# Off-label prescribing in the midst of a pandemic

## *The case of hydroxychloroquine*

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**IN THE MIDDLE AGES,** the deadly, feverish illness endemic throughout most of the world was known as ague. The term 'mal'aria' was unknown in English until the 18th century, but the alleged cure, derived from the South American cinchona tree, had already been in use for 100 years.[1] In the treatment of malaria, quinine (the active ingredient in cinchona bark) and its chemical successors chloroquine and hydroxychloroquine have largely been superseded by more effective, less toxic medications; hydroxychloroquine is reserved for still significant but less common conditions.

However, following US President Donald Trump's declaration that hydroxychloroquine is a potential 'game changer' in the fight against COVID-19,[2] there have been anecdotal reports of widespread off-label prescribing by medical doctors and dentists, including for themselves and their families. This has prompted Pharmaceutical Society of Australia President Dr Chris Freeman to write an open letter to prescribers on 21 March calling for an end to prescribing of hydroxychloroquine unless there is a genuine need.[3] Dr Freeman went as far as to suggest that pharmacists should refuse to dispense hydroxychloroquine unless they are satisfied it has been prescribed for an approved indication – rheumatoid arthritis, mild systemic and discoid lupus erythematosus, or the suppression and treatment of malaria.[4]

Off-label prescribing refers to a situation in which a medication is prescribed for an indication, route of administration or patient group not included in the product information.[5] The Therapeutic Goods Administration (TGA) has not approved any medications for the prophylaxis or treatment of COVID-19, so all medication prescribing for this purpose is considered off-label. Off-label prescribing is not new, nor does it necessarily represent poor prescribing. Prescribing for patient groups underrepresented in clinical trials and not covered in the product information is often off-label. Off-label prescribing may also occur in the absence of alternatives when there are grounds to suspect a medication is effective based on its known mechanism of action.[5] This is the rationale that has been put forward for the use of hydroxychloroquine for prophylaxis of COVID-19.

Off-label prescribing of hydroxychloroquine (or the closely related anti-malarial medication chloroquine) for prophylaxis of COVID-19 raises important safety concerns. It has been suggested that medical doctors may perform their own benefit-versus-risk analysis before deciding whether it is safe to use hydroxychloroquine.[6] The mechanism of action for antiviral activity is not clear, and evidence for clinical benefits is weak. Hydroxychloroquine interferes with the acidification of host cell lysosomes, and it is proposed that this could inhibit viral entry into host cells. In vitro studies do show that chloroquine and hydroxychloroquine can inhibit SARS-CoV-2 viral replication,[7,8] but at approximately 100-fold weaker potency than their activity against malaria parasites. Chloroquine and hydroxychloroquine accumulate to high concentrations within tissues, and modelling suggests that effective antiviral concentrations could theoretically be achieved in lung tissue with acceptable dosing protocols. However, chloroquine has proven ineffective in randomised controlled trials for other viruses.[9,10] There are currently no convincing data from human studies to support the efficacy of hydroxychloroquine for prophylaxis or treatment of COVID-19. The much-publicised non-randomised French trial of 20 patients with at least six days' follow-up reported that hydroxychloroquine and azithromycin combination lowered viral load, but this small trial had methodological flaws that limit conclusions that can be drawn.[11] In contrast to the lack of efficacy data, the side-effect profile of hydroxychloroquine is well established following more than 70 years of clinical use as an anti-malarial and immunomodulatory agent. Infrequent and rare side effects include retinal toxicity, cardiac toxicity, QT interval prolongation and agranulocytosis. Cardiac side effects may be of particular relevance given that COVID-19 is more severe in older people who are also likely to have cardiovascular comorbidity. A chart review of 355 people who died from COVID-19 in Italy reported 30% had ischaemic heart disease, 25% had atrial fibrillation and 10% had prior stroke.[12]

There are also important ethical considerations related to prescribing off-label hydroxychloroquine. Widespread off-label prescribing has led to hydroxychloroquine becoming out of stock at many pharmacies. This has meant

that people using hydroxychloroquine for approved and evidenced-based indications such as rheumatoid arthritis may no longer be able to access this treatment. These concerns have prompted the TGA to amend the current Poisons Standard to require initial treatment be authorised by a specialist in dermatology, intensive care medicine, paediatrics and child health, physician or emergency medicine.[13]

While there is a rational mechanistic basis to investigate the potential of hydroxychloroquine for the management of COVID-19, questions remain regarding its mechanism of action. Evidence to date from human trials has been inconclusive, and it is common for compounds with promising in vitro data to fail to produce meaningful clinical outcomes. The World Health Organization has included chloroquine or hydroxychloroquine as one of four potential treatments in the new multi-country SOLIDARITY trial.[9] However, there is currently no robust evidence to support prescribing hydroxychloroquine as a treatment or prophylaxis for COVID-19. Doing so risks unnecessarily exposing people to side effects and depriving people with approved indications from accessing their medication.

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