

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists and pharmacy technicians will be able to:

- Describe emerging information about the COVID-19 pandemic
- Use this information to answer patients' questions



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.1 CEU (1 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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\$3 for technicians

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To obtain CPE credit, visit the UConn Online CE Center

<https://pharmacyce.uconn.edu/login.php>.

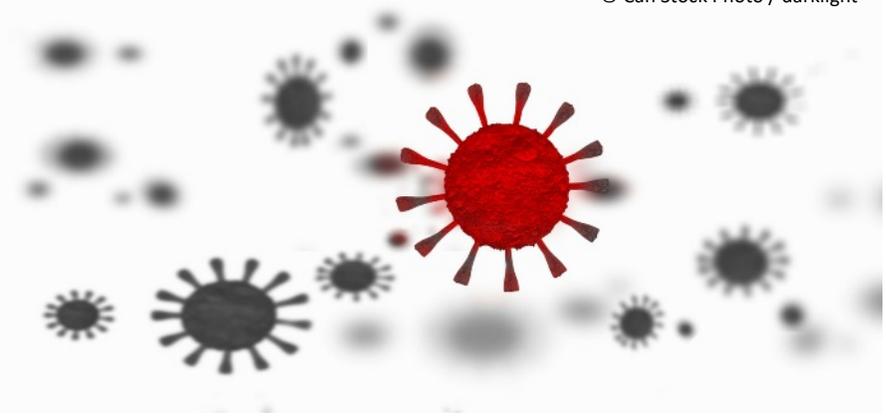
Use your NABP E-profile ID and the session code 20YC38-WXF49 for pharmacists or 20YC38-FTC42 for pharmacy technicians

to access the online quiz and evaluation. First-time users must pre-register in the Online CE Center. Test results will be displayed immediately and your participation will be recorded with CPE Monitor within 72 hours of completing the requirements.

For questions concerning the online CPE activities, email joanne.nault@uconn.edu.

You Asked for It! CE

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UConn UPDATE #1: SARS-CoV-2 and COVID-19

ABSTRACT: UConn faculty assembled this homestudy in response for a high demand to reliable education on coronavirus. It answers questions proposed by our learners.

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DISCLOSURE OF DISCUSSIONS of OFF-LABEL and INVESTIGATIONAL DRUG USE: This activity may contain discussion of off label/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

INTRODUCTION

This is an update to the University of Connecticut School of Pharmacy's continuing education (CE) activity on coronavirus. Interested individuals can find the original activity here: <https://pharmacy.uconn.edu/wp-content/uploads/sites/2740/2020/03/CORONAVIRUS-MAR2020-FINAL.pdf>.

Please feel free to share it with others.

As the SARS-CoV-2 virus spreads and the number of infections with and deaths from this virus grows, new questions emerge daily. Many pharmacists and pharmacy technicians who took the CE activity mentioned above have sent additional questions and asked for periodic updates. This update answers five of the questions we hear most often. We hope that it will provide the information you need to educate patients and answer questions.

We are aware that misinformation flourishes at a time like this. We believe something we read on a tee shirt today: **Science doesn't care what you think.** We hope you believe this too—that science is about facts, not beliefs—and will find value in the evidence we present below.

TO REGISTER and PAY FOR THIS CE, go to: https://pharmacyce.uconn.edu/program_register.php

Is there anything that you wrote in the initial activity that needs to be corrected?

No. We've reviewed that activity, and it is still correct. One area that can be amended, however, is information about making hand sanitizer. The International Pharmaceutical Federation has now issued *CORONAVIRUS SARS-CoV-2/COVID-19 PANDEMIC: Information and Interim Guidelines for Pharmacists and the Pharmacy Workforce*.¹ You can find it here: <https://tinyurl.com/r8kvt29>. It provides guidance (not rules or regulations) on how to make large batches of alcohol-based hand rub (among other things). Many states have issued their own rules and regulations for compounding pharmacies that wish to make hand sanitizer, so interested parties should check with their individual states.

Can patients with COVID-19 take NSAIDs?

This has been a common question since France's Health Minister announced that patients should not take NSAIDs and instead use acetaminophen preferentially. A number of news outlets broadcast this information, despite its preliminary nature. And it is still VERY preliminary. The World Health Organization (WHO) initially endorsed the Health Minister's statement, but then quickly adjusted its stance to indicate that no evidence supports this recommendation.² The French Health Minister's recommendation may have been based on a piece of *correspondence* published in *The Lancet Respiratory Medicine* that *hypothesized* that when combined with anti-inflammatory drugs such as ibuprofen, an enzyme could facilitate more COVID-19 infections and worsen symptoms.³ We added emphasis here to show that this concern's origin is based on a *hypothesis* proposed in *correspondence*. We are monitoring recent pre-publication manuscripts for COVID-19 specifics with regards to this potential concern. In short, no current evidence suggests that ibuprofen specifically or NSAIDs in general influence COVID-19 disease risk of infection, or severity of infection once acquired.

Pharmacists can counsel patients that until further research is available, they should start with acetaminophen to target fever provided it's safe for them to take acetaminophen (see Sidebar).

Pharmacy staff should remember that the vast majority of COVID-19 infected patients will experience only mild fever and illness, and most will have few comorbidities. For patients with mild symptoms, ibuprofen, naproxen, or any NSAID would be likely to provide symptomatic relief with risk of harm that is similar to acetaminophen. If patients have these OTC medications on hand, avoiding a trip to the grocery store or pharmacy just for acetaminophen helps maintain social distancing practices.

Patients at risk of more severe disease (elderly with comorbid hypertension, cardiovascular disease, diabetes, renal/

SIDEBAR: Who can—and cannot—take acetaminophen?^{4,5}

Acetaminophen is used widely alone and in combination with other OTC and prescription drugs. It's critical for pharmacists and technicians to know who should not take acetaminophen. It is contraindicated for patients who have the following conditions:

- Regular alcohol consumption of three or more drinks/day
- Caloric undernutrition
- The following liver conditions
 - Elevated liver enzymes
 - Acute liver failure
 - Acute hepatic inflammation associated with hepatitis C
- Severe renal impairment

Patients also need to be aware that acetaminophen overdose is possible. The maximum daily dose for adults is 4 grams (and one manufacturer recommends 3.25 grams), and older adults should take no more than 2.4 grams daily. Overdose requires immediate medical attention.

Remember (and tell patients) that acetaminophen has a number of names: acetaminophen, paracetamol, APAP, N-acetyl-para-aminophenol, acet, acetamin, or acetaminoph. Any of these names may appear on labels.

respiratory disease, etc.) generally need to avoid NSAIDs regardless of COVID-19, as they have the potential to worsen these patient's underlying conditions. For these patients, acetaminophen has a neutral effect on heart health.

What are the guidelines for pregnant and breast-feeding patients?

Limited data exists about pregnancy and COVID-19 infection, given that the disease only recently emerged. It is not known whether pregnant women have a higher chance of contracting COVID-19 than the general public, but pregnancy does cause physiological and immunological changes that increase risk of serious illness. It is currently unknown whether COVID-19 infection could cause pregnancy complications or affect the baby's health after birth. Current Centers for Disease Prevention and Control (CDC) guidelines suggest pregnant women take the same precautions as everyone else: cough or sneeze into your elbow or a tissue, avoid sick people, and clean your hands often using soap and water or alcohol-based hand sanitizer.⁶

Many hospitals are limiting hospital visitors to a single birthing partner, and in rare cases, no partner. Expectant mothers close to delivery should revise their birth plan to accommodate these changes. For example, consider a virtual doula or look into a virtual lactation consultant. Also, expectant women can have a reliable video chat service ready and know how to use it. They need to plan how to prop up a computer or phone to allow support

people to be present virtually during labor and delivery. Most importantly, they will need birth plan flexibility. Focusing on the “big picture” can reduce stress and anxiety about the smaller details.⁷

A series of nine COVID-19 positive, pregnant women in China found no mother-child transmission but one newborn born to a COVID-19 infected mother had an elevated IgM antibodies to SARS-CoV-2.⁸ In limited studies, COVID-19 and other coronaviruses have not been detected in breast milk, but we still do not know whether breastfeeding mothers can transmit the virus via breastfeeding. The most likely form of spread from mother to child would be after birth and mainly via SARS-CoV-2 contaminated respiratory droplets.

A mother with confirmed COVID-19 or whose symptoms suggest she may have the virus should⁶:

- wash her hands before touching the infant
- wear a face mask if possible while breastfeeding
- wash her hands before touching any breast pump or bottle parts
- consider having someone who is well feed the expressed milk to the infant



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Should people taking ARBs and ACE inhibitors be concerned?

In our initial publication, we noted that SARS-CoV-2 seems to be more similar to SARS-CoV than to MERS-CoV. Both SARS-CoV and SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE2) as a receptor when they bind to human cells. That fact has galvanized conversation in the science community, and that conversation has spilled over into the non-science community. Even the most educated among the conversation’s participants have questions.

ACE inhibitors (lisinopril, enalapril, ramipril) and angiotensin receptor blockers (ARBs; losartan, valsartan, candesartan) are the 4th and 11th most utilized drug classes in the U.S., with approximately 250 million prescriptions filled annually.⁹ In a rapid response letter in the *British Medical Journal* on February 28, 2020, two infectious disease specialists reported that ACE inhibitors and ARBs increase the amount of ACE2 in the body.¹⁰ Social media picked up threads of the letter’s content, and some people (who may not have the scientific training to make recommendations) began advising patients to stop taking their ACE inhibitors and ARBs immediately to prevent coronavirus spread.¹¹ Social media members’ hypothesis—and it is just a hypothesis—is that the SARS-CoV-2 virus uses ACE2 to enter human cells, so more ACE2 means more infection. The uninformed conjecture is that people with cardiovascular disease are more likely to have serious outcomes once infected with COVID-19; people with cardiovascular disease are more likely to receive ACE inhibitors and ARBs (because they have cardiovascular disease) than others.

It is not that simple.

The European Society of Cardiology and the American College of Cardiology, worried about the social media amplification, strongly suggest patients continue to take ACE inhibitors and ARBs.¹² There is no sound scientific basis to stop using them. One of this activity’s authors (Dr. White) is a pharmacist and cardiovascular researcher who has written extensively about ACE inhibitors and ARBs.^{13,14} He supports the two organizations’ recommendation for two reasons.

(1) Avoiding or stopping ARBs and ACE inhibitors without the prescriber’s knowledge in the presence of hypertension,¹⁵ chronic kidney disease,¹⁶ a past heart attack,¹⁷ or heart failure¹⁸ is known to cause cardiac and renal damage and increase mortality risk. Both organizations are skeptical of the claim that the slight increase in ACE2 with ACE inhibitor or ARB therapy will make people more susceptible to COVID-19 disease.

(2) ACE inhibitors and ARBs might actually protect patients with COVID-19 infections. Understanding the yin and the yang of the renin and angiotensin system in the body offers a clue to this hypothesis. Angiotensin converting enzyme creates angiotensin II, a chemical that causes blood vessels to constrict and the kidneys to conserve sodium and water.¹⁹ These effects are

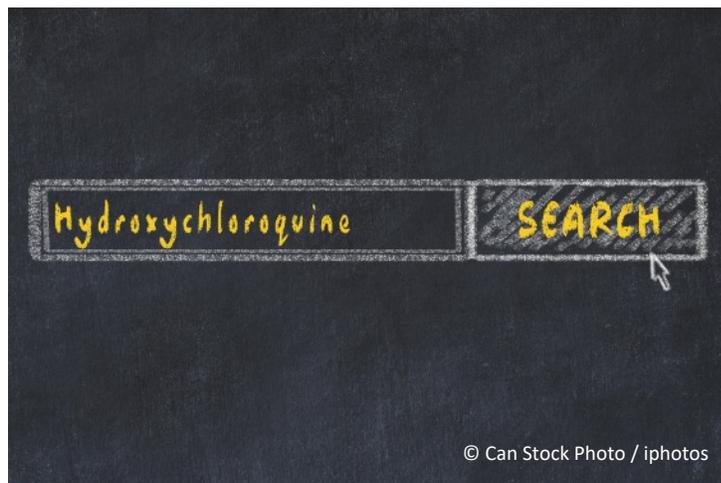
beneficial when the blood pressure is too low. Unfortunately, if there is too much angiotensin II (which can occur in patients with diabetes, heart attack, heart failure, or kidney damage), it causes the body to waste serum potassium; that can cause arrhythmias and damage the heart and kidneys by inducing local inflammation.²⁰ The body uses ACE2 to break down excessive angiotensin II, which helps to maintain a safe balance and simultaneously creates angiotensin 1-7. Angiotensin 1-7 opposes angiotensin II's actions.^{20,21}

The damage caused by COVID-19 infection suggests that the body's ACE2 effects are too small and no longer balanced with those of ACE. In 138 hospitalized COVID-19 patients, 20% developed lung injury (acute respiratory distress syndrome), 17% developed a heart arrhythmia, 7% developed acute heart injury, and 4% developed kidney injury.^{22,23} This is similar to other reports on COVID-19 infection and from reports of coronavirus MERS where cardiac injury and inflammation were commonly seen.²⁴

Even more compelling, mice infected with the original SARS-CoV developed acute lung injury, but blocking angiotensin II prevented this damage.²⁵ Furthermore, certain genetic changes in the ACE gene are risk factors for developing cardiovascular and kidney disease; when researchers assessed Vietnamese patients with the original SARS disease (SARS-CoV), patients with worse outcomes had these genetic variants.²⁶

In a prepublication of observational data from China assessing outcomes in 511 COVID-19 patients with hypertension, those receiving ARBs were at lower risk of developing severe lung dysfunction than those receiving no antihypertensive drugs (OR=0.343, 95% CI 0.128-0.916, p=0.025). Calcium channel blockers did not provide lung benefit compared to no antihypertensives while the sample sizes for beta-blockers, thiazides, and ACE inhibitors were too limited to make any statements of effect. This is interesting data supporting the imbalance in angiotensin II and angiotensin 1-7 created by COVID-19 but controlled trials are needed to know if ARB therapy truly provides patient benefit and if that benefit extends to the patient without heart disease.²⁷

The bottom line is that patients should not stop taking ACE inhibitors or ARBs in fear of contracting COVID-19. Patients need these drugs to treat underlying cardiovascular diseases. While ACE2 is needed for SARS-CoV-2 to enter cells, the slight decrease in ACE2 pursuant to discontinuation of ACE inhibitors or ARBs is unlikely to prevent infection. Furthermore, the predominance of angiotensin II in COVID-19 patients stopping ACE inhibitors and ARBs might increase risk of cardiac or renal damage.



Uninfected patients concerned about COVID-19 are interested in buying hydroxychloroquine and azithromycin from Internet pharmacies, what should I tell them?

First, let's address the issue of treating COVID-19 with hydroxychloroquine or azithromycin. We can find no large sample size, prospective, properly-controlled, randomized clinical studies; published papers; or evidenced-based recommendations that either of these drugs can prevent or successfully treat COVID-19 infection. To date (3/27/2020), only three reports describe the potential benefits of either chloroquine, hydroxychloroquine, or the combinations of hydroxychloroquine + azithromycin in patients with COVID-19 infection.^{28,29} Press release reports from China stated that "results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course." Researchers have not released any manuscript yet for peer review by the scientific community.

Another investigation that has received much attention was a small prospective non-randomized observational investigation that described the use of hydroxychloroquine alone (n=14), or, combined with azithromycin (n=6).²⁹ This article has been accepted for publication and is currently "in press." These researchers only added azithromycin to these patient's therapy if they had concerns of possible bacterial infections. Use of hydroxychloroquine was reported to decrease the time to negative nasopharyngeal polymerase chain reaction (PCR) for detection of SARS-CoV-2 compared to control patients who did not receive either of these two drugs. Interestingly, the patients who received the combination of hydroxychloroquine + azithromycin all had negative PCRs by day 5 of therapy. While this finding is cause for cautious optimism and some hope, this investigation is fraught with many important methodological and scientific limitations that are beyond the scope of this update. Those interested in learning more could review this website: <https://pubpeer.com/publications/E09AC9D25125B0AB077971FBA6DD7B>. It is an virtual "journal club" discussion of the article.

Finally, a small (n=30) prospective randomized pilot investigation described the effect of adding hydroxychloroquine to “standard therapy” (which included at least two other drugs with possible antiviral and/or immunomodulating activity).³⁰ The numbers of patients who had throat swabs negative for SARS-CoV-2 via PCR was similar in both groups (87% hydroxychloroquine + standard therapy, 93% for standard therapy only).

On March 26, 2020, clinicaltrials.gov indicated that 14 studies have registered to treat coronaviruses with hydroxychloroquine. More than half of them are not yet recruiting. Three are complete, but these are older studies that did not look specifically at COVID-19. However, the University of Minnesota is conducting an active innovative Internet-based multicenter study of hydroxychloroquine’s effects in asymptomatic persons with high-risk exposure and symptomatic persons. The study had already enrolled 455 patients as of March 26, 2020

(https://twitter.com/boulware_dr).³¹ Patients and healthcare providers in the United States and Canada who are interested in learning more about this study can either email covid19@umn.edu (to receive an automated response email with details about the study) or can visit is.gd/covid19pep. In summary, although some data exists, it is still very premature to consider chloroquine, hydroxychloroquine, or hydroxychloroquine + azithromycin effective prophylactic or treatment measures for COVID-19.³² But more rigorous data on these potential therapies may be available in as soon as two to four weeks.

So when patients indicate they might order hydroxychloroquine from the Internet, what can pharmacy staff tell them? Tell them that ordering medication on the Internet is unwise.

Here, the pharmacy community needs to turn to the lessons we have learned from experience. From 2005 to 2010, many Internet pharmacies shipped “TamiFlu (oseltamivir)” into the US.³³ These tablets had no active ingredient and some had vitamin C instead while others contained the penicillin cloxacillin placing people at risk of anaphylactic reactions.³⁴ Internet pharmacies exploited the H1N1 pandemic and concurrent shortages of oseltamivir in the US.

An even greater potential for counterfeit antiviral medication exists for the COVID-19 pandemic today. In August 2017, the National Association of Boards of Pharmacy analyzed Internet pharmacies and found that 96% did not comply with U.S. federal or state laws. Of these, almost 90% shipped prescription medication without a valid prescription and two-thirds do not reveal their physical location.³⁵ Counterfeit drugs provided by Internet pharmacies—some lacking any active ingredient and others with other drugs that do not appear on the label or banned substances—are a pervasive problem.³⁶

It goes without saying that people should not take chloroquine or hydroxychloroquine meant to clean aquariums or treat animals.

SIDEBAR: Summing It Up

1. Follow state regulations about compounding hand sanitizer
2. Patients should use acetaminophen preferentially if possible and if readily available, but NSAIDs have not been proven unsafe in COVID; patients, in most cases, need not make a special trip to the store for acetaminophen.
3. Pregnant patients should follow the same precautions as the general public and revise birthing plans where necessary. COVID-19 positive moms should take extra precautions while breastfeeding an infant.
4. Patients should never discontinue ACE inhibitors or ARBs without consulting their physicians; risk of worsening COVID-19 infection does not outweigh cardiovascular benefit.
5. No treatment has been proven effective for the prevention or treatment of COVID-19, and advise patients to never buy drugs from an online pharmacy due to lack of regulation.

Two people in the US recently found that out the hard way, with one dying and the other hospitalized after taking chloroquine meant for a fish tank.³⁷

For an updated list of all the known clinical trials of drugs being tested for COVID-19 infections, please go to the American Society of Healthcare Pharmacists’ website at: <https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx>. At this point, the currently evaluated drugs were promising *in vitro* or in small animals but far from proven effective in humans. The hope is that if one of these off-the-shelf remedies is effective, it could be rapidly deployed rather than using a typical Food and Drug Administration approval path that would take several years to test and amp up production.

CONCLUSION

This concludes our update. Please know that we appreciate your questions and comments, and we know how hard you are working. We continue to monitor this pandemic, and will provide updates as information becomes available. And don’t forget: Science doesn’t care what we think—we need to rely on the best available facts.

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