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Time to Stop Using Ineffective Covid-19 Drugs

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In practicing evidence-based medicine, physicians use the best evidence currently available on safety and efficacy in making decisions on treatment choices for their patients. During the Covid-19 pandemic, some of the early treatment trials were rushed, leading to studies that were badly conducted[1] or had too few patients.[2] As a result, initial evidence of the efficacy of some Covid-19 treatments could not be replicated,[3,4] but these drugs were already in widespread use by then, and some clinicians have been reluctant to change to proven efficacious alternatives. Ivermectin and fluvoxamine, in particular, are still widely prescribed, even though evidence has been steadily accumulating to indicate that both treatments at acceptable doses are not effective for Covid-19.[3-5]

In this issue of the *Journal*, Bramante et al.[6] report the results of the COVID-OUT randomized, controlled trial of oral metformin, ivermectin, and fluvoxamine for the early treatment of SARS-CoV-2 infection in 1323 outpatients. The investigators found no reductions in hypoxemia, emergency department visits, hospitalization, or death associated with any of the three drugs. A strength of the trial is the selection of adults between the ages of 30 and 85 years who were at high risk for severe Covid-19 because of overweight or obesity. However, as a result, the trial may not be readily generalizable to patients at lower risk for severe disease. One secondary analysis, which should be interpreted with caution, suggested that metformin may reduce a composite of emergency department visit, hospitalization, or death in this population with overweight or obesity, a finding that indicates no more than the need for further investigation at this time.

When this trial was initiated in 2020, evidence on the three treatments was either unavailable or equivocal. Since then, data have been accumulating from several clinical trials, including meta-analyses of metformin, ivermectin, and fluvoxamine. In a combined analysis of antidiabetic agents involving more than 3 million patients with diabetes and Covid-19 in 24 observational studies and 110 patients in one clinical trial,[7] the investigators found that the use of metformin before hospital admission, but not in-hospital use, correlated with reduced mortality. In a meta-analysis of fluvoxamine involving 2208 outpatients with nonsevere cases of Covid-19 in three trials,[8] investigators found that those who received fluvoxamine did not have a lower incidence of hospitalization, mechanical ventilation, or death than those in the control groups. For ivermectin, a meta-analysis of 16 trials[8] involving 2407 patients with both severe and nonsevere illness showed no reliable evidence of reductions in mechanical ventilation,

hospital admission, duration of hospitalization, clinical severity, or mortality; in addition, the investigators found no effect related to the dose of ivermectin. In light of this available evidence of nonefficacy for ivermectin and fluvoxamine, how much evidence of nonefficacy is enough?

The treatment guidelines of the World Health Organization (WHO) provide a barometer for such decisions that is based on the latest evidence (as interpreted by experts from many countries) to provide recommendations regarding each candidate drug, with an indication of the quality of its evidence. The most recent WHO guidelines,[9] which do not include the results of the COVID-OUT trial, stipulate explicit recommendations against the use of fluvoxamine and ivermectin but provide no recommendation with respect to metformin. The guidelines also provide explicit recommendations regarding treatments that should be prescribed (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

Despite this WHO guidance, drugs with unproven efficacy against Covid-19 continue to be prescribed by some physicians. The results of the COVID-OUT trial provide persuasive additional data that increase the confidence and degree of certainty that fluvoxamine and ivermectin are not effective in preventing progression to severe disease. There are no evidence-based grounds to continue prescribing ivermectin and fluvoxamine when other efficacious treatments are available for patients with nonsevere Covid-19.

Prescribing nonefficacious treatments is not a neutral or harmless option. In addition to denying patients the appropriate treatment, such prescribing can lead to side effects without any therapeutic benefit and to drug shortages for patients who need the medications for other conditions. Hence, it is important to have reliable evidence of nonefficacy and to have journals publish such studies. It is also important that multiple rigorous randomized, controlled trials be performed to provide unequivocal evidence on the efficacy of new treatments, as the Covid-19 experience has shown.

As the American Board of Internal Medicine[10] pointed out regarding the promotion of misinformation by physicians, "There aren't always right answers, but some answers are clearly wrong." With respect to clinical decisions about Covid-19 treatment, some drug choices, especially those that have negative WHO recommendations, are clearly wrong. In keeping with evidence-based medical practice, patients with Covid-19 must be treated with efficacious medications; they deserve nothing less.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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