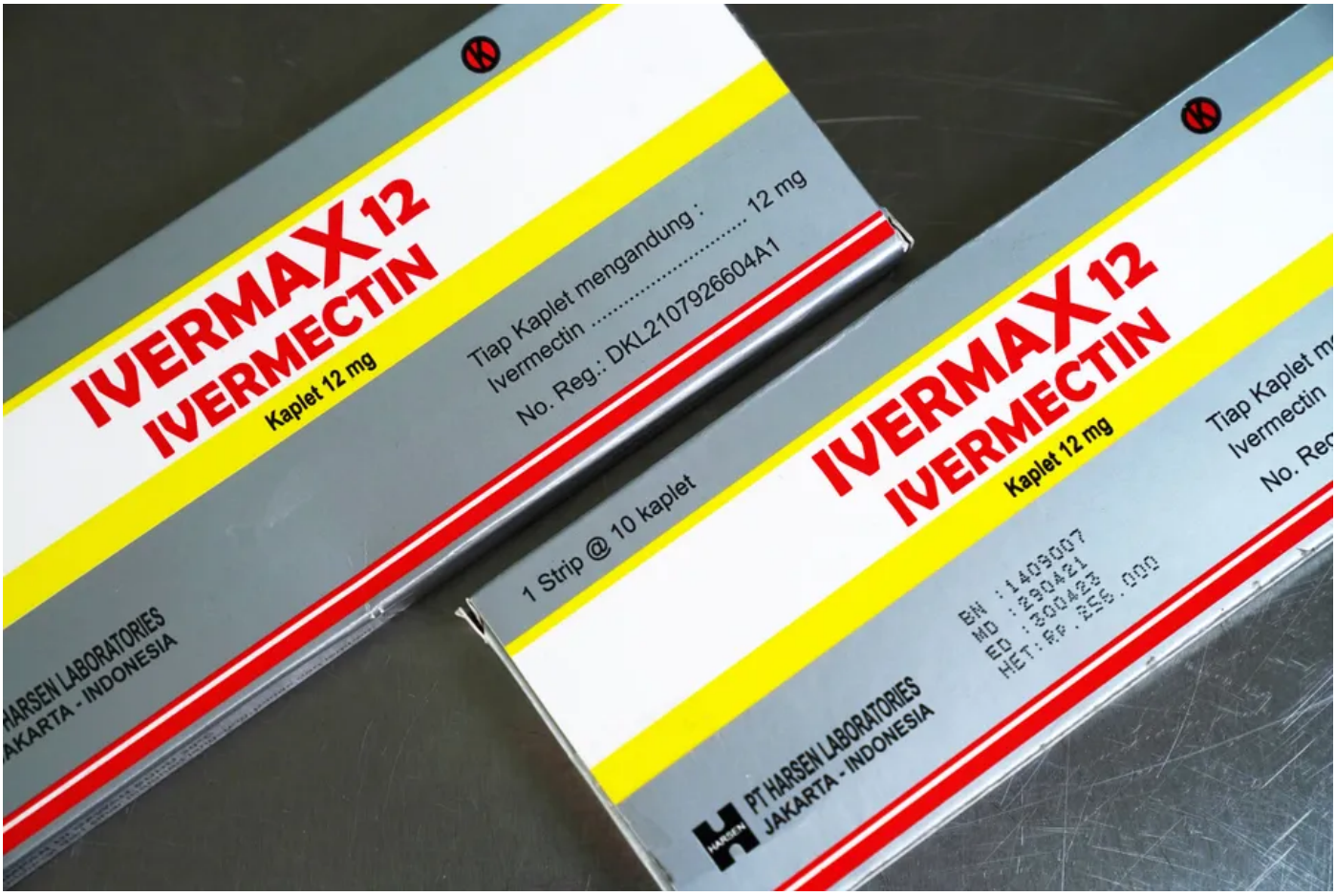
Better Data on Ivermectin Is Finally on Its Way

Studies have been small and often not great. The best info so far says don't use it, get vaccinated, and hang in there for the more promising meds being tested.

Adam Rogers 09.08.2021 07:00 AM



Ivermectin prescriptions spiked to nearly 100,000 in August, 20 times their pre-pandemic level.Photograph: Dimas Ardian/Bloomberg/Getty Images

Edward Mills came to the meeting last month with very good data. A clinical trials expert at McMaster University, Mills was presenting new results from a

trial that is looking at how well half a dozen different drugs treat Covid-19—not for the people so sick they're in the emergency room or the hospital, but in people whose symptoms haven't gotten that bad yet. People sick at home, in other words.

At his online talk, put on by the National Institutes of Health, Mills' slides told the tale: A relatively safe, familiar, cheap drug reduced the relative risk of mild Covid getting worse by nearly 30 percent. The drug is fluvoxamine, a selective serotonin reuptake inhibitor—an antidepressant. (It's also an anti-inflammatory, and inflammation and an overreacting immune system are hallmarks of serious Covid infection, so that might be why it seems to help). Get a bunch of people with Covid and randomize them into two groups; 739 get fluvoxamine and 733 get a placebo. Only 77 of the fluvoxamine-takers end up in the hospital; 109 of the placebo group do. This is exciting.

"This is the first time these results have been presented in a public forum?" asked the moderator, Adrian Hernandez, director of the Duke Clinical Research Institute.

"Yeah," Mills answered. "You are hearing it for the first time."

"Well, simply, wow," Hernandez said. If the data bears out, it'll be only the second repurposed drug that works for outpatient Covid-19. (The other is a steroid called budesonide; other drugs you might have heard of, like remdesivir or dexamethasone, are for people who are severely ill and hospitalized.) The team's results haven't been peer-reviewed or officially published yet, but the Together trial, on which Mills is co-principal investigator, is well-designed and respected. Now, to be clear, fluvoxamine is still a ways off from becoming part of the standard of care for people with Covid-19. Once the Together trial's results get published, guideline-setting organizations like the US Food and Drug Administration and the World

Health Organization will have to take a look. But the Together trial data, if it holds up, seems positive for the SSRI.

But wait! There's more! In the very same presentation, the very same trial that showed this antidepressant might lessen the symptoms of Covid-19 *also* showed that the antiparasitic drug ivermectin—you've heard about that one, right?—doesn't help at all. In the Together trial, that drug, commonly used against things like river blindness and intestinal roundworms, didn't keep anyone with Covid out of the hospital any better than a placebo. Of 677 people with Covid who got 400 micrograms per kilogram of weight per day for three days, 86 ended up in the ER or hospital; of the 678 people who got a placebo, 95 went. That's not a significant difference, and Mills' team dropped it from the study. (Vaccination, I should add, is still the most effective, safest, cheapest, and easiest way to avoid getting sick.)

Ivermectin had some promising early results against the virus in petri dishes and in smaller and observational studies, but it still hasn't aced a trial. Of two apparent large-scale confirmations of its effects, one (a preprint from researchers in Egypt) got retracted over concerns about plagiarism and fake data. Scientists and journalists at BuzzFeed have found irregularities in the data from another. A separate, positive review of all the data on ivermectin was rejected from a journal after provisional acceptance for concerns about research integrity and conflicts of interest, while a strict meta-analysis of *all* the randomized, controlled trials of ivermectin against Covid found no positive effect for the drug. The FDA says people shouldn't take it. The American Medical Association and two pharmacist associations have issued a statement recommending that none of their members prescribe ivermectin for Covid-19 outside of a clinical trial. (Oh, and a physician in Arkansas gave the drug to unknowing, unconsenting prison inmates, which generally is not the side of history you want to be on.)

Yet ivermectin is still a big deal in the US. Prescriptions spiked to nearly 100,000 in August, 20 times their pre-pandemic level. Talk show hosts, right-wing propagandists, and some physicians are still claiming that the drug is miraculously effective. Shortages and lack of access to prescriptions have led some people to turn to the more readily available veterinary formulations of the drug—horse and cow deworming agents. That's dangerous, to be sure, though perhaps not enough people *actually* did it to warrant an unusual amount of snark from a federal agency warning against interspecies self-medication.

All this confusion and misinformation filled what has been an information vacuum. No one had rock-solid data on cheap, workhorse drugs to fight "mild" outpatient Covid. The need for them became apparent early in the pandemic, and it hasn't gone away. Vaccines are powerful armor against the virus, but money, policy, and logistics mean most of the world can't get them, and pockets of political opposition and structural obstacles remain in wealthier countries like the United States. Combine that real need with snake-oil grifterism and political opportunism and you get crazes like this one for ivermectin or last year's for hydroxychloroquine (which mostly faded when big randomized trials like Recovery in England and another at the University of Minnesota found that it had no effect, and doctors stopped prescribing it). Maybe hydroxychloroquine's journey will be a template. "There was noise on both sides in terms of, is it a cure-all or does it have safety issues? But when the Recovery trial came out with a rigorous, definitive answer of 'No, it doesn't work,' everything quieted down," says Hernandez. "That's the crisis. We haven't had a national system that can rigorously evaluate these in a rapid fashion. That's kind of what we need now to address the ivermectin question, a definitive answer to 'does it work or not?'"

In North America, trials to get those answers have begun. The Together trial

is an adaptive, multi-arm trial—which means it enrolls people on an ongoing basis and uses statistical techniques to swap drugs in and out as they either succeed or fail. Besides helping dispatch hydroxychloroquine, the Together trial has now similarly shown that the antidiabetes (and sometimes anti-aging) drug metformin doesn't make much of a difference, either.

But political activists didn't turn metformin into a rhetorical tool; ivermectin has stans so aggressive they make Gamergaters seem chill. Mills says he and his colleagues have been abused and threatened by ivermectin adherents; the trial designers even went through the rigorous process of changing the dosage administered to comport better to the fans' preferred regimen of three days instead of just one. "We tested, what, seven other drugs? Nobody abuses us about the other drugs. We even showed one of them worked," Mills tells me. His team touted positive results for fluvoxamine, "and that crowd doesn't seem to care. If you ask them, 'Why do you feel so strongly about ivermectin?' they will say, 'Because we feel there should be a cheap, effective drug that can be used by poor people.' OK, well, we have that. We have it with fluvoxamine, and with inhaled budesonide. Why do they not care about those drugs? They don't have an answer. They just want to talk about ivermectin."

I've written about this problem before. Since the pandemic began, physicians and researchers have launched hundreds of trials for Covid-19 drugs, involving thousands of volunteer participants. But drug trials are complicated and expensive. Taken individually, few of those trials had the rigorous design or statistical power to give results robust enough to change the standard of care. A few did, of course. The drug remdesivir—in a trial partially supported by a pharma company—showed some success. Expensive monoclonal antibodies (touted by Florida governor Ron DeSantis as an alternative to vaccines or masks) were hits, too. But a health care worker has to administer them. "There was this notion of a 1,000 flowers

blooming, all these individual sites doing local trials. But there was no integration of those, so you couldn't generate answers that would change guidelines," Hernandez says.

A big, multicenter trial Hernandez is running—the sixth in a series of NIH-funded studies called Accelerating Covid-19 Therapeutic Interventions and Vaccines, or Activ-6—will also look at fluvoxamine, a steroid called fluticasone, and, yes, ivermectin, but at different doses than the Together trial administered. "People recognized back in the spring that there was a gap in the Activ programs, which is how to study drugs that were easily administered at home and had a long safety record," Hernandez says. In his trial, people can sign up from anywhere and get their drugs (or placebos) by mail. It's a convenient way to get data, and it also gets around another problem with drug trials. Over the course of a fast-moving pandemic, a local wave of patients might crest and then break before an academic hospital can set up the infrastructure to actually do the study. But people can sign up for Activ-6 from home, making it a lot more flexible. (Together dealt with that issue by studying people in Brazil, where it was easier to find sick people.)

Why do another trial at all if the evidence for ivermectin's usefulness is collapsing? Well, for one thing, the researchers started planning it before the collapse began. It takes a while for a big trial to change course. Methodologically and bureaucratically, a lot of groups have to sign off, and researchers and administrators have been planning Activ-6 for months—since the days when ivermectin looked like a better bet. "Based on the existing data, particularly the Together trial, there is not any evidence that ivermectin has any role in the outpatient realm," says David Boulware, an infectious disease physician and researcher at the University of Minnesota who is cochair of the Activ-6 steering committee. "There's no data on clinical benefit. Does it prevent hospitalization or ER visits? Does it reduce severity or duration of symptoms? When you put the data together, there's nothing

conclusive. The point of Activ-6 is: Let's get a definitive answer, because people are using it."

Much of the US response to the pandemic has been exactly this backward—responsive to misinformation rather than getting out in front of it. This has been going on for long enough that the pandemic itself has changed. Vaccination does an excellent job keeping people out of the hospital, but people get breakthrough cases, albeit relatively mild ones, even where vaccination is common. Everyone would benefit from something their physician could prescribe that'd make them feel better and keep ERs clear for the desperately ill—with Covid, or anything else. A drug that actually worked in people, with good data behind it? That'd be worth a "wow."

More From WIRED on Covid-19

- 📩 The latest on tech, science, and more: Get our newsletters!
- Vaccine mandates work—but only if they're done right
- The US is getting Covid booster shots. The world is furious
- The Delta variant has warped our risk perception
- How to find a vaccine appointment and what to expect
- Need a face mask? Here are ones we like to wear
- Read all of our coronavirus coverage here