

Will the COVID-19 Pandemic Finally Fuel Drug Repurposing Efforts?

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The coronavirus disease 2019 (COVID-19) pandemic has turned the health care world upside down. Research and medical institutions have delved deeply into health care arsenals to identify some unlikely heroes that have helped to treat a disease that seemingly evolves with each passing day. In a controlled, open-label trial of hospitalized COVID-19 patients, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) Collaborative Group found that the use of dexamethasone, a cheap generic drug commonly used to treat a variety of inflammatory conditions, resulted in lower 28-day mortality in COVID-19 patients receiving respiratory support.¹ This is not the only incidence of older generic drugs being repurposed to combat the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus; however, it is one of the more successful stories. The urgency to find effectiveness in older drugs has come with some serious pitfalls. Chloroquine phosphate and hydroxychloroquine sulfate, 2 drugs originally used for malaria, were broadcast at the beginning of the pandemic as possible “cures” for the new virus. Ensuing demand for these products threatened to interrupt chronic therapy among patients using the drugs for evidence-based indications such as lupus, only for the Food and Drug Administration (FDA) to revoke their Emergency Use Authorization (EUA) for COVID-19 because of reports of ineffectiveness and serious cardiac adverse events.²

Drug repurposing is a process that involves identifying an alternative use for medications that are already on the market or investigational medications that are being studied for a different indication. For patients with limited life expectancy or few treatment

options, earlier access to potential new therapeutics is a benefit of repurposing older, cheaper drugs that are already on the market. For example, glucagon-like peptide 1 (GLP-1) agonists, indicated for type 2 diabetes, are being integrated into clinical practice for patients with nonalcoholic steatohepatitis based on evidence from a mix of clinical trials and observational studies.³ A major advantage of drug repurposing is that preclinical and safety studies have already been conducted, and for medications that have been approved, there exists a body of real-world evidence on utilization and safety.⁴ Therefore, the safety profile of the medications is already well understood and fewer studies will need to be conducted for regulatory approval, which may shorten the notoriously long drug development process significantly. This decreases the cost of development and reduces the risk of failure in the later stages of clinical development to much lower levels compared with a completely new molecular entity.⁴ Although less costly, 3 years of market protection provided by the FDA is often not enough time to recover accumulated expenses and may leave the company open to competition from off-label use of generics.⁵ Consequently, there have been relatively few instances of pharmaceutical companies seeking and gaining approval for new indications of repurposed generic drugs.

There are different methods to identify candidate drugs for repurposing, including computational approaches and experimental approaches. Computational approaches include analysis of genomic and proteomic data, chemical structure, and retrospective observational studies.⁵ Observational studies occupy a critical intermediary position in the drug repurposing process. They are one of the more accessible pathways for developing evidence to support the drug repurposing efforts, capitalizing on already existing data that only need to be extracted and not created. Once drugs are identified as potential candidates for repurposing (eg, based on an understanding of their mechanisms of action), observational studies that leverage existing data sources can identify signals of clinical effectiveness (or a lack thereof) to support or refute the need for expensive clinical trials, while also informing trial design. Positive signals from observational studies should be confirmed with

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randomized controlled trials before repurposed drugs are integrated into clinical practice.

Electronic health records (EHRs), administrative databases (eg, health care claims), and registries are common resources used for observational studies of drugs being examined for repurposing.⁵ EHRs have assets of large amounts of data on structured patient outcomes, including laboratory tests, drug prescribing data, and diagnostic and pathophysiologic data. EHRs also contain an abundance of unstructured data, including signs and symptoms of a specific disease and imaging data. These rich data sources, sometimes referred to as “big data,” can support rigorous drug development research. Because of substantial diversity in EHR systems used to host this type of data, there is a need for technological and automation solutions for appropriate analysis. However, large data sources, such as EHRs, are beneficial for multiple reasons. First, in large data sets, it is easier to find multiple signals of effectiveness (eg, changes in symptomatology and health care utilization). Second, large sample sizes allow for increased power at lower cost, facilitating detection of smaller effect sizes than would be identified in a small clinical trial. This is important because a modest statistical effect size can have large clinical implications. Third, because the data have already been collected, studies that use large existing databases to test hypotheses regarding new indications can be conducted within months rather than years.

Researchers seeking to conduct observational research to support drug repurposing may encounter several challenges. Access to big data in a format that is suitable for rigorous pharmacoepidemiologic research is typically tightly restricted to protect patient privacy. Distributed research networks such as the FDA's Sentinel Initiative and the Healthcare Systems Research Network overcome such barriers by applying common data models and permitting individual institutions to maintain local control over their data resources, while allowing external scientists to implement protocols that use these data as part of larger studies involving data from several organizations.^{6,7} Although, traditionally, analysis of data across institutions would have required substantial staff time to adapt code to address the nuances of each organization's data model, use of a common data model is comparatively much more efficient. An individual analyst can develop a standard program that can be run in parallel on-site at each organization, with the aggregate results later combined without any need to exchange sensitive personal health information. This is not to say that progress in expanding access to big data is not needed. Access to these types of research

networks is often closed to researchers unaffiliated with participating institutions, or may be costly, as is the case with data from the Centers for Medicare & Medicaid Services.⁸ Efforts should be made to allocate resources and establish processes to ensure that data are not only organized in a standardized format but also widely usable by researchers.

It is evident that drug repurposing cannot be done without a wealth of resources often housed at different institutions. The likely partners for drug repurposing initiatives include large pharmaceutical companies that have libraries of compounds, academic institutions with diverse areas of scientific expertise, and government agencies that are data stewards and are able to fund grants that promote public health.⁹ Pharmaceutical companies can act as the backbone for projects because they contain the molecular libraries and preliminary safety data that can serve as the foundation for successful ventures. Moreover, these companies have cross-functional teams that are already well versed in regulatory drug approval processes and can streamline successfully repurposed drugs through FDA reviews. Small upstart biotech companies also should be included to take advantage of their new and innovative methods in drug development.⁹ Funding of such projects is a large burden that can be relieved by government-led programs such as the Discovering New Therapeutic Uses for Existing Molecules initiative by the National Institutes of Health-National Center for Advancing Translational Sciences, which has already partnered with 8 pharmaceutical companies.⁵ For COVID-19 specifically, the US Defense Advanced Research Projects Agency has signed a \$16 million contract with the Wyss Institute for Biologically Inspired Engineering at Harvard University to identify and test FDA-approved drugs to treat or prevent COVID-19.¹⁰ Researchers also should turn to nonprofit organizations such as Cures Within Reach, the Michael J. Fox Foundation, and the Alzheimer's Drug Discovery Foundation that also have funded programs for drug repurposing studies and can bring in a much needed patient perspective on access and unmet needs.⁹ Only through strategic, cross-sectoral partnerships can current and future drug repurposing studies be translated into new therapeutic options that ultimately benefit patients.

The COVID-19 pandemic has shown us that both the medical community and general public are interested in drug repurposing. Although drug repurposing represents an opportunity for faster access to new therapeutic options compared with development of new molecular entities, it is important to note that lowering established evidentiary thresholds and

pushing new therapeutic applications into the clinic on the back of preliminary results is not what drug repurposing aims to do. The repurposing of hydroxychloroquine, for which the EUA was rushed without sufficient evidence, represents a cautionary example. It is paramount that scientists in industry, academic, and regulatory settings apply the consistently high standards for evidence of safety and effectiveness that have been established for new molecular entities to repurposed drugs as well. In our modern era where scientific expertise is actively undermined in the public sphere, the scientific community's transparent stewardship of public health has only become more important. Ultimately, a systematic, collaborative, and well-resourced initiative to discover and study new indications for existing drugs may help fulfill the nation's thirst for more therapeutic options and lower pharmaceutical costs.

Conflicts of Interest

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