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MAYO CLINIC

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

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As of April 12, 2020, the Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome (SARS)−CoV-2 virus has affected more than 550,000 Americans, and claimed more than 21,000 lives.[1,2] In just 2 months, the number of deaths is projected to reach over 60,000 — despite current levels of social distancing and other preventive measures.[3,4] Health care workers are placing their lives at risk, and are facing enormous physical and emotional stress. The shortage of testing, masks, other personal protective equipment, 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 such as midazolam and propofol which are needed for patients who are being intubated and placed on mechanical ventilation.[6] This impacts patients seriously ill with COVID-19, as well as patients with respiratory failure due to other causes who need critical care, and those who need emergency surgeries under general anesthesia. The active pharmaceutical ingredients for many commonly used medications come from China, and many of our generics are manufactured and imported from other countries, including India. Since the pandemic has affected manufacturing and exports worldwide, the shortages exemplified by antimicrobials and sedatives will soon impact numerous medications unrelated to the treatment of COVID-19.[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 must act now with urgency. The US 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. Because of various barriers for some generic drugs, we have only one or two FDA-approved versions 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 lowers cost.[8] Here are the steps we as a nation must take (Table):

First, 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

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TABLE. Immediate Actions Needed to Boost Medication Supply and Ensure Equitable Access

Boost medication supply	Minimize cost
• Mobilize any state or federal government stockpiles of critical medications to hospitals experiencing surges in patients.	• Use a "Netflix" option for new antiviral drugs and vaccines.
• Institute a 24-h turnaround for approving the importation of generic drugs or grant immediate reciprocal approval for selected generic drugs manufactured in other countries.	• Authorize Medicare to negotiate prices for COVID-19–related drugs.
• Work with major brand-name and generic pharmaceutical companies to boost mass manufacturing of approved drugs in short supply.	• Be willing to issue compulsory licensing for medications.
• Encourage and fund nonprofit generic drug manufacturing in the United States.	• Prohibit deductibles and rebates for COVID-19–specific drugs.
• Increase the domestic manufacturing of active pharmaceutical ingredients.	
• Establish centralized systems to track need, based on patient caseload, to inform manufacturing needs and shift supply rapidly and equitably.	

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 must encourage and fund nonprofit 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 must consider long-term because generic drugs with small profit margins are unattractive to for-profit companies despite critical need.

Fourth, in addition to negotiating with China to increase supply, the United States must consider increasing the domestic manufacture of active pharmaceutical ingredients.[10] 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 backup 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 to inform manufacturing requirements, 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 (Table). 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 before 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. The role PBMs play in contributing to increased prescription drug costs is best illustrated by insulin prices that have increased several fold over the past 10 years even for older insulin preparations.[13] The resulting higher retail prices disproportionately affect uninsured and under-insured people. To prevent these problems, the federal government must prohibit deductibles and rebates for COVID-19–specific drugs.

SUMMARY

Similar to 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.

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