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# Careful, medicines can also be poisons

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By **ALASTAIR STEWART**
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The impact of COVID-19 has stirred emotional and politically flavoured commentary on matters that normally are the province of scientific reasoning. Terry McCrann ("When one man's poison is another's medicine", August 7) berated the Therapeutic Goods Administration for defining hydroxychloroquine as a poison and later urged us to embrace hydroxychloroquine plus zinc as COVID-19 treatment.

Paracelsus, an early 16th-century physician, defined all cures as poisons, with only the dose determining whether a cure might provide more benefit than harm to patients. This is the principle highlighted in Adrien Albert's landmark 1951 book, Selective Toxicity. It is axiomatic to the discipline of pharmacology that all drugs are poisons. We teach our biomedicine and medical students to rationalise this core principle, using evidence to support the truth of a statement that has been cast to protect the community from the harms drugs may cause.

Hydroxychloroquine is and will always be a poison. Hippocrates advised to "do no harm". As educators, practitioners and scientists we apply this concept to drug treatments with a modern refinement: that drug treatment should produce a net improvement in the quality and/or duration of the patient's life. The positive impacts of modern drug therapies are immense, in large part because of the efforts of scientists, clinicians and regulators.

McCrann expresses frustration at the "expertism" and "bureaucratic" processes that serve to protect the community from drug harms. One man's "bureaucratic expertism" is

another's informed and reasoned decision-making process that values careful, dispassionate assessment of all the reliable evidence by university-educated scientists and clinicians.

Objective clinical trial evidence of "substantial efficacy and safety" on populations of patients is required to persuade the US Food and Drug Administration and our TGA to register a therapeutic. How else should we reach decisions on whether the public interest is served by granting authorisation for the sale of a therapeutic good for use in specific conditions?

Hydroxychloroquine has been used for prophylaxis in travellers to regions with a high prevalence of malaria. As noted by McCrann, this agent is used to treat a subset of patients with auto-immune diseases such as lupus in whom it provides an effective and inexpensive option. Does this long history of hydroxychloroquine use make this drug safe in all patients? No.

Hydroxychloroquine has the well-known side effects of heart arrhythmias and the risk of blindness with prolonged use. When prescribing, practitioners pay attention to coexisting medical conditions such as eye complaints and heart disease, and monitor responses and the duration of treatment to promptly stop or avoid treatment in patients who appear at risk of harm. The dose used for auto-immune disease has sometimes been exceeded in clinical trials of hydroxychloroquine in patients with COVID-19 or those at risk in an attempt to achieve therapeutic concentrations. Although these higher, more frequent doses may fail to achieve effective antiviral concentrations, a beneficial anti-inflammatory effect may yet be obtained.

Is the evidence supporting a net benefit of hydroxychloroquine in COVID-19 sufficient to warrant its off-label usage outside of well-designed and closely monitored clinical trials? Clearly not, according to the most recent editorial in the New England Journal of Medicine commenting on a study published on August 6, and previous studies that collectively provide no evidence of benefit for hydroxychloroquine when used as prophylaxis in those at risk, those with known COVID-19 exposure or in those with mild or severe COVID-19 disease. That editorial acknowledges that there is still some uncertainty as to whether hydroxychloroquine has benefit in any of the circumstances so far subjected to clinical trial, and therefore advocates the need for more definitive clinical trials.

A final word on poison. McCrann's definition, "a substance that is capable of causing the illness or death of a living organism when introduced or absorbed", is accurate. Hydroxychloroquine fits this definition.

However, to be fair, the ire of McCrann was primarily directed towards the reclassification by government of hydroxychloroquine with restricted PBS availability to preserve limited supplies for patients requiring it for evidence-based medical treatment. He characterised this amendment as newly classifying hydroxychloroquine as a poison, implying that it had not previously been regulated by the poisons standard.

This is incorrect. All therapeutic drugs are incorporated into the poisons standard. The Department of Health exercised discretionary power to amend the poisons standard 52D(2) (a) of the Therapeutic Goods Act 1989, enabling rescheduling of hydroxychloroquine, listing it under Schedule 4, Appendix D. Hydroxychloroquine has not been newly classified as a poison by this amendment. We note that salbutamol supplies have been protected by the same amendment, without any expression of concern.

Desperate times require desperate measures. In our opinion, the government-TGA action has avoided harms to COVID-19 patients in whom benefit from hydroxychloroquine is unlikely based on the most reliable evidence, and its potential for harm in these patients remains uncertain. The restriction in access has the dual benefits of maintaining supplies for those selected patients with auto-immune conditions who benefit from it, while preventing potential toxicity of off-label use in COVID-19 patients. No harm done.

Our TGA experts have served the Australian community well in providing an effective antidote to the rhetoric of domestic and international politicians and celebrities that regularly poisons community thinking on science and evidence-based medicine. This is not about US President Donald Trump, it is about science and high-quality clinical trial evidence.

*This opinion was written by Alastair Stewart, director of the ARC Centre for Personalised Therapeutics Technologies, in collaboration with his University of Melbourne colleagues Phillip Reece, honorary senior fellow, department of pharmacology and therapeutics; David Story, deputy director, Centre for Integrated Critical Care; and Megan Munsie, deputy director, Centre for Stem Cell Systems.*

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