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To dispense or not to dispense: Lessons to be learnt from ethical challenges faced by pharmacists in the COVID-19 pandemic

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Abstract

The year 2020 is facing one of the worst public health situations in decades. The world is experiencing a pandemic that has triggered significant challenges to health-care systems in both high and low-middle income countries (LMICs). Government policymakers and healthcare personnel are experiencing real-life ethical dilemmas and are pressed to respond to these situations. Many possible treatments are being investigated, one of which is the use of hydroxychloroquine or chloroquine. These drugs are approved for use by patients with systemic lupus erythematosus (SLE), rheumatoid arthritis, and malaria. The demand for these products has increased, and the stocks are depleting for the patient population for whom the drugs are intended initially. Although both innovator and generic pharmaceutical manufacturers are making plans for increased production, there are challenges with global supply chains disruption and the retention of supplies for local markets. This may cause countries that rely on the importation of pharmaceuticals to be out of stock of supplies for an extended period. There are allegations of off-label prescribing and hoarding. Pharmacists are the custodians and dispensers of medications and are faced with the task of assessing prescriptions and making decisions about the allocation of these products. This paper seeks to 1) highlight some of the ethical challenges of dispensing hydroxychloroquine by pharmacists during the COVID-19 pandemic, 2) identify some of the responses to these issues from various regulatory authorities in the USA, and 3) recommend approaches to assist pharmacists in their decision-making process, especially in LMICs.

KEYWORDS

COVID-19 pandemic, pharmacist, hydroxychloroquine, off-label, ethical challenges, moral distress

1 | INTRODUCTION

On March 11, 2020, the Director-General of the World Health Organisation (WHO) declared that COVID-19, the illness caused by the virus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was officially a pandemic.[1] At the time of writing this paper, there are over 190 countries affected across the globe. COVID-19 has created a healthcare crisis, unlike any other many have seen in a lifetime.[2] Globally, there are over 1900 studies registered on Clinicaltrials.gov, demonstrating that researchers are seeking to develop evidence-based effective treatment modalities.[3] Some established drugs are being explored, four of which are being compared to standard treatment in the World Health Organisation (WHO), global clinical trial endeavor called "solidarity." These are 1) remdesivir, 2) lopinavir/ritonavir, 3) lopinavir/ritonavir with interferon beta-1a, and 4) hydroxychloroquine or chloroquine.[4] The promotion of hydroxychloroquine as a possible treatment for COVID-19 has been controversial and created challenges for Lupus patients, pharmaceutical manufacturers, and healthcare professionals globally.[5] In early March 2020, preliminary data indicating that hydroxychloroquine showed promise in treating COVID-19 was released in preprints and then circulated widely on various media platforms.[6] This abetted widespread prescribing and dispensing of the drug and the initiation of multi-country clinical trials, including the solidarity trials. Regulatory bodies such as the US Food and Drug Administration (FDA) as well as the European Union's Medicine Agency (EMA) issued emergency approval for its use in clinical trials and hospitalized patients.[7,8] The preliminary data were from researchers in China and France, who reported possible benefits of using hydroxychloroquine/chloroquine in COVID-19 patients.[9] Subsequent trials, however, have yielded preliminary results that indicate the drugs did not benefit COVID-19 patients, but may, in fact, cause harm.[10] One of these studies, an observational study based on the health records of almost 100,000 patients around the world and published in the Lancet recently,[11] indicated that hydroxychloroquine had a sharply higher risk of death and heart problems in patients compared to those who did not receive the drug and that it did not provide a benefit. This study was, however, retracted by the authors on June 4, 2020 due to doubts about the veracity of the data used and the analyses conducted.[12] Another study with healthy individuals, published in the New England Journal of Medicine on June 3, 2020 found that taking hydroxychloroquine after high-risk or moderate-risk exposure to SARS-CoV-2 did not prevent illness.[13]

Prior to the emergency approval, community pharmacists observed a surge in prescriptions for hydroxychloroquine resulting in shortages in both high and low-middle income countries (LMIC).[14,15,16] To further complicate the matter, one of the largest generic suppliers of hydroxychloroquine to LMICs, India, decided to put an export ban on the product, which they withdrew shortly after, but this created a disruption in the global supply chain, particularly affecting LMICs.[17] The experience of dispensing hydroxychloroquine for the treatment of COVID-19 highlighted ethical issues that may have generated moral distress among some pharmacists due to the uncertainties regarding the drug. Some pharmacists may not wish to dispense, while others support "a right to try" even in the outpatient

[1] Ducharme, J. (2020). The WHO Just Declared Coronavirus COVID-19 a Pandemic | Time. Retrieved March 31, 2020, from https://time.com/5791661/who-coronavirus-pandemic-declaration/.

[2] Russell, P., & Locke, T. (2020). PM: COVID-19 "Worst Public Health Crisis in a Generation." Retrieved April 6, 2020, from : https://www.medscape.com/viewarticle/926710.

[3] US National Library of Medicine. (2020). COVID-19 - List Results - ClinicalTrials.gov. Retrieved May 7, 2020, from https://clinicaltrials.gov/ct2/results?cond=COVID-19%26term=%26cntry=%26state=%26city=%26dist=%26Search=Search.

[4] WHO. (2020). Solidarity clinical trial for COVID-19 treatments. Retrieved May 7, 2020, from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.

[5] Boseley, S. (2020, March 27). Vital drug for people with lupus running out after unproven Covid-19 link. The Guardian. Retrieved July 25, 2020, from https://www.theguardian.com/world/2020/mar/27/vital-drug-people-lupus-coronavirus-covid-19-link-hydroxychloroquine.

[6] Gautret, P., Lagier, J. C., Parola, P., et al., D. (2020). Hydroxychloroquine and Azithromycin as a treatment of COVID-19: preliminary results of an open-label non-randomized clinical trial. MedRxiv, 2020.03.16.20037135. https://doi.org/10.1101/2020.03.16.20037135.

[7] European Medicines Agency. (2020). COVID-19: chloroquine and hydroxychloroquine only to be used in clinical trials or emergency use programmes.. Retrieved April 1, 2020, from https://www.ema.europa.eu/en/news/covid-19-chloroquine-hydroxychloroquine-only-be-used-clinical-trials-emergency-use-programmes.

[8] Rowland, C. (2020, March 30). FDA authorizes emergency use of unapproved drugs to treat coronavirus. The Washington Post. Retrieved July 25, 2020, from https://www.washingtonpost.com/business/2020/03/30/coronavirus-drugs-hydroxychloroquin-chloroquine/.

[9] Wong, J. (2020, April 24). Hydroxychloroquine and coronavirus: a guide to the scientific studies so far. The Guardian. Retrieved July 25, 2020, from https://www.theguardian.com/world/2020/apr/22/hydroxychloroquine-coronavirus-scientific-studies-research.

[10] Ibid.

[11] Mehra, M.R., Desai, S.S., Ruschitzka, F., and Patel, A.N. (2020). Hydroxychloroquine or chloroquine with or without macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. https://doi.org/10.1016/s0140-6736(20)31180-6.

[12] Mehra, M.R., Ruschitzka, F., and Patel, A.N. (2020). Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. https://doi.org/10.1016/s0140-6736(20)31324.

[13] Boulware, D.R., Pullen, M.F., Bangdiwala, A.S., et al. (2020). A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. New England Journal of Medicine. https://doi.org/10.1056/nejmoa2016638.

[14] Bebinger, M. (2020). Hydroxychloroquine May Not Work Against COVID-19, But Hoarding's Already A Problem : Shots. NPR. Retrieved July 25, 2020, from https://www.npr.org/sections/health-shots/2020/03/23/820228658/why-hoarding-of-hydroxychloroquine-needs-to-stop.

[15] Boseley, op. cit. note 5.

[16] Hibbert, K. (2020, April 5). COVID-19 demand makes lupus drug scarce. Jamaica Observer. Retrieved July 25, 2020 from http://www.jamaicaobserver.com/news/covid-19-demand-makes-lupus-drug-scarce_191388?profile=1373.

[17] Cortez, M., Che, C., Altstedter, A., Shrivastava, B., Lyu, D., & Gale, J. (2020, March 25). Global Rush for Trump-Backed Virus Drug Sparks India Export Ban. Bloomberg News. Retrieved July 25, 2020 from https://www.bloomberg.com/news/articles/2020-03-25/india-bans-exports-of-trump-backed-virus-drug-as-demand-surges.

setting.[18,19] The initial outcry regarding hydroxychloroquine by pharmacists was due to concerns regarding 1) shortage of medication for regular patients suffering from serious chronic diseases such as systemic lupus erythematosus (SLE), malaria and rheumatoid arthritis (RA), 2) misuse and hoarding of drugs through physician prescribing for self and loved ones, and 3) prescribing in response to patient demand.[20,21,22] However, in late March, 2020, the US National Community Pharmacy Association (NCPA)'s survey indicated that despite the shortage and challenges faced by Lupus patients, 84% of community pharmacists believed the drug should be dispensed for the off-label use once the patient is under the physician's care.[23] The International Pharmaceutical Federation's (FIP) Code of Ethics states that "*the pharmacist is recognized as the expert on medicines. Pharmacists are given the responsibility, within the overall health system, to help people to maintain good health, to avoid ill health and, where medication is appropriate, to promote the responsible use of medicines*.[24] In this current crisis, the pharmacist- the custodian of medicines-, regarding responsible use (dispensing) of medicines becomes paramount. When confronted with this kind of scenario, for those pharmacists who wish to refuse to dispense, this creates a kind of moral distress due to the plethora of questions ruminating in his/her mind within a limited time constraint. These questions include whether a pharmacist has the right to refuse to dispense based on perceived misuse? If yes, on what grounds. If no, how does she/he dispense against her/his better professional judgement? What will be the consequences of refusal? How will her/his refusal affect the relationship with the physician, the patient, and the business? To adequately respond to these questions of an ethico-legal nature, the pharmacist must be guided by law, professional Codes of Ethics, and an evidence-based standard of practice. This paper will address the concerns by examining recent policies, position statements, and responses of professional boards and associations, drug regulatory agencies, and the application of ethical principles to assist pharmacists in their decision-making process.

2 | RESPONSIBLE USE – A REVIEW OF US BOARDS OF PHARMACY RESPONSES

The pursuit of the right medicine for the treatment of any disease is hinged on the core ethical principles of beneficence (acting to benefit), non-maleficence (avoiding/minimising harm), and respecting patients' autonomy. It is for these reasons; that there are systems in place to regulate drug development governed by various legislations and guidelines. The results of carefully vetted clinical research to verify the efficacy and safety of a drug before it is made publicly available for an approved condition is the foundation of evidence-based clinical practice. An approved drug is a drug that has undergone all the processes to receive approval for indications by a competent regulatory authority. Hydroxychloroquine is still under investigation in various clinical trials to establish efficacy and safety profiles. The use of the drug in the treatment of COVID-19, would either be based on emergency use in a hospital setting/clinical trial or off-label use in the community/retail pharmacy setting.[25] The crux of having regulatory systems for pharmaceuticals from development to being accessed by patients is based on the fundamental ethical principles of maximizing benefits and minimizing harm. This controlled approach for drugs is explained by the WHO as the responsible use of medicines. The "*…responsible use of medicines' implies that the activities, capabilities and existing resources of health system stakeholders are aligned to ensure patients receive the right medicines at the right time, use them appropriately, and benefit from them*".[26] The alignment of all stakeholders is crucial to address this situation. Although the FDA and the EMA issued statements and advisories 1) restricting the prescribing and dispensing of

[18] In the health care ethics literature the concept of 'moral distress' covers situations in which it is impossible to do the right thing and situations where it is possible to do the right thing but costly for the agent, and often emphasizes actions guiding recommendations about to find moral compromises. For this concept, see e.g. Rushton, C., and A. Carse. (2016). Towards a New Narrative of Moral Distress: Realizing the Potential of Resilience. The Journal of Clinical Ethics. 27, no. 3: 214-8; Campbell, S.M., Ulrich, C.M., & Grady, C. A. (2016). Broader Understanding of Moral Distress. The American Journal of Bioethics. 16;12; 2-9; and Ulrich, C.M., & Grady, C. (2018). Moral Distress in the Health Professions. Dordrecht: Springer. In the last paragraph, I will discuss the relevance of this concept for pharmacists.

[19] Volansky, R. (2020). Rheumatologists, pharmacists' debate "right to try" hydroxychloroquine for COVID-19. Retrieved May 7, 2020, from https://www.healio.com/rheumatology/lupus/news/online/%7B3cc706de-0e7e-4433-956b-0b778af95d91%7D/rheumatologists-pharmacists-debate-right-to-try-hydroxychloroquine-for-covid-19.

[20] Bebinger, op. cit. note 14.

[21] Boseley, op. cit. note 5.

[22] Lupkin, S. (2020). Malaria Drugs Get FDA "Emergency Use Authorization" For COVID-19 : Coronavirus Live Updates : NPR. Retrieved April 1, 2020, from https://www.npr.org/sections/coronavirus-live-updates/2020/03/30/823987540/fda-oks-addition-to-stockpile-of-malaria-drugs-for-covid-19.

[23] Murphy, J. (2020). NCPA Survey Finds 84% of Local Pharmacists Say Patients Should Have Access to COVID-19 Treatments. Pharmacy Times. Retrieved June 4, 2020, from https://www.pharmacytimes.com/ajax/ncpa-survey-finds-84-of-local-pharmacists-say-patients-should-have-access-to-covid-19-treatments.

[24] FIP. (2014). FIP STATEMENT OF PROFESSIONAL STANDARDS Codes of ethics for pharmacists. Retrieved July 25, 2020, from www.fip.org/statements.

[25] Off label use is defined as the unapproved use of an approved medication that is "situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information". Lenk, C., & Duttge, G. (2014). Ethical and legal framework and regulation for off-label use: European perspective. Therapeutics and clinical risk management, 10, 537–546. https://doi.org/10.2147/tcrm.s40232. Off-label differs from emergency use which is the authorization of a product(s) "*…to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by a chemical, biological, radiological or nuclear (CBRN) agent when there are no adequate, approved, and available alternatives*." This occurs during public health emergencies such as the current pandemic. The regulatory authority stipulates the conditions for emergency use e.g. in clinical trials or hospitals only. Finally, compassionate use is the use of a drug that is still in developmental stage but permission is granted by the regulatory authority for use by a patient outside of a clinical trial. This is for life-threatening situations outside of the context of a public health emergency but on an evaluated case by case basis. See: American Cancer Society. (2020). Compassionate Drug Use. Retrieved June 10, 2020, from https://www.cancer.org/treatment/treatments-and-side-effects/clinical-trials/compassionate-drug-use.html, and FDA. (2017). Emergency Use Authorization of Medical Products and Related Authorities. Retrieved June 10, 2020, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities.

[26] WHO. (2012). The Pursuit of Responsible Use of Medicines: Sharing and Learning from Country Experiences The benefits of responsible use of medicines: Setting policies for better and cost-effective health care. Retrieved July 25, 2020, from www.who.int.

hydroxychloroquine to clinical trials and hospitalized patients, 2) concerning the potential side-effects, and 3) cautioning against outpatient use, these statements do not explicitly prohibit clinicians from practicing off-label prescribing within the outpatient setting or pharmacists from dispensing.[27,28] Some prescribers and pharmacists are of the opinion that patients have a right to try these drugs while others are concerned about shortages. To address this conundrum, 39 US Boards of Pharmacy issued directives to pharmacists instructing them 1) to use professional judgement, 2) limit quantities of drugs sold, and 3) to verify diagnosis before dispensing. Twenty-four Us Boards of Pharmacy explicitly requested that doctors indicate a diagnosis on the prescriptions with supporting evidence, 9 instructed the pharmacists to refuse to dispense, and 10 issued precautionary statements but left the decision to the pharmacist.[29] A joint statement issued by the American Medical Association, the American Pharmacists Association, and the American Society of Health-System Pharmacists supports the position that while off-label prescribing remains a part of the established practice, the prescribing of a medication must be for "legitimate medical reasons" that is based on "evidence-based science".[30] The statement further supported the right of the pharmacist to make queries to establish the appropriate use of prescribed medicine".[31] However, the state to state regulatory positions on whether to dispense hydroxychloroquine were inconsistent. While some of the US Boards of Pharmacy clearly forbid the use of hydroxychloroquine/chloroquine in the treatment of COVID-19, there were some who indicated conditions for dispensing while some noted that this is the remit of the prescriber, pharmacist and patients. The National Community Pharmacy Association notes "that the decision to use hydroxychloroquine was a clinical one and not a regulatory one[32]." North Carolina Pharmacy board notes:

> Pharmacists are reminded of their capacity to refuse to fill prescriptions that, in the pharmacist's professional judgment, are not clinically appropriate. And exercising that professional
>
> judgment may include setting reasonable policies designed to ensure that prescription drugs are
>
> available for all patients, including by use of partial fills of limited days' supply and otherwise
>
> ensuring that patients taking these medications for established, and approved, indications do
>
> not have their drug therapy interrupted.[33]

However, other boards such as the Board of Pharmacy in Indiana warned against interpreting the advisory as a right to refuse but that pharmacists should exercise caution: The advisory states:

> The **Board is not recommending that pharmacies refuse to fill**, the Board is recommending that pharmacies use caution. While both Boards are recommending caution, licensees should avoid interruptions in care for patients previously established on these medications with an appropriate medical diagnosis. The Boards recognize this may be a difficult balance; however, licensees should make a good faith effort to ensure appropriate prescribing, dispensing, and patient care.[34]

Hence the moral conundrum of to dispense or not dispense continues.

3 | A RIGHT TO TRY VERSUS A RIGHT TO REFUSE

Clinical practice remains the remit of the clinician, and when a drug is prescribed by a clinician, it is usually based on the premise that the clinician is acting in the best interests of the patient. Off-label use of medication is widely practiced globally. Drugs that do not have regulatory approval for a medical indication are prescribed. In an ideal scenario, it is expected that the clinician would have discussed with the patient the reason for the off-label prescribing and obtained the consent of that patient to proceed. The clinician would then manage his/her patient to verify the outcome. Usually, off-label prescribing does not create a challenge to the extent that it contributes to a global shortage, as with the COVID-19 situation. If the off-label prescribing/dispensing related to hydroxychloroquine takes place outside the conditions stipulated by the regulatory authorities, it requires serious consideration of what are and should be the role and ethical obligations of pharmacists in the responsible use of hydroxychloroquine. Some USA healthcare personnel, including pharmacists, have argued that the patients have a right to try off-label prescribed medications. However, this argument ought to be

[27] FDA. (2020). 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 | FDA. Retrieved May 7, 2020, from https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or.

[28] EMA. op. cit. note 7.

[29] National Alliance of State Pharmacy Associations. (2020). COVID-19: Hydroxychloroquine, Chloroquine, and Azithromycin. Retrieved May 7, 2020, from https://naspa.us/resource/hydroxychloroquine-chloroquine-and-azithromycin/.

[30] American Medical Association. (2020). Joint statement of the American Medical Association, American Pharmacists Association and American Society of Health-System Pharmacists. Retrieved July 25, 2020, from https://www.ama-assn.org/delivering-care/public-health/joint-statement-ordering-prescribing-or-dispensing-covid-19.

[31] Ibid.

[32] Murphy, op. cit. note 23.

[33] American Medical Association. (2020). Boards of pharmacy and other actions relating to COVID-19 prescribing. Select resources and other information. Retrieved July 25, 2020, from https://www.ama-assn.org/system/files/2020-04/board-of-pharmacy-covid-19-prescribing.pdf.

[34] Ibid.

dismissed for the following reason. The USA passed a "right to try" law in 2018 to provide non-FDA approved access to experimental drugs for treating patients with life-threatening conditions. These persons are usually not able to access the drugs through clinical trials and would have already exhausted all available treatment. The patient would have to give written consent that he/she is aware of the risks involved.[35,36] Since hydroxychloroquine was given emergency use approval for the seriously ill COVID-19 patient in a hospital setting, the reasonable decision for the community pharmacist to make would be to refuse to dispense as the patient that would ordinarily meet the "right to try" criteria should have access in the hospital. The real challenge, therefore, is the use of the drug prophylactically or to treat persons with mild-moderate COVID-19 symptoms, which can be managed at home. Therefore, any use of hydroxychloroquine in the community setting can be reasonably assumed to be for regular patients or off-label for COVID-19 patients who are not critically ill.

When a prescription is reviewed by a pharmacist, unless the physician notes the medical indication, the use of drugs would be left to speculation until additional steps are taken to confirm a diagnosis. In many countries, the writing of the diagnosis on the prescription is not common practice, although it is one that has been lobbied for by pharmacists but resisted by physicians. Indication-based prescriptions have many benefits, such as improving healthcare team communication, medication safety, and facilitate medication reconciliation.[37] In the context of COVID-19, the enforcement of writing the medical indication supported by a positive test by the US boards of pharmacy empowered community pharmacists to assess prescriptions completely before deciding to dispense. Additionally, some of the boards restricted the off-label prescribing for COVID-19 to infectious disease specialists.[38] The International Pharmaceutical Federation (FIP) Code of Ethics states that a pharmacist should:

> cooperate and collaborate with colleagues, other health professionals, consumers, patients, carers and other actors in the healthcare delivery system to ensure that the best possible quality of healthcare is provided both to individuals and the community at large, while always considering the limitations of available resources and the principles of equity and justice.[39]

Contemplating this obligation, to achieve equity and justice, the pharmacist may need to apply a risk-benefit assessment to help guide in the decision-making process.[40] There are several possible risks in this situation: 1) perceived risk of harm by preventing the SARS-CoV-2 positive patient from receiving medicine that could improve health, 2) perceived risk of harm to the SARS-CoV-2 positive patient due to adverse effects from an unproven medicine, and 3) potential risk of harm to the patients with SLE and RA who cannot access their usual medicines because of shortages. The potential benefits would be the respective patient groups accessing the medications and overall improvement of health. If the first risk is considered plausible and the pharmacist decides to cooperate with the physician and dispense to the COVID-19 patient, one can assert that the pharmacist assumes a beneficent role, which is a duty to support the treatment decision of the physician by dispensing the medicine to the patient.[41] In this context, the duty would be to dispense, albeit off-label.[42] However, as noted earlier, in a situation of scarcity, fulfilling the preceding duty could cause harm to another patient group, the SLE/RA patients. In assessing this potential risk, the pharmacist assumes a non-maleficent role, a duty to avoid harm.[43] This duty would be relevant to both patient groups, and since the pharmacist must decide between the two, another ethical principle may be applied, that is, justice. Justice is the fair distributions of benefits and burdens. This ethical principle may tip the scale in favour of the SLE/RA patients. The reasons are 1) the drugs are approved for these conditions (legal support), 2) the adverse effects for these patient groups are documented and known, and 3) the patients are already on these medicines. It would be unfair to deprive a patient group of a drug that was approved for them in favour of a medical condition for which the risk/benefit ratio is under investigation due to genuine uncertainty. Off-label use does have a place in medicine, but in a crisis, such as the one we are currently experiencing, the pharmacist ought to judiciously review each prescription in favour of the patients for whom the drugs are approved, and he/she would be justified in refusing to dispense prescriptions for SARS-CoV-2 positive patients. The compromise of dispensing indication-based prescriptions could also be a reasonable one if supplies are adequate.

4 | MISUSE DUE TO PROPHYLAXIS AND PANIC PRESCRIBING

The US FDA notes that

> If physicians use a product for an indication, not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on

[35] FDA. (2020). Right to Try. Retrieved May 7, 2020, from https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try.

[36] American Cancer Society. op. cit. note 25.

[37] Schiff, G. D., Seoane-Vazquez, E., & Wright, A. (2016). Incorporating Indications into Medication Ordering — Time to Enter the Age of Reason. New England Journal of Medicine. 375(4), 306–309. https://doi.org/10.1056/nejmp1603964.

[38] NASPA. op. cit. note 29; American Medical Association, op. cit. note 30.

[39] FIP, op. cit. note 24.

[40] Duffull, S. B., Wright, D. F. B., Marra, C. A., & Anakin, M. G. (2018). A philosophical framework for pharmacy in the 21st century guided by ethical principles. Research in Social and Administrative Pharmacy, 14(3), 309–316. https://doi.org/10.1016/j.sapharm.2017.04.049.

[41] Ibid.

[42] Furey, K., & Wilkins, K. (2016). Prescribing "off-label": What should a physician disclose? AMA Journal of Ethics, 18(6), 587–593. https://doi.org/10.1001/journalofethics.2016.18.6.ecas3-1606.

[43] Duffull, et al., op. cit. note 40.

> firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.[44]

The term panic prescribing, not a standard scientifically accepted jargon, was used to describe physicians writing prescriptions to ensure they have stock for themselves, loved ones, and in response to patient demands.[45] This implies that there is no immediate medical indication for the drug, but it is being hoarded for future use. This misuse has occurred in both high and low-middle-income countries and has been heavily criticized by pharmacists, physicians, and patient groups.[46,47,48] While the US boards of pharmacy have taken steps to resolve this by issuing directives, either prohibiting the use of the drug or restricting the use by enforcement of indication-based prescribing, in LMICs, if a pharmacist identifies panic prescribing and hoarding, what can he/she do in this situation? How does the pharmacist prove misuse without accompanying proof of diagnosis? Furthermore, if proven, are there enough ethical justifications, without legislative support, that would support a right to refuse? The US response requiring community pharmacists to ask the prescriber for proof of diagnosis is a meaningful step that other countries could follow in law or policy. Additionally, their Drug Utilization Review (DUR) strategy supported by law offers support to pharmacists in assessing prescriptions to prevent clinical misuse and abuse of prescription drugs.[49] DUR is defined as

> An authorized and structured ongoing review of practitioner prescribing, pharmacist dispensing, and patient use of medications. The purpose of DUR is to ensure drugs are used appropriately, safely and effectively to improve patient health status.[50]

The Board of Pharmacy in Vermont advised their pharmacists to use an "enhanced DUR" to dispense hydroxychloroquine.[51] The DUR could be submitted as a policy response to the misuse of hydroxychloroquine in institutional settings such as government hospitals because of the overarching goal of:

> "improv*ing* the quality of care for patients, individually and as populations, by striving to prevent the use of unnecessary or inappropriate drug therapy, prevent adverse drug reactions and improve overall drug effectiveness".[52]

Governments and local pharmacy groups in LMICs may be able to decide on a DUR policy for in-demand medications during epidemics in their countries to guide pharmacists on judiciously dispensing to prevent panic prescribing, off-label use, and hoarding of these drugs. However, a policy is only as good as the extent to which there is compliance. If similar policies regarding indication-based prescribing or enhanced DUR are adopted, there is another challenge to be addressed by the community pharmacists, that of compromised professional autonomy. In a survey by Astbury and Gallagher on moral distress experienced by community pharmacists in the UK, challenges with being able to assert professional judgement, dispensing off-licence (off-label) products, and time constraints due to expectations of pharmacy owners were cited as some causes of distress.[53] Community pharmacists are answerable to pharmacy owners who may assert that all legally written prescriptions should be dispensed. Refusing to dispense prescriptions based on ethical considerations may not be supported by some business owners, especially when this refusal is interfering with the revenue stream of the retail business.[54,55] For many owners, this is business and the medication, once available, and the prescription, once ordered by a licensed physician; ought to be dispensed. For the community pharmacist to exercise his/her autonomy, he/she would need the support of both policymakers and pharmacy owners. Some jurisdictions have taken steps to address this at a policy level.[56,57]

Astbury and Gallagher conclude that the key to addressing the issue of moral distress would require strategies that facilitate "moral competency, support the enactment of moral agency, and enhance the moral habitability of community pharmacy environments".[58] The pharmacist, as a moral agent, ought to have the freedom to assert her/his professional autonomy in promoting the responsible use of medications.

[44] FDA. (1998). "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices. Retrieved May 10, 2020, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices.

[45] Lynch, H., Bateman-House, A., & Caplan, A. (2020). 'Panic Prescribing' Untested Coronavirus Treatments: A Danger to Patients Today and Tomorrow. Health Affairs. Retrieved April 6, 2020, from https://www.healthaffairs.org/do/10.1377/hblog20200330.265604/full/.

[46] Bebinger, op. cit. note 14.

[47] Hibbert, op. cit. note 16.

[48] Lynch, Bateman-House, & Caplan, op cit. note 45.

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5 | GLOBAL DEMAND AND MEDICATION SHORTAGE

As the global demand for these drugs increases during the COVID pandemic, pharmacists are faced with another issue of managing resources during a period where demand exceeds supply.[59] Certainly, the effects of the global demand will be felt much greater and for much longer in LMICs. This is primarily because these countries rely on the importation of these drugs. Some innovator and generic companies in the USA and Europe are making commitments to boost production; however, these will be relevant only for those countries in which they already have existing marketing authorizations.[60,61,62] For many LMICs that depend on drug manufacturers located in countries like India, there are three major challenges: 1) export restrictions from manufacturing countries, 2) competing with high-income countries and, 3) disruption in the global supply chain in the shipping and airline industries. Since it may take some time before normalcy is restored post-COVID-19, affected governments will have to seek out generic drug alternatives and carefully assess and expedite required marketing authorizations as well as implement policies at a local level on how to handle the existing limited supply in the market. However, on the community level, reviewing the US Boards of Pharmacy responses, the various guidelines required 1) a restriction against supplying hydroxychloroquine for prophylaxis, 2) a restriction of 14 day supply of hydroxychloroquine for SARS-CoV-2 positive patients with no refills, and 3) either no restrictions or limits of 30 day supply of hydroxychloroquine for regular SLE/RA patients. There were some US states such as New York which completely prohibited the off-label dispensing of hydroxychloroquine for COVID-19 for the duration of the crisis.[63]

6 | CONCLUDING REMARKS AND THE WAY FORWARD

Lisa Tessman, in a recently published paper on moral distress in healthcare, presents a compelling argument that there is a place for reflection and personal growth when a medical practitioner experiences moral distress.[64] Her adopted definition of moral distress as "one or more negative self-directed emotions or attitudes that arise in response to one's perceived involvement in a situation that one perceives to be morally undesirable" is suitable to describe the situation faced by pharmacists during the COVID-19 pandemic.[65] The plethora of uncertainties surrounding the acceptability of hydroxychloroquine in the treatment of COVID-19, coupled with shortages associated with over-prescribing and misuse, has created a morally undesirable situation for community pharmacists. While two of the most influential regulatory agencies, the US FDA and the EMA issued emergency use orders for hospitalized patients and clinical trial use only, off-label prescribing remains a concern.[66] A review of the policy positions of boards of US boards of pharmacy revealed a lack of consensus on whether pharmacists should dispense the drug to SARS-CoV-2 positive patients except on the issue of prophylactic use. The general guidance in some US states was for the verification of medical indication on the prescription, which would either determine quantity dispensed or whether the pharmacist could dispense. Some regulators completely disagreed with the use of hydroxychloroquine for the treatment of COVID-19 citing insufficient clinical data or adherence to the FDA guidelines, while some allow a ten 10 to 14 day supply of hydroxychloroquine for SARS-CoV-2 positive patients and restricted prescribing to infectious disease specialists. The struggle for community pharmacists in the USA seems to be more about the shortage of hydroxychloroquine to supply regular patients and not so much about the therapeutic efficacy or dangers of using the drug in treating COVID-19. It seems pharmacists are inclined to believe that once the patient is under physician care, she/he has a right to try hydroxychloroquine. The California Board of Pharmacy notes that to dispense hydroxychloroquine would be considered "professional misconduct" and pharmacists ought to "…follow the law, standard of care, and professional codes of ethics in serving their patients and public health."[67] However, the Board of Pharmacy in Indiana suggested that the pharmacist may not have a right to refuse. The professional associations of medicine and pharmacy in the USA have issued a joint statement calling for the prescribing of a medication to be for "legitimate medical reasons" that is based on "evidence-based science" which would strengthen the decision to refuse to dispense.[68] However, a survey organized by the National Community Pharmacy Association (NCPA), a US pharmacy owners' association, identified that the majority of community pharmacists support

[59] Balfour, H. (2020, April 1). COVID-19 update: coronavirus and the pharmaceutical supply chain. Retrieved April 1, 2020, from https://www.europeanpharmaceuticalreview.com/article/116145/covid-19-update-coronavirus-and-the-pharmaceutical-supply-chain/.

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[61] Lupkin, op. cit. note 22.

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[63] NASPA. op. cit. note 29.

[64] Tessman, L. (2020). Moral distress in health care: when is it fitting? Medicine, Health Care and Philosophy, 23(2), 165–177. https://doi.org/10.1007/s11019-020-09942-7.

[65] Ibid.

[66] On June 15, 2020, the US FDA revoked the emergency authorization for the use of Hydroxychloroquine in the treatment of COVID-19. The letter stated "Based on its ongoing analysis of the EUA and emerging scientific data, the FDA determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweigh the known and potential risks for the authorized use". FDA. (2020). Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine . Retrieved July 19, 2020, from https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and.

[67] American Medical Association, op. cit. note 33.

[68] American Medical Association, op. cit. note 30.

dispensing hydroxychloroquine.[69] It was not clear whether the pharmacists in this survey were also owners as this presented additional consideration of whether the financial implications of not dispensing the drug influenced their opinion. Pharmacists also faced challenges of inter-professional conflicts with physicians, warnings of professional misconduct, and the lack of consensus from regulators. It would be important to explore whether the COVID-19 pandemic situation has affected community pharmacists in terms of moral distress and the associated challenges outlined in this paper. The reflective aspect when one experiences moral distress helps to guide the moral agent in how she/he conducts her/himself in future scenarios. In their recommendation to address moral distress among community pharmacists, Astbury and Gallagher, suggest a "systemic approach to further enquiry and evaluation that seeks to promote the competency and confidence of pharmacists as moral agents whilst addressing the structural barriers to morally congruent practice".[70] The lessons from the experiences and responses in the USA can guide policymakers in LMICs. The need for medical indications to be written on prescriptions played a significant role in strengthening the professional autonomy of the pharmacist in making decisions. The decision to dispense or not dispense a prescription must be made by morally competent, fully autonomous pharmacists, along with the support of policymakers and other healthcare professionals. Healthcare professionals are expected to act in such a way to minimize harm and maximize benefits for their patients, but these principles are challenged in the face of a global pandemic when resources are scarce, and people (including physicians and other healthcare professionals) are scared. LMICs must act swiftly to establish national protocols for the judicious prescribing and dispensing of these vital medicines in the time of COVID-19.

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CONFLICT OF INTEREST

I have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest on the subject matter or materials discussed in this manuscript.

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[69] Murphy, op. cit. note 23.

[70] Astbury, & Gallagher, op. cit. note 53.