

## Why Are Patients With COVID-19 at Risk for Drug-Drug Interactions?

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The goal of this column is to provide information to health care professionals about drug-drug interactions (DDIs) and why DDIs are important to consider in those at serious risk of illness with Coronavirus Disease 2019 (COVID-19). Important considerations discussed in this column include the frequency and complexity of multiple medication use, particularly important for the older patient who often has multiple comorbid illnesses. The column covers the following issues: (1) Why patients at high risk for serious illness from COVID-19 are also at high risk for DDIs. (2) Application of results of pharmacoepidemiological studies to the population at risk for serious COVID-19 illness. (3) Mechanisms underlying DDIs, frequency and potential complexity of DDIs, and how DDIs can present clinically. (4) Methods for preventing or mitigating DDIs. (5) An introduction to the University of Liverpool drug interaction checker as a tool to reduce the risk of adverse DDIs while treating patients for COVID-19. Commentary is also provided on issues related to specific psychiatric and nonpsychiatric medications a patient may be taking. A subsequent column will focus on DDIs between psychiatric medications and emerging COVID-19 treatments, as a detailed discussion of that topic is beyond the scope of this column.

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**KEY WORDS:** Coronavirus Disease 2019 (COVID-19), drug-drug interactions, polypharmacy, multiple medication use, psychiatric medications, cytochrome P450 enzymes, University of Liverpool drug interaction checker

The goal of this column is to help health care professionals understand why patients with Coronavirus Disease 2019 (COVID-19) who are at high risk for serious illness are also at increased risk for drug-drug interactions (DDIs) that can have an impact on the outcome. This column will cover the following main points:

- (1) Why patients at high risk for serious illness from COVID-19 are also at high risk for DDIs.
- (2) Application of results of pharmacoepidemiological studies to the population at risk for serious COVID-19 illness.
- (3) Mechanisms underlying DDIs, frequency and potential complexity of DDIs, and how DDIs can present clinically.
- (4) Methods for preventing or mitigating DDIs.
- (5) An introduction to the University of Liverpool drug interaction checker as a tool to reduce the risk of adverse DDIs when treating patients for COVID.

### BACKGROUND ON COVID-19

Sudden acute respiratory syndrome (SARS) is the most serious form of COVID-19. The name given to the virus which causes this illness is SARS coronavirus-2 (SARS-CoV-2) to distinguish it from the first coronavirus discovered to be capable of causing SARS in 2003 (SARS-CoV-1).

During the early stages of the COVID-19 pandemic in December 2019, little was known about this virus and the range of illnesses it could cause from mild cold-like symptoms to severe respiratory failure and death. However, since the beginning of

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2020, much has been learned about risk factors for more severe forms of the disease. Those at high risk for having serious COVID-19 illness are the elderly, pregnant women, and people of any age who have the following comorbid illnesses—respiratory diseases such as asthma and chronic obstructive pulmonary disease, obesity, serious heart conditions such as heart failure, coronary artery disease and/or cardiomyopathies, cardiovascular disease, hypertension, diabetes mellitus, sickle cell disease—and those who are immunocompromised for reasons such as organ transplant, immunosuppression, and/or cancer.<sup>1</sup> Parenthetically, individuals with one of the comorbid conditions listed above are at increased risk for a second, third, or even more of these comorbid illnesses.

**WHY PATIENTS AT HIGH RISK FOR SERIOUS COVID-19 ILLNESS ARE ALSO AT HIGH RISK FOR DDIs**

Patients with multiple comorbid illnesses are likely to be taking multiple medications and seeing > 1 prescriber for their health care needs. Obviously, the more medications a patient is taking, the more likely he or she is to experience a DDI, and one that is complex, as discussed in an earlier column and illustrated by the case described in Table 1.<sup>2</sup> This situation can lead to an increased probability of experiencing unplanned and adverse DDIs, which can contribute to or directly cause a poor outcome including death.

No studies have yet been published concerning how many medications those at high risk of a severe form of COVID-19 are taking. However, pharmacoepidemiological studies about the frequency and complexity of multiple medication use (MMU) in the

United States and other industrialized societies have been published, and these data can be generalized to high-risk COVID-19 patients.

**FINDINGS FROM PHARMACOEPIDEMOLOGICAL STUDIES**

**VISN 15 Study**

A pharmacoepidemiological study by Preskorn and colleagues<sup>3,4</sup> published in 2005 examined MMU and the complexity of drug regimes in an adult outpatient population of United States veterans treated in Region 15 of the Veterans Affairs (VA) Integrated Service Network (VISN 15). The objective of the study was to examine the extent and nature of MMU in relation to several factors including patient age and number of prescribers treating the patient. The outcomes were the complexity and uniqueness of the drug regimens in relation to the numbers of different medications patients were taking. Medications counted in the study were limited to those that acted systemically or gastrointestinally (“SG” drugs) because these agents are of particular concern given their potential to interact with each other [Systemically active drugs are absorbed and act on mechanisms within the body. Gastrointestinally active drugs are not systemically absorbed but act in the GI tract where they can interact with systemically absorbed drugs principally by affecting their absorption (eg., certain antacids that bind to other drugs and block their absorption)].

The drug regimens of 5003 patients were assessed, and the researchers found that a total of 394 different SG drugs were prescribed to this population of 5003 patients. Only 88 (22%) of these 394 drugs were used in at least 1% of patients

**TABLE 1. Medication Regimen of a Patient Seeing 4 Physicians\*** © Preskorn 2001

<i>Drug</i>	<i>Indication</i>	<i>Prescriber</i>
Codeine	Pain	Primary care physician
Erythromycin	Infection	Infectious disease specialist
Metoprolol	Hypertension	Cardiologist
Paroxetine	Depression	Psychiatrist

\*These medications could have been prescribed by a physician in any one of these specialties, but, in this case, the patient happened to be seeing 4 different prescribers.

(ie,  $\geq 50$  patients). The remaining 306 drugs were used in  $<1\%$  of the patients. Of the 5003 patients, 80% had current prescriptions for at least 2 SG drugs and 38% were receiving 5 or more drugs. There were 3819 different drug regimens used in this population, 3553 of which were used in only 1 patient. Thus, 71% of the patients in this population of 5003 patients were receiving a unique drug regimen (ie, the patient was the only one in the population taking that same total regimen of drugs without regard to dose or schedule). If dosing and scheduling were also considered, even more patients would have been considered unique with regard to their drug treatment. These results indicate that treatment for most of these patients was quite individualized—but based on what rationale and experience?

Figure 1 illustrates the rate at which the prevalence of a specified drug combination decreases when the number of drugs in the combination increases. This figure shows the most common 4-drug combination used in the population in this VA study. Of the 5003 patients, 26.5% received aspirin and 10.6% received furosemide, but only 4.2% received both aspirin and furosemide. Fewer than 2% of the patients took a combination of aspirin, furosemide, and a third SG drug, digoxin, and the percentage decreased further, to  $<1\%$  of patients, who were receiving a combination of those 3 SG drugs plus lisinopril—despite the fact that each of the 4 drugs was among the most commonly prescribed drugs in this population. Of the 28 patients taking this 4-drug combination, only 1 patient received only these 4 drugs, 2 others received the same regimen plus a fifth drug (another cardiovascular-related agent,

simvastatin), and the remaining 25 were on unique drug regimens of 5 or more drugs.

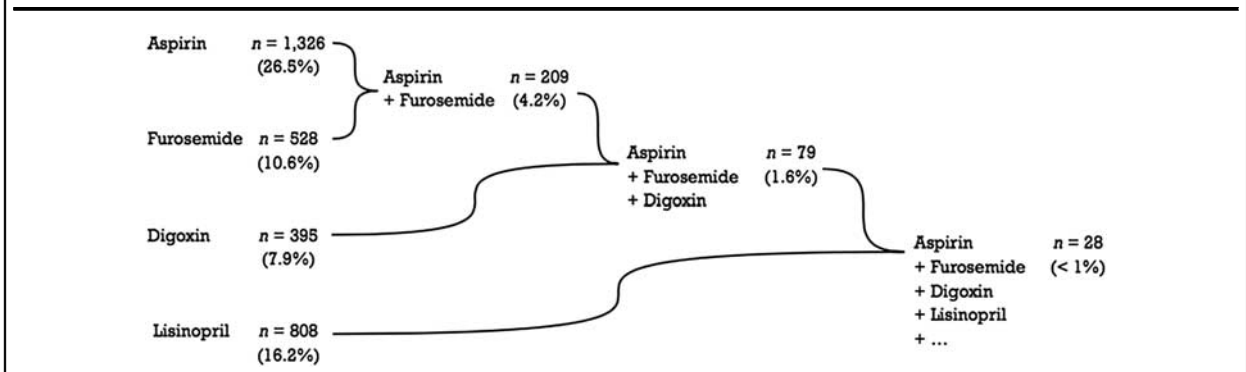
**Slone Survey**

The Slone survey, published by Kaufman et al<sup>5</sup> in 2002, was also conducted in the United States. It obtained self-reported information about prescription, over the counter, and herbal drugs from adult outpatients 18 years of age and older. This general survey of 2590 adults found that 7% had taken 5 or more prescription medications in the previous week. Women 65 years of age and older were the highest consumers of medications. In this population, 94% took at least 1 medication, 57% took 5 or more medications, and 12% took 10 or more medications. Rates of prescription drug use were similarly high in men and women in the oldest age group.

**Studies Done in Europe**

The findings from the VISN 15 study were similar to those of pharmacoepidemiological studies done in Europe. A series of studies<sup>6-8</sup> looked at reimbursement for prescription medications on an average day in Fünen County, Denmark in 1994. Bjerrum et al<sup>6</sup> found that 8.7% (SD = 0.2%) of the individuals were taking to 2 to 4 drugs and 1.2% were taking 5 or more drugs. The proportion of individuals receiving 5 or more medications increased with age up to 90 years so that two thirds of individuals 70 years of age and older were receiving 5 or more medications. In another study, Rosholm et al<sup>7</sup> found that 26,337 elderly individuals 70 years of age or older were receiving 21,293 different

**FIGURE 1. An example illustrating how patients become pharmacologically unique (N = 5003)** © Preskorn 2005



drug combinations and that the 10 most prevalent combinations were found in only 2.7% of the elderly individuals. In the third study, Bjerrum et al<sup>8</sup> examined drug combinations in 5443 individuals 16 years of age or older who were receiving 5 drugs. They found a total of 3890 different drug combinations, of which the 10 most prevalent combinations occurred in only 3% of individuals.

A pharmacoepidemiology study done in Italy by Valent et al<sup>9</sup> assessed the prevalence of MMU in the general population of Udine, Italy during 2017. The results of this study were comparable to those of the VISN 15 study: 63.7% of the general population were prescribed at least 1 medication during the year. MMU was also more common among the elderly, especially those 80 years of age and older, compared with the rest of the adult population, with 31.7% of those 65 years of age and older prescribed  $\geq 5$  medications at least once during the study year.

Taken together, these studies demonstrate that the frequency and complexity of MMU are similar across different Western countries.

### Why Unique Drug Combinations Are Common

The fact that there are numerous medications available to treat any one condition and multiple options within specific pharmacological classes of drugs (eg, multiple beta-blockers or serotonin reuptake inhibitors) helps explain the multitude of different combinations of medications that an elderly individual or an individual with multiple comorbid conditions may be taking. On the basis of the studies discussed above, it is clear that many individuals are receiving a unique drug regimen (“unique” referring to the total specific drug entities an individual is receiving, regardless of dose, formulation, or administration schedule), meaning that no other individual in the population sampled will be taking the same regimen. That in turn means that no single prescriber is likely to have extensive clinical experience with even a small fraction of the multiple total drug regimens his or her patients are taking.

### DDIs: AN OVERVIEW

A DDI, by definition, occurs when the presence of a coprescribed drug (the perpetrator) alters the nature, magnitude, or duration of effect of a given dose of another drug (the victim).

To understand DDIs, it is important to know how medications act, because their action determines whether and how they will interact pharmacodynamically with other medications. It is also important to know their pharmacokinetics (the mechanisms underlying their absorption into the body, their distribution throughout the body, their metabolism, and their elimination), because that is the second way that drugs can interact. As noted above, medications that act systemically or gastro-intestinally (referred to as SG medications) are of most concern because they have the greatest potential to interact. Therefore, identifying frequently used combinations of SG medications is the first step in addressing potentially hazardous combinations.

### Mechanisms of DDIs

Drugs can interact in 2 ways: pharmacodynamically and/or pharmacokinetically. The word “pharmacodynamics” refers to the action of a drug on a specific site of action and the biochemical and physiological effect it produces via that site of action. It is the body’s response to the drug. The word “pharmacokinetics” refers to the movement of a drug through the body: its absorption into the body from the site of administration (usually oral), its distribution from the central compartment (ie, blood) to peripheral compartments (ie, various organs including the brain), its metabolism (ie, its movement through the pathways of biotransformation), and finally its excretion from the body (usually via the kidneys).

DDIs can be therapeutic or adverse, planned or unplanned. A planned DDI is when the prescriber knows that adding another medication to the existing medication regime, thereby creating a combination regime, will enhance the efficacy or tolerability of the treatment. An example of a planned DDI is adding an adjunctive medication such as bupropion to a selective serotonin reuptake inhibitor to boost the antidepressant effect that a patient experiences.

To understand and avoid DDIs, it is important to be familiar with Equations (1) and (2).<sup>10</sup> The 3 variables in Equation (1) determine the effect a drug will produce in a patient. First, the drug must work on a site of action that is capable of producing the effect observed. The site of action for most drugs is a receptor, transporter (uptake pump), enzyme, or ion channel. By

<b>Equation 1</b>		© Preskorn 2007	
Clinical response	= Affinity for and intrinsic activity at the site of action (pharmacodynamics)	X Drug concentration at site of action (pharmacokinetics) (ADME)	X Underlying biology of patient (GADE)
		<ul style="list-style-type: none"> <li>○ Absorption</li> <li>○ Distribution</li> <li>○ Metabolism</li> <li>○ Elimination</li> </ul>	<ul style="list-style-type: none"> <li>○ Genetics</li> <li>○ Age</li> <li>○ Disease</li> <li>○ Environment</li> </ul>

binding to the target(s), the drug can alter its functional status and thus alter human physiology. The second variable is the drug's pharmacokinetics, which is the ability of the drug to move through the body. This is dependent on the absorption, distribution, metabolism, and elimination of the drug. The third variable involves the interindividual differences among patients, which shift the dose-response curve, making patients either more or less sensitive to the effect of the drug.

Equation (2) simply illustrates that drug concentration is a function of the dosing rate a patient is actually taking (rather than what has been prescribed) in relation to their ability to clear the drug.

<b>Equation 2</b>	© Preskorn 2007
Concentration = dosing rate / clearance	

**Time Course of DDIs**

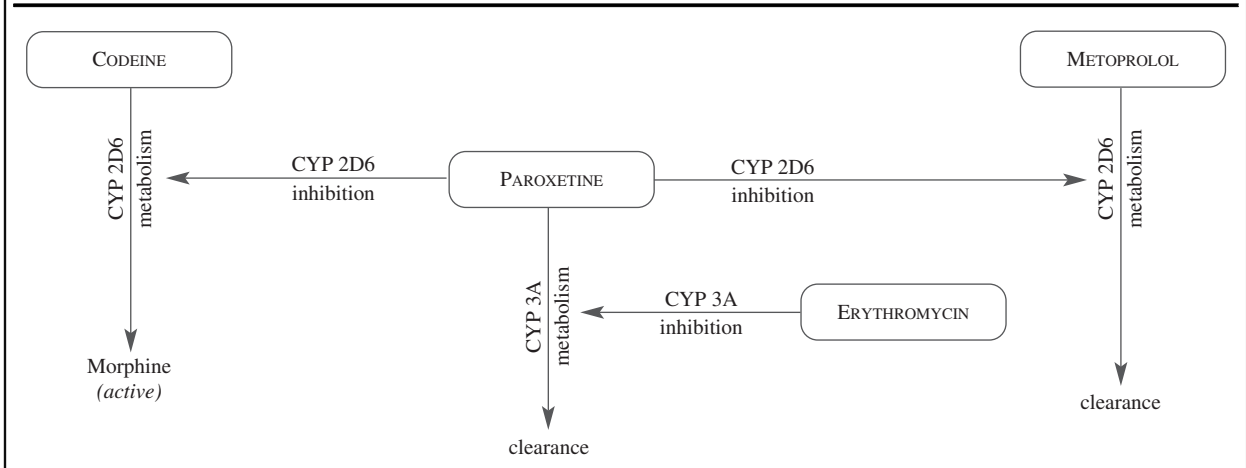
The time course of potential DDIs varies depending on how long the drugs (or their effects) persist in the body. The potential for an interaction may therefore last for days to even months after a medication has been discontinued. For example, a medication like fluoxetine can remain in the system for many weeks (5 wk or more depending on the half-life of the parent drug and its essentially equally active major metabolite, norfluoxetine, in a given patient). A drug may also have induced a change in the body which then may persist for weeks after the drug has been discontinued. Examples of such drugs are those that induce (turn on the promoter genes for) cytochrome P450 drug-metabolizing enzymes (eg, carbamazepine) or drugs that covalently bind to and deactivate an enzyme (eg, most monoamine oxidase inhibitors). Hence, it is important to elicit a detailed medication

history, not only of the medications the patient is currently taking but also of medications the patient has previously been taking in the past few months before being seen by a new prescriber.

**How Do DDIs Present?**

DDIs can present in a myriad of ways ranging from common everyday problems (which are more common but more easily missed outcomes) to catastrophic adverse effects (which are much rarer but also more easily detectable outcomes). Catastrophic adverse events due to DDIs can include sudden death, seizures, cardiac rhythm disturbances, serotonin syndrome, malignant hypertension, neuroleptic malignant syndrome, and delirium to name a few. In terms of common everyday problems, DDIs can make a patient appear to have poor tolerability for medication(s) or to be nonresponsive (ie, lack of efficacy) to the medication(s). They may also cause symptoms that mimic the worsening of a preexisting illness or the emergence of a new illness. The pitfall with worsening of symptoms is that it may lead the prescriber to stop a potentially efficacious treatment because of the belief that the medication that has been added is itself causing the adverse effect, rather than identifying the DDI which is the true culprit leading to the untoward outcome. If the potential for a DDI is recognized, then the prescriber can make whatever adjustments are needed (eg, lowering the dose or switching to a different agent within a class of medications, such as changing from 1 selective serotonin reuptake inhibitor to another that does not inhibit a specific cytochrome P450 enzyme) so that the patient can benefit from the efficacy of the medication without having the adverse effect(s). Alternatively, the emergence of new symptoms as a result of a DDI may lead to a misdiagnosis, which may result in the addition of new medications to

**FIGURE 2. Cytochrome P450 (CYP)-mediated drug-drug interactions involving codeine, erythromycin, metoprolol, and paroxetine** © Preskorn 2001



treat the apparent worsening of an existing illness or the apparent emergence of a new illness.

**Example of a Patient Receiving Multiple Medications**

Table 1 shows an example of a 4-medication regimen that a patient was receiving via prescriptions from 4 different prescribers. This patient was one of the 5003 in the Preskorn and colleagues’ VISN 15 study<sup>3,4</sup> described above. This patient was taking codeine for pain, erythromycin for an infection, paroxetine for depression, and metoprolol for hypertension. Parenthetically, the pharmacoepidemiological studies reviewed earlier in this paper documented that patients receiving such multiple medication regimens are common in clinical practice. The clinically relevant questions are: Do two or more of these drugs interact? If so, how does that interaction present and what might one or more of the prescribers do in reaction to that presentation?

Figure 2 illustrates the known potential interactions among the 4 medications this patient was taking. Codeine is an inactive prodrug that must be converted by CYP 2D6 to morphine to produce analgesia. Metoprolol is a beta-blocker whose clearance is principally dependent on CYP 2D6-mediated biotransformation to polar metabolites which can subsequently be eliminated via the kidneys. Paroxetine substantially to completely inhibits CYP 2D6 at the usual dose needed

to produce an antidepressant response. While paroxetine is metabolized by CYP 2D6 at low concentrations, it saturates this enzyme under usual dosing conditions. At higher concentrations, paroxetine is likely dependent on CYP 3A mediated biotransformation for its elimination. CYP 3A is substantially inhibited by erythromycin under usual dosing conditions. The inhibition of CYP 3A by erythromycin will produce an increased accumulation of paroxetine, which in turn would produce more inhibition of CYP 2D6, which in turn would lead to less conversion of codeine to morphine and more accumulation of metoprolol. This is an example of a complex or multiple DDI. Such DDIs can cause many adverse effects.

Figure 2 also illustrates the complex and hidden way in which such a DDI can present. Due to the inability to convert codeine to morphine, the patient will have less than optimal pain control, which may be construed as the lack of efficacy of the codeine and/or as opiate seeking behavior by the patient and/or as worsening depression. The increased accumulation of metoprolol can cause hypotension and the patient may subjectively complain of increased fatigue, which can again be misconstrued as a worsening of depression. The increased accumulation of paroxetine can cause more insomnia, decreased emotional reactivity, and decreased libido which can also look like worsening of depression. If the prescriber observes this increase in depression-like symptoms and concludes that the depressive episode is worsening, she or he may increase the dose of paroxetine, further

worsening the problem. This scenario illustrates the “hidden” way in which a DDI can present and how it can perhaps lead the clinician and the patient dangerously astray.

## PREVENTING OR MITGATING DDIs IN PATIENTS WITH COVID-19

### Why It Is Important to Consider DDIs in Those Diagnosed With COVID-19, Especially Those With Severe Illness

The discussion of multiple medications and DDIs presented in the preceding section is directly applicable to patients who are at high risk for having serious COVID-19 illness, because these individuals are likely to be taking multiple medications and unique combinations of those medications. These patients will often be prescribed additional medications to treat their COVID-19 illness along with their regular medication regimen, which will further increase the risk of experiencing DDIs. Therefore, it is important for prescribers to be aware of and understand the implications of (1) the extent and complexity of MMU, (2) how common it is for patients to be on unique medication regimens, and (3) how to help prevent immediate and long-term adverse effects, unexpected outcomes, and mortality.

In addition to the medication(s) the patient has been taking before presenting with COVID-19, many of the emerging treatments for COVID-19 have the potential to interact with the other medications the patient is taking. If the patient is in the intensive care unit, then the treating physician may simplify the medication regimen by stopping some or perhaps all of the medications the patient had previously been taking. If that approach is taken, the important questions are: Which medications can be abruptly and safely stopped and why? Which other medications may need to be tapered to avoid withdrawal or rebound phenomena? The answer to these questions depends on the specific agent being taken and the indication.

When patients with COVID-19 are hospitalized but not in the intensive care unit, their usual medications may be continued as these patients may require more supportive treatment (eg, intravenous fluids) rather than the addition of specific anti-COVID-19 medications. The determination would be made on a case-by-case basis considering both the status of the patient and his or her medication list.

The challenge for prescribers and health care professionals, in general, is the rapid expansion of our knowledge about COVID-19 and its treatment, as illustrated by the exponential growth in clinical trials and clinical experience with this illness. As just one example, at the end of August 2020, the US Food and Drug Administration broadened the indication for remdesivir (Veklury) to all hospitalized COVID-19 patients.<sup>11</sup> When considering the wider use of this drug, it is important to note that it has the potential to interact with other drugs. For example, while the usefulness of chloroquine phosphate or hydroxychloroquine sulfate remains uncertain, some providers may consider using it in combination with remdesivir. If so, the prescriber should be aware of the potential for interaction between these 2 treatments. The fact sheet concerning remdesivir issued as part of the Emergency Use Authorization from the Food and Drug Administration<sup>12</sup> states that “In vitro, remdesivir is a substrate for drug-metabolizing enzymes CYP 2C8, CYP 2D6, and CYP 3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP.” With regard to DDIs, the fact sheet states “Drug-drug interaction trials of Veklury (remdesivir) and other concomitant medications have not been conducted in humans. Due to antagonism observed in vitro, concomitant use of Veklury with chloroquine phosphate or hydroxychloroquine sulfate is not recommended.”

### Caveats About Specific Psychiatric Medications

Some specific psychiatric medications to consider when dealing with a COVID-19 patient on multiple medications include fluoxetine and long-acting depot antipsychotics, because of the long time they persist in the body even after they are discontinued. Other agents to consider are certain anticonvulsants such as carbamazepine because of their ability to induce specific CYP enzymes such as CYP 3A, with the inducted state persisting for at least a few weeks after the inducer has been stopped. For the same reason, it is important to determine if these types of medications had recently been discontinued before patients were hospitalized,

because their effects may persist for days to weeks after the drugs are discontinued.

### A TOOL FOR MINIMIZING DDIs

If some of the patient's usual medications cannot be stopped because of potential adverse health consequences or because of the potential for clinically meaningful withdrawal symptoms, then the physician or health care provider has to consider how these medications can interact with those being added to treat the COVID-19 illness. In this regard, the University of Liverpool provides access to a tool to minimize DDIs when prescribing medications for COVID-19 patients. This is a free drug interaction checker which prescribers can access on the website: [www.covid19-druginteractions.org](http://www.covid19-druginteractions.org).<sup>13,14</sup> This website lists all of the medications currently being used to treat COVID-19 and potential DDIs with other medications, and it is updated regularly as new treatment regimens for COVID-19 emerge. The checker is broken down in a table format showing interactions according to the drug class.

### CONCLUSIONS

The goal of this column was to provide information to health care professionals about DDIs and why DDIs are important to consider in those at serious risk of illness with COVID-19. The important considerations presented in this column include the frequency and complexity of MMU, particularly the older patients are and the more comorbid illnesses they have, and the basic conceptualization of how and why drugs may interact and how such interactions can present clinically. This information is important for patients with serious forms of COVID-19 because they are a population likely to be receiving MMU before they become ill with COVID-19 and then are likely to be treated with additional medicines for their COVID-19 illness. Factors to consider and general actions that can be taken to prevent or mitigate untoward DDIs have been discussed. A link to the website developed by the University of Liverpool is given so that readers can access this tool to better understand how treatments for COVID-19 may interact with other medications that a patient may be taking. Comments have also been provided concerning issues related to

specific psychiatric medications patients may be taking. A subsequent article will focus on DDIs between psychiatric medications and emerging COVID-19 treatments, as a detailed discussion of this topic is beyond the scope of this column.

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