Ther Adv Psychopharmacol
2020, Vol. 10: 1–15
DOI: 10.1177/2045125320935306

Emerging and experimental treatments for COVID-19 and drug interactions with psychotropic agents

Delia Bishara, Chris Kalafatis and David Taylor

***Abstract*:** As yet, no agents have been approved for the treatment of COVID-19, although several experimental drugs are being used off licence. These may have serious adverse effects and potential drug interactions with psychotropic agents. We reviewed the common agents being used across the world for the treatment of COVID-19 and investigated their drug interaction potential with psychotropic agents using several drug interaction databases and resources. A preliminary search identified the following drugs as being used to treat COVID-19 symptoms: atazanavir (ATV), azithromycin (AZI), chloroquine (CLQ)/hydroxychloroquine (HCLQ), dipyridamole, famotidine (FAM), favipiravir, lopinavir/ritonavir (LPV/r), nitazoxanide, remdesivir, ribavirin and tocilizumab. Many serious adverse effects and potential drug interactions with psychotropic agents were identified. The most problematic agents were found to be ATV, AZI, CLQ, HCLQ, FAM and LPV/r in terms of both pharmacokinetic as well as serious pharmacodynamic drug interactions, including QTc prolongation and neutropenia. Significant caution should be exercised if using any of the medications being trialled for the treatment of COVID-19 until robust clinical trial data are available. An even higher threshold of vigilance should be maintained for patients with pre-existing conditions and older adults due to added toxicity and drug interactions, especially with psychotropic agents.

Keywords: adverse effects, drug-interactions, psychotropic drugs, treatment COVID-19

Received: 16 April 2020; revised manuscript accepted: 25 May 2020.

Introduction

Although no treatments have been approved or shown to be safe and effective for the treatment of COVID-19, there are several treatments being used off licence either on a compassionate-use basis or as part of a randomised controlled trial. The South London and Maudsley NHS Foundation Trust does not currently recommend initiating these drugs. However, clinicians need to be aware of their adverse effects and potential drug interactions with psychotropic agents in case they are prescribed elsewhere to patients from our services.

Serious adverse effects are associated with these drugs, and these may overlap with the clinical manifestations of COVID-19. Chloroquine (CLQ)/hydroxychloroquine (HCLQ), azithromycin (AZI), and lopinavir/ritonavir (LPV/r) are associated with a range of adverse effects, including QTc prolongation, torsade de pointes, hepatitis, acute pancreatitis and neutropenia.[1] Considering that most patients who have died from COVID-19 were elderly and had underlying health conditions including cardiovascular comorbidities, CLQ/HCLQ, AZI, and LPV/r could potentially increase the risk of cardiac death. In addition, hepatitis and leucopoenia are clinical manifestations of COVID-19, and so the use of these drugs could worsen both hepatic and bone marrow dysfunction. It would also be almost impossible to differentiate the drug-related adverse effects from the disease manifestations.[1]

Several clinical trials are currently underway. The World Health Organisation and its partners have launched the Solidarity trial,[2] a large international study to compare different treatments and ensure

Correspondence to:
Delia Bishara
Maudsley Hospital, Denmark Hill, Camberwell, London SE5 8AZ, UK
delia.bishara@slam.nhs.uk

Chris Kalafatis
David Taylor
South London and Maudsley NHS Foundation Trust, London, UK

clear evidence of which treatments are most effective. The study will have five arms: standard of care; remdesivir (RDV); LPV/r; LPV/r plus interferon (IFN) beta; and CLQ. The University of Oxford have launched the Recovery trial,[3] which will be testing some of these suggested treatments: LPV/r, low-dose dexamethasone, HCLQ and inhaled IFN-beta1a.

The purpose of this review was to identify the main experimental drugs that are being trialled or used off licence to treat patients with COVID-19. For each drug we aimed to examine trial outcome data, dosing regimens, adverse effects, drug interaction potential and specific drug interactions with commonly used psychotropic agents in the United Kingdom (UK).

Methods

A preliminary search identified several drugs that were being used off licence around the world for the treatment of COVID-19 either as part of a clinical trial or on a compassionate basis. For each drug identified, we summarised any available published data on trial outcome, dosing regimens and potential adverse effects. We then used the following drug-interaction databases and on-line resources to identify potential drug interactions with the commonly used psychotropic agents in the UK: Stockley's Drug Interactions Checker, Product Information, the University of Liverpool human immunodeficiency virus (HIV) drug interactions website, drug interaction checker, the interaction sections of the drugs.com website, Drugbank and the Liverpool Drug Interactions Group online.[4–9]

For each drug identified, trial outcome data, dosing regimens, adverse effects and drug interaction potential are reported in the following. For specific drug interactions with psychotropic agents, see Table 1.

Atazanavir

An antiretroviral medication used to treat and prevent the human immunodeficiency virus (HIV)

Dosage information. Some reports have emerged where the following regimen was used for COVID-19 pneumonia: ATV 400 mg daily for 2 weeks in combination with oseltamivir 150 mg twice daily +/– methylprednisolone 40 mg twice daily for 5 days. However, there are no published data for its use to support this.

Adverse effects. ATV can cause serious, life-threatening adverse effects, including heart rhythm abnormalities, severe rash and hepatic disorders, as well as life-threatening drug interactions.

Drug interactions. ATV is metabolised principally by cytochrome P450 (CYP) 3A4. It is an inhibitor of CYP3A4 and a weak inhibitor of CYP2C8. When co-administered with ATV, increased serum levels of psychotropics that are substrates of CYP3A4 can occur. This is especially true for lurasidone, quetiapine and ziprasidone. Their levels can be raised significantly, thus increasing the risk of serious adverse effects, including prolongation of QTc interval. These combinations should be avoided if possible. Other CYP3A4 substrates, such aripiprazole, clozapine, haloperidol, iloperidone, risperidone and zuclopentixol, as well as some benzodiazepines (e.g. clonazepam, diazepam and midazolam) and certain antidepressants (e.g. citalopram, escitalopram, clomipramine, imipramine and mirtazapine, amongst others) can also be affected in the same way when co-administered with ATV and may require dose adjustments or monitoring. Carbamazepine and ATV together can lead to increased levels of carbamazepine and reduced levels of ATV and this combination should be avoided (see Table 1). Co-administration with drugs highly dependent on CYP2C8 with narrow therapeutic indices is not recommended (no psychotropic meets this definition).

Dose-related asymptomatic prolongations in the PR interval with ATV have been observed in clinical studies. Caution should be used when prescribing ATV with medicinal products that have the potential to increase the QT interval; a potential effect of many antipsychotic drugs and some antidepressants, and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances according to the Liverpool Drug Interaction Group)[9]; see Table 1.

Azithromycin

AZI is a macrolide antibiotic used in combination with HCLQ (for dosage information see HCLQ).

Adverse effects. Adverse effects include gastrointestinal effects, arrhythmias, QT prolongation and hepatic disorders.

Drug interactions. AZI does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo pharmacokinetic

Table 1. Drug interactions for COVID-19 drugs and psychotropics.[4–9]

Antipsychotics	ATV	AZI	CLQ	DIP	FAM	FAVI	HCLQ	LPV/r	NITAZ	RDV	RBV	TCZ
Amisulpride	↔	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↔	↔	↔	↔	↔
Aripiprazole	↑A	↔	↑A	↔	↔ (QTc)	↑A (t)	↑A	↑A	↔	↔	↔	↔
Chlorpromazine	↔ (QTc)	↔ (QTc)	↑CPM (QTc)	↔	↔ (QTc)	↔	↑CPM (QTc)	↑C (QTc)	↔	↔	↔	↔
Clozapine	↑ATV/C (QTc)	↔ (QTc)	↔ (QTc, FBC)	↔	↑C (t) (QTc)	↑C (t)	↔ (QTc, FBC)	↑C (QTc)	↔	↓C(t)	↑RBV (FBC)	↔ (FBC)
Fluphenazine	↔ (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↑F (QTc)	↔	↔	↔	↔
Haloperidol	↑H (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↑H (QTc)	↔	↔	↑RBV	↔
Iloperidone	↑I (QTc)	↔ (QTc)	↑I (QTc)	↔	↔ (QTc)	↑I (t)	↑I (QTc)	↑I (QTc)	↔	↔	↔	↔
Levomepromazine	↔ (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↑L (QTc)	↔	↔	↔	↔
Lurasidone	↑L (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↑L (t)	↔ (QTc)	↑L (QTc)	↔	↔	↔	↔
Olanzapine	↔	↔ (QTc)	↑O (QTc)	↔	↑O (t) (QTc)	↑O (t)	↑O (QTc)	↓O	↔	↓O (t)	↔	↔
Paliperidone	↑P	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↑P	↔ (QTc)	↑P	↔	↔	↑P	↔
Pipotiazine	↔ (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↑P (QTc)	↔	↔	↔	↔
Quetiapine	↑Q (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↑Q (t)	↔ (QTc)	↑Q (QTc)	↔	↔	↑Q	↔
Risperidone	↑R (QTc)	↔ (QTc)	↑R (QTc)	↔	↔ (QTc)	↑R (t)	↑R (QTc)	↑R (QTc)	↔	↔	↔	↔
Sulpiride	↔ (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↔ (QTc)	↔	↔	↔	↔
Ziprasidone	↑Z (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↑Z (t)	↔ (QTc)	↑Z (QTc)	↔	↔	↔	↔
Zuclopentixol	↑Z (QTc)	↔ (QTc)	↑Z (QTc)	↔	↔ (QTc)	↑Z (t)	↑Z (QTc)	↑Z (QTc)	↔	↔	↔	↔
Antidepressants												
Agomelatine	↔	↔	↔	↔	↑A (t)	↑A (t)	↔	↓A	↔	↓A (t)	↔	↔
Amitriptyline	↔ (QTc)	↔ (QTc)	↑CLQ(t) (QTc)	↔	↔ (QTc)	↔	↑CLQ(t) (QTc)	↑A (QTc)	↔	↔	↑RBV	↔
Buproprion	↔	↔	↑CLQ(t) (seizure)	↔	↔	↔	↑CLQ(t) (seizure)	↓B	↔	↓B (t)	↑B	↔
Citalopram	↑C (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↑C (QTc)	↔	↔	↔	↔
Clomipramine	↑C (QTc)	↔ (QTc)	↑C(t) (QTc)	↔	↔ (QTc)	↑C (t)	↑C(t) (QTc)	↑C (QTc)	↔	↔	↑C	↔
Desipramine	↔ (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↑ (QTc)	↔	↔	↑D	↔
Duloxetine	↔	↔	↑CLQ(t)	↔	↔	↔	↑CLQ(t)	↑↓D	↔	↔	↑RBV	↔
Escitalopram	↑E (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↑E (t)	↔ (QTc)	↑E (QTc)	↔	↔	↔	↔

(Continued)

Table 1. (Continued)

Antipsychotics	ATV	AZI	CLQ	DIP	FAM	FAVI	HCLQ	LPV/r	NITAZ	RDV	RBV	TCZ
Fluoxetine	↔	↔ (QTc)	↑CLQ /F (QTc)	↔	↔ (QTc)	↑F (t)	↑CLQ /F (QTc)	↑F	↔	↔	↔	↔
Imipramine	↑I (QTc)	↔ (QTc)	↑I (QTc)	↔	↔ (QTc)	↑I (t)	↑I (QTc)	↑I (QTc)	↔	↔	↑RBV	↔
Mirtazapine	↑M	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↑M (t)	↔ (QTc)	↑M	↔	↔	↔	↔
Nortriptyline	↔ (QTc)	↔ (QTc)	↑N (QTc)	↔	↔ (QTc)	↑N (t)	↑N (QTc)	↑N (QTc)	↔	↔	↔	↔
Paroxetine	↑↓?	↔ (QTc)	↑CLQ(t) (QTc)	↔	↔ (QTc)	↔	↑CLQ(t) (QTc)	↑↓?	↔	↔	↔	↔
Phenelzine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑RBV	↔
Reboxetine	↑R	↔	↔	↔	↔	↑R (t)	↔	↑R	↔	↔	↔	↔
Sertraline	↑S	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↓S	↔	↔	↔	↔
Tranylcypromine	↑T	↔	↔	↔	↔	↔	↔	↑T	↔	↔	↔	↔
Trazodone	↑T (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↑T (t)	↔ (QTc)	↑T (QTc)	↔	↔	↔	↔
Trmipramine	↔	↔ (QTc)	↑T (QTc)	↔	↔ (QTc)	↑T (t)	↑T (QTc)	↑T	↔	↔	↔	↔
Venlafaxine	↑V	↔ (QTc)	↑V(t) (QTc)	↔	↔ (QTc)	↑V (t)	↑V(t) (QTc)	↑V	↔	↔	↑RBV	↔
Vortioxetine	↔	↔	↑V (t)	↔	↔	↑V (t)	↑V (t)	↑V	↔	↔	↑V	↔
Benzo/hypnotics												
Clonazepam	↑C	↔	↔	↔	↔	↑C (t)	↔	↑C	↑C (t)	↔	↑C	↔
Diazepam	↑D	↔	↔	↔	↔	↔	↔	↑D	↑D	↔	↑D	↔
Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↑L	↔	↔	↔
Midazolam (oral)	↑M	↔	↔	↔	↔	↑M (t)	↔	↑M	↑M	↔	↑RBV	↔
Midazoalm (parenteral)	↑M	↔	↔	↔	↔	↑M (t)	↔	↑M	↑M	↔	↑RBV	↔
Oxazepam	↔	↔	↔	↔	↔	↔	↔	↔	↑O	↔	↑O	↔
Zolpidem	↑Z	↔	↔	↔	↔	↑Z (t)	↔	↑Z	↔	↔	↔	↔
Zopiclone	↑Z	↔	↔	↔	↔	↑Z	↔	↑Z	↔	↔	↔	↔
Mood stabilisers												
Carbamazepine	↑C ↓ATV	↔	↓CLQ (FBC, seizure)	↔	↔	↑C (t)	↓CLQ (FBC, seizure)	↑C↓LPV/r	↔	↓ RDV	↑C (FBC)	↓C (FBC)
Lamotrigine	↔	↔	↔ (seizure)	↔	↔	↑L (t)	↔ (seizure)	↓L	↔	↔	↑RBV	↔
Lithium	↔ (QTc)	↔ (QTc)	↔ (QTc)	↔	↔ (QTc)	↔	↔ (QTc)	↔ (QTc)	↔	↔	↑L	↔
Valproate	↔	↔	↔ (seizure)	↔	↔	↑V	↔ (seizure)	↓V	↑V	↔	↔	↔

(Continued)

Table 1. (Continued)

Antipsychotics	ATV	AZI	CLQ	DIP	FAM	FAVI	HCLQ	LPV/r	NITAZ	RDV	RBV	TCZ
Dementia drugs												
Donepezil	↑D	↔ (QTc)	↔	↔	↔ (QTc)	↑D (t)	↔	↑D	↔	↔	↔	↔
Rivastigmine	↔	↔ (QTc)	↔	↔	↔ (QTc)	↔	↔	↔	↔	↔	↔	↔
Galantamine	↑G	↔ (QTc)	↑G	↔	↔ (QTc)	↑G (t)	↑G	↑G	↔	↔	↔	↔
Memantine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Other												
Pregabalin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑RBV	↔

ATV, atazanavir; AZI, azithromycin; CLQ, chloroquine; CYP, cytochrome P450; DIP, dipyridamole; ECG, electrocardiogram; FAM, famotidine; FAVI, favipiravir; FBC, full blood count; HCLQ, hydroxychloroquine; LPV/r, lopinavir/ritonavir; NITAZ, nitazoxanide; RDV, remdesivir; RBV, ribavirin; TCZ, tocilizumab.

Text Legend

↑	Potential increase exposure of drug specified
↓	Potential decrease exposure of drug specified
↔	No significant effect on drug serum levels
QTc	One or both drugs may cause QT and/or PR prolongation. ECG monitoring advised
FBC	One or both drugs may cause bone marrow suppression. Monitor FBC
Seiz	One or more drugs may reduce seizure threshold. Monitor closely.
(t)	Theoretical drug interaction based on CYP metabolism, however no specific reports
	These drugs should not be co-administered
	Potential interaction which may require a dose adjustment or close monitoring
	Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required
	No clinically significant interaction expected

drug interactions. Hepatic cytochrome P450 induction or inactivation *via* cytochrome-metabolite complex does not occur with AZI. AZI is known to be a P-glycoprotein (P-gp) inhibitor and, if co-administered with P-gp substrates (e.g. digoxin, colchicine), it has been reported to result in increased serum levels, requiring monitoring.[10] Psychotropics are not known to be P-gp substrates.

Whilst pharmacokinetic drug interactions are not a problem with AZI, it is important to note that serious pharmacodynamic drug interactions do exist when co-administered with psychotropic agents. Since QTc prolongation can be an effect of AZI, and of many antipsychotic and some antidepressant drugs (see Table 1), caution should be exercised when used together as the risk for QTc prolongation is further increased. In addition, some psychotropics are known to cause neutropenia or agranulocytosis (particularly clozapine and carbamazepine), which is also a potential adverse effect of AZI.

Chloroquine and hydroxychloroquine

CLQ and HCLQ are oral drugs that have been used for the prophylaxis and treatment of malaria, and the treatment of certain inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus. Both drugs are currently being trialled in patients with mild-to-severe COVID-19.[2] HCQL is also being trialled for post-exposure prophylaxis to prevent progression to symptomatic disease after known exposure. CLQ is being trialled for prevention of COVID-19 in the healthcare setting.[11]

Chloroquine. Use of CLQ is included in treatment guidelines from China's National Health Commission and was reportedly associated with reduced progression of disease and decreased duration of symptoms; however, there are no published data. An expert consensus guideline in China recommends CLQ in mild to severe cases of COVID-19 as it may improve the success rate of treatment, shorten hospital stay and improve patient outcome.[12]

Dosing information. According to a consensus statement from a multicentre collaboration group in China, they recommend a CLQ-phosphate tablet, 500 mg twice per day for 10 days for patients diagnosed as having mild, moderate or severe cases of novel coronavirus pneumonia and without contraindications to CLQ.[12]

Hydroxychloroquine. There is a considerable interest for the use of HCLQ to treat COVID-19 disease; however, significant methodological limitations do not allow for definitive conclusions.

A small randomised controlled trial (20 patients) found that HCLQ (with or without AZI) was efficient in reducing viral nasopharyngeal carriage of SARS-CoV-2 in 3–6 days in most patients. The addition of AZI (to six patients) was thought to be synergistic and the combination was found to be significantly more efficient for virus elimination[13]; however the sample was small, the majority of patients presented with mild symptoms and the authors did not describe whether the participants suffered from other significant co-morbidities.

A similar combination trial of HCLQ and AZI in 11 participants did not replicate the previously mentioned results. Crucially, 8 out of 11 had significant comorbidities associated with poor outcomes.[14]

Another randomised open-label study in 30 Chinese participants (1:1 randomisation) did not offer conclusive results on the efficacy of HCLQ.[15]

The only publicly available randomised control trial of HCLQ in 62 Chinese participants remains in pre-publication, therefore not peer-reviewed, and the authors have not elaborated on participant co-morbidities.[16]

HCLQ /AZI combination is associated with high risk of QTc prolongation. In 84 adult patients with SARS-CoV-2 infection treated with this combination, QTc was significantly prolonged from baseline between days 3 and 4. In 30% of patients QTc increased by greater than 40 ms. In 11% of patients QTc increased to >500 ms, representing a high risk group for arrhythmia. The development of acute renal failure but not baseline QTc was a strong predictor of extreme QTc prolongation.[17]

Dosing information. HCLQ 200 mg three times a day for 10 days. (Recent studies linking HCLQ treatment to viral load reduction in COVID-19 patients did so with higher dose treatment, using either a 600 mg daily dose or 1000 mg daily dose).[18] AZI dosage used was (500 mg daily day 1 followed by 250 mg per day, the next 4 days). It has been suggested that early treatment is important.[3]

Adverse effects for CLQ/HCLQ. Gastrointestinal effects, such as vomiting and diarrhoea, are the most common adverse effects of these two drugs. Patients with long-term exposure to CLQ suffer from severe side effects such as retinopathy and cardiotoxic effects.[19] CLQ and HCLQ have been shown to prolong the QTc interval in some patients and should therefore be used with caution in patients receiving concomitant drugs known to prolong the QT interval or where a drug interaction may increase CLQ or HCLQ exposure (see drug interactions in the following). Electrocardiogram (ECG) monitoring would be recommended in these instances.[9] Caution is also advised when considering these drugs in patients with chronic medical conditions (e.g. renal failure, hepatic disease).

HCLQ has similar therapeutic effects to CLQ, but less severe adverse effects. It is considered safe in pregnancy and is more readily available in some countries. More importantly, the maximum dose for HCLQ is 1200 mg, which has an antiviral effect equivalent to 750 mg CLQ (for which the maximum tolerable dose can be 500 mg). Hence, HCLQ can be administered at a higher equivalent dosage and may therefore achieve more powerful antiviral effect.[20]

The United States Food and Drug Administration (FDA) has recently issued a warning that CLQ and HCLQ should be used for COVID-19 only when patients can be appropriately monitored in the hospital setting or are enrolled in a clinical trial with appropriate screening and monitoring. The FDA is currently reviewing the safety of their use for COVID-19 outside the hospital setting after reports of QT interval prolongation and ventricular tachycardia.[21]

Drug interactions. CLQ and HCLQ undergo CYP-mediated metabolism by CYPs 2C8, 3A4 and 2D6. Co-administration with inhibitors and inducers of these isoenzymes may increase or decrease exposure to them, respectively, and dose changes or additional monitoring could be considered. Fluoxetine and paroxetine are inhibitors of both CYP3A4 and CYP2D6 and can therefore lead to increased levels of CLQ and HCLQ, in turn increasing the risk of QTc prolongation. Other psychotropics that are important inhibitors of CYP2D6 include amitriptyline, bupropion and duloxetine. Carbamazepine induces CYP3A4 and can lead to reduced levels of CLQ and HCLQ. CLQ and HCLQ are moderate inhibitors of CYP2D6 and P-gp, and caution may be required when co-administering medication with a narrow therapeutic index that are metabolised or transported by these pathways.[9] Psychotropics that are substrates of CYP2D6 and that will undergo reduced metabolism and have increased levels when co-administered with these drugs include aripiprazole, chlorpromazine, iloperidone, olanzapine, risperidone, zuclopentixol, clomipramine, imipramine, nortriptyline, trimipramine and venlafaxine (see Table 1).

The following pharmacodynamic drug interactions should be considered carefully. Since CLQ and HCLQ have been shown to prolong QTc interval, caution should be used when co-administered with most antipsychotics and some antidepressant drugs, such as tricyclic antidepressants, citalopram, escitalopram, venlafaxine, trazodone and lithium (see Table 1), as they too can prolong QTc. In addition, CLQ and HCLQ have been reported to cause bone marrow failure, neutropenia and agranulocytosis Therefore, co-administration with carbamazepine should be avoided, and if used with clozapine, cautious use and close monitoring are advised. Furthermore, CLQ and HCLQ may lower the convulsive threshold and thus antagonise the actions of antiepileptics such as carbamazepine, lamotrigine or sodium valproate. They should also be used with caution with bupropion, which can also reduce seizure threshold.

Dipyridamole

Dipyridamole (DIP) is an antiplatelet agent and acts as a phosphodiesterase (PDE) inhibitor that increases intracellular cAMP/cGMP. Apart from the well-known antiplatelet function, DIP may provide potential therapeutic benefits to patients with COVID-19. Published studies, including clinical trials conducted in China, have demonstrated that it has a broad spectrum antiviral activity, particularly efficacious against positive-stranded RNA viruses; it suppresses inflammation and promotes mucosal healing, and, as a pan-PDE inhibitor, it may also prevent acute injury and progressive fibrosis of the lung, heart, liver and kidneys.[22]

COVID-19 infection can cause acute respiratory distress syndrome, hypercoagulability, hypertension and multiorgan dysfunction. In an analysis of a randomly collected cohort of 124 patients with the disease, researchers from China found that hypercoagulability as

indicated by elevated concentrations of D-dimers was associated with disease severity. They identified DIP, which suppressed COVID-19 replication *in vitro*.[22]

Dosage information. The daily treatment protocol comprises oral DIP 150 mg in three separate doses for 14 consecutive days.

Adverse effects. Gastrointestinal adverse effects are common with DIP, and thrombocytopenia and tachycardia have been reported although frequency is not known.[23] Because DIP is a PDE inhibitor and can exacerbate bronchospasm (frequency not known), particularly in patients with reactive airway disease and/or chronic obstructive pulmonary disease (COPD). Therapy with DIP is contraindicated in patients with active wheezing and should be administered cautiously in patients with asthma or COPD and therefore in COVID-19 patients as well.[24]

Drug interactions. Metabolism of DIP occurs in the liver. DIP is metabolized by conjugation with glucuronic acid to form mainly a monoglucuronide and only small amounts of diglucuronide. In plasma, about 80% of the total amount is parent compound, 20% of the total amount is monoglucuronide with oral administration.[23]

The bleeding risk associated with DIP might be further increased by the concurrent use of a serotonin reuptake inhibitors (SRIs). Serotonin release by platelets plays an important role in haemostasis, thus SRIs may alter platelet function and induce bleeding. Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic agents that interfere with serotonin reuptake. Bleeding events related to SRIs have ranged from ecchymosis, haematoma, epistaxis and petechiae to life-threatening haemorrhages.[25] Therefore, caution should be used with citalopram, escitalopram, fluoxetine, paroxetine and sertraline as well as clomipramine, duloxetine, venlafaxine and vortioxetine. Monitor closely for bleeding. Gastroprotection (such as a proton pump inhibitor) in those at high risk of gastrointestinal bleeding (e.g. history of gastrointestinal bleeding, the elderly) should be considered.[4]

DIP may also increase the hypotensive effect of psychotropic drugs that reduce blood pressure and may counteract the anticholinesterase effect of cholinesterase inhibitors.[23,26]

Famotidine

Famotidine (FAM) is a H_2 antagonist use to treat heartburn, ulcers and Zollinger–Ellison syndrome. Earlier in the outbreak, doctors who worked with coronavirus patients in Wuhan, China discovered that, although one in five COVID-19 patients over the age of 80 died, many of those who survived had been taking the heartburn medication FAM. In fact, hospitalized COVID-19 patients on FAM appeared to be dying at a rate of about 14% compared with 27% for those not on the drug, and, although the analysis was crude, the result was not statistically significant and studies on the Chinese patients have not yet been published, the findings were enough to encourage US scientists to explore FAM's potential.[27]

As part of a clinical trial, patients at New York City's Northwell Health have been receiving FAM intravenously, at a dose nine times greater than what people typically take for heartburn (specific dosing details are not available). The randomised, double-blind trial, which began on 7 April 2020, has enrolled 187 participants to date, but expects to expand to a total of 1174 individuals in critical status, including many on ventilators.[27]

Adverse effects. ECG changes are seen; prolonged QT interval has been reported in patients with moderate-to-severe renal impairment. The FDA has received reports of torsades de pointes occurring with FAM. There have also been rare reports of seizures, thrombocytopenia, leukopenia, agranulocytosis, pancytopenia intrahepatic cholestasis, jaundice and increased liver enzyme abnormalities. In addition, it can very rarely cause psychiatric effects such as depression, anxiety and hallucinations.[28]

Drug interactions. FAM is considered a weak CYP1A2 inhibitor and may lead to substantial increases in blood concentrations of CYP1A2 substrates. Whilst there are no reports, theoretically, co-administration can lead to increased levels of clozapine, olanzapine and agomelatine as they are predominantly CYP 1A2 substrates.[29]

FAM may cause QTc prolongation. Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. According to the manufacturer, prolongation of

the QT interval has been reported very rarely in patients with impaired renal function whose dose/dosing interval of FAM may not have been adjusted appropriately. In general, the risk of an individual agent, or a combination of these agents, causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease and electrolyte disturbances (e.g. hypokalemia, hypomagnesemia). In addition, the extent of drug-induced QT prolongation is dependent on the particular drug(s) involved and dosage(s) of the drug(s). Acetylcholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes, which occasionally manifest as bradycardia or heart block (<2%). Because bradycardia is a risk factor for torsade de pointes, a theoretical risk exists when combined with agents that prolong the QT interval.[30] See Table 1 for drug interactions with psychotropic agents.

Favipiravir

Favipiravir (FAVI) is an anti-viral drug [used in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)] that has secured approval from the National Medical Products Administration of China to treat coronavirus COVID-19. An open-label study compared FAVI (35 patients) with LPV/r (45 patients) for the treatment of COVID-19.[31] FAVI was noted to have shown significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance.

Available dosage information. Patients in the study received oral FAVI (day 1: 1600 mg twice daily; day 2–14 600 mg twice daily) plus IFN-α by aerosol inhalation (5 million U twice daily) or LPV/r (days 1–14: 400 mg/100 mg twice daily plus IFN-α by aerosol inhalation (5 million U twice daily).[31]

Adverse effects. In the small study described previously, two patients reported diarrhoea, one had liver injury and one had poor diet.[31]

Drug interactions. FAVI is a weak inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 and showed little or no induction of CYPs 1A2, 2C9, 2C19 and 3A4 in human hepatocytes. FAVI inhibits CYP2C8 and caution is required in combination with drugs metabolised *via* this route. It is also a moderate inhibitor of OAT1 and OAT3. A study showed increased areas under the plasma concentration-time curves (AUC) of paracetamol, and as a result maximum dose should be 3000 mg/day. The QT interval prolongation risk is considered to be low with FAVI.[9]

Based on the information previously mentioned, some psychotropic levels are expected be increased due to weak CYP inhibition by FAVI, but since there are no reports of this, they are theoretical interactions only (t) and are highlighted in yellow in Table 1. A dose change may not therefore be required but it is important to be aware of a potential interaction. Caution is recommended when FAVI is co-administered with zopiclone as it is a CYP2C8 substrate.

Lopinavir/ritonavir

LPV/r is an oral antiretroviral protease inhibitor currently approved for the treatment of HIV infection. LPV/r has been used in clinical trials for the treatment of COVID-19. Results from one small case series found that evidence of clinical benefit with LPV/r was equivocal.[32] A randomised controlled trial of 199 patients in China found that treatment with LPV/r was not beneficial compared with standard care alone (primary outcome was time to improvement) in hospitalised patients with severe COVID-19.[12]

Dosing information. LPV/r (400 mg and 100 mg) orally twice daily, plus standard care for 14 days was used in the clinical trial.[33]

Adverse effects. In the trial, gastrointestinal adverse events including nausea, vomiting and diarrhoea were more common in the LPV/r group than in the standard-care group, but serious adverse events were more common in the standard-care group.

Drug interactions. Lopinavir is metabolised extensively by the hepatic cytochrome P450 system, almost exclusively by CYP3A. Ritonavir is also noted to be extensively metabolised by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform. Ritonavir is a potent CYP3A and CYP2D6 inhibitor, and is given with lopinavir to increase plasma levels of lopinavir. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19, thereby increasing the biotransformation of some drugs metabolised by these pathways. This may result in decreased systemic exposure of these agents.[34]

As carbamazepine is a potent inducer and a substrate of CYP3A4, co-administration can lead to both reduced LPV/r levels and increased carbamazepine levels. Many psychotropic drugs are metabolised by CYP3A4, and so the majority will experience reduced metabolism and increased serum levels when administered with LPV/r (see Table 1). The effects and associated risks are highest with lurasidone, quetiapine and ziprasidone, and these combinations should be avoided. In contrast, the following psychotropics are expected to have reduced serum levels when administered with LPV/r: olanzapine, agomelatine, bupropion, sertraline, lamotrigine, valproate and methadone. Of the psychotropics evaluated, the levels of the following drugs are not expected to be affected: amisulpride, sulpiride, phenelzine, lorazepam, oxazepam, lithium, rivastigmine, memantine and pregabalin. For duloxetine and paroxetine, there are reports of both increase and decrease in levels when given with LPV/r.

LPV/r has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd and 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities in patients receiving drugs known to prolong the PR interval (e.g. verapamil or ATV) have been reported. LPV/r should be used with caution in such patients.[9] As many antipsychotic drugs, some antidepressants and lithium can also cause cardiac adverse effects, co-administration with LPV/r can cause pharmacodynamic drug interactions leading to increased cardiac risks. In addition, LPV/r is reported to commonly cause respiratory infections and neutropenia, both of these will be added risk factors in patients with COVID-19, especially in those on psychotropics that can also cause neutropenia, for example clozapine and carbamazepine.

Nitazoxanide

Nitazoxanide (NITAZ) an antiprotozoal that is currently FDA approved for treating cryptosporidium and giardia shown to have broad antiviral activity and has been approved in some countries for treating noro and rota viruses.[35]

Proposed dosing regimen[36]

1) HCLQ 400 mg twice a day for 2–3 days (loading) then 200 mg twice a day for 4 days[37];
2) NITAZ (600 mg -SR tabs) twice a day; if unavailable, using the immediate release formulation 500 mg three times a day for 7 days (absorption better with food) should achieve adequate trough levels that easily exceeds the EC50 of SARS-CoV2. The duration of treatment can likely be adjusted based on clinical response.

Adverse effects. NITAZ has an excellent safety record, though some gastrointestinal adverse effects are reported.

Drug interactions. Although no drug–drug interaction studies have been conducted *in vivo*, it is expected that no significant interactions would occur when NITAZ is co-administered with drugs that either are metabolised by or inhibit CYP 450 enzymes. Caution should, however, be used when administering NITAZ concurrently with other highly plasma protein-bound drugs with narrow therapeutic index, as competition for binding sites may occur. NITAZ can therefore increase levels of benzodiazepines and valproate when co-administered (see Table 1). Close monitoring for adverse effects of benzodiazepines is recommended, especially with regards to respiratory depression as this can be an issue in patients with COVID-19, who already may be experiencing respiratory distress.

When administered with food, the AUC of NITAZ in oral form increased by around 50% and subsequently is recommended to be taken with food. No clinically significant effect on QTc prolongation has been observed.[9]

Remdesivir-GS-5734®

Remdesivir-GS-5734® (RDV) is a novel, investigational, intravenous nucleoside analogue (originally used to treat Ebola) with broad antiviral activity that shows *in vitro* activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[38] Several clinical trials with RDV are underway in patients with mild-to-severe COVID-19.[39] It has been used on a compassionate-use basis in areas where clinical trials are not available; however, the manufacturer has paused access to the drug *via* this route due to overwhelming demand while they transition to an expanded access programme. Exceptions will be made for patients with severe illness, and pregnant women and children with confirmed infection.[40]

In a recent cohort of 61 hospitalised patients who received RDV on a compassionate basis, clinical improvement was observed in 36 of 53 patients (68%). A total of 25 patients (47%) were discharged, and 7 patients (13%) died.[41]

Dosing information. Limited data available; dosing used in clinical trials: 200 mg as a single dose on day 1, followed by 100 mg once daily until day 5 or 10 in addition to standard care.[42,43]

Adverse effects. The information on adverse effects is also limited however it has been reported to cause nausea and increase liver enzymes (which may or may not indicate liver damage). It does not prolong QTc interval.[44]

Drug interactions. Based on rapid distribution, metabolism and clearance, the likelihood of clinically significant interactions is low. RDV is a substrate of CYP 2C8, CYP 2D6, CYP 3A4 and transporters OATP1B1 and P-gp *in vitro*, but co-administration with inhibitors of these CYP isoforms and transporters is unlikely to increase its levels.[9] RDV can be impacted by strong inducers (e.g. carbamazepine) thus co-administration is not recommended. RDV is an inducer of CYP 1A2 and CYP 2B6 *in vitro* but, considering the exposure, it is unlikely to translate into clinically significant interaction with substrates of these enzymes.[9] However, caution should be used when co-administered with clozapine (CYP1A2 substrate) and methadone (CYP2B6 substrate) as, theoretically, levels of these drugs could be reduced (see Table 1 for effects on other psychotropics as well).

Since there are limited data on the tolerability and adverse effect profile of RDV, it is difficult to predict whether any pharmacodynamic interactions with psychotropics exist. Reports of increased liver enzymes may suggest that monitoring may be warranted in some patients, especially if co-prescribed psychotropics that can also increase liver enzymes or affect liver function for example, agomelatine, monoamine oxidase inhibitors, carbamazepine or haloperidol.

Ribavirin

Ribavirin (RBV) is an antiviral used to treat hepatitis and has been used previously to manage SARS and MERS patients. An open-label, randomised controlled trial currently underway in China included three regimens with the following dosage[45]:

RBV (intravenous loading dose of 2 g, followed by oral doses of 400–600 mg every 8 h depending on the patient's weight, for 14 days);
LPV/r (oral, 400 mg/100 mg per dose, twice a day, for 14 days);
IFN-α-1b (atomizing inhalation, 5 million U or 50 μg per dose, twice a day, for 14 days).

And comparing the effectiveness of:

- RBV plus IFN-α1b (arm A);
- LPV/r plus IFN-α1b (arm B); and
- RBV plus LPV/r plus IFN-α1b (arm C)

for the treatment of COVID-19.

Adverse effects[46]*.* Pancytopenia and bone marrow suppression have been reported with RBV. No effect on QTc prolongation has been observed. There are several serious adverse reactions associated with the combination therapy of RBV with (peg)IFN-α . These include:

- Severe psychiatric and central nervous system effects (such as depression, suicidal ideation, attempted suicide and aggressive behaviour, etc.);
- Severe ocular disorders;
- Dental and periodontal disorders.

Drug interactions. RBV has two pathways of metabolism: a reversible phosphorylation pathway and a degradative pathway. Both RBV and metabolites are excreted renally. Results of *in vitro* studies indicated no CYP 450 enzyme-mediated metabolism of RBV. RBV does not inhibit CYP 450 enzymes and there is no evidence from toxicity studies that it induces liver enzymes, therefore potential for P450-based interactions is minimal.[9]

Information on drug interactions with RBV is limited. The Drugbank database lists potential pharmacokinetic drug interactions leading to increased RBV levels with the following psychotropic agents: clozapine, haloperidol, amitriptyline, duloxetine, imipramine, phenelzine, venlafaxine, midazolam, lamotrigine and pregabalin. It is not clear whether these are actual reports of interactions or theoretical considerations, and the mechanisms are not clear. Similarly, Drugbank also notes that RBV may lead to increased levels of the following psychotropic agents: paliperidone, quetiapine, bupropion, clomipramine, desipramine, vortioxetine, clonazepam, diazepam, oxazepam, carbamazepine and lithium.

Pharmacodynamic interactions with psychotropics include infections and neutropenia, which have both been reported with RBV use – a significant risk for patients infected with COVID-19, particularly if also taking clozapine or carbamazepine, also known to cause neutropenia. In addition, combination therapy of RBV with (peg)IFN-α has been associated with severe psychiatric effects, another serious concern if used in psychiatric patients.

Tocilizumab

Tocilizumab (TCZ) is an interleukin (IL)-6 receptor inhibiting monoclonal antibody that is currently approved for rheumatological conditions such as rheumatoid arthritis and cytokine release syndrome. TCZ is being trialled in patients with severe COVID-19 to see whether it is effective in reducing the virus-induced cytokine storm, thereby potentially reducing complications.[47] However, the decision to suppress the immune system of a critically unwell patient with COVID-19 is a difficult one; the beneficial anti-inflammatory effects of TCZ (or any other anti-inflammatory drug) must be weighed against the possibly detrimental effects of impairment of immunity.[48]

Reported dosage has been:

- The initial dose should be 4–8 mg/kg, with the recommended dosage being 400 mg;
- Dilute with 0.9% saline to 100 ml and infuse over the course of more than 1 h;
- Repeat once after 12 h (same dosage) if the response to the first dose was poor, maximum two cumulative doses;
- Single maximum dose is 800 mg.

There are no published papers on this.

Drug interactions. TCZ has no direct inhibitory or inducing effects on CYP enzymes *per se*. However, it reverses IL-6 induced suppression of cytochromes (elevation of IL-6 during inflammation has been shown to inhibit CYP 3A4, CYP2C19, CUP2C9 and CYP1A2 activity, resulting in higher drug exposure of substrate drugs), which, prior to treatment with TCZ, has been adjusted to the metabolism of individuals. When treatment with TCZ is started, cytochrome activity normalises, thus leading to reduced exposure of drugs, which, prior to treatment, had been adjusted to the metabolism of individuals with the rheumatic disease that it is usually used for.[9]

Patients with COVID-19 experience an elevation of IL-6. However, since co-medication will not have been adjusted to the acute inflammatory COVID-19 state, and since treatment with TCZ would have been initiated very rapidly (and only up to two doses given), no prior adjustment of CYP substrates is needed. But the effect of acute COVID-19 infection on drugs with narrow therapeutic index is unclear.[9] TCZ may decrease blood levels of carbamazepine, which may require dose adjustment.

Caution is required when co-administering with myelotoxic drugs such as clozapine or carbamazepine due to the potential additive haematological toxicity. No clinically significant effect on QT prolongation was observed in healthy subjects.[9]

Other drugs

Intravenous immunoglobulin is being trialled in some patients with COVID-19; however, there are no data to support this. Angiotensin-II receptor antagonists such as losartan are being investigated as a potential treatment because it is thought that the angiotensin-converting enzyme-2 (ACE2) receptor is the main binding site for the virus.[35,36]

In addition, researchers at the Murdoch Children's Research Institute in Australia are set to conduct a randomised, multi-centre clinical trial to test the use of tuberculosis vaccine BCG against Covid-19. The BRACE trial is intended for healthcare workers. It is based on previous study findings that BCG decreases the level of virus in patients infected by viruses similar to SARS-CoV-2.[49] BCG vaccine's heterologous beneficial effect against non-tuberculosis infections is well known. The vaccine works on the innate immune system and produces a memory like response termed 'trained immunity' that helps in faster recognition, triggering a quicker inflammatory response. Recent studies have also suggested that it has the potential to protect against experimental infection with yellow fever vaccine strain and to enhance immune responses to other vaccines in general including influenza vaccination.[50]

Conclusion

We urge clinicians to exercise significant caution in the use of any of the previously mentioned medications even on a compassionate-use basis in the absence of adequately powered and/or

peer-reviewed safety and randomised controlled trials for the treatment of COVID-19 patients. An even higher threshold of vigilance should be maintained for patients with pre-existing conditions and older adults due to added toxicity and drug interactions. It is clear from this review that many psychotropic agents can interact with agents used in COVID-19, leading to serious adverse effects including QTc prolongation thus increasing the risk of torsades de pointes and bone marrow suppression. Identifying and avoiding these interactions can be vital to improving survival in COVID-19 patients.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Delia Bishara https://orcid.org/0000-0002-6254-2054

David Taylor https://orcid.org/0000-0002-2557-1710

Note

This paper was accepted on the basis of one independent review due to the Covid-19 pandemic and the ongoing commitments of our Editors and reviewers.

References

1. Kalil AC. Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA*. Epub ahead of print 24 March 2020. DOI: 10.1001/jama.2020.4742.
2. Sayburn A. Covid-19: trials of four potential treatments to generate "robust data" of what works. *BMJ* 2020; 368: m1206.
3. Recovery: Randomised Evaluation of COVID-19 Therapy. This nation clinical trials aims to identify treatments that may be beneficial for adults hospitalised with confirmed COVID-19, https://www.recoverytrial.net/ (accessed 27 March 2020).
4. Medicines Complete. Stockley's interactions checker, https://about.medicinescomplete.com/publication/stockleys-interactions-checker/ (accessed 06 May 2020).
5. HIV Drug Interactions. Interaction checker. University of Liverpool, www.hiv-druginteractions.org (accessed 06 May 2020).
6. RxList. Drug interations checker, https://www.rxlist.com/drug-interaction-checker.htm (accessed 06 May 2020).
7. Drugs.com. Find drugs & conditions, www.Drugs.com (accessed 06 May 2020).
8. Drugbank, https://www.drugbank.ca/ (accessed 06 May 2020).
9. University of Liverpool. Covid-19 drug interactions, https://covid19-druginteractions.org/ (accessed 06 May 2020).
10. Medicines.org.uk. Azithromycin 250mg capsules. EMC, https://www.medicines.org.uk/emc/product/8663/smpc#PHARMACOKINETIC_PROPS (accessed 02 April 2020).
11. ClinicalTrials.gov. Chloroquine/hydrocloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting (COPCOV), https://www.clinicaltrials.gov/ct2/show/NCT04303507 (accessed 27 March 2020).
12. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 2020; 43: 185–188.
13. Gautret P, Lagier JC, Parola P, *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. Epub ahead of print 20 March 2020. DOI: 10.1016/j.ijantimicag.2020.105949.
14. Molina JM, Delaugerre C, Goff JL, *et al.* No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 Infection, *Med Mal Infect.* Epub ahead of print 30 March 2020. DOI: 10.1016/j.medmal.2020.03.006.
15. Chen J, Liu D, Liu L, *et al*, A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ* 2020; 49: 215–219.
16. Chen Z, Hu J, Zhang Z, *et al.* Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv* 2020. DOI: 10.1101/2020.03.22.20040758.
17. Chorin E, Dai M, Shulman E, *et al.* The QT interval in patients with SARS-CoV-2 infection treated with hydroxychloroquine/azithromycin. *MedRxiv* 2020. DOI: https://doi.org/10.1101/2020.04.02.20047050.

18. BMJ. Rapid response: use of hydroxychloroquine for COVID-19: risk of ocular toxicity, https://www.bmj.com/content/368/bmj.m1166/rr (accessed 02 May 2020).
19. Schrezenmeier E and Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol* 2020; 16: 155–166.
20. Zhou D, Dai SM and Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother*. Epub ahead of print 20 March 2020. DOI: 10.1093/jac/dkaa114.
21. U.S. Food & Drug Administration. Hydrochloroquine or chloroquine for COVID-19: drug safety communication – FDA cautions against use outside of the hospital setting or a clinical trial due to risk of heart rhythm, https://www.fda.gov/safety/medical-product-safety-information/hydroxychloroquine-or-chloroquine-covid-19-drug-safety-communication-fda-cautions-against-use (accessed 02 May 2020).
22. Liu X, Li Z, Liu Z, *et al.* Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. *Acta Pharm Sin B.* Epub ahead of print 20 April 2020. DOI: 10.1016/j.apsb.2020.04.008.
23. Medicines.org.uk. Dipyridamole 100mg tablets. EMC, https://www.medicines.org.uk/emc/product/3557/smpc (accessed 05 May 2020).
24. Drugs.com. Dipyridamole disease interactions, https://www.drugs.com/disease-interactions/dipyridamole.html (accessed 05 May 2020).
25. Drugs.com. Drug interactions between dipyridamole and paroxetine, https://www.drugs.com/drug-interactions/dipyridamole-with-paroxetine-914-0-1800-0.html?professional=1 (accessed 05 May 2020).
26. Medicines.org.uk. Persatin 100mg tablets, EMC, https://www.medicines.org.uk/emc/product/3817/smpc#PHARMACOKINETIC_PROPS (accessed 05 May 2020).
27. Borrell B. New York clinical trial quietly tests heartburn remedy against coronavirus. *Science*, 2020. DOI: 10.1126/science.abc4739.
28. Drugs.com. Famotidine side effects, https://www.drugs.com/sfx/famotidine-side-effects.html#for-professionals (accessed 03 May 2020).
29. Taylor D, Barnes TRE and Young AH. *The Maudsley prescribing guidelines in psychiatry*. 13th ed. Hoboken, NJ: Wiley, 2018.
30. Drugs.com. Famotidine drug interactions, https://www.drugs.com/drug-interactions/famotidine-index.html (accessed 03 May 2020).
31. Cai Q, Yang M, Liu D, *et al.* Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering (Beijing)*. Epub ahead of print 18 March 2020. DOI: 10.1016/j.eng.2020.03.007.
32. Young BE, Ong SWX, Kalimuddin S, *et al.* Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA*. Epub ahead of print 3 March 2020, DOI: 10.1001/jama.2020.3204.
33. Cao B, Wang Y, Wen D, *et al.* A trial of lopinavir–ritonavir in adults hospitalized with severe covid-19. *N Engl J Med*. Epub ahead of print 18 March 2020. DOI: 10.1056/NEJMoa2001282.
34. Medicines.org.uk. Norvir 100mg film-coated tablets. EMC, https://www.medicines.org.uk/emc/product/510/smpc (accessed 03 March 2020).
35. Rossignol JF. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antivir Res* 2014; 110: 94–103.
36. Padmanabhan S. Potential dual therapeutic approach against SARS-CoV-2/COVID-19 with Nitazoxanide and Hydroxychloroquine. 2020. DOI: 10.13140/RG.2.2.28124.74882.
37. Yao X, Ye F, Zhang M, *et al.* In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. Epub ahead of print 9 March 2020. DOI: 10.1093/cid/ciaa237.
38. Wang M, Cao R, Zhang L, *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; 30: 269–271.
39. ClinicalTrials.gov. 12 studies found for remdesivir, https://www.clinicaltrials.gov/ct2/results?cond=&term=remdesivir++&cntry=&state=&city=&dist=&Search=Search (accessed 27 March 2020).
40. BMJ Best Practice. Coronavirus disease 2019 (COVID-19), https://bestpractice.bmj.com/topics/en-gb/3000168/emergingtxs (accessed 27 March 2020).
41. Grein J, Norio Ohmagari N, Shin D, *et al.* Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med*. Epub ahead of print 10 April 2020. DOI: 10.1056/NEJMoa2007016.

42. Gilead sciences initiates two phase 3 studies of investigational antiviral remdesivir for the treatment of COVID-19, https://www.gilead.com/news-and-press/press-room/press-releases/2020/2/gilead-sciences-initiates-two-phase-3-studies-of-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19 (accessed 27 March 2020).

43. NIH clinical trial of remdesivir to treat COVID-19 begins, https://www.nih.gov/news-events/news-releases/nih-clinical-trial-remdesivir-treat-covid-19-begins (accessed 27 March 2020).

44. MedicineNet. Remdesivir (RDV): experimental antiviral for coronavirus (COVID-19), https://www.medicinenet.com/remdesivir_rdv_ebola_covid-19_coronavirus_trial/article.htm#what_is_remdesivir_rdv (accessed 27 March 2020).

45. Zeng YM, Xu XL, He XQ, *et al.* Comparative effectiveness and safety of ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha and ribavirin plus lopinavir/ritonavir plus interferon-alphain in patients with mild to moderate novel coronavirus pneumonia. *Chin Med J (Engl)* 2020; 133: 1132–1134.

46. Medicines.org.uk. Ribavirin 200mg film-coated tablets. EMC, https://www.medicines.org.uk/emc/product/7108/smpc. (accessed 28 March 2020).

47. ClinicalTrial.gov. Tocilizumab in COVID-19 pneumonia (TOCIVID-19) (TOCIVID-19), https://clinicaltrials.gov/ct2/show/NCT04317092 (accessed 31 March 2020).

48. Ritchie AI and Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? *Lancet* 2020; 395: 1111.

49. ClinicalTrials.gov. BCG vaccination to protect healthcare workers against COVID-19 (BRACE), https://clinicaltrials.gov/ct2/show/NCT04327206. (accessed 14 April 2020).

50. Mahase E. Covid-19: what treatments are being investigated? *BMJ* 2020; 368: m1252.