tags

Prof Salim Abdool Karim, Centre for the Aids Programme of Research, Durban, ministerial advisory committee, Ivermectin, fluvoxamine, metformin, World Health Organization, American Board of Internal Medicine,

Dump those ineffective COVID drugs: Abdool Karim

Despite WHO guidance, drugs with unproven efficacy against COVID-19 continue to be prescribed by some doctors, who ignore the wealth of evidence, and ample data showing these are not in their patients’ best interests.

In practicing evidence-based medicine, physicians should use the best evidence currently available on safety and efficacy in making decisions on treatment choices for their patients.

Prof Salim Abdool Karim, Centre for the Aids Programme of Research and former head of the COVID-19 ministerial advisory committee, in an editorial in the latest edition of The New England Journal of Medicine, wrote that during the pandemic, some early treatment trials were rushed, leading to studies that were badly conducted or had too few patients.

As a result, initial evidence of the efficacy of some treatments could not be replicated, 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, he wrote, even though evidence has been steadily accumulating to indicate that both treatments at acceptable doses are not effective for COVID-19.

Findings of a study conducted by researchers, also published in The New England Journal of Medicine, show the results of the COVID-Out randomised, controlled trial of oral metformin, Ivermectin and fluvoxamine for the early treatment of infection in 1,323 outpatients: they found no reductions in hypoxaemia, emergency department visits, hospitalisation, 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 generalisable to patients at lower risk for severe disease,” he wrote.

“One secondary analysis, which should be interpreted with caution, suggested that metformin may reduce a composite of emergency department visit, hospitalisation, or death in this population with overweight or obesity, a finding that indicates no more than the need for further investigation at this time.”

He wrote that 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 anti-diabetic agents involving more than 3m patients with diabetes and COVID in 24 observational studies and 110 patients in one clinical trial, 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 2,208 outpatients with non-severe cases of COVID-19 in three trials, investigators found that those given fluvoxamine did not have a lower incidence of hospitalisation, mechanical ventilation, or death than those in the control groups.

“For Ivermectin, a meta-analysis of 16 trial[s](https://www.nejm.org/doi/full/10.1056/NEJMe2209017?query=TOC&cid=NEJM%20eToc,%20August%2018,%202022%20DM1352386_NEJM_Non_Subscriber&bid=1121481433) involving 2,407 patients with both severe and non-severe illness showed no reliable evidence of reductions in mechanical ventilation, hospital admission, duration of hospitalisation, clinical severity, or mortality; in addition, the investigators found no effect related to the dose of Ivermectin.

“In light of this available evidence of non-efficacy for Ivermectin and fluvoxamine, how much evidence of non-efficacy 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, 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.

“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 non-severe COVID-19.

“Prescribing non-efficacious 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 non-efficacy and to have journals publish such studies. It is also important that multiple rigorous randomised, 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 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 must be treated with efficacious medications; they deserve nothing less.”

Study details

Randomised Trial of Metformin, Ivermectin, and Fluvoxamine for COVID-19

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Abstract

## BACKGROUND

Early treatment to prevent severe coronavirus disease 2019 (COVID-19) is an important component of the comprehensive response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

## METHODS

In this phase 3, double-blind, randomised, placebo-controlled trial, we used a 2-by-3 factorial design to test the effectiveness of three repurposed drugs — metformin, Ivermectin, and fluvoxamine — in preventing serious SARS-CoV-2 infection in nonhospitalised adults who had been enrolled within 3 days after a confirmed diagnosis of infection and less than 7 days after the onset of symptoms. The patients were between the ages of 30 and 85 years, and all had either overweight or obesity. The primary composite end point was hypoxemia (≤93% oxygen saturation on home oximetry), emergency department visit, hospitalisation, or death. All analyses used controls who had undergone concurrent randomization and were adjusted for SARS-CoV-2 vaccination and receipt of other trial medications.

## RESULTS

A total of 1,431 patients underwent randomisation; of these patients, 1323 were included in the primary analysis. The median age of the patients was 46 years; 56% were female (6% of whom were pregnant), and 52% had been vaccinated. The adjusted odds ratio for a primary event was 0.84 (95% confidence interval [CI], 0.66 to 1.09; P=0.19) with metformin, 1.05 (95% CI, 0.76 to 1.45; P=0.78) with Ivermectin, and 0.94 (95% CI, 0.66 to 1.36; P=0.75) with fluvoxamine. In prespecified secondary analyses, the adjusted odds ratio for emergency department visit, hospitalisation, or death was 0.58 (95% CI, 0.35 to 0.94) with metformin, 1.39 (95% CI, 0.72 to 2.69) with Ivermectin, and 1.17 (95% CI, 0.57 to 2.40) with fluvoxamine. The adjusted odds ratio for hospitalisation or death was 0.47 (95% CI, 0.20 to 1.11) with metformin, 0.73 (95% CI, 0.19 to 2.77) with ivermectin, and 1.11 (95% CI, 0.33 to 3.76) with fluvoxamine.

## CONCLUSIONS

None of the three medications that were evaluated prevented the occurrence of hypoxemia, an emergency department visit, hospitalisation, or death associated with COVID-19.

The NEJM article – Time to Stop Using Ineffective Covid-19 Drugs (Open access)

https://www.nejm.org/doi/full/10.1056/NEJMe2209017?

The NEJM study – Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19 (Open access)

https://www.nejm.org/doi/full/10.1056/NEJMoa2201662?

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