

SUPPORTING OUR PHARMACY STAKEHOLDERS DURING THE COVID-19 CRISIS

# MEDICATIONS AND COVID-19: FACTS AND CONTROVERSIES

This COVID-19 pandemic has fundamentally changed the way people live their lives today. Technology plays a crucial role in keeping people connected, but it is also the source of numerous messages from various sources, some of which offer hope to those concerned about, or dealing with, COVID-19 illness. Pharmacists have an important role to play on the front lines, providing credible, evidence-based information and advice to Canadians. This document was created to enable and support pharmacists in helping patients sort through the “noise” during this crisis.

## OBJECTIVES:

*This document will address the following four questions:*

- 1 Do ibuprofen and other NSAIDs increase the risk of serious illness with COVID-19, and should I be telling my patients not to use them?
- 2 What should I tell my patients who are taking ACE inhibitors and ARBs about their risk of becoming more ill if they get COVID-19?
- 3 Should patients be prescribed hydroxychloroquine with azithromycin for COVID-19?
- 4 What other treatments are being tested for COVID-19?



## 1 IBUPROFEN AND OTHER NSAIDS

Concerns were raised amongst the general public regarding the use of ibuprofen and other NSAIDs in those with COVID-19 after the health minister in France tweeted a message stating that NSAIDs and corticosteroids could worsen COVID-19 infection. He tweeted his comment after a letter by Fang et al,<sup>1</sup> posted on *Lancet* online, raised some theoretical concerns.

The letter was based on the observation of comorbidities, specifically cardiovascular disease and diabetes, identified in patients who were hospitalized with COVID-19 in China. The authors suggested that ibuprofen, thiazolidinediones, ACE inhibitors, and ARBs increase the expression of the enzyme ACE2 (angiotensin converting enzyme 2). The SARS-CoV-2 (coronavirus) attaches to lung cells via this enzyme, thus theoretically increasing the risk of severe or fatal COVID-19 in those who are taking these medications.<sup>1</sup>

### What does this mean for patient care?

There is currently no evidence to show that people with asymptomatic or mild COVID-19 are at higher risk of complications if they take NSAIDs. If people are taking one of these medications for a reason prior to contracting COVID-19, they can continue treatment.<sup>2</sup>

When it comes to treating fever, it is important to consider, as always, whether the fever needs to be treated. If a patient is very uncomfortable, then treatment with an antipyretic medication may be warranted but not necessary. Ibuprofen has risks in those with advanced age and in those with certain medical conditions, such as hypertension, so acetaminophen may be a safer choice in these individuals.<sup>3</sup>

## 2 ACE INHIBITORS AND ARBs AND INCREASED RISKS OF COVID-19

Following on the letter that was published in the *Lancet*<sup>1</sup>, it was theorized that because SARS-CoV-2, or COVID-19, uses the SARS-COV receptor angiotensin converting enzyme (ACE) 2 to attach to target cells in the lungs, an increase in ACE2 could increase the risk of serious or fatal disease.<sup>4</sup> Thus, it would appear that the use of ACE inhibitors and ARBs would increase the risk of worse outcomes with COVID-19 infection. However, there have been no clinical trials that have shown that patients who take these medications have worse outcomes.

Although Fang et al. state in their author's reply to the original letter published in *Lancet* that it is unclear as to whether ACE inhibitors and ARBs do more harm than good during COVID-19 infection,<sup>5</sup> the Canadian Cardiovascular Society has stated that patients taking ACE inhibitors/ARBs/angiotensin-neprilysin inhibitors for hypertension or heart failure should continue to take these medications unless otherwise advised by their physician. They have also indicated that these medications should not be stopped if there is a suspected or confirmed diagnosis of COVID-19 unless there is a compelling reason to do so.<sup>6</sup> A statement from the American Heart Association, Heart Failure Society of America, and the American College of Cardiology states that patients are advised to continue treatment with ACE inhibitors or ARBs as prescribed unless otherwise advised by their primary care provider.<sup>7</sup>

### What does this mean for patient care?

Patients are prescribed ACE inhibitors and ARBs most often for conditions such as heart failure, hypertension, and protection associated with the negative vascular effects of diabetes. Stopping these medications can pose

significant risks of worsening heart failure or increased blood pressure and subsequent increased morbidity and mortality. As of March 30, 2020, there is no clinical evidence to support stopping these medications for patients. Continue to educate patients on physical distancing measures to prevent the spread of COVID-19 and other strategies to maintain cardiovascular wellness.

### 3 HYDROXYCHLOROQUINE WITH/WITHOUT AZITHROMYCIN TO TREAT COVID-19

Hydroxychloroquine and chloroquine have been used for years to treat malaria and some autoimmune conditions, such as rheumatoid arthritis.

Recent trials in China have shown some benefits of chloroquine phosphate in patients with COVID-19, associated pneumonia and have suggested that this drug be included in the treatment guidelines for pneumonia caused by COVID-19, published by the Health Commission of the People's Republic of China.<sup>9</sup> The in-vitro effectiveness of hydroxychloroquine against SARS-CoV-2 has been documented.<sup>10</sup> Azithromycin has been found to be active in vitro against Zika virus.<sup>11</sup>

There has been increasing interest in the use of hydroxychloroquine with azithromycin to treat COVID-19, primarily in response to a study that was posted before publication on March 20, 2020. This small, open-label, non-randomized trial was conducted in Marseille and surrounding areas in France to test the impact of hydroxychloroquine on viral load in patients with COVID-19. The primary endpoint was viral clearance at day six of treatment.<sup>8</sup>

The clinical trial conducted in Marseille included patients who were all over 12 years of age with laboratory-confirmed COVID-19

and were either asymptomatic or had upper respiratory tract infection (e.g., rhinitis, pharyngitis) or lower respiratory tract infection (i.e., pneumonia or bronchitis).<sup>8</sup> The treatment group (20 patients) received 600 mg hydroxychloroquine daily for 10 days, and the control group (16 patients) did not receive any medication. Some patients also received azithromycin to prevent bacterial super-infection based on clinician judgment. Investigators checked viral loads each day using nasopharyngeal wash. The investigators found that by day six, 70% of people in the treatment group no longer carried the virus, compared to 12.5% in the control group. Investigators also concluded that the combination of hydroxychloroquine with azithromycin was more effective than hydroxychloroquine alone.<sup>8</sup>

Although the investigators for this French study were encouraged by the outcomes and recommended the use of hydroxychloroquine with azithromycin to “cure” COVID-19, the research had some flaws and significant limitations. First, the study did not measure clinical outcomes, only viral load. Second, six patients dropped out of the study, but this was not accounted for; many of those were sicker patients. Third, the rationale for using azithromycin was not articulated in this study, as it was based on clinician judgment. The sample size was also small, and the follow-up period was short.<sup>8</sup>

#### What does this mean for patient care?

There is insufficient data from this small, nonrandomized trial to make recommendations for treatment of COVID-19. More research is needed. Furthermore, what has not been studied is the safety of hydroxychloroquine and azithromycin when used together in patients with COVID-19. Both medications can cause QT interval prolongation, and this is particularly concerning because the sickest patients with COVID-19 tend to be those with comorbidities, such as cardiovascular disease.

## 4 CURRENT RESEARCH ON COVID-19

In light of the fact that a vaccine against COVID-19 could be at least one year away, the World Health Organization (WHO) has started a megatrial, referred to as SOLIDARITY, to test several medications for their effectiveness and safety in treating this coronavirus.<sup>12</sup> All the medications have previously shown some evidence of effectiveness against the coronavirus, either in vitro or in animal studies.<sup>13</sup> As of March 30, 2020, several countries have confirmed their participation in this trial, including Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland, and Thailand.<sup>12</sup> Patients in this trial will be randomized to one of the four treatments listed below or the local standard of care. To expedite the process, the trial will not be double-blinded. Note that the design of the trial, and the medications included, may change over time. Here is a brief review of the medications that will be included in this trial.<sup>12,14</sup>

### REMDESIVIR

- This antiviral drug was created by Gilead Sciences as a treatment for Ebola virus. It was not shown to be effective to treat Ebola but has been shown in vitro to inhibit MERS (Middle East respiratory syndrome) and SARS (severe acute respiratory syndrome) viruses.
- When the first reported case of COVID-19 was identified in the US in Washington state earlier in 2020, the patient was hospitalized and treated with remdesivir, obtained through compassionate use. The patient's symptoms improved the next day, such that he no longer needed oxygen therapy and experienced only mild symptoms.<sup>15</sup>
- Remdesivir is currently available through the Special Access Programme of Canada, determined on a case-by-case basis. The criteria for consideration are for those who

are hospitalized, confirmed COVID-19 positive, and have significant clinical manifestations. Physicians can also enrol patients in current clinical trials to access this drug (<https://rdvcu.gilead.com>).

### CHLOROQUINE AND HYDROXYCHLOROQUINE

- These antimalarial medications have been studied for other viruses (e.g., dengue, Chikungunya) but have not been shown to be effective. It has been suggested that high doses may be needed to suppress viruses, so medication toxicity may be an issue.
- The commentary in question 3 above addresses the recent interest in the use of these medications for COVID-19.

### RITONAVIR/LOPINAVIR (KALETRA®)

- This combination of drugs, both protease inhibitors, is indicated for the treatment of HIV infection.
- It has been suggested that this medication combination may be able to inhibit the proteases of coronaviruses (enzymes necessary to cut long chains of viral proteins into functional smaller segments), and it has shown some benefits for treatment of MERS in marmosets.
- This combination was tried in China in close to 200 patients with severe COVID-19 and was not found to be effective.<sup>16</sup>
- There are several potential drug interactions and some safety and monitoring considerations.

### RITONAVIR/LOPINAVIR (KALETRA®) AND INTERFERON-BETA

- Interferon-beta, a cytokine used to treat autoimmune disease, has shown some promise in treating MERS in marmosets.

**What does this mean for patient care?**

This study exemplifies how the world is coming together to tackle this important public health crisis. It is hoped that this megatrial will provide good evidence to support a pharmacologic treatment for COVID-19. According to the Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19), in critically ill adults with COVID-19, the consensus is not to use ritonavir/lopinavir or antivirals routinely.<sup>17</sup>

While the news of this study offers a glimmer of hope for everyone, it is important to share with patients the importance of credible, well-designed trials to test both safety and effectiveness of any treatment, including those for COVID-19.

**For more clinical guidance, click on the following link to view the International Pharmaceutical Federation (FIP) guidelines for pharmacists and the pharmacy workforce:**  
**<https://www.fip.org/coronavirus>.**

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