COVID-19 Pandemic: Considerations for Safe Medication Use in Older Adults with Multimorbidity and Polypharmacy

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Background

The COVID-19 (Coronavirus Disease-2019) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a serious risk to older adults' health worldwide. As of April 17th 2020, there are over 1.9 million confirmed cases with 131,037 deaths[1]. Most deaths in China, the United States (US) and Europe (Italy, Spain, Germany) occurred among adults aged ≥60 years[2-4].

Multimorbidity, the co-occurrence of two or more chronic conditions[5], and polypharmacy, the use of five or more medicines, are highly prevalent in older adults[6]. Achieving optimal medication use in this population is complex and challenging under normal circumstances. Given the disproportionate effect of COVID-19 on older adults, particularly those with multimorbidity, this challenge only increases. In this article, we therefore aim to highlight considerations to support safe medication use in older adults during the current COVID-19 pandemic.

Considerations for COVID-19 treatment in older adults

Clinical Trials

Current clinical management of COVID-19 infection focuses on early recognition, isolation, infection control measures and provision of supportive care[7,8]. Researchers have identified actions to help recognize COVID-19 symptoms early in older adults and provide appropriate management of the disease[9,10]. While there is no specific antiviral treatment for COVID-19, the World Health Organization (WHO) has prioritized some medications to be further investigated in clinical trials based on *in-vitro* clinical effectiveness and available safety data[11]. These include oseltamavir/remdesivir, lopinavir/ritonavir, chloroquine phosphate/(hydroxy)chloroquine sulfate.[10,11] The Clinicaltrials.gov registry has over 200 registered studies investigating COVID-19 and the Chinese Clinical Trial registry has over 500[12,13]. **Table 1** lists dosing and safety considerations in older adults for the above medications[14].

Of note, chloroquine and hydroxychloroquine have received attention for potential prevention and/or treatment of COVID-19. Both these medications are 4-aminoquinoline derivatives that differ only by a hydroxy group[14]. They have similar pharmacokinetic (PK) profiles **(Table 1)** and are immunomodulant drugs that are used to prevent and treat malaria, and in the treatment of rheumatoid arthritis and lupus[15]. *In-vitro*, chloroquine and hydroxychloroquine have been shown to reduce viral replication of SARS-CoV-2.[15] This has sparked interest to investigate their efficacy and clinical safety *in-vivo*.

Of the clinical trials registered on Clinicaltrials.gov[13], four aim to investigate chloroquine as a potential therapeutic agent for treating COVID-19 and 13 aim to investigate hydroxychloroquine. Three studies are investigating chloroquine or hydroxychloroquine in combination with other therapeutic agents (e.g. zinc, azithromycin, protease inhibitors). Many of these registered clinical trials for hydroxychloroquine and chloroquine, however, have exclusion criteria that prevent involvement of many older adults with multimorbidity. Of the trials that included details of inclusion/exclusion criteria (14 trials):

- Four exclude those with chronic kidney disease (glomerular filtration rate < 30 ml/min/1.73 m^2) or who are on hemodialysis
- Four exclude those who have a prolonged QT syndrome (QT_C > 450 milliseconds for men for women) or are prescribed medications that prolong QT_C
- Four exclude those with retinopathy/retinal disease/ macular degeneration/ changes in visual fields
- Three exclude those with chronic hepatic disease /liver cirrhosis/abnormal liver tests over 3 x upper limit of normal
- Three exclude those with reduced left ventricular function or who use digoxin
- Two exclude those prescribed psychoactive drugs or who have a severe mental illness
- One excludes those with ventricular arrythmias
- One excludes those with pancreatitis

To date, the average age of participants in published pilot studies of hydroxychloroquine is well below the age of patients who are the most affected by severe COVID-19. In the open label study of Gautret and colleagues[16], the 36 participants had a mean age of 45.1 (standard deviation, SD=22.0). Chen and colleagues included 62 participants with an average age of 44.7 (SD = 15.3) years[17].

When extrapolating current and future trial data to the multimorbid older adult, it is important to consider several factors, including pharmacokinetic (PK) changes with aging[18]. Cumulatively, these changes can increase the exposure to medications, increasing older adults' risk of type-A dose-related adverse drug reactions (ADRs)[18]. All of the aforementioned medications, considered as a priority for investigation to treat COVID-19, are metabolized by the liver and most of their metabolites are excreted renally **(Table 1)**. Many older adults have reduced liver/kidney function[19] and COVID-19 is thought to contribute to liver/kidney injury[20]. This could lead to significantly reduced metabolism and excretion of these agents, as well as medications prescribed for pre-existing conditions, increasing the risk of toxicity. Additionally, numerous drug-drug interactions between commonly prescribed medications (e.g. statins, warfarin) could occur with potential COVID-19 treatments. Conversely, oseltamivir, requires conversion via the liver to the active metabolite, and as such could have lower efficacy in those with liver dysfunction (if found to be effective). Adjusting medication doses with consideration of these PK changes and drug-drug interactions could decrease the likelihood of ADRs and improve outcomes for older adults.

Controversial issues with commonly prescribed medications in people with COVID-19

A number of controversial links have been made between certain medications and the risk of infection with and severity from COVID-19 infection.[21] These are particularly relevant to older people, who have a high prevalence of medication use for management of chronic diseases[5]. These associations are currently being investigated in pharmacovigilance studies and interventional clinical trials.

I. Angiotensin Converting (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

Chronic administration of ACE inhibitors and ARBs can lead to the increased expression of Angiotensin converting enzyme 2 (ACE2)[21], an enzyme that mediates the entry of SARS-CoV-2 into cells[22]. The clinical relevance of these claims is currently unclear and subject to confounding[23]. International cardiology societies currently recommend to continue using these medications[24,25].

II. Non-steroidal anti-inflammatory drugs (NSAIDs)

The use of ibuprofen and other NSAIDs, has been raised as a concern in people with COVID-19[26]. Similar to ACE inhibitors and ARBs, long-term exposure to NSAIDs has been reported to increase ACE2 expression[21,23]. Albeit controversial, long-term use of NSAIDs has also been associated with an increased risk of cardiovascular (CV) outcomes (e.g. stroke, myocardial infarction)[27]. Considering the higher risk of CV events during any acute respiratory tract infection, using NSAIDs (even short-term) is thought to increase this risk in

people with COVID-19[26]. Additionally, there is a concern that fever and/or dehydration due to COVID-19 in combination with NSAID use could lead to nephrotoxicity[28]. Prescribing NSAIDs in older adults for any indication has been identified as potentially inappropriate due to the risk of several ADRs[6].

The World Health Organization (WHO) does not endorse claims that the use of NSAIDs worsens outcomes in COVID-19[7]. Current guidance recommends acetaminophen as first line treatment for fever in COVID-19[29]. When considering the use of NSAIDs in older adults, risks and benefits should be individually assessed and carefully balanced[23].

III. Corticosteroids

Judicious use of corticosteroids such as one or two doses, to reduce immunopathological damage in the acute phase of an infection, has been proposed for COVID-19 treatment[30]. This is currently being evaluated in clinical trials. However, prolonged administration beyond the early stage of the disease has been shown to enhance viral replication (i.e. viral rebound) and increase the risk of adverse events (e.g. acute respiratory distress syndrome)[30]. Therefore, current recommendations suggest avoiding corticosteroids when treating COVID-19 outside a clinical trial setting, unless indicated for other reasons such as septic shock or exacerbation of pre-existing chronic obstructive pulmonary disease[7,24].

Considerations for safe prescribing and administration for older adults

With the increased complexity of medication regimens and increased strains on the healthcare system due to COVID-19, medication errors and medication-related problems are more likely and can lead to significant negative health consequences. Increased vigilance to prevent errors is needed. Geriatric syndromes, including falls and delirium may be precipitated by pre-existing medications and/or by COVID-19 and could be more difficult to manage considering required COVID-19-specific infection control measures. Determining if medications contributed to falls/delirium and deprescribing (discontinuing) them may prevent further complications[6].

In general, simplifying medication regimens in all older adults as much as possible could reduce the risk of medication-related harm[31]. It could also reduce infection risk and use of Personal Protection Equipment (PPE) by health care workers administering medications. In palliative patients, medication burden can be reduced by deprescribing medications where the time to benefit is discordant with comfort care (e.g. aspirin, statins)[32,33]. This extends to COVID-19 patients nearing end of life. Comprehensive guides on optimizing therapy for people with COVID-19 in post-acute and long-term care settings[32] as well as in palliative care[34] are now available.

Another priority is ensuring older adults have accurate and up-to-date medication lists. This could be important in the case of an unplanned hospital admissions due to COVID-19 [35]. Optimizing medication management and ensuring accurate medications lists can be achieved by the continuity of services such as medication reviews (e.g. via Telehealth) before, during or after a COVID-19 diagnosis.

Reports have been received internationally of consumers stockpiling certain medications (e.g.: acetaminophen, asthma inhalers). Physicians and non-medical prescribers are also prescribing medications (e.g. hydroxychloroquine) for potential COVID-19 infections based on limited evidence. The Food and Drug Administration (FDA) authorized emergency use of hydroxychloroquine from the US national stockpile for hospitalized patients unable to participate in clinical trials[36].

Therefore, medication shortages and stock delays are a real concern[37]. Older adults are particularly vulnerable to the consequences. For example, lack of supply could lead to abrupt medication discontinuation which can cause unwanted adverse drug withdrawal effects (ADWEs). Healthcare governance systems responsible for the regulation of pharmaceuticals, are adapting quickly to address and prevent these issues[37-39]. As an example, we have summarized some key legislative changes made in Australia regarding medication supply and services in response to COVID-19[37,38] **(Figure 1)**. New Zealand introduced similar legislative/funding changes to protect health professionals and high-risk/vulnerable patients[39,40].

Conclusion

Here we described three main considerations for medication management in older adults during COVID-19; pharmacokinetics and drug interactions when considering investigational therapies, medication reviews to simplify existing regimens and minimize iatrogenic geriatric syndromes and responding to supply shortages. Cumulatively, these considerations can help prevent avoidable drug-related adverse events and facilitate the recovery of older adults affected by COVID-19.

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Medication/MOA	Metabolism & Elimination	PK changes	Dosing in renal impairment	Dosing in liver impairment	Serious adverse drug reactions	Drug-drug interactions
Oseltamivir [14] Unspecified antiviral effects against SARS-CoV-2	**Metabolism:** Oseltamivir is a pro-drug converted to the active metabolite by hepatic esterases **Elimination:** The active substance is eliminated	• Exposure to the active metabolite is inversely proportional to declining renal function. • Exposure to the active metabolite at steady	• Moderate impairment (CrCl > 30 - 60 mL/min): 30 mg orally twice daily for 5 days • Severe impairment (CrCl > 10 - 30 mL/min): 30 mg orally	Mild or moderate impairment: No adjustment recommended	• Stevens-Johnson syndrome • Elevated liver enzymes and hepatitis	Concurrent use of oseltamivir and warfarin may result in an increased risk of bleeding

	entirely (> 99%) by renal excretion. .	state was 25% to 35% higher in older adults compared to young adults • Half-lives observed in older adults were similar to those seen in young adults.	once daily for 5 days • ESRD not on dialysis: Use not recommended .			

Remdesivir[14] Nucleotide analog, may inhibit viral nucleotide synthesis to stop viral replication	Public information lacking as this is an investigational product	When administered under expanded access (compassionate use) for 4 to 10 days, the following adverse effects were noted: • Transient GI symptoms (nausea, vomiting) • Hepatic effects (elevated aminotransferase levels)	Public information lacking as this is an investigational product

Lopinavir/Ritonavir[14,41,42] Viral protease inhibitors – available combined in dosage formulations (e.g. Brand name: Kaletra)	**Metabolism:** • Lopinavir is extensively metabolised by the CYP3A isozyme • Ritonavir is a potent CYP3A inhibitor, which	Geriatric-specific dosing advice is lacking as clinical studies did not include a representative sample of older adults	No specific dosing recommendations in renal impairment	• Mild or moderate impairment: No dose adjustment is necessary • Severe hepatic impairment: Use is not recommended	• **Cardiovascular:** Syncope, atrioventricular block • **Dermatologic:** Stevens-Johnson syndrome • **Endocrine:** Hyperglycemia • **Hepatic:** Elevated levels of aminotransferases	• Inhibitor of cytochrome P450 3A (CYP3A). Co-administration with medicines primarily metabolised by CYP3A (e.g. calcium channel blockers, statins, immunosuppressants) can increase their plasma levels. • Potent inducer of

	inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. **Elimination:** Mostly fecal elimination of metabolites					CYP2C19. If co-administered, medicines metabolised by CYP2C19 (e.g.: warfarin, glipizide, losartan) can have varying plasma levels.

Chloroquine Phosphate[14] May elevate endosomal pH and interfere with ACE2 glycosylation which is theorized to have antiviral effects against SARS-CoV-2	**Metabolism:** Using human liver microsomes (HLM) and cytochrome P450 (CYP450) including CYP2D6, 2C8,	No specific information related to age-related PK changes exists	Severe renal failure (GFR<10 mL/min): 50% of the normal dose should be administered. If prolonged treatment is necessary, the dosage should be	No specific dosing recommendations in liver impairment	• **Cardiovascular:** Atrioventricular block, cardiomyopathy • **Neurological:** Extrapyramidal disease • **Endocrine:**	Some major/significant interactions include concomitant use with QT prolonging medications (e.g. donepezil, amiodarone, tricyclic antidepressants)

	3A4 and 3A5 **Elimination:** Mainly renal excretion of metabolites		further reduced to 50 to 100 mg/day		hypoglycemia	
Hydroxychloroquine sulfate[14,43] Unspecified antiviral effects against SARS-CoV-2	**Metabolism:** Using human liver microsomes (HLM) and cytochrome P450 (P450) including CYP2D6, 2C8, 3A4 and 3A5	No specific information related to age-related PK changes exists	No specific dosing recommendations in renal impairment	No specific dosing recommendations in liver impairment	• **Cardiovascular:** Torsades de pointes • **Endrocrine:** Hypoglycemia • **Otic/Optic:** Hearing loss. Retinal damage	Some major/significant interactions include concomitant use with QT prolonging medications (e.g. amiodarone, tricyclic antidepressants)

	Elimination: Mainly renal excretion of metabolites					

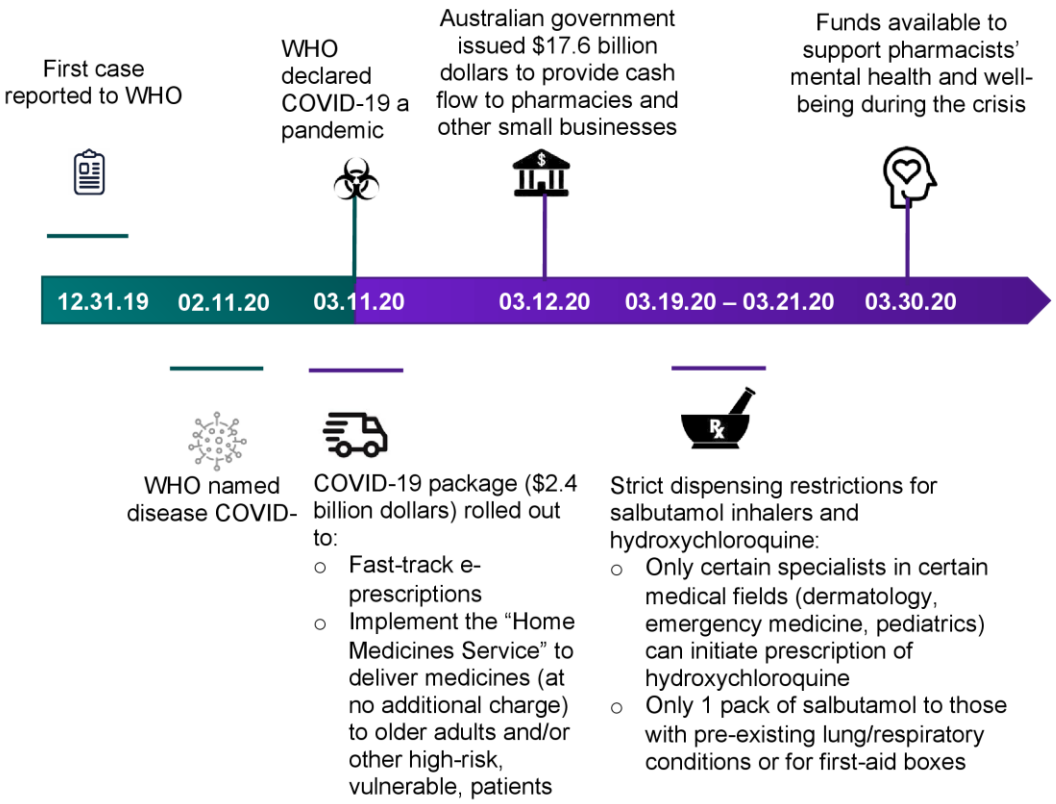
MOA: Mechanism of action; PK: pharmacokinetic; CrCl: Creatinine Clearance; ESRD: End-stage Renal Disease, ACE2: Angiotensin Converting Enzyme 2; GFR: Glomerular Filtration Rate.
The information in this table was extracted from IBM Micromedex Drug Consult and medication product information sheets

Table caption and Figure legend

Table 1: Dosing considerations of COVID-19 medications in older adults

Figure 1: Timeline for legislative changes in Australia related to medication supply and services in response to COVID-19

Figure 1


First case reported to WHO
WHO declared COVID-19 a pandemic
Australian government issued $17.6 billion dollars to provide cash flow to pharmacies and other small businesses
Funds available to support pharmacists' mental health and well-being during the crisis
12.31.19
02.11.20
03.11.20
03.12.20
03.19.20 – 03.21.20
03.30.20
WHO named disease COVID-
COVID-19 package ($2.4 billion dollars) rolled out to:
Fast-track e-prescriptions
Implement the "Home Medicines Service" to deliver medicines (at no additional charge) to older adults and/or other high-risk, vulnerable, patients
Strict dispensing restrictions for salbutamol inhalers and hydroxychloroquine:
Only certain specialists in certain medical fields (dermatology, emergency medicine, pediatrics) can initiate prescription of hydroxychloroquine
Only 1 pack of salbutamol to those with pre-existing lung/respiratory conditions or for first-aid boxes