The Use of "Novel Pharmacology" in the Treatment of COVID-19 and Potential Psychiatric Risks

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The coronavirus disease 2019 (COVID-19) pandemic continues to generate understandable mass panic as the number of fatalities linked to the disease rise. The trajectory of the viral pathogenesis varies among the population, with 80% of patients experiencing mild illness, 14% presenting with moderate illness, and 5% having a critical form of disease.[1] This pathogenesis may include progressive pneumonia, acute respiratory distress syndrome, myocardial injury, arrhythmias, signs of disseminated intravascular coagulation, multiorgan failure, and death.[1,2] D-dimer levels have been suggested as possible biomarkers for disease severity and mortality.[3]

Specific groups including the elderly and those with existing comorbidity can have worse prognostic outcomes.[1] Those with psychiatric illness commonly fall into these categories, as coexisting physical illness is rife in this community. The virus may present in an atypical fashion in vulnerable groups with abrupt deterioration to the extent that subjects require hospitalization[1] and assisted ventilation in the critical or intensive care setting.

Various novel pharmacologic treatments are being considered for COVID-19. We briefly discuss some of these proposed treatments and their possible psychiatric adverse effects.

Chloroquine/Hydroxychloroquine

The antimalarial drug chloroquine and its safer derivative hydroxychloroquine have been permitted for use by the US Food and Drug Administration.[4] Both drugs have generated significant interest as potential antiviral treatments. In vitro testing in China demonstrated inhibition of severe acute respiratory syndrome (SARS) coronavirus 2, but there is no robust evidence at the time of this writing to confirm clinical efficacy in human subjects.[5] Speculation about potential curative effects of these treatments has allegedly led to supply shortages and even fatal overdoses.[6]

These medications have potential lethal effects at higher dosage, which can include QTc prolongation and, rarely, sudden cardiac death. The cardiac risk is greater if used in combination with azithromycin. Azithromycin also can lengthen QTc, compounding dangers from chloroquine products.[4] A study[7] reported promising data with superior viral clearance found with the addition of azithromycin. Both chloroquine and hydroxychloroquine have potential neuropsychiatric adverse effects including anxiety, irritability, emotional difficulties, agitation, and, rarely, psychosis.[8,9] Their interaction with psychotropic medications would require close monitoring given the strong association with some antipsychotics and QTc prolongation.

Interferon-α, Interferon-β, Lopinavir/Ritonavir, and Ribavirin

The immunomodulatory agents have been studied for potential use, with interferon-β having demonstrated some activity against middle east respiratory syndrome.[7] There is limited published evidence for these treatments with conflicting current clinical data. Most of the published studies have reported the effects of these agents when combined with the antiretroviral lopinavir/ritonavir or the guanine analog ribavirin, which inhibits viral RNA-dependent RNA polymerase.[7]

Interferon-α is most commonly used in the treatment of hepatitis C. Severe fatigue and insomnia are common side effects.[10] A psychiatric opinion is advisable before treatment with interferon-α and more so in cases wherein there is predisposing vulnerability because of the potential serious psychiatric adverse effects including increased risk of suicidal ideation.[10] Of those treated with interferon-α, 10%–40% can develop a clinical depression that manifests in various biological and cognitive symptoms.[10] For patients with a history of major depressive disorder, prophylactic treatment with a selective serotonin reuptake inhibitor should be considered when starting interferon, as this appears to reduce the incidence of developing depression by approximately half.[10] Up to 25% of patients can develop anger and irritability with subsequent impairment of quality of life. Less frequent psychiatric complications can include mania, delirium, and psychosis.[10] There is also the possibility of inducement of a manic state when this drug is withdrawn.[10]

The coadministration of the antiviral protease inhibitor lopinavir with ritonavir (ritonavir used to increase the half-life of lopinavir) can inhibit cytochrome P450 3A4, which can lead to increased plasma levels of various psychiatric

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Box 1. Medications That May Prolong the QTc Interval[13,14]

- Antipsychotic medications: pimozide, ziprasidone, haloperidol, phenothiazines, olanzapine, risperidone, quetiapine, trifluoperazine, droperidol
- Antidepressant medications: selective serotonin reuptake inhibitors (citalopram, fluoxetine, paroxetine), serotonin-norepinephrine reuptake inhibitors (venlafaxine), and various tricyclic antidepressants (amitriptyline, desipramine, imipramine, doxepin)
- Anticonvulsants: phenytoin, carbamazepine
- Other: methadone, lithium, domperidone, quinine, tamoxifen, indapamide, furosemide
- Antihistamines: diphenhydramine, hydroxyzine
- Antibiotics: erythromycin, azithromycin, clarithromycin, levofloxacin, trimethoprim
- Antifungals: ketoconazole, fluconazole
- Antiarrhythmic medications
- Antidiarrheal agent: loperamide
- Migraine treatments: sumatriptan, zolmitriptan
- Anesthetic drugs

medications.[10] Adverse effects of this combination include gastrointestinal disturbance and hepatotoxicity.[7] Nausea and diarrhea can occur in up to 28% of patients,[7] and caution should be applied if the patient is prescribed lithium, as these symptoms may lead to lithium toxicity or can be a manifestation of this. We would advise frequent monitoring of plasma levels in such patients.

The combination of lopinavir/ritonavir was also associated with QTc prolongation, which is a concern when using concurrent psychiatric medications.[2] Ribavirin is commonly added to this combination, and this can cause severe dose-dependent hematologic toxicity and hepatotoxicity.[7] These potential adverse effects are important for psychiatrists to keep in mind, particularly as some psychotropic medications can also cause hepatic and hematologic dysfunction.

Zhang et al[11] advise that if a patient with psychiatric comorbidity is treated with these medications for COVID-19, then these agents should be combined with the appropriate psychotropic medication for treatment of the mental illness as there is a risk of relapse. Specialist psychiatric advice should be sought to keep the drug interactions at a minimum.

Corticosteroids

The evidence for use of steroids in the treatment of COVID-19 is limited, with the possible rationale being to decrease host inflammatory response in the lungs.[7] Steroids are well known to have various psychiatric adverse effects including inducing affective and psychotic states in some. There is caution with regard to their routine use in COVID-19 patients due to lack of evidence for their effectiveness.[7] Cheng et al[12] reported on psychiatric complications in patients during the acute treatment phase of SARS and attributed the use of steroids as a possible causal factor.[12] The authors[12] add that these patients responded to haloperidol (doses ranging from 1.5–5 mg daily) with prompt resolution of symptoms within 3–5 days.

Conclusions

Epidemiologic strategies have been implemented by governments to provide containment of the COVID-19 outbreak. There is an urgency to develop efficacious pharmacologic treatments and a potential vaccination to prevent infection. Various drug treatments have been proposed, though no therapeutic agent has yet proved effective in the treatment of severe disease.[2] The current gold-standard treatment remains supportive care.[7] A number of controlled trials are currently underway[7] to establish the efficacy, safety, and tolerability of these prospective treatments. Psychiatrists should be particularly mindful of the cardiac adverse effects of some of these proposed treatments and their interaction with psychotropic medications (Box 1).

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REFERENCES

1. Beeching NJ, Fletcher TE, Fowler R. Coronavirus disease 2019 (COVID-19). BMJ Best Practice website. https://bestpractice.bmj.com/topics/en-us/3000168. Accessed May 11, 2020.
2. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19 [published online ahead of print March 18, 2020]. *N Engl J Med*. 2020;NEJMoa2001282.
3. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thromb Haemost*. 2020;120(5):876–878.
4. Jaffe S. Regulators split on antimalarials for COVID-19. *Lancet*. 2020;395(10231):1179.
5. Owens B. Excitement around hydroxychloroquine for treating COVID-19 causes challenges for rheumatology. *Lancet Rheumatology*. 2020;2(5):e257.
6. Newton PN, Bond KC; 53 signatories from 20 countries. COVID-19 and risks to the supply and quality of tests, drugs, and vaccines. *Lancet Glob Health*. 2020;S2214-109X(20)30136-4.
7. Sanders JM, Monogue ML, Jodlowski TZ, et al. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review [published online ahead of print April 13, 2020]. *JAMA*. 2020.
8. Ali SS, Jones H. 23. An adverse neuropsychiatric reaction following treatment with hydroxychloroquine: a case report. *Rheumatol Adv Pract*. 2018;2(suppl 1):rky033.014.
9. Manzo C, Gareri P, Castagna A. Psychomotor agitation following treatment with hydroxychloroquine. *Drug Saf Case Rep*. 2017;4(1):6.
10. Lotrich FE. Psychiatric clearance for patients started on interferon-alpha-based therapies. *Am J Psychiatry*. 2013;170(6):592–597.
11. Zhang K, Zhou X, Liu H, et al. Treatment concerns for psychiatric symptoms in COVID-19–infected patients with or without psychiatric disorders [published online ahead of print April 9, 2020]. *Br J Psychiatry*. 2020.
12. Cheng SKW, Tsang JSK, Ku KH, et al. Psychiatric complications in patients with severe acute respiratory syndrome (SARS) during the acute treatment phase: a series of 10 cases. *Br J Psychiatry*. 2004;184(4):359–360.
13. Al-Khatib SM, LaPointe NMA, Kramer JM, et al. What clinicians should know about the QT interval. *JAMA*. 2003;289(16):2120–2127.
14. Dave J, Bessette MJ, Setnik G, et al. Torsade de pointes. Medscape website. https://emedicine.medscape.com/article/1950863-overview. 2017. Accessed May 7, 2020.