Metformin and COVID-19: An old drug with compelling anti-viral properties

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With the COVID pandemic approaching the end of its fifth year, the ninth major wave of infections is washing across the global population infecting tens of millions of people each day. The return to school and the winter holidays in the Northern Hemisphere will only cause the number of infections to swell, raising both the number of deaths and the ranks of the invisible millions suffering from Long COVID.

Both in the United States and worldwide, capitalist political authorities have effectively ended any effort to protect the population from this deadly disease. The "forever COVID" policy, as the WSWS has termed it, or declaring COVID to be "endemic," as Dr. Mandy Cohen, director of the Centers for Disease Control and Prevention, did last month, means more than just shutting down the collection of data on the number of infections, hospitalizations and deaths, or the number affected by Long COVID.

Willful blindness to the extent of the pandemic has been combined with near-abandonment of efforts to develop more powerful therapies against the disease, even as previously discovered therapies are of sharply declining effectiveness, because of the constant mutation of SARS-CoV-2, the virus which causes COVID.

Notably, the FDA pulled the emergency use authorization (EUA) of the monoclonal antibody Evusheld in January 2023. Only 14 months later, in March 2024, it supplanted this with pemivibart as COVID pre-exposure treatment for people with moderate to severe immune system dysfunction—solid organ transplant recipients, cancer patients receiving CAR T-cell therapy or stem cell transplants, or those with hematologic cancers that cannot mount a response to COVID vaccines, as well as others such as advanced HIV patients.

This treatment is extremely costly, with a two-hour infusion administered in a medical setting every three months, coming with a price tag of more than $6,000 for one course, not including the additional medical fees for the facility, nursing and physician costs that go into administering the treatment.

Additionally, for most of the world's population, access to the anti-viral treatments by Pfizer (Paxlovid) and Moderna (Lagevrio) has been thwarted due to lack of availability or the horrendous cost for such treatments. Pfizer announced last year that a five-day course of Paxlovid would cost nearly $1,400.

For patients with health conditions at risk for severe disease, Paxlovid can potentially reduce their risk of hospitalization by nearly half if taken early in the course of illness. But for the standard risk population, the treatment didn't show such benefits. And complications with the treatment include multiple drug interactions and a virological "rebound" that can extend the duration of the period when the patient is infectious to others.

Similarly, Remdesivir and Lagevrio have proven ineffective in patients with prior vaccine immunity or infections. The known safety concerns with these medications also mean potential complications for little benefit.

This is the reality behind Dr. Cohen's declaration that "we have the tools" to fight the virus that causes COVID, and her implicit blaming of patients who don't take advantage of the tools, rather than the profit-based medical system supposedly supplying them.

The development of new therapies is held back by a health system rooted in capitalist profit interests. Specifically, issues around intellectual property rights, how they are reformulated, regulatory blocks and financialization of the drugs pose significant challenges. Additionally, there are problems in convincing the population to accept new therapies, given the anti-scientific reaction and quackery that was the hallmark of the early days of the pandemic, with fascistic figures like Donald Trump and Brazil's Jair Bolsonaro promoting hydroxychloroquine and ivermectin.

The promising results with metformin

Still, one recent medication that has appeared to overcome some of these hurdles is an old drug that has been used to treat diabetes, called metformin. Known to have anti-viral properties, its cheap price, favorable side-effect profile and widespread availability have aroused interest in its potential benefit to treat COVID.

What follows is a summary of significant research on the anti-Covid properties of Metformin, and must not be read as a recommendation for its use without consultation with a well-informed physician familiar with a patient's medical history and overall condition. Moreover, Metformin may produce side-effects and is not well-tolerated by all patients to whom it is prescribed.

Discovered in 1922, metformin didn't become widely used until the mid-1990s when broad population-based studies proved its benefits. It is now the most widely used oral therapy for regulating blood sugar levels in diabetics. It has been proven to lower risks of age-related conditions like cardiovascular diseases and cancers as well as reduce all-cause mortality in diabetics. In 2022, it was the second most prescribed drug in the US.

As authors of a 2023 review paper on metformin noted, "Interestingly, metformin was originally investigated as an anti-influenza drug in the early 1940s and showed some promise in improving flu symptoms coupled with reducing blood glucose levels. While it was not directly pursued as an anti-influenza drug, metformin showed promise in a variety of infections. Further retrospective studies suggest that metformin has protective benefits during flu infection as well. For example, obese patients with a history of metformin treatment have been shown to have a lower rate of influenza mortality. Another study demonstrated that in diabetics, metformin treatment reduced overall risk for hospitalization due to infections compared to other oral hypoglycemics such as sulfonylureas."

Complications associated with COVID disproportionately affect the

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elderly, mainly due to their decline in immune function and ability to fend off infections. Also, those with comorbidities like diabetes and obesity can also develop severe reactions from a COVID infection. Preexisting diabetes has also been a risk factor after infection with SARS-CoV-1 and MERS-CoV coronaviruses. Moreover, patients treated in ICUs for severe complications with these viruses fared better when their blood glucose levels were kept in normal ranges.

The exact mechanisms for metformin's health benefits have not been completely worked out. But some researchers have pointed to the possibility that metformin through its ability to cause changes to the ACE2 receptor—it adds a phosphate group to this receptor, causing conformational and functional changes—it could decrease the binding of the virus to respiratory cells.

It has also been theorized that metformin's anti-viral properties stem from its ability to block a crucial signaling pathway used by the coronavirus. A study published in January 2023 in the journal *Virus Research* found that in cell culture the administration of metformin to SARS-COV-2-infected cells led to a dramatic decline in viral proteins and viral life cycle, thus protecting these cells. A small group of patients treated with metformin in the study showed a drop in their viral titers, underscoring that their "results unambiguously demonstrated a potent anti-SARS-CoV-2 effect of metformin."

Moreover, irrespective of one's diabetic state, metformin has been shown to ameliorate the immune system's response to inflammatory pathways, reducing cytokine levels, which have been implicated for development of severe COVID. As the authors of the above review underscored:

> Metformin has the capability to impact immune responses through its modulation of inflammation, the microenvironment, and via metabolic and non-metabolic action on immune cells themselves. These findings highlight the ability of metformin to modulate immune cell function, specifically in T cells, macrophages, and B cells which are essential for controlling responses to infection and generating long-term immunological memory.

One of the first reports on the potential for metformin to mitigate the deadly consequences of SARS-CoV-2 infection was published online in May 2020 from researchers in Wuhan, China. In their retrospective analysis of diabetic patients hospitalized with confirmed COVID from January 27, 2020 to March 24, 2020, in-hospital mortality for the metformin group was 2.9 percent (3 of 104 patients), versus 12.3 percent (22 of 179 patients) for the group not taking metformin.

Another early observational report was published in preprint form in June 2020 by Dr. Carolyn Bramante from the University of Minnesota and colleagues. In that retrospective cohort analysis utilizing data extracted from the insurance company UnitedHealth Group's Clinical Discovery Database, they analyzed the impact of COVID-19 on 6,256 patients admitted to US hospitals, of whom 2,333 were taking metformin in an outpatient setting. Interestingly, the study showed that there was a statistically significant reduction in mortality, but only for women.

The COVID-OUT clinical trial

Nonetheless, with respect to gender, the above work prompted the Minnesota group to initiate the COVID-OUT clinical trial that enrolled participants, either overweight or clinically obese, from December 30, 2020 to January 28, 2022, to investigate three medications: immediate-release metformin, ivermectin (anti-parasite drug), and fluvoxamine (an anti-depression medication from the group known as selective serotonin reuptake inhibitors). The trial included 1,126 people who gave their consent to participate and completed at least one long-term follow-up survey 180 days after starting in the trial. There were six subgroups, one each for metformin plus ivermectin, placebo plus ivermectin, metformin plus fluvoxamine, placebo plus fluvoxamine, metformin plus placebo, and placebo plus placebo.

The study was "quadruple blinded," which meant that neither the investigators, the individuals who assessed outcomes (i.e., Long COVID), the treating clinicians, nor the participants themselves knew which combination of drugs any participant was receiving.

The analysis of the impact of metformin on Long COVID was published in *Lancet Infectious Diseases*, showing that the drug metformin lowered one's risk of developing Long COVID by 41.3 percent, while no such reduction was seen with ivermectin or fluvoxamine.

The overall incidence of Long COVID in the metformin group nearly one year out from their initial infection was 6.3 percent compared to 10.6 percent in the placebo group. Earlier initiation of metformin during acute COVID-19 resulted in a greater reduction in risk. Initiating metformin within four days of symptom onset reduced risk by 63 percent versus 36 percent for initiation after. The strain of the virus did not affect the incidence of Long COVID. Vaccination status also did not impact the results; the reduction in risk was the same for both vaccinated and unvaccinated individuals.

Most recently, their latest publication in the journal of *Clinical Infectious Diseases* demonstrated a dramatic 3.6-fold reduction in SARS-CoV-2 viral load by day 10. Those receiving metformin were less likely to have detectable viral load than placebo by day five or day 10. The reviewers of the study commented that this

> study makes a strong case for a potential effect of metformin on COVID-19 virologic decay and prompts reevaluation of existing data in support of its use. In vitro studies have identified both antiviral and anti-inflammatory activities of the drug, and the investigators initially identified metformin as a promising agent through use of sophisticated in silico modeling.

Furthermore, observational studies have suggested that individuals treated with metformin for diabetes have improved COVID-19 outcomes compared with those not on this drug. While cross-study comparisons have limitations, it is notable that the absolute risk reduction for hospitalization or death for metformin versus placebo in COVID-OUT was nearly identical to that from a recent study that compared nirmatrelvir-ritonavir (Paxlovid) to lack of treatment in a propensity-scored matched analysis in the vaccination era (i.e., 1 percent versus 3 percent).

The fact that more than 50 percent of participants in COVID-OUT were vaccinated further amplifies the relevance of the study results to the current immunologic profile of today's population, where nearly everyone has been vaccinated, or had COVID-19, or both.

The authors of the COVID-OUT studies should be commended for their initiative, which has provided compelling evidence for the benefits offered by Metformin. Further work to confirm these benefits should be expedited and consideration given to bringing other treatments forward to address the vacuum that exists in the treatment of COVID.

Clearly, the paucity of effective treatments for COVID and mitigating Long COVID in a period where mass infection has been normalized is part and parcel of the logic of "forever COVID." The need for treatments

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to address the harms caused by repeat infections with SARS-CoV-2 underscores the irrational and reactionary character of the policy of mass infection.

Unlike the flu, where adults may catch the influenza virus on average twice per decade, serial viral infection with COVID is commonplace. There have been more than 1.1 billion infections across the US during the COVID pandemic; on average, every person in the US and, by extension, the rest of the world, can expect to be infected annually. And given the long-term consequences of repeat COVID infections to respiratory, cardiovascular, neurological and metabolic systems, many have predicted that chronic health conditions will disable millions more and these illnesses will begin appearing at earlier ages than previously expected.

As has been previously stated, SARS-CoV-2, like any virus, lacks consciousness. Its constant mutation is part of its nature. The conscious factor in the pandemic, up to now, has been the decision made by the ruling elites that public health initiatives cannot encroach on the need to maximize the extraction of profit from the international working class. This needs to be countered by the conscious political mobilization of the working class, allied with principled scientists, to make the survival and welfare of working people, not profit, the basis of healthcare and society as a whole.

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