# International Union for Basic and Clinical Pharmacology (IUPHAR) Clinical Division considerations in the context of COVID-19 pandemics

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## Warnings on self-medication and stopping medicines

In the midst of an endless stream of often contradictory information on medicines, IUPHAR clinical division wishes to emphasise the danger of stopping medicines by patients suffering from chronic diseases. Patients should be strongly advised to contact their primary care doctor before considering any modification. Primary care doctors should contact the relevant specialist before considering any changes from standard care. Existing national/international guidelines should be followed; at this stage, there is no good evidence to deviate from existing guidelines. This includes medicines that have been the subject of scrutiny, in particular:

- ACE inhibitors or Angiotensin II receptor blockers (sartans) should not be discontinued.

- Long term Non Steroidal Anti-inflammatory Drugs (NSAIDs) for chronic inflammatory condtions should not be discontinued.  Short-term NSAID use for fever, headache or muscle aches should be discouraged, and paracetamol favored (max 3 g per day).

- Low-dose aspirin has no anti-inflammatory action and should not be discontinued

- Corticosteroids and other immune modulatory therapies: long term use should not be discontinued if currently indicated for disease management.  Some of these therapies are being investigated in clinical trials for treatment of COVID-19 at different stages of disease.

Self-medication (medication not prescribed by a licensed healthcare professional) is a well-known challenge, associated with wastage of resources, adverse drug reactions and drug-drug interactions (DDI). Necessary steps should be taken to avoid self-medication. Potential risks of self-medication include incorrect self-diagnosis, failure to seek medical advice promptly, failure to recognize pharmacological risks (contra-indications, drug-drug interactions, dose adaptation), and duplication of medication resulting in toxicity (such as using more than one paracetamol-containing preparation) or inadequate dosage. Health professionals should be actively involved in preventing risks of self-medication by appropriately informing, educating and giving scientifically rational therapeutic advice to patients, as well as warning patients on false "miracle cures" in the context of COVID-19.

*Some useful links:*
*https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19*
*https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19*
*https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang*

*https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2020/04/07/12/25/coronavirus-disease-2019-infection-and-ras*
*https://www.sifweb.org/en/covid-19/sif-documents*
*https://www.hug-ge.ch/coronavirus/recommandations-pour-professionnels-sante#considerations*
*https://www.medicinesinformation.co.nz/2020/03/20/medicines-and-covid-19/*
*https://sfpt-fr.org/covid19-presentation*

## Special pharmacological considerations in the older population

Older people everywhere are highly vulnerable to death from COVID-19. Key points to consider in management of geriatric patients are:

- Changes in ageing physiology that impact on pharmacokinetics and pharmacodynamics. This applies to experimental therapies used in COVID-19, where dose may need to be reduced to adjust for reduced volume of distribution and clearance, and an increased susceptibility to adverse drug effects;
- Lack of clinical trial data in geriatric patients, who appear to have been generally excluded from published and registered drug trials due to age, comorbidities and comedications;
- Higher prevalence of polypharmacy and multimorbidity, resulting in more use of medications that may affect the prognosis of COVID-19 described above;
- Medication management challenges including the impact of reduced drug supply, resulting in acute withdrawal or confusion around therapeutic substitution. Strategies such as medication simplification have been recommended.

*Useful links:*

*COVID-19 Pandemic: Considerations for Safe Medication Use in Older Adults with Multimorbidity and Polypharmacy. J Gerontol A Biol Sci Med Sci. 2020 Apr 30. pii: glaa104. doi: 10.1093/gerona/glaa104. PMID: 32353109*
*https://www.pharmacy.umaryland.edu/PALTC-COVID19-MedOpt*

## Medication errors, drug interactions and adverse drug reactions

Errors increase in times of pressure. Medication errors are a common cause of patient harm. There have been big changes in the way we do things, including decreased face to face contact for patient counselling and development of telemedicine. Health professionals and patients should be encouraged to check and question any changes in medicines.

The risk of drug-drug interactions increases when there is rapid uptake of new treatments. A pharmacokinetic example, lopinavir/ritonavir inhibits CYP3A4/5, responsible for the metabolism of many other drugs currently on the market. A pharmacodynamic example is combination of azithromycin and hydroxychloroquine, contributing to prolonged QT interval and increased risk of cardiac arrest in patients treated with other QT-prolonging drugs such as some antipsychotics.

Close monitoring of adverse drug reactions in patients with COVID-19 is needed, in particular when drugs are used outside of clinical trials. Increased safety monitoring is essential in a time when risks are high (eg. unusual care context or to patients different from those for which they are normally intended). Both individual reporting and systemic surveillance are needed. Pharmacovigilance allows a qualitative analysis of those cases spontaneously declared to national databases. Well-described underreporting of adverse drug reactions

may be accentuated in a period of high tension in hospital services. Clinical pharmacologist and pharmacovigilance networks have a key role to play to identify potential harms and signals. Cardiovascular risks of chloroquine, hydroxychloroquine, azithromycin and lopinavir/ritonavir, used alone or in combination, are of particular concern.

## Off label/compassionate drug use

Off label use is the unapproved use of an approved drug; i.e. a drug used to treat a different condition/population than it was originally approved to treat. The decision to prescribe off-label must take into account the risks and the benefits to the patient, as well as the evidence supporting the efficacy and safety of the proposed treatment. In such case, healthcare providers do not need special government approval but the patient has to be informed of such non-approved use in most countries (such as in the UK, Switzerland or New Zealand). Written informed consent is recommended for off label use in some circumstances (exceptional use or conditional use with evidence development) in some countries (such as Australia). A clear record of the medication(s) prescribed and reason for prescribing should be kept and the potential risks and benefits should be clearly communicated in order to provide appropriate informed consent. Outcomes, efficacy and adverse events should be monitored carefully.

Compassionate drug use is defined as the use of a new or unapproved drug to treat a severe or life-threatening health condition when no other treatments are available. Requirements for government approval differ from country to country. They can be made through a clinical trial or through special programs such as "expanded access" (USA), "special access" (Canada), "EU-wide and country-specific compassionate use" (EU), "special access scheme" (Australia), "Korean compassionate use system" (Korea) or "Japanese compassionate use system" (Japan).

*Useful links:*
*https://www.nejm.org/doi/full/10.1056/NEJMhle1409465*
*http://www.catag.org.au/wp-content/uploads/2012/08/OKA9963-CATAG-Rethinking-Medicines-Decision-Making-final1.pdf*

## Supply management: a worldwide problem - demand management: a local challenge/solution.

Supply management is likely to become a major problem with some short-term reduction in Chinese supply, and ongoing reduction of supply from India. Shortages of a wide range of medicines, including anaesthetic agents, muscle relaxants, benzodiazepines as well hydroxychloroquine or lopinavir/ritonavir.

Strategies may include:

- Identification of first, second and third line treatment options by specialist groups for common conditions;
- National and local priority setting and co-ordinated approach to supply and reduced wastage;

Another major concern of supply chain problems is the possibility of counterfeit drugs entering the market.

## Misleading claims and fraud

Exaggerated claims of benefit are common in health care and healthcare professionals and patients are especially vulnerable to these claims in situation of despair like during this unexpected pandemic, which can lead to reckless unintended risk-taking. Misleading claims may come both from well-meaning but misinformed sources and from those seeking financial gain. IUPHAR clinical division would seek to remind everyone about the importance of thinking critically, checking the primary sources of any claims and seeking out trusted sources of advice through the usual channels in national health services.

With increased shortage comes increased fraud, and a higher risk of counterfeit products entering the supply chains. A careful verification of Good Manufacturing Procedures (GMP) is particulary important.

## Clinical research

There are many hundreds of COVID-19 clinical trials registered world-wide and the numbers are increasing daily. IUPHAR clinical division would like to reinforce the following key points when conducting clinical research on medications:

- Be careful about translating between *in vitro* data to *in vivo* use. Examples are provided by chloroquine and hydroxychloroquine, ivermectin (where concentrations used in many *in vitro* studies are not compatible with human dosing), and by cases where metabolism/excretion are not adequately considered. *In vitro* data may speak for an antiviral efficacy but do not always reflect clinical efficacy as suggested by the hydroxychloroquine data with another RNA virus chikungunya.

- Do not cut corners with study design - whatever the emergency, well conducted and appropriately powered clinical trials are still needed in humans, in particular randomized double blinded standard-of-care controlled trials in order to avoid bias and recognize the importance of a control group to rule out the normal course of the disease. The opportunity should be sought to use adaptive study designs, in large and adequately powered studies, to remove treatments that are clearly ineffective and add new potential candidates as the trial proceeds.

- Drug testing needs rational use especially knowledge of PK/PD, drug regimen (e.g. hydroxychloroquine has a long half-life and requires a loading dose), knowledge of drug-drug interactions, contra-indications, pharmacogenomics and clear pharmacovigilance (e.g. long QT for hydroxychloroquine, azithromycin and lopinavir/ritonavir).

- Patient inclusion/exclusion criteria should be clearly defined and ideally standardized, in particular: clear definition of the disease and its severity (e.g. method for COVID-19 confirmation: RT-PCR, clinical, radiological? clinical or radiological definition of severity? supplemental O2 or ventilation requirement?). Underlying conditions/co-medications should be clearly listed, and a core decision protocol is needed.

- Primary and secondary outcomes should be clearly defined and standardized, and clinically relevant to assess efficacy and safety. Examples of clinically relevant outcomes are: mortality, duration of intensive care unit stay/ventilation period, mean duration of hospital stay, 7-point scoring (Discovery trial). Viral clearance/shedding are not be considered clinically relevant outcomes.

- Ensure proper regulatory and peer review, including ethical review and pre-registration of the trial, with proper power calculations, managements of patients' consent, use of data management tools, data monitoring, publication in peer-reviewed journals, grant access to raw data, and disseminate results in English.

- Ethics Committees need to be sensitized about the urgency of studies especially observational with minimal or no risk for expedited review or waiver -guidelines and guidance needed.

-The access to drugs required for the intervention arms should be guaranteed.  It is recommended to prioritise supply for clinical trials over off-label use.

-The futility of clinical trials should be assessed, for example there are currently many trials of hydroxychloroquine, some of which are poorly designed and good information should be available before many of these can finish and report. This use of resource appears unethical.

- The same GCP standards should be applied to clinical studies with traditional medicines/herbal drugs. The use of a standardized product is essential (as per pharmacopoeia) and should be ensured.

- IUPHAR wishes to promote the design of a collaborative common database (registry) to encourage healthcare professionals to collect data on covid19 patients across countries that is intended to provide answers to hypothesis-driven studies and epidemiological studies, while being efficient and not duplicate efforts. Indeed, it would foster collaboration and prevent fragmentation of research efforts.  Professionals including cases in the database should be given credit in publications derived from this work.

*Useful links:*
*https://www.transparimed.org/single-post/2020/03/27/COVID-19-clinical-trials-information-source*
*http://covid19.trialstracker.net/index.html*
*https://isaric.tghn.org/covid-19-clinical-research-resources/*


Useful ressources on drugs used in COVID-19:

*Drug-drug interactions:*
https://www.covid19-druginteractions.org/
https://crediblemeds.org

*Current evidence:*
https://iuphar.org/coronavirus-news/
https://covid-evidence.org/
https://covid-19.cochrane.org/
http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx
https://covid19treatmentguidelines.nih.gov/introduction/
https://bibliovid.org
https://www.bps.ac.uk/covid-19/resources-and-trusted-information