

# The Medical Letter<sup>®</sup>

## on Drugs and Therapeutics

Volume 65

May 29, 2023

ISSUE No.  
**1677**

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# The Medical Letter®

## on Drugs and Therapeutics

Volume 65 (Issue 1677)

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### COVID-19 Update

#### Metformin to Prevent Long Covid?

Results from a double-blind trial suggest that off-label use of the oral antihyperglycemic drug metformin in patients with COVID-19 may decrease the risk of post-acute sequelae of SARS-CoV-2 infection ("long COVID").

**LONG COVID** – The presentation and severity of long COVID varies widely; symptoms can include fatigue with pain or mood swings, cognitive impairment, and ongoing respiratory problems. In a meta-analysis of 54 studies and 2 databases, the prevalence of long COVID 3 months after SARS-CoV-2 infection was estimated to be 6.2% (95% CI 2.4%-13.3%). Long COVID was more common in COVID-19 patients who required care in an ICU or a general hospital ward than in those who did not (43.1% and 27.5% vs 5.7%). It was most prevalent in adult females.<sup>1</sup>

**MECHANISM OF ACTION** – The mechanism by which metformin could decrease the risk of long COVID is unclear. Metformin has antiviral effects *in vitro* and can decrease levels of inflammatory biomarkers such as interleukins 1 $\beta$  and 6.<sup>2,3</sup>

**CLINICAL STUDY** – In a randomized, double-blind trial (COVID-OUT), 1431 adults 30-85 years old with an elevated body mass index who had tested positive for SARS-CoV-2 infection  $\leq 3$  days previously and experienced symptom onset  $\leq 7$  days previously received either metformin or placebo for 14 days; some patients also received the antiparasitic drug ivermectin or the antidepressant fluvoxamine. None of these drugs decreased the incidence of severe COVID-19 within 14 days, the primary endpoint, compared to placebo.<sup>4</sup> In a prespecified secondary analysis (available only as a preprint), among 1125 patients who completed monthly follow-up surveys from day 60 to day 300, those who took metformin were significantly less likely than those who took placebo to report a diagnosis of long COVID (6.3% vs 10.6%; absolute risk reduction 4.3% [95% CI 1.1%-

7.6%]; NNT 23.3). The effect was greatest in patients who started taking metformin within 4 days after symptom onset.<sup>5</sup>

**ADVERSE EFFECTS** – Metformin can cause GI adverse effects, including a metallic taste, nausea, diarrhea, and abdominal pain. Lactic acidosis occurs rarely; because of this risk, metformin is contraindicated for use in patients with an eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>, and starting the drug in patients with an eGFR of 30-45 mL/min/1.73 m<sup>2</sup> is not recommended.

**DRUG INTERACTIONS** – Metformin is a substrate of organic cation transporter 1 (OCT1) and the multidrug and toxin extrusion (MATE) transporter; inhibitors of these transporters (e.g., codeine, cimetidine) can increase its serum concentrations and inducers of these transporters (e.g., metoprolol) can decrease them. Use of metformin with other products that increase the risk of lactic acidosis (e.g., alcohol, carbonic anhydrase inhibitors, iodinated contrast media) can result in additive effects. Metformin can decrease the anticoagulant effect of warfarin.

**DOSAGE, ADMINISTRATION, AND COST** – The dosage of metformin used in the COVID-OUT trial was 500 mg once on day 1, 500 mg twice daily on days 2-5, and 500 mg each morning and 1000 mg each evening on days 6-14.<sup>5</sup> The cost for a 14-day supply of metformin at this dosage is about \$1.50.<sup>6</sup>

**CONCLUSION** – In a double-blind trial, adults with SARS-CoV-2 infection who took metformin for 2 weeks were less likely than those who took placebo to later report a diagnosis of long COVID. The drug did not decrease the risk of severe COVID-19. Off-label use of metformin to prevent long COVID in high-risk patients with normal renal function is reasonable, but confirmatory data from a trial more specifically focused on long COVID would be welcome. ■

1. Global Burden of Disease Long COVID Collaborators. Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. *JAMA* 2022; 328:1604.

2. DE Gordon et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; 583:459.
3. TS Postler et al. Metformin selectively dampens the acute inflammatory response through an AMPK-dependent mechanism. *Sci Rep* 2021; 11:18721.
4. CT Bramante et al. Randomized trial of metformin, ivermectin, and fluvoxamine for Covid-19. *N Engl J Med* 2022; 387:599.
5. C Bramante et al. Outpatient treatment of COVID-19 and the development of long COVID over 10 months: a multi-center, quadruple-blind, parallel group randomized phase 3 trial. *Lancet* 2023 March 6 (preprint). Available at: <https://bit.ly/3ZVuPZv>. Accessed May 11, 2023.
6. Approximate WAC for the dosage used in COVID-OUT. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. May 5, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. [www.fdbhealth.com/policies/drug-pricing-policy](http://www.fdbhealth.com/policies/drug-pricing-policy).

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