparticle delivered ivermectin is able to inhibit the nuclear transport activities mediated through proteins such as importin alpha/beta1 heterodimer as a possible mechanism of action. This study sheds light on ivermectin-loaded, orally administrable, biodegradable nanoparticles to be a potential treatment option for the novel coronavirus through a multilevel inhibition. As both ACE2 targeting and the presence of spike protein are features shared among this class of virus, this platform technology has the potential to serve as a therapeutic tool not only for COVID-19 but for other coronavirus strains as well.Copyright © 2020 American Chemical Society. All rights reserved.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=7aec54f17f63e52ea36fd3bd49c56af9)

1. **Clinically Approved Antiviral Drug in an Orally Administrable Nanoparticle for COVID-19**  
   Surnar Bapurao ACS pharmacology & translational science 2020;3:1371-1380.

There is urgent therapeutic need for COVID-19, a disease for which there are currently no widely effective approved treatments and the emergency use authorized drugs do not result in significant and widespread patient improvement. The food and drug administration-approved drug ivermectin has long been shown to be both antihelmintic agent and a potent inhibitor of viruses such as Yellow Fever Virus. In this study, we highlight the potential of ivermectin packaged in an orally administrable nanoparticle that could serve as a vehicle to deliver a more potent therapeutic antiviral dose and demonstrate its efficacy to decrease expression of viral spike protein and its receptor angiotensin-converting enzyme 2 (ACE2), both of which are keys to lowering disease transmission rates. We also report that the targeted nanoparticle delivered ivermectin is able to inhibit the nuclear transport activities mediated through proteins such as importin alpha/beta1 heterodimer as a possible mechanism of action. This study sheds light on ivermectin-loaded, orally administrable, biodegradable nanoparticles to be a potential treatment option for the novel coronavirus through a multilevel inhibition. As both ACE2 targeting and the presence of spike protein are features shared among this class of virus, this platform technology has the potential to serve as a therapeutic tool not only for COVID-19 but for other coronavirus strains as well. Copyright © 2020 American Chemical Society.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=bee634ed3b3cb5249942fd9a80ddfa89)

1. **Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq**  
   Hashim Hashim 2020;:No page numbers.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=059b7cceb9bbcd887028da567053d541)

1. **COVID-19 and nutriceutical therapies, especially using zinc to supplement antimicrobials**  
   Butters D. Inflammopharmacology 2020;:No page numbers.

The nutritional status of a patient can be critical for the efficacy of other pharmaceuticals, especially organic antibiotics, to treat viral pandemics. There may be political and scientific difficulties in achieving a constructive synergy of nutritional and prescribed allopathic remedies. For adequate treatment, timelines may need to extend well beyond eliminating viral proliferation, e.g., with vaccines, to include the goals of (a) reducing post-viral fatigue, (b) promoting earliest recovery, and (c) future resistance in often poorly nourished patients, e.g., obese (!). Many trace minerals (TM) and vitamins may need to be replenished. This review focusses only upon zinc to illustrate some problems in rectifying these TM deficiencies affecting the balance between continued ill-health ('illth') or regaining optimal physical and mental wellbeing. Ultimately, this is a matter of behaviour, lifestyle, and informed choice(s). See Hetzel and McMichael 1959.Copyright © 2020, Springer Nature Switzerland AG.

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1. **Current status and strategic possibilities on potential use of combinational drug therapy against COVID-19 caused by SARS-CoV-2**  
   Siddiqui Arif Jamal Journal of biomolecular structure & dynamics 2020;:1-14.

The spread of new coronavirus infection starting December 2019 as novel SARS-CoV-2, identified as the causing agent of COVID-19, has affected all over the world and been declared as pandemic. Approximately, more than 8,807,398 confirmed cases of COVID-19 infection and 464,483 deaths have been reported globally till the end of 21 June 2020. Until now, there is no specific drug therapy or vaccine available for the treatment of COVID-19. However, some potential antimalarial drugs like hydroxychloroquine and azithromycin, antifilarial drug ivermectin and antiviral drugs have been tested by many research groups worldwide for their possible effect against the COVID-19. Hydroxychloroquine and ivermectin have been identified to act by creating the acidic condition in cells and inhibiting the importin (IMPalpha/beta1) mediated viral import. There is a possibility that some other antimalarial drugs/antibiotics in combination with immunomodulators may help in combatting this pandemic disease. Therefore, this review focuses on the current use of various drugs as single agents (hydroxychloroquine, ivermectin, azithromycin, favipiravir, remdesivir, umifenovir, teicoplanin, nitazoxanide, doxycycline, and dexamethasone) or in combinations with immunomodulators additionally. Furthermore, possible mode of action, efficacy and current stage of clinical trials of various drug combinations against COVID-19 disease has also been discussed in detail. Communicated by Ramaswamy H. Sarma.

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1. **Development of a Minimal Physiologically-Based Pharmacokinetic Model to Simulate Lung Exposure in Humans Following Oral Administration of Ivermectin for COVID-19 Drug Repurposing**  
   Jermain B. Journal of Pharmaceutical Sciences 2020;109:3574-3578.

SARS-CoV-2 utilizes the IMPalpha/beta1 heterodimer to enter host cell nuclei after gaining cellular access through the ACE2 receptor. Ivermectin has shown antiviral activity by inhibiting the formation of the importin-alpha (IMPalpha) and IMPbeta1 subunits as well as dissociating the IMPalpha/beta1 heterodimer and has in vitro efficacy against SARS-CoV-2. Plasma and lung ivermectin concentrations vs. time profiles in cattle were used to determine the apparent plasma to lung tissue partition coefficient of ivermectin. This coefficient, together with a simulated geometric mean plasma profile of ivermectin from a published population pharmacokinetic model, was utilized to develop a minimal physiologically-based pharmacokinetic (mPBPK) model. The mPBPK model accurately described the simulated ivermectin plasma concentration profile in humans. The mPBPK model was also used to simulate human lung exposure to ivermectin after 12, 30, and 120 mg oral doses. The simulated ivermectin lung exposures reached a maximum concentration of 772 ng/mL, far less than the estimated 1750 ng/mL IC50 reported for ivermectin against SARS-CoV-2 in vitro. Further studies of ivermectin either reformulated for inhaled delivery or in combination with other antivirals with differing mechanisms of action is needed to assess its therapeutic potential.Copyright © 2020

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1. **Diagnostic approaches and potential therapeutic options for coronavirus disease 2019**  
   Khan Z. New Microbes and New Infections 2020;38:100770.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan city of China in late December 2019 and identified as a novel coronavirus. Due to its contagious nature, the virus spreads rapidly and causes coronavirus disease 2019 (COVID-19). The global tally of COVID-19 was 28 million in early September 2020. The fears and stress associated with SARS-CoV-2 has demolished the socio-economic status worldwide. Researchers are trying to identify treatments, especially antiviral drugs and/or vaccines, that could potentially control the viral spread and manage the ongoing unprecedented global crisis. To date, more than 300 clinical trials have been conducted on various antiviral drugs, and immunomodulators are being evaluated at various stages of COVID-19. This review aims to collect and summarize a list of drugs used to treat COVID-19, including dexamethasone, chloroquine, hydroxychloroquine, lopinavir/ritonavir, favipiravir, remdesivir, tociluzimab, nitazoxanide and ivermectin. However, some of these drugs are not effective and their use has been suspended by WHO.Copyright © 2020 The Authors

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1. **Drug repositioning: New approaches and future prospects for life-debilitating diseases and the COVID-19 pandemic outbreak**  
   Low Z. Y. Viruses 2020;12:1058.

Traditionally, drug discovery utilises a de novo design approach, which requires high cost and many years of drug development before it reaches the market. Novel drug development does not always account for orphan diseases, which have low demand and hence low-profit margins for drug developers. Recently, drug repositioning has gained recognition as an alternative approach that explores new avenues for pre-existing commercially approved or rejected drugs to treat diseases aside from the intended ones. Drug repositioning results in lower overall developmental expenses and risk assessments, as the efficacy and safety of the original drug have already been well accessed and approved by regulatory authorities. The greatest advantage of drug repositioning is that it breathes new life into the novel, rare, orphan, and resistant diseases, such as Cushing's syndrome, HIV infection, and pandemic outbreaks such as COVID-19. Repositioning existing drugs such as Hydroxychloroquine, Remdesivir, Ivermectin and Baricitinib shows good potential for COVID-19 treatment. This can crucially aid in resolving outbreaks in urgent times of need. This review discusses the past success in drug repositioning, the current technological advancement in the field, drug repositioning for personalised medicine and the ongoing research on newly emerging drugs under consideration for the COVID-19 treatment.Copyright © 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

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1. **Has Ivermectin Virus-Directed Effects against SARS-CoV-2? Rationalizing the Action of a Potential Multitarget Antiviral Agent**  
   Francés-Monerris Antonio 2020;:No page numbers.

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1. **HIV-1 versus SARS-CoV-2 infection: understanding the population genetic aspects of drug inefficacy (especially ivermectin) in the integrase-importin complex**  
   Felix Pierre Teodosio 2020;:No page numbers.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=09602d726bcbe83cdd6819da68c493cd)

1. **Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view**  
   Momekov Georgi 2020;:No page numbers.

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1. **Ivermectin as a promising RNA-dependent RNA polymerase inhibitor and a therapeutic drug against SARS-CoV2: Evidence from in silico studies**  
   Swargiary Ananta 2020;:No page numbers.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=533e0e844054378e57df716c7d5f58ff)

1. **Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial**  
   Niaee Morteza Shakhsi 2020;:No page numbers.

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1. **Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2**  
   Lehrer S. In Vivo 2020;34:3023-3026.

Background/Aim: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). One drug that has attracted interest is the antiparasitic compound ivermectin, a macrocyclic lactone derived from the bacterium Streptomyces avermitilis. We carried out a docking study to determine if ivermectin might be able to attach to the SARS-CoV-2 spike receptor-binding domain bound with ACE2. Material(s) and Method(s): We used the program AutoDock Vina Extended to perform the docking study. Result(s): Ivermectin docked in the region of leucine 91 of the spike and histidine 378 of the ACE2 receptor. The binding energy of ivermectin to the spike-ACE2 complex was -18 kcal/mol and binding constant was 5.8 e-08. Conclusion(s): The ivermectin docking we identified may interfere with the attachment of the spike to the human cell membrane. Clinical trials now underway should determine whether ivermectin is an effective treatment for SARS-Cov2 infection.Copyright © 2020 International Institute of Anticancer Research. All rights reserved.

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1. **Ivermectin for COVID-19 Treatment: Clinical Response at Quasi-Threshold Doses Via Hypothesized Alleviation of CD147-Mediated Vascular Occlusion**  
   Scheim David 2020;:No page numbers.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=6ce6a15401034f358f456036d70e8e2b)

1. **Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19**  
   DiNicolantonio James J. Open heart 2020;7:No page numbers.

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1. **Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19): a structured summary of a study protocol for a randomized controlled trial**  
   Vallejos Julio Trials 2020;21:965.

OBJECTIVES: To assess the efficacy of ivermectin in addition to standard treatment compared to standard treatment alone in reducing hospitalizations in the COVID-19 patient population., TRIAL DESIGN: IVERCOR-COVID19 will be a single-center, prospective, randomized, double-blind, parallel group (1:1 ratio), placebo-controlled study., PARTICIPANTS: Patients who meet the following criteria will be invited to participate: Inclusion criteria: (1) Over 18 years of age who reside in the province of Corrientes at the time of diagnosis. (2) Confirmed diagnosis of COVID-19 by polymerase chain reaction (PCR) test for detection of SARS-CoV2 in the last 48 h. (3) In the case of women of childbearing age, they must be using a contraceptive method of proven efficacy and safety (barrier, hormonal, or permanent contraceptives) for at least 3 months prior to inclusion in the present study and for the entire period of time for the duration of the study and until at least 30 days after the end of this study. A woman will be considered to have no reproductive capacity if she is postmenopausal (at least 2 years without her menstrual cycles) or if she has undergone surgical sterilization (at least 1 month before the time of inviting her to participate in this study). (4) Weight at the time of inclusion greater than 48 kg. (5) That they sign the informed consent for participation in the study., EXCLUSION CRITERIA: (1) pregnant or breastfeeding women; (2) known allergy to ivermectin or some of the components of ivermectin tablets or placebo; (3) current use of home oxygen; (4) require hospitalization due to COVID-19 at the time of diagnosis or history of hospitalization for COVID-19; (5) presence of mal-absorptive syndrome; (6) presence of any other concomitant acute infectious disease; (7) known history of severe liver disease, for example liver cirrhosis; (8) need or use of antiviral drugs at the time of admission for another viral pathology other than COVID-19; (9) need or use of hydroxychloroquine or chloroquine; (10) use of ivermectin up to 7 days prior to randomization; (11) patients on dialysis or who have required it in the last 2 months or who plan to do it in the next 2 months; and (12) current participation or in the last 30 days in a research study that has included the administration of a drug (Table 1). Table 1 Ivermectin/placebo dose according to patient weight Patient weight Ivermectin/placebo dose Total dose (mg) Equal to or greater than 48 kg and less than 80 kg 2 tablets of 6 mg each at the time of inclusion and 2 tablets 24 h after the first intake 24 Equal or greater than 80 kg and less than 110 kg 3 tablets of 6 mg each at the time of inclusion and 3 tablets 24 h after the first intake 36 Equal or greater than 110 kg 4 tablets of 6 mg each at the time of inclusion and 4 tablets 24 h after the first intake 48 The study will be carried out by the Ministry of Public Health of the Province of Corrientes (Argentina) in coordination with the Institute of Cardiology of Corrientes in the Province of Corrientes, Argentina., INTERVENTION AND COMPARATOR: Intervention group: patients who are randomized to ivermectin will receive the dose according to their weight (patients up to 80 kg will receive 2 tablets of 6 mg ivermectin; patients with more than 80 kg and up to 110 kg will receive 3 tablets of 6 mg of ivermectin; patients weighing more than 110 kg will receive 4 tablets of 6 mg ivermectin) the day they enter the study and the same dose 24 h after the first dose., CONTROL GROUP: patients who are randomized to placebo will receive the dose according to their weight (patients up to 80 kg will receive 2 tablets of 6 mg placebo; patients with more than 80 kg and up to 110 kg will receive 3 tablets of 6 mg of placebo; patients weighing more than 110 kg will receive 4 tablets of 6 mg placebo) on the day they enter the study and the same dose 24 h after the first dose (Table 2). Table 2 Inclusion and exclusion criteria Inclusion criteria Exclusion criteria 1. Over 18 years of age who reside in the province of Corrientes at the time f diagnosis 1. Pregnant or breastfeeding women 2.Confirmed diagnosis of COVID-19 by polymerase chain reaction test for detection of SARS-CoV2 in the last 48 h 2. Known allergy to ivermectin or some of the components of ivermectin tablets or placebo 3. In case of being women of childbearing age, they must be using a contraceptive method of proven efficacy and safety (barrier, hormonal, or permanent contraceptives) for at least 3 months prior to inclusion in the present study, during the entire period of time for the duration of the study, and until at least 30 days after the end of this study. A woman will be considered to have no reproductive capacity if she is postmenopausal (at least 2 years without her menstrual cycles) or if she has undergone surgical sterilization (at least 1 month before the time of inviting her to participate in this study) 3. Current use of home oxygen 4. Weight at the time of inclusion equal to or greater than 48 kg 4. That require hospitalization due to COVID-19 at the time of diagnosis or history of hospitalization for COVID-19 5. That they sign the informed consent for participation in the study 5. Presence of mal-absorptive syndrome 6. Presence of any other concomitant acute infectious disease 7. Known history of severe liver disease, for example liver cirrhosis 8. Need or use of antiviral drugs at the time of admission for another viral pathology other than COVID-19 9. Need or use of hydroxychloroquine or chloroquine 10. Use of ivermectin up to 7 days prior to randomization 11. Patients on dialysis or who have required it in the last 2 months or who plan to do it in the next 2 months 12. Current participation or in the last 30 days in a research study that has included the administration of a drug MAIN OUTCOMES: Primary outcome will be the percentage of hospitalizations in patients with COVID-19 in the intervention and control groups., SECONDARY OUTCOMES: time to hospitalization in each of the arms of the study: number of days elapsed from the inclusion in the study until the hospitalization of the patient; percentage of use of invasive mechanical ventilation in each of the study arms: every patient who is connected to invasive mechanical ventilation after signing the informed consent and before the final study visit; time to invasive mechanical ventilation in each of the arms of the study: number of days elapsed from inclusion in the study to connection to invasive mechanical ventilation of the patient; percentage of patients requiring dialysis in each of the study arms: all patients who require renal replacement therapy of any kind, temporary or permanent, and which begins after signing the informed consent and before the final visit; mortality from all causes in each of the two trial groups: death of the patient, from any cause. Negative PCR swab at 3 +/- 1 and 12 +/- 2 days after entering the study. Ivermectin safety: it will be analyzed according to the incidence of adverse events that patients present in the intervention and control groups. The end of study (EOS) is recorded as the day the patient is discharged or death. Discharge will be granted according to the current recommendations of the Ministry of Public Health of the Province of Corrientes. A follow-up visit (EOF) will be made by phone 30 days after the EOS when vital status will be verified., RANDOMIZATION: Randomization will be done through a web system with randomly permuted blocks. Randomization will be carried out by one of the investigators who will not participate in the inclusion of patients or in the delivery of medication (Table 3). Table 3 EOS end of study, EOF end of follow-up Visit Basal and randomization, day 0 Day 3 +/- 1 Day 12 +/- 2 V#1 V#2 V#3 EOS EOF Informed consent X - - - - Inclusion/exclusion criteria X - - - - Demographic data and medical history X - - - - Concomitant medication X - - - - Vital signs\* X X - - - Anthropometric data^ X - - - - Basal laboratory X - - - - PCR swab - X X - - Assessment of adverse events - X X X - Final objective evaluation - X X X X Randomization X - - - - Adherence to trea ment X X - - - \*Includes heart rate, temperature, and oxygen saturation by a digital saturometer ^Includes weight and height BLINDING (MASKING): The participants, investigators, care providers, and outcome assessors will be blinded., NUMBERS TO BE RANDOMIZED (SAMPLE SIZE): We will include a total of 500 patients (250 patients in each group)., TRIAL STATUS: This is version 1.0, 17 August 2020. The recruitment started on 19 August 2020, and we anticipate the trial will finish recruitment on 31 December 2020., TRIAL REGISTRATION: ClinicalTrials.gov NCT04529525 . Registered on 26 August 2020 FULL PROTOCOL: The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest of expediting the dissemination of this material, the familiar formatting has been eliminated; this letter serves as a summary of the key elements of the full protocol.

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1. **Ivermectin: Potential Role as Repurposed Drug for COVID-19**  
   Dixit Alok The Malaysian journal of medical sciences : MJMS 2020;27:154-158.

Severe acute respiratory illness caused by 2019 novel coronavirus (2019-nCoV), officially named severe acute respiratory syndrome coronavirus (SARS-CoV-2) in late December 2019 is an extremely communicable disease. World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a pandemic as it has spread to at least 200 countries in a short span of time. Being a new disease there is lack of information about pathogenesis and proliferation pathways of this new coronavirus. Currently there is no effective treatment for coronavirus infection; major effort is to develop vaccine against the virus and development of therapeutic drugs for the disease. The development of genome-based vaccine and therapeutic antibodies require thorough testing for safety and will be available after some time. In the meanwhile, the available practical approach is to repurpose existing therapeutic agents, with proven safety record as a rapid response measure for the current pandemic. Here we discuss the presently used repurposed drugs for COVID-19 and the potential for ivermectin (IVM) to be used as a therapeutic option in COVID-19. Copyright © Penerbit Universiti Sains Malaysia, 2020.

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1. **Ivermectin: repurposing a multipurpose drug for Venezuela's humanitarian crisis**  
   Perez-Garcia Luis A. International journal of antimicrobial agents 2020;56:106037.

Ivermectin (IVM) is a robust antiparasitic drug with an excellent tolerance and safety profile. Historically it has been the drug of choice for onchocerciasis and lymphatic filariasis global elimination programs. IVM is an oral insecticide and is a standard treatment against intestinal helminths and ectoparasites. The current humanitarian crisis in Venezuela is a regional public health threat that requires immediate action. The public health system in Venezuela has crumbled because of a 70% shortage of medicines in public hospitals, low vaccination campaigns, and the mass exodus of medical personnel. Herein we discuss the repurposing of IVM to attenuate the burden imposed by the most prevalent neglected tropical diseases (NTDs) in Venezuela, including soil-transmitted helminths, ectoparasites and, possibly, vector-borne diseases, such as malaria. In addition, novel experimental evidence has shown that IVM is active and efficacious in vitro against Chagas disease, Leishmaniases, arboviruses, and SARS-CoV-2. In crisis-hit Venezuela, all these infectious diseases are public health emergencies that have long been ignored and require immediate attention. The versatility of IVM could serve as a powerful tool to tackle the multiple overlapping endemic and emergent diseases that currently affect Venezuela. The repurposing of this multipurpose drug would be a timely therapeutic approach to help mitigate the tremendous burden of NTDs nationwide. Copyright © 2020. Published by Elsevier Ltd.

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1. **Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients**  
   Camprubi Daniel PloS one 2020;15:e0242184.

Ivermectin has recently shown efficacy against SARS-CoV-2 in-vitro. We retrospectively reviewed severe COVID-19 patients receiving standard doses of ivermectin and we compared clinical and microbiological outcomes with a similar group of patients not receiving ivermectin. No differences were found between groups. We recommend the evaluation of high-doses of ivermectin in randomized trials against SARS-CoV-2.

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1. **Nitazoxanide/azithromycin combination for COVID-19: A suggested new protocol for early management**  
   Kelleni M. T. Pharmacological Research 2020;157:104874.

Azithromycin has been shown to have a clinical efficacy against severe acute respiratory syndrome coronavirus 2; ivermectin has also demonstrated a remarkable experimental efficacy with a potential to be used for Coronavirus disease 2019. Further, BCG vaccination is being considered for clinical trials aiming to test its potential for lowering COVID-19 morbidity and mortality. This article illustrates some structural and functional relationships that may gather these drugs and the author, basing on a combined pathophysiological and pharmacological approach, recommends the FDA-approved antidiarrhea drug; nitazoxanide, which has been previously suggested but unfortunately widely ignored, to be tested in combination with azithromycin for their potential activity against SARS CoV-2, soonest. The author also recommends testing their combined administration as early during the clinical course of COVID-19 as possible. Further, basing on the same represented concept, the author suggests more trials for interferons to be tested against SARS CoV-2, especially in severe and critical COVID-19 cases.Copyright © 2020 Elsevier Ltd

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1. **Old and re-purposed drugs for the treatment of COVID-19**  
   Jean S. S. Expert Review of Anti-Infective Therapy 2020;18:843-847.

Introduction: The coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has developed since December 2019. It has caused a global pandemic with more than three hundred thousand case fatalities. However, apart from supportive care by respirators, no standard medical therapy is validated. Areas covered: This paper presents old drugs with potential in vitro efficacy against SARS-CoV-2. The in vitro database, adverse effects, and potential toxicities of these drugs are reviewed regarding their feasibility of clinical prescription for the treatment of patients with COVID-19. To obtain convincing recommendations, we referred to opinions from the US National Institute of Health regarding drugs repurposed for COVID-19 therapy. Expert opinion: Although strong evidence of well-designed randomized controlled studies regarding COVID-19 therapy is presently lacking, remdesivir, teicoplanin, hydroxychloroquine (not in combination with azithromycin), and ivermectin might be effective antiviral drugs and are deemed promising candidates for controlling SARS-CoV-2. In addition, tocilizumab might be considered as the supplementary treatment for COVID-19 patients with cytokine release syndrome. In future, clinical trials regarding a combination of potentially effective drugs against SARS-CoV-2 need to be conducted to establish the optimal regimen for the treatment of patients with moderate-to-severe COVID-19.Copyright © 2020 Informa UK Limited, trading as Taylor & Francis Group.

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1. **Potential diagnostics and therapeutic approaches in COVID-19**  
   Kumari P. Clinica Chimica Acta 2020;510:488-497.

The most important aspect of controlling COVID-19 is its timely diagnosis. Molecular diagnostic tests target the detection of any of the following markers such as the specific region of the viral genome, certain enzyme, RNA-dependent RNA polymerase, the structural proteins such as surface spike glycoprotein, nucleocapsid protein, envelope protein, or membrane protein of SARS-CoV-2. This review highlights the underlying mechanisms, advancements, and clinical limitations for each of the diagnostic techniques authorized by the Food and Drug Administration (USA). Significance of diagnosis triaging, information on specimen collection, safety considerations while handling, transport, and storage of samples have been highlighted to make medical and research community more informed so that better clinical strategies are developed. We have discussed here the clinical manifestations and hospital outcomes along with the underlying mechanisms for several drugs administered to COVID-19 prophylaxis. In addition to favourable clinical outcomes, the challenges, and the future directions of management of COVOD-19 are highlighted. Having a comprehensive knowledge of the diagnostic approaches of SARS-CoV-2, and its pathogenesis will be of great value in designing a long-term strategy to tackle COVID-19.Copyright © 2020 Elsevier B.V.

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1. **Remdesivir-Ivermectin combination displays synergistic interaction with improved in vitro antiviral activity against SARS-CoV-2**  
   Jeffreys Laura 2020;:No page numbers.

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1. **Repurposing Drugs for COVID-19: An Approach for Treatment in the Pandemic**  
   Khadka S. Alternative therapies in health and medicine 2020;26:100-107.

Context: Drug repurposing is a relevant approach during the COVID-19 pandemic, because development of new drugs is time-consuming and costly, and the safety of new drugs is paramount. Drug repurposing focuses on researching new indications for existing drugs and can reduce the challenges faced in drug development. Objective(s): The current review intended to examine the current status of drugs being repurposed for COVID-19 treatment. Design(s): The research team performed a literature review, searching relevant literature databases to find abstracts of relevant articles in journals published from 2010 until May 16, 2020. The sources of data included Google Scholar, PubMed, and ScienceDirect. The search terms used included repositioning of drugs, repurposing of drugs and COVID-19 therapy, and SARS-CoV-2 therapy. Setting(s): The research team conducted this study at the Department of Pharmacology, Punjab University College of Pharmacy, University of the Punjab, Lahore, Pakistan; Mangalbare Hospital, Morang, Nepal; and Dr Iwamura Memorial Hospital, Bhaktapur, Nepal. Result(s): Repurposing of drugs from different pharmacological groups including antivirals like remdesivir, lopinavir, ritonavir, arbidol, oseltamivir, penciclovir, favipiravir, ganciclovir, and ribavirin; other antibiotics like azithromycin, ivermectin, eravacycline, valrubicin, streptomycin, nitazoxanide, teicoplanin, caspofungin, and colistin; and other agents like hydroxychloroquine, chloroquine, tocilizumab, camostat, nafamostat, carfilzomib, interferon, aprepitant, and dexamethasone can be considered for COVID-19 therapy. Conclusion(s): Although current results are promising, limitations to drug repurposing, such as a low success rate and the possibility of adverse events, can't be overlooked. With continuous research and technical advancements, repurposing will no doubt provide a notable scientific contribution to innovation in drug development and pharmacotherapy practice for the treatment of new diseases or existing diseases in a new way.

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1. **Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study**  
   Behera Priyamadhaba 2020;:No page numbers.

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1. **The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19**  
   Schmith Virginia D. Clinical pharmacology and therapeutics 2020;108:762-765.

Caly et al.1 reported that ivermectin inhibited severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) in vitro for up to 48 hours using ivermectin at 5 muM. The concentration resulting in 50% inhibition (IC50 ; 2 microM) was > 35x higher than the maximum plasma concentration (Cmax ) after oral administration of the approved dose of ivermectin when given fasted. Simulations were conducted using an available population pharmacokinetic model to predict total (bound and unbound) and unbound plasma concentration-time profiles after a single and repeat fasted administration of the approved dose of ivermectin (200 mug/kg), 60 mg, and 120 mg. Plasma total Cmax was determined and then multiplied by the lung:plasma ratio reported in cattle to predict the lung Cmax after administration of each single dose. Plasma ivermectin concentrations of total (bound and unbound) and unbound concentrations do not reach the IC50 , even for a dose level 10x higher than the approved dose. Even with the high lung:plasma ratio, ivermectin is unlikely to reach the IC50 in the lungs after single oral administration of the approved dose (predicted lung: 0.0873 microM) or at doses 10x higher that the approved dose administered orally (predicted lung: 0.820 microM). In summary, the likelihood of a successful clinical trial using the approved dose of ivermectin is low. Combination therapy should be evaluated in vitro. Repurposing drugs for use in coronavirus disease 2019 (COVID-19) treatment is an ideal strategy but is only feasible when product safety has been established and experiments of repurposed drugs are conducted at clinically relevant concentrations. Copyright © 2020 The Authors. Clinical Pharmacology & Therapeutics published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

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1. **The Battle against COVID 19 Pandemic: What we Need to Know Before we "Test Fire" Ivermectin**  
   Banerjee Kushal Drug research 2020;70:337-340.

The world is faced with the dire challenge of finding an effective treatment against the rampaging COVID 19 pandemic. Amidst the crisis, reports of in vitro inhibitory activity of ivermectin, an approved anthelmintic, against the causative SARSCoV2 virus, have generated lot of optimism. In this article, we have fished and compiled the needed information on the drug, that will help readers and prospective investigators in having a quick overview. Though the primordial biological action of the drug is allosteric modulation of helminthic ion channel receptor, its in vitro activity against both RNA and DNA viruses is known for almost a decade. In the past two years, efficacy study in animal models of pseudorabies and zika virus was found to be favourable and unfavourable respectively. Only one clinical study evaluated the drug in dengue virus infection without any clinical efficacy. However, the proposed mechanism of drug action, by inhibiting the importin family of nucleus-cytoplasmic transporters along with favourable pharmacokinetics, warrants exploration of its role in COVID 19 through safely conducted clinical trials. Being an available and affordable drug, enlisted in WHO List of Essential Medicine, and a long track record of clinical safety, the drug is already in clinical trials the world over. As the pandemic continues to ravage human civilisation with unabated intensity, the world eagerly waits for a ray of hope emanating from the outcome of the ongoing trials with ivermectin as well as other drugs. Copyright © Georg Thieme Verlag KG Stuttgart . New York.

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1. **The COVID-19 pandemic-A global public health crisis: A brief overview regarding pharmacological interventions**  
   Haque M. Pesquisa Brasileira em Odontopediatria e Clinica Integrada 2020;20:1-15.

WHO reported that viral diseases remain as an international public health concern. Quite a lot of viral outbreaks such as the SARS coronavirus from 2002 to 2003, H1N1 influenza in 2009, and the MERS syndrome coronavirus in 2012, in the last two decades. The recent outburst of COVID-19 disease has to turn out a global public health catastrophe that has a profound consequence on every aspect of human life. Currently, national governments, international health agencies, UN different bodies are working relentlessly to find the best way to save and mitigate our world from the shattering effects of COVID-19. Simultaneously, all related scientists around the planet determinedly made enormous efforts to find the COVID-19 transmission process, clinicopathological issues, diagnostics tools, and prevention policy planning and pharmacological intervention approaches. There are many problems that are not resolved regarding COVID-19, like the virus-host relations and the development and progression of the pandemic, with precise reference to the times when the current pandemic will reach its ultimate level to produce maximum damage. At this moment in time, yet we do not possess and definite and specific treatment options to fight with the COVID-19 viral infectious diseases. Currently, the majority of the scientist is involved in finding a way through drug repurposing. Up to the present time lot of medicines were identified that possess definite antiviral effects against COVID-19 but need to go a long way with well-designed study to obtain the best possible answer. After that, to this point, supportive and preventive remain as the best weapon.Copyright © 2020, Association of Support to Oral Health Research (APESB). All rights reserved.

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1. **The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial**  
   Chaccour Carlos 2020;:No page numbers.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=83c5ebddb848978f547b8bb6e8387331)

1. **The SARS-CoV-2 Ivermectin Navarra-ISGlobal Trial (SAINT) to Evaluate the Potential of Ivermectin to Reduce COVID-19 Transmission in low risk, non-severe COVID-19 patients in the first 48 hours after symptoms onset: A structured summary of a study protocol for a randomized control pilot trial**  
   Chaccour Carlos Trials 2020;21:498.

OBJECTIVES: The primary objective is to determine the efficacy of a single dose of ivermectin, administered to low risk, non-severe COVID-19 patients in the first 48 hours after symptom onset to reduce the proportion of patients with detectable SARS-CoV-2 RNA by Polymerase Chain Reaction (PCR) test from nasopharyngeal swab at day 7 post-treatment. The secondary objectives are: 1.To assess the efficacy of ivermectin to reduce the SARS-CoV-2 viral load in the nasopharyngeal swab at day 7 post treatment.2.To assess the efficacy of ivermectin to improve symptom progression in treated patients.3.To assess the proportion of seroconversions in treated patients at day 21.4.To assess the safety of ivermectin at the proposed dose.5.To determine the magnitude of immune response against SARS-CoV-2.6.To assess the early kinetics of immunity against SARS-CoV-2., TRIAL DESIGN: SAINT is a single centre, double-blind, randomized, placebo-controlled, superiority trial with two parallel arms. Participants will be randomized to receive a single dose of 400 mug/kg ivermectin or placebo, and the number of patients in the treatment and placebo groups will be the same (1:1 ratio)., PARTICIPANTS: The population for the study will be patients with a positive nasopharyngeal swab PCR test for SARS-CoV-2, with non-severe COVID-19 disease, and no risk factors for progression to severity. Vulnerable populations such as pregnant women, minors (i.e.; under 18 years old), and seniors (i.e.; over 60 years old) will be excluded. Inclusion criteria 1. Patients diagnosed with COVID-19 in the emergency room of the Clinica Universidad de Navarra (CUN) with a positive SARS-CoV-2 PCR. 2. Residents of the Pamplona basin ("Cuenca de Pamplona"). 3. The patient must be between the ages of 18 and 60 years of age. 4. Negative pregnancy test for women of child bearing age\*. 5. The patient or his/her representative, has given informed consent to participate in the study. 6. The patient should, in the PI's opinion, be able to comply with all the requirements of the clinical trial (including home follow up during isolation). Exclusion criteria 1. Known history of ivermectin allergy. 2. Hypersensitivity to any component of ivermectin. 3. COVID-19 pneumonia. Diagnosed by the attending physician.Identified in a chest X-ray. 4. Fever or cough present for more than 48 hours. 5. Positive IgG against SARS-CoV-2 by rapid diagnostic test. 6. Age under 18 or over 60 years. 7. The following co-morbidities (or any other disease that might interfere with the study in the eyes of the PI): Immunosuppression.Chronic Obstructive Pulmonary Disease.Diabetes.Hypertension.Obesity.Acute or chronic renal failure.History of coronary disease.History of cerebrovascular disease.Current neoplasm. 8. Recent travel history to countries that are endemic for Loa loa (Angola, Cameroon, Central African Republic, Chad, Democratic Republic of Congo, Ethiopia, Equatorial, Guinea, Gabon, Republic of Congo, Nigeria and Sudan). 9. Current use of CYP 3A4 or P-gp inhibitor drugs such as quinidine, amiodarone, diltiazem, spironolactone, verapamil, clarithromycin, erythromycin, itraconazole, ketoconazole, cyclosporine, tacrolimus, indinavir, ritonavir or cobicistat. Use of critical CYP3A4 substrate drugs such as warfarin. \*Women of child bearing age may participate if they use a safe contraceptive method for the entire period of the study and at least one month afterwards. A woman is considered to not have childbearing capacity if she is post-menopausal (minimum of 2 years without menstruation) or has undergone surgical sterilization (at least one month before the study). The trial is currently planned at a single center, Clinica Universidad de Navarra, in Navarra (Spain), and the immunology samples will be analyzed at the Barcelona Institute for Global Health (ISGlobal), in Barcelona (Spain). Participants will be recruited by the investigators at the emergency room and/or COVID-19 area of the CUN. They will remain in the trial for a period of 28 days at their homes since they will be patients with mild disea e. In the interest of public health and to contain transmission of infection, follow-up visits will be conducted in the participant's home by a clinical trial team comprising nursing and medical members. Home visits will assess clinical and laboratory parameters of the patients., INTERVENTION AND COMPARATOR: Ivermectin will be administered to the treatment group at a 400mug/Kg dose (included in the EU approved label of Stromectol and Scabioral). The control group will receive placebo. There is no current data on the efficacy of ivermectin against the virus in vivo, therefore the use of placebo in the control group is ethically justified., MAIN OUTCOMES: Primary Proportion of patients with a positive SARS-CoV-2 PCR from a nasopharyngeal swab at day 7 post-treatment. Secondary 1.Mean viral load as determined by PCR cycle threshold (Ct) at baseline and on days 4, 7, 14, and 21.2.Proportion of patients with fever and cough at days 4, 7, 14, and 21 as well as proportion of patients progressing to severe disease or death during the trial.3.Proportion of patients with seroconversion at day 21.4.Proportion of drug-related adverse events during the trial.5.Median levels of IgG, IgM, IgA measured by Luminex, frequencies of innate and SARS-CoV-2-specific T cells assessed by flow cytometry, median levels of inflammatory and activation markers measured by Luminex and transcriptomics.6.Median kinetics of IgG, IgM, IgA levels during the trial, until day 28., RANDOMISATION: Eligible patients will be allocated in a 1:1 ratio using a randomization list generated by the trial statistician using blocks of four to ensure balance between the groups. A study identification code with the format "SAINT-##" (##: from 01 to 24) will be generated using a sequence of random numbers so that the randomization number does not match the subject identifier. The sequence and code used will be kept in an encrypted file accessible only to the trial statistician. A physical copy will be kept in a locked cabinet at the CUN, accessible only to the person administering the drug who will not enrol or attend to patient care. A separate set of 24 envelopes for emergency unblinding will be kept in the study file., BLINDING (MASKING): The clinical trial team and the patients will be blinded. The placebo will not be visibly identical, but it will be administered by staff not involved in the clinical care or participant follow up., NUMBERS TO BE RANDOMISED (SAMPLE SIZE): The sample size is 24 patients: 12 participants will be randomised to the treatment group and 12 participants to the control group., TRIAL STATUS: Current protocol version: 1.0 dated 16 of April 2020. Recruitment is envisioned to begin by May 14th and end by June 14th., TRIAL REGISTRATION: EudraCT number: 2020-001474-29, registered April 1st. Clinicaltrials.gov: submitted, pending number FULL PROTOCOL: The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.

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1. **The use of compassionate Ivermectin in the management of symptomatic outpatients and hospitalized patients with clinical diagnosis of COVID-19 at the Medical Center Bournigal and the Medical Center Punta Cana, Rescue Group, Dominican Republic, from may 1 to august 10, 2020**  
   Morgenstern José 2020;:No page numbers.

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1. **Three novel prevention, diagnostic, and treatment options for COVID-19 urgently necessitating controlled randomized trials**  
   Horowitz Richard I. Medical hypotheses 2020;143:109851.

PURPOSE: Asymptomatic or minimally symptomatic infection with COVID-19 can result in silent transmission to large numbers of individuals, resulting in expansion of the pandemic with a global increase in morbidity and mortality. New ways of screening the general population for COVID-19 are urgently needed along with novel effective prevention and treatment strategies., HYPOTHESIS: A hypothetical three-part prevention, diagnostic, and treatment approach based on an up-to-date scientific literature review for COVID-19 is proposed. Regarding diagnosis, a validated screening questionnaire and digital app for COVID-19 could help identify individuals who are at risk of transmitting the disease, as well as those at highest risk for poor clinical outcomes. Global implementation and online tracking of vital signs and scored questionnaires that are statistically validated would help health authorities properly allocate essential health care resources to test and isolate those at highest risk for transmission and poor outcomes. Second, regarding prevention, no validated protocols except for physical distancing, hand washing, and isolation exist, and recently ivermectin has been published to have anti-viral properties against COVID-19. A randomized trial of ivermectin, and/or nutraceuticals that have been published to support immune function including glutathione, vitamin C, zinc, and immunomodulatory supplements (3,6 Beta glucan) could be beneficial in preventing transmission or lessening symptomatology but requires statistical validation. Third, concerning treatment, COVID-19 induced inflammation and "cytokine storm syndrome" with hemophagocytic lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS) have resulted in extreme morbidity and mortality in those with certain comorbidities, secondary to "acute respiratory distress syndrome" (ARDS) and multiorgan dysfunction with disseminated intravascular coagulation (DIC). Deficiency in red blood cell, serum and alveolar glutathione has been published in the medical literature for ARDS, as well as viral and bacterial pneumonias, resulting from increased levels of free radical/oxidative stress. A randomized controlled trial of blocking NF-kappaB and cytokine formation using glutathione precursors (N-acetyl-cysteine [NAC] and alpha lipoic acid) and PO/IV glutathione with associated anti-viral effects should be performed, along with an evaluation of Nrf2 activators (curcumin, sulforaphane glucosinolate) which have been scientifically proven to lower inflammation. Since high mortality rates from sepsis induced DIC due to COVID-19 infection has also been associated with thrombotic events and elevated levels of D-dimer, randomized controlled trials of using anticoagulant therapy with heparin is urgently required. This is especially important in patients on ventilators who have met certain sepsis induced coagulopathy (SIC) criteria. The use of acetazolamide with or without sildenafil also needs to be explored with or without heparin, since increased oxygen delivery to vital organs through prevention of thrombosis/pulmonary emboli along with carbonic anhydrase inhibition may help increase oxygenation and prevent adverse clinical outcomes., CONCLUSION AND IMPLICATIONS: A three-part prevention, diagnostic, and treatment plan is proposed for addressing the severe complications of COVID-19. Digital monitoring of symptoms to clinically diagnose early exposure and response to treatment; prevention with ivermectin as well as nutritional therapies that support a healthy immune response; treatment with anti-inflammatory therapies that block NF-kappaB and activate Nrf2 pathways, as well as novel therapies that address COVID-19 pneumonia and ARDS with DIC including anticoagulation and/or novel respiratory therapies with or without acetazolamide and sildenafil. These three broad-based interventions urgently need to be subjected to randomized, controlled trials. Copyright © 2020 The Authors. Published by Elsevier Ltd.. All rights reserved.

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1. **Treatment Options for COVID-19: A Review**  
   Ali Mukarram Jamat Frontiers in medicine 2020;7:480.

Background: The recent COVID-19 pandemic sweeping the globe has caused great concern worldwide. Due to the limited evidence available on the dynamics of the virus and effective treatment options available, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a huge impact in terms of morbidity and mortality. The economic impact is still to be assessed. Aims: The purpose of this article is to review the evidence for the multiple treatment options available, to consider the future of this global pandemic, and to identify some potential options that could revolutionize the treatment of COVID-19. Moreover, this article underscores the sheer importance of repurposing some of the available antiviral and antimicrobial agents that have long been in use so as to have an effective and expeditious response to this widespread pandemic and the need to conduct a multicenter global randomized controlled trial to find an effective single antiviral agent or a cocktail of available antimicrobial agents. Method: We thoroughly searched and reviewed various case reports, retrospective analyses, and in vitro studies published in PubMed, EMBASE, and Google Scholar regarding the treatment options used for SARS-CoV, MERS-CoV, and SARS-CoV-2 since its outbreak in an attempt to highlight treatments with the most promising results. Conclusion: We are currently facing one of the worst pandemics in history. Although SARS-CoV-2 is associated with a lower mortality rate than are SARS-CoV and MERS-CoV, its higher infectivity is making it a far more serious threat. Unfortunately, no vaccine against SARS-CoV-2 or effective drug regimen for COVID-19 currently exists. Drug repurposing of available antiviral agents may provide a respite; moreover, a cocktail of antiviral agents may be helpful in treating this disease. Here, we have highlighted a few available antimicrobial agents that could be very effective in treating COVID-19; indeed, a number of trials are underway to detect and confirm the efficacy of these agents. Copyright © 2020 Ali, Hanif, Haider, Ahmed, Sundas, Hirani, Khan, Anis and Karim.

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1. **Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019: The ICON Study**  
   Rajter Juliana Cepelowicz Chest 2020;:No page numbers.

BACKGROUND: Ivermectin was shown to inhibit severe acute respiratory syndrome coronavirus 2 replication in vitro, which has led to off-label use, but clinical efficacy has not been described previously., RESEARCH QUESTION: Does ivermectin benefit hospitalized coronavirus disease 2019 (COVID-19) patients?, STUDY DESIGN AND METHODS: Charts of consecutive patients hospitalized at four Broward Health hospitals in Florida with confirmed COVID-19 between March 15 and May 11, 2020, treated with or without ivermectin were reviewed. Hospital ivermectin dosing guidelines were provided, but treatment decisions were at the treating physician's discretion. The primary outcome was all-cause in-hospital mortality. Secondary outcomes included mortality in patients with severe pulmonary involvement, extubation rates for mechanically ventilated patients, and length of stay. Severe pulmonary involvement was defined as need for Fio2 >= 50%, noninvasive ventilation, or invasive ventilation at study entry. Logistic regression and propensity score matching were used to adjust for confounders., RESULTS: Two hundred eighty patients, 173 treated with ivermectin and 107 without ivermectin, were reviewed. Most patients in both groups also received hydroxychloroquine, azithromycin, or both. Univariate analysis showed lower mortality in the ivermectin group (15.0% vs 25.2%; OR, 0.52; 95% CI, 0.29-0.96; P = .03). Mortality also was lower among ivermectin-treated patients with severe pulmonary involvement (38.8% vs 80.7%; OR, 0.15; 95% CI, 0.05-0.47; P = .001). No significant differences were found in extubation rates (36.1% vs 15.4%; OR, 3.11; 95% CI, 0.88-11.00; P = .07) or length of stay. After multivariate adjustment for confounders and mortality risks, the mortality difference remained significant (OR, 0.27; 95% CI, 0.09-0.80; P = .03). One hundred ninety-six patients were included in the propensity-matched cohort. Mortality was significantly lower in the ivermectin group (13.3% vs 24.5%; OR, 0.47; 95% CI, 0.22-0.99; P < .05), an 11.2% (95% CI, 0.38%-22.1%) absolute risk reduction, with a number needed to treat of 8.9 (95% CI, 4.5-263)., INTERPRETATION: Ivermectin treatment was associated with lower mortality during treatment of COVID-19, especially in patients with severe pulmonary involvement. Randomized controlled trials are needed to confirm these findings. Copyright © 2020 The Authors. Published by Elsevier Inc. All rights reserved.

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1. **White paper on Ivermectin as a potential therapy for COVID-19**  
   Vora Agam The Indian journal of tuberculosis 2020;67:448-451.

A group of senior doctors with vast clinical experience met on 19th July'20 under the aegis of Academy of Advanced Medical Education. The panel looked at Ivermectin, one of the old molecule and evaluated it's use in COVID 19 (Novel Coronavirus Disease 2019) management. After critical panel discussion, all the attending doctors came to a conclusion that Ivermectin can be a potential molecule for prophylaxis and treatment of people infected with Coronavirus, owing to its anti-viral properties coupled with effective cost, availability and good tolerability and safety. Copyright © 2020 Tuberculosis Association of India. Published by Elsevier B.V. All rights reserved.

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| 21. | embase | 17 and 20 | 79 |

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