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Ten Common Questions (and Their Answers) About Off-label Drug Use

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Abstract

The term *off-label drug use* (OLDU) is used extensively in the medical literature, continuing medical education exercises, and the media. Yet, we propose that many health care professionals have an underappreciation of its definition, prevalence, and implications. This article introduces and answers 10 questions regarding OLDU in an effort to clarify the practice's meaning, breadth of application, acceptance, and liabilities. Off-label drug use involves prescribing medications for indications, or using a dosage or dosage form, that have not been approved by the US Food and Drug Administration. Since the Food and Drug Administration does not regulate the practice of medicine, OLDU has become common. It occurs in every specialty of medicine, but it may be more common in areas of medicine in which the patient population is less likely to be included in clinical trials (eg, pediatric, pregnant, or psychiatric patients). Pharmaceutical companies are not allowed to promote their medications for an off-label use, which has lead to several large settlements for illegal marketing. To limit liability, physicians should prescribe medications only for indications that they believe are in the best interest of the patient. In addition, health care professionals should educate themselves about OLDU to weigh the risks and benefits and provide the best possible care for their patients.

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The term *off-label drug use* (OLDU) is used extensively in the medical literature, continuing medical education (CME) exercises, and the media. It is a polarizing term because it can be associated with great benefit or harm to patients.[1] In addition, OLDU, along with allegations of pharmaceutical company promotion of OLDU, has been the cause of major lawsuits and historically large out-of-court legal settlements.[2-7] Therefore, all health care professionals have likely heard the term *OLDU* used, yet we propose that many have an underappreciation of its definition, prevalence, and implications. This article introduces and answers 10 questions regarding OLDU in an effort to clarify the practice's meaning, breadth of application, acceptance, and liabilities.

QUESTION 1: WHAT IS THE DEFINITION OF OLDU?

The most common form of OLDU involves prescribing currently available and marketed medications but for an indication (eg, a disease or a symptom) that has never received Food and Drug Administration (FDA) approval.[8,9] Hence, the specific use is "off-label" (ie, not approved by the FDA and not listed in FDA-required drug-labeling information). The term *OLDU* can also apply to the use of a marketed medication in a patient population (eg, pediatric), dosage, or dosage form that does not have FDA approval.

The current role of the FDA is to control which medications are available commercially. Historically, the Food, Drug, and Cosmetic Act of 1938 required only that a new medication be safe.[9] In 1962, the Kefauver-Harris Amendment mandated that FDA-approved new drugs also must have evidence that they are effective.[9] Therefore, the FDA approves new medications that have been shown to be safe and effective for specific indications (ie, "on-label" prescribing). The FDA does not limit or control how the medications are prescribed by physicians once the medications are available on the market. By definition, OLDU is prescribing for an indication, or employing a dosage or dosage form, that has not been approved through the FDA process.

Off-label drug use can be motivated by several factors. First, a medication may not have been studied and approved for a specific population (eg, pediatric, geriatric, or pregnant patients).[10] Second, a life-threatening or terminal medical condition may motivate a health care professional to give any treatment that is logical and available, whether approved by the FDA or not. Third, if one medication from a class of drugs has FDA approval, physicians commonly use other medications in the same class without specific FDA approval for that use for the same indication.[8,9] In addition, if the pathologic or physiologic features of 2 conditions are similar, a physician may use a medication approved for 1 of these conditions for both (eg, diabetes and metabolic syn-

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drome; psychiatric diseases such as anxiety and posttraumatic stress disorder).[8]

QUESTION 2: IS OLDU COMMON?

Indeed, OLDU is common. Radley et al[1] reported in 2006 that in a group of commonly used medications, 21% of prescriptions were for an off-label use. In certain subpopulations of patients, this rate may be even higher. For example, a study by Shah et al[11] found that 78.9% of children discharged from pediatric hospitals were taking at least 1 off-label medication. In addition, in a pediatric emergency department, the rate of OLDU was estimated to be 26.2%.[2] The off-label use of antidepressant, anticonvulsant, and antipsychotic medications is high and is more prevalent with increasing patient age.[12] In an intensive care unit, Lat et al[13] reported that 36.2% of medication orders were for an off-label use. In addition, β-adrenergic blocking agents are commonly prescribed for an off-label indication, and specialists may more commonly prescribe for off-label β-blocker use than primary care physicians.[10] In a headache specialty practice, Loder and Biondi[14] reported that off-label use accounted for 47% of prescriptions written.

QUESTION 3: CAN AN OLDU FOR A GIVEN DRUG BECOME A WIDELY ACCEPTED PRACTICE OR EVEN A STANDARD OF CARE?

Off-label drug uses can become widely entrenched in clinical practice and become predominant treatments for a given clinical condition. For example, tricyclic antidepressants do not have FDA approval as a treatment for neuropathic pain, yet this class of drugs is considered a first-line treatment option.[15] The use of aspirin provides another interesting example of OLDU. Aspirin was widely used before the introduction of the Food, Drug, and Cosmetic Act of 1938. Therefore, aspirin was grandfathered and approved as an existing drug without the rigorous testing that modern medications undergo. Currently, aspirin is FDA approved for use in patients with pain, fever, rheumatic diseases, cardiovascular diseases (eg, acute myocardial infarction, previous myocardial infarction, angina pectoris, and previous cerebrovascular disease), and a history of a revascularization procedure (eg, coronary artery bypass grafting and carotid endarterectomy).[16] However, aspirin does not have an indication for coronary disease prophylaxis in diabetic patients, yet guidelines recommend its use in these patients.[8] Therefore, aspirin prophylaxis for coronary disease in high-risk patients is an off-label use.

Elsewhere, medications are often prescribed for OLDU with poor or absent clinical evidence. Radley et al[1] reported that 73% of medications prescribed for an off-label use had poor or no scientific support. In critical care patients, OLDU was without adequate evidence 48.3% of the time.[13] Because OLDU is typically less critically evaluated than is on-label drug use, OLDU may be associated with an increase in medication errors.[17] Rinke et al[17] studied pediatric antidepressant drug use in a national error-reporting database and found that 77% involved off-label prescribing.

QUESTION 4: WHAT ARE SOME EXAMPLES OF WIDELY PRACTICED OLDUs?

There are examples of widely practiced OLDUs in every specialty of medicine (Table). Since the patient population in pediatrics is often excluded from clinical drug studies, examples of OLDU are especially abundant. For example, morphine has never received an FDA indication for pain treatment in children, but it is extensively used for this indication in hospitalized pediatric patients.[11] In another example, researchers discovered in the 1970s that the nonsteroidal anti-inflammatory agent indomethacin was efficacious as a medical therapy for closing a persistent, symptomatic patent ductus arteriosus in newborns.[18] Thus, a trial of indomethacin became the treatment of choice for many affected newborns in an attempt to avoid curative surgery. Indomethacin has never been approved for this indication and, as such, this use remains an OLDU. In addition, many inhaled bronchodilators, antimicrobials, anticonvulsants, and proton pump inhibitors are often used in the pediatric population without formal FDA approval.[30]

The FDA has attempted to lessen the gap between FDA approval and contemporary drug-prescribing practices in pediatrics through the FDA Modernization Act of 1997. This Act created incentives, including exclusive marketing and patent extension, for pharmaceutical companies to test medications on children.[31]

Medications for psychiatric disorders are also frequently used for unapproved indications.[12,32] Patients with psychiatric disorders are often excluded from clinical trials, and these disorders are inherently difficult to study. Moreover, there is often crossover in symptoms from disease state to disease state, which has lead physicians to use psychiatric medications approved for one psychiatric condition for additional unapproved indications. For example, selective serotonin reuptake inhibitors have been used off-label for rare or difficult-to-study disorders, such as borderline personality disorder, stuttering, pathologic gambling, and alcoholism.[16] Moreover, selective serotonin reuptake inhibitors (eg, paroxetine, sertraline, and fluoxetine) are considered first-line treatments for premature ejaculation, another off-label use.[33] In recent years, antipsychotic drug use

TABLE. Examples of Common Off-label Uses of Drugs

Category and drug	Off-label use(s)[a]
Allergy	
Diphenhydramine	Chemotherapy-related emesis, insomnia[16]
Anesthesiology	
Propofol	Intracranial hypertension
Dexamethasone, propofol	Postoperative nausea
Meperidine	Postanesthetic shivering
Cardiology	
Amiodarone	Supraventricular tachycardia[16]
Aspirin	Antithrombosis in atrial fibrillation, Kawaskai disease[16]
Atorvastatin, simvastatin	Extended-interval dosing for hyperlipidemia[16]
Indomethacin	Pharmacologic closure of patent ductus arteriosus[18]
Dermatology	
Azathioprine	Atopic dermatitis, pemphigus; psoriasis[19]
Biologic agents (eg, etanercept, infliximab, intravenous immunoglobulin, rituximab)	Alopecia areata, atopic dermatitis, Behçet disease, dermatomyositis, hidradenitis suppurativa, pemphigoid, pityriasis, vasculitis[20]
Gastroenterology	
Erythromycin	Gastroparesis[21]
Omeprazole	Reflux-related laryngitis[16]
Hematology/oncology	
Alendronate	Hypercalcemia of malignancy[16]
Dabigatran	Venous thromboembolism prophylaxis after orthopedic surgery[22]
Doxorubicin	Refractory multiple myeloma[16]
Furosemide (nebulized)	Dyspnea[16]
Rituximab	Idiopathic thrombocytopenic purpura, Waldenström macroglobulinemia[16]
Infectious disease	
Linezolid	Infective endocarditis[16]
Sulfamethoxazole-trimethoprim	Sinusitis[16]
Nephrology	
Acetylcysteine	Prevention of contrast nephrotoxicity[16]
Albuterol	Hyperkalemia[16]
Erythropoietin	Anemia of chronic disease[16]
Neurology	
Atenolol, metoprolol, propranolol	Migraine prophylaxis[10]
Isoflurane	Seizure, status epilepticus
Donepezil	Frontotemporal dementia[23]
Gabapentin	Bipolar disorder, diabetes, fibromyalgia, neuropathic pain symptoms, headache, hiccups, hot flashes, restless leg syndrome[24]
Lidocaine	Postherpetic neuralgia[24]
Tricyclic antidepressants	Bulemia, insomnia, irritable bowel syndrome, neuropathic pain symptoms[15,16,24]
Obstetrics	
Magnesium sulfate	Premature labor[16]
Volatile anesthetics (eg, enflurane, isoflurane, halothane)	Intraoperative uterine contraction
Pediatrics	
Amoxicillin (high dose)	Otitis media in children[16]
Atenolol	Hypertension in children[16]
Intranasal desmopressin	Nocturnal enuresis[25]

(continued)

TABLE. Continued

Category and drug	Off-label use(s)[a]
Pediatrics (continued)	
Morphine	Pain in children[11]
Sildenafil	Pulmonary hypertension in children[16]
Pulmonary	
Volatile anesthetics (eg, enflurane, isoflurane, halothane)	Status asthmaticus[26]
Psychiatry	
Atypical antipsychotics (eg, risperidone, olanzapine, quetiapine)	Anxiety, dementia, eating disorders, obsessive-compulsive disorder, personality disorders, posttraumatic stress disorder, substance abuse[27]
β-Blockers	Social phobia, public speaking[28]
Citalopram	Alcoholism, fibromyalgia, irritable bowel syndrome, obsessive-compulsive disorder, pathologic gambling, stuttering[16]
Fluoxetine	Borderline personality disorder, diabetic neuropathy, fibromyalgia, hot flashes, premature ejaculation[24]
Trazodone	Insomnia in elderly patients[16]
Urology	
Sildenafil	Sexual dysfunction symptoms in women[29]

[a]This table is not comprehensive and is not intended as an endorsement of these off-label drug uses.

for unapproved FDA indications has increased. Alexander et al[32] estimated that the cost of off-label antipsychotic drug use in 2008 was $6.0 billion.

During the 1970s and 1980s, there was a proliferation of cardiac surgery to repair or replace diseased heart valves. Disease in many of these patients was the result of rheumatic abnormalities in patient populations with inadequate or no antibiotic drug treatment of infections earlier in their lives. In these patient populations, hemodynamic stability was of utmost concern during anesthesia, surgery, and the immediate postoperative course. Lowenstein[34] reported that high-dose morphine, combined with amnestic agents, could provide the type of stable anesthetic required for these patients and that the beneficial effects of the anesthetic would continue into the postoperative intensive care period. With the later introduction of the short-acting opioid fentanyl, it was infused in doses much greater than approved by the FDA, thus converting a short-acting drug into a long-acting drug. High-dose morphine- and fentanyl-based anesthetics, highly favored therapy for valve replacement surgery, were retained as core anesthetics with the introduction of coronary artery bypass graft surgery. Today, patients are typically brought to surgery much earlier in the disease course (hence, they tend to be more stable hemodynamically), and there is a focus on shortening stays in the intensive care unit after cardiac surgery. In addition, improvements in surgical technique have shortened operation times. For these reasons, high-dose opioid anesthesia is less common than in the past, although it is still used. These high doses of morphine and fentanyl have never been approved by the FDA, and, therefore, their use has always been off-label.

Postoperative nausea and vomiting in surgical patients can add to patient morbidity and the cost of health care. Postoperative nausea is common, occurring in nearly 70% to 80% of high-risk patients.[35] Because of this, practitioners have empirically explored a variety of antiemetic therapies. In patients at high risk for postoperative nausea and vomiting, bolus or infused propofol and bolus dexamethasone have gained favor as antiemetic regimens. However, these treatments have never been approved by the FDA for this indication. As such, they represent OLDUs.

QUESTION 5: IF EFFICACIOUS, WHY IS GOVERNMENT APPROVAL NOT OBTAINED TO CONVERT OFF-LABEL USES OF DRUGS TO ON-LABEL USES?

Obtaining a new FDA approval for a medication can be costly and time-consuming. To add additional indications for an already approved medication requires the proprietor to file a supplemental drug application, and, even if eventually approved, revenues for the new indication may not offset the expense and effort of obtaining approval.[8] Finally, generic medications may not have the requisite funding foundations needed to pursue FDA-approval studies.[8] For these financial reasons, drug proprietors may never seek FDA approval for a new drug indication.

QUESTION 6: DO PHYSICIANS EXPOSE THEMSELVES TO LEGAL VULNERABILITY FOR INCLUDING OLDUs IN THEIR CLINICAL PRACTICES, PARTICULARLY IF THE PATIENT EXPERIENCES AN ADVERSE REACTION RELATED TO AN OLDU?

Physicians have been involved in legal claims due to an adverse reaction related to a medication prescribed for an off-label use.[8,36] The legal theories used in these lawsuits include unregulated use of a research drug, failure to provide adequate informed consent for an OLDU, and medical negligence.[37] In developing legal precedents for off-label therapies, the courts have typically treated drugs and devices as coequals. As such, many of the courts' views on OLDU have evolved from decisions regarding off-label uses of medical devices.

Research vs Practice

The FDA makes it clear that it does not regulate the practice of medicine and that the federal Food, Drug, and Cosmetic Act of 1938 will not play a role in creating physician liability for OLDU.[38] However, the FDA requires stringent review before drugs and medical devices are involved in research to ensure that steps are taken to properly protect human study participants. When not classified as tools involved in research, medications can be prescribed and medical devices can be used in an off-label manner without FDA regulatory oversight. Regarding this point, during its evaluation of possible harm arising from placement of an orthopedic spine medical device, an Ohio appellate court stated that "the off-label use of a medical device is merely a matter of medical judgment and, as such, subjects a physician to professional liability for exercising professional medical judgment, but off-label use of a medical device is not barred by the U.S. Food and Drug Administration."[38,39] By way of legal precedent and similar FDA regulatory processes, the same standard would apply to OLDU.

Drawing a clear line of demarcation between a drug's use in research vs practice can often be difficult. Prescribing a drug in a new and yet untested manner does not alone brand it as an interest of research.[38] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has attempted to define whether a drug's use might be classified as a practice or research tool, and their definitions follow. The goal of medical practice is to "provide diagnosis, preventative treatment or therapy."[38] Research, on the other hand, is "designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge."[38] When not deemed research, legal claims brought solely on the basis of failure to gain adequate FDA approval before prescribing an off-label drug will likely be struck down. However, physicians may not be sheltered from other forms of liability theories.

Medical Malpractice: Informed Consent

No court decision to date has mandated that a physician must disclose, through an informed consent process, the off-label use of a drug.[40] Two arguments are often voiced by those who oppose any routine requirement for disclosure: (1) disclosure may unduly frighten patients and (2) the extensive burden placed on physicians to constantly review and communicate medication risk and benefit information may divert attention away from other more important patient care issues.[40]

Perhaps the most cited modern legal case involving the medical informed consent process is *Canterbury v Spence*.[41] The Canterbury court held that "the test for determining whether a particular peril must be divulged is its *materiality* to the patient's decision."[41] A material risk is one in which "a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to forego the proposed therapy."[41]

Many courts have not considered OLDU to be an independent material issue requiring disclosure during the consent process.[38] A 1996 Ohio court held that off-label use of medical devices was a "matter of medical judgment."[38,42] According to the court, physicians may be subject to professional liability for medical negligence involving OLDU but will not be held liable for nondisclosure.[38,42]

The results of a 2006 nationwide poll on the public's view of OLDU may precipitate concerns for future court challenges not fully appreciated by previous legal opinion. Half of the poll's respondents falsely believed that a drug could be prescribed only for its primary FDA-approved use.[43] An almost similar percentage felt that physicians should be prohibited from prescribing drugs for off-label use. Nearly two-thirds of those responding felt that except for use in clinical trials, OLDU should be completely banned.[43] This is a remarkable aggregate response given that a considerable fraction of those responding negatively to OLDU had likely benefited from the practice at some point in their lives (although they were probably unaware).

Although many courts do not require physicians to disclose OLDU, patients may have a different belief and concern regarding their use. Whether these matters will develop into a greater expectation for adequate disclosure remains unknown. Some physicians have suggested that providing patients with information about OLDU may afford greater protection from future liability suits.[38]

Medical Malpractice: Negligence

Medical malpractice is a broad term that includes the action of negligence. In fact, 4 elements of tort law dealing with negligence must be proved before liability can be found to exist: (1) the prescribing physician must have a duty to the patient, (2) that duty must be breached, (3) there must be some injury requiring compensation, and (4) there must be a causal link between the breech and that injury.

A physician's duty of care is defined as the same degree of care provided by other physicians practicing under similar circumstances. Use of off-label medication alone does not result in liability under negligence standards.[44] When a patient believes that he or she was harmed by an off-label use of a medication, it must be established that the prescribing physician deviated from the standard of practice.[38] Because the FDA prohibits manufacturers from sponsoring physician education for off-label use of their medications, physicians may find it difficult to establish how others in their field are using medications outside their FDA-approved uses.[37] As peer-reviewed published evidence focusing on a drug's off-label use grows over time, new standards of practice involving the off-label use of a drug begin to develop.[38]

To help determine whether the standards of practice are being met when prescribing medications for OLDU, physicians should first ask themselves several questions[38,45,46]: (1) Does the native drug have FDA approval? (2) Has the off-label use been subjected to substantial peer review? (3) Is the off-label use medically necessary for treatment? (4) Is the use of the medication nonexperimental? To mitigate the risk of liability, physicians should always prescribe off-label drugs in "good faith, in the best interest of the patient, and without fraudulent intent."[45] This 3-pronged approach to prescribing medications will also ensure that the tenets of the FDA's requirement are met; specifically, physicians prescribing medications for off-label use should "be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."[47]

QUESTION 7: WILL INDEXED MEDICAL JOURNALS PUBLISH ARTICLES ON OLDU?

Reports on OLDU, particularly original observations, are not only tolerated by indexed medical journals but also may actually be encouraged. The most welcomed reports may follow several patterns, the 2 most common of which are described in the following subsections.

Reports to Evaluate New Drug Therapies Seeking FDA Approval

Before a drug use can be approved by the FDA, drug utilization for this specific application must undergo extensive studies of efficacy and safety in humans. The data from multiple phases of study are needed for the drug's proprietor to file a New Drug Application to the FDA. Studies of new drugs or studies involving expanded use of an existing drug are, by definition, "off-label" indications until FDA approval is obtained. These studies may take the form of phase 0 (pharmacokinetic and pharmacodynamic studies of subtherapeutic drug doses in small numbers of patients), phase 1 (small studies of drug pharmacodynamic properties in healthy volunteers), phase 2 (larger studies of drug pharmacology, safety, and efficacy in volunteers and patients), and phase 3 (large, randomized, multicenter trials of drug safety and efficacy; drug compared with a placebo or an existing treatment standard) trials.[48] In addition, phase 4 trials are completed after FDA approval to further delineate the drug's effects and adverse reactions.[48]

Although preliminary research on drug pharmacology and safety intended to support a petition for FDA approval may be important to the proprietor and the FDA, articles based on these data may be difficult to publish in competitive biomedical journals because the data may not be of interest to the journal's target audience. As such, initial research may not pass peer review because of journal priorities. However, as subsequent trials evaluate drug efficacy and safety using methods that mimic the drug's use in clinical practice, journals' interest in the research will be piqued. The more novel the therapy (eg, a new class of drug for a common application, in contrast to a "me too drug"), the more likely the research data will be competitive for publication in better-quality medical journals. In fact, journals may introduce the reports with editorials and engage in media promotion of the discoveries, both testaments to the value the journals place on the research.

Reports to Evaluate Off-label Uses, or Describe Adverse Effects, of Drugs Approved for Other Indications

As previously described, a large fraction of drug use is off-label, and these indications may even become the standard of care (see Question 3). In these instances, the FDA will have previously approved the drug for clinical practice but for an indication other than the one under question. Medical journals and their readers may have a keen interest in original observations related to this form of drug use. Articles may not only become accepted for publication but may also get journal promotion (editorials and media promotion) reserved for the highest-priority articles. Clearly, a journal's enthusiasm for these types of articles is coupled with the quality and statistical power of the data, the novelty of the obser-

vation, the generalizability of the results, and the relevance of the observations to the intended audience's interests. As such, a journal may publish OLDU articles on drugs' effects and adverse effects related to indications for which FDA approval may never be sought.

Prospective trials of drug use in humans must conform to federal regulations, be approved by the institutional review boards of all participating institutions, and be registered in one of many appropriate registries (eg, ClinicalTrials.gov) to be considered for publication in biomedical journals.[49,50] Retrospective OLDU observations in patients, whether of a drug's effects or adverse effects, also must have accompanying institutional review board approval before reporting the observations to a biomedical journal. However, the standards of approval for retrospective observations are much less stringent than for prospective research.

Indexed biomedical journals are less likely to publish review articles on drugs that are seeking FDA approval for a first use. Reviews with the best probability of getting published are those that describe novel drug mechanisms or success in treating conditions in which other drugs have limited efficacy. Articles primarily intended to support a marketing angle for the proprietor (ie, seeding reports)[51] have difficulty getting published in the most competitive medical journals. In contrast, journals may welcome review articles that address a widely applied OLDU. As information on a given OLDU grows, journals may even welcome updated reviews or new reviews that address novel aspects of the OLDU experience (eg, new information on a drug's effects or adverse effects, updates on the operant mechanisms of action, and articles on drug-use adherence and economics).

QUESTION 8: CAN SPEAKERS DISCUSS OLDU DURING ACCREDITED CME COURSES?

Speakers at accredited CME courses are allowed to discuss OLDU during their presentations. The Accreditation Council for Continuing Medical Education historically required that all discussions of OLDU be disclosed during the CME presentation. However, current Accreditation Council for Continuing Medical Education requirements state that all clinical presentations should be based on "evidence that is accepted within the profession of medicine."[52] If the discussion of OLDU conforms to this mandate, no specific disclosure is required.

QUESTION 9: CAN DRUG COMPANIES PROMOTE OLDU?

The 1938 Food, Drug, and Cosmetic Act gave the FDA the power to regulate promotional materials on medications.[53] Two provisions from the FDA prohibit most promotion of off-label uses of medications by pharmaceutical manufacturers and marketers. First, the FDA requires approval before distribution into interstate commerce of all medication labeling (including the package insert, print and broadcast advertisements, brochures, and patient education materials).[53] Second, the FDA prohibits "misbranding" of medications. Misbranding includes labeling a medication with misleading information, including off-label uses.[53]

Although pharmaceutical manufacturers are not allowed to promote off-label uses of medications, they are allowed to respond to unsolicited questions from health care professionals about off-label use and to distribute peer-reviewed publications regarding off-label use.[53] Responses to questions regarding off-label use must be completed by the manufacturer's medical affairs office and not their sales representatives, and interactions with the questioner must be documented.[53]

Historically, the 1997 FDA Modernization Act allowed manufacturers to distribute to health care providers peer-reviewed journal articles about unapproved uses of medications.[54,55] If a given drug company chose to engage in distribution of this type of information, it was required to submit an application for approval of that indication within a rigid and prespecified period. These requirements were subsequently revised in 2009 with the approval of new FDA guidelines.[53] The new guidelines clarified existing rules and allowed distribution of information on off-label uses by pharmaceutical manufactures if specific regulations were followed.[53] After 2009, pharmaceutical manufacturers could distribute information, including journal articles and textbook chapters, describing unapproved uses for their medications. The FDA demanded that the information in these OLDU publications be accurate, the relationship between the distribution of information and the sponsoring drug manufacturer be disclosed, and the published material not be edited or presented in an abridged form.[53] In addition, the manufacturer is no longer required to submit an application for approval for that indication.[53]

With the increase in direct-to-consumer marketing by pharmaceutical manufacturers, in 2010 the FDA introduced the Truthful Prescription Drug Advertising and Promotion (Bad Ad) Program. This program provides a mechanism by which health care professionals and patients can report illicit OLDU promotion to the FDA.

Despite regulations that ban pharmaceutical manufacturers and marketers from promoting OLDUs, some have ignored this mandate. In fact, one study found that off-label marketing by drug companies was one of the most common causes of

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Medicaid fraudulent claim investigations.[2,56] In addition, marketing of off-label uses has been the source of costly lawsuits and out-of-court penalties for pharmaceutical manufacturers. In 2012, GlaxoSmithKline paid a record $3 billion to settle a dispute, including alleged illegal off-label marketing involving paroxetine in children (approved only for use in adults), the antidepressant bupropion as a weight loss aid, and failure to report safety information about the antidiabetes medication rosiglitazone.[5] In 2012, Abbott paid $1.6 billion in penalties for alleged off-label marketing of valproic acid.[7] In 2009, Eli Lilly paid $1.4 billion in a settlement for alleged off-label marketing of olanzapine for dementia.[3] That same year, Pfizer paid $2.3 billion for alleged off-label marketing of 4 of its medications.[4]

QUESTION 10: WHAT IS THE DIFFERENCE BETWEEN OLDU AND ORPHAN USE OF DRUGS?

Orphan drugs are medications that are developed and used for rare, or orphan, diseases. Owing to a drug's limited clinical use for an orphan indication, it will typically generate insufficient profitability for the drug's sponsor to seek FDA approval for the narrow indication. As such, practitioners are typically forced to use medications in an off-label manner to treat orphan diseases. Therefore, orphan drugs are often a subtype of OLDU. However, in 1983, the FDA implemented the Orphan Drug Act, which offered incentives to pharmaceutical manufacturers that developed and marketed new drugs for rare diseases.[57] Incentives include tax breaks, exclusive marketing rights, and reduced drug application fees. In addition, the FDA has offered grants for the development of drugs for rare diseases. These measures have been successful in increasing the development of new, FDA-approved (ie, "on-label") drugs for orphan diseases.[57] Examples of off-label uses of medications for orphan disease include aspirin for Kawasaki disease and rituximab for Behçet disease.[16,20]

OLDU SUMMARY

Off-label drug use involves prescribing medications for an indication, or using a dosage or dosage form, that has not been approved by the FDA. Since the FDA does not regulate the practice of medicine, OLDU has become common. It occurs in every specialty of medicine, but it may be more common in areas of medicine in which the patient population is less likely to be included in clinical trials (eg, pediatric, pregnant, or psychiatric patients). Pharmaceutical companies are not allowed to promote their medications for an off-label use, which has lead to several large settlements for illegal marketing. To limit liability, physicians should prescribe medications only for indications that they believe are in the best interest of the patient on the basis of the most credible available evidence. In an era of global exchange of medical information, this approach to physician prescribing practices may have greater utility than restricting practices solely to indications approved by a US-based pharmaceutical labeling system. Health care professionals should continually educate themselves about OLDU to weigh the risks and benefits and provide the best possible care for their patients.

Abbreviations and Acronyms: **CME** = Continuing Medical Education; **FDA** = Food and Drug Administration; **OLDU** = off-label drug use

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OFF-LABEL FACT SHEET

Prevalence of Off-label Drug Use (OLDU)[1]

- "The most common form of OLDU involves prescribing currently available and marketed medications but for an indication (eg, disease or a symptom) that has never received [FDA] approval."
- "OLDU is common."
- Study of commonly used medications showed that 21% of prescriptions for those medications were for off-label use
- In intensive care units, it was found to be much higher at 36.2%
- OLDU's "can become widely entrenched in clinical practice and become predominant treatments...."
- Approval for OLDU's is sought primarily if a drug company wishes to promote the use, but often profit outlooks do not support it irrespective of effectiveness (which can easily be true if the original patent has already expired or is near to expiration)

Ivermectin[2]

- Ivermectin has safely been used in humans since the 1980's, is FDA approved, and led to a Nobel prize in 2015
- The World Health Organization recognized ivermectin as one of its "Essential Medicines"
- Before the pandemic, studies evidenced both anti-inflammatory properties as well as anti-viral properties (with the latter showing benefits against RNA viruses specifically)
- Since 1987, more than 3.7 billion doses have been administered to humans
- 88,000 ivermectin prescriptions are issued per week
- While some uncertainty exists as is often the case in the practice of medicine, numerous studies along with epidemiological evidence support the use of ivermectin as a treatment for COVID

Hydroxychloroquine[3]

- FDA approved since 1955 with millions of doses prescribed annually (5.4M in US in 2019 alone)
- HCQ is safe and even often taken daily for years at a time as a prophylaxis and/or treatment, including with success against auto-immune diseases given its "anti-inflammatory and immunomodulatory effects"
- Lab studies before the pandemic of the related chloroquine drug (for which HCQ is a derivative) have demonstrated promising effects against SARS-CoV specifically
- Recognized as generally safe, even for prescriptions for "children of all ages"
- 5 observational studies including over thirty thousand outpatients showed a 69% reduction in mortality from COVID-19
- Risks do exist to be weighed by a patient's doctor with informed consent of patient, as per standard

Note:

"[T]he FDA regulates the marketing & distribution of drugs, not the practice of medicine."[4]

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[1] https://www.mayoclinicproceedings.org/action/showPdf?pii=S0025-6196%2812%2900683-0

[2] https://ago.nebraska.gov/sites/ago.nebraska.gov/files/docs/opinions/21-017_0.pdf

[3] *Id.*

[4] Cordray v Planned Parenthood, 911 N.E.2d 871, 875 (Ohio 2009).

History of Hydroxychloroquine (HCQ)

Hydroxychloroquine is on the WHO model list of essential medicines.

*more detailed information on back

1955
HCQ Approved by the FDA

August 2005
NIH Study Finds Chloroquine to be Effective Against Coronaviruses

March 2020
Dr. Didier Raoult's Early Treatment Success; Dr. Fauci's First Attack on HCQ

April 2020
More Early Treatment Success by Dr. Zelenko and Other U.S. Doctors

May 2020
Dr. Harvey Risch's Study on Early Treatment Success; Fraudulent Trials by The Lancet, WHO, and UK; Switzerland Sees Death Rates Fall with HCQ Use

June 2020
Early Treatment Success in Other Countries; FDA Revokes the EUA for HCQ and Sends Alert that HCQ is Dangerous; WHO Calls for Halt on HCQ Trials

July 2020
Henry Ford Health System Study Shows Early Treatment Success; Continued Attacks on HCQ by Dr. Fauci

August 2020
France Study Finds Early Treatment Success; Dr. Fareed Reports to Dr. Fauci His Report of Success Using HCQ to Treat COVID

February 2022
Current Studies Show the Efficacy of HCQ

For complete timeline and source links visit www.KSHF.org/timeline or scan our QR code.

Expanded History of HCQ

1955
HCQ was approved by the FDA.

August 2005
NIH study found Chloroquine to be effective against coronaviruses.

March 2020
Dr. Didier Raoult's report on 36 patients treated successfully with HCQ and AZ. Dr. Fauci launched his concerted attack on HCQ, including a New York Times article to defame Dr. Raoult. Dr. Fauci declared that HCQ should only be used as part of a clinical trial.

April 2020
Dr. Vladimir Zelenko reproduced Dr. Raoult's success, dramatically reducing expected mortality among the 800 patients he treated with the HCQ cocktail. Since that time Dr. Zelenko has successfully treated thousands of COVID patients. US doctors widely prescribed HCQ to patients and family members, reported outstanding results, and took it themselves prophylactically.

May 2020
Dr. Harvey Risch published the most comprehensive study, to date, on HCQ's efficacy against COVID, concluding that evidence is unequivocal for early and safe use of the HCQ cocktail. The Lancet published an HCQ study which later had to be retracted (June 4, 2020) because it was found that the data was fabricated. Clinical trials were suspended and the damage was done to discredit HCQ. WHO and UK trials of HCQ used potentially lethal hydroxychloroquine doses, concluding that those given HCQ had a higher death rate than those in the control arm. Switzerland banned the use of HCQ; 2 weeks into the ban Switzerland's death rates tripled for about 15 days, then Switzerland reintroduced HCQ and death rates fell back to their baseline.

June 2020
AAPS filed a court filing comparing the national death rates among countries with varying policies governing access to HCQ. Many countries with underdeveloped health care systems used HCQ early and achieved far lower mortalities than in the United States. FDA revoked the EUA for HCQ and sent an alert that HCQ was dangerous, and was only to be used in hospitals, while continuing to encourage its use for other health issues. With the encouragement of Dr. Fauci and other HHS officials, many states simultaneously imposed restrictions on HCQ's use and state pharmacy boards began refusing orders from physicians and retailers. Hospitals commanded doctors to cease treating their patients with HCQ. The WHO called for the halt of HCQ trials in hundreds of hospitals across the world and the WHO Chief ordered nations to stop using HCQ and CQ.

July 2020
A Detroit Henry Ford Health System study found that HCQ significantly cut death rates even in mid-to-late COVID cases, and without any heart-related side effects. Dr. Fauci testified before Congress that the Detroit Henry Ford Health System's results were "flawed."

August 2020
An HCQ study revealed outcomes of 3,737 COVID-19 patients treated with HCQ-AZ and other regimens in France that concluded "early treatment of COVID-19 patients lead to a significantly better clinical outcome and a faster viral load reduction than other treatments." Dr. George Fareed wrote an Open Letter to Dr. Anthony Fauci regarding the use of HCQ for treating COVID. Dr. Fareed has currently treated 7000+ COVID patients successfully, with no deaths or hospitalizations.

February 2022
Currently there are 313 studies from 4,971 scientists, 426,562 patients, in 50 countries, that show statistically significant improvement for mortality, hospitalization, recovery, cases, and viral clearance. In addition, they show 64% improvement for early treatment, 20% improvement for late treatment, 45% improvement in eight early treatment random controlled trials, and 74% less death in 14 early treatment trials.

For complete timeline and source links
visit www.KSHF.org/timeline or scan our QR code.

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DOUGLAS J. PETERSON
ATTORNEY GENERAL

No. 21-017

STATE OF NEBRASKA
OFFICIAL
OCT 14 2021
DEPT. OF JUSTICE

SUBJECT: Prescription of Ivermectin or Hydroxychloroquine as Off-Label Medicines for the Prevention or Treatment of Covid-19

REQUESTED BY: Dannette R. Smith
Chief Executive Officer
Nebraska Department of Health and Human Services

WRITTEN BY: Douglas J. Peterson, Attorney General
James A. Campbell, Solicitor General
Mindy L. Lester, Assistant Attorney General

INTRODUCTION

On September 16, 2021, you requested our opinion on whether it would be "deemed unlawful or otherwise subject to discipline under [Neb. Rev. Stat. § 38-186] for an appropriately licensed health care provider, once informed patient consent has been appropriately obtained, to prescribe" ivermectin, hydroxychloroquine, or other "off label use" medications "for the treatment or prevention of COVID-19." You requested this opinion in your role as Chief Executive Officer of the Nebraska Department of Health and Human Services ("Department"). Neb. Rev. Stat. § 84-205(4) gives you, as the head of an executive department, the authority to ask our office's opinion on legal questions like this one.

The Department, acting through its Division of Public Health, enforces the Nebraska Uniform Credentialing Act ("UCA"). The purpose of the UCA is to protect public

health, safety, and welfare.[1] One way in which the Department protects the public is by investigating complaints alleging that licensed healthcare professionals have committed UCA violations.[2] After the Department completes an investigation, it refers the matter to the appropriate professional board to consider and make a recommendation to the Attorney General. Neb. Rev. Stat. § 38-186 then gives the Attorney General the authority to file a petition for discipline against the healthcare provider if such action is warranted.

You indicate in your request that "[c]onsumers and health care providers have been and continue to be inundated with information and opinions[] regarding COVID-19 treatment and prevention." You also note that due to the "sheer volume" of conflicting information, questions have been raised "regarding the permissibility of certain medications for the treatment or prevention of COVID-19." This observation is consistent with questions that our office has received from constituents and discussions that our office has witnessed at some of the professional boards' meetings.

After receiving your question and conducting our investigation, we have found significant controversy and suspect information about potential COVID-19 treatments. A striking example features one of the world's most prestigious medical journals—the Lancet. In the middle of the COVID-19 pandemic, the Lancet published a paper denouncing hydroxychloroquine as dangerous.[3] Yet the reported statistics were so flawed that journalists and outside researchers immediately began raising concerns.[4] Then after one of the authors refused to provide the analyzed data, the paper was retracted,[5] but not before many countries stopped using hydroxychloroquine and trials were cancelled or interrupted. The Lancet's own editor in chief admitted that the paper was a "fabrication," "a monumental fraud,"[6] and "a shocking example of research misconduct in the middle of

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1 Neb. Rev. Stat. § 38-128(1).

2 Neb. Rev. Stat. § 38-1,124.

3 Mandeep R. Mehra et al., *Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis*, The Lancet (May 22, 2020), *available at* https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931180-6 (last visited Oct. 14, 2021).

4 Melissa Davey, *Questions raised over hydroxychloroquine study which caused WHO to halt trials for Covid-19*, The Guardian (May 27, 2020), *available at* https://www.theguardian.com/science/2020/may/28/questions-raised-over-hydroxychloroquine-study-which-caused-who-to-halt-trials-for-covid-19 (last visited Oct. 14, 2021).

5 Sarah Boseley & Melissa Davey, *Covid-19: Lancet retracts paper that halted hydroxychloroquine trials*, The Guardian (Jun. 4, 2020), *available at* https://www.theguardian.com/world/2020/jun/04/covid-19-lancet-retracts-paper-that-halted-hydroxychloroquine-trials (last visited Oct. 14, 2021).

6 Roni Caryn Rabin, *The Pandemic Claims New Victims: Prestigious Medical Journals*, New York Times (Jun. 14, 2020), *available at* https://www.nytimes.com/2020/06/14/health/virus-journals.html (last visited Oct. 14, 2021).

a global health emergency."[7] When fraudulent information is published in a leading medical journal, it understandably leads to skepticism in some physicians and members of the public. Mindful of these concerns about misunderstandings and mistrust, we have drafted a rather lengthy opinion that aims to address the public confusion and outline the relevant scientific literature that supports our legal conclusions.

At the outset, we pause to delineate the parameters of this opinion. The question presented asked about ivermectin, hydroxychloroquine, and other drugs used "off label"—that is, for a purpose other than the specific use approved by the U.S. Food and Drug Administration ("FDA"). To enable us to respond in a timely manner, we have confined our discussion to ivermectin and hydroxychloroquine only. But in doing so, we do not mean to rule out the possibility that other off-label drugs might show promise—either now or in the future—as a prophylaxis or treatment against COVID-19. Also, because our investigation has revealed that physicians who currently use hydroxychloroquine for COVID-19 do so as either a prophylaxis or an early treatment for outpatients (as opposed to a late treatment in hospitalized patients), we will confine our consideration of hydroxychloroquine to those two uses. In addition, we note that there are treatment options the FDA has approved, either through an Emergency Use Authorization ("EUA") or through the regular FDA drug-approval process, for COVID-19 prophylaxis or treatment. These include monoclonal antibodies, vaccines, and remdesivir. We do not take any position on those options because they are outside the scope of the question asked.

In the end, as we explain below, we find that the available data does not justify filing disciplinary actions against physicians simply because they prescribe ivermectin or hydroxychloroquine to prevent or treat COVID-19. If, on the other hand, healthcare providers neglect to obtain informed consent, deceive their patients, prescribe excessively high doses, fail to check for contraindications, or engage in other misconduct, they might be subject to discipline. But based on the evidence that currently exists, the mere fact of prescribing ivermectin or hydroxychloroquine for COVID-19 will not result in our office filing disciplinary actions. While our terminology throughout this opinion focuses on physicians prescribing these medicines, what we conclude necessarily applies to other licensed healthcare professionals who prescribe, participate in, or otherwise assist with a treatment plan utilizing these medications.

ANALYSIS

1. The Nebraska Uniform Credentialing Act and Other Relevant Law

The UCA was enacted by the legislature to license and regulate persons and businesses that provide healthcare and health-related services.[8] The UCA was adopted

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7 Boseley & Davey, *supra*.

8 Neb. Rev. Stat. §§ 38-102 & 38-104.

to protect public health, safety, and welfare, and to provide for the efficient, adequate, and safe practice of credentialed persons and businesses.[9] "It is the intent of the Legislature," the UCA explains, "that quality health care services and human services be provided to the public" and "that professionals be regulated by the state only when it is demonstrated that such regulation is in the best interest of the public."[10]

The UCA grants the Director of Public Health of the Department's Division of Public Health the authority to deny a credential, refuse a credential renewal, or discipline a credential holder, although the Chief Medical Officer (if one is appointed) shall perform the Director's duties for decisions in contested administrative cases.[11] The Department must provide "the Attorney General with a copy of all complaints it receives and advise the Attorney General of investigations it makes" regarding possible violations of the UCA.[12] Following review and recommendation from the appropriate professional health board, the Attorney General must then determine whether the credential holder has violated any statutes or regulations and decide whether to proceed with administrative action.[13]

If the Attorney General determines that a violation has occurred, he "shall" file a petition for disciplinary action with the Department.[14] The Attorney General cannot prevail in disciplinary proceedings against a licensed healthcare professional unless he proves the claim by clear and convincing evidence.[15]

The grounds for disciplinary action are set forth in Neb. Rev. Stat. § 38-178 and include, among other things, acting with "gross incompetence or gross negligence," practicing in "a pattern of incompetent or negligent conduct," or engaging in "unprofessional conduct" as set forth in Neb. Rev. Stat. § 38-179.[16] Gross incompetence is a very high standard; it occurs only when there is "such an extreme deficiency on the part of a physician in the basic knowledge and skill necessary for diagnosis and treatment that one may reasonably question his or her ability to practice medicine at the threshold level of

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9 Neb. Rev. Stat. § 38-103.

10 Neb. Rev. Stat. § 38-128(1).

11 Neb. Rev. Stat. §§ 38-176(1) & 38-1,101.

12 Neb. Rev. Stat. § 38-1,107(1).

13 Neb. Rev. Stat. §§ 38-1,107 & 38-1,108.

14 Neb. Rev. Stat. § 38-186.

15 *Poor v. State*, 266 Neb. 183, 190, 663 N.W.2d 109, 115 (2003); *Davis v. Wright*, 243 Neb. 931, 936-37, 503 N.W.2d 814, 818 (1993).

16 Neb. Rev. Stat. § 38-178(6), (24).

professional competence."[17] Neb. Rev. Stat. § 38-179 generally defines unprofessional conduct as a "departure from or failure to conform to the standards of acceptable and prevailing practice of a profession or the ethics of the profession, regardless of whether a person, consumer, or entity is injured, or conduct that is likely to deceive or defraud the public or is detrimental to the public interest."[18] Along these same lines, the regulation governing physicians states that unprofessional conduct includes:

> [c]onduct or practice outside the normal standard of care in the State of Nebraska which is or might be harmful or dangerous to the health of the patient or the public, not to include a single act of ordinary negligence.[19]

Healthcare providers do not violate the standard of care when they "select between two reasonable approaches to . . . medicine."[20] Regulations also indicate that physicians may utilize reasonable "investigative or unproven therapies" that reflect a reasonable approach to medicine so long as physicians obtain "written informed patient consent."[21] "Informed consent concerns a doctor's duty to inform his or her patient," and it includes telling patients about "the nature of the pertinent ailment or condition, the risks of the proposed treatment or procedure, and the risks of any alternative methods of treatment, including the risks of failing to undergo any treatment at all."[22] Regulations require physicians "to keep and maintain" records that disclose the "advice and cautionary warnings provided to the patient."[23]

Prescribing medicines for off-label use—that is, for some purpose other than the use approved by the FDA—often falls within the standard of care. Indeed, "[o]ff-label use is legal, common, and necessary,"[24] and "[c]ourts have repeatedly recognized the propriety of off-label use."[25] This includes the U.S. Court of Appeals for the Eighth Circuit, which has acknowledged that "[d]octors may prescribe an FDA-approved drug for

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17 *Langvardt v. Horton*, 254 Neb. 878, 895, 581 N.W.2d 60, 70-71 (1998).

18 Neb. Rev. Stat. § 38-179.

19 172 Neb. Admin. Code § 88-009(Q).

20 *Whittle v. Dep't of Health & Hum. Servs.*, 309 Neb. 695, 721-22, 962 N.W.2d 339, 356-57 (2021).

21 172 Neb. Admin. Code § 88-009(B).

22 *Curran v. Buser*, 271 Neb. 332, 337, 711 N.W.2d 562, 568 (2006) (citations omitted).

23 172 Neb. Admin. Code § 88-009(B).

24 James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L.J. 71, 76 (1998) (capitalization omitted).

25 *Id.* (collecting cases).

nonapproved uses."[26] And the U.S. Supreme Court, in an analogous context, has affirmed that "'off-label' usage of medical devices" is an "accepted and necessary" practice.[27] Even the FDA recognizes that off-label use is legitimate: it has said for many decades that once it approves a drug, "a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling."[28] Expanding on that point, the FDA has explained that "healthcare providers generally may prescribe [a] drug for an unapproved use when they judge that it is medically appropriate for their patient."[29] Nothing in the federal Food, Drug, and Cosmetic Act ("FDCA") "limit[s] the manner in which a physician may use an approved drug."[30]

Based on these principles, we conclude that governing law allows physicians to use FDA-approved medicines that are unproven for a particular off-label use so long as (1) reasonable medical evidence supports that use and (2) a patient's written informed consent is obtained. In the context of this ever-changing global pandemic, we note that it is appropriate to consider medical evidence outside of Nebraska and to give physicians who obtain informed consent an added measure of deference on their assessment of the available medical evidence.

2. COVID-19 and SARS-CoV-2

The disease known as COVID-19 and the virus that causes it—SARS-CoV-2—took the world by storm in late 2019 and early 2020. While there is still so much that the medical community does not know about SARS-CoV-2 and COVID-19, it is widely recognized that COVID-19 is a multifaceted disease. "[A]dults with SARS-CoV-2 infection can be grouped" into at least three different categories depending on the progression of their disease.[31] The first group has an asymptomatic or presymptomatic infection, meaning that those individuals have "test[ed] positive for SARS-CoV-2" but "have no symptoms

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26 *Rhone-Poulenc Rorer Pharms., Inc. v. Marion Merrell Dow, Inc.*, 93 F.3d 511, 514 n.3 (8th Cir. 1996).

27 *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001).

28 FDA Drug Bulletin at 5 (Apr. 1982), *available at* https://play.google.com/books/reader?id=3f3YC3Gw6sEC&pg=GBS.PA6&hl=en (last visited Oct. 14, 2021).

29 U.S. Food & Drug Administration, Understanding Unapproved Use of Approved Drugs "Off Label" (Feb. 5, 2018), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label (last visited Oct. 14, 2021).

30 FDA Drug Bulletin, *supra*, at 5. Because the question posed to us asks about prescribing drugs for off-label use, any view on the legality of efforts to market drugs for off-label use is outside the scope of this opinion.

31 National Institutes of Health, Clinical Spectrum of SARS-CoV-2 Infection, COVID-19 Treatment Guidelines (Apr. 21, 2021), *available at* https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ (last visited Oct. 14, 2021).

that are consistent with COVID-19."[32] A second group experiences a mild illness that manifests itself through "any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell)" but does not include "shortness of breath, dyspnea, or abnormal chest imaging."[33] And a third group suffers from a more severe illness marked by "evidence of lower respiratory disease" and deficient "oxygen saturation" levels.[34] When people in this third category reach a critical level, they often "have respiratory failure, septic shock, and/or multiple organ dysfunction."[35]

A recently published paper on COVID-19 recognized that "for reasons that are yet to be clarified, early treatment has not been emphasized" in Western countries like the United States.[36] Despite this, many healthcare providers in the United States advocate for early treatment, particularly for high-risk patients. In fact, scores of treating and academic physicians have published papers in well-respected journals like the American Journal of Medicine explaining that the "multifaceted pathophysiology of life-threatening COVID-19 illness . . . warrants early interventions"[37] and encouraging "outpatient treatment of the illness with the aim of preventing hospitalization or death."[38] Also, a declaration of the International Alliance of Physicians and Medical Scientists—which is apparently signed by over 10,000 physicians and scientists, more than 60 of whom are publicly identified online—supports a doctor's choice to provide early COVID-19 care rather than "advising their patients to simply go home . . . and return when their disease worsens."[39]

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32 *Id.*

33 *Id.*

34 *Id.*

35 *Id.*

36 Matthieu Million et al., *Early combination therapy with hydroxychloroquine and azithromycin reduces mortality in 10,429 COVID-19 outpatients*, 22 Reviews in Cardiovascular Medicine 1063, 1063 (Sept. 2021), https://rcm.imrpress.com/article/2021/2153-8174/2153-8174-22-3-1063.shtml (last visited Oct. 14, 2021).

37 Peter A. McCullough et al., *Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)*, 21 Reviews in Cardiovascular Medicine 517, 518 (Dec. 2020), *available at* https://rcm.imrpress.com/article/2020/2153-8174/RCM2020264.shtml (last visited Oct. 14, 2021) (including 57 co-authors) (hereinafter, "McCullough, *Multifaceted*").

38 Peter A. McCullough et al., *Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection*, 134 American Journal of Medicine 16, 16 (Jan. 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7410805/pdf/main.pdf (last visited Oct. 14, 2021) (including 23 co-authors) (hereinafter, "McCullough, *Pathophysiological*").

39 Physicians Declaration, Global COVID Summit, International Alliance of Physicians and Medical Scientists (Sept. 2021), https://doctorsandscientistsdeclaration.org/ (last visited Oct. 14, 2021).

These groups of physicians have established protocols for early treatment, and ivermectin and hydroxychloroquine are staples of those treatments.[40] As discussed in greater detail below, while the scientific literature is continuing to grow, some data suggest that ivermectin- or hydroxychloroquine-based early treatments of COVID-19 can be effective in thwarting hospitalization and death.[41]

3. Ivermectin

A. History of Ivermectin

Researchers discovered ivermectin in the 1970s, and while its first use was to treat parasites in animals, ivermectin has been used in humans since the 1980s.[42] In the early years, ivermectin effectively stymied the scourge of two devastating parasitic diseases—onchocerciasis (also known as river blindness) and lymphatic filariasis—"among poverty-stricken populations throughout the tropics."[43] These are two of the most "disfiguring diseases" that "have plagued the world's poor . . . for centuries."[44] Later, the use of ivermectin was expanded to include "the treatment of scabies and lice."[45]

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40 *E.g.*, McCullough, *Multifaceted*, *supra*, at 519 Table 1 (listing early treatment kits that include both ivermectin and hydroxychloroquine); McCullough, *Pathophysiological*, *supra*, at 18–19 (discussing hydroxychloroquine).

41 *E.g.*, Flavio A. Cadegiani et al., *Early COVID-19 therapy with azithromycin plus nitazoxanide, ivermectin or hydroxychloroquine in outpatient settings significantly improved COVID-19 outcomes compared to known outcomes in untreated patients*, New Microbes and New Infections (Sept. 2021), *available at* https://www.sciencedirect.com/science/article/pii/S2052297521000792 (last visited Oct. 14, 2021) (finding that "the use of nitazoxanide, ivermectin[,] and hydroxychloroquine demonstrated unexpected improvements in COVID-19 outcomes when compared to untreated patients").

42 Andy Crump, *Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations*, 70 The Journal of Antibiotics 495, 495 (2017), *available at* https://www.nature.com/articles/ja201711.pdf (last visited Oct. 14, 2021) (hereinafter, "Crump, *Ivermectin*").

43 *Id.*

44 Andy Crump & Satoshi Ōmura, *Ivermectin, 'wonder drug' from Japan: the human use perspective*, 87 Proceedings of the Japan Academy, Series B, Physical and biological sciences 13, 13 (2011), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3043740/pdf/pjab-87-013.pdf (last visited Oct. 14, 2021).

45 Andrew Bryant et al., *Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines*, 28 American Journal of Therapeutics 434, 435 (Jul./Aug. 2021), *available at* https://journals.lww.com/americantherapeutics/fulltext/2021/08000/ivermectin_for_prevention_and_treatment_of.7.aspx (last visited Oct. 14, 2021) (hereinafter, "Bryant, *Ivermectin*").

Given its track record as a medicine for humans, ivermectin has long since been "approved as an antiparasitic" by the World Health Organization (WHO) and the FDA.[46] The WHO has also recognized ivermectin as one of its "Essential Medicines."[47] Further recognizing the importance of this drug, in 2015 its discoverers won the Nobel Prize in Medicine for their work in uncovering it and bringing it to market.[48]

In the decade leading up to the COVID-19 pandemic, studies began to show ivermectin's surprising versatility. By 2017, ivermectin had "demonstrate[d] antiviral activity against several RNA viruses by blocking the nuclear trafficking of viral proteins."[49] One recent systematic review cited more than a handful of studies to "demonstrate that ivermectin has antiviral properties against an increasing number of RNA viruses, including influenza, *Zika*, HIV, [and] *Dengue*."[50] And another review summarized the "antiviral effects of ivermectin" demonstrated through "studies over the past 50 years."[51]

Before the pandemic, scholarly literature had also recognized ivermectin's "anti-inflammatory capacity."[52] Doctors thus have been using ivermectin to treat "rosacea, a chronic inflammatory disease," that manifests itself as a reddening of the face, and the FDA has approved ivermectin for that purpose.[53] Ivermectin's ability to "curb inflammation," one reviewer wrote, may also "be useful in treating . . . inflammatory airway diseases."[54] Summing it up, that same reviewer recognized that "ivermectin is continuing

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46 *Id.*

47 *Id.*

48 The Nobel Prize, Press Release for The Nobel Prize in Physiology or Medicine 2015 (Oct. 5, 2015), https://www.nobelprize.org/prizes/medicine/2015/press-release/ (last visited Oct. 14, 2021).

49 Crump, *Ivermectin*, *supra*, at 500.

50 Pierre Kory et al., *Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19*, 28 American Journal of Therapeutics 299, 301 (2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8088823/ (last visited Oct. 14, 2021).

51 Fatemeh Heidary & Reza Gharebaghi, *Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen*, 73 The Journal of Antibiotics 593, 593 (2020), *available at* https://www.nature.com/articles/s41429-020-0336-z.pdf (last visited Oct. 14, 2021) ("Several studies reported antiviral effects of ivermectin on RNA viruses . . . . Furthermore, there are some studies showing antiviral effects of ivermectin against DNA viruses . . . .").

52 Crump, *Ivermectin*, *supra*, at 499.

53 Leon H. Kircik et al., *Over 25 Years of Clinical Experience With Ivermectin: An Overview of Safety for an Increasing Number of Indications*, 15 Journal of Drugs in Dermatology 325, 325 (Mar. 2016), *available at* https://jddonline.com/articles/dermatology/S1545961616P0325X (last visited Oct. 14, 2021).

54 Crump, *Ivermectin*, *supra*, at 499; *see also* Arianna Portmann-Baracco et al., *Antiviral and anti-inflammatory properties of ivermectin and its potential use in Covid-19*, 56 Archivos De Bronconeumologia

to surprise and excite scientists, offering more and more promise to help improve global public health by treating a diverse range of diseases."[55]

For more than three decades, ivermectin has also shown itself to be very safe. Indeed, the National Institutes of Health ("NIH") recognize that "ivermectin has been widely used and is generally well tolerated."[56] One recent systematic review similarly states that "ivermectin at the usual doses . . . is considered extremely safe for use in humans."[57] Other studies have noted that the medicine "has an established safety profile for human use,"[58] and it "provide[s] a high margin of safety for a growing number of indications."[59] Notably, a December 2018 WHO-supported application to add ivermectin as an essential medicine for scabies reviewed the data and concluded that the adverse events associated with ivermectin are "primarily minor and transient."[60]

The available data support this conclusion. The WHO's VigiAccess database, which compiles adverse drug reactions from throughout the world, breaks down the reported side effects for drugs into different categories.[61] The largest reported categories for ivermectin include skin issues, headaches, dizziness, and gastrointestinal disturbances such as diarrhea and nausea.[62] The NIH confirms that ivermectin's primary adverse side effects "include dizziness, pruritis [itchy skin], nausea, or diarrhea."[63] And

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831, 831 (2020), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7578741/pdf/main.pdf (last visited Oct. 14, 2021) ("Ivermectin has a demonstrated anti-inflammatory effect *in vivo* and *in vitro*").

55 Crump, *Ivermectin*, *supra*, at 495.

56 National Institutes of Health, COVID-19 Treatment Guidelines: Ivermectin, https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ivermectin/ (last visited Oct. 14, 2021) (hereinafter, "NIH, COVID-19 and Ivermectin").

57 Bryant, *Ivermectin*, *supra*, at 435.

58 Leon Caly et al., *The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro*, Antiviral Research 178 at 3 (June 2020), *available at* https://www.sciencedirect.com/science/article/pii/S0166354220302011 (last visited Oct. 14, 2021).

59 Kircik, *Ivermectin*, *supra*, at 325.

60 WHO Expert Committee on the Selection and Use of Essential Medicines: Application for inclusion of ivermectin on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) for the indication of Scabies at 19 (Dec. 2018), *available at* https://www.who.int/selection_medicines/committees/expert/22/applications/s6.6_ivermectin.pdf (last visited Oct. 14, 2021).

61 VigiAccess, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, http://www.vigiaccess.org/ (last visited Oct. 14, 2021).

62 *Id.*

63 NIH, COVID-19 and Ivermectin, *supra*.

a recent review of ivermectin similarly describes the common side effects as "itching, rash, swollen lymph nodes, joint pain[], fever, and headache."[64]

The data show not only that the adverse side effects are minor, but also that the percentage of people who report experiencing any adverse events is vanishingly small. The latest statistics available through VigiAccess report only 5,674 adverse drug reactions from ivermectin between 1992 and October 13, 2021.[65] This number is incredibly low considering that "more than 3.7 billion doses" of ivermectin have been administered to humans worldwide since the 1980s.[66]

To illustrate the safety of ivermectin, compare its VigiAccess report to that of remdesivir, an FDA-approved treatment for COVID-19.[67] Remdesivir was not released for widespread use until 2020. Yet in the short period of time that it has been on the market, people have reported at least 7,491 adverse drug reactions on VigiAccess, more than ivermectin has registered over the last 30 years.[68] What's more, serious adverse reactions from remdesivir are reported in high numbers. For example, in less than two years, those who have used remdesivir have reported over 560 deaths, 550 serious cardiac disorders (such as bradycardia and cardiac arrest), and 475 acute kidney injuries.[69] Since that safety profile is sufficient to retain FDA approval, ivermectin's safety record cannot reasonably be questioned.

B. Ivermectin and COVID-19

As discussed above, ivermectin had shown its antiviral and anti-inflammatory properties long before the pandemic began. So when COVID-19 began to spread across the globe, some in the medical community quickly identified ivermectin as a potential drug for the prevention and treatment of COVID-19. Initially, a group of researchers found that ivermectin significantly inhibited replication of SARS-CoV-2 in cell cultures.[70] Dismissing

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64 Kory, *supra*, at 314.

65 VigiAccess, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, http://www.vigiaccess.org/ (last visited Oct. 14, 2021).

66 Morimasa Yagisawa et al., *Global trends in clinical studies of ivermectin in COVID-19*, 74 The Japanese Journal of Antibiotics 44, 46 (Mar. 2021), *available at* http://jia-contents.wdc-jp.com/pdf/JJA74/74-1-open/74-1_44-95.pdf (last visited Oct. 14, 2021).

67 U.S. Food and Drug Administration, *FDA Approves First Treatment for COVID-19* (Oct. 22, 2020), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19 (last visited Oct. 14, 2021).

68 VigiAccess, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, http://www.vigiaccess.org/ (last visited Oct. 14, 2021).

69 *Id.*

70 Caly, *supra*, at 1.

that finding, ivermectin doubters argued that too much of the drug would be needed to achieve this antiviral activity in humans.[71] But peer-reviewed models undermined those concerns by showing that the predicted accumulation of ivermectin in the lungs—the site in the body where the medicine is most needed—would be over 10 times higher than necessary for antiviral activity.[72] In layman's terms, these models indicated that an effective level of the medicine can be reached in lung tissue without creating toxicity in the blood. Plus, other pro-ivermectin doctors have explained that the amount of the drug "required for an effect in cell culture models bear[s] little resemblance to human physiology" because cell cultures lack "an active immune system working synergistically with" the medicine.[73]

The doctors who believed that ivermectin could be effective against COVID-19 also identified its anti-inflammatory properties as an important countermeasure to the disease. One reason why COVID-19 progresses to its severe phase, many believe, is "the provocation of an overwhelming and injurious inflammatory response."[74] Thus, ivermectin's anti-inflammatory effects suggest that it can help COVID-19 patients as the disease worsens.

i. Ivermectin Studies and Meta-analyses

Since the COVID-19 pandemic began, researchers have conducted over 20 randomized controlled trials (RCTs) and more observational trials to evaluate ivermectin's effectiveness in the prevention and treatment of COVID-19.[75] Many of those trials showed promise. On the question of COVID-19 prevention, the Shouman study out of Egypt—a RCT—evaluated ivermectin as a potential prophylaxis for close family members of COVID-19 patients.[76] The test group included 203 family members who took

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71 Virginia D. Schmith et al., *The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19*, 108 Clinical Pharmacology & Therapeutics 762, 762 (Oct. 2020), *available at* https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1889 (last visited Oct. 14, 2021).

72 Usman Arshad et al., *Prioritization of Anti-SARS-Cov-2 Drug Repurposing Opportunities Based on Plasma and Target Site Concentrations Derived from their Established Human Pharmacokinetics*, 108 Clinical Pharmacology and Therapeutics 775, 785 (Oct. 2020), *available at* https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1909 (last visited Oct. 14, 2021).

73 Kory, *supra*, at 301.

74 *Id.*

75 Bryant, *Ivermectin*, *supra*, at 435.

76 Waheed M. Shouman et al., *Use of Ivermectin as a Potential Chemoprophylaxis for COVID-19 in Egypt: A Randomised Clinical Trial*, 15 Journal of Clinical and Diagnostic Research 27, 27 (Feb. 2021), *available at* https://www.jcdr.net/articles/PDF/14529/46795_CE[Ra]_F(Sh)_PF1(SY_OM)_PFA_(OM)_PN(KM).pdf (last visited Oct. 14, 2021).

ivermectin, and only 15 of them (7.4%) developed COVID-19.[77] Compare that to the 101 family members in the control group, 59 of whom (58.4%) tested positive during the study.[78] These outcomes prompted the research team to conclude that ivermectin is "a promising, effective[,] and safe chemoprophylactic drug in management of COVID-19."[79] Also, the Behera study in India tested ivermectin as a prophylaxis in a group of 3,532 healthcare workers.[80] Of the 2,199 workers who took two doses of ivermectin prophylaxis three days apart, only 45 (2%) tested positive for COVID-19.[81] But of the 1,147 workers who did not take ivermectin, 133 (11.6%) contracted the disease.[82] Behera's team thus announced that two doses of ivermectin "as chemoprophylaxis among [healthcare workers] reduced the risk of COVID-19 infection by 83% in the following month."[83]

Moving beyond ivermectin's role as a prophylaxis, other studies have demonstrated its potential as a COVID-19 treatment. The Mahmud study—a RCT that explored ivermectin as an early treatment for 363 individuals—concluded that "[p]atients with mild-to-moderate COVID-19 infection treated with ivermectin plus doxycycline recovered earlier, were less likely to progress to more serious disease, and were more likely to be COVID-19 negative . . . on day 14."[84] And Niaee's research team found that ivermectin can help even hospitalized patients.[85] That group conducted a "randomized, double-blind, placebo-controlled, multicenter clinical trial" with 180 hospitalized patients diagnosed with COVID-19.[86] They concluded that ivermectin "reduces the rate of

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77 *Id.*

78 *Id.*

79 *Id.*

80 Priyamadhaba Behera et al., *Prophylactic Role of Ivermectin in Severe Acute Respiratory Syndrome Coronavirus 2 Infection Among Healthcare Workers*, Cureus, at 1 (Aug. 2021), *available at* https://assets.cureus.com/uploads/original_article/pdf/64807/20210904-4912-omcmtf.pdf (last visited Oct. 14, 2021).

81 *Id.* at 5.

82 *Id.*

83 *Id.* at 1.

84 Reaz Mahmud et al., *Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial*, Journal of International Medical Research 49(5) (Apr. 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8127799/pdf/10.1177_03000605211013550.pdf (last visited Oct. 14, 2021).

85 Morteza Shakhsi Niaee et al., *Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial*, 14 Asian Pacific Journal of Tropical Medicine 266, 266 (2021), *available at* https://www.apjtm.org/temp/AsianPacJTropMed146266-5371482_145514.pdf (last visited Oct. 14, 2021).

86 *Id.*

mortality . . . and duration of hospitalization in adult COVID-19 patients," and "[t]he improvement of other clinical parameters showed that the ivermectin, with a wide margin of safety, had a high therapeutic effect on COVID-19."[87]

As the data accumulated, scholars began conducting and publishing meta-analyses of the available studies. One such analysis—the Bryant review—focused on 24 total RCTs involving 3,406 participants and found "with moderate certainty that ivermectin treatment in COVID-19 provides a significant survival benefit."[88] It also concluded that "[u]sing ivermectin early in the clinical course may reduce numbers progressing to severe disease" and that "[t]he apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally."[89] Following Bryant's publication of his team's review, the Elgazzar study—one of the RCTs included in the meta-analysis—was questioned and is now under review. This prompted Bryant's team to reanalyze the data without the Elgazzar study, and that review still found "a clear result, showing a 49% reduction in mortality in favor of ivermectin."[90]

Another meta-analysis known as the Popp review has reached more skeptical conclusions. That analysis, which excluded some of the RCTs that Bryant considered, evaluated only 14 studies with 1,678 participants and determined that the "completed studies are small and few are considered high quality."[91] Thus, the authors expressed "uncertain[ty] about the efficacy and safety of ivermectin used to treat or prevent COVID-19."[92] Recently, however, the Bryant team critiqued the Popp review, highlighting, among other things, that although "Popp claims to provide a 'complete evidence profile,'" it actually "excludes most of the available evidence."[93]

In further contrast, a third meta-analysis expressed doubt about ivermectin. That one—the Roman review—restricted the pool of RCTs even further, considering only 10

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87 *Id.*

88 Bryant, *Ivermectin*, *supra*, at 451.

89 *Id.* at 435.

90 Andrew Bryant et al., *Letter to the Editor: Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines*, 28 American Journal of Therapeutics 573, 573 (Sept./Oct. 2021), *available at* https://covid19critical care.com/wp-content/uploads/2021/09/Response-to-Elgazzar.pdf (last visited Oct. 14, 2021).

91 Maria Popp et al., *Ivermectin for preventing and treating COVID-19*, Cochrane Database of Systematic Reviews, at 2 (July 28, 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8406455/pdf/CD015017.pdf (last visited Oct. 14, 2021).

92 *Id.*

93 Edmund J. Fordham et al., *The uses and abuses of systematic reviews: the case of ivermectin in Covid-19*, OSF Preprints, at 7 (Sept. 3, 2021), *available at* https://osf.io/pegcj/ (last visited Oct. 14, 2021).

of them.[94] After doing this, the authors concluded that ivermectin does "not reduce all-cause mortality, [length of hospital stay], or viral clearance . . . in patients with mostly mild COVID-19."[95] As a result, the researchers announced that ivermectin "is not a viable option to treat patients with COVID-19."[96]

In the days since its publication, the Roman review has drawn some harsh criticism. In particular, the authors of the Bryant review have highlighted four categories of flaws with Roman's work: (1) "mis-reporting of source data," (2) "highly selective study inclusion," (3) "'cherry picking' of data within included studies," and (4) "conclusions that do not follow from the evidence."[97] To illustrate these flaws, consider that Roman's paper initially inverted the treatment and control arms for the Niaee study and thus indicated less mortality in the control group when in fact the opposite was true.[98] Once that error was fixed, the numbers no longer supported the conclusion that ivermectin does "not reduce all-cause mortality."[99] Yet the Roman team did not adjust that statement, and thus its "conclusions are no longer based on the data."[100]

Furthermore, in a letter to the editor of the *American Journal of Therapeutics*, two researchers recently explained that Roman's conclusion of no mortality reduction "is not based on the results of the statistical analysis of the data . . . ; instead, it was based on a somewhat vague and possibly biased subjective assessment of the quality of the trials

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94 Yuani M. Roman et al., *Ivermectin for the treatment of Coronavirus Disease 2019: A systematic review and meta-analysis of randomized controlled trials*, Clinical Infectious Diseases, at 1 (June 28, 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8394824/pdf/ciab591.pdf (last visited Oct. 14, 2021).

95 *Id.*

96 *Id.*

97 Letter from Andrew Bryant et al. to Robert T. Schooley, MD, Editor in Chief, Clinical Infectious Diseases, at 3, *available at* https://covid19criticalcare.com/wp-content/uploads/2021/07/RomanRebuttal_v7_EF_letterhead_ML-1.pdf (last visited Oct. 14, 2021) (hereinafter, "Bryant Letter to Schooley").

98 *Compare* Yuani M. Roman et al., *Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials*, Preprint Version 1, at 27 Figure 2 (May 25, 2021), *available at* https://www.medrxiv.org/content/10.1101/2021.05.21.21257595v1.full.pdf (last visited Oct. 14, 2021) (listing the Niaee study as having four deaths in the control arm and 11 in the ivermectin arm), *with* Yuani M. Roman et al., *Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials*, Preprint Version 2, at 27 Figure 2 (May 26, 2021), *available at* https://www.medrxiv.org/content/10.1101/2021.05.21.21257595v2.full.pdf (last visited Oct. 14, 2021) (correcting the Niaee study to list 11 deaths in the control arm and four in the ivermectin arm).

99 Bryant Letter to Schooley, *supra*, at 2.

100 *Id.*

themselves."[101] Those researchers conducted their own Bayesian analysis, a method of statistical inference, and found that the "probability for the hypothesis of a causal link between COVID-19 severity, ivermectin, and mortality is over 99%."[102] As they concluded, "[i]n our view, this Bayesian analysis, based on the statistical study data, provides sufficient confidence that ivermectin is an effective treatment for COVID-19 and this belief supports the conclusions of Bryant over those of Roman."[103] Those scholars have since published their full analysis in a paper available online.[104]

Additional supportive evidence for Bryant's conclusions is a non-peer-reviewed website that currently maintains a running list of 64 COVID-19-related ivermectin studies—RCTs and others—which include all the relevant ivermectin studies except the few (such as Elgazzar) whose data have been called into question.[105] Of those 64 studies, 31 are RCTs and 44 have been peer-reviewed.[106] That site posts multiple meta-analyses of different groupings of the data and concludes that "[m]eta analysis using the most serious outcome reported shows" that ivermectin leads to 66% "improvement for early treatment" and an 86% "improvement for . . . prophylaxis."[107] These "[r]esults are very robust," the site reports, because "in worst case exclusion sensitivity analysis 53 of 64 studies must be excluded to avoid finding statistically significant efficacy."[108]

Finally, a recent mini-review of ivermectin and COVID-19 considered the studies analyzing ivermectin's safety specifically in the context of COVID-19 treatments.[109] That mini-review—which was authored by Yale Professor Alessandro D. Santin—observed

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101 Martin Neil & Norman Fenton, *Bayesian Hypothesis Testing and Hierarchical Modeling of Ivermectin Effectiveness*, 28 American Journal of Therapeutics 576, 576 (Sept./Oct. 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8415515/pdf/ajt-28-e576.pdf (last visited Oct. 14, 2021).

102 *Id.*

103 *Id.* at 578.

104 Martin Neil & Norman Fenton, Bayesian hypothesis testing and hierarchical modelling of ivermectin effectiveness in treating Covid-19 (Oct. 1, 2021), *available at* https://arxiv.org/ftp/arxiv/papers/2109/2109.13739.pdf (last visited Oct. 14, 2021).

105 Ivermectin for COVID-19: Real-time meta analysis of 64 studies (Oct. 8, 2021), https://ivmmeta.com/ (last visited Oct. 14, 2021).

106 *Id.*

107 *Id.*

108 *Id.*

109 Alessandro D. Santin et al., *Ivermectin: a multifaceted drug of Nobel prize-honoured distinction with indicated efficacy against a new global scourge, COVID-19*, New Microbes New Infections (Aug. 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8383101/pdf/main.pdf (last visited Oct. 14, 2021).

that ivermectin "has been safely used in 3.7 billion doses since 1987" and that the medicine has been "used without serious [adverse effects]" in multiple "COVID-19 treatment studies."[110]

The existing ivermectin studies and meta-analyses are subject to vigorous ongoing disputes, and there are large ongoing studies, at least one of which includes the NIH as a collaborator, that will hopefully provide additional clarity.[111] But based on the existing medical literature, we do not find clear and convincing evidence that a physician who prescribes ivermectin for COVID-19 after obtaining informed consent engages in unprofessional conduct or otherwise violates the UCA.

While we find the studies and meta-analyses sufficient to resolve this question, we note that epidemiological evidence—derived by analyzing COVID-related data from various states, countries, or regions—is also instructive in the context of a global pandemic. We highlight just a few examples.

One set of scholars analyzed data comparing the COVID-19 rates of countries that routinely administer ivermectin as a prophylaxis and countries that do not.[112] The research revealed that "countries with routine mass drug administration of prophylactic . . . ivermectin have a significantly lower incidence of COVID-19."[113] This "highly significant" correlation manifests itself not only "in a worldwide context" but also when comparing African countries that regularly administer prophylactic "ivermectin against parasitic infections" and African countries that do not.[114] Based on these results, the researchers surmised that these results "may be connected to ivermectin's ability to inhibit SARS-CoV-2 replication, which likely leads to lower infection rates."[115]

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110 *Id.* at 4.

111 *E.g.*, U.S. National Library of Medicine, ACTIV-6: COVID-19 Study of Repurposed Medications, https://clinicaltrials.gov/ct2/show/NCT04885530?term=activ-6&draw=2&rank=1 (last visited Oct. 14, 2021) (purpose of this trial involving an estimated 15,000 participants is "to evaluate the effectiveness of repurposed medications" that include ivermectin "in reducing symptoms of non-hospitalized participants with mild to moderate COVID-19"); U.S. National Library of Medicine, COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 Infection (COVID-19), https://clinicaltrials.gov/ct2/show/NCT04510194?_term=ivermectin+boulware&draw=2&rank=1 (last visited Oct. 14, 2021) (purpose of this trial involving 1,160 participants is to understand whether ivermectin is superior to other options, including placebo, in "non-hospitalized adults with SARS-CoV-2 disease for preventing Covid-19 disease progression").

112 Martin D. Hellwig & Anabela Maia, *A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin*, International Journal of Antimicrobial Agents (2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7698683/pdf/main.pdf (last visited Oct. 14, 2021).

113 *Id.* at 1.

114 *Id.*

115 *Id.*

More specifically, Peru's COVID-19 statistics, which have been analyzed in pre-print studies and discussed in published ivermectin reviews, are also informative.[116] Peru deployed mass ivermectin-based COVID-19 treatments from April 2020 through November 2020 throughout its 25 states.[117] In ten of those states, a maximal amount of "mass [ivermectin] treatments of COVID-19 were conducted through a broadside, army-led effort, *Mega-Operación Tayta (MOT).*"[118] Fourteen other states had a medium distribution of ivermectin administered at the local level.[119] And one state, Lima, distributed a minimal amount of ivermectin due to restrictive government policies.[120] "The mean reduction in excess deaths 30 days after peak deaths was 74% for the maximal [ivermectin] distribution group, 53% for the medium group[,] and 25% for Lima."[121] Furthermore, throughout the country of Peru, "excess deaths decreased 14-fold over four months" leading up to December 1, 2020, "after which deaths then increased 13-fold when [ivermectin] use was restricted under a new president."[122]

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116 Juan J. Chamie-Quintero et al., *Ivermectin for COVID-19 in Peru: 14-fold reduction in nationwide excess deaths, p < 0.002 for effect by state, then 13-fold increase after ivermectin use restricted* (Mar. 2021), *available at* https://osf.io/9egh4/ (last visited Oct. 14, 2021); *see also* Santin, *supra*, at 3–4 (discussing the Peruvian data); Kory, *supra*, at 311–13 (same).

117 Chamie-Quintero, *supra*, at 2.

118 Santin, *supra*, at 3.

119 Chamie-Quintero, *supra*, at 2.

120 *Id.*

121 *Id.*

122 *Id.*

Ivermectin for COVID-19 in Peru: 14-fold reduction in nationwide excess deaths, p=.002 for effect by state, then 13-fold increase after ivermectin use restricted

Juan J. Chamie-Quintero,[a] Jennifer A. Hibberd,[b] David E Scheim[c]

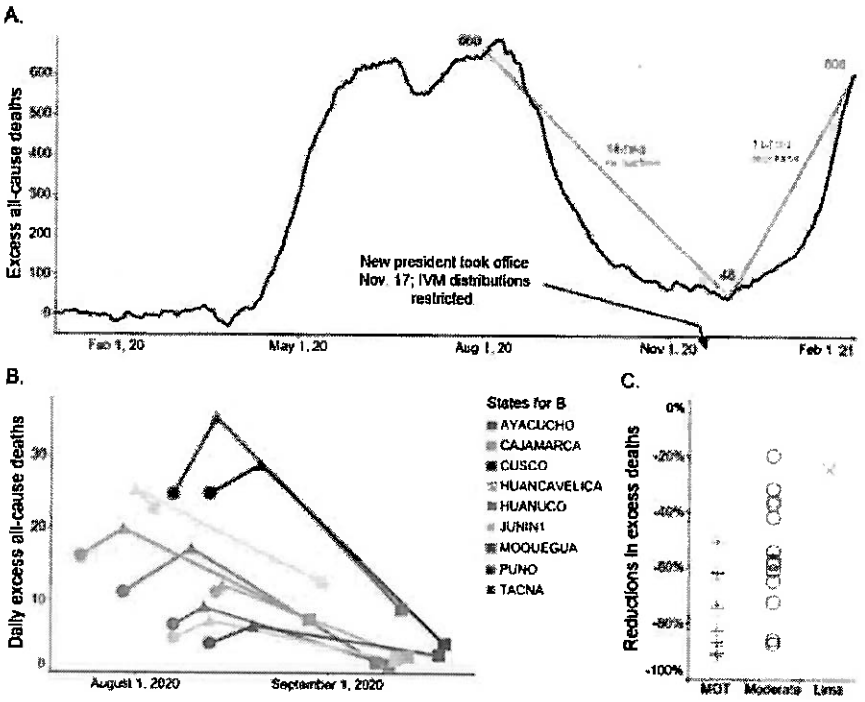

Figure 1. A) Excess all-cause deaths (all ages), national population of Peru. These decreased 14-fold August 1 through December 1, 2020; then, after IVM use was restricted, increased 13-fold through February 1. All y values are 7-day moving averages; for B,C, ages ≥ 60. Data are from Peru's National Death Information System (SINADEF).[12] B) Drops in excess deaths for all states of operation *MOT*, an army-led program of mass IVM distributions, but Pasco, which had them on 3 dates. ● *MOT* start date: ▲ peak deaths: ■ day of peak deaths + 30 days. Junin also distributed IVM 13 days before *MOT* start. C) Reductions in excess deaths at +30 days after peak deaths for the 25 states by extent of IVM distributions: maximal-*MOT* (+), mean -74%; moderate-local distributions (○), mean -53%; and minimal-Lima (x), -25%. These reductions for the 25 states correlated with extent of IVM distributions with Kendall τ_b p=0.002.

"Potential confounding factors, including lockdowns and herd immunity, were ruled out using Google community mobility data, seropositivity rates, population densities and geographic distributions of SARS-CoV-2 genetic variations."[123] While these figures do not prove causation, they demonstrate a strong correlation between ivermectin use and mortality reductions.

Moving from Peru to India, the government in the State of Uttar Pradesh—a jurisdiction with a population of more than 200 million—"introduced a large-scale 'prophylactic and therapeutic' use of [i]vermectin" that enabled it "to maintain a lower fatality and

123 Santin, *supra*, at 4.

positivity rate as compared to other states" in India.[124] As one state official explained, "Uttar Pradesh was the first state in [India] to introduce large-scale prophylactic and therapeutic use of Ivermectin."[125] The state's health department introduced ivermectin "as prophylaxis for close contacts of [COVID-19] patients" and "health workers," "as well as for the treatment of the patients themselves."[126] "Despite being [India's] state with the largest population base and a high population density," that state official added, Uttar Pradesh has "maintained a relatively low positivity rate and cases per million of population."[127] Although these statements from the Uttar Pradesh government do not prove ivermectin's effectiveness, they are informative and worthy of some consideration.

ii. U.S. Public Health Agencies on Ivermectin

Many public health agencies in the United States have now addressed the topic of ivermectin and COVID-19. The NIH has adopted a neutral position, saying that "[t]here is insufficient evidence . . . to recommend either for or against the use of ivermectin for the treatment of COVID-19."[128] This position, which the NIH adopted in January 2021, overrode its prior stance of "recommend[ing] against the use of ivermectin for the treatment" of COVID-19.[129] The reason for the change, the NIH recognized, was that "several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals."[130] And some of those studies reported positive outcomes, including "shorter time to resolution of disease manifestations that were attributed to COVID-19, greater reduction in inflammatory marker levels, shorter time to viral clearance, [and] lower mortality rates in patients who received ivermectin than in patients who received comparator drugs or placebo."[131] The NIH nevertheless decided not to recommend the use of ivermectin for COVID-19 because other studies suggest "no benefits" and the NIH thought that the available studies

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124 Maulshree Seth, *Uttar Pradesh government says early use of Ivermectin helped to keep positivity, deaths low*, The Indian Express (May 12, 2021), *available at* https://indianexpress.com/article/cities/lucknow/uttar-pradesh-government-says-ivermectin-helped-to-keep-deaths-low-7311786/ (last visited Oct. 14, 2021), and https://www.msn.com/en-in/news/other/uttar-pradesh-government-says-early-use-of-ivermectin-helped-to-keep-positivity-deaths-low/ar-BB1gDp5U (last visited Oct. 14, 2021).

125 *Id.*

126 *Id.*

127 *Id.*

128 NIH, COVID-19 and Ivermectin, *supra*.

129 Yagisawa, *supra*, at 65.

130 NIH, COVID-19 and Ivermectin, *supra*.

131 *Id.*

generally suffered from "methodological limitations."[132] By making a neutral recommendation, the NIH—which is continuing to collaborate on at least one study investigating ivermectin as a treatment for "mild to moderate COVID-19"[133]—clearly signaled that physicians should use their discretion in deciding whether to treat COVID-19 patients with ivermectin.

Ignoring the NIH's official position, officials within its agencies have sent contradictory messages. On August 29, 2021, Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID) within the NIH, went on CNN and announced that "there is no clinical evidence" that ivermectin works for the prevention or treatment of COVID-19.[134] Expanding on that point, he reiterated that "there is no evidence whatsoever" that it works.[135] Yet this definitive claim directly contradicts the NIH's recognition that "several randomized trials . . . published in peer-reviewed journals" have reported data indicating that ivermectin is effective as a COVID-19 treatment.[136]

The FDA has similarly charted a course of confusion. In March 2021, the FDA posted a webpage entitled "Why You Should Not Use Ivermectin to Treat or Prevent COVID-19."[137] Although the FDA's concern was stories of some people using the animal form of ivermectin or excessive doses of the human form, the title broadly condemned any use of ivermectin in connection with COVID-19. Yet there was no basis for its sweeping condemnation. Indeed, the FDA itself acknowledged on that very webpage (and continued to do so until the page changed on September 3, 2021) that the agency had *not* even "reviewed data to support use of ivermectin in COVID-19 patients to treat or to prevent COVID-19."[138] But without reviewing the available data, which had long

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132 *Id.*

133 U.S. National Library of Medicine, ACTIV-6: COVID-19 Study of Repurposed Medications, https://clinicaltrials.gov/ct2/show/NCT04885530?term=activ-6&draw=2&rank=1 (last visited Oct. 14, 2021).

134 CNN Health, *'Don't do it': Dr. Fauci warns against taking Ivermectin to fight Covid-19* (Aug. 29, 2021), https://edition.cnn.com/videos/health/2021/08/29/dr-anthony-fauci-ivermectin-covid-19-sotu-vpx.cnn (last visited Oct. 14, 2021).

135 *Id.*

136 NIH, COVID-19 and Ivermectin, *supra.*

137 U.S. Food and Drug Administration, Why You Should Not Use Ivermectin to Treat or Prevent COVID-19 (archived Mar. 5, 2021), https://web.archive.org/web/20210305163946/https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19 (last visited Oct. 14, 2021) (hereinafter, "FDA, Why You Should Not Use Ivermectin (Mar. 5, 2021)").

138 *Id.*; *see also* U.S. Food and Drug Administration, Why You Should Not Use Ivermectin to Treat or Prevent COVID-19 (archived Sept. 2, 2021), https://web.archive.org/web/20210902231921/https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19 (last visited Oct. 14, 2021) (hereinafter, "FDA, Why You Should Not Use Ivermectin (Sept. 2, 2021)").

since been available and accumulating, it is unclear what basis the FDA had for denouncing ivermectin as a treatment or prophylaxis for COVID-19.

On that same webpage, the FDA also declared that "[i]vermectin is not an anti-viral (a drug for treating viruses)."[139] It did so while another one of its webpages[140] simultaneously cited a study in *Antiviral Research* that identified ivermectin as a medicine "previously shown to have *broad-spectrum anti-viral activity*."[141] It is telling that the FDA deleted the line about ivermectin not being "anti-viral" when it amended the first webpage on September 3, 2021.[142]

The FDA has additionally assailed ivermectin's safety by suggesting, though not outright stating, that even a proper dose of human ivermectin might be dangerous when used to treat COVID-19. For example, the FDA announced that "[t]aking a drug for an unapproved use can be very dangerous" and "[t]his is true of ivermectin."[143] Yet this ignores the fact that, as discussed above, doctors routinely prescribe medicines for off-label use and that ivermectin is a particularly well-tolerated medicine with an established safety record. Moreover, it is inconsistent for the FDA to imply that ivermectin is dangerous when used to treat COVID-19 while the agency continues to approve remdesivir[144] despite its spottier safety record, as discussed above.

The FDA has also called into question ivermectin's potential effectiveness. When updating the "Why You Should Not Use Ivermectin" webpage on September 3, 2021, the FDA added this entry: "Currently available data do not show ivermectin is effective against COVID-19."[145] But this claim fails to recognize that several RCTs and at least one meta-analysis suggest that ivermectin is effective against COVID-19.

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139 FDA, Why You Should Not Use Ivermectin (Mar. 5, 2021), *supra*.

140 U.S. Food and Drug Administration, FAQ: COVID-19 and Ivermectin Intended for Animals (Sept. 3, 2021), https://www.fda.gov/animal-veterinary/product-safety-information/faq-covid-19-and-ivermectin-intended-animals (last visited Oct. 14, 2021).

141 Caly, *supra*, at 1 (emphasis added).

142 U.S. Food and Drug Administration, Why You Should Not Use Ivermectin to Treat or Prevent COVID-19 (updated Sept. 3, 2021), https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19 (last visited Oct. 14, 2021) (hereinafter, "FDA, Why You Should Not Use Ivermectin (Sept. 3, 2021)").

143 FDA, Why You Should Not Use Ivermectin (Mar. 5, 2021), *supra*.

144 U.S. Food and Drug Administration, FDA Approves First Treatment for COVID-19 (Oct. 22, 2020), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19 (last visited Oct. 14, 2021).

145 FDA, Why You Should Not Use Ivermectin (Sept. 3 2021), *supra*.

Moreover, a review of the studies on remdesivir makes it difficult to understand why the FDA would condemn the data supporting ivermectin. The NIH reports only five studies testing remdesivir's efficacy against COVID-19.[146] Three of those five studies show *no benefit* from remdesivir, with the largest of those concluding that remdesivir "did not decrease in-hospital mortality in hospitalized patients."[147] Even the two remaining studies are far from compelling. One found that "[h]ospitalized patients . . . who received 5 days of [remdesivir] had better outcomes," but the difference "was of uncertain clinical importance."[148] And while the other study indicated that remdesivir "reduced time to clinical recovery" for "patients with severe COVID-19," it also found "[n]o observed benefit . . . in patients with mild or moderate COVID-19" and "[n]o statistically significant difference in mortality."[149] Beyond that, in September 2021, the Lancet published the results of a large RCT (the DisCoVeRy trial) that found "[n]o clinical benefit . . . from the use of remdesivir in patients who were admitted to hospital for COVID-19, were symptomatic for more than 7 days, and required oxygen support."[150] The data on ivermectin thus appears at least as strong as the data on remdesivir.

The FDA's most controversial statement on ivermectin came on August 21, 2021, when it posted a link on Twitter to its "Why You Should Not Use Ivermectin" webpage with this message: "You are not a horse. You are not a cow. Seriously, y'all. Stop it."[151]

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146 National Institutes of Health, Remdesivir: Selected Clinical Data, https://www.covid19treatmentguidelines.nih.gov/tables/table-2a/ (last visited Oct. 14, 2021).

147 *Id.*

148 *Id.*

149 *Id.*

150 Florence Ader et al., *Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial*, The Lancet, at 1 (Sept. 14, 2021), *available at* https://www.thelancet.com/action/showPdf?pii=S1473-3099%2821%2900485-0 (last visited Oct. 14, 2021).

151 U.S. FDA, Twitter, https://twitter.com/us_fda/status/1429050070243192839 (last visited Oct. 14, 2021).

This message is troubling not only because it makes light of a serious matter but also because it inaccurately implies that ivermectin is only for horses or cows.

Despite its attempts to impugn ivermectin, the FDA appears to recognize that doctors may prescribe it for COVID-19. On September 3, 2021, a change in its website makes this clear. The "Why You Should Not Use Ivermectin" webpage originally said that "[i]f you have a prescription for ivermectin for an FDA-approved use, get it from a legitimate source and take it exactly as prescribed."[152] That same sentence now omits the limitation on prescriptions to FDA-approved uses. It says that "[i]f your health care provider writes you an ivermectin prescription, fill it through a legitimate source such as a pharmacy, and take it *exactly* as prescribed."[153] This change implicitly acknowledges that ivermectin may be prescribed off-label for COVID-19.

The CDC has followed in the FDA's footsteps of implying that ivermectin is unsafe. On August 26, 2021, the CDC issued an official advisory entitled "Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19."[154] Like the FDA, the CDC's

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152 FDA, Why You Should Not Use Ivermectin (Mar. 5, 2021), *supra*.

153 FDA, Why You Should Not Use Ivermectin (Sept. 3, 2021), *supra*.

154 Centers for Disease Control and Prevention, *Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat*

sweeping title implies that severe illnesses are arising from the prescribed use of human ivermectin to combat COVID-19, but it supplies no data to indicate that human ivermectin in appropriate doses is harming anyone. On the contrary, the CDC's advisory acknowledges that the actual concerns arise from the "use of veterinary products not meant for human consumption" and that the reported "[a]dverse effects [are] associated with ivermectin misuse and overdose."[155] The CDC's instructions to the public confirm that its concerns arise from the improper use of ivermectin creams or animal formulas: "Do not swallow ivermectin products that should be used on skin (e.g., lotions and creams) or are not meant for human use, such as veterinary ivermectin products."[156]

None of this undermines the use of human ivermectin in proper doses for the treatment or prevention of COVID-19. If anything, the reported uptick in people resorting to animal ivermectin simply reinforces that COVID-19 patients should be encouraged to discuss human ivermectin with their healthcare providers and that those providers should be allowed to consider the available data with their patients. That would be more beneficial for public health than attempting to obscure the demonstrated safety profile of ivermectin.

The media has added to the confusion and misinformation. On August 30, 2021, the New York Times published an article about ivermectin stating that "Mississippi's health department said earlier this month that *70 percent* of recent calls to the state poison control center had come from people who ingested ivermectin from livestock supply stores."[157] Yet two weeks later, on September 13, 2021, the Times amended its story by deleting that sentence and adding this note after the article: "An earlier version of this article misstated the percentage of recent calls to the Mississippi poison control center related to ivermectin. It was 2 percent, not 70 percent."[158]

Similarly, on September 3, 2021, Rolling Stone published a story entitled "Gunshot Victims Left Waiting as Horse Dewormer Overdoses Overwhelm Oklahoma Hospitals,

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COVID-19, Health Advisory, at 1 (Aug. 26, 2021), *available at* https://emergency.cdc.gov/han/2021/pdf/CDC_HAN_449.pdf (last visited Oct. 14, 2021).

155 *Id.*

156 *Id.* at 3.

157 Emma Goldberg, *Demand Surges for Deworming Drug for Covid, Despite No Evidence It Works*, New York Times (Aug. 30, 2021), *available at* https://web.archive.org/web/20210830091038/https://www.nytimes.com/2021/08/30/health/covid-ivermectin-prescriptions.html (last visited Oct. 14, 2021) (emphasis added).

158 Emma Goldberg, *Demand Surges for Deworming Drug for Covid, Despite No Evidence It Works*, New York Times (amended Sept. 28, 2021), *available at* https://www.nytimes.com/2021/08/30/health/covid-ivermectin-prescriptions.html (last visited Oct. 14, 2021).

Doctor Says."[159] Soon thereafter, one the hospitals where this doctor supposedly works denied that claim, and "the doctor [did] not respond[] to requests for further comment."[160] Rather than delete the article or substantially rewrite it, Rolling Stone left the article largely unchanged and amended the title to say: "One Hospital Denies Oklahoma Doctor's Story of Ivermectin Overdoses Causing ER Delays for Gunshot Victims."[161] In addition, the magazine added an "update" message stating, among other things, that "[o]ne hospital has denied [the doctor's] claim that ivermectin overdoses are causing emergency room backlogs and delays in medical care in rural Oklahoma, and Rolling Stone has been unable to independently verify any such cases as of the time of this update."[162] In other words, the publication allowed a story based on a discredited and nonresponsive source to remain available to the public. It is no wonder that some people are unsure what to believe about ivermectin.

iii. Foreign Public Health Agencies on Ivermectin

Looking abroad, in March 2021, the WHO "recommend[ed] not to use ivermectin in patients with COVID-19 except in the context of a clinical trial."[163] The basis for this recommendation rested not on proof that ivermectin is ineffective, but on the WHO's belief that the existing studies were of too low quality to support any conclusive determinations.[164] Notably, though, while the WHO questioned the quality of the evidence, its analysis determined, based on data from 1,419 patients in seven studies, that patients treated with ivermectin had a 14 per 1,000 chance of death while patients in the control groups had a 70 per 1,000 chance of death.[165] Also, the WHO considered only

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159 Peter Wade, *Gunshot Victims Left Waiting as Horse Dewormer Overdoses Overwhelm Oklahoma Hospitals, Doctor Says*, Rolling Stone (Sept. 3, 2021), *available at* https://web.archive.org/web/20210903231939/https://www.rollingstone.com/politics/politics-news/gunshot-victims-horse-dewormer-ivermectin-oklahoma-hospitals-covid-1220608/ (last visited Oct. 14, 2021).

160 Peter Wade, *One Hospital Denies Oklahoma Doctor's Story of Ivermectin Overdoses Causing ER Delays for Gunshot Victims*, Rolling Stone (amended Sept. 5, 2021), *available at* https://www.rollingstone.com/politics/politics-news/gunshot-victims-horse-dewormer-ivermectin-oklahoma-hospitals-covid-1220608/ (last visited Oct. 14, 2021).

161 *Id.*

162 *Id.*

163 World Health Organization, Therapeutics and COVID-19: Living Guideline, at 20 (July 6, 2021), *available at* https://files.magicapp.org/guideline/a6e3f83e-bff5-481c-90ab-130aa86bbe83/published_guideline_5486-6_1.pdf (last visited Oct. 14, 2021) (hereinafter, "WHO COVID-19 Guidelines").

164 *Id.*

165 *Id.* at 23.

ivermectin's effectiveness as a COVID-19 treatment and did not assess its potential as a prophylaxis.[166]

Public health authorities in other countries have declined to follow the WHO's guidance. Most importantly, the NIH continues to embrace its neutral recommendation on ivermectin. Also, in May 2021, the State of Goa in India announced, through its health minister Vishwajit Rane, that "it would give [ivermectin] to all its adult residents" in its efforts to combat COVID-19.[167] Likewise, as discussed above, India's Uttar Pradesh continues to distribute ivermectin to people diagnosed with COVID-19. And El Salvador's Ministry of Public Health has included ivermectin as part of its recommendations for early COVID-19 treatment via home patient kit.[168] We did not conduct an exhaustive search on other countries' practices, so this list is simply intended to be illustrative.

iv. Professional Associations and Physicians on Ivermectin

Professional associations, both here in the United States and abroad, have adopted conflicting positions on ivermectin and COVID-19. The American Medical Association (AMA), American Pharmacists Association (APhA), and American Society of Health-System Pharmacists (ASHP) have issued a statement that "strongly oppose[s] the ordering, prescribing, or dispensing of ivermectin to prevent or treat COVID-19 outside of a clinical trial."[169] But this statement relies solely on the FDA's and CDC's statements. Consider the AMA, APhA, and ASHP's claim that "[u]se of ivermectin for the prevention and treatment of COVID-19 has been demonstrated to be harmful to patients."[170] Their only support for that alarming statement is the CDC Health Alert discussed above.[171] But as we explained, that CDC advisory gave no indication that any severe adverse effects are occurring from the use of human ivermectin in appropriate doses.

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166 *Id.* at 18.

167 Siladitya Ray, *Indian State Will Offer Ivermectin To Entire Adult Population — Even As WHO Warns Against Its Use As Covid-19 Treatment*, Forbes (May 11, 2021), *available at* https://www.forbes.com/sites/siladityaray/2021/05/11/indian-state-will-offer-ivermectin-to-entire-adult-population---even-as-who-warns-against-its-use-as-covid-19-treatment/?sh=3d45adce6d9f (last visited Oct. 14, 2021).

168 *El Salvador Minister of Public Health Includes Ivermectin as COVID-19 Pandemic Continues*, TrialSite News (Aug. 26, 2021), *available at* https://trialsitenews.com/el-salvador-minister-of-public-health-includes-ivermectin-as-covid-19-pandemic-continues/ (last visited Oct. 14, 2021).

169 American Medical Association, AMA, APhA, ASHP statement on ending use of ivermectin to treat COVID-19 (Sept. 1, 2021), *available at* https://www.ama-assn.org/press-center/press-releases/ama-apha-ashp-statement-ending-use-ivermectin-treat-covid-19 (last visited Oct. 14, 2021) (hereinafter, "AMA, APhA, and ASHP Statement on Ivermectin").

170 *Id.*

171 *Id.*

Those groups' opposition to ivermectin also conflicts with their otherwise steadfast support for healthcare providers' rights to prescribe medicines for off-label use. They call for ivermectin's ban because the FDA has not approved it "to prevent or treat COVID-19" and some public-health agencies have found "insufficient evidence" to support its use.[172] But just last year, these same professional associations, when discussing prescriptions for hydroxychloroquine to treat COVID-19, affirmed that "[n]ovel off-label use of FDA-approved medications is a matter for the physician's or other prescriber's professional judgment."[173] Moreover, the AMA elsewhere recognizes "its strong support for the autonomous clinical decision-making authority of . . . physician[s]" to "lawfully use an FDA approved drug product . . . for an off-label indication when such use is based upon sound scientific evidence."[174] In their recent ivermectin statement, however, the AMA, APhA, and ASHP ignore that some sound scientific evidence, including meta-analyses of RCTs, supports the use of ivermectin for COVID-19.

The AMA, APhA, and ASHP mentioned the statement of Merck—the original patentholder on ivermectin—as an additional basis for their position.[175] Yet that does not provide persuasive support for their opposition to ivermectin. Merck's February 2021 statement expressed its view that there is "[n]o meaningful evidence for . . . clinical efficacy in patients with COVID-19,"[176] but this simply ignores the RCTs demonstrating ivermectin's efficacy. Merck then claimed that there is "[a] concerning lack of safety data in the majority of studies."[177] While worded vaguely, this statement, when read carefully, says next to nothing. It simply acknowledges that many of the studies it references did not track safety data. It is not saying, though it might be implying, that the studies showed the medicine to be dangerous. But Merck, of all sources, knows that ivermectin is exceedingly safe, so the absence of safety data in recent studies should not be concerning to the company.

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172 *Id.*

173 American Medical Association, Joint statement on ordering, prescribing or dispensing COVID-19 medications (Apr. 17, 2020), *available at* https://www.ama-assn.org/delivering-care/public-health/joint-statement-ordering-prescribing-or-dispensing-covid-19 (last visited Oct. 14, 2021).

174 American Medical Association, Patient Access to Treatments Prescribed by Their Physicians, https://policysearch.ama-assn.org/policyfinder/detail/Patient%20Access%20to%20Treatments%20Prescribed%20by%20Their%20Physicians%20H-120.988%20%20?uri=%2FAMADoc%2FHOD.xml-0-201.xml (last visited Oct. 14, 2021).

175 AMA, APhA, and ASHP Statement on Ivermectin, *supra*.

176 Merck, Merck Statement on Ivermectin use During the COVID-19 Pandemic (Feb. 4, 2021), https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/ (last visited Oct. 14, 2021).

177 *Id.*

Why would ivermectin's original patentholder go out of its way to question this medicine by creating the impression that it might not be safe? There are at least two plausible reasons. First, ivermectin is no longer under patent, so Merck does not profit from it anymore. That likely explains why Merck declined to "conduct[] clinical trials" on ivermectin and COVID-19 when given the chance.[178] Second, Merck has a significant financial interest in the medical profession rejecting ivermectin as an early treatment for COVID-19. "[T]he U.S. government has agreed to pay [Merck] about $1.2 billion for 1.7 million courses of its experimental COVID-19 treatment, if it is proven to work in an ongoing large trial and authorized by U.S. regulators."[179] That treatment, known as "molnupiravir, aims to stop COVID-19 from progressing and can be given early in the course of the disease."[180] On October 1, 2021, Merck announced that preliminary studies indicate that molnupiravir "reduced hospitalizations and deaths by half,"[181] and that same day its stock price "jumped as much as 12.3%."[182] Thus, if low-cost ivermectin works better than—or even the same as—molnupiravir, that could cost Merck billions of dollars.

While one side of the "professional associations" ledger includes the AMA, APhA, and ASHP (with Merck's backing), other associations disagree with their stance. In particular, the Association of American Physicians and Surgeons (AAPS)—a long-established group that has represented doctors in all specialties since 1943—has raised questions concerning those associations' "startling and unprecedented position that American physicians should immediately stop prescribing, and pharmacists should stop honoring their prescriptions for ivermectin for COVID-19 patients."[183] The AAPS pointed "out that many physicians disagree with the AMA, writing around 88,000 ivermectin

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178 Yagisawa, *supra*, at 61.

179 *U.S. signs $1.2 bln deal for 1.7 mln courses of Merck's experimental COVID-19 drug*, Reuters (Jun. 9, 2021), *available at* https://www.reuters.com/business/healthcare-pharmaceuticals/merck-says-us-govt-buy-about-17-mln-courses-cos-covid-19-drug-2021-06-09/ (last visited Oct. 14, 2021).

180 *Id.*

181 Matthew Perrone, *Merck says COVID-19 pill cuts risk of death, hospitalization*, Associated Press (Oct. 1, 2021), *available at* https://apnews.com/article/merck-says-experimental-covid-pill-cuts-worst-effects-a9a2245fdcee324f6bbd776a0fffcc60 (last visited Oct. 14, 2021).

182 Lewis Krauskopf & Manojna Maddipatla, *Merck COVID-19 pill success slams Moderna shares, shakes up healthcare sector*, Reuters (Oct. 1, 2021), *available at* https://www.reuters.com/business/healthcare-pharmaceuticals/merck-covid-19-pill-success-slams-moderna-shares-shakes-up-healthcare-sector-2021-10-01/ (last visited Oct. 14, 2021).

183 Association of American Physicians and Surgeons, AAPS Challenges the AMA on Efforts to Suppress Ivermectin Use in COVID (Sept. 4, 2021), *available at* https://aapsonline.org/aaps-challenges-the-ama-on-efforts-to-suppress-ivermectin-use-in-covid/ (last visited Oct. 14, 2021).

prescriptions per week."[184] The AAPS has thus publicly resisted these groups' call to "stop[] the off-label use of long-approved drugs."[185]

In addition, the Tokyo Metropolitan Medical Association, as explained by its chairman Haruo Ozaki, recommended the use of ivermectin for COVID-19 patients in February 2021.[186] That organization emphasized that ivermectin should be administered to people diagnosed with COVID-19 because, among other reasons, it has been effective when used in other countries.[187] Other doctors' groups similarly advocate for ivermectin as a staple of early COVID-19 treatment. The Front Line COVID-19 Critical Care Alliance has been an outspoken supporter. Its organization "regard[s] ivermectin as a core medication in the prevention and treatment of COVID-19,"[188] and it includes a five-day course of ivermectin as part of its COVID-19 early treatment protocol.[189] Also, the British Ivermectin Recommendation Development Group (BIRD) is a UK-based association of "clinicians, health researchers[,] and patient representatives from all around the world" that collectively "advocate[s] for the use of ivermectin" against COVID-19.[190]

In summary, the evidence discussed above shows (1) that ivermectin has demonstrated some effectiveness in preventing and treating COVID-19 and (2) that its side effects are primarily minor and transient. Thus, the UCA does not preclude physicians from considering ivermectin for the prevention or treatment of COVID-19.

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184 *Id.*

185 *Id.*

186 Tokyo Metropolitan Medical Association recommends ivermectin administration to prevent aggravation, Nikkei (Feb. 9, 2021), https://www.nikkei.com/article/DGXZQOFB25AAL0V20C21A1000000/ (last visited Oct. 14, 2021).

187 *Id.*

188 Front Line COVID-19 Critical Care Alliance, Ivermectin in COVID-19, https://covid19criticalcare.com/ivermectin-in-covid-19/ (last visited Oct. 14, 2021).

189 Front Line COVID-19 Critical Care Alliance, Prevention & Treatment Protocols for COVID-19, https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Alliance-I-MASKplus-Protocol-ENGLISH.pdf (last visited Oct. 14, 2021).

190 British Ivermectin Recommendation Development Group, Who are the BIRD Group, https://bird-group.org/who-are-bird/ (last visited Oct. 14, 2021).

4. Hydroxychloroquine

A. History of Hydroxychloroquine

Hydroxychloroquine, a less toxic derivative of a medicine named chloroquine, was first developed in 1946[191] and approved by the FDA in 1955.[192] Since that time, hydroxychloroquine has been widely used as a prophylaxis and treatment for malaria.[193] It has also "prove[n] to be effective in a number of autoimmune diseases," including systemic lupus erythematosus,[194] primary Sjögren's syndrome, and rheumatoid arthritis, and for those uses, it is often taken daily for years at a time.[195] Hydroxychloroquine's success against these autoimmune diseases "is linked to its anti-inflammatory and immunomodulatory effects."[196] Because of its versatility and efficacy, "[m]illions of hydroxychloroquine doses are prescribed annually."[197] In just the year 2019, hydroxychloroquine was prescribed over 5.4 million times in the United States alone.[198]

In 2004, long before the COVID-19 pandemic began, a lab study revealed that chloroquine is "an effective inhibitor of the replication of the severe acute respiratory syndrome coronavirus (SARS-CoV) in vitro" and thus that it should "be considered for immediate use in the prevention and treatment of SARS-CoV infections."[199] The following

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191 National Institutes of Health, COVID-19 Treatment Guidelines: Chloroquine or Hydroxychloroquine and/or Azithromycin, https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/chloroquine-or-hydroxychloroquine-and-or-azithromycin/ (last visited Oct. 14, 2021) (hereinafter, "NIH, COVID-19 and Hydroxychloroquine").

192 Georgi Fram et al., *Cardiac Complications Attributed to Hydroxychloroquine: A Systematic Review of the Literature Pre-COVID-19*, 17 Current Cardiology Reviews 389, 389 (2021), *available at* https://www.eurekaselect.com/186876/article (last visited Oct. 14, 2021).

193 *Id.*

194 Claudio Ponticelli & Gabriella Moroni, *Hydroxychloroquine in systemic lupus erythematosus (SLE)*, 16 Expert Opinion on Drug Safety 411, 411 (2017), *available at* https://www.tandfonline.com/doi/full/10.1080/14740338.2017.1269168?scroll=top&needAccess=true (last visited Oct. 14, 2021).

195 Eliise Laura Nirk et al., *Hydroxychloroquine in rheumatic autoimmune disorders and beyond*, EMBO Molecular Medicine, at 1 (Aug. 2020), *available at* https://www.embopress.org/doi/epdf/10.15252/emmm.202012476 (last visited Oct. 14, 2021).

196 *Id.*

197 Fram, *supra*, at 389.

198 ClinCalc, Hydroxychloroquine Drug Usage Statistics, United States, 2013–2019, https://clincalc.com/DrugStats/Drugs/Hydroxychloroquine (last visited Oct. 14, 2021).

199 Els Keyaerts et al., *In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine*, 323 Biochemical and Biophysical Research Communications 264, 264 (2004), *available at* https://www.sciencedirect.com/science/article/pii/S0006291X0401839X (last visited Oct. 14, 2021).

year, another paper explained that "chloroquine has strong antiviral effects on SARS-CoV infection" and "is effective in preventing the spread of SARS[-]CoV in cell culture."[200]

It is widely recognized in the medical community that hydroxychloroquine is generally safe, so safe in fact that it may be prescribed to pregnant women[201] and "children of all ages."[202] During the beginning of the pandemic, the FDA Commissioner stated that hydroxychloroquine has "a well-established safety profile" for malaria, lupus, and rheumatoid arthritis.[203] According to the CDC, hydroxychloroquine's "most common adverse reactions reported" are minor issues such as "stomach pain, nausea, vomiting, . . . headache," and "itching."[204] While the CDC recognizes that high doses, "such as those used to treat rheumatoid arthritis, have been associated with retinopathy," a serious eye condition, that side effect is "extremely unlikely" when hydroxychloroquine is used in short durations with moderate doses.[205] Notably, the CDC's guidance on hydroxychloroquine does not mention any concerns about cardiac disorders stemming from the drug.

B. Hydroxychloroquine and COVID-19

At the outset of the pandemic, researchers found—consistent with the prior studies demonstrating chloroquine's efficacy against SARS-CoV—that hydroxychloroquine "can efficiently inhibit SARS-CoV-2 infection in vitro."[206] These COVID-19 studies specifically

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200 Martin J. Vincent et al., *Chloroquine is a potent inhibitor of SARS coronavirus infection and spread*, Virology Journal, at 1 (Aug. 2005), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1232869/pdf/1743-422X-2-69.pdf (last visited Oct. 14, 2021).

201 Ponticelli & Moroni, *supra*, at 411; *see also* Ewa Haładyj et al., *Antimalarials - are they effective and safe in rheumatic diseases?*. 56 Reumatologia 164, 171–72 (2018), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6052376/pdf/RU-56-33240.pdf (last visited Oct. 14, 2021) (noting that hydroxychloroquine "can be continued in the treatment of rheumatic diseases during pregnancy and lactation").

202 Centers for Disease Control and Prevention, Medicines for the Prevention of Malaria While Traveling Hydroxychloroquine (Plaquenil™), https://www.cdc.gov/malaria/resources/pdf/fsp/drugs/Hydroxychloroquine.pdf (last visited Oct. 14, 2021) (hereinafter, "CDC, Malaria Travel").

203 U.S. Food & Drug Administration, Bringing a Cancer Doctor's Perspective to FDA's Response to the COVID-19 Pandemic (Mar. 29, 2020), https://www.fda.gov/news-events/fda-voices/bringing-cancer-doctors-perspective-fdas-response-covid-19-pandemic (last visited Oct. 14, 2021) (hereinafter, "FDA, Bringing Perspective").

204 CDC, Malaria Travel, *supra*.

205 Centers for Disease Control and Prevention, Yellow Book, Chapter 4: Travel-Related Infectious Diseases – Malaria (2020), *available at* https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria#1939 (last visited Oct. 14, 2021).

206 Jia Liu et al., *Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro*, Cell Discovery, at 4 (2020), *available at* https://www.nature.com/articles/s41421-020-0156-0.pdf (last visited Oct. 14, 2021).

showed that hydroxychloroquine "can inhibit [SARS-CoV-2] virus entry, transmission[,] and replication."[207] In addition to this "antiviral activity," hydroxychloroquine also has "anti-inflammatory properties" that help regulate "pro inflammatory cytokines."[208] These characteristics—both the antiviral properties and the anti-inflammatory activity—are important countermeasures against COVID-19.

i. Hydroxychloroquine Studies and Meta-analyses

Many large observational studies suggest that hydroxychloroquine significantly reduces the risk of hospitalization and death when administered to outpatients—particularly high-risk outpatients—as part of early COVID-19 treatment. For example, the Mokhtari study "was a multicenter, population-based national retrospective-cohort investigation of 28,759 adults with mild COVID-19 seen . . . between March and September 2020 throughout Iran."[209] The data showed that "[t]he odds of hospitalization . . . reduced by 38%" and the chance of death decreased by 73% for those who took hydroxychloroquine.[210] Critically, those "effects were maintained after adjusting for age, comorbidities, and diagnostic modality," and "[n]o serious [hydroxychloroquine]-related adverse drug reactions were reported."[211]

In the same vein, the recently published Million study evaluated 10,429 "adult outpatients" in France infected with SARS-CoV-2 who were "treated early" with hydroxychloroquine plus azithromycin.[212] Only five deaths occurred among the 8,315 patients who received hydroxychloroquine plus azithromycin—a mere 0.6 per 1,000 patients—while 11 died among the 2,114 who received either no treatment or azithromycin alone—a much higher rate of 5.2 per 1,000 patients.[213] Based on these figures, the study's authors found that hydroxychloroquine "was associated with a lower risk of death, independently of age, sex[,] and epidemic period."[214] Million's team thus concluded that

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207 Jyoti Bajpai et al., *Hydroxychloroquine and COVID-19 - A narrative review*, 67 Indian Journal of Tuberculosis 147, 148 (Dec. 2020), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7836863/pdf/main.pdf (last visited Oct. 14, 2021).

208 *Id.*

209 Majid Mokhtari et al., *Clinical outcomes of patients with mild COVID-19 following treatment with hydroxychloroquine in an outpatient setting*, International Immunopharmacology, at 1 (Jul. 2021), *available at* https://www.sciencedirect.com/science/article/pii/S1567576921002721 (last visited Oct. 14, 2021).

210 *Id.*

211 *Id.*

212 Million, *supra*, at 1063.

213 *Id.* at 1066.

214 *Id.* at 1063.

"[e]arly ambulatory treatment of COVID-19" with hydroxychloroquine plus azithromycin "is associated with very low mortality" and it "improve[s] COVID-19 survival compared to other regimens."[215]

Another group of researchers assessed an elderly population living in a nursing home in the small European state of Andorra.[216] Their study included "100 COVID-19 confirmed cases" in the nursing home "from March 15 to June 5, 2020."[217] After evaluating the numbers, these researchers concluded that "[t]reatment with hydroxychloroquine and azithromycin was associated with lower mortality in these patients."[218] And "the multivariate logistic regression analysis identified hydroxychloroquine plus azithromycin treatment as an independent factor favoring survival compared with no treatment or other treatments."[219] The study also reinforced hydroxychloroquine's longstanding safety profile because "[c]ardiac monitoring was performed by electrocardiogram, and no rhythm changes were observed . . . in any patient."[220]

Added to all this, a preprint of another large observational study by Sulaiman supports the use of hydroxychloroquine as part of early COVID-19 treatment.[221] This "study took place in 238 ambulatory fever clinics in Saudi Arabia" during June 2020.[222] Of the 5,541 participating patients, 1,817 were given hydroxychloroquine, and 3,724 received only supportive care.[223] The researchers found that early hydroxychloroquine-based "therapy was associated with a lower hospital admission" of 9.4% compared to 16.6% for supportive care alone, which equated to a relative risk reduction of 43%. "Adjusting for age, gender, and major comorbid conditions, a multivariate logistic regression model" further confirmed the significant decrease in the hospitalization risk of

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215 *Id.*

216 Eva Heras et al., *COVID-19 mortality risk factors in older people in a long-term care center*, 12 European Geriatric Medicine 601, 601 (2021), *available at* https://link.springer.com/content/pdf/10.1007/s41999-020-00432-w.pdf (last visited Oct. 14, 2021).

217 *Id.*

218 *Id.*

219 *Id.* at 606.

220 *Id.* at 603.

221 Tarek Sulaiman et al., *The Effect of Early Hydroxychloroquine-based Therapy in COVID-19 Patients in Ambulatory Care Settings: A Nationwide Prospective Cohort Study*, Preprint, at 1 (2020), *available at* https://www.medrxiv.org/content/10.1101/2020.09.09.20184143v1.full.pdf (last visited Oct. 14, 2021).

222 *Id.*

223 *Id.*

patients who received hydroxychloroquine.[224] Regression analysis also demonstrated that hydroxychloroquine reduced the mortality risk by an odds ratio of .36, which equates to a threefold drop in deaths.[225] Other observational studies further suggest that hydroxychloroquine has value as an early COVID-19 treatment.[226]

We acknowledge that other studies and meta-analyses have concluded that hydroxychloroquine has little to no effect on COVID-19.[227] Yet those materials generally blur the important distinction between hydroxychloroquine's efficacy as an early treatment for mild COVID-19 in nonhospitalized patients and its efficacy as a late treatment for severe COVID-19 in hospitalized patients.[228] As explained above, COVID-19 in its early stages, which consists primarily of cold- and flu-like symptoms, is very different from severe COVID-19, which is a lower respiratory disease often accompanied by respiratory failure and multiple organ dysfunction. Thus, evidence about hydroxychloroquine's use "in inpatients[] is irrelevant with regard to the efficacy of [the drug] in early high-risk outpatient disease."[229] So even if hydroxychloroquine is not effective against severe COVID-19, that does not disprove its value as an early treatment against the disease.

The key, then, is to focus on data that assess hydroxychloroquine's effectiveness in early treatment. A prime example of that is a recently published meta-analysis that combined the Million, Mokhtari, and Sulaiman studies discussed above with two other

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224 *Id.*

225 *Id.* at 14.

226 *E.g.*, Andrew Ip et al., *Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: a multi-center observational study*, BMC Infectious Diseases (2021), *available at* https://bmcinfectdis.biomedcentral.com/track/pdf/10.1186/s12879-021-05773-w.pdf (concluding in a study of 1,274 outpatients with SARS-CoV-2 infection that "there was an association between exposure to hydroxychloroquine and a decreased rate of hospitalization from COVID-19"); Yi Su, *Efficacy of early hydroxychloroquine treatment in preventing COVID-19 pneumonia aggravation, the experience from Shanghai, China*, 14 BioScience Trends 408, 408 (2020), *available at* https://www.jstage.jst.go.jp/article/bst/14/6/14_2020.03340/_pdf/-char/en (last visited Oct. 14, 2021) (finding in a study of 616 individuals that "[t]he early use of hydroxychloroquine decreased the improvement time and the duration of COVID-19 detection in throat and stool swabs").

227 Tawanda Chivese et al., *Efficacy of chloroquine and hydroxychloroquine in treating COVID-19 infection: A meta-review of systematic reviews and an updated meta-analysis*, Travel Medicine and Infectious Disease, at 1 (Sept./Oct. 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8273040/pdf/main.pdf (last visited Oct. 14, 2021) (concluding that hydroxychloroquine is "not effective in treating COVID-19").

228 *Id.* at 3 (noting that this meta-analysis considered studies of people with "confirmed COVID-19, regardless of . . . the severity of illness").

229 Harvey A. Risch, *Early Outpatient Treatment of Symptomatic, High-Risk COVID-19 Patients That Should Be Ramped Up Immediately as Key to the Pandemic Crisis*, 189 American Journal of Epidemiology 1218, 1218 (Nov. 2020), *available at* https://academic.oup.com/aje/article/189/11/1218/5847586 (last visited Oct. 14, 2021).

outpatient studies.[230] Those five studies together included 32,124 total outpatients, and the analysis revealed that hydroxychloroquine is associated with a 69% reduction in mortality when used as an early COVID-19 treatment.[231] In addition, a few months ago, another team of researchers reviewed "nine reports of early treatment outcomes in COVID-19 nursing home patients."[232] Data from those studies revealed that "hydroxychloroquine-based multidrug regimens were associated with a statistically significant > 60% reduction in mortality."[233] And another scholar, Dr. Harvey A. Risch, Professor of Epidemiology at Yale School of Public Health, has published online a non-peer-reviewed meta-analysis of ten studies exploring hydroxychloroquine as an early COVID-19 treatment.[234] He concluded that for people receiving that treatment the odds ratio of hospitalization was .56 and the odds ratio of death was .25. In other words, his meta-analysis demonstrated that when hydroxychloroquine is administered as an early COVID-19 treatment, it can reduce the risk of death by 75%.

To be sure, these data derive from large-scale observational studies rather than RCTs, and we understand that RCTs are considered the gold standard in medicine. But for at least two reasons, we find these observational studies sufficient for our purposes. First, our role is not to set a standard for the practice of medicine. Rather, we must simply confirm whether reasonable medical evidence supports the use of hydroxychloroquine as an early COVID-19 treatment, and we determine that a collection of large-scale observational studies suffices for that purpose. Second, a seminal review of the scientific literature has revealed that "on average, there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions."[235] There is thus no basis to cast aside the observational studies demonstrating hydroxychloroquine's efficacy as an early COVID-19 treatment.

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230 Million, *supra*, at 1070.

231 *Id.*

232 Paul E. Alexander et al., *Early multidrug treatment of SARS-CoV-2 infection (COVID-19) and reduced mortality among nursing home (or outpatient/ambulatory) residents*, Medical Hypotheses, at 1 (2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8178530/pdf/main.pdf (last visited Oct. 14, 2021).

233 *Id.*

234 Harvey A. Risch, *Hydroxychloroquine in Early Treatment of High-Risk COVID-19 Outpatients: Efficacy and Safety Evidence*, at 11 (Jun. 17, 2021), *available at* https://earlycovidcare.org/wp-content/uploads/2021/09/Evidence-Brief-Risch-v6.pdf (last visited Oct. 14, 2021).

235 Andrew Anglemyer et al., *Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials*, Cochrane Database of Systematic Reviews, at 1 (2014), *available at* https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.MR000034.pub2/epdf/full (last visited Oct. 14, 2021).

We turn now to discuss the use of hydroxychloroquine as a prophylaxis, and although the data on that point seem to be smaller, there is some evidence suggesting that it might work for that purpose too. One study was a RCT of migrant workers quarantined in a large dormitory in Singapore, and it compared a group who used hydroxychloroquine as a prophylaxis to a group that received only vitamin C.[236] The hydroxychloroquine group included 432 people, and only 31 of them (7.2%) contracted COVID-19 with acute respiratory symptoms.[237] In contrast, 619 individuals were in the vitamin C group, and 69 of them (11.1%) developed COVID-19 with acute respiratory symptoms.[238] Thus, the researchers concluded that prophylaxis with hydroxychloroquine is "superior to oral vitamin C in reducing SARS-CoV-2 infection."[239] Additionally, an observational study of healthcare workers in Bulgaria found that out of 156 workers who used hydroxychloroquine as a prophylaxis, none of them presented with COVID-19 symptoms.[240] By contrast, in the group of 48 workers who did not take hydroxychloroquine, three of them developed a symptomatic case of COVID-19.[241] These results prompted the administrators at the Bulgarian Cardiac Institute to start a prophylactic strategy for their workers that "includes alternative months of [hydroxychloroquine] intake (200 mg daily) and months without therapy."[242] In addition to these studies, there are a few others, some of which suggest marginal benefits, and some of which suggest that there might not be any. We are not aware of any of these studies showing serious adverse effects from use of low-dose hydroxychloroquine as a COVID-19 prophylaxis.

We pause here to reiterate that it is not our role to resolve the debate on hydroxychloroquine's effectiveness, either as an early COVID-19 treatment or as a preventative measure. These are matters for individual healthcare providers to assess based on the available data in consultation with their patients. Our only point is that reasonable data support the use of hydroxychloroquine as an early COVID-19 treatment and as a prophylaxis, and in light of that, we cannot find clear and convincing evidence

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236 Raymond Chee Seong Seet et al., *Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: An open-label randomized trial*, 106 International Journal of Infectious Diseases 314, 314 (2021), *available at* https://www.ijidonline.com/action/showPdf?pii=S1201-9712%2821%2900345-3 (last visited Oct. 14, 2021).

237 *Id.* at 319.

238 *Id.*

239 *Id.* at 314.

240 Iana Simova et al., *Hydroxychloroquine for prophylaxis and treatment of COVID-19 in health-care workers*, New Microbes and New Infections, at 1 (Nov. 2020), *available at* https://www.sciencedirect.com/science/article/pii/S2052297520301657#! (last visited Oct. 14, 2021).

241 *Id.*

242 *Id.*

to file disciplinary actions against physicians who prescribe hydroxychloroquine for either of those purposes.

ii. Hydroxychloroquine, COVID-19, and Safety

During the pandemic, the FDA raised questions about hydroxychloroquine and adverse cardiac events.[243] These kinds of concerns prompted one group of scholars to conduct a systematic review of the hydroxychloroquine safety literature pre-COVID-19. Their review of the data indicated that people taking that medication in appropriate doses "are at very low risk of experiencing cardiac [adverse events], particularly with short term administration" of the drug.[244] The pre-COVID-19 data showed that heart issues occurred—albeit infrequently—only when patients took hydroxychloroquine in dangerously high doses or for many years on end.[245]

As to the increase of adverse cardiac events associated with COVID-19, the researchers questioned the prevalence of the problem by noting that several COVID-19 studies recorded "the use of [hydroxychloroquine] at variable doses without significant cardiac toxicity."[246] They also observed that COVID-19 itself often causes heart issues. As they explained, "[t]he underlying pathophysiology of SARS-CoV-2 contributes to cardiac complications in the population it infects, with estimates ranging from 20-40% incidence."[247] In particular, "[c]ardiac complications of cytokine storm have been well documented to involve fatal cardiac dysrhythmias and acute systolic heart failure."[248] These researchers thus concluded that "the reported increased arrhythmic events in the COVID-19 era appear to be more related with the direct inflammatory effect of the virus (myocarditis) or the concomitant administration of multiple drugs capable of prolonging QT intervals rather than to hydroxychloroquine itself."[249] They did not seem to think the medication itself had "change[d] after 70 years" of widespread use.[250]

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243 U.S. Food and Drug Administration, FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems, https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or (last visited Oct. 14, 2021).

244 Fram, *supra*, at 391.

245 *Id.* at 390–92.

246 *Id.* at 393.

247 *Id.* at 392.

248 *Id.* at 393.

249 *Id.* at 394.

250 *Id.*

Others echoed these views. Another group reviewed the relevant studies and observed that "[m]ost of the available and credible data suggest that [hydroxychloroquine] is a safe drug."[251] That includes the pre-COVID-19 data—in "decades of . . . use by rheumatologists, . . . cardiac toxicity was rarely ever seen"—as well as the COVID-19-related studies—for example, the RECOVERY trial found "no cardiotoxicity" by hydroxychloroquine.[252] Indeed, the RECOVERY trial "prove[d] that [hydroxychloroquine] did not increase cardiac complications in COVID-19 cases despite using 4 times higher dosage than that used by rheumatologists."[253] These authors also emphasized that "[m]ultiple mechanisms cause cardiac complications in patients with COVID-19 infection";[254] thus, the infection's propensity to cause "intrinsic cardiac abnormalities . . . is probably acting as a confounder."[255]

Still another set of researchers reevaluated hydroxychloroquine's safety during the pandemic. They conducted a "meta-analysis to compare the safety of [hydroxychloroquine] versus placebo" for any indication.[256] Although their "meta-analysis of RCTs found a significantly higher risk of skin pigmentation [issues] in [hydroxychloroquine] users versus placebo," they did not find any statistically significant increases in other adverse events, including "cardiac toxicity."[257]

In addition to these data tending to confirm hydroxychloroquine's safety when used in appropriate doses, a few other factors further lessen the cardiac concerns. For starters, one piece of key evidence contributing to the safety concerns surrounding hydroxychloroquine rested on admittedly fraudulent data. As discussed above, it was a study published in the Lancet on May 22, 2020.[258] That study claimed that hydroxychloroquine was "associated with . . . an increased frequency of ventricular

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251 Shivraj Padiyar & Debashish Danda, *Revisiting cardiac safety of hydroxychloroquine in rheumatological diseases during COVID-19 era: Facts and myths*, 8 European Journal of Rheumatology 100, 100 (2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8133889/pdf/ejr-8-2-100.pdf (last visited Oct. 14, 2021).

252 *Id.*

253 *Id.* at 102.

254 *Id.* at 102.

255 *Id.* at 100.

256 Khalid Eljaaly et al., *Hydroxychloroquine safety: A meta-analysis of randomized controlled trials*, Travel Medicine and Infectious Disease at 1 (Jul./Aug. 2020), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7342171/ (last visited Oct. 14, 2021).

257 *Id.*

258 Mehra, *supra.*

arrhythmias when used for treatment of COVID-19."[259] That supposed finding was so startling that "major drug trials" involving hydroxychloroquine "were immediately halted";[260] the WHO started pressuring countries like Indonesia that were widely using hydroxychloroquine to ban it;[261] and some countries—including France, Italy, and Belgium—decided to stop using it for COVID-19.[262]

The problem, however, is that the study was based on false data from a company named Surgisphere, whose founder and CEO Sapan Desai was a co-author on the published paper.[263] The data were so obviously flawed that journalists and outside researchers began raising concerns within days of the paper's publication.[264] Even the Lancet's editor in chief, Dr. Richard Horton, admitted that the paper was a "fabrication," "a monumental fraud,"[265] and "a shocking example of research misconduct in the middle of a global health emergency."[266] Approximately two weeks after its publication, the paper was retracted.[267] An article published in *The Guardian* declared that "[g]iven the seriousness of the topic and the consequences of the paper, this [was] one of the most consequential retractions in modern history."[268] Despite calls to "publish full explanations

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259 *Id.* at 1.

260 James Heathers, *The Lancet has made one of the biggest retractions in modern history. How could this happen?*, The Guardian (Jun. 5, 2020), *available at* https://www.theguardian.com/commentisfree/2020/jun/05/lancet-had-to-do-one-of-the-biggest-retractions-in-modern-history-how-could-this-happen (last visited Oct. 14, 2021).

261 Kate Lamb & Tom Allard, *Indonesia, major advocate of hydroxychloroquine, told by WHO to stop using it*, Reuters (May 26, 2020), *available at* https://www.reuters.com/article/us-health-coronavirus-indonesia-chloroqu/exclusive-indonesia-major-advocate-of-hydroxychloroquine-told-by-who-to-stop-using-it-idUSKBN23227L (last visited Oct. 14, 2021).

262 *France, Italy, Belgium act to stop use of hydroxychloroquine for COVID-19 on safety fears*, Reuters (May 27, 2020), *available at* https://www.reuters.com/article/health-coronavirus-hydroxychloroquine-fr/update-1-france-italy-belgium-act-to-stop-use-of-hydroxychloroquine-for-covid-19-on-safety-fears-idUKL1N2D911J (last visited Oct. 14, 2021).

263 Boseley & Davey, *supra*.

264 Davey, *supra*.

265 Rabin, *supra*.

266 Boseley & Davey, *supra*.

267 *Id.*

268 Heathers, *supra*.

of what happened," the Lancet has "declined to provide details regarding the retracted stud[y]."[269]

Further reducing the cardiac concerns is important information on the FDA's own website. The FDA "cautions against use of hydroxychloroquine . . . for COVID-19 *outside of the hospital setting* or a clinical trial due to risk of heart rhythm problems."[270] But the agency's referenced support for this cautionary statement concerning *nonhospitalized patients* is its "review of safety issues with the use of hydroxychloroquine . . . to treat *hospitalized patients* with COVID-19."[271] It is questionable, however, to theorize about risks to nonhospitalized patients with mild COVID-19 based on data about heart issues in hospitalized patients with severe COVID-19 because, as explained above, cardiac complications often accompany the late stages of COVID-19. The FDA's concerns thus derive from a context—using hydroxychloroquine to treat hospitalized patients—that we are not addressing in this opinion.

It is important to note that although the medical literature tends to confirm that hydroxychloroquine is a safe medication when used in appropriate doses, any concerns about heart issues, even if resting on limited evidence, are serious. Prevailing principles of informed consent likely require physicians who present patients with the option of using hydroxychloroquine for early treatment of COVID-19 to inform them about the cardiac concerns that the FDA has identified. Also, for patients who have underlying cardiac issues, physicians should carefully consider whether hydroxychloroquine is the right choice for them. Finally, physicians should pay attention to which drugs they combine with hydroxychloroquine and evaluate the potential cardiac risks of those combinations. Failure to take such precautions could result in disciplinary action.

iii. U.S. Public Health Agencies on Hydroxychloroquine

The public health agencies in the United States have addressed the topic of hydroxychloroquine and COVID-19. The NIH "recommends against" its use "for the treatment of COVID-19 in hospitalized patients . . . and in nonhospitalized patients."[272] To justify its position against hydroxychloroquine for nonhospitalized patients, the NIH relied heavily on a RCT conducted by Mitja.[273] While that study did not show great advantages in the hydroxychloroquine group, that group did have, as the NIH's own

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269 Rabin, *supra*.

270 U.S. Food and Drug Administration, FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems, https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or (last visited Oct. 14, 2021) (emphasis added).

271 *Id.* (emphasis added).

272 NIH, COVID-19 and Hydroxychloroquine, *supra*.

273 *Id.*

website reports, a slight reduction in the risk of hospitalization (7.1% risk in the control arm versus 5.9% risk in the treatment arm) and in the time to resolution of symptoms (12 days in the control arm versus 10 days in the treatment arm).[274] As for serious adverse events, more (12) were reported in the control group than the hydroxychloroquine group (8), and the researchers determined that the serious adverse events in the hydroxychloroquine group were not related to the drug.[275] Thus, this study, particularly when considered in light of the large-scale observational studies discussed above, appears to be an insufficient basis to definitively recommend against using hydroxychloroquine as an early COVID-19 treatment.

The FDA, for its part, has questioned not only hydroxychloroquine's safety, as we discussed above, but also its efficacy. The agency's position grew out of its approval and subsequent disapproval of an Emergency Use Authorization (EUA) involving hydroxychloroquine. That EUA was issued on March 28, 2020, and it authorized licensed healthcare providers to use hydroxychloroquine donated to the Strategic National Stockpile to treat patients hospitalized with COVID-19.[276] Though this EUA was necessary to authorize the use of a specific source of hydroxychloroquine for a specific purpose, it was not required to allow healthcare providers to prescribe hydroxychloroquine off-label for COVID-19. That option was already available, as our prior discussion of off-label use makes clear. When the FDA revoked the EUA a few months later, on June 15, 2020, that is when it stated its current position on hydroxychloroquine and COVID-19.[277]

In that revocation, the FDA said that it no longer "believe[s] that oral formulations of [hydroxychloroquine] . . . may be effective in treating COVID-19" or that "that the known and potential benefits of these products outweigh their known and potential risks."[278]

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274 National Institutes of Health, Table 2b. Chloroquine or Hydroxychloroquine and/or Azithromycin: Selected Clinical Data, https://www.covid19treatmentguidelines.nih.gov/tables/table-2b/ (last visited Oct. 14, 2021) (discussing Oriol Mitjà, *Hydroxychloroquine for Early Treatment of Adults With Mild Coronavirus Disease 2019: A Randomized, Controlled Trial*, Clinical Infectious Diseases (2020), *available at* https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1009/5872589 (last visited Oct. 14, 2021)).

275 *Id.* (discussing Mitjà, *supra*).

276 Letter from Denise M. Hinton, Chief Scientist, U.S. Food and Drug Administration, to Dr. Rick Bright, Director of Biomedical Advanced Research and Development Authority (BARDA), Office of Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS) (Mar. 28, 2020), *available at* https://www.fda.gov/media/136534/download (last visited Oct. 14, 2021).

277 Letter from Denise M. Hinton, Chief Scientist, U.S. Food and Drug Administration, to Gary L. Disbrow, Deputy Assistant Secretary, Director of Medical Countermeasure Programs, Biomedical Advanced Research and Development Authority (BARDA), Office of Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS) (Jun. 15, 2020), *available at* https://www.fda.gov/media/138945/download (last visited Oct. 14, 2021).

278 *Id.* at 2.

Because both the EUA and its revocation deal only with hydroxychloroquine's use in hospitalized patients, they do not address the treatment topic that we are considering in this opinion—hydroxychloroquine's use as an early COVID-19 treatment.

The FDA's EUA revocation included four justifications, none of which establishes—let alone by clear and convincing evidence—that hydroxychloroquine is ineffective as an early treatment of COVID-19. First, the FDA said that the "suggested dosing regimens . . . are unlikely to produce an antiviral effect" because they will not create sufficient "drug concentration" in the body.[279] But as the FDA's revocation itself acknowledged, hydroxychloroquine's "immunomodulatory effects," as opposed to its antiviral effects, are not "predicated on achieving [certain hydroxychloroquine] concentration[]" levels.[280] Moreover, the FDA based its views on the assumption that "free drug concentration in the plasma" are "likely to be equal to free extracellular tissue concentration."[281] But other researchers' simulations showed that hydroxychloroquine's "concentration in lung tissue was much higher than in plasma,"[282] leading them to conclude that moderate doses are "recommended to treat SARS-CoV-2 infection."[283] Thus, the FDA's pessimism about hydroxychloroquine's potential antiviral capacity is open to reasonable debate in the scientific community.

Second, the FDA wrote that "[e]arlier reports of decreased viral shedding" with hydroxychloroquine "treatment have not been consistently replicated."[284] Notice that the FDA did not say that the studies have *disproven* a reduction in viral shedding; rather, the agency recognized that the evidence was still evolving and that some studies did in fact observe a positive "impact on viral shedding."[285] This criticism, on its face, is thus insufficient to dismiss hydroxychloroquine's use as an early COVID-19 intervention. Additionally, doubts about hydroxychloroquine's effect on viral shedding question only one of the drug's many possible mechanisms of action against COVID-19. More salient

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279 U.S. Food and Drug Administration, Memorandum Explaining Basis for Revocation of Emergency Use Authorization for Emergency Use of Chloroquine Phosphate and Hydroxychloroquine Sulfate, at 1, 4, *available at* https://www.fda.gov/media/138945/download (last visited Oct. 14, 2021) (hereinafter, "FDA EUA Revocation Memo").

280 *Id.* at 4.

281 *Id.*

282 Xueting Yao et al., *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)*, Clinical Infectious Diseases, at 13 (2020), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7108130/pdf/ciaa237.pdf (last visited Oct. 14, 2021).

283 *Id.* at 2.

284 FDA EUA Revocation Memo, *supra*, at 1.

285 *Id.* at 6.

information is whether the drug is actually decreasing hospitalization and mortality rates when used as an outpatient treatment. As we discussed above, many large observational studies strongly suggest that hydroxychloroquine does in fact keep people diagnosed with COVID-19 out of the hospital and alive. That evidence is far more relevant of the drug's potential efficacy as an early COVID-19 treatment than debates about viral shedding.

Third, the FDA found it compelling that "NIH guidelines now recommend against" using hydroxychloroquine "outside of a clinical trial."[286] But as previously explained, the NIH's recommendation concerning COVID-19 outpatients does not rest on undisputed support. Thus, the NIH's guidelines should not be considered a basis upon which to ban healthcare providers from using hydroxychloroquine for COVID-19.

Fourth, the FDA stressed that "[r]ecent data from a large randomized controlled trial"—the RECOVERY trial mentioned above—"showed no evidence of benefit . . . of [hydroxychloroquine] treatment in hospitalized patients with COVID-19."[287] Yet as we have already discussed, a study about hospitalized patients does not address hydroxychloroquine's efficacy as an outpatient COVID-19 treatment. Indeed, the RECOVERY team itself reported that while its "findings indicate that hydroxychloroquine is not an effective treatment for hospitalized patients with Covid-19," it does "not address [the drug's] use as prophylaxis or in patients with less severe SARS-CoV-2 infection managed in the community."[288] In sum, none of the FDA's four reasons, in isolation or taken together, clearly establish that hydroxychloroquine is ineffective as an early treatment against COVID-19.

Despite raising doubts about hydroxychloroquine's use against COVID-19, the FDA has consistently affirmed that healthcare providers retain the right to use hydroxychloroquine as a part of early COVID-19 treatment. At least four statements demonstrate this.

First, the FDA's current website says (and has said since July 2020) that "[i]f a healthcare professional is considering use of hydroxychloroquine or chloroquine to treat or prevent COVID-19, FDA recommends checking www.clinicaltrials.gov for a suitable clinical trial and consider enrolling the patient." This plainly assumes that healthcare providers have the right to use hydroxychloroquine to treat COVID-19.

Second, on May 29, 2020, then-FDA Commissioner Stephen Hahn acknowledged that "[m]any physicians have . . . prescribed [hydroxychloroquine] for patients with COVID-19 based on an individual assessment of the potential benefits versus the risks

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286 *Id.* at 1.

287 *Id.*

288 RECOVERY Collaborative Group, *Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19*, 383 The New England Journal of Medicine 2030, 2038 (Nov. 2020), *available at* https://www.nejm.org/doi/pdf/10.1056/NEJMoa2022926?articleTools=true (last visited Oct. 14, 2021).

for an individual patient."[289] He added that "[p]rescribing a product for uses not specifically included in the official labeling is common in the practice of medicine" and that the FDA does not "prohibit[] physicians from prescribing medications" because the agency does "not regulate the practice of medicine."[290] These statements are still posted on the FDA's website, and we are not aware of any subsequent FDA statements revoking them.

Third, in June 2020, after the FDA revoked the hydroxychloroquine EUA, Health and Human Services Secretary Alex Azar said: "At this point, hydroxychloroquine and chloroquine are just like any other approved drug in the United States. They may be used in hospital, they may be used in out-patient, they may be used at home—all subject to a doctor's prescription."[291] Leaving no doubt about this point, Secretary Azar added that "[i]f a doctor wishes to prescribe [hydroxychloroquine], working with a patient, they may prescribe it for any purpose that they wish."[292] We are not aware of any subsequent statement revoking this guidance.

Fourth, in late July 2020, then-FDA Commissioner Hahn reiterated that "whether people should take hydroxychloroquine as a treatment" for COVID-19 is a decision that "should be made between a doctor and a patient."[293] He specifically stated: "A doctor and a patient need to assess the data that's out there, FDA does not regulate the practice of medicine, and that in the privacy of the doctor-patient relationship is where that decision should be made."[294]

iv. Foreign Public Health Agencies, Professional Associations, and Physicians on Hydroxychloroquine

The WHO "recommend[s] against administering hydroxychloroquine . . . for treatment of COVID-19" for "patients with any disease severity and any duration of symptoms."[295] It reached this recommendation after concluding that hydroxychloroquine

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289 FDA, Bringing Perspective, *supra*.

290 *Id.*

291 Trump White House Archives, Remarks by President Trump in Roundtable Discussion on Fighting for America's Seniors (Jun. 15, 2020), *available at* https://trumpwhitehouse.archives.gov/briefings-statements/remarks-president-trump-roundtable-discussion-fighting-americas-seniors/ (last visited Oct. 14, 2021).

292 *Id.*

293 Tal Axelrod, *FDA chief: Hydroxychloroquine use a decision between doctor and patient*, The Hill (Jul. 30, 2020), https://thehill.com/policy/healthcare/509733-fda-chief-hydroxychloroquine-use-a-decision-between-doctor-and-patient?rl=1 (last visited Oct. 14, 2021).

294 *Id.*

295 WHO COVID-19 Guidelines, *supra*, at 26.

"probably do[es] not reduce mortality" and that its "effect on . . . admission to hospital . . . remains uncertain."[296] To the extent that this recommendation purports to address hydroxychloroquine's effectiveness as an early treatment for COVID-19, it arguably rests on weak evidence. Although it is difficult to determine how many of the studied individuals were outpatients, it appears that most were hospitalized. For instance, the WHO says that it consulted 29 studies in concluding that "[h]ydroxychloroquine probably does not reduce mortality," but the only study specifically cited is the RECOVERY trial,[297] which, as we already indicated, included only patients hospitalized with COVID-19.[298] In addition, the WHO's statistics on hospitalization rates, which consisted of one RCT that included 465 outpatients, suggests hydroxychloroquine's efficacy.[299] That trial revealed a hospitalization rate of 47 per 1,000 people in the control group but only 19 of 1,000 people in the hydroxychloroquine arm.[300] It thus seems as if the WHO may have overreached in definitively declaring that hydroxychloroquine holds no promise as an early COVID-19 treatment.

The WHO also "recommend[s] against administering hydroxychloroquine prophylaxis to individuals who do not have COVID-19" because it believes that prophylaxis "hydroxychloroquine has a small or no effect on death and hospital admission" and that it "probably has a small or no effect on laboratory-confirmed COVID-19."[301] Disagreeing with this, the team of researchers conducting the COPCOV trial on prophylaxis hydroxychloroquine has announced that the WHO's conclusions are "scientifically unsound."[302] In their statement on this topic, the COPCOV team explained that the available RCTs "suggest substantial uncertainty as to the benefit of hydroxychloroquine in preventing COVID-19," but the "overall trend [is] towards benefit."[303]

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296 *Id.* at 27.

297 *Id.* at 28.

298 RECOVERY Collaborative Group, *supra*, at 2030.

299 WHO COVID-19 Guidelines, *supra*, at 29.

300 *Id.*

301 World Health Organization, WHO Living guideline: Drugs to prevent COVID-19, at 12 (Mar. 2, 2021), *available at* https://apps.who.int/iris/bitstream/handle/10665/339877/WHO-2019-nCoV-prophylaxes-2021.1-eng.pdf?sequence=13&isAllowed=y (last visited Oct. 14, 2021).

302 The COPCOV Trial's position statement on "A living WHO guideline on drugs to prevent COVID-19," MORU Tropical Health Network (Mar. 5, 2021), https://www.tropmedres.ac/news/copcov-response-to-latest-who-guidelines-on-hydroxychloroquine-for-covid-19-trials-1 (last visited Oct. 14, 2021).

303 *Id.*

As for the professional associations' and physician groups' views on hydroxychloroquine, it appears that they generally adopt the same position they took on ivermectin. Those like the AAPS that support ivermectin as an option for early COVID-19 treatment generally support hydroxychloroquine too, while those like the AMA, APhA, and ASHP that oppose one typically resist the other. Additionally, many physician groups use early COVID-19 treatment protocols that include hydroxychloroquine. For example, an article co-authored by over 50 doctors in Reviews in Cardiovascular Medicine outlines an early treatment protocol that includes hydroxychloroquine as a key component.[304]

Considering the evidence discussed above, we do not find that clear and convincing evidence would warrant disciplining physicians who prescribe hydroxychloroquine for the prevention or early treatment of COVID-19 after first obtaining informed patient consent.

CONCLUSION

Based on the available data, we do not find clear and convincing evidence that a physician who first obtains informed consent and then utilizes ivermectin or hydroxychloroquine for COVID-19 violates the UCA. This conclusion is subject to the limits noted throughout this opinion. Foremost among them are that if physicians who prescribe ivermectin or hydroxychloroquine neglect to obtain informed consent, deceive their patients, prescribe excessively high doses, fail to check for contraindications, or engage in other misconduct, they might be subject to discipline, no less than they would be in any other context.

As we have stressed throughout, this opinion is based only on the data and information available at this time. If the relevant medical evidence materially changes, that could impact our conclusions. Also, though an opinion from our office about possible UCA violations would ordinarily focus on healthcare practices within Nebraska, the context of a global pandemic necessitates looking for evidence far beyond our State's borders, as we have done here. Thus, the analytical roadmap in this opinion likely has limited application outside the circumstance of a global pandemic.

We emphasize in closing that our office is not recommending any specific treatments for COVID-19. That is not our role. There are multiple treatment options outside the scope of this opinion—including treatments that have been officially approved by the FDA—that physicians and their patients should carefully consider. This opinion takes no position on them. Rather, we address only the off-label early treatment options discussed in this opinion and conclude that the available evidence suggests that they might work for some people. Allowing physicians to consider these early treatments will free them to evaluate additional tools that could save lives, keep patients out of the hospital, and provide relief for our already strained healthcare system.

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304 McCullough, *Multifaceted*, *supra*, at 522-23.

Very truly yours,

DOUGLAS J. PETERSON
Attorney General

James A. Campbell
Solicitor General

Mindy L. Lester
Assistant Attorney General

Approved by:

Attorney General

COLORADO
Department of
Regulatory Agencies
Division of Professions and Occupations

PERSONAL AND CONFIDENTIAL

January 3, 2022

Dr. Rae Ann Weber
[redacted]

RE: License Number: DR. 0051917
Case Number: 2021-8097- Panel B

Dear Dr. Weber:

The Colorado Medical Board ("Board") has received information from you that implicates your conduct as a licensed physician, more specifically, a possible violation of the Medical Practice Act. Based on the information, the Board has made the determination to open a matter against your license and investigate. The first step in this process is to obtain your response to the questions identified below. At this point, no assumption has been made about the truth or validity of any information provided to the Board. Please provide a written response to the questions below:

1. Provide a list of all patients for whom you have provided treatment for COVID19 in Colorado, along with copies of their medical records.
2. Provide a list of COVID19 patients with COVID19 to whom you have prescribed either Ivermectin or Hydroxychloroquine, along with copies of their medical records.
3. Discuss your current process and practices for evaluating and treating patients with COVID19.
4. Identify and discuss any public communications that you have made in your capacity as a physician regarding masking, vaccinations, or treatment of patients with COVID19.
5. Please feel free to include any other information you feel is pertinent to the investigation of this matter.

Please provide a written response **within thirty days of the date of this letter**. An earlier response may expedite the Board's review of this matter. To facilitate an efficient and timely review, please type your response. If this is not possible, please legibly print your response. Also, please be sure that any copies submitted with your response are legible. Be sure to include the case number listed above on all correspondence.

We encourage you to respond electronically. If you do so, please submit the response to dora_medicalboard@state.co.us.

It is the policy of the Board to copy your attorney on all correspondence in order to assure that your attorney is aware of developments in your case. If you are represented by an attorney in this matter, please provide your attorney's contact information to the Board in writing. If the Board already has your attorney's contact information, your attorney's name should be identified below as a carbon copy or "cc," indicating that a copy of this letter was sent to that attorney. If at any time it appears that the Board does not have the correct information regarding your legal representation, please update the Board and provide your attorney with a copy of all correspondence from the Board.

We strongly encourage you to begin preparing your response to the complaint as soon as possible, as extensions to the thirty-day response time will not be granted except in very limited circumstances. Additionally, if you choose to be represented by an attorney, please contact him or her immediately. A delay in doing so will not be grounds for an extension.

The Medical Practice Act requires you to respond to this letter. Please be aware that the failure to respond in a materially factual and timely manner may constitute grounds for disciplinary action against your license pursuant to section 12-240-125(4)(a)(I), C.R.S. Please be advised that no reminder letters or other notices will be sent to you regarding this matter.

Following receipt of your response, the Board will review the complaint and your response thereto. The Board will then determine what further action, if any, is warranted. Please note you will be advised in writing of the Board's disposition of this complaint.

Healthcare Professions Profile Program (HPPP) requirements: Pursuant to section 12-30-102, C.R.S, your Healthcare Professions Profile must be updated within 30 days of any reportable event. To ensure compliance, you must regularly review and update your profile. Failure to comply with HPPP requirements may result in an administrative fine of up to $5,000, a hold on license renewal and possible disciplinary action. To access your profile, go to www.colorado.gov/dora/hppp and click the "Create/Update a Profile" link. For any questions, please contact dora_dpo_hppp@state.co.us.

Thank you for your cooperation and prompt attention to this matter.

Sincerely,

FOR THE COLORADO MEDICAL BOARD

Paula E. Martinez

Paula E. Martinez
Program Director
Paula.martinez@state.co.us

cc: Lisanne Leasure