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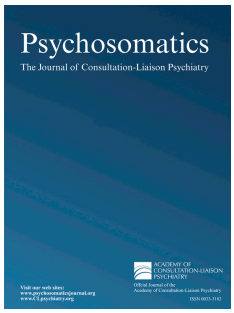

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PII: S0033-3182(20)30144-4

DOI: https://doi.org/10.1016/j.psym.2020.05.006

Reference: PSYM 1107

To appear in: *Psychosomatics*

Received Date: 24 April 2020

Revised Date: 11 May 2020

Accepted Date: 12 May 2020

Please cite this article as: Bilbul M, Paparone P, Kim AM, Mutalik S, Ernst CL, Psychopharmacology of COVID-19, *Psychosomatics* (2020), doi: https://doi.org/10.1016/j.psym.2020.05.006.

Title: Psychopharmacology of COVID-19

Melanie Bilbul[1], Patricia Paparone[1], Anna M. Kim[1], Shruti Mutalik[1] and Carrie L. Ernst[1,2]

1. Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY
2. Department of Medical Education, Icahn School of Medicine at Mount Sinai, New York, NY

Corresponding Author: Carrie L. Ernst
Corresponding Author Address: One Gustave L. Levy Place, Box 1230, New York, NY 10029
Corresponding Author Email: carrie.ernst@mssm.edu
Corresponding Author Phone: 212-659-8856

Declarations of Interest: Dr. Ernst receives royalties from American Psychiatric Publishing, Inc; the other authors have no interests to declare

Abstract

BACKGROUND: With the rapid, global spread of SARS-CoV-2, hospitals have become inundated with patients suffering from COVID-19. Consultation-liaison psychiatrists are actively involved in managing these patients and should familiarize themselves with how the virus and its proposed treatments can affect psychotropic management. The only FDA approved drug to treat COVID-19 is remdesivir, and other off-label medications used include chloroquine and hydroxychloroquine, tocilizumab, lopinavir/ritonavir, favipiravir, convalescent plasma therapy, azithromycin, vitamin C, corticosteroids, interferon and colchicine.

PURPOSE: To provide an overview of the major safety considerations relevant to clinicians who prescribe psychotropics to patients with COVID-19, both related to the illness and its proposed treatments.

METHODS: In this targeted review we performed structured literature searches in PubMed to identify articles describing the impacts of COVID-19 on different organ systems, the neuropsychiatric adverse effects of treatments, and any potential drug interactions with psychotropics. The articles most relevant to this manuscript were included.

RESULTS: COVID-19 impacts multiple organ systems, including gastrointestinal, renal, cardiovascular, pulmonary, immunological, and hematological systems. This may lead to pharmacokinetic changes that impact psychotropic medications and increase sensitivity to psychotropic-related adverse effects. Additionally, several proposed treatments for COVID-19 have neuropsychiatric effects and potential interactions with commonly used psychotropics.

CONCLUSION: Clinicians should be aware of the need to adjust existing psychotropics or avoid using certain medications in some COVID-19 patients. They should also be familiar with neuropsychiatric effects of medications being used to treat this disease. Further research is needed to identify strategies to manage psychiatric issues in this population.

Keywords: COVID-19, psychotropic, psychopharmacology, side effects

Introduction

With the rapid, global spread of SARS-CoV-2, hospitals have become inundated with patients suffering from COVID-19 infection. Remdesivir was recently approved by the US Food and Drug Administration (FDA) to treat severe COVID-19 (1), and many other medications are either being studied in clinical trials or being used off-label and/or for compassionate use (2).

As the pandemic spreads, Consultation Liaison (CL) psychiatrists are being called upon to help manage the psychiatric conditions of individuals with COVID-19 and are encountering challenging clinical scenarios of multiple medical comorbidities and unfamiliar drugs. Psychiatrists should familiarize themselves with the mechanism of action of these treatments, neuropsychiatric side effects and possible interactions with psychotropics. Additionally, since COVID-19 affects multiple organ systems, psychiatrists will need to be aware of safety concerns inherent in prescribing psychotropics to these patients.

This article is divided into 2 main sections. The first provides an update on the organ systems that may be negatively impacted by COVID-19 and recommendations for safer use of psychotropics in these patients. The second section reviews potential neuropsychiatric side effects of the early approved and investigational treatments for COVID-19 as well as pharmacokinetic and pharmacodynamic drug-interactions when used concurrently with psychotropics. COVID-19 therapies reviewed include remdesivir, chloroquine, hydroxychloroquine, azithromycin, tocilizumab, lopinavir/ritonavir, favipiravir, convalescent plasma therapy, corticosteroids, interferon, vitamin C, and colchicine.

Given the limited literature in this area, we undertook a non-systematic narrative review that was focused on practical clinical concerns. We utilized a structured PubMed search using the following search terms in combination with the names of the medications mentioned above: “COVID-19,” “coronavirus,” “Psychotropic medications,” “QT prolongation,” “Psychiatric side effects,” “Neuropsychiatric side effects,” “drug interactions,” and pertinent organ systems, e.g. “hepatic,” “renal,” “hematological,” “pulmonary,” and “cardiac.” This was followed by a search of manufacturer’s package inserts for pertinent facts about specific medications, including drug interactions.

We selected the above medications as they were the ones most commonly being used in healthcare settings and clinical trials at the time of preparation of this manuscript, although we are aware that this is a rapidly evolving field and thus this list is not meant to be comprehensive.

Impact of COVID-19 on Psychotropic Drug Safety

COVID-19 is believed to impact multiple organs, including the liver, kidneys, lungs and heart, as well as the immune and hematological systems (3). Damage to these organs or systems may lead to pharmacokinetic changes that impact absorption, distribution, metabolism and/or excretion of psychotropic medications as well as increased sensitivity to certain psychotropic-related adverse effects. As such, clinicians should be aware of the potential need to make adjustments to existing psychotropic regimens or avoid using certain psychotropic agents if such safety concerns arise (Tables 1 and 2).

Hematological Effects

An early report noted the presence of lymphopenia (lymphocyte count less than 1.0 x 109/L) in 63% and leukopenia (white blood cell count less than 4 x109/L) in 25% of COVID-19 patients (4). It has been proposed that lymphopenia is a feature of severe COVID-19 cases and may serve as a poor prognostic factor. Contributing factors likely include direct infection of lymphocytes and cytokine storm (5) It therefore seems prudent to utilize caution and consider avoiding medications which have the potential to further impact white blood cell production, particularly lymphocytes. By contrast, clinicians might determine that it is acceptable from a safety standpoint to continue psychotropics which have only been associated with agranulocytosis and neutropenia, assuming the patient does not have a secondary bacterial infection. Several psychotropics have been implicated in hematological adverse effects, including leukopenia, neutropenia, and agranulocytosis. The most commonly implicated psychotropics include carbamazepine and clozapine, but there is a class effect FDA warning on all first and secondary generation antipsychotics for the potential association with leukopenia, neutropenia and agranulocytosis as well as a number of published case reports. Carbamazepine is more likely to be associated with an early transient leukopenia, but has also been associated with agranulocytosis and aplastic anemia (6).

While the leukopenia and lymphopenia observed in COVID-19 patients may be less of a concern for clozapine prescribers in the setting of a normal neutrophil count, clozapine deserves unique mention given several potential challenges associated with its use during the COVID-19 pandemic. These challenges have been recently reviewed along with recommendations for management in a consensus statement by Siskind and colleagues (7). Patients on clozapine may have difficulty accessing routine absolute neutrophil count (ANC) monitoring and the Food and Drug Administration (FDA) has released guidance allowing healthcare providers to use medical judgment to delay laboratory testing for drugs subject to Risk Evaluation and Mitigation Strategy (REMS) (8). While there is no data yet available on COVID-19 in patients on clozapine, it has been suggested that clozapine is associated with a higher risk of pneumonia and its complications. Explanations include aspiration, sialorrhea, sedation, and poorly understood effects on the immune system (7,9). Patients should be educated on symptoms of pneumonia and urgently evaluated by a clinician if symptoms of infection emerge. Complicating the picture further, elevation of clozapine levels has been observed with multiple acute viral and bacterial infections. This may in part be related to effects of systemic infection and inflammation on CYP450 enzymes (10). Clinicians should closely monitor clozapine levels and consider reducing the dose by up to a half in patients with fever and other signs of infection.

Coagulation abnormalities such as PT and aPTT prolongation, thrombocytopenia and disseminated intravascular coagulation (DIC) are also frequently observed in COVID-19 patients. At the same time, many COVID-19 patients experience increased thrombotic risk and may be prescribed prophylactic anti-coagulants(5). These factors may impact the decision to prescribe psychotropics that have been associated with platelet dysfunction and increased bleeding risk (e.g. selective serotonin reuptake inhibitors and valproic acid). Clinicians should be especially mindful of using these medications in patients who have other risk factors for bleeding, such as concomitant anti-coagulation therapy and history of significant bleeding event.

Cardiac Effects

There is limited available information regarding cardiovascular involvement due to COVID-19 infection, although tachyarrhythmias and heart failure have been described with other severe acute respiratory syndrome (SARS) beta-coronavirus infections (11). A recent report described acute myopericarditis in a patient with COVID-19 (12) and a meta-analysis found acute cardiac injury in at least 8% of patients with COVID-19 (13). It has been suggested that COVID-19 most likely has an arrhythmogenic effect (14). Proposed mechanisms of myocardial injury include derangement of Angiotensin Converting Enzyme 2 (ACE2) signal pathways, cytokine storm and myocarditis. Additionally, several medications being utilized off-label in the management of COVID-19 (azithromycin, hydroxychloroquine, chloroquine, and lopinavir/ritonavir) have been reported to prolong the QT interval. QT prolongation, particularly in those with underlying medical risk factors, has been linked to lethal ventricular arrhythmias, such as Torsades de Pointes (TdP).

A complete discussion of the cardiac side effects of psychotropics is beyond the scope of this paper, except to note that it has been well described in the literature that a number of psychotropic medications can prolong the QT interval. Although the data are often difficult to interpret due to confounding factors, antipsychotics, tricyclic antidepressants and the SSRI citalopram, appear to be the agents of most concern. It is difficult to stratify antipsychotic medications by QT prolongation risk. Of the typical antipsychotics, thioridazine causes the greatest QT prolongation, although IV haloperidol has also been implicated. The greatest risk among the atypicals appears to be related to ziprasidone and possibly iloperidone. Aripiprazole and possibly lurasidone have been associated with the lowest risk based on available data (15).

Health care providers should be aware of the baseline corrected QT interval (QTc) and all concomitant medications, labs, medical comorbidities and family history prior to prescribing psychotropics in COVID-19 patients. Caution should be used in patients with a baseline prolonged QTc and/or other risk factors for drug-induced QT prolongation and TdP: use of QT prolonging medications, cardiac comorbidities, age >65, female sex, family history of sudden cardiac death, hypokalemia/hypomagnesemia, and illicit substance use. If QT-prolonging medications are used in a patient with a QTc>500ms or other significant risk factors, ECGs should be monitored frequently (daily in high risk cases), potassium and magnesium should be repleted, cardiology involvement should be considered, and every attempt made to reduce risk factors (15). In patients who test positive for COVID-19 but are already taking a psychotropic drug that has inherent potential for QTc prolongation, risk-benefit decisions must be made on a case-by-case basis regarding continuation versus switching to an alternative medication.

Hepatic Effects

Several studies have reported acute liver injury, particularly in severe COVID-19 cases (4,16,17). The etiology of the liver injury is not known and hypotheses include viral infection, drug-induced liver injury, and systemic inflammation due to cytokine storm or hypoxia (16). Lab abnormalities observed include elevated AST, ALT and bilirubin (17). Liver function tests should be monitored and, if abnormal, consideration given to avoiding psychotropics that can also cause hepatic injury or making dose adjustments if heavily dependent on hepatic metabolism. Since most psychotropics are lipid soluble and require hepatic metabolism prior to clearance, clinicians should review the package insert to determine if a dose adjustment is

needed. Additionally, many psychotropics (valproate, carbamazepine, tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors and second-generation antipsychotics) have been associated with mild hepatoxicity that manifests with modest, transient increases in liver enzymes. Only a few, are thought to have a high risk of causing serious drug-induced liver injury (DILI), including chlorpromazine, carbamazepine, valproate, duloxetine and nefazodone (18,19). Such high risk psychotropics should be preferentially avoided in patients with COVID-19 associated liver disease.

Renal Effects

Acute kidney injury has been observed, particularly in patients with COVID-19-associated acute respiratory distress syndrome (ARDS) and pre-existing chronic kidney disease. Several causes have been proposed, including impaired gas exchange, hemodynamic alterations, sepsis, and an inflammatory/immune reaction involving release of circulating mediators that cause injury to kidney cells (20). In such patients, avoiding potentially nephrotoxic drugs, such as lithium, may be required. Additionally, psychiatrists should be aware of any renal impairment and make necessary dose adjustments as per the manufacturer's prescribing information. Psychotropics highly dependent on renal excretion include lithium, gabapentin, topiramate, pregabalin and paliperidone. Many other psychotropics have renally excreted active metabolites. Levels of these medications or their metabolites can increase in the setting of impaired renal clearance such that reduced dosing or avoiding the medication may be required. For example, administration of duloxetine is not recommended for patients with severe renal impairment (CrCL of <30 mL/min) (18).

Neurological Effects

Based on similarities between SARS-CoV2 and other coronaviruses, it is thought likely that SARS-CoV2 has neuroinvasive potential (21) but there remain many unanswered questions about neurological manifestations of COVID-19. Initial observations note a variety of neurological syndromes in COVID-19 patients, particularly the more severely affected. These include stroke, delirium, seizures, and an encephalitis-type presentation. A recent paper from Wuhan (22) reports neurologic symptoms in 36.4% of COVID-19 patients, falling into 3 categories: 1) Central nervous system symptoms or diseases (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and seizure); 2) Peripheral nervous system symptoms (impairment in taste, vision and smell, neuropathic pain) and 3) Skeletal muscular injury. It is not known whether these neurologic syndromes are a direct effect of the virus entering the central nervous system or an indirect response to the cytokine storm that patients are experiencing. A specific prevalence rate of delirium was not reported but is presumed to be very high and to contribute to poor adherence with care and other safety concerns. Certainly, for patients with severe COVID-19 infections, there are many other potential etiologies of delirium, including organ failure, hypoxia, sepsis, medication effects, and electrolyte/metabolic abnormalities. Observational studies have in fact reported high rates of benzodiazepine use for sedation in ventilator-dependent COVID-19 patients (23). Environmental factors such as isolation from family members and difficulty mobilizing patients also contribute (24).

In COVID-19 patients with delirium, clinicians should be mindful about prescribing benzodiazepines, opioids and drugs with strong anticholinergic properties (tertiary amine tricyclic antidepressants, low potency antipsychotics, benztropine and diphenhydramine) as these

medications have the potential to cause or exacerbate confusion, sedation and/or falls. Clinicians should also be cautious about prescribing psychotropics that can lower the seizure threshold in patients with seizures or structural brain lesions. Such medications include most antipsychotics (especially clozapine, quetiapine, olanzapine and first generation antipsychotics) (25) and certain antidepressants (bupropion, tricyclics) (26).

Pulmonary Effects

As the lung is considered the primary organ that is affected by COVID-19, most patients present with respiratory symptoms, such as cough and shortness of breath. Affected individuals may develop pneumonia and acute respiratory distress syndrome leading to high supplemental oxygen requirements and in the most severe cases, invasive ventilation (4). Psychiatric consultants may be asked to evaluate and manage COVID-19 patients with anxiety or panic symptoms in addition to respiratory distress. While there may be circumstances in which the use of small doses of a benzodiazepine is appropriate, it is important to be aware of the potential for benzodiazepines to suppress respiratory drive, particularly at higher doses. Clinicians therefore need to consider risks versus benefits in using benzodiazepines in patients with prominent respiratory symptoms.

Psychiatric considerations of proposed COVID-19 Treatments

Many of the proposed COVID-19 treatments have the potential for neuropsychiatric side effects as well as drug-drug interactions. These are reviewed in the section below and summarized in Table 3.

Remdesivir

Remdesivir is an antiviral medication that interacts with RNA polymerase and evades proofreading by viral exonuclease leading to a decrease in viral RNA (27). On May 1, 2020, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to use remdesivir for treatment of suspected or confirmed severe COVID-19 infection (1), with severe defined as "patients with an oxygen saturation $\leq$ 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO)". The EUA was based on early promising data from a randomized double-blinded, placebo-controlled (28) and an open-label trial (29). Remdesivir is administered by infusion, with a treatment course of 5 or 10 days, depending on severity of disease.

Neuropsychiatric effects

No information is available regarding neuropsychiatric side effects, but administration has been associated with infusion-related reactions that can present with hypotension, diaphoresis and shivering (1). Such symptoms might be misconstrued as a panic attack.

Psychotropic Considerations

Remdesivir carries a risk of transaminase elevations (30), specifically but not limited to alanine aminotransferase (ALT) elevations up to 20 times the upper limit of normal (1). This may impact the decision to use hepatically metabolized psychotropics, such as valproic acid.

Chloroquine and Hydroxychloroquine

Chloroquine, a synthetic form of quinine used for the treatment and prophylaxis of malaria, and hydroxychloroquine a derivative compound used in the treatment of inflammatory disorders such as rheumatic arthritis and systemic lupus erythematosus, are being considered as a possible treatment for COVID-19 infection. Interest in these medications is in part due to their potential for interference with virus-receptor binding and immune-modulating effects (31). The most promising study is a small open-label trial from France (32), although a recent large observational study showed that the risk of intubation or death was not significantly higher or lower among patients who received the drug than among those who did not (33). The authors suggest that their findings do not support continued use of the drug in COVID-19 patients outside of clinical trials. *Neuropsychiatric effects*

Neuropsychiatric side effects of chloroquine and hydroxychloroquine include psychosis, delirium, agitation, suicidality, personality changes, depression, and sleep disturbances (34,35). Risk factors for hydroxychloroquine-induced neuropsychiatric effects may be concurrent use of CYP3A4 inhibitors or low-dose glucocorticoids, alcohol intake, family history of psychiatric disease, female gender, low body weight and supratherapeutic dosing (36).

A number of mechanisms have been postulated for the pathogenesis of hydroxychloroquine-induced neuropsychiatric effects, such as cholinergic imbalance due to acetylcholinesterase inhibition, inhibition of the serotonin transporter protein, and NMDA and GABA antagonism (34).

Psychotropic Considerations

Hydroxychloroquine and chloroquine can cause heart conduction disorders, including QT interval prolongation, bundle branch block, AV block, and torsades de pointes (37). On April 24, 2020, the FDA issued a safety announcement against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems (38). Caution should be used when combining them with QT prolonging psychotropics. These agents can also be hepatotoxic (39) and epileptogenic (40), so caution should be exercised in patients with hepatic disease, or in conjunction with psychotropics that may be hepatotoxic or may lower the seizure threshold.

Both chloroquine and hydroxychloroquine are metabolized by CYP3A4 (41), so CYP3A4 inhibitors (e.g. fluvoxamine), could raise plasma levels and increase the potential for adverse effects. By contrast, CYP3A4 inducers, such as carbamazepine, oxcarbazepine and modafinil could decrease levels of chloroquine or hydroxychloroquine, potentially rendering them less effective. Given hydroxychloroquine's long half-life (40 hours), the potential for continued adverse effects and drug-interactions may continue for days after the drug has been discontinued (35).

Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody that acts as an interleukin-6 (IL-6) receptor inhibitor (42) and is FDA approved to treat several types of arthritis (43). Tocilizumab is being trialed in severe COVID-19 patients with elevated IL-6 because IL-6 appears to be involved in cytokine storms that have been observed in critically ill patients with COVID-19 (44).

Neuropsychiatric effects

Data from rheumatic arthritis patients suggest that Tocilizumab may have some positive effects on depressive symptoms in rheumatoid arthritis (45,46), however unpublished data from a small study surprisingly suggests that patients who received tocilizumab following allogeneic hematopoietic cell transplantation experienced worse symptoms of depression, anxiety, pain, and sleep (47).

Psychotropic Considerations

No major interactions have been reported.

Favipiravir

Favipiravir is an antiviral thought to act as an RNA dependent RNA polymerase inhibitor (48). It was approved in China in February 2020 for treatment of influenza (48) and there are current trials evaluating its efficacy on SARS-Cov-2. It is not currently approved for use in the United States.

Neuropsychiatric effects

No published information is available.

Psychotropic Considerations

There is no published information available. One published case report suggested a mild QT prolongation in an Ebola virus patient who received favipiravir (49).

Lopinavir/Ritonavir (Kaletra)

Lopinavir/Ritonavir is an antiviral medication used to treat HIV-1 infection (50) The two medications work synergistically: lopinavir is a protease inhibitor and ritonavir helps to boost plasma levels of lopinavir by inhibiting its metabolism(50). Unfortunately, a recently published randomized, controlled, open-label trial found no additional benefit with lopinavir-ritonavir treatment in hospitalized patients with SARS-CoV-2 as compared with standard care (51).

Neuropsychiatric effects

The manufacturer's prescribing information lists possible psychiatric side effects, including abnormal dreams, agitation, anxiety, confusion and emotional lability although there is limited information in published case reports or trials regarding the incidence of such effects (50). Protease inhibitors as a class have been associated with neurological adverse events, such as paresthesias, taste alterations, and neurotoxicity (52).

Psychotropic Considerations

Protease inhibitors are extensively metabolized by the cytochrome P450 system and have been shown to interact with many drugs, including psychotropics (53). Use of Ritonavir may lead to increased concentrations of co-administered drugs that are CYP3A4 or CYP2D6 substrates or decreased concentrations of CYP1A2 or CYP2B6 substrates, many of which are psychotropics.

Use of Lopinavir/Ritonavir is contraindicated with medications that include pimozide, midazolam, and triazolam due to increased drug levels and potentiation of adverse effects. Use of benzodiazepines not dependent on CYP metabolism (lorazepam, temazepam or oxazepam) is recommended. Due to CYP450 enzyme or glucuronidation inducing effects, Ritonavir-boosted protease inhibitors also have been shown to lower concentrations of some psychotropics (e.g. bupropion, methadone, lamotrigine and olanzapine), thus leading to increased dose requirements for these medications (53).

Since most psychotropics are substrates for CYP isoenzymes, there are many additional theoretical interactions, but the clinical significance varies by agent. Clinicians should assess each potential interaction individually by reviewing available literature and manufacturer prescribing information.

Other potential non-psychiatric side effects that may have implications for psychiatrists include the following: Stevens Johnson syndrome, diabetes mellitus, QTc prolongation, pancreatitis, neutropenia, hepatotoxicity and chronic kidney disease (50).

Convalescent plasma therapy

Antibody containing convalescent plasma from recovered patients has been used with some success as a last resort to treat severe viral respiratory infections such as SARS-CoV, MERS-CoV, and Ebola although large clinical trials are absent (54). Trials are currently underway to study the effectiveness of convalescent plasma therapy in the treatment of individuals with severe respiratory failure associated with COVID-19.

Neuropsychiatric effects

When used for the treatment of other severe acute viral respiratory infections, convalescent plasma therapy was not associated with serious adverse events (55), although in general, plasma transfusions can cause a range of adverse events from mild fever and allergic reactions to life threatening bronchospasm/anaphylaxis, transfusion-related acute lung injury and transfusion associated circulatory overload (56).

Specific neuropsychiatric effects have not been reported, although allergic reactions, cardiovascular complications and bronchospasm can produce symptoms such as shortness of breath and palpitations that mimic panic attacks.

A potential psychological adverse effect of convalescent plasma therapy relates to ethical concerns about coercion, confidentiality, and privacy for the prospective donors that were initially raised during the Ebola outbreak (57) and led to a World Health Organization document providing guidance on the ethical use of convalescent plasma (58).

Psychotropic Considerations

There are no specific interactions between psychotropics and plasma transfusions, but patients who develop transfusion reactions might receive steroids or diphenhydramine which can have negative synergistic effects with existing psychotropics.

Azithromycin

Azithromycin is an antibacterial agent which may have antiviral and anti-inflammatory activity (32). It is under investigational use for treatment of COVID-19 when given in conjunction with chloroquine or hydroxychloroquine. In one small French study (n=20), azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination as compared to hydroxychloroquine alone (32).

Neuropsychiatric effects

Side effects that have been reported include psychotic depression, catatonia, delirium, aggressive reaction, anxiety, dizziness, headache, vertigo and somnolence (59,60).

Psychotropic Considerations

Azithromycin has not been implicated in pharmacokinetic interactions with psychotropics but has been associated with QTc prolongation and life-threatening TdP arrhythmias. It has also been associated with hepatotoxicity (61).

Vitamin C

High dose intravenous vitamin C (ascorbic acid), an antioxidant and reducing agent, has been investigated in the treatment of sepsis due to its enhancement of the immune response (62). In the intensive care setting, vitamin C administration has been correlated with preventing progressive organ dysfunction and reducing mortality in sepsis and acute respiratory distress syndrome (ARDS) (63), and is being investigated in critically ill patients with COVID-19.

Neuropsychiatric effects

There are no known adverse neuropsychiatric consequences of high-dose IV vitamin C administration, but some studies have associated lower levels of vitamin C with depression, confusion and anger (64). Vitamin C deficiency has also been identified as a possible risk factor for delirium (65).

Psychotropic Considerations

Coadministration with barbiturates may decrease the effects of vitamin C (62).

Corticosteroids

Corticosteroids are involved in immune function, inflammation, and carbohydrate metabolism and are used in the treatment of endocrinopathies, autoimmune disorders, and asthma/allergies (66). In previous pandemics, such as SARS and MERS, corticosteroids were not recommended due to concern that they may exacerbate lung injury (67). Given evidence suggesting that severe COVID-19 may be associated with a cytokine storm and hyperinflammation syndrome (67), corticosteroids may have a role in treatment.

Neuropsychiatric effects

The neuropsychiatric side effects of corticosteroids have been well described in the literature and include depression, mania, agitation, mood lability, anxiety, insomnia, catatonia, depersonalization, delirium, and psychosis (66). The majority of neuropsychiatric side effects occur early in treatment course, usually within days, and dosing is the most significant risk factor (i.e. at prednisone equivalents of >40mg/day) (66).

Psychotropic considerations

Corticosteroids have been inconsistently reported to be weak CYP 3A4 and CYP2C19 inducers (68), which could lead to decreased effects of CYP3A4 or CYP2C19 substrate psychotropics (69). Additionally, phenytoin has been shown to increase hepatic metabolism of systemic corticosteroids (70).

Interferon

Interferons (IFNs) are glycoproteins that have immunomodulatory, antiproliferative, and hormone-like activities (71). IFN alpha and beta have anti-SARS-CoV-1 activity in vitro and IFN beta reduces the replication of MERS-CoV (72,73) in vitro. Based on this information, IFN has been considered as a potential treatment for COVID-19, including in combination with Ribavirin, a guanosine analogue with broad spectrum antiviral potency (74).

Neuropsychiatric effects

IFN alpha has a boxed warning for “life threatening or fatal neuropsychiatric disorders” (75). Specific effects include fatigue, mood disorders, suicidality, anxiety disorders, irritability, lability, apathy, sleep disturbance, and cognitive deficits (76). Side effects of IFN beta can

include fatigue, weight loss, myalgia and arthralgia (77), but not generally depression. Given the potential for significant psychiatric side effects of IFN alpha, it is important for clinicians to screen for baseline psychiatric history and monitor closely for emergence of any symptoms.

Psychotropic Considerations

There are no known pharmacokinetic interactions with psychotropics but clinicians should be mindful of the potential for bone marrow suppression which may raise safety concerns with concurrent use of psychotropics, such as carbamazepine, valproate and clozapine. Additionally, seizures in conjunction with bupropion use have been reported (78).

Colchicine

Colchicine is a plant-derived alkaloid with anti-inflammatory properties that is used for a variety of rheumatological and cardiac conditions (79). It is hypothesized that colchicine could treat COVID-19 through targeting the overactive IL-6 pathway (80).

Neuropsychiatric effects

Colchicine does not typically produce any neuropsychiatric effects, but at toxic doses, can cause delirium, seizures and muscle weakness.. (81).

Psychotropic Considerations

Colchicine has a narrow therapeutic index and attention must be paid to potential drug interactions that might increase cause toxicity. Colchicine is metabolized by CYP3A4 and excreted via the P-glycoprotein (P-gp) transport system as well as cleared by the kidneys through glomerular filtration. Dose adjustment is recommended with concurrent use of CYP 3A4 or P-gp inhibitors as well as in patients with hepatic or renal impairment (82). CYP3A4 inducers can lead to increased metabolism, and theoretically decreased effectiveness of colchicine.

Discussion

COVID-19 and its treatments can impact many organ systems and contribute to a host of drug interactions and neuropsychiatric effects. This can have safety implications for use of psychotropics, which are highly metabolized by the hepatic cytochrome p450 system and carry their own potential for drug-interactions and end-organ adverse effects.

While there are no absolute contraindications to use of psychotropics in COVID-19 patients, psychiatrists must be mindful of potential adverse effects and conduct a thoughtful risk-benefit analysis as part of their clinical decision-making process. For example, chloroquine, hydroxychloroquine, and azithromycin have the potential for QT prolongation, which can be problematic in patients with tenuous cardiac status. Generally, psychiatrists might avoid antipsychotic medications in the setting of a prolonged QT interval. However, in our experience, hyperactive delirium in COVID-19 patients is highly prevalent and manifests with severe agitation that can be difficult to treat and leads to dangerous behaviors such as removing oxygen or assaulting staff. While there is limited evidence to support the use of any interventions in the

management of agitation in COVID-19 associated delirium, most CL psychiatrists consider antipsychotics such as haloperidol the gold standard for managing agitation in delirious patients. In these situations, the CL psychiatrist should assist the medical team in reasoning through the cardiac risks of using an antipsychotic balanced against effective management of the agitation. Use of an antipsychotic with cardiology involvement and frequent EKG monitoring or telemetry may be deemed acceptable. Alternatives such as alpha-2 agonists (dexmedetomidine and clonidine) or anti-epileptics (valproic acid) should be considered if the individual patient's cardiac risk is determined to be high and/or if the antipsychotic is clinically ineffective. Melatonin has been proposed for addressing consciousness and sleep-wake cycle disturbances in delirious COVID-19 patients, especially given its potential for anti-oxidative, anti-inflammatory and immune-enhancing effects (83). With the exception of patients who chronically use alcohol or benzodiazepines and may be at risk for withdrawal, benzodiazepines should be avoided if possible and considered only as a last resort for highly agitated delirious patients for whom other treatments are unavailable or ineffective. Early delirium screening and non-pharmacological strategies to prevent or treat delirium such as frequent orientation and early mobilization should be employed if practically feasible (24).

As another example, we have observed many non-delirious COVID-19 patients with significant anxiety in the setting of respiratory distress. In some cases, the anxiety leads to requests to leave against medical advice or refusal to remain isolated. For these patients, psychiatrists should consider whether the benefit of a low dose benzodiazepine outweighs the potential risk of respiratory depression. Use of benzodiazepines may be reasonable in patients with adequate oxygen saturation and absence of confusion or a depressed sensorium. Depending on the individual patient's circumstances and symptoms, alternative medications such as gabapentin, buspirone, hydroxyzine, a low dose atypical antipsychotic, or a selective serotonin reuptake inhibitor (SSRI) may be appropriate. Non pharmacological/psychosocial interventions (eg, behaviorally oriented therapies) should also be utilized.

Other important tasks for the psychiatrist treating a COVID-19 patient include review of all medications, monitoring for neuropsychiatric side effects of medications such as hydroxychloroquine or corticosteroids and differentiating between primary psychiatric symptoms versus those that are secondary to COVID-19 or other medications.

Interestingly, several psychotropics, including haloperidol and valproic acid were recently named on a list of FDA approved medications with potential for in vitro action against SARS-CoV-2 (84) Fluvoxamine is also under investigation for its potential to reduce the inflammatory response during sepsis by inhibiting cytokine production(85), and melatonin for its anti-oxidative and anti-inflammatory properties (86). If more data becomes available, psychiatrists might consider preferentially using these agents if clinically appropriate.

In summary, psychiatrists must be aware of the likelihood of encountering patients with COVID-19 infection and must remain cognizant of the neuropsychiatric effects and drug-drug interactions of COVID-19 treatments as well as the end-organ effects of COVID-19.

Disclosures

Dr. Ernst receives royalty payments from American Psychiatric Publishing, Inc. The other authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1. Potential Psychotropic Safety Concerns in COVID-19 Organized by Drug Class

Drug Class	Specific Drugs	Problem	Solution
Antipsychotics	Clozapine	Patients with difficulty accessing ANC monitoring	Reduce frequency of ANC monitoring at discretion of provider
		May be associated with increased risk of pneumonia and its complications	Education of patients and urgent clinical assessment including ANC for those with symptoms of infection
		Levels can increase with acute infection leading to clozapine toxicity	Consider halving clozapine dose in patients with fever, pneumonia and/or flu-like symptoms; temporarily discontinue clozapine if toxicity emerges
		COVID-19 associated with leukopenia and lymphopenia; unclear impact on neutrophils; clozapine associated with neutropenia and agranulocytosis and more rarely lymphopenia or aplastic anemia	Monitor complete blood count (CBC); if persistent white blood cell abnormalities, weigh risks vs benefits of continuing clozapine; when total white blood cell count is decreased but neutrophil count is normal, consider continuing clozapine
		COVID-19 associated with seizures; clozapine can lower seizure threshold	Recognize potential for lowered seizure threshold; assure non-toxic clozapine level; consider holding clozapine, decreasing dose, or adding anti-epileptic
	Other Antipsychotics	COVID-19 associated with decreased white blood cell and lymphocyte counts; rare reports of antipsychotic-associated aplastic anemia or lymphopenia, especially with phenothiazines (chlorpromazine, fluphenazine, thioridazine)	Monitor CBC; if persistent hematologic abnormalities (eg, lymphopenia, neutropenia, thrombocytopenia) weigh risks vs benefits of continuing antipsychotic agent
		Coagulation abnormalities (PT and aPTT prolongation, thrombocytopenia) are observed in COVID-19 patients; rare reports of thrombocytopenia associated with multiple antipsychotics	
		Concern for COVID-19 associated tachyarrhythmias and cardiac injury and potential for several medications being used to treat COVID-19 to cause QT prolongation; all antipsychotics with potential for QT prolongation	Baseline EKG for QTc; caution in patients with baseline prolonged QTc and/or other risk factors for drug-induced QT prolongation and TdP; daily EKG and electrolyte monitoring, reduce other risk factors, and cardiology consult in high risk cases if opt to use antipsychotic; case-by-case

		Acute liver injury in COVID-19 patients; antipsychotics (especially chlorpromazine) with potential for drug-induced liver injury COVID-19 associated with seizures; all anti-psychotics can lower seizure threshold	risk-benefit discussion Monitor liver function tests and avoid chlorpromazine in patients with liver injury; risk vs benefit assessment for other antipsychotic use Consider avoiding antipsychotics (especially clozapine, quetiapine, olanzapine and first generation drugs) or adding anti-epileptic drug in patients who have seizures
Anti-Epileptic Drugs (AED)	Carbamazepine	COVID-19 associated with leukopenia and lymphopenia; leukopenia and rare reports of aplastic anemia associated with carbamazepine use; Acute liver injury in COVID-19 patients; carbamazepine with potential for drug-induced liver injury	Monitor CBC; if persistent white blood cell abnormalities or aplastic anemia, use alternative AED Monitor liver function tests and avoid carbamazepine in patients with liver injury
	Valproic Acid	Coagulation abnormalities (PT and aPTT prolongation, thrombocytopenia) observed in COVID-19 patients; valproic acid associated with thrombocytopenia Acute liver injury in COVID-19 patients; valproic acid with potential for drug-induced liver injury	Monitor platelet count; avoid valproic acid if thrombocytopenia Monitor liver function tests and avoid valproic acid in patients with liver injury
	Gabapentin	COVID-19 with potential for acute kidney injury; gabapentin clearance dependent on intact renal function	Adjust gabapentin dose based on renal function
Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	(all)	Coagulation abnormalities observed in COVID-19 patients and many COVID-19 patients receiving anticoagulation; SSRIs and SNRIs associated with impaired platelet aggregation and abnormal bleeding Concern for COVID-19 associated tachyarrhythmias and cardiac injury and potential for several medications being used to treat COVID-19 to cause QT prolongation; citalopram with potential for QT prolongation	Monitor coagulation factors and platelet count; weigh risks and benefits for individual patient but consider avoiding SSRIs and SNRIs in patients with recent bleeding or high risk for bleeding (eg, thrombocytopenia, concurrent anticoagulation therapy, history of hemorrhage); can instead use non serotonin reuptake inhibitor antidepressant such as bupropion Baseline EKG for QTc; caution in patients with baseline prolonged QTc and/or other risk factors for drug-induced QT prolongation and TdP; consider using SSRI other than citalopram in high risk cases

		Acute liver injury in COVID-19 patients; duloxetine with potential for drug-induced liver injury	Monitor liver function tests avoid duloxetine in patients with liver injury
Bupropion		COVID-19 associated with seizures; bupropion can lower seizure threshold	Avoid bupropion in patients with seizures or lowered seizure threshold
Lithium		COVID-19 with potential for acute kidney injury; lithium clearance dependent on intact renal function; lithium with nephrotoxic potential	Adjust lithium dose based on renal function; consider temporarily holding lithium until acute kidney injury resolves
Benzodiazepines	(all)	COVID-19 associated with delirium; benzodiazepines can exacerbate delirium COVID-19 associated with prominent respiratory symptoms; benzodiazepines can suppress respiratory drive Lopinavir/Ritonavir contraindicated with midazolam and triazolam (and can raise levels of some other benzodiazepines) due to CYP450 inhibition	Avoid or taper existing benzodiazepines in patients with delirium if possible Weigh risks vs benefits in using benzodiazepines in patients with prominent respiratory symptoms; a low dose may be able to be used safely in non-delirious patients Avoid midazolam and triazolam and consider using lorazepam, temazepam or oxazepam in patients taking Lopinavir/Ritonavir

Table 2. Potential Psychotropic Safety Concerns in COVID-19 Organized by Organ System

Organ System affected by COVID-19	Systemic Effects and Symptoms	Potential Psychotropic Safety Concerns
Hematologic	Lymphopenia Coagulopathy (increased PT, aPTT; decreased platelets)	Consider avoiding medications that can negatively impact white blood cell (WBC) production Highest risk: carbamazepine, clozapine, olanzapine Moderate risk: all 1st and 2nd generation antipsychotics (especially low potency conventionals) Rare reports: TCAs, benzodiazepines (chlordiazepoxide), gabapentin, and valproate Consider avoiding medications that can increase bleeding risk (via thrombocytopenia or impaired platelet aggregation): valproic acid, SSRIs, SNRIs
Cardiac	Concern for tachyarrhythmias, heart failure, myopericarditis, acute cardiac injury Several medications being utilized for COVID-19 (azithromycin, hydroxychloroquine, chloroquine, lopinavir/ritonavir) reported to prolong QT interval	Caution with psychotropics known to prolong QTc and in patients with other underlying risk factors for QT prolongation Highest risk: antipsychotics, citalopram, tricyclic antidepressants
Hepatic	Risk of acute liver injury, especially in severe cases	In patients with hepatic injury or failure: Consider avoiding psychotropics that can also cause serious drug-induced liver injury (DILI): chlorpromazine, carbamazepine, valproate, duloxetine and nefazodone. Refer to prescribing information to determine if dose adjustments are needed
Renal	Acute kidney injury has been observed, particularly in patients with COVID-19-associated acute respiratory distress syndrome (ARDS) and pre-existing chronic kidney disease	Consider dose adjustment with some psychotropics (e.g. lithium, gabapentin, topiramate, pregabalin, paliperidone, and duloxetine) Consider avoiding potentially nephrotoxic drugs
Nervous system	Central Nervous System: headache, dizziness, impaired consciousness, ataxia, stroke, delirium, seizures Peripheral nervous system: impaired taste/smell/vision, neuropathic pain	In patients with delirium, caution with deliriogenic medications: benzodiazepines, opioids, sedative-hypnotics, and those drugs with strong anticholinergic effects (tertiary amine tricyclic antidepressants, low potency first generation antipsychotics, some second-generation antipsychotics, benztropine and diphenhydramine Caution with medications that can lower seizure threshold: antipsychotics and certain antidepressants (bupropion, tricyclics)
Pulmonary	Cough, shortness of breath, pneumonia and acute respiratory distress syndrome	In COVID-19 patients with anxiety or panic symptoms, weigh risks vs benefits in using benzodiazepines in patients with prominent respiratory symptoms, given potential to suppress respiratory drive

Table 2. Psychiatric Side Effects and Drug Interactions with Proposed COVID-19 Treatments

Proposed COVID 19 treatment	Mechanism of Action	Psychiatric side effects	Drug-drug Interactions
Azithromycin	Used with hydroxychloroquine. Antibacterial (primarily) Antiviral and anti-inflammatory (potential)	Psychotic depression, catatonia, delirium, aggressive reaction, anxiety, dizziness, headache, vertigo and somnolence	• Risk of QTc prolongation – caution with psychotropics known to prolong QTc • Risk of hepatotoxicity- caution with hepatotoxic drugs
Chloroquine and hydroxychloroquine	Anti-inflammatory Antiviral: interference with virus-receptor binding Immune modulating effects	Psychosis, delirium, suicidality, personality changes, depression, nervousness, irritability, compulsive impulses, preoccupations, and aggressiveness	• Risk of QTc prolongation – caution with QT prolonging drugs. Do not use outside of the hospital setting or a clinical trial due to risk of heart rhythm problems (FDA) • Metabolized by CYP3A4 – potential drug interactions with CYP3A4 inhibitors (eg, fluvoxamine) and inducers (eg, carbamazepine, oxcarbazepine, modafinil) • Risk of hepatotoxicity- caution with hepatotoxic drugs • Risk of seizures- caution with psychotropics that can lower the seizure threshold • Higher risk of neuropsychiatric side effects when combined with CYP3A4 inhibitors, low-dose glucocorticoids, alcohol intake, family history of psychiatric disease, female gender, low body weight and supratherapeutic dosing • Long half-life (40 hours) - adverse effects and drug-interactions may continue for days after the drug has been discontinued
Colchicine	Anti-inflammatory Immune modulator: targets IL-6 pathway, inhibition of NLRP3 inflammasome. May attenuate cytokine storm.	At toxic doses: delirium, seizures, muscle weakness, depressed reflexes	• Narrow therapeutic index – potential for toxicity • Caution in renal and hepatic failure • Caution with P-gp and CYP 3A4 inhibitors (eg, fluvoxamine) • CYP3A4 inducers may decrease levels
Convalescent plasma therapy	Antibody containing convalescent plasma from patients who have recovered from viral infections	No specific psychiatric effects (N.B. allergic reactions can produce shortness of breath and palpitations that mimic panic attacks) Potential psychological effects for donors	• There are no specific interactions (N.B. patients who develop transfusion reactions might receive steroids or diphenhydramine which can have negative synergistic effects with existing psychotropics).
Corticosteroids	Immune modulators and anti-inflammatory: may lessen cytokine storm and hyperinflammation syndrome	Depression, mania, agitation, mood lability, anxiety, insomnia, catatonia, depersonalization, delirium, dementia, and psychosis	• Inconsistently reported to be weak CYP 3A4 and CYP2C19 inducers • Phenytoin – increases hepatic metabolism of systemic corticosteroids • Caution with bupropion- lowers seizure threshold • Majority of neuropsychiatric side effects occur early in treatment course, usually within days, and dosing is the most significant risk factor

			(i.e. at prednisone equivalents of >40mg/day)
Favipiravir	Anti-viral: RNA dependent RNA polymerase inhibitor	No information	• Possible QT prolongation
Interferon	Immune modulator, antiproliferative, and hormone-like activities Anti-viral	IFN alpha: boxed warning for "life threatening or fatal neuropsychiatric disorders." Specific effects include fatigue, mood disorders, suicidality, anxiety disorders, irritability, lability, apathy, sleep disturbance, and cognitive deficits IFN beta: fatigue, weight loss, myalgia, arthralgia	• No known pharmacokinetic interactions with psychotropics • Potential for bone marrow suppression - safety concerns with some psychotropics (eg, carbamazepine, valproate and clozapine) • May lower seizure threshold: caution with psychotropics that also lower seizure threshold
Lopinavir/Ritonavir	Anti-viral Lopinavir: protease inhibitor Ritonavir: boosts plasma levels of lopinavir	Possible abnormal dreams, agitation, anxiety, confusion and emotional lability All protease inhibitors associated with paresthesias, taste alterations, and neurotoxicity	• Extensively metabolized by cytochrome P450 – risk of multiple possible interactions • May get increased concentrations of co-administered CYP3A4 or CYP2D6 substrates • May get decreased concentrations of CYP1A2 or CYP2B6 substrates • Contraindicated with pimozide, midazolam, and triazolam due to increased drug levels and potentiation of adverse effects • Lowers concentrations of some psychotropics (e.g., bupropion, methadone, lamotrigine and olanzapine) • • Other potential side effects that may impact psychotropic use: Stevens Johnson syndrome, diabetes mellitus, QTc prolongation, pancreatitis, neutropenia, hepatotoxicity and chronic kidney disease
Remdesivir	*Only FDA-approved medication for severe COVID-19 Interacts with RNA polymerase, leads to decrease in viral RNA	No information	• No information is available about pharmacokinetic drug-drug interactions • Risk of elevated aminotransferase levels (e.g. ALT up to 20x upper limit of normal)– caution with potentially hepatotoxic psychotropics
Tocilizumab	Immune modulator: recombinant humanized monoclonal antibody that acts as an IL-6 inhibitor; may lessen cytokine storm	Possible positive effects on depressive symptoms	• No major interactions reported
Vitamin C	Enhances immune response, antioxidant and reducing agent	No evidence for neuropsychiatric adverse effects; Of note, lower levels associated with depression, confusion, anger, delirium	• Coadministration with barbiturates may decrease the effects of vitamin C