Given the global magnitude of morbidity and mortality attributed to coronavirus disease 2019 (COVID-19), it is critically important to establish therapeutic options to treat patients with disease and to prevent infection among individuals who have been exposed to the virus. At the time of this writing, there are no medications or other therapeutic modalities that have been approved by U.S. Food and Drug Administration (FDA) as treatment for or prophylaxis against COVID-19. Chloroquine (CQ) and hydroxychloroquine (HCQ), structurally related antimalarial drugs with an identical mechanism of action, have emerged as potential therapeutic options and have been the subject of much attention in the media. CQ has been FDA approved since 1949 for the treatment of malaria and other parasitic diseases. HCQ, which differs from CQ by a single hydroxyl group, has been approved since 1955 for the prevention and treatment of uncomplicated malaria as well as autoimmune diseases, such as rheumatoid arthritis and lupus. While the safety profile of these agents is well characterized for the approved indications, the efficacy and safety for treating or preventing COVID-19 have not yet been confirmed.

Community pharmacists are uniquely accessible healthcare providers during the COVID-19 pandemic, and as such may be fielding questions related to highly publicized potential therapies such as CQ and HCQ. In addition, they are impacted by a dwindling supply chain of HCQ and may struggle with interpretations of prescription legitimacy as it relates to investigational COVID-19 therapies. This article seeks to summarize the current body of evidence for the efficacy and safety of CQ and HCQ in the treatment of COVID-19.
body of evidence for CQ and HCQ in the context of issues that impact community pharmacists.

Interpreting the Literature in Infectious Diseases Therapeutics

The efficacy of an antimicrobial agent for an infectious syndrome is established both by its in vitro activity in the laboratory and studies in patients with the disease of interest. Clinical studies provide crucial information, as there are many examples in the infectious diseases literature where in vitro activity does not translate into in vivo effectiveness.12-22 Importantly, CQ and HCQ have historically demonstrated in vitro activity against several other viruses for which they were not found to be clinically useful as treatment, including chikungunya, dengue, and Ebola.22,23

The level of evidence needed to support drug efficacy for a particular disease depends on a number of factors, but general U.S. FDA guidance is that “at least two adequate and well-controlled studies” are needed to establish efficacy.24 A study is deemed adequate and well-controlled if its design minimizes bias, if the data were collected and analyzed appropriately, and if the study population adequately represents the population of interest. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework, which describes 4 levels of evidence from high to very low, is a commonly utilized scale for standardizing communication about the quality of a body of literature.25 The highest quality of evidence comes from prospective, randomized controlled trials in which investigators have taken steps, such as blinding, to minimize the risk of bias and in which there is a control group to support causal inferences about efficacy. Lower quality evidence comes from observational studies that describe outcomes in a population that has not proactively been assigned to one treatment or another.25-26

The ideal means of communicating the results of drug efficacy trials is in a peer-reviewed medical journal, which provides a mechanism for other field experts to critique the study design, analysis, and conclusions prior to wide dissemination.

Literature Review

CQ and HCQ have demonstrated potent in vitro activity against SARS-CoV-2, the virus that causes COVID-19.27,28 Off-label use of CQ and HCQ have been reported worldwide in patients with COVID-19, but much of the initial efficacy data consist of brief reports or observational cohorts published in non-peer-reviewed form.23 A widely circulated paper, cited by more than 300 publications, reported that more than 100 patients were treated with CQ in China and that it was associated with superior clinical endpoints compared to control treatment.29 The source of this information was a news briefing in China, as the study results were not available in a full manuscript. Reports of HCQ efficacy from France have also been broadly discussed in both medical and lay media. Gautret and colleagues published initial findings from a nonrandomized study of 20 HCQ-treated patients and 16 control patients and described higher rates of viral elimination from the nasopharynx with HCQ, particularly in combination with the antibiotic azithromycin.30 The groups in the study were not perfectly matched in terms of several disease-related characteristics at baseline and the viral elimination analysis excluded patients who died, deteriorated, or had adverse effects, factors which may have influenced the results.5,30 Clinicians have struggled to interpret the relevance of viral elimination as an endpoint because no studies to date have described the relationship between viral elimination and clinical outcomes, such as time spent in an intensive care unit or death.

Gautret and colleagues wrote a follow-up report describing a prospective observational study of combination HCQ and azithromycin in inpatients with mild COVID-19 upper or lower respiratory tract infection. They included 80 patients, six of whom had been described in the earlier report. They demonstrated that 81.3% of patients were clinically stable enough for discharge from the unit at the time of writing, and that 83% of patients had a negative viral test at 7 days.31 Similarly positive results were reported by the same research group in over 1000 patients with confirmed SARS-CoV-2 who were treated with at least three days of HCQ 600 mg daily and azithromycin. The majority of studied patients had mild COVID-19, and were reported to have a 4.3% rate of poor clinical outcomes.32 A challenge with these observational studies is the absence of a control group of patients who did not receive treatment, which prevents clinicians from comparing the outcomes with HCQ and azithromycin to the natural course of untreated mild disease in an environment with the same testing and supportive care procedures.

Several recent observational studies have compared patients who received HCQ to
those who did not. Mahevas and colleagues described the use of HCQ 600 mg daily at 4 French hospitals among inpatients with COVID-19 pneumonia.\textsuperscript{20} The cohort included 84 patients who received HCQ and 97 patients who did not; patients who were prescribed other experimental drugs for COVID-19 were excluded. There was a similar risk in both groups of being transferred to a critical care unit or dying within 7 days- 20.2\% of HCQ patients and 22.1\% of non-HCQ patients (RR 0.91, 95\% CI 0.47-1.8). Eight patients receiving HCQ required discontinuation due to QTc prolongation.\textsuperscript{20} Magagnoli and colleagues conducted an observational study using the national database of U.S. Veterans Health Administration medical centers with a primary endpoint of death and need for mechanical ventilation.\textsuperscript{17} They included 368 male inpatients with confirmed SARS-CoV-2 infection, of whom 97 received HCQ, 113 received HCQ and azithromycin, and 158 received only supportive care. Complex statistical analyses were performed to correct for differences in the cohorts, including propensity score adjustment to account for the fact that patients were not randomly assigned to the three treatment groups. In the cohort, patients who received HCQ had a higher mortality rate than those who did not (adjusted HR 2.61, 95\% CI 1.10-6.17, \(p = 0.03\)). There were no differences when compared to the combination therapy group, or in the endpoint of mechanical ventilation risk.\textsuperscript{17} These observational studies must be interpreted with caution, as even with statistical corrections there can be residual confounding variables and selection bias, as well as heterogeneity in the timing and dosing of HCQ.

Three small prospective randomized controlled studies have been published to date on non-peer-reviewed websites.\textsuperscript{11-13} Chen and colleagues at Zhejiang University in China described a trial with 30 patients with COVID-19 who were prescribed HCQ plus standard care or standard care alone.\textsuperscript{12} Standard care at this center included antiviral medications, so patients may also have received interferon, umifenovir, or lopinavir/ritonavir. The investigators did not find a difference in the amount of time it took for patients to have a negative SARS-CoV-2 test or the number of days it took to have a normal temperature.\textsuperscript{12} The second trial in Wuhan, China randomized 62 patients with mild COVID-19 to receive HCQ plus standard care or standard care alone. The primary endpoint was time to resolution of fever or cough and improvement of chest imaging.\textsuperscript{11} The authors reported that HCQ improved chest imaging and reduced the time to clinical improvement, with an average difference in time to improvement of 1 day for both fever and cough. Four patients in the study progressed from mild to severe disease, all of whom were in the group that did not receive HCQ.\textsuperscript{11} Given the small number of patients, this evidence is not strong enough to support the hypothesis that HCQ can prevent disease progression from mild disease. Finally, a non-blinded, randomized trial conducted at 16 centers in China reported the preliminary trial results from 150 inpatients with mild-moderate COVID-19. The study described 75 patients who had been assigned to receive HCQ and 75 who received only standard care. The rate of viral elimination was similar between the two groups at all time points up to 28 days, and the rate of improvement of symptoms (disappearance of all respiratory symptoms and fever) was also similar at 28 days.\textsuperscript{13}

Preliminary results from the CloroCovid-19 trial in Brazil supported

### TABLE 1. Clinical Practice Guidelines that Address Hydroxychloroquine for COVID-19

<table>
<thead>
<tr>
<th>Organization</th>
<th>Statement</th>
<th>Level of Evidence</th>
<th>Literature Review Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Society of Critical Care Medicine\textsuperscript{7}</td>
<td>Critically ill adults with COVID-19: insufficient evidence to issue a recommendation on the use of hydroxychloroquine.</td>
<td>N/A</td>
<td>Through March 2020</td>
</tr>
<tr>
<td>American Thoracic Society\textsuperscript{a}</td>
<td>Outpatients with COVID-19 or hospitalized patients with no evidence of pneumonia: no suggestion either for or against hydroxychloroquine.</td>
<td>Outpatients: 18% of responding experts for intervention, 36% no suggestion, and 46% against.</td>
<td>Expert survey March 23-25, 2020</td>
</tr>
<tr>
<td></td>
<td>Hospitalized patients with COVID-19 who have evidence of pneumonia: suggest hydroxychloroquine on a case-by-case basis.</td>
<td>Hospitalized without pneumonia: 8% for intervention, 50% no suggestion, and 42% against.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospitalized patients with COVID-19 who have evidence of pneumonia: suggest hydroxychloroquine on a case-by-case basis.</td>
<td>Hospitalized with COVID pneumonia: 73% for intervention, 16% no suggestion, and 11% against.</td>
<td></td>
</tr>
<tr>
<td>Infectious Diseases Society of America\textsuperscript{a}</td>
<td>Hospitalized patients with COVID-19: recommend hydroxychloroquine in the context of a clinical trial.</td>
<td>Very low</td>
<td>April 4, 2020</td>
</tr>
<tr>
<td></td>
<td>Hospitalized patients with COVID-19: recommend hydroxychloroquine plus azithromycin only in the context of a clinical trial.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Institutes of Health\textsuperscript{10}</td>
<td>Insufficient clinical data to recommend either for or against using hydroxychloroquine for the treatment of COVID-19.</td>
<td>A-III (strong recommendation based on expert opinion)</td>
<td>Updated continuously</td>
</tr>
</tbody>
</table>
the early discontinuation of one of the study arms due to safety concerns. Borba and colleagues designed a prospective, double-blinded, randomized trial of two different doses of CQ in combination with azithromycin in hospitalized patients with clinical suspicion of COVID-19. Of the 81 patients enrolled, 41 received high dose CQ (1200 mg daily) and 40 received low dose CQ (900 mg on day 0, 450 mg on days 1-4). The two groups were not perfectly matched, since patients in the high dose CQ group were more likely to have heart disease and be older than 75 years of age. Patients in the high dose group were more likely to have a QTc > 500 msec and two patients experienced ventricular tachycardia before death without torsade de pointes, prompting the safety oversight board for the study to recommended termination of the high dose arm. Preliminary clinical efficacy outcomes were published, but the investigators had not yet enrolled the number of patients that were needed to find a difference between the two arms from a statistical standpoint.

There is no published evidence to date regarding the efficacy of CQ or HCQ in the prevention of COVID-19 in high risk populations such as healthcare workers or close household contacts of patients with COVID-19.

**Expert Consensus**

Clinical practice guidelines that address the use of CQ and HCQ for COVID-19 have been published by several American organizations to date: the European Society of Intensive Care Medicine and Society of Critical Care Medicine, an international task force of the American Thoracic Society, the Infectious Diseases Society of America, and the National Institutes of Health (Table 1). These guidelines did not include in their review recently published pre-print studies, including the French observational studies, the largest prospective Chinese trial, Veterans Affairs study, or Cloro-Covid19. In light of emerging data, the U.S. FDA recently released a drug safety communication alerting prescribers to the risks of CQ and HCQ, specifically QTc interval prolongation and risk of severe hypoglycemia. Healthcare professionals are encouraged to utilize CQ and HCQ in the context of a clinical trial or among hospitalized patients who can be monitored for QTc prolongation.

**Supply Chain Concerns**

The supply chain for HCQ has been impacted by increasing off-label demand for COVID-19, with most major manufacturers listed on the American Society of Health-System Pharmacists’ (ASHP) Drug Shortage Bulletin. The risk of interrupted therapy for patients who require chronic HCQ for diseases with well-established efficacy, such as rheumatoid arthritis and lupus, is significant. Pharmacists should be aware that wholesalers may have supplies of HCQ set aside for patients with chronic conditions; pharmacies affected by drug shortages should communicate with their purchasing contacts to obtain necessary stock.

Wisconsin has not passed formal regulations with regards to outpatient prescribing of HCQ. That said, major medical societies such as the American Medical Association, American Pharmacists Association, and ASHP have all formally addressed the responsibility that pharmacists have in stewardship of hydroxychloroquine to ensure a consistent supply for patients on chronic therapy for approved indications. In a joint statement, these organizations strongly advised against the practice of prophylactic use of HCQ for COVID-19, particularly the identified practice of self-prescribing or providing prescriptions for family members and colleagues. Pharmacists are encouraged to have a conversation with prescribers to determine whether HCQ prescriptions have been written for a legitimate medical purpose. In addition, pharmacists are asked not to stockpile excessive amounts of HCQ in anticipation of increased COVID-19 utilization. The Wisconsin Medical Society and the Pharmacy Society of Wisconsin issued an affirmation of this joint statement. In the context of the previous paragraphs, it is clear that no data exist to support prophylactic use of HCQ and that no major medical societies recommend outpatient use of HCQ outside of clinical trials.

**Conclusion**

Pharmacists play an important role in providing medication expertise and stewardship related to potential therapies for COVID-19. This review highlights current literature and pharmacist considerations related to CQ and HCQ.

Kristen Bunnell is an Assistant Professor of Clinical Sciences at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI. Sara Revolinski is the Director of Experiential Education and Assistant Professor at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI. Drs. Bunnell and Revolinski practice as antimicrobial stewardship pharmacists at Froedtert Hospital in Milwaukee, WI. Njeri Wainaina is an Associate Professor of Medicine and Surgery and Medical Director at Froedtert Hospital Preoperative Clinic, Enterprise Medical Director for Antimicrobial Stewardship at Froedtert Health in Milwaukee, WI.

This information is up to date as of April 26, 2020. Please note that the data for COVID-19 are rapidly evolving, and the key points above are subject to change.

Acknowledgements: We appreciate the following colleagues who provided critical review and content expertise in the creation of this article: Lisa Brauer, RPh, Shannon Werner, PharmD, Mary Frances Piccone, PharmD, and the MCW librarians who performed an initial literature search.

Disclosure: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

**References**


www.pswi.org

3.

References