SARS-Cov-2 and drug shortages - Trends and lessons from a Caribbean perspective

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INTRODUCTION

Coronavirus SARS-CoV-2 first reported in Wuhan, China in December 2019 has rapidly infected millions, claimed the lives of a large global population, crippled economies, created a new 'normal' and continues to flog the health care system. The pandemic seems to have affected supply and demand of pharmaceutical entities as an early concern was that medications for patients on ventilators would soon run out. Critical points for management of the pandemic were highlighted in China and even with adequate ICU beds and frontline workers, shortage of emergency medications remained a major concern (1). As the surge began, sedatives and painkillers were soon in short supply at hospital pharmacies and clinical pharmacists began to spend more time on drug acquisition and conservation than on patient care (2). While drug shortages are not uncommon, the titanic surge of SARS-CoV-2 has led to the use of alternative drugs in place of first line analgesics, neuromuscular blockers, vasopressors and antimicrobials in the United States (3). Europe is experiencing scarcities of critical drugs needed to manage patients with COVID-19 such as sedatives, analgesics, bronchodilators, antimicrobials and antimalarial agents (4). The American Society of Health-System Pharmacists (ASHP) has been conducting weekly reports on drug availability and has proposed methods for therapeutic assessment, drug shortage impact analysis, and alternate available options (3). Clinical pharmacists have been actively identifying drugs in short supply, considering alternatives and assessing the risks when using these agents. They have also been monitoring drug use and reducing drug wastage, which is of paramount importance when there are drug shortages.

With increasing patient numbers overwhelming the hospitals, availability of drugs decreased and the number of prescriptions being filled for sedatives, muscle relaxants, anesthetic agents for the pain and distress in mechanically ventilated patients dropped by 4-7% in just one week and analgesic prescriptions stayed at 69% (5). The United States Drug Enforcement Agency (DEA) promptly approved a 15% increase in production quotas for controlled substances like fentanyl, morphine, hydromorphone, codeine, ephedrine, and pseudoephedrine, and in parallel will permit increased

imports of ketamine, diazepam, midazolam, lorazepam, and phenobarbital (6).

DISCUSSION

Drug shortages- why do they occur?

The COVID-19 pandemic has worsened some shortages and created others. Roughly half of all drugs in shortage are injectable, including analgesics, sedatives and paralytics needed to intubate critically ill patients (3). Shortages in drug supply are generally consequent to issues with quality control, such as when a product may be recalled or destroyed. Drugs with low frequency use or demand are manufactured in limited amounts, and shortages are precipitated in an acute high demand scenario. The pandemic has triggered sudden global demands for certain pharmaceuticals, placing a high burden on manufacturers- some of whom are adversely affected by the pandemic themselves and forced to shut down operations, due to the inability to source raw materials and active pharmaceutical ingredients (APIs).

There is also the artificial shortage from claims of efficacy of agents purported to treat COVID-19.

Hydroxychloroquine has dominated sales beyond its true indications despite robust evidence of its efficacy in COVID-19 (7). Like a grocery item, fueled by anecdotal media reports and touted as a game changer, it underwent panic buying and stockpiling for possible treatment and even prophylaxis (8). As of June 8th 2020, if the planned 212 clinical trials worldwide go ahead, patients, who rely on hydroxychloroquine for its licensed indications of rheumatoid arthritis and systemic lupus erythematosus (SLE) will face an escalated shortage. The increased demand for enoxaparin to treat COVID-19 associated coagulation disorders in the United Kingdom, amidst acute scarcity and quality issues saw forced imports from Italy (9). The National Health Service (NHS) subsequently banned the export of 82 drugs out of the UK to preserve supplies for their patients (10). India also restricted export of 26 drugs and drug ingredients, amid disruption of services at its manufacturing plants, prioritizing supply for its own people, provoking drug shortages worldwide, though India later opened her doors to exports (11).

Recognizing the projected impact of COVID-19 on drug shortages the NHS, England noting that community

pharmacies are running out of supplies urged doctors not to overprescribe or over-order during this time, to avoid further pressures on the supply chain (12). Many of these reports address the acute shortage, but the reduced availability of APIs could mean chronic disease medications may be in the 'out of stock' list soon.

Active pharmaceutical ingredients

When China was recognized as the epicenter of the pandemic, there were concerns about the availability of raw materials and APIs for drug manufacture. China's supply of APIs has more than doubled in the last decade to 13% of the pharmaceutical market in the USA. The Indian pharmaceutical industry, the world's third largest drug manufacturer of medications at affordable prices, supplies medicines to a vast portion of the global population, and supplies more than 250 US FDA and UK Medicine and Healthcare Products Regulatory Agency (MHRA) approved plants (12). The majority of APIs for generic drug manufacturing globally are sourced from India, which also supplies approximately 30 percent of the generic APIs in the USA; COVID-19 has highlighted global dependence on these two pharmaceutical titans putting severe strain on the world's Pharmaceutical Industry (13).

Trinidad and Tobago has experienced the situation of anxious patients hoarding medications, anticipating the fury of COVID-19 will threaten drug supplies particularly for chronic non-communicable diseases. An overnight 300% hike in drug prices for some agents, could not be controlled by the local Pharmacy Board which passed the blame to the wholesalers (14). Trinidad and Tobago's Minister of Health made an impassioned public appeal in one of the daily press conferences of the Ministry of Health, urging retailers to desist from spiraling prices and even suggested patients hoarding hydroxychloroquine should return supplies to the retail pharmacy so that patients with autoimmune disorders could avail their treatment without financial liability.

Challenges- counterfeit medications

The dearth of much needed pharmaceuticals has opened doors for the entry of counterfeit medications. Patients generally do not suspect counterfeit or substandard

medicines when doing online shopping. To highlight the significance and dangers of fake medicines, officials from 90 countries during 3 - 10 March 2020, inspected over 326,000 packages and seized more than 48,000, with a total worth of 4 billion US dollars (15). A total of 4.4 million units of illicit pharmaceuticals were seized worldwide. The most common items detected were erectile dysfunction pills, anti-cancer medication, hypnotic and sedative agents, anabolic steroids, analgesics/painkillers, nervous system and dermatological agents and vitamins. These bogus agents may also be found on pharmacy shelves in some countries where it is illegally imported, putting patients at high risk for adverse events. Thus, the unsuspecting consumer would experience worsening of their chronic disease, additionally burdening the health care system.

Can drug shortages be mitigated?

COVID-19 is likely to persist for the foreseeable future, mandating the critical management of scarce resources to ensure optimal patient care and to protect public health. There should be equitable access to drugs so that those who require drugs for specific conditions are able to obtain them, rather than bulk-buying by those with the means to do so. Allowing importation of generic drugs with proven quality assurance studies from approved manufacturers can prevent shortages and even control prices. Prescribing proven generics should be encouraged and pharmacists can educate patients on their cost-efficacy, if the prescription does not forbid switching the brand. Pharmaceutical manufacturers can be requested to repurpose their production facilities to manufacture generic drugs that are facing shortages, similar to General Motors shifting to ventilators in the best interest of the nation's health. Measures should be implemented to produce generic drugs with small profit margins as these are unattractive to pharmaceutical companies despite their critical need. Responsible reporting of the results of drug trials and of potential candidates for treating COVID-19 can prevent panic bulk buying which causes societal health inequity from artificial drug shortages and price increases, which will have negative implications for medications unrelated to the treatment of COVID-19.

CONCLUSION

The Ministry of Health in conjunction with the Pharmacy Board can develop policies in the short term to maximize available pharmaceuticals with minimal wastage in treating COVID-19 patients. Public education is imperative for the unsuspecting consumer and the community to be made aware of any impending drug shortages with recommended changes in therapy to prevent the unknowing purchase of false products. A major issue for global consideration is the dependence on just a few nations for the bulk of the world's supply of APIs. Serious consideration by relevant stakeholders can encourage and support more centres for worldwide pharmaceutical manufacturing, to ensure a reliable supply of medications in the event that the current plants are unable to operate. Measures to ensure that patients can access good quality, low priced pharmaceuticals to contain chronic diseases and avoid overwhelming the health care system during or post- COVID-19 scene, would be a welcome initiative by health authorities and care givers.

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