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April 2020 ~ Resource #360423

COVID-19 and Pharmacotherapy

The **first chart below** provides information or resources on pharmacotherapy of interest for COVID-19, the disease caused by the SARS-CoV-2 virus. Additional resources on pharmacotherapy, which are frequently updated, include:

- The **American Society of Health-System Pharmacists** evidence table of COVID-19 treatments (https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table).
- The **British Columbia Ministry of Health** evidence review (http://www.bccdc.ca/Health-Professionals-Site/Documents/Guidelines_Unproven_Therapies_COVID-19.pdf).

At this point, no pharmacotherapy has been proven effective for COVID-19, so treatment is largely supportive. Resources pertinent to supportive therapy include:

- The **World Health Organization** guidance for the treatment of suspected COVID-19 severe acute respiratory infection (https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected).
- The **Surviving Sepsis Campaign** COVID-19 guidelines (https://sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19).
- The **NIH** general treatment guidelines (https://covid19treatmentguidelines.nih.gov/).

The **second chart below** addresses common questions about pharmacotherapy as it relates to COVID-19.

Search **www.clinicaltrials.gov for the latest information on COVID-19 clinical trials.**

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; CT = computed tomography; EUA = Emergency Use Authorization; IDSA = Infectious Diseases Society of America; IL = interleukin; NSAIDs = nonsteroidal anti-inflammatory drugs; SARS = severe acute respiratory syndrome; SARS-CoV-2 = the virus that causes COVID-19 disease; tPA = tissue plasminogen activator; TNF = tumor necrosis factor

TREATMENTS OF INTEREST

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Anakinra (*Kineret*)	• Anakinra is an IL-1 antagonist. IL-1 may have a role in ARDS.[65] • Anakinra 5 mg/kg twice daily intravenously in moderate to severe ARDS (non-ventilator) and inflammation (elevated C-reactive protein and/or ferritin) (n=29) was associated with improved survival compared to a similar historical cohort (90% vs 56%, p = 0.009).[65] These patients also received hydroxychloroquine and lopinavir/ritonavir.[65] A lower dose of anakinra (100 mg twice daily subcutaneously) did not seem to provide benefit.[65]

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Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Azithromycin	• Macrolides have *in vitro* antiviral (e.g., Zika, Ebola), anti-inflammatory, and immunomodulatory activity.[2,7] • Insufficient evidence to support widespread use [Evidence level C].[2,28] • Was used in a small, widely publicized study with hydroxychloroquine in six patients **to prevent bacterial superinfection** in COVID-19 patients (See hydroxychloroquine, below).[2] Subsequent observational data including 74 additional patients suggests that the combination can reduce viral load and perhaps improve the clinical course, but there was no comparator group.[28] • NIH guidelines recommend against the use of azithromycin plus hydroxychloroquine outside of a clinical trial.[50] • Studies for COVID-19 treatment include various dosing regimens (usually azithromycin 500 mg x 1 then 250 mg once daily for four days) **WITH** chloroquine, hydroxychloroquine, or other antimicrobials. See www.clinicaltrials.gov for the latest information on these studies. • When used with hydroxychloroquine or chloroquine (and other QT prolonging medications), QT prolongation is of increased concern.[2,6]
Aviptadil	• **Investigational** synthetic form of vasoactive intestinal polypeptide. Has anti-IL-6 and anti-TNF activity. Phase I trial suggests benefit in ARDS. No COVID-19 data. • Clinical trial is planned for COVID-19-associated ARDS. See www.clinicaltrials.gov for more information.
Baloxavir (*Xofluza*)	• No COVID-19 data.
Chloroquine phosphate* *Chloroquine phosphate 500 mg = chloroquine base 300 mg[6] *Continued…*	Efficacy • Inhibits SARS-CoV-2 *in vitro*,[2] but clinical trials have not shown benefit against other viruses.[18] Also has immunomodulating effects.[26] Early reports suggested that for COVID-19 pneumonia, it could speed clinical improvement and viral clearance.[3] • The FDA has **revoked its EUA** for chloroquine because it is unlikely to be effective, based on data from the EUA and elsewhere.[73] • Clinical trials are planned on the use of chloroquine to prevent COVID-19 in healthcare workers. • See www.clinicaltrials.gov for regimens being studied. Dosing • The FDA suggested, as part of their now-**revoked** EUA for chloroquine, for patients weighing ≥50 kg, a chloroquine phosphate dose of 1 g on day one, followed by 500 mg once daily for four to seven days.[4] This suggested dosing regimen is **unlikely to produce an antiviral effect**.[73]

More. . .

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Chloroquine, continued	Safety • In addition to efficacy concerns, the FDA's revocation of its EUA for chloroquine was based on adverse effects; its known and potential benefits no longer outweigh the known and potential side effects (e.g., serious cardiac events and other serious side effects).[33] • The FDA recommends **against** chloroquine use for COVID-19 outside of a clinical trial.[33] • **Adverse effects** are not well-characterized at the doses studied for COVID-19. In general, potential adverse effects include: gastrointestinal side effects (take with food or milk), headache, hypoglycemia, QT prolongation and other conduction disturbances (especially with hypokalemia, hypomagnesemia, or heart disease), cardiomyopathy, myopathy, movement disorders, neurotoxicity, ocular toxicity, ototoxicity, anemia, thrombocytopenia, neutropenia, bone marrow suppression, serious dermatologic reactions, and psoriasis flare.[4,27] **Monitor** electrolytes, glucose, complete blood count, electrocardiogram, baseline renal and hepatic function, knee and ankle reflexes, vision, and mental status.[4,6,27] • A Brazilian study of chloroquine phosphate 600 mg twice daily vs 450 mg twice daily stopped the high-dose arm due to higher instance of QT prolongation >500 milliseconds (18.9% vs 11.1%) and mortality (39% vs 15%).[41] All patients received azithromycin.[41] • When used with azithromycin (and other QT-prolonging medications), QT prolongation is of increased concern.[2,4,6]
Colchicine	• Based on its anti-inflammatory effect, there is interest in using colchicine to alter the clinical course of COVID-19 in both inpatients and higher-risk outpatients. • Clinical trials are underway. See www.clinicaltrials.gov for more information. • Keep in mind colchicine's toxicities and drug interactions. See our chart, *Colchicine Dosing and Interactions*, for details.
Convalescent Plasma (COVID-19)	• No large studies have been published, but small case series in patients hospitalized with severe COVID-19 show promise (e.g., defervescence, radiographic improvement, improved oxygen support requirements, viral clearance, improved clinical condition).[62-64] It appears well-tolerated.[62-64] Concerns include allergic reaction, viral infection, and increased clotting risk.[70,71] • There are three pathways for administering or studying COVID-19 convalescent plasma: clinical trials (www.clinicaltrials.gov or https://covidcp.org/), expanded access (https://uscovidplasma.org), or single patient emergency IND. The FDA has guidance for use of **convalescent plasma** at https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. • See https://www.ccpp19.org/ or https://uscovidplasma.org to find out how recovered **patients can donate** their plasma.

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Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Corticosteroids	• The World Health Organization Guidelines recommends that at this time, **outside of clinical trials**, corticosteroids should be reserved for patients with specific indications for them (e.g., sepsis, **COPD**, **asthma**, **septic shock**, **ARDS**) with consideration to risk vs benefit.[10] • The CDC recommends that corticosteroids be avoided because of the potential for prolonging viral replication, as observed in MERS-CoV and influenza patients, **unless indicated for other reasons**.[11] • The IDSA recommends corticosteroids only for patients with ARDS, in the context of a clinical trial.[46] • NIH guidelines relating to corticosteroid use are available at https://covid19treatmentguidelines.nih.gov/concomitant-medications/. • Corticosteroids appeared to be ineffective and possibly harmful for SARS, but are being studied for COVID-19.[9,10] In one institution in China, methylprednisolone use in patients with COVID-19 ARDS was associated with reduced mortality.[16] Conversely, a meta-analysis of over 5,000 patients found longer hospital stays and higher mortality.[9] • Unpublished data from the RECOVER trial, in which 2,104 patients were randomized to dexamethasone 6 mg/day for 10 days, suggests a mortality benefit for COVID-19 patients requiring oxygen, especially for those requiring ventilation, over usual care (n = 4,321).[31] NNT = 8 to prevent one death in ventilated patients, or 25 in patients requiring oxygen but not ventilation. • Ciclesonide (*Alvesco*) is being studied for treatment of outpatients with COVID-19. See www.clinicaltrials.gov for more information.
Dapagliflozin	• No data. • Dapagliflozin is being studied in COVID-19 patients with respiratory failure and with hypertension, diabetes, heart disease, or advanced renal disease to prevent organ failure, based on its known renal and cardiac benefit (DARE-19 study). • See www.clinicaltrials.gov for more information.
Famotidine	• Interest in famotidine as a COVID-19 treatment stems from observations in China that patients who were taking famotidine who were infected with COVID-19 had better outcomes.[55] • In a retrospective U.S. study (n = 1,620), famotidine use (10 to 40 mg/day; n = 84) within 24 hours of admission was associated with reduced risk of death or intubation in **hospitalized** COVID-19 patients.[67] • A clinical trial using high-dose intravenous famotidine is underway. See www.clinicaltrials.gov for more information.
Hydroxy-chloroquine *Continued…*	Efficacy • Is a more potent inhibitor of SARS-CoV-2 than chloroquine *in vitro*.[2] Also has immunomodulating effects.[27] • The FDA has **revoked its EUA** for hydroxychloroquine because it is unlikely to be effective, based on data from the EUA and elsewhere.[73] • The hydroxychloroquine arm of the large RECORD study was also stopped due to lack of efficacy.[31]

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Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Hydroxy-chloroquine, continued *Continued…*	• Early enthusiasm for hydroxychloroquine was based on a widely publicized open-label, randomized study in hospitalized patients testing positive for SARS-CoV-2.[2] Six of 26 hydroxychloroquine patients were lost to follow-up: one due to death, three due to intensive care admission, one due to side effects (nausea), and one who left the hospital. Viral clearance at day six was 70% in the 20 remaining hydroxychloroquine patients vs 12.5% of the control patients (n = 16).[2] Six treated patients also received azithromycin 500 mg on day one, then 250 mg on days two through five to prevent bacterial infection.[2] In the combination group, viral clearance was 100% at day six vs 57.1% in the hydroxychloroquine-alone group.[2] Also see subsequent observational data under "Azithromycin," above. • In a pilot study in China, 30 patients were randomized to hydroxychloroquine 400 mg/day (it is unclear if this was divided) for five days, or usual care. There was no difference between groups in viral clearance at day seven, length of stay, or time to defervescence.[29] In a study of 62 hospitalized patients with mild disease, 31 patients were randomized to hydroxychloroquine 200 mg twice daily. Time to recovery (defervescence and cough remission) was shortened by about one day in the treatment group. On day six, pneumonia was improved per CT in more patients in the treatment group. Four patients progressed to severe disease, all in the control group.[39] A subsequent open-label Chinese study (n=150) randomized patients to usual care or hydroxychloroquine 1,200 mg/day for three days, then 800 mg/day for two (mild to moderate disease) or three weeks (severe disease).[42] Viral clearance was similar on days 4, 7, 10, 14, 21, and 28 for the two groups. Hydroxychloroquine did not seem to hasten symptom improvement. Thirty percent of hydroxychloroquine patients had adverse effects. • A retrospective French cohort study found no benefit of early hydroxychloroquine administration to 84 hospitalized patients in regard to need for intensive care, or mortality.[43] • Similarly, in a retrospective U.S. Veterans Affairs study (n=368), hydroxychloroquine, alone or with azithromycin, was not associated with reduced need for mechanical ventilation in hospitalized patients. Mortality was higher in patients who received hydroxychloroquine alone vs no hydroxychloroquine.[49] • Other retrospective U.S. studies suggest no benefit. In one (n = 1,376), patients received hydroxychloroquine 600 mg twice daily on day 1, then 400 mg daily for a median of five days. Some patients also received azithromycin or sarilumab. About half of patients began treatment within 24 hours of presentation. Hydroxychloroquine use was not associated with a reduced risk of a composite outcome of death or intubation.[60] In another study (n=1,438), neither hydroxychloroquine alone, azithromycin alone, nor the combination was associated with improved in-hospital mortality, but the combination was associated with cardiac arrest.[66] • The FDA suggested, as part of their now-**revoked** Emergency Use Authorization for hydroxychloroquine, for hospitalized patients weighing ≥50 kg, a dose of 800 mg on day one, followed by 400 mg once daily for four to seven days.[31] This suggested dosing regimen is **unlikely to produce an antiviral effect**.[73] • Clinical trials are ongoing on the use of hydroxychloroquine to prevent COVID-19 in healthcare workers. • See www.clinicaltrials.gov for regimens being studied.

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Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Hydroxy-chloroquine, continued	Safety • In addition to efficacy concerns, the FDA's revocation of its EUA for hydroxychloroquine was based on adverse effects; its known and potential benefits no longer outweigh the known and potential side effects (e.g., serious cardiac events and other serious side effects).[33] • Due to the risk of arrhythmias, the FDA recommends **against** hydroxychloroquine use for COVID-19 outside of a clinical trial.[33] • **Adverse effects** are not well-characterized at the doses studied for COVID-19. In general, potential adverse effects include: gastrointestinal side effects (take with food or milk), headache, hypoglycemia, QT prolongation and other conduction disturbances (especially with hypokalemia, hypomagnesemia, or heart disease), cardiomyopathy, myopathy, movement disorders, neurotoxicity, ocular toxicity, ototoxicity, anemia, thrombocytopenia, neutropenia, bone marrow suppression, serious dermatologic reactions, and psoriasis flare.[27,31] **Monitor** electrolytes, glucose, complete blood count, electrocardiogram, baseline renal and hepatic function, knee and ankle reflexes, vision, and mental status.[6,27,31] • When used with azithromycin (and other QT-prolonging medications), **QT prolongation** is of increased concern.[2,6] Information on managing QT prolongation risk in these patients is available at https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.047521.
IL-6 antagonist Tocilizumab (*Actemra*); sarilumab (*Kevzara*); siltuximab (*Sylvant*).	• Anti-IL-6 monoclonal antibody. • Some, but not all, data from China suggests an association between elevated IL-6 and severe COVID-19 disease.[18] • Anecdotal reports and case series suggest benefit for tocilizumab (*Actemra*).[18,68] One or two doses of 400 to 800 mg (4 to 8 mg/kg) has been used.[18,68] • May cause increased infections, neutropenia, thrombocytopenia, and elevated liver enzymes.[1,34-38] • Not for routine use. Clinical trials are planned or underway for treatment of pneumonia or cytokine storm. See www.clinicaltrials.gov for more information. • Outside of a clinical trial, limit to patients with evidence of cytokine storm (e.g., elevated ferritin, elevated IL-6, etc), with specialist consultation.[44]
Janus Kinase Inhibitors (Ruxolitinib [*Jakafi*], etc)	• No data. • Interest based on potential to block IL-6 effects, reduce cytotoxic T cells, and increase regulatory T cells. • See www.clinicaltrials.gov for more information.

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Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Lopinavir/ ritonavir (*Kaletra*)	• Lopinavir/ritonavir has not demonstrated anti-SARS-CoV-2 activity in humans.[15] Small study suggested benefit (reduced composite endpoint of ARDS or death) for 2003 SARS vs historical control.[17] • Results from a randomized, open-label study (n=199) suggest it might reduce complications such as acute kidney injury, secondary infections, or need for mechanical ventilation in patients with COVID-19 pneumonia.[15] However, time to clinical improvement was not reduced (main outcome measure).[15] Gastrointestinal adverse effects may limit use.[15,30] • There is interest in studying lopinavir/ritonavir earlier in the disease course, or in combination with other medications.[15] Use with **ribavirin** and interferon beta-1b early in the disease course (mean five days from symptom onset) was compared to lopinavir/ritonavir alone in hospitalized patients (n=127).[58] In this open-label study, median time to viral clearance was seven days with combination therapy vs 12 days for lopinavir/ritonavir alone.[58] Alleviation of symptoms occurred in four days vs eight days, respectively ($p<0.0001$).[58] • Additional clinical trials are planned or underway. See www.clinicaltrials.gov for more information.
Losartan, Telmisartan	• Studies in mice suggest that ARBs can reduce lung damage caused by SARS-CoV.[13] • Clinical trials are underway for treatment of COVID-19. See www.clinicaltrials.gov for more information.
Oseltamivir	• Not expected to be effective against SARS-CoV-2 because SARS-CoV-2 does not use neuraminidase.[26] • Has been used for COVID-19 pneumonia, but there is no efficacy data.[12]
Remdesivir *Continued…*	• Remdesivir has *in vitro* activity against SARS-CoV-2.[40] • In a cohort of 53 evaluable patients treated with remdesivir for severe COVID-19 disease, use was associated with clinical improvement in regard to oxygen support requirements in 68% of patients.[40] Mortality was 13%, which is less than in other case series and cohorts.[40] The most common adverse events were liver enzyme elevation (23%), diarrhea (9%), rash, renal impairment, hypotension (8%), acute kidney injury, atrial fibrillation, multiorgan dysfunction, hypernatremia, and venous thrombosis (6%).[40] Causality could not be assessed due to the effects of COVID-19 itself.[40] Based on previous data, mild to moderate transaminase elevations are expected with remdesivir.[40] Viral load was not evaluated,[40] but in a previous case report, virologic improvement was seen.[8] • Preliminary analysis of a double-blind, placebo-controlled trial (n = 1,063), remdesivir seemed to shorten time to recovery (11 days vs 15 days; $p<0.001$), but mortality was not statistically different (8% vs 11.6%; $p = 0.059$).[54,72] Similarly, a Chinese study found a nonsignificant trend toward faster recovery.[61] • **U.S.**: Remdesivir is being distributed to select hospitals by the government through Emergency Use Authorization.[57] This is a rapidly changing situation. For other potential opportunities for availability, see www.clinicaltrials.gov, www.gilead.com/remdesivir, or contact Gilead at 833-445-3230 (GILEAD-0) or GileadClinicalTrials@gilead.com. • The FDA has a fact sheet on remdesivir, including criteria for use, adverse effects, dosing, and more

More. . .

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Remdesivir, continued	(https://www.fda.gov/media/137566/download). • **Canada**: Remdesivir is available through an Expanded Access Treatment Protocol at approved clinical trial sites. A list of active sites is available at https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-clinical-trials/list-authorized-trials.html and at www.clinicaltrials.gov. At this point, Gilead is not accepting more sites for consideration. Compassionate use requests continue to be reviewed for pregnant women and children <18 years of age with confirmed severe COVID-19.[59] • **Coadministration of remdesivir and chloroquine or hydroxychloroquine is not recommended** based on *in vitro* data showing that these drugs might interfere with the metabolic activation and antiviral activity of remdesivir.[53]
Ribavirin	• Not potent enough to be effective at safe doses; hematologic toxicity precludes use.[26] See lopinavir/ritonavir section for information on combination use.
Statins	• No data. • Interest based on cardiovascular damage noted in COVID-19 patients and anti-inflammatory effects. Simvastatin might also block viral cell entry. • NIH guidelines recommend against use specifically for COVID-19 treatment outside of a clinical trial. • See www.clinicaltrials.gov for more information on planned or ongoing studies.
tPA (alteplase)	• No data. • Interest based on reports of hypercoagulability in COVID-19 patients.[19] • Studies underway to treat ARDS in COVID-19 patients.[19]
Vaccines	• Due to evidence of a non-specific protective effect against respiratory infections, BCG vaccine is being studied to prevent COVID-19 disease in healthcare workers. See www.clinicaltrials.gov for more information. • Oral polio vaccine has been mentioned on the internet, but no trials are planned at this time.
Vitamin C	• Intravenous vitamin C is being studied for treatment of severe COVID-19 disease based on previous data in sepsis and ARDS. However, there is no clear evidence of benefit even for these conditions.[48] • Oral vitamin C is being studied for treatment of COVID-19 disease in the outpatient setting, and as prophylaxis. • See www.clinicaltrials.gov for more information on these planned or ongoing studies.
Vitamin D	• There is false information circulating that **vitamin D** is recommended by health officials. Interest in vitamin D stems from its effects on the immune system and pulmonary ACE2 expression. Studies are planned or underway using vitamin D for prevention or as a treatment adjunct. See www.clinicaltrials.gov for more information.

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Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Zinc	• Zinc has *in vitro* activity against SARS-CoV.[47] • Studies of oral zinc, alone or in combination (e.g., with vitamin C, **vitamin D**, hydroxychloroquine [purported to help zinc get inside the cells[47]], azithromycin) to prevent COVID-19 disease are planned or ongoing. • See www.clinicaltrials.gov for more information.

FAQs ABOUT COVID-19 AND PHARMACOTHERAPY

There is a lot of misinformation regarding COVID-19 on the internet. Use this table to help answer patient questions and correct misconceptions.

Clinical question	Pertinent information or resource

Do ACE inhibitors or ARBs make COVID-19 worse?	• The SARS-CoV-2 virus uses ACE2 to enter cells.[13] ACE inhibitors and ARBs may upregulate ACE2.[13] In theory, these drugs could thereby facilitate virus entry into cells.[13] But on the other hand, blocking angiotensin could reduce lung injury.[13]
	• No evidence suggests that patients taking an ACEI or ARB are more susceptible to COVID-19 infection, or that these medications worsen outcomes.[14,51,52,69] One cohort study even suggests reduced mortality in COVID-19 patients taking them for other indications.[51] Furthermore, we know that these drugs benefit patients with diabetic nephropathy and cardiovascular disease, populations at risk of severe COVID-19 disease.[13,22]
	• Patients should continue these medications. See statements from:
	  • the **American Heart Association**, the **Heart Failure Society of America**, and the **American College of Cardiology** at https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unless-otherwise-advised-by-their-physician.
	  • the **Canadian Cardiovascular Society** at https://www.ccs.ca/images/Images_2020/CCS_CHFS_Update_COVID__CV_medications_Mar20.pdf.
	  • the **European Society of Cardiology** at https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang.

Can NSAIDs be used in COVID-19-infected patients?	• Anecdotal reports regarding worse COVID-19 outcomes in patients taking NSAIDs have spread in the media and on social media, including via a tweet from a French health official.[14,23] In 2019, a French report suggested that NSAIDs could worsen infections, mainly Strep, perhaps by masking symptoms.[24,25] However, there is currently no reliable clinical data supporting worse outcomes in patients taking NSAIDs or aspirin.[14,20] Preclinical data is mixed on the potential effects of NSAIDs on COVID-19 (increased expression of ACE2, which the virus uses to enter cells, vs potential antiviral activity of NSAIDs).[14] • Patients taking low-dose aspirin should not stop taking it because of COVID-19 concerns.[14] • Neither the FDA nor Health Canada is advising changes to NSAID use due to COVID-19.[20,21]

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Clinical question	Pertinent information or resource
Are any supplements effective for prevention or treatment of COVID-19?	• There is no scientific evidence that any alternative remedies can prevent or treat COVID-19, and some products may not be safe.[5] See our *Natural Medicines* database (www.naturaldatabase.com) for information on efficacy and safety of specific alternative medicines. • A study using **honey** as an adjunct to standard care for treatment of COVID-19 is planned. • Several studies are looking at multivitamin/mineral combos as adjuncts for treatment or prevention. See www.clinicaltrials.gov for more information. For information on **zinc**, **vitamin C**, and **vitamin D** see the "Treatments of Interest" chart, above.
Are heartburn drugs effective for treating or preventing COVID-19?	• For information on famotidine, see the "Treatments of Interest" chart, above.
Does nicotine protect against COVID-19?	• In China, there was an unexpectedly low prevalence of smoking among patients hospitalized with COVID-19. Low smoking prevalence among hospitalized COVID-19 patients has also been seen in the U.S.[56] • Nicotine, through its cholinergic agonist activity, blocks production of inflammatory cytokines such as IL-6.[56] • There is interest in using nicotine, either as currently available products, or perhaps via nebulization, as an adjunct for COVID-19 treatment.[56] • Continue to use nicotine replacement products for nicotine users who are hospitalized for COVID-19, and for anyone who desires to quit smoking.[56]

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

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Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*****	1. High-quality RCT 2. SR/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*****	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).
RCT = randomized controlled trial; **SR** = systematic review
[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. http://www.aafp.org/afp/2004/0201/p548.pdf.]

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