



## FRONTIERS

## New Coronavirus Drug Paxlovid: Highly Effective, But In Short Supply

By SPENCER SHORKEY

**MILLERS FALLS** – No introduction to the topic of COVID-19 is needed. My deep gratitude to anyone working in health care over the past couple years, and sorrow for the near million lives lost due to coronavirus in this country, with over 20,000 counted in Massachusetts.

Distrust in medicine has heightened in recent years, coinciding with new, more complex therapeutic technologies being phased into modern medicine – although I think it may be better to say that trust in many institutions has been altered by the emergence of complex technologies in general.

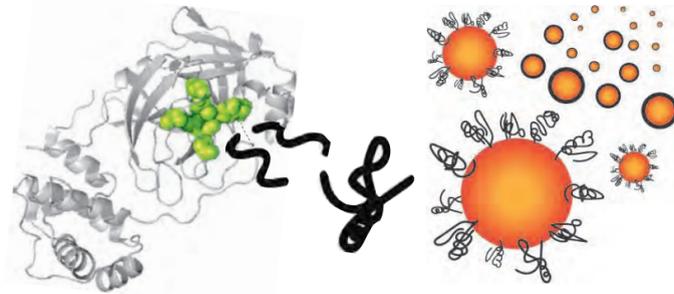
The life-saving RNA-nanoparticle vaccine has become emblematic of modern biomedical technologies. In terms of the COVID-19 pandemic in the United States, vaccines are estimated to have saved over 200,000 lives, and prevented over a million hospitalizations. However, old medical technologies such as small-molecule drugs in pill form, or covering your face holes (wearing masks), are still useful for managing disease situations.

Emergency Use Authorizations (EUAs) were granted in late December 2021 by the Food and Drug Administration for two new coronavirus drugs, Paxlovid and molnupiravir. In clinical trials, these new small-molecule drugs each lowered the risk of hospitalization and death when administered to actively infected patients. Paxlovid, made by Pfizer, reduced hospitalization and death by 88% – tenfold lower odds! Molnupiravir, marketed by Merck, showed a 30% reduction in hospitalizations and deaths.

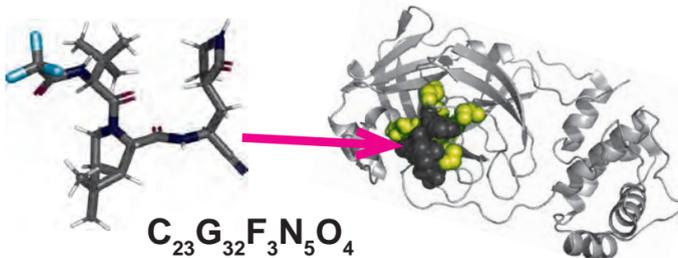
Paxlovid is a protease inhibitor and prevents virus components from being built correctly, and molnupiravir is a nucleic-acid analog that causes faulty replication of the virus's RNA genome.

Other small molecules, ivermectin and hydroxychloroquine, apparently showed some ability to block coronavirus activities in lab tests, but have failed to yield any benefit in clinical trials. One clinical trial completed in November 2020, for example, found that “[i]n non-critical hospitalized patients with COVID-19 pneumonia, neither ivermectin nor hydroxychloroquine decreases the number of in-hospital days, respiratory deterioration, or deaths,” as documented on the medical pre-print archive medRxiv.

Paxlovid and molnupiravir have known molecular mechanisms for blocking coronavirus activities,



The coronavirus protease, a string of nearly 5,000 atoms, is shown as a cartoon resembling a strange-looking pasta noodle (left). This nano-machine cuts the virus components up into their correct forms, a crucial step of its replication. The spheres shown in green are atoms known to contribute directly to the protease's holding and cutting actions.



A Paxlovid molecule, shown in black spheres, jams this machine. The drug's nearly 70 atoms apparently fit well into the protease, and block its function. (The 3D view can be accessed in a web browser at [rcsb.org/3d-view/7VH8](https://rcsb.org/3d-view/7VH8).)

while ivermectin and hydroxychloroquine mechanisms are speculative at best – i.e., they are unknown or may not be real at all.

How is it that we can have positive lab test tube results, which do not hold up when tested in human bodies? Well, it's actually more common than you might think. Over 90% of drugs entering clinical trials do not succeed. False positive results in drug-screening experiments can occur for a multitude of reasons, a common one being that the drug being tested could be too sticky or reactive, which can alter the experimental signal itself more than actually blocking its intended target.

You may be wondering how exactly these new drugs which are proven to actually work in clinical trials impact coronavirus infections. I'll tell you about one of them, Paxlovid, in more detail.

Humans and viruses are built and maintained by molecular machines, nanoscopically small (microscopic at a nano-scale), which are susceptible to being blocked by small-molecule drugs. Imagine throwing a big wrench into some complicated industrial machinery with many moving parts. The wrench can get stuck, jam the machine, and block it from functioning.

In a virus, one such machine is the protease, an enzyme that cuts virus building blocks into the right shapes for proper assembly – a kind

of nanoscale molecular scissors. Paxlovid sticks to the coronavirus protease, and in doing so inhibits its function, preventing the virus from replicating itself. By jamming these molecular scissors with Paxlovid, no new viruses can be built.

Pfizer has agreed with the Medicines Patent Pool to allow Paxlovid to be manufactured and sold in 95 countries, and plans to produce 120 million courses worldwide. Supply is limited at the moment, however: according to the National Institute for Health's online Therapeutics Locator, out of the 232,240 courses of Paxlovid that have been allocated, only 60,191 are available. (For molnupiravir, 370,730 courses remain of 758,500 allocated.)

ABC News reports that California received just under 10,000 Paxlovid courses during the last full week of January, which is unfortunately an undersupply, considering the state saw hundreds of thousands of cases that week, and over a thousand deaths. ABC also found that only about a quarter of counties had Paxlovid on hand.

Hannah Curtiss, PharmD, my cousin who runs a small town pharmacy in upstate New York, told me that Paxlovid and molnupiravir are “completely unavailable to community pharmacists at this point,” and that the “largest drug wholesaler in the US doesn't even have it listed as available to order.” This makes

## MEDICINE

## Protect Your Heart!

By CATHERINE DODDS, MD

**TURNERS FALLS** – February is National Heart Month. As Valentine's Day approaches, our thoughts turn to the heart. Not only the proverbial heart that helps you find that Hallmark Movie-worthy special someone, but also the heart that beats in your chests to keep you alive.

Heart disease is a broad term. In my work as a primary care physician, patients often tell me heart disease runs in their family, but that can mean many things, including heart failure, atrial fibrillation, or heart murmurs. Medically speaking, heart disease usually refers to atherosclerotic cardiovascular disease, a term that includes narrowing or blockage of blood vessels to the brain (cerebrovascular disease, including strokes), the heart (coronary artery disease, including heart attacks), or the legs (peripheral vascular disease).

So how can you tell when your heart is not working like it should be?

Early medical studies generally included only men, so there is a divide between classic signs of a heart attack such as central chest pain “like an elephant sitting on your chest,” and so-called atypical symptoms that are actually more common in both sexes and may include nausea, dizziness, fatigue, sweats, palpitations/heart racing, shortness of breath, or even just feeling “off.” Symptoms of heart disease often start during physical exertion and improve with rest, but a sudden onset of these symptoms is concerning, even when resting or sleeping.

You are the one who knows your body best, so if you are ever concerned you may be having symptoms of a heart attack, seek emergency care right away. Evaluation for a heart attack is straightforward – typically, an electrocardiogram (EKG) is done to look at the electrical activity of the heart and a blood test called troponin is checked to look for heart muscle damage.

If both of these are normal but symptoms are still concerning for

coronary artery disease, a stress test may be done. In some cases, a direct view of the coronary arteries that bring blood to the heart is needed – this is called a cardiac (heart) catheterization.

What can we do to keep our hearts healthy and happy? Besides love, red roses, and dark chocolate – keeping the chocolate in moderation – there's a lot we can do to prevent heart disease. Even with all the available medical interventions and prescription medications, the basics are still important.

Eat a healthy diet with lots of vegetables and minimal processed or fast food. “Dietary Approaches to Stop Hypertension” (DASH) and a Mediterranean-style diet are two of the most widely recommended specific heart-healthy diets.

Your heart loves to work. In general, aim for a minimum of 150 minutes of exercise per week. Some people like aerobics classes for the social aspect. Some run marathons. Others are “weekend warriors” who are intensely active for hours, once per week. Some people stay active in their daily lives, walking briskly at least 10,000 steps (around 5 miles) per day in the course of their usual routine.

All of these have similar benefits for your heart. The most important thing about exercise is not the specific type, but simply to add more physical activity to your life.

If you smoke, make it a top priority to quit. Becoming a non-smoker is among the best things you can do for your heart, and for your health in general.

Heart disease is one of the most common chronic medical conditions, affecting half of us over our lifetimes, and it is the leading cause of death in the United States. Once heart disease is diagnosed, there are several prescription medications that have proven benefit to reduce risk of further heart damage. If you are concerned about heart disease risk or symptoms, consult with your healthcare provider.

Catherine Dodds, M.D.  
lives in Turners Falls.

sense; given the currently limited supplies, the drugs must be rationed to higher-risk infections at this time.

“But,” Curtiss added, “I am still getting a few calls a week asking whether we dispense ivermectin for COVID.” She said these are scripts she will not fill, given the scientific evidence and advisories by both the FDA and the CDC against this usage. Curtiss mentioned that certain pharmacies in her region are still willing

to fill ivermectin scripts, and certain MD's continue to write the scripts.

The over 100,000 Paxlovid courses administered thus far are sure to have saved lives during this current wave. The drug's availability and impact are likely to be greater during any future waves – Pfizer plans to provide the USA with 10 million doses by June, and 10 million more by September.

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