


# COVID-SAFER: Deprescribing Guidance for Hydroxychloroquine Drug Interactions in Older Adults

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**BACKGROUND/OBJECTIVES:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes high morbidity and mortality in older adults with chronic illnesses. Several trials are currently underway evaluating the antimalarial drug hydroxychloroquine as a potential treatment for acute infection. However, polypharmacy predisposes patients to increased risk of drug-drug interactions with hydroxychloroquine and may render many in this population ineligible to participate in trials. We aimed to quantify the degree of polypharmacy and burden of potentially inappropriate medications (PIMs) that older hospitalized adults are taking that would interact with hydroxychloroquine.

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**METHODS:** We reanalyzed data from the cohort of patients 65 years and older enrolled in the MedSafer pilot study. We first identified patients taking medications with potentially harmful drug-drug interactions with hydroxychloroquine that might exclude them from participation in a typical 2019 coronavirus disease (COVID-19) therapeutic trial. Next, we identified medications that were flagged by MedSafer as potentially inappropriate and crafted guidance around medication management if contemplating the use of hydroxychloroquine.

**RESULTS:** The cohort contained a total of 1,001 unique patients with complete data on their home medications at admission. Of these 1,001 patients, 590 (58.9%) were receiving one or more home medications that could potentially interact with hydroxychloroquine, and of these, 255 (43.2%) were flagged as potentially inappropriate by the MedSafer tool. Common classes of PIMs observed were antipsychotics, cardiac medications, and antidiabetic agents.

**CONCLUSION:** The COVID-19 pandemic highlights the importance of medication optimization and deprescribing PIMs in older adults. By acting now to reduce polypharmacy and use of PIMs, we can better prepare this vulnerable population for inclusion in trials and, if substantiated, pharmacologic treatment or prevention of COVID-19. *J Am Geriatr Soc* 68:1636-1646, 2020.

**Keywords:** polypharmacy; potentially inappropriate medications; hydroxychloroquine; COVID-19; deprescribing

The first cluster of cases of 2019 coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported to

the World Health Organization (WHO) on December 31, 2019.<sup>1,2</sup> On March 11, 2020, the WHO declared COVID-19 a pandemic,<sup>3</sup> and at the time of writing, greater than 4.3 million laboratory-confirmed cases have been documented globally, with more than 290,000 related deaths.<sup>4</sup> In response, more than 600 interventional trials have been registered to investigate whether existing medications are safe and effective for the treatment of COVID-19.<sup>5</sup>

One class of medications that has demonstrated therapeutic properties *in vitro* are the antimalarial agents chloroquine and hydroxychloroquine.<sup>6</sup> Following results from the early emerging literature, including several small clinical trials,<sup>7-10</sup> an uncontrolled case series,<sup>11</sup> and an open-label nonrandomized study from France,<sup>12</sup> the U.S. Food and Drug Administration (FDA) granted an Emergency Use Authorization for hydroxychloroquine for hospitalized patients with COVID-19 who are unable to participate in clinical trials.<sup>13-15</sup> These studies were heavily referenced in the media despite inconclusive data, and trials for use as prophylaxis and treatment are ongoing.<sup>12,16</sup> More recently, an observational study on hydroxychloroquine was published showing no improvement in clinical outcomes in patients hospitalized with COVID-19.<sup>17</sup> At the present time, the FDA and the Infectious Diseases Society of America recommend against its use outside of clinical trials.<sup>18</sup> The results of randomized controlled trials are forthcoming, and the medication may still be prescribed outside of a trial, for lack of any alternative treatment.

One population in critical need of effective treatments for COVID-19 are older adults with comorbidities such as diabetes, hypertension, and cardiac conditions. Studies suggest older adults are more susceptible to infection with COVID-19 and at a higher risk of severe complications when compared with the general population.<sup>19,20</sup> Outbreaks in long-term care facilities resulting in death have emphasized the vulnerability of this population.<sup>21</sup> With increasing age, higher rates of medical conditions are observed, leading to a higher prevalence of polypharmacy (taking multiple medications).<sup>22,23</sup> As many as 56.7% of community-dwelling North Americans older than 65 years of age are taking five or more regular medications.<sup>24,25</sup> Polypharmacy is harmful, given the association with falls, fractures, and other adverse drug events.<sup>26</sup> However, we are now encountering another problem from taking multiple medications: a substantial risk of drug-drug interactions with potential therapies for COVID-19.<sup>27</sup> Many of these interacting medications are potentially inappropriate medications (PIMs) that themselves carry an increased risk for adverse drug events and could be deprescribed (stopped, tapered, or switched to a safer alternative).<sup>28-31</sup>

We hypothesized that due to polypharmacy and clinically significant drug-drug interactions, many older adults with their current drug regimens will be ineligible for COVID-19 therapeutic trials and/or treatment with medications that are currently under investigation, including, but not limited to, the antimalarial hydroxychloroquine. This despite older adults being at an increased risk of complications as a result of COVID-19 and representing a population most likely to benefit from different therapeutic options. We postulated that many of these drug-drug interactions are due to PIMs that could be deprescribed proactively. In light of a recent FDA warning regarding risk of

QTc prolongation, we examined hydroxychloroquine<sup>14</sup> (as a test case) to estimate the prevalence of prescribed medications with drug-drug interactions in a cohort of hospitalized older adults with polypharmacy. We aimed to better characterize the burden of PIMs that could be deprescribed with the impetus of the COVID-19 pandemic.

## METHODS

The MedSafer pilot study<sup>32</sup> was a large controlled before and after deprescribing trial that took place between September 2016 and May 2017 on four Canadian academic internal medicine clinical teaching units. The trial was designed to assess whether a computer-assisted medication review tool augmented the deprescribing of PIMs at discharge in a population of hospitalized older adults with polypharmacy. The software's algorithm identified PIMs and provided deprescribing recommendations for each individual patient by applying rules derived from widely available consensus documents for safer prescribing in older adults.<sup>30,31,33</sup>

Details of the trial are described elsewhere.<sup>32</sup> Briefly, patients were identified on admission via the emergency department to one of the designated units after discussion with the treating team to see if they met the broad inclusion criteria of 65 years and older and taking five or more medications. Patient data concerning medical conditions, validated medications, and some lab results were collected and entered into the MedSafer deprescribing electronic decision support software that identified PIMs through drug-disease combinations, drug-drug interactions, or those that should be avoided or used with caution in older adults. The MedSafer system generated a report of the PIM that included a level of harm (high risk, intermediate risk, or low risk but little added value), the rationale for deprescribing, and, when appropriate, a tapering protocol.

For the present study, we reanalyzed the MedSafer data as a representative sample of vulnerable older adults with polypharmacy. We first searched the literature for medications with known drug-drug interactions with hydroxychloroquine by examining the product monograph,<sup>34</sup> referring to drug-drug interaction websites,<sup>35,36</sup> and reviewing the exclusion criteria for a currently enrolling FDA and Health Canada approved hydroxychloroquine trial for COVID-19 (NCT04308668).<sup>5,37,38</sup> Medications with known interactions with hydroxychloroquine were grouped according to the American Hospital Formulary Service classification<sup>39</sup> (Table 1) and divided into two categories: chronic medications and medications typically prescribed for a short course such as antibiotics. We analyzed all patients in the MedSafer study who consented to participate in the deprescribing trial and who had a complete medication reconciliation performed on admission.

We theoretically "exposed" this patient cohort to treatment with hydroxychloroquine (minimum 5 days at a minimum dose of 600 mg daily as in NCT04308668) and identified possible drug interactions, as well as potential harmful outcomes such as increased toxicity of hydroxychloroquine, risk of QTc prolongation or malignant cardiac arrhythmia, or risk of other adverse drug events requiring closer monitoring during therapy such as severe hypoglycemia (Table 2). From all interacting medications

**Table 1. Medications with Potential Drug-Drug Interactions with Hydroxychloroquine**

AHFS drug class	Drug name	PIM <sup>a</sup> (Y/N)	Potential interaction with hydroxychloroquine
<b>Chronic medications</b>			
<i>Cardiac medications (risk of QTc prolongation)</i>			Rare but serious and potentially life-threatening side effects may occur. Can result in an increase of irregular heart rhythm, QTc prolongation, and malignant arrhythmia. Increased risk with underlying cardiac conditions or congenital/preexisting long QTc.
24,040,404	Procainamide	Y	
24,040,412	Flecainide, Propafenone		
24,040,420	Amiodarone, Ibutilide, Dofetilide		
242,400	Sotalol		
<i>Medications acting on the CNS (risk of QTc prolongation)</i>			
28,160,416	Venlafaxine	Y	
28,160,420	Citalopram, Escitalopram, Fluoxetine, Sertraline		
28,160,428	Amitriptyline, Desipramine, Imipramine, Doxepin	Y	
28,160,808	Typical antipsychotics (eg, haloperidol)	Y	
28,160,824			
28,160,804	Atypical antipsychotics (eg, quetiapine)	Y	
28,160,424	Trazodone	Y	
282,492	Droperidol	N	
2,828	Lithium	N	
404	Promethazine	Y	
404	Hydroxyzine	Y	
1,204	Donepezil	Y	
122,004	Cyclobenzaprine	Y	
<i>Gastrointestinal/Miscellaneous (risk of QTc prolongation)</i>			
563,200	Domperidone	Y	
562,220	Ondansetron	N	
861,204	Solifenacin	Y	
<i>Other drug classes requiring increased monitoring or dose adjustment</i>			
81,692	Dapsone	N	Concomitant use of HCQ with antimalarial agents may increase the risk of hemolytic reactions. Concomitant use may increase the risk of nerve damage with longer term use (months/years). May require dose adjustment or more frequent monitoring.
240,408	Digoxin	Y	Concomitant use may result in increased serum digoxin levels. Serum digoxin levels should be closely monitored in patients receiving combined therapy.
681,612	Tamoxifen	N	Increased risk of retinal toxicity when used in combination with HCQ; greater risk with longer therapy (months/years)
<i>Medications for diabetes<sup>b</sup></i>			
682,005	DPP-4 inhibitors	Y	Risk of hypoglycemia
682,006	GLP-1 receptor agonist	Y	
682,008	Insulin	Y	
682,016	Meglitinides	Y	
682,018	SGLT2 inhibitors	Y	
682,020	Sulfonylureas	Y	
602,028	Thiazolidinedione	Y	
<b>Short-term use medications</b>			
8,121,204	Erythromycin	N	Rare but serious and potentially life-threatening side effects may occur. Can result in an increase of irregular heart rhythm, QTc prolongation and malignant arrhythmia. Increased risk with underlying cardiac conditions or congenital/preexisting long QTc.
8,121,292	Azithromycin (Exception: Sometimes used Chronically) Clarithromycin	N	

(Continues)

Table 1 (Contd.)

AHFS drug class	Drug name	PIM <sup>a</sup> (Y/N)	Potential interaction with hydroxychloroquine
81,218	Levofloxacin, Ciprofloxacin, Moxifloxacin	N	
81,408	Ketoconazole, Itraconazole	N	
83,092	Chloroquine	N	
280,808	Methadone	Y	
83,092	Artemether, Lumefantrine	N	Coadministration may increase the toxic effect of antimalarials
83,092	Mefloquine	N	Coadministration of HCQ and mefloquine may increase the risk of seizure; avoid concurrent use (contraindicated)
283,228	Sumatriptan, Zolmitriptan	N	Rare but serious and potentially life-threatening side effects may occur. Can result in an increase of irregular heart rhythm, QTc prolongation, and malignant arrhythmia. Increased risk with underlying cardiac conditions or congenital/preexisting long QTc.

Abbreviations: CNS, central nervous system; HCQ, hydroxychloroquine; N, no; PIM, potentially inappropriate medication; Y, yes.

<sup>a</sup>Many of these medications are potentially inappropriate only under certain clinical circumstances (Table 2 lists potential triggering conditions).

<sup>b</sup>Metformin was not considered to be at risk of causing hypoglycemia for the purposes of this analysis.

we ran the MedSafer algorithms to determine the proportion of medications that were PIMs and that could be deprescribed. We also identified the triggering condition associated with each PIM (eg, atrial fibrillation, heart failure, dementia, delirium, or renal failure).

Finally, we developed recommendations for how to manage potential drug interaction including the option of not receiving hydroxychloroquine. Recommendations were based on the literature and expert consensus generated by the authors (experts in infectious diseases [T.C.L.], general internal medicine [T.C.L., E.G.M., J.D., B.R., and P.E.W.], clinical pharmacy [R.W., K.B., S.P., and L.P.F.], geriatrics [A.H. and L.P.F.], and clinical pharmacology/toxicology [P.E.W.]). Ideally PIMs would be deprescribed proactively, before infection with COVID-19, but logistically this may not always be feasible, and thus we have made recommendations for these patients. Examples of recommendations included medications that can be safely and abruptly held during treatment, those that require monitoring if there is to be ongoing use, and medications that likely cannot be stopped due to risk of an adverse drug withdrawal event.

## RESULTS

The MedSafer<sup>32</sup> cohort contained 1,001 patients with complete data on their home medications. The median age of the cohort was 80 years; approximately 50% were women. More than one-half had hypertension, approximately 40% had diabetes, and close to 50% were moderately to severely frail as defined by the Clinical Frailty Scale.<sup>40</sup> All patients were hospitalized in a tertiary care hospital and admitted to one of four general medical wards in one of three Canadian academic centers in Montreal, Ottawa, and Toronto.

We analyzed 1,001 participants and found that 590 (58.9%) were prescribed one or more usual home medications that could potentially interact with hydroxychloroquine. The most commonly prescribed drug classes with known interactions were antidiabetic medications

(330/1001 [33%]), the selective serotonin/norepinephrine reuptake inhibitors (SSRIs/SNRIs) (173/1001 [17.3%]), antipsychotics (typical and atypical) (136/1001 [13.6%]), and antiarrhythmics such as digoxin and amiodarone (64/1001 [6.4%]) (Table 3). The most common classes of antidiabetics were insulin, 138 of 1,001 (13.8%), and sulfonylureas, 90 of 1,001 (9.0%) (Table 3). The most serious interaction identified was a risk of QTc prolongation, torsade de pointes, and sudden death. A common but less severe interaction was a risk of hypoglycemia requiring increased monitoring. Lowering of the seizure threshold and pharmacokinetic interactions leading to increased hydroxychloroquine levels was uncommon.

We then determined how many PIMs (as identified by the MedSafer tool) with known interactions with hydroxychloroquine presented an opportunity to be deprescribed proactively. Of the 590 of 1,001 (58.9%) of participants who were prescribed a medication that could interact with hydroxychloroquine, 255 patients had the respective medication identified as a PIM, representing 43.2% of all patients with an interacting medication. Some common deprescribing opportunities that were identified included (1) too high a dose of digoxin for a patient's renal function, (2) antipsychotic use in patients with a known history of delirium or neurocognitive disorder (risk of stroke, falls, confusion), and (3) insulin and sulfonylureas in patients with a history of hypoglycemia and/or tight glycemic control (hemoglobin [Hb]A<sub>1c</sub> <7.5%) (Table 4).

We prepared recommendations for the management of interacting medications in patients with COVID-19 who may want to receive treatment with hydroxychloroquine if found to be effective. Examples include holding low doses of antipsychotics or antidepressants during therapy, QTc monitoring and electrolyte optimization with continued use of QTc prolonging agents, and glucose monitoring with concurrent diabetes medications. We also highlight medications such as amiodarone that cannot be stopped on short notice for inclusion in clinical trials, due to its prolonged half-life (Table 2).

**Table 2 Medication Management for Potentially Inappropriate Medications with Hydroxychloroquine Interaction<sup>a</sup>**

AHFS drug class	Drug name	Triggering condition	General rationale for deprescribing	Suggested medication management for hydroxychloroquine interaction <i>if</i> unable to deprescribe in advance
24,040,404 24,040,412 24,040,420 24,040,412 242,400	Procainamide Flecainide Dofetilide Sotalol Propafenone	Atrial fibrillation	Data suggest that rate control yields better balance of benefits and harms than pharmacologic rhythm control for most older adults.	If unable to deprescribe or hold during coadministration, use likely precludes HCQ given known risk of TdP for all medications listed apart from propafenone (conditional risk of TdP). Risk of sudden death.
24,040,420	Amiodarone	Atrial fibrillation	Amiodarone is associated with multiple toxicities including thyroid disease, pulmonary disorders, and QT interval prolongation. Consider a safer alternative.	The half-life of amiodarone is 60 to 142 days for long-term oral maintenance therapy. If unable to deprescribe well in advance (weeks); likely precludes use of HCQ given known risk of TdP and risk of sudden death.
240,408	Digoxin	Heart failure; chronic kidney disease; atrial fibrillation	Higher dosages of digoxin are not associated with any additional benefit and may increase risk of toxicity, especially in the presence of renal insufficiency.	If low dose (<125 µg daily) may consider holding during coadministration. Consider alternate means of rate control. If given for HF: consider holding or reducing dose during HCQ treatment. Monitor for arrhythmia, monitor electrolytes (Na, K, Mg). Monitor digoxin level if available (coadministration may increase digoxin levels).
280,808	Methadone	Triggered for all patients (unless active cancer or palliative treatment)	Do not initiate or maintain opioids long-term for chronic pain until there has been a trial of nonpharmacologic treatment and of nonopioid medications.	Chronic methadone therapy likely precludes use of HCQ given known risk of TdP, sudden death, and risk of withdrawal syndrome from holding methadone therapy.
28,160,416 28,160,420	Venlafaxine Citalopram, Escitalopram, Fluoxetine, <sup>b</sup> Sertraline	HypoNa Recurrent falls	SSRIs/SNRIs increase the risk of hyponatremia and also increase the risk of recurrent falls in older adults.	If low dose, consider holding during therapy and monitor for early withdrawal symptoms: dizziness, GI upset, flu-like symptoms, paresthesias, insomnia, and psychiatric problems. For higher doses, suggest avoiding HCQ with (es) citalopram given known risk of TdP and sudden death. Possible risk of TdP for venlafaxine and conditional risk for fluoxetine and sertraline (coadministration requires careful electrolyte and QTc monitoring).
28,160,424	Trazodone	Flagged for all older adults	Do not use trazodone for sleep disorders or as first choice for behavioral symptoms unless agitation is severe and nonpharmacologic interventions have failed. Increased risk of falls, daytime drowsiness, and impaired cognition.	If low dose, consider holding during therapy and monitor for withdrawal symptoms. For higher doses, may consider reducing dose with careful QTc monitoring or avoiding HCQ altogether given possible risk of TdP.
28,160,428	Tricyclic antidepressants, Desipramine, Imipramine, Doxepin	Dementia; urinary retention; BPH;	Alone or in combination may precipitate or worsen delirium, urinary retention,	If low dose, consider holding during therapy and monitor for early withdrawal symptoms:

*(Continues)*

Table 2 (Contd.)

AHFS drug class	Drug name	Triggering condition	General rationale for deprescribing	Suggested medication management for hydroxychloroquine interaction if unable to deprescribe in advance
		delirium; interactions with anticholinergics	constipation, glaucoma, urinary retention, and adverse CNS effects through anticholinergic effects.	dizziness, muscular pain, GI upset, headache, malaise, trouble sleeping, irritability, hyperthermia, mania. For higher doses, suggest avoiding HCQ. If used concurrently, would require QTc and electrolyte monitoring. Amitriptyline and doxepin have a conditional risk of TdP. Nortriptyline and desipramine have a possible risk of TdP.
28,160,804 28,160,804 28,160,808 28,160,824	Typical and atypical antipsychotics	Triggered for all patients unless history of schizophrenia or bipolar disorder	Do not use antipsychotics for sleep disorders or as first choice for behavioral symptoms unless agitation is severe and nonpharmacologic interventions have failed. Antipsychotics increase risk of stroke, falls, confusion, extrapyramidal side effects, aspiration, and death.	If low dose, consider holding during HCQ co-administration and monitoring closely for emergence of behavioral symptoms. For higher doses, may consider reducing dose with careful QTc monitoring, or alternatively, avoiding HCQ altogether (haloperidol has a known risk of TdP and sudden death). Quetiapine, risperidone, and olanzapine have a conditional risk of TdP.
1,204	Donepezil	Flagged in combination with beta-blockers; history of falls; orthostatic hypotension	In combination with beta-blockers can lead to bradycardia; on its own, can increase the risk of falls.	Hold medication during co-administration with HCQ but monitor for changes in behavior and development of confusion/delirium; may consider reducing dose with careful QTc monitoring, or alternatively, avoiding HCQ altogether due to known risk of TdP and sudden death.
404	Promethazine Hydroxyzine	Flagged for all older adults	Highly anticholinergic.	Hold medications during coadministration with HCQ due to possible risk of TdP.
122,004	Cyclobenzaprine	Flagged for all older adults	Most muscle relaxants are poorly tolerated by older adults because of anticholinergic adverse effects, sedation, risk of fracture; effectiveness at dosages tolerated by older adults is questionable. Side effects are even more likely in patients with dementia or delirium.	Taper ahead of time to avoid symptoms of withdrawal. If low dose, consider holding during HCQ coadministration and monitoring closely for behavioral symptoms. For higher doses, may consider reducing dose with careful QTc monitoring given possible QTc prolongation.
861,204	Solifenacin	Flagged for most older adults	Medications for overactive bladder symptoms may add to pill burden, contribute to adverse events from anticholinergic side effects, and the benefits rarely outweigh the harms.	Hold medication during coadministration with HCQ or monitor QTc and electrolytes due to conditional risk of QTc prolongation.
563,200	Domperidone	Parkinson's disease	Increased risk of sudden death in Parkinson's.	Hold medication during coadministration with hydroxychloroquine due to known risk of QTc prolongation and risk of sudden death.

(Continues)

Table 2 (Contd.)

AHFS drug class	Drug name	Triggering condition	General rationale for deprescribing	Suggested medication management for hydroxychloroquine interaction if unable to deprescribe in advance
682,005	DPP-4 inhibitors	Diabetes; hypoglycemia; heart failure (for thiazolidinediones)	Consider decreasing if your patient had a recent hemoglobin A <sub>1c</sub> measurement <7.5%. Avoid using medications known to cause hypoglycemia. In many adults ≥65 years who are frail or with a reduced life expectancy, moderate control (HbA <sub>1c</sub> 8%-8.5%) is reasonable. Consider decreasing or stopping this medication.	Consider holding medications as per sick day protocol and monitoring glycemias closely.
682,006	GLP-1 receptor agonist			
682,008	Insulin			
682,016	Meglitinides			
682,018	SGLT2 inhibitors			
862,020	Sulfonylureas			
682,028	Thiazolidinedione			

Abbreviation: AHFS, America hospital formulary service; BPH, benign prostatic hypertrophy; HCQ, hydroxychloroquine; HF, heart failure; K, potassium; Mg, magnesium; Na, sodium; TdP, torsade de pointes.

<sup>a</sup>Risk of QTc prolongation and TdP is classified according to the following: *Known risk of TdP* (substantial evidence and clear risk); *possible risk of TdP* (substantial evidence for QTc prolongation but insufficient evidence that the drug causes TdP); *conditional risk of TdP* (substantial evidence of QTc prolongation and but risk of TdP only under certain conditions such as hypokalemia, excessive dosing, congenital long QTc syndrome or through drug-drug interactions such as with HCQ) as per crediblemeds.org.

<sup>b</sup>Fluoxetine has a prolonged half-life of deprescribing and needs to take place well in advance (4-6 weeks) of combining with hydroxychloroquine.

Table 3 Drug Interactions with Hypothetical Hydroxychloroquine on Admission

AHFS	Generic medication name	n (%) (N = 1,001)
Cardiac medications		
240,408	Digoxin	42 (4.2)
24,040,420	Amiodarone	17 (1.7)
242,400	Sotalol	2 (.2)
24,040,412	Flecainide	2 (.2)
24,040,420	Ibutilide	1 (.1)
24,040,420	Dofetilide	0 (0)
24,040,412	Propafenone	0 (0)
24,040,404	Procainamide	0 (0)
Medications acting on the CNS		
28,160,804	Atypical antipsychotics	128 (12.8)
28,160,420	Citalopram	87 (8.7)
28,160,424	Trazodone	56 (5.6)
28,160,428	Tricyclic antidepressants	38 (3.8)
1,204	Donepezil	37 (3.7)
28,160,416	Venlafaxine	29 (2.9)
28,160,420	Sertraline	27 (2.7)
28,160,420	Escitalopram	24 (2.4)
404	Hydroxyzine	22 (2.2)
280,808	Methadone	8 (.8)
28,160,808	Haloperidol	8 (.8)
28,160,420	Fluoxetine	6 (.6)
122,004	Cyclobenzaprine	3 (3.0)
2,828	Lithium	3 (.3)
404	Promethazine	0 (0)
28,160,824	Thioridazine	0 (0)
282,492	Droperidol	0 (0)
Gastrointestinal/Miscellaneous medications		
563,200	Domperidone	19 (1.9)

(Continues)

Table 3 (Contd.)

AHFS	Generic medication name	n (%) (N = 1,001)
861,204	Solifenacin	14 (1.4)
8,121,292	Azithromycin	13 (1.3)
562,220	Ondansetron	9 (.9)
81,692	Dapsone	3 (.3)
681,612	Tamoxifen	3 (.3)
Medications for diabetes		
682,008	Insulin	138 (13.8)
682,020	Sulfonylureas	90 (9.0)
682,005	DPP-4 inhibitors	77 (7.7)
682,016	Meglitinides	12 (1.2)
682,018	SGLT2 inhibitors	6 (.6)
682,028	Thiazolidinedione	4 (.4)
682,006	GLP-1 receptor agonist	3 (.3)

Abbreviations: AHFS, American Hospital Formulary Service; CNS, central nervous system.

## DISCUSSION

We reanalyzed data from the MedSafer pilot and found that one in two older adults with polypharmacy in our cohort have a chronically prescribed medication that could potentially interact with hydroxychloroquine, half of which were PIMs that could be deprescribed. The number of medical conditions and associated polypharmacy of the cohort places them at high risk of complications from COVID-19 but also potentially at risk of harm from treatments. We identified several common drug classes, many of which are also PIMs, that would preclude many older adults from enrolling in a trial. A main finding was that many older adults were taking medications that carry a known risk of

prolonging the QTc. This finding should caution against routine prescribing of QTc prolonging COVID-19 treatments outside of a clinical study because there is real potential for harm. Importantly, more than 50% of interacting drugs were identified as a PIM that could be proactively deprescribed, rendering the person more likely to be eligible for a trial and increasing the generalizability of study findings to this population.

In this analysis, we chose to focus on a specific drug, hydroxychloroquine. Of note, debate is ongoing regarding the safety

of hydroxychloroquine for treatment of COVID-19, and studies into its efficacy are still ongoing. The risks associated with a medication such as hydroxychloroquine are likely higher for older adults with polypharmacy, especially given the common coadministration of QTc prolonging medications and the prevalence of underlying cardiac conditions.<sup>41</sup> Many patients in our cohort were also overprescribed oral hypoglycemic agents (HbA<sub>1c</sub><7.5% or a history of hypoglycemia) that when co-prescribed with hydroxychloroquine could increase the risk of hypoglycemia. Older adults may have decreased oral intake as a

**Table 4 Proportion of Potentially Inappropriate Medications That Interact with Hydroxychloroquine According to MedSafer**

Drug class or drug name	Rule (shortened): drug with triggering condition	n (%) (total N = by class)
<b>Agents acting on the CNS</b>		
Atypical antipsychotics (N = 128 patients)	High risk of urinary retention	17 (13.3)
	Risk of extrapyramidal symptoms in patients with parkinsonism	9 (7.0)
	Risk of stroke, falls, confusion, and extrapyramidal symptoms in patients with delirium or dementia	40 (31.3)
Haloperidol (N = 8 patients)	Risk of extrapyramidal symptoms in parkinsonism	1 (12.5)
	Should be avoided in patients with delirium or dementia	4 (50.0)
Citalopram	May contribute to additional fall risk	6 (4.2)
Escitalopram	Risk of exacerbating or precipitating hyponatremia	9 (6.3)
Fluoxetine		
Sertraline (N = 144 patients)		
Tricyclic antidepressants (N = 38 patients)	May lead to or worsen urinary retention or delirium in patients with delirium or dementia	5 (13.2)
Trazodone (N = 56 patients)	Risk of falls and impaired cognition	56 (100)
Donepezil (N = 37 patients)	Risk of falls and of heart block in combination with beta-blockers	22 (59.5)
Hydroxyzine (N = 22 patients)	Risk of falls and impaired cognition	22 (100)
Cyclobenzaprine (N = 3 patients)	Anticholinergic; sedating; risk of falls and fracture	3 (100)
solifenacin (n = 14 patients)	Highly anticholinergic	12 (85.7)
Methadone (n = 8 patients)	Consider risks with patient before prescribing opioid analgesics as long-term therapy to treat chronic noncancer pain	3 (37.5)
Domperidone (n = 19 patients)	Increased risk of sudden death in Parkinson's	1 (5.1)
<b>Cardiac medications</b>		
Digoxin (n = 42 patients)	Higher dosages of digoxin may increase toxicity without additional benefit, particularly in heart failure and renal failure	39 (92.9)
Amiodarone (N = 17 patients)	Rate control yields better balance of benefits and harms than rhythm control for most older adults	12 (72.2)
	Associated with thyroid and pulmonary toxicity and QT prolongation	10 (61.1)
Class 1c antiarrhythmics (eg, flecainide, propafenone) (n = 2 patients)	Rate control yields better balance of benefits and harms than rhythm control for most older adults	2 (100)
Sotalol (n = 2 patients)	Rate control yields better balance of benefits and harms than rhythm control for most older adults	1 (50.0)
<b>Diabetic agents</b>		
Sulfonylureas (N = 90 patients)	High risk of hypoglycemia (especially glyburide)	32 (35.6)
Insulin (N = 138 patients)	And/or	39 (28.3)
DPP-4 inhibitors (N = 77 patients)	Consider decreasing or stopping in patients with HbA <sub>1c</sub> <7.5%.	8 (10.4)
Meglitinides (N = 12 patients)	Moderate control (8%-8.5%) is acceptable in patients who are frail or have reduced life expectancy	4 (33.3)
SGLT2 inhibitors (N = 6 patients)		4 (66.7)
GLP-1 receptor agonist (N = 3 patients)		2 (66.7)
Thiazolidinedione (N = 4 patients)		1 (25.0)
Thiazolidinedione (N = 4 patients)	Potential to promote fluid retention and exacerbate heart failure	1 (25.0)

Note: No patients were on thioridazine, procainamide, or promethazine.

No patients had venlafaxine flagged as potentially inappropriate.

Abbreviation: CNS, central nervous system; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>.



result of COVID-19 infection and subsequent dehydration, electrolyte disturbances, nausea, and gastrointestinal upset, which are also common adverse effects of hydroxychloroquine and may further exacerbate severe cardiac dysrhythmias.<sup>42</sup>

We have identified medications that may interact with study drugs that could be deprescribed proactively or at the time of treatment (eg, off-label low-dose quetiapine for sleep and agitation). Others, if stopped abruptly, could lead to serious adverse drug withdrawal events or uncomfortable withdrawal symptoms (eg, methadone or higher doses of SSRIs).<sup>43</sup> Finally, some medications have long half-lives that require weeks to months to discontinue safely and avoid interactions. In this case, it may not be possible to stop the medication in time for treatment, and thus the risk of interaction will not be reduced (eg, azithromycin,<sup>44</sup> fluoxetine, and amiodarone). Of note, although there is a risk of potential interactions between medications, this does not necessarily mean there will be any clinical manifestations.

Currently, the use of antimalarials for the treatment or prevention of COVID-19 has extremely limited evidence.<sup>27</sup> If robust evidence demonstrating efficacy in the treatment of COVID-19 is established, some clinicians might opt to continue certain medications that cannot be stopped abruptly or where symptoms of withdrawal are thought to be significant. In most cases, this would involve judicious monitoring of the QTc and minimizing other risk factors (electrolyte abnormalities, bradycardia). Although cardiac monitoring is generally available for hospitalized patients, and perhaps at select nursing homes, this is likely not the case for most outpatients. Finally, it is important to consider the half-life of the treatment medication to know for how long symptoms should be monitored and when it is safe to restart medications (hydroxychloroquine, range = 20-120 days; mean = 40 days).<sup>45-47</sup> The risk of QTc prolongation may persist beyond the treatment period and remain clinically relevant for an unclear duration.

Of note, the optimal effective dose of hydroxychloroquine is not known. Our referenced study uses a daily dose of 600 mg, but in practice doses are variable, and some jurisdictions may prescribe lower doses of 400 mg daily that may have an impact on the risk of drug interactions and of side effects. These considerations aside, for medications that are PIMs, their interactions with possible COVID-19 therapies are yet another reason to evaluate these medications for safe deprescribing immediately.<sup>48</sup> Any concern for abrupt discontinuation can be avoided by deprescribing in advance of acute illness.<sup>48</sup>

Although we used hydroxychloroquine as a test case, this should not be interpreted as an endorsement of the medication. The clinical scenario described here is not limited to hydroxychloroquine. Other treatments including but not limited to lopinavir-ritonavir, colchicine, and dapsone have also been proposed. These treatments similarly do not have significant evidence to support their use presently, but they also carry risks of serious drug-drug interactions.<sup>48,49</sup> Clinicians may be tempted and indeed are prescribing medications out of desperation to provide patients with some form of treatment for COVID-19, but caution and a rigorous review of possible interactions is warranted, especially in older adults with polypharmacy. Notably, this population will often be underrepresented in clinical trials and even if proven effective, harms may still outweigh benefits

for some therapies. An individualized approach should always be taken. Presently, although some medications have shown promise, such as hydroxychloroquine and more recently remdesivir,<sup>49</sup> no medication for the treatment of COVID-19 has been proven effective, and so we would suggest that outside of a clinical trial, the potential harms of off-label prescribing likely outweigh benefits. In the meantime, it is important that we reduce the number of PIMs patients are taking because it may facilitate more treatment options once clinical evidence is established.

Strengths of this study include a large cohort of older adults from a multisite trial with polypharmacy, a thorough review of the literature to outline potential drug interactions, and clear instructions for medication management in the setting of drug interactions. This cohort also reflects the latest FDA recommendation that hydroxychloroquine should not be used outside of a clinical trial or a hospitalized setting.<sup>14</sup>

Our study also has several limitations. Because they were all hospitalized, the patients in this study likely represent those who are most likely to experience harm as a result of widespread prescribing of hydroxychloroquine. Future work should focus on finding safe and effective treatments in long-term care facilities where the burden of polypharmacy is high, there is an increased risk for COVID-19 exposure, and effective treatments may decrease the risk of hospitalization. We chose to focus on hydroxychloroquine as a test case to provide realistic examples of harm that could result from widespread prescribing. Reviewing all potential therapies and their subsequent drug-drug interactions was beyond the scope of this article. However, similar recommendations could be generated for other potential treatments and may be more complex. For example, interactions with lopinavir-ritonavir are more extensive than we have outlined for hydroxychloroquine.

Additionally, the clinical significance of the interactions identified vary with cardiac complications, with sudden death the most severe, whereas absolute risks of seizure or hypoglycemia are less well defined. All patients in our cohort were on at least five medications. This is the case for approximately 50% of older Americans.<sup>24,25</sup> For those on fewer medications, the risk of drug-drug interactions is less. However, this study only looked at interactions with home medications. Patients who are hospitalized may have an even higher risk of interactions because they receive additional treatments (eg, concurrent antibiotics that prolong the QTc, antipsychotics for the management of delirium, insulin, etc). Finally, although the population of patients we analyzed is Canadian, the problem of polypharmacy has been widely described in the United States and countries across the world, so the principles outlined in the discussion can be extrapolated to other jurisdictions.

In conclusion, polypharmacy has many unpredictable consequences. There are well-described harms (eg, falls, fractures, and cognitive impairment),<sup>2,3</sup> but we describe an emerging concern in the era of COVID-19. Patients may not be eligible for COVID-19 trials to study the effectiveness and safety of the medications under investigation. Others may be subject to harm as a result of off-label prescribing due to the risk of drug-drug interactions. Now more than ever, we should examine the medication lists of older adults with a focus on medication optimization and

stopping PIMs, particularly those that may interact with potential COVID-19 therapies.

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