Can Generic Drugs Be Repurposed for COVID-19 Treatment?

Dr. Buse:
In addition to new therapies, generic medications can be repurposed for use in treatment of several conditions, but are metformin, ivermectin and fluvoxamine viable treatment options for COVID-19?

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And joining us to share her research on the use of these drugs to treat COVID-19 is Dr. Carolyn Bramante. Dr. Bramante is an assistant professor in the Division of Geriatrics, Palliative and Primary Care at the University of Minnesota Medical School.

Dr. Bramante, thanks for joining me today.

Dr. Bramante:
Thanks so much for having me.

Dr. Buse:
Can you give our audience some background about what initially encouraged you to conduct a study of repurposing drugs for the treatment of COVID-19?

Dr. Bramante:
Well, the pandemic in general was just a very compelling, you know, urgent public health crisis, so, initially, I started to get involved in a little COVID research to better understand how much obesity was a risk factor, but then colleagues here at the university invited me to help with an observational analysis, because they had predicted metformin may be protective by looking at a big computer simulator that is normally used to simulate cancer cells and drug therapy targets, and early in 2020, the engineers who run the simulator created a simulator of SARS-CoV-2 and then identified proteins that they thought were important for the viral life cycle. And then other colleagues here at the university used natural language processing to cull the medical literature and find existing medications active on those proteins, one of which was metformin, active against the protein mTORC. And then we were able to use a large database early in the pandemic from United Health Group, their insurance claim data, and we saw an association between people who were already on metformin seem less likely to have severe COVID than similar individuals not on metformin, but that was just an observational analysis, and those are never conclusive, but we also found, uh, data published by UCSF in 2020 that they had tested metformin against SARS-CoV-2 in the test tube, so in vitro assays showing efficacy against SARS-CoV-2.

So, with the Insilico data, the in vitro data and then our observational data, it seemed worth doing a trial because metformin is very safe, widely available, very inexpensive, has few interactions. It's even used in children and during pregnancy, so it was a compelling therapy to want to understand better.

Dr. Buse:
That's, that's really compelling. So, can you tell us a bit about the design of the COVID-OUT study that you recently reported?

Dr. Bramante:
Yeah. So the COVID-OUT study actually included three medications, metformin, ivermectin and fluvoxamine, and it used a 2x3 factorial design, which is a clinical trial design of where you test parallel treatments and you're able to share control groups, so it's an efficient trial design. And with these three medications, because they are all oral pills, we could do this design and keep participants blinded to which medication they were receiving. And all of the medications had exact matching placebo pills in the trial. So that's a little bit about the sort of clinical trial methodology behind the three medications in the trial.

And then this was a remotely delivered trial, so that's a fairly new approach to clinical trials. So we did have participants submit proof of their positive SARS-CoV-2, but everything was done remotely through, e-mail secure databases, and we delivered the medications to patients. They were never in person with our study staff.

Dr. Buse:

Well, that's very cool. So, tell us about the results. What were the key findings regarding metformin, ivermectin, and fluvoxamine?

Dr. Bramante:

Well, among the top findings, none of the medications had any impact on the primary outcome. The primary outcome was a four-part composite outcome, so whether or not someone had hypoxemia on a home oximeter that we mailed them or if they had to go to the ER or hospitalized or died from COVID. So, having any one of those components meant they had the primary outcome. So, none of the meds showed any efficacy against the primary outcome. Secondary outcomes are a bit more interesting though. Neither fluvoxamine or ivermectin showed impact on our key secondary outcome, which was the primary outcome excluding the oxygen data. So the key secondary outcome was whether someone needed to go to the ER, be hospitalized, or died from COVID. Metformin did lower the odds of that key secondary outcome by over 40 percent, and in a subgroup of people who received the medications in less than four days of symptoms, it was over 50 percent. But this is a secondary outcome, so strictly speaking we are not able to say if that's statistically significant or not.

Dr. Buse:

Right. So, technically, it would be something that generates a very strong hypothesis that metformin works to reduce hospitalizations, ER visits and death for COVID-19 infection, but it wouldn't constitute proof.

Dr. Bramante:

No. I mean, some clinicians might see our results and view, view them as metformin is an easily accessible early outpatient treatment option, but as a researcher, I see this as an important contribution to the literature and in need for more research.

Dr. Buse:

Wonderful. For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and today I'm speaking with Dr. Carolyn Bramante about metformin, ivermectin and fluvoxamine for the treatment of COVID-19.

Iif you look at the results even further you know, and think about the 50 percent reduction in the secondary endpoint for patients that get metformin early in their course with COVID-19, have you started to change the way the practice is done in Minnesota?

Dr. Bramante:

Right, the fact that it seems to work earlier in the course of the disease is another bit of evidence that suggests there really is an effect there. That combined with the fact that the point estimate, the odds ratio gets lower as the severity of the outcome gets worse, so ER visit, hospitalization, so these all point towards metformin probably does have an effect. And, yeah, the interpretation of clinical trials should be nuanced and not necessarily black and white.

As far as treatment, you know, would this change treatment guidelines here in Minnesota or elsewhere? That's a discussion that we're just starting to have, but we're also working on important other analyses from the trial. So we had an optional substudy where patients could self-swab their anterior, anterior nose for viral load, so we are completing those analyses now, and I think that will be an important piece of evidence for people on guideline committees to see and to inform whether or not they think metformin should be included in treatment guidelines.

I myself don't work in primary care. I only work in our weight management clinics, so I'm not seeing patients with COVID. They're not reaching out to me for treatment.

Dr. Buse:

Yeah, and similarly, I haven't yet treated a patient with active COVID. Do you have any thoughts about the high risk of poor outcomes in patients with diabetes and the fact that many of them are treated with metformin at background?

Dr. Bramante:

Yeah, so that's really interesting. So there have been a number of observational analyses looking at, you know, metformin use and is it associated with less severe COVID, and the quality of these observational analyses is really hard to, to do well because there's a lot of confounding by indication. Right? People are on metformin most often because they have diabetes. Diabetes is a risk factor for poor outcomes from most infections. But yes, all these observational analyses point towards people who were on metformin before they got COVID having less severe COVID. And then we are looking at whether or not the portion of people who die from COVID, the portion who have diabetes, is that higher or lower than the portion of people who die from influenza who have diabetes. That's just a population-

level way of understanding if, if diabetes is a much bigger risk factor for poor outcomes in COVID compared to similar infections, like influenza.

Dr. Buse:

Well, it's really been a pleasure to talk to you Carolyn. Do you have any final messages you'd like to leave our audience with?

Dr. Bramante:

I think I'd love for the audience to read clinical trials very critically, read the supplements. All of these things take time though, and everyone is strapped for time. So we will hope to keep contributing to evidence around metformin for COVID. We hope others study it as well. And then we all do rely on guideline committees to help synthesize entire bodies of evidence.

Dr. Buse:

Well, thank you. As we come to a close, I'd like to thank my guest, Dr. Carolyn Bramante, for sharing her research on metformin, ivermectin and fluvoxamine for the treatment of COVID-19. Carolyn, again, thank you for joining us today.

Dr. Bramante:

Thank you for having me.

Dr. Buse:

For ReachMD, I'm Dr. John Buse. To access this episode and others from our series, visit ReachMD.com/DiabetesDiscourse where you can be Part of the Knowledge. Thanks for listening.