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HVPA Rx Update on COVID-19 –March 24, 2020

CDC Update on Therapeutic Options for COVID-19

Our patients are reading and hearing so many things about COVID-19 and are frightened. Unfortunately, there is a lot of misinformation or unclear messaging being provided that may make this crisis even more complicated.

The drug chloroquine has been noted as a potential treatment for seriously ill COVID-19 patients, however, some people are acquiring the chemical chloroquine phosphate through the internet, including products used to clean fish tanks, and ingesting those chemicals to prevent COVID-19 infection. We are starting to see case reports of deaths and hospitalizations due to use of this chemical without a health care professional supervision.

The FDA-approved indication for chloroquine is for malaria or off-label for some types of lupus, but not as a first-line drug.

I remember from pharmacy school that this drug has very ugly side-effects: Major toxicities include:

- Severe hypoglycemia
- Extrapyramidal effects
- Myopathy and neuromyopathy
- Retinal toxicity, including irreversible retinopathy
- Agranulocytosis and aplastic anemia
- Seizures
- Cardiomyopathy, fatal cardiac failure and QT prolongation

Use of this drug in unsupervised settings may cause severe harm and even death.

Hydroxychloroquine sulfate has also been noted as a potential treatment for seriously ill COVID-19 patients. It is FDA-approved to treat malaria, lupus erythematosus and rheumatoid arthritis.

Hydroxychloroquine sulfate also shares some of the same major toxicities as chloroquine, such as:

- Retinal toxicity
- Cardiomyopathy including fatal cardiac failure
- Myopathy and neuromyopathy
- Psychiatric effects
- Bone marrow suppression

Some of my fellow pharmacists have told me that they have encountered “stockpiling” prescriptions for chloroquine and hydroxychloroquine for patients and prescribers themselves without a history of malaria, lupus or rheumatoid arthritis. We should not be diverting prescriptions from the critically ill “just in case” someone may get symptoms of COVID-19. Most health plans will be placing limitations on

the use of these medications to ensure patients with FDA-approved indications and the critically ill will still have access to these medications.

So where is the best source of information on the drugs under investigation for COVID-19?
I have provided the most recent update from the CDC as of 3/21/2020 (see pages below). It provides the status of clinical trials and expanded access availability. This will be a very fluid situation and it will be important that health care providers have a source of this information. It can be found at:
https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html

Remote Prescribing through e-Prescribing as we Move to Telemedicine
Using technology to provide telemedicine visits to patients is currently one of the most effective tools to safeguard both patients and health care providers from unnecessary exposure to COVID-19 yet still providing effective care and treatment. Th Centers for Medicare and Medicaid Services (CMS) and health plans are expanding coverage of telemedicine benefits to allow more patients to receive care through technology.

Electronic prescribing (e-prescribing) is another technology that safeguards patients as well as prescribers and pharmacists. Use of e-prescribing in conjunction with telemedicine visits has many benefits. Pharmacies are also on the front line in caring for patients. Volumes of phone calls and prescriptions to be filled have tripled and quadrupled for some busy pharmacy settings.

Use of e-prescribing has the following benefits:

- Prevention of prescription errors
- Immediate access to medication history and drug-drug interaction notifications
- Clinical alerts such as allergies and duplicate therapies
- Prevention of controlled substance misuse
- Facilitates verification of insurance/formulary coverage of medications
- Reduction of provider calls into the pharmacy; more calls into the pharmacy can increase the risk of a medication order translation error

One major challenge with telemedicine and e-prescribing involves the prescribing of controlled substances. On January 31, 2020, the Secretary of the Department of Health and Human Services issues a public health emergency.

https://www.deadiversion.usdoj.gov/coronavirus.html

Question: Can telemedicine now be used under the conditions outlined in Title 21, United States Code (U.S.C.), Section 802(54)(D)?

Answer: Yes. While a prescription for a controlled substance issued by means of the Internet (including telemedicine) must generally be predicated on an in-person medical evaluation (21 U.S.C. 829(e)), the Controlled Substances Act contains certain exceptions to this requirement. One such exception occurs when the Secretary of Health and Human Services has declared a public health emergency under 42 U.S.C. 247d (section 319 of the Public Health Service Act), as set forth in 21 U.S.C. 802(54)(D). Secretary Azar declared such a public health emergency with regard to COVID-19 on January 31, 2020 (https://www.hhs.gov/about/news/2020/01/31/secretary-azar-declares-public-health-emergency-us-

2019-novel-coronavirus.html). On March 16, 2020, the Secretary, with the concurrence of the Acting DEA Administrator, designated that the telemedicine allowance under section 802(54)(D) applies to all schedule II-V controlled substances in all areas of the United States. Accordingly, as of March 16, 2020, and continuing for as long as the Secretary's designation of a public health emergency remains in effect, DEA-registered practitioners in all areas of the United States may issue prescriptions for all schedule II-V controlled substances to patients for whom they have not conducted an in-person medical evaluation, provided all of the following conditions are met:

- The prescription is issued for a legitimate medical purpose by a practitioner acting in the usual course of his/her professional practice;
- The telemedicine communication is conducted using an audio-visual, real-time, two-way interactive communication system; and
- The practitioner is acting in accordance with applicable federal and state laws.

Provided the practitioner satisfies the above requirements, the practitioner may issue the prescription using any of the methods of prescribing currently available and in the manner set forth in the DEA regulations. Thus, the practitioner may issue a prescription either electronically (for schedules II-V) or by calling in an emergency schedule II prescription to the pharmacy, or by calling in a schedule III-V prescription to the pharmacy.

The term "practitioner" in this context includes a physician, dentist, veterinarian, or other person licensed, registered, or otherwise permitted, by the United States or the jurisdiction in which s/he practices to prescribe controlled substances in the course of his/her professional practice (21 U.S.C. 802(21)).

Important note: If the prescribing practitioner has previously conducted an in-person medical evaluation of the patient, the practitioner may issue a prescription for a controlled substance after having communicated with the patient via telemedicine, or any other means, regardless of whether a public health emergency has been declared by the Secretary of Health and Human Services, so long as the prescription is issued for a legitimate medical purpose and the practitioner is acting in the usual course of his/her professional practice. In addition, for the prescription to be valid, the practitioner must comply with applicable Federal and State laws.

Michigan regulations do require the existence of a prior provider-patient relationship before medication can be prescribed, but nothing in the law or regulations requires that the relationship be established in person.

Pursuant to the definition of Telemedicine (defined by MCL 500.3476) states that "Telemedicine" means the use of an electronic media to link patients with health care professionals in different locations. To be considered telemedicine under this section, "the health care professional must be able to examine the patient via a real-time, interactive audio or video, or both, telecommunications system and the patient must be able to interact with the off-site health care professional at the time the services are provided.

Information for Clinicians on Therapeutic Options for COVID-19 Patients – Published by the CDC 3/21/2020

There are no U.S. Food and Drug Administration (FDA)-approved drugs specifically for the treatment of patients with COVID-19. At present, clinical management includes infection prevention and control measures and supportive care, including supplementary oxygen and mechanical ventilatory support when indicated. An array of drugs approved for other indications as well as several investigational drugs are being studied in several hundred clinical trials that are underway across the globe. The purpose of this document is to provide information on two of the approved drugs (chloroquine and hydroxychloroquine) and one of the investigational agents (remdesivir) currently in use in the United States.

Remdesivir

Remdesivir is an investigational intravenous drug with broad antiviral activity that inhibits viral replication through premature termination of RNA transcription and has in-vitro activity against SARS-CoV-2 and in-vitro and in-vivo activity against related betacoronaviruses [1-3].

There are currently four options for obtaining remdesivir for treatment of hospitalized patients with COVID-19 and pneumonia in the United States:

- A National Institutes of Health (NIH)-sponsored adaptive double-blinded, placebo-controlled trial of remdesivir versus placebo in COVID-19 patients with pneumonia and hypoxia is enrolling non-pregnant persons aged 18 years and older with oxygen saturation of ≤94% on room air or requiring supplemental oxygen or mechanical ventilation (https://clinicaltrials.gov/ct2/show/NCT04280705external icon). Exclusion criteria include alanine aminotransaminase or aspartate aminotransaminase levels >5 times the upper limit of normal, stage 4 severe chronic kidney disease or a requirement for dialysis (i.e., estimated glomerular filtration rate (eGFR) <30);

- Two phase 3 randomized open-label trials of remdesivir (5-days versus 10-days versus standard of care) are open to enrollment in persons aged 18 years and older with COVID-19, radiographic evidence of pneumonia and oxygen saturation of ≤94% on room air (severe disease https://clinicaltrials.gov/ct2/show/NCT04292899external icon) or >94% on room air (moderate disease https://clinicaltrials.gov/ct2/show/NCT04292730external icon). Exclusion criteria include alanine aminotransaminase or aspartate aminotransaminase levels >5 times the upper limit of normal, participation in another clinical trial of an experimental treatment for COVID-19, requirement for mechanical ventilation, or creatinine clearance <50 mL/min; and

- Finally, in areas without clinical trials, COVID-19 patients in the United States and other countries have been treated with remdesivir on an uncontrolled compassionate use basis. The manufacturer is currently transitioning the provision of emergency access to remdesivir from individual compassionate use requests to an expanded access program. The expanded access program for the United States is under rapid development. Further information is available at: https://rdvcu.gilead.com/external icon

Hydroxychloroquine and Chloroquine

Hydroxychloroquine and chloroquine are oral prescription drugs that have been used for treatment of malaria and certain inflammatory conditions. Chloroquine has been used for malaria treatment and chemoprophylaxis, and hydroxychloroquine is used for treatment of rheumatoid arthritis, systemic lupus erythematosus and porphyria cutanea tarda. Both drugs have in-vitro activity against SARS-CoV, SARS-CoV-2, and other coronaviruses, with hydroxychloroquine having relatively higher potency against SARS-CoV-2 [1,4,5]. A study in China reported that chloroquine treatment of COVID-19 patients had clinical and virologic benefit versus a comparison group, and chloroquine was added as a recommended antiviral for treatment of COVID-19 in China [6]. Based upon limited in-vitro and anecdotal data, chloroquine or hydroxychloroquine are currently recommended for treatment of hospitalized COVID-19 patients in several countries. Both chloroquine and hydroxychloroquine have known safety profiles with the main concerns being cardiotoxicity (prolonged QT syndrome) with prolonged use in patients with hepatic or renal dysfunction and immunosuppression but have been reportedly well-tolerated in COVID-19 patients.

Due to higher in-vitro activity against SARS-CoV-2 and its wider availability in the United States compared with chloroquine, hydroxychloroquine has been administered to hospitalized COVID-19 patients on an uncontrolled basis in multiple countries, including in the United States. One small study reported that hydroxychloroquine alone or in combination with azithromycin reduced detection of SARS-CoV-2 RNA in upper respiratory tract specimens compared with a non-randomized control group but did not assess clinical benefit [7]. Hydroxychloroquine and azithromycin are associated with QT prolongation and caution is advised when considering these drugs in patients with chronic medical conditions (e.g. renal failure, hepatic disease) or who are receiving medications that might interact to cause arrythmias.

Hydroxychloroquine is currently under investigation in clinical trials for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection, and treatment of patients with mild, moderate, and severe COVID-19. In the United States, several clinical trials of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection are planned or will be enrolling soon. More information on trials can be found at: https://clinicaltrials.gov/external icon.

There are no currently available data from Randomized Clinical Trials (RCTs) to inform clinical guidance on the use, dosing, or duration of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection. Although optimal dosing and duration of hydroxychloroquine for treatment of COVID-19 are unknown, some U.S. clinicians have reported anecdotally different hydroxychloroquine dosing such as: 400mg BID on day one, then daily for 5 days; 400 mg BID on day one, then 200mg BID for 4 days; 600 mg BID on day one, then 400mg daily on days 2-5.

Other Drugs

Lopinavir-ritonavir did not show promise for treatment of hospitalized COVID-19 patients with pneumonia in a recent clinical trial in China [8]. This trial was underpowered, and lopinavir-ritonavir is under investigation in a World Health Organization study.

Several other drugs are under investigation in clinical trials or are being considered for clinical trials of prophylaxis or treatment of COVID-19 in the United States and worldwide. Information on registered clinical trials for COVID-19 in the United States is available at: https://clinicaltrials.gov/external icon.

References

1. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020 Mar;30(3):269-271.

2. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE, Bauer L, Sellers S, Porter D, Feng JY, Cihlar T, Jordan R, Denison MR, Baric RS. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020 Jan 10;11(1):222.

3. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, Leist SR, Pyrc K, Feng JY, Trantcheva I, Bannister R, Park Y, Babusis D, Clarke MO, Mackman RL, Spahn JE, Palmiotti CA, Siegel D, Ray AS, Cihlar T, Jordan R, Denison MR, Baric RS. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017 Jun 28;9(396).

4. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020 Mar 4:105932. doi: 10.1016/j.ijantimicag.2020.105932. [Epub ahead of print]

5. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9. pii: ciaa237. doi: 10.1093/cid/ciaa237. [Epub ahead of print]

6. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020 Mar 16;14(1):72-73

7. Gautret P, Lagier J, Parola P, Hoang V, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents. In Press.

8. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 Mar 18. doi: 10.1056/NEJMoa2001282. [Epub ahead of print]