Elias Khawam, MD
Department of Psychiatry and Psychology, Neurologic Institute, Cleveland Clinic

Hassan Khouli, MD
Department of Critical Care Medicine, Respiratory Institute, Cleveland Clinic

Leo Pozuelo, MD
Department of Psychiatry and Psychology, Neurologic Institute, Cleveland Clinic

Treating acute anxiety in patients with COVID-19

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ABSTRACT

At present, there are no firm guidelines for the treatment of COVID-19–related emotional distress. The current approach is based on our knowledge of how to manage anxiety in medically ill patients, taking into consideration all associated medical comorbidities, drug-drug interactions, and the patient's specific needs and preexisting mental illness. Interventions should be implemented at the bedside to augment the patient's own resiliency in coping with these stressful events. A targeted combination of psychopharmacology (targeting acute anxiety and panic symptoms) and psychotherapy (relaxation techniques, breathing exercises, and encouragement) is recommended.

CASE PRESENTATION

A 62-year-old woman with a history of diabetes mellitus and hypertension presented to the emergency department with worsening shortness of breath, fatigue, severe headache, nausea, poor oral intake, and ongoing fever during the past 3 days despite using acetaminophen and ibuprofen. She reported flu-like symptoms for the past week and possible exposure to a COVID-19–positive neighbor.

In the emergency room, her temperature was 99°F, heart rate 105 beats per minute, blood pressure 130/78 mm Hg, respiratory rate 24 breaths per minute, and oxygen saturation 88% on room air. Chest radiography revealed bilateral peripheral mid- and lower-lung field infiltrates. She tested positive for COVID-19 and was admitted to a regular COVID-19 nursing floor for management.

She was placed on supplemental oxygen at 3 L/min by nasal cannula, with improvement in oxygen saturation to 96%. She was started on intravenous ceftriaxone for possible super imposed bacterial pneumonia and enrolled in a hydroxychloroquine research trial for patients with COVID-19 infection. In the setting of social distancing (no visitors, communication with family only by iPad), she exhibited several acute anxiety attacks, with episodes of chest tightness, fear, and hyperventilation. Her primary team requested psychiatry consult to help the patient manage her emotional distress.

During the virtual psychiatric interview, the patient reported worsening anxiety over the past couple weeks. She denied any previous psychiatric treatment but reported being a lifelong generalized worrier, with increasing anxiety ever since the governor of her state ordered all residents to shelter in place. She felt isolated and scared and started experiencing insomnia, anxiety, decreased appetite, and low energy at home. Her mood was increasingly worried and sad. There was no evidence of confusion, mania, or psychosis during the interview. She had experienced 1 acute panic attack in the past when she was involved in a motor vehicle accident. She is divorced mother of 2 grown children and is a retired librarian. The clinical impression was acute panic attacks and worsening of generalized anxiety disorder.

Laboratory testing results were remarkable only for absolute lymphopenia and an elevated C-reactive protein (CRP) level of 2.8 mg/L. Her electrolyte levels and kidney function were normal.

Electrocardiography showed sinus tachycardia, with a heart rate of 115 beats per minute; the corrected QT (QTc) interval was prolonged at 570 ms. Her respiratory rate remained elevated at 28 breaths per minute, and her oxygen saturation by pulse oximetry was 95% while receiving supplemental oxygen at 3 L/min by nasal cannula. The patient was awake and alert and reported feeling very stressed. There were no signs of accessory respiratory muscle use during physical examination. There was no wheezing, but scattered scant bilateral crackles were heard.

She was given low-dose lorazepam, 0.5 mg intra-

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TABLE 1
Medications for the treatment of acute anxiety in hospitalized patients with COVID-19 infection

Medication	Dose	Route	Caution
Alprazolam	0.125–0.25 mg, 3 times daily	By mouth	Respiratory depression
Lorazepam	0.5–1 mg, 3 times daily	By mouth, intramuscular, intravenous[a]	Respiratory depression
Gabapentin	100–300 mg, 3 times daily	By mouth	Renal clearance
Hydroxyzine	25–50 mg, 3 times daily	By mouth	QTc monitoring
Olanzapine	2.5–5 mg, 3 times daily	By mouth	QTc monitoring
Quetiapine	25–50 mg, 3 times daily	By mouth	QTc monitoring
Haloperidol	0.5–1 mg, 3 times daily	By mouth, intramuscular, intravenous[a]	QTc monitoring

[a]For intravenous dosing, use half of the oral dose.

venously every 8 hours as needed, for breakthrough panic. After 1 dose of the lorazepam, there was a subjective drop in panic symptoms and an objective decrease in respiratory rate to 20 breaths per minute. She remained awake and alert. Her oxygen saturation remained unchanged at 95% to 96% on the supplemental oxygen.

She was started on gabapentin 100 mg three times daily for anxiety, and melatonin 5 mg every night at bedtime for insomnia. The gabapentin dose was increased gradually to 300 mg three times daily with good results. The lorazepam was continued on an as-needed basis. Daily supportive psychotherapy (via cellphone) was provided. Her anxiety symptoms improved commensurately with her respiratory symptoms. She did not require admission to an intensive care unit and was discharged home after a 6-day hospitalization stay with low-flow oxygen. Psychiatry recommended a low-dose selective serotonin reuptake inhibitor for long-term management of her generalized anxiety disorder.

DISCUSSION

The emergence of the COVID-19 pandemic has affected individuals and society on multiple levels. The overall focus has been on preventing the spread of the disease and discovering treatment options. However, the psychological impact of the illness should not be overlooked.

Patients face multiple stressors due to the COVID-19 crisis including but not limited to fear of becoming infected and of infecting others, inadequate access to testing, disrupted regular medical care, financial losses, distress related to social distancing and quarantine, and uncertainty of the duration of the pandemic.[1] Some reports raise concerns of a long-lasting mental health impact as a consequence of the pandemic.

Research on previous viral outbreaks revealed significant and wide-ranging psychosocial distress that impacted individuals and communities. Anxiety, panic, and stress have been linked to infectious epidemics. It is anticipated that patients infected with COVID-19 may suffer from mood dysregulation, anxiety, anger, and worsening of any preexisting mental illness.[2] Patients are also at risk for social stigma and xenophobia. In the hospital setting, with prolonged hospitalization and the potential need for intubation and mechanical ventilation, light sedation is recommended to minimize risk of post-intensive care unit syndrome and adverse outcomes (90-day mortality, cognitive dysfunction, physical disability, post-traumatic stress disorder, anxiety, and depressive symptoms).[3]

At present, there are no firm guidelines for the treatment of COVID-19–related emotional distress. The current approach is based on our knowledge on how to manage anxiety in medically ill patients, taking into consideration all associated medical comorbidities, drug-drug interactions, and the patient's specific needs and preexisting mental illness. Interventions should be implemented at the bedside to augment the patient's own resiliency in coping with these stressful events. A targeted combination of psychopharmacology (targeting acute anxiety and panic symptoms) and psychotherapy (relaxation techniques, breathing exercises, and encouragement) is recommended.

There are multiple pharmacologic agents that can be used to treat acute anxiety in hospitalized patients with COVID-19 infection (**Table 1**).

Benzodiazepines produce an immediate anxiolytic effect. Low-dose alprazolam can be used for patients with anxiety and panic symptoms in the presence of

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mild respiratory distress. Alprazolam works rapidly and is eliminated quickly, having a short half-life. Alprazolam is available only in oral form whereas lorazepam can be given orally, intravenously, and intramuscularly. We prefer these short-acting agents to the benzodiazepines with a longer half-life (eg, diazepam and chlordiazepoxide).

Benzodiazepines should be used cautiously in patients with underlying acute or chronic respiratory illness to avoid respiratory depression and precipitating acute respiratory failure. Anxiety and agitation can be part of the presentation of acute respiratory decompensation, and they may be further aggravated by the administration of anxiolytics such as benzodiazepines. It is important to carefully evaluate the etiology of anxiety and agitation before considering benzodiazepines. The evaluation may include assessing the patient's mental status, use of accessory muscles of breathing, vital signs, and oxygen saturation as well as ordering additional laboratory tests and imaging studies when clinically indicated.[4] Close monitoring of respiratory, cardiovascular, and neurological status are paramount to detect early signs of potential clinical deterioration from benzodiazepine use. Yet, anxiety-induced hyperventilation can compromise lung function, which was the case in our patient.

Benzodiazepines can be used judiciously in anxious patients with COVID-19 infection to provide symptomatic relief. The lowest possible dose of alprazolam or lorazepam is recommended 4 times daily to achieve a uniform 24-hour effect. Of course, any patient who was taking benzodiazepines prior to admission should have them continued at the lowest daily dose to avoid benzodiazepine withdrawal-induced delirium.

In rare cases, patients can have a paradoxical reaction to benzodiazepines that is characterized by increased agitation, restlessness, and hostility. Increasing the dose may worsen the agitation. Appropriate management involves discontinuing the benzodiazepine and using an alternative sedative. While benzodiazepines can increase the risk for delirium in critically ill patients, a continuous infusion may be used as an alternative sedative agent in critically ill, mechanically ventilated COVID-19–infected patients to achieve light sedation with daily sedation interruption.[5]

Second-tier options for anxiolysis include gabapentin, an anticonvulsant GABA analogue. Although it has not been approved by the US Food and Drug Administration (FDA) for treatment of anxiety, it has been used in anxiety disorders and alcohol withdrawal with mild to moderate success.[6] Another option is the FDA-approved anxiety treatment hydroxyzine, which is a histamine H1 receptor antagonist with a very low anticholinergic profile; it is mostly used in children and young adults.

Both of these options are viable when benzodiazepines are contraindicated (concern with respiratory depression) or benzodiazepines could aggravate the risk for delirium. With both of these medications, sedation is minimal and there is no major respiratory depression. Furthermore, they can be administered using an optimal three-times-a-day dosing schedule. These medications are also less likely to cause delirium in the medically ill. Gabapentin use should be monitored in patients with decreased renal clearance and the dose adjusted accordingly. Hydroxyzine increases the risk for prolongation of the QTc interval.

Buspirone, a non-benzodiazepine, non-sedating medication indicated for generalized anxiety disorder, has a delayed onset of effect to that of traditional antidepressants (2 to 3 weeks), and thus is ineffective in an acute anxiety state.

Antipsychotics are not approved by the FDA for the treatment of anxiety but there are data supporting their efficacy.[7] Low-to-moderate doses of olanzapine or quetiapine can be effective for anxiety, rumination, and insomnia. These agents can be sedating but do not suppress respiratory drive. However, when using both olanzapine and lorazepam, they must be administered at least 1 hour apart to avoid the risk of respiratory depression.

The risk of QTc prolongation may be of concern when antipsychotics are combined with QTc-prolonging agents for treatment of COVID-19 infection (eg, hydroxychloroquine, chloroquine, and azithromycin). Haloperidol, when given intravenously in low dosages, can also have anxiolytic effects with minimal sedation. It can be used in agitated patients but should be administered with the patient on telemetry due to risk of QTc prolongation and ventricular arrhythmias.[8]

Psychotherapeutic techniques are valuable in managing anxiety in medically ill patients and should be used to allow the patient to successfully cope with the index hospitalization. A supportive psychotherapy approach is recommended, which includes active and empathic listening to the patient's concerns and fears, providing education and encouragement about the treatment for anxiety, and regularly updating the patient on his or her care team's goals and objectives. Relaxation techniques and mindfulness exercises can be of added value, especially as they lend themselves to digital platforms.

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As we continue to learn and adapt our diagnostic and therapeutic knowledge to the physical needs of the COVID-19 patient, we should be vigilant and address their emotional needs as well during the continuum of care.

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