



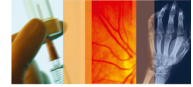
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Journal Pre-proof



MAYO CLINIC
PROCEEDINGS



Medication Shortages During the COVID-19 Crisis: What We Must Do

Esther K. Choo, MD, MPH, S. Vincent Rajkumar, MD

PII: S0025-6196(20)30320-7

DOI: <https://doi.org/10.1016/j.mayocp.2020.04.001>

Reference: JMCP 2843

To appear in: *Mayo Clinic Proceedings*

Received Date: 1 April 2020

Accepted Date: 2 April 2020

Please cite this article as: Choo EK, Rajkumar SV, Medication Shortages During the COVID-19 Crisis: What We Must Do, *Mayo Clinic Proceedings* (2020), doi: <https://doi.org/10.1016/j.mayocp.2020.04.001>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Mayo Foundation for Medical Education and Research

Medication Shortages During the COVID-19 Crisis: What We Must Do

Esther K. Choo, MD, MPH,¹ and S. Vincent Rajkumar, MD²

From the ¹Department of Emergency Medicine, Oregon Health and Science University, Portland,

Oregon; and ²Division of Hematology, Mayo Clinic, Rochester, Minnesota

Supported in part by grants CA 107476 and CA 168762 from the National Cancer Institute,

Rockville, MD, USA.

Corresponding Author:

S. Vincent Rajkumar, MD
Division of Hematology,
Mayo Clinic
200 First Street SW
Rochester, Minnesota 55905
rajkumar.vincent@mayo.edu

As of April 2, 2020, the Coronavirus Disease 2019 (COVID-19) caused by the SARS-CoV-2 virus has affected more than 200,000 Americans, and claimed over 5000 lives.^{1,2} In just 2 months, the number of deaths is projected to reach nearly 100,000— despite current levels of social distancing and other preventive measures.^{3,4} Healthcare workers are placing their lives at risk, and are facing enormous physical and emotional stress. The shortage of testing, masks and other personal protective equipment (PPE), and ventilators threatens to make our predicament worse. But unfortunately, we are already in the midst of *another* devastating problem: the shortage of medications that are critical for the management of COVID-19.

Medication shortages, anticipated to worsen with time, affect patients with COVID-19 directly, but also pose a threat to the health and safety of patients with other diseases who do not have COVID-19. Shortages include medications that have been touted as promising therapies against COVID-19, such as chloroquine and hydroxychloroquine.⁵ In fact, due to off-label prescriptions and hoarding, hydroxychloroquine is now difficult to obtain for patients without COVID-19 who need this drug to manage rheumatoid arthritis and other autoimmune disorders. Even more worrisome is the shortage of sedatives like midazolam and propofol that are needed for patients who are being intubated and placed on mechanical ventilation.⁶ This impacts patients seriously ill with COVID-19 patients, as well as patients who have respiratory failure due to other causes and need critical care. Such shortages as exemplified by sedatives may apply to a host of other drugs including antibiotics and vasopressors. It unfortunately gets worse: the active pharmaceutical ingredient (API) for many commonly used medications comes from China, and many of our generics are manufactured and imported from other countries, including India.

There are shortages of numerous medications that are unrelated to COVID-19, and since the pandemic has limited manufacturing and export worldwide this situation is bound to get worse.⁷

Recommendations to boost drug supply: We are exceeding capacity in terms of our vital medication supply. The usual supply chains, mechanisms, and administrative processes are inadequate for this crisis. We need to act now with urgency. Here are the steps that we as a nation must take. First, the Food and Drug Administration (FDA) must revamp its regulatory procedures and dramatically accelerate its processes to ensure that important medications are available to the public. Many of the drug shortages are going to be generic drugs. Due to various barriers, for some generic drugs we have only one or two FDA approved versions that are available for sale in the United States. In contrast, in some countries in Europe, and in India, each brand name drug may have multiple generic versions made by different manufacturers. The multiplicity of manufacturers acts as a protection against shortages in these countries, and also lowers cost.⁸

We recommend that the FDA institute a 24-hour turnaround for approving the importation of generic drugs that are in short supply from established manufacturers in other countries. Alternatively, the FDA can also grant immediate reciprocal approval for selected generic drugs manufactured in other countries.⁹ *Not having access to a drug must be considered far worse for the public the agency is charged to protect than any safety concerns that arise with the use of a generic drug that is made by an established manufacturer hitherto not authorized to sell in the United States.*

Second, the federal government must work with major brand name and generic pharmaceutical companies to boost mass manufacturing of approved drugs that are in short supply. If General Motors can repurpose its factories to make ventilators, then big pharmaceutical companies can be requested to divert their factories to manufacture generic drugs that are facing shortages. If companies that have the infrastructure are not willing to do this voluntarily, in the national interest, then the administration must invoke the Defense Production Act to compel them to meet the needs of the country.

Third, we need to encourage and fund non-profit generic drug manufacturing in the United States. Civica Rx, for instance, was founded with the goal of overcoming drug shortages and to manufacture and supply at reduced cost. This concept needs to be expanded. Although it will take time to set up, government manufacturing of essential drugs is something we have to consider longterm because generic drugs with small profit margins are unattractive to for-profit companies despite critical need.

Fourth, most APIs (the active chemical substance in prescription drugs) are currently manufactured in China.¹⁰ As well as negotiating with China to increase the supply, the United States must consider increasing the domestic manufacture of these substances. Since factories closed in China, and India shut down exports of medications, we have been under the threat of shortages in multiple medications.^{11,12} There have since been some signs of improvement, but the situation is fluid, and may worsen. This pandemic reminds us of the importance of having back up manufacturing within the United States, supported by taxpayer funds if needed.

Finally, any state or federal government stockpiles of critical medications should be mobilized, now, to hospitals experiencing surges in patients. Delay in providing these to cities in

need will cause major harm and loss of trust. For critical hospital medications, the government should establish centralized systems to track need, based on patient caseload, in order to inform manufacturing needs, and to shift supply rapidly and equitably. States and cities should be willing to share supplies of vital medications with other states as their own needs diminish when disease control is achieved within the state.

Recommendations to control cost: Even as we increase the amounts of available drugs, we must take steps to keep costs down. As we have witnessed with hand sanitizers and masks, if supplies are limited, prices go up dramatically. In the case of prescription drugs, we already have major problems controlling price, even prior to this pandemic.¹³ If we fail to take strict measures, access to life saving medications will be limited by cost, and this will disproportionately affect uninsured people and the elderly—the ones most vulnerable to COVID-19. Making treatment (and vaccines, as they become available) accessible and affordable is therefore critical.

We must pursue contracts with manufacturers especially for new antiviral drugs and vaccines for a “Netflix” option, in which they receive a fixed reimbursement for an unlimited supply.¹⁴ The Netflix model has been very successful in providing hepatitis C drugs to the State of Louisiana. We also recommend that laws be enacted to immediately authorize Medicare to negotiate price for COVID-19 related drugs. There has always been overwhelming public support for Medicare negotiation, and this is something we must do now more than ever because it can help keep prices lower.¹⁵ As a last resort, the federal government should be willing to issue compulsory licensing, if negotiations with companies fail to reach agreement on a reasonable price.¹⁶ Compulsory licensing permitted by the World Trade Organization Doha declaration in

2001, allows governments to license the use of a patented invention to a third party or government agency without the consent of the patent-holder if negotiations with the patent owner are unsuccessful.¹⁷

Another major factor that can increase the prices of COVID-19 related drugs in the United States are pharmacy benefit managers (PBMs), who normally act as middlemen between drug manufacturers, pharmacies and insurers. PBMs are supposed to deliver value to insurers and the insured public by identifying the best options for formulary placement and negotiating for lower prices. However, this is not always the case. PBMs may favor expensive drugs over inexpensive alternatives, and best illustrated by insulin prices that steadily contribute to increases in the list prices of even older insulin preparations.¹³ The resulting higher retail prices disproportionately affect the uninsured and under-insured public. To prevent these problems, the federal government must prohibit deductibles and rebates for COVID-19 specific drugs.

Like many at-risk resources in this crisis, medication shortages have been invisible but are threatening not only our ability to overcome this pandemic, but also the health of patients who have other diseases. The fragility of the complex medication supply chain was not created overnight, and yet we must overcome its limitations rapidly and decisively. And we must act before it is too late.

References:

1. Worldometers. COVID-19. Coronavirus Pandemic. 2020:<https://www.worldometers.info/coronavirus/country/us/>. Accessed April 2, 2020.
2. Shah A, Kashyap R, Tosh P, Sampathkumar P, O'Horo JC. Guide to understanding the 2019 novel Coronavirus [published online ahead of print February 28, 2020]. *Mayo Clin Proc.* 2020;95(4):646-652.
3. Wedell K, Mansfield E, Pulver D. US coronavirus deaths predicted to peak by mid-April if all States impose restrictions. . 2020:<https://www.usatoday.com/story/news/nation/2020/03/31/us-coronavirus-deaths-could-peak-mid-april-restrictions-states/5100513002/>. Accessed April 1, 2020.
4. Evaluation IfHMa. COVID-19 Projections. 2020:<https://covid19.healthdata.org/projections>. Accessed April 1, 2020.
5. Lee J. There's scant evidence so far for chloroquine as a COVID-19 drug — but there's already a shortage. 2020:<https://www.marketwatch.com/story/theres-scant-evidence-for-chloroquine-so-far-as-a-covid-19-drug-but-theres-already-a-shortage-2020-03-30>. Accessed April 1, 2020.
6. Silverman E. A new Covid-19 problem: Shortages of medicines needed for placing patients on ventilators. 2020:<https://www.statnews.com/pharmalot/2020/03/31/a-new-covid-19-problem-shortages-of-medicines-needed-for-placing-patients-on-ventilators/>. Accessed April 1 2020.
7. Byrnes H, Harrington J. Prescription unfilled? These 30 drugs are in short supply in the US right now. 2020:<https://www.usatoday.com/story/money/2020/03/10/fda-shortage-30-drugs-currently-in-short-supply-in-the-us/111402408/>. Accessed April 1, 2020.
8. Administration FaD. Generic Competition and Drug Prices: New Evidence Linking Greater Generic Competition and Lower Generic Drug Prices. 2019:<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices>. Accessed April 1, 2020.
9. Cohen M, Gupta R, Bollyky TJ, Ross JS, Kesselheim AS. Policy Options For Increasing Generic Drug Competition Through Importation. Health Affairs Blog 2019:<https://www.healthaffairs.org/doi/10.1377/hblog20190103.333047/full/>. Accessed November 16, 2019.
10. Huang W. The Coronavirus Outbreak Could Disrupt the U.S. Drug Supply. 2020:<https://www.cfr.org/in-brief/coronavirus-disrupt-us-drug-supply-shortages-fda>. Accessed

April 1, 2020.

11. Palmer E. Chinese APIs flowing but India ban hinders U.S. approval of hydroxychloroquine. 2020:<https://www.fiercepharma.com/manufacturing/chinese-apis-flowing-but-indian-ban-hinders-u-s-approval-hydroxychloroquine>. Accessed April 1, 2020.
12. Palmer E. How much does U.S. rely on China for drugs? FDA simply doesn't know. 2020:<https://www.fiercepharma.com/manufacturing/how-much-does-u-s-rely-china-for-drugs-fda-simply-doesn-t-know>. Accessed April 1, 2020.
13. Rajkumar SV. The High Cost of Insulin in the United States: An Urgent Call to Action. *Mayo Clin Proc.* 2020;95(1):22-28.
14. Trusheim MR, Cassidy WM, Bach PB. Alternative State-Level Financing for Hepatitis C Treatment-The "Netflix Model". *JAMA.* 2018;320:1977-1978.
15. Venker B, Stephenson KB, Gellad WF. Assessment of Spending in Medicare Part D If Medication Prices From the Department of Veterans Affairs Were Used. *JAMA Intern Med.* 2019;179:431-433.
16. Stavropoulou C, Valletti T. Compulsory licensing and access to drugs. *Eur J Health Econ* 2015;16:83-94.
17. Organization WH. The DOHA Declaration on the TRIPS agreement and public health.https://www.who.int/medicines/areas/policy/doha_declaration/en/. Accessed April 1, 2020.

Table 1: Immediate actions needed to boost medication supply and ensure equitable access

Boost medication supply	Minimize cost
<ul style="list-style-type: none"> • Mobilize any state or federal government stockpiles of critical medications to hospitals experiencing surges in patients • Institute a 24-hour turnaround for approving the importation of generic drugs or grant immediate reciprocal approval for selected generic drugs manufactured in other countries • Work with major brand name and generic pharmaceutical companies to boost mass manufacturing of approved drugs in short supply • Encourage and fund non-profit generic drug manufacturing in the United States • Increase the domestic manufacturing of active pharmaceutical ingredients (APIs) • Establish centralized systems to track need, based on patient caseload, in order to inform manufacturing needs, and shift supply rapidly and equitably 	<ul style="list-style-type: none"> • Utilize a “Netflix” option for new antiviral drugs and vaccines • Authorize Medicare to negotiate prices for COVID-19 related drugs • Be willing to issue compulsory licensing for medications • Prohibit deductibles and rebates for COVID-19 specific drugs