Can Prozac treat COVID? Perhaps, but a related drug may be better

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The rise of Omicron, the latest SARS-CoV-2 variant of concern, reminds us how quickly things can change during the pandemic.

Only a few weeks ago, we were hearing about a range of potential new COVID-19 antiviral drugs and antibody treatments. Now researchers are asking if such drugs will still work to treat Omicron, with its multiple new mutations. We'll be hearing more about this in coming weeks.

> Signs are emerging that some COVID-19 antibody drugs don't work as well against Omicron and may need to be modified, with Regeneron reporting that preliminary testing indicates its therapy loses effectiveness https://t.co/puh48CLvJ8
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> — Anthony DeRosa (@Anthony) November 30, 2021

However, another approach to treating COVID is to "treat the host." Rather than target the virus itself, this involves treating the body's overwhelming response to the virus. This approach is less susceptible to new viral variants.

And for this, we have some progress with, at first glance, an unlikely group of drugs to treat COVID-19—antidepressants. These include fluoxetine (for example, Prozac) and the related drug fluvoxamine (for example, Luvox). It's early days yet. But here's what we know so far.

How could antidepressants treat COVID?

The antidepressants under investigation are SSRIs or selective serotonin reuptake inhibitors. These commonly prescribed mood-altering drugs block "reuptake" of the naturally occurring chemical messenger, serotonin, by nerve cells in the brain; some antidepressants stop serotonin being broken down. These mechanisms leave more serotonin available to pass messages between nearby nerve cells.

There are two ways SSRIs could have an effect on COVID-19.

First, human biology is frugal

Biological "frugality" sets the scene. It takes a lot of effort for the body to make a single important molecule and a huge undertaking if you need hundreds of them. So, biology directs important molecules to multi-task.

For example, we all make serotonin by introducing a few changes to the chemical structure of the essential amino acid tryptophan, commonly present in food.

Serotonin is then tasked with being:

- a messenger in the brain
- a molecule to cause contraction in the gut
- an inducer of platelet clotting, and
- a modulator of how blood vessels work, including how they constrict and how they interact with the immune system.

The virus responsible for COVID-19 drives a devastating hyperinflammation in serious disease. This involves many of the systems serotonin strongly regulates—inflammation, platelet clotting and proper functioning of blood vessels.

So there's a potential link between drugs that influence serotonin, and COVID-19.

Second, drugs can open different locks

Drugs often act as a "key" to open certain locks in the body. However, in some cases, the "key" is not that specific and can surprise us by opening additional, unrelated locks.

This is called a pleiotropic response and is the basis of using existing drugs for new purposes (repurposing).

This may also explain why a mood-altering drug may be effective in serious infection. As we'll see later, it may open the lock to influence inflammation.

Have people tried SSRIs for COVID?

There have been a number of clinical trials showing favorable COVID-19 outcomes for people taking SSRIs.

In a preliminary study, outpatients with COVID-19 symptoms treated with fluvoxamine were less likely to deteriorate over 15 days compared with those taking the placebo.

Another study found patients hospitalized for COVID-19 who took antidepressants—including the SSRI fluoxetine, and non-SSRI antidepressants—within 48 hours of admission were less likely to be intubated or die than those who didn't take an antidepressant.

The latest evidence comes from a major independent study published online in late October. This found people diagnosed with COVID-19 who took fluvoxamine reduced their chance of symptoms deteriorating or needing to go to hospital, compared to those who took the placebo.

Although few studies have directly compared fluvoxamine with fluoxetine to treat COVID-19, the bulk of the best quality evidence suggests to date suggests fluvoxamine may have the greatest promise.

However, there are a number of studies on broader effects of other SSRIs including fluoxetine.

What could be happening?

It is likely our frugal biology is at work, in particular the influence of serotonin on platelets and blood clotting.

SSRIs may be reducing the incidence or size of blood clots, heart attacks and strokes we'd usually see in severe COVID-19.

SSRIs could also switch on anti-inflammatory pathways in the body, independent of any serotonin effect. Different SSRIs have different capacities to do this, which may explain why some SSRIs seem to have a greater effect on COVID-19 than others.

For instance, fluvoxamine is a more powerful key to unlock the sigma-1 receptor, which has a significant role in controlling inflammation. Fluvoxamine may also increase melatonin, which has anti-inflammatory effects.

What we still want to find out

Despite promising clinical trials, in particular for fluvoxamine, researchers still want to know:

- is this a class effect? In other words, would all SSRIs work? Although fluvoxamine is widely available, it is not on the World Health Organization's list of essential medicines, whereas fluoxetine is. So we need to know if these drugs are interchangeable within the class of SSRIs, or even with antidepressants more broadly
- we still don't know the precise mechanism behind why these drugs seem to work. But how much more data would we need before we start treating these patients in hospital?

- could fluvoxamine work for vaccinated people? Or is the potential mainly for those unvaccinated, and more likely to have severe disease?
- we need further information on possible side-effects of using SSRIs in COVID-19 patients, particularly if we are using doses different to the standard antidepressant dose. However, since SSRIs are existing and commonly used drugs, we already know a lot about how they work in the body, and any possible adverse reactions.

That said, based on the results to date with fluvoxamine in particular, we consider it needs to be added to the list of candidate COVID-19 drugs for further testing and evaluation.

Omicron may not be the last variant of concern. And by "treating the host" with existing drugs—SSRIs being just one example—we can offer patients options that are not at the mercy of future, unknown variants.

SSRIs can be dangerous if used in a dose that is too high for a particular person. These drugs should only be prescribed by your doctor. The drugs also have a number of potential drug interactions, increasing the risk of serotonin syndrome, which can be life-threatening.

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