

## Prescribing medications responsibly in a pandemic

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As COVID-19 continues to ravage populations worldwide and the search for effective treatments for those who become ill goes on, patients and physicians have looked to novel interventions for hope. Some suggestions have been highly unscientific and dangerous, such as recommendations to ingest household cleaning products that circulated widely early in the pandemic. Others have been more plausible, such as recommendations for “off label” use of medications already approved by the U.S. Food and Drug Administration (FDA) to treat conditions other than COVID-19.

Two prominent examples of off label use have involved hydroxychloroquine and, more recently, ivermectin. Hydroxychloroquine, which was briefly available for treatment of COVID-19 under an Emergency Use Authorization between late March and mid-June 2020<sup>1</sup>, has since been demonstrated in clinical trials not to be effective<sup>2</sup>. Ivermectin, an antiparasitic drug approved in humans for treatment of certain tropical diseases, is also reportedly being prescribed off label for COVID-19, although the FDA has warned against use<sup>3,4,5</sup> and the National Institutes of Health (NIH) have concluded that evidence from clinical trials is not sufficient to “recommend either for or against the use of ivermectin for the treatment of COVID-19”<sup>6</sup>.

Now that the first COVID-19 vaccine has received full FDA approval through a Biological License Application for use in persons over 16 years of age, the American Academy of Pediatrics has warned physicians not to prescribe the vaccine for children under 12 while clinical trials are still underway.<sup>7</sup>

Off-label prescribing occurs frequently<sup>8</sup> and can seem especially promising in the face of a pandemic disease that carries significant risk of severe illness and death for which there are few or no effective treatments. But novel use even of approved medications raises concerns for both science and ethics. Scientifically, lack of data raises questions about appropriate dosing, safety or efficacy in the populations for whom novel use is proposed. Ethically, questions arise about how physicians should responsibly make a decision to offer a particular medication off label.

Physicians are expected to prescribe drugs “based solely on medical considerations, patient need, and reasonable expectations of effectiveness for the particular patient” (Opinion 9.6.6, “Prescribing and Dispensing Drugs and Devices,” *AMA Code of Medical Ethics*). When prescribing off label, however, physicians must determine what count as “reasonable expectations” under conditions of greater than usual uncertainty given the absence of relevant data for the intended use, in addition to

determining appropriate dose and route of administration.

Responsibly prescribing an approved medication for a novel, off label use requires that the physician reflect critically on the evidence that is available, seek input from knowledgeable colleagues or other medical professionals, and attend carefully to minimizing the risks to the patients for whom the physician intends to prescribe for an unapproved use (Opinion 1.2.11, “Ethically Sound Innovation in Medical Practice,” *AMA Code of Medical Ethics*).

Physicians must explicitly seek the patient’s consent to the off-label use and candidly disclose:

- | How the diagnostic or therapeutic service differs from the standard therapeutic approach (when there is one).
- | Why the physician is recommending the innovative modality.
- | The known or anticipated risks, benefits and burdens of the recommended therapy and any alternatives.
- | Experience with the innovative use in the professional community in general and the physician’s individual experience with the innovative use.
- | Any conflicts of interest the physician may have with respect to the therapy.

Having prescribed an innovative therapy, physicians must monitor and discontinue any therapy that is not benefitting the patient. To promote patient safety and quality of care, physicians should also share their findings with peers, including both positive and negative outcomes.

If the intervention in question is under study in a clinical trial designed to test the novel use, physicians should recommend that patients enroll in the study. If the patient does not meet inclusion/exclusion criteria or is unable to enroll for other reasons, it may be appropriate to consider seeking access under FDA’s “expanded access” program (Opinion 7.3.10, “Expanded access to investigational therapies,” *AMA Code of Medical Ethics*).

To best fulfill the fundamental ethical commitment to promote patients’ well-being, physicians must not allow the laudable goal of providing help and support in the face of a devastating public health crisis to overcome thoughtful, evidence-based judgment as medical professionals.

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1. Thomson K, Nachlis H. Emergency use authorizations during the COVID-19 pandemic: lessons from hydroxychloroquine for vaccine authorization and approval. *JAMA* 2020;324:1282-1283.
  2. National Institutes of Health. COVID-19 treatment guidelines: chloroquine or hydroxychloroquine and/or azithromycin, July 8, 2021. Accessed Aug. 28, 2021.
  3. Bellware K. Jail doctor prescribes livestock drug ivermectin to detainees with covid-19 despite FDA warnings. *Washington Post*. Aug. 25, 2021.
  4. Food and Drug Administration. Why you should not use ivermectin to treat or prevent COVID-19.

Accessed Aug. 28, 2021.

5. Food and Drug Administration. FAQ: COVID-19 and ivermectin intended for use in animals. Accessed Aug. 28, 2021.
6. National Institutes of Health. COVID-19 treatment guidelines: ivermectin. Accessed Aug. 28, 2021.
7. Jenco M. Don't use COVID-19 vaccine off label for children. *AAP News*; Aug. 23, 2021. See also Jenco M. CDC: Clinicians administering COVID-19 vaccines off-label risk losing liability protection, payment. *AAP News*; Aug. 24, 2021.
8. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. *Mayo Clin Proc.* 2012;87(10):982-990.

## **Additional ethics guidance in a pandemic**

The AMA offers an overview of foundational guidance regarding medical ethics for health care professionals and institutions responding to the COVID-19 pandemic.