# is illegal to post this copyrighted PDF on any website. Prompt Use of Benzodiazepines for Anxiety Management in COVID-19–Positive Patients With Tracheostomy

Terence L. Howard, MS<sup>a</sup>; Haarika Korlipara, BS<sup>a</sup>; and Nidhi Sharoha, DO<sup>b,\*</sup>

The novel coronavirus disease 2019 (COVID-19) pandemic has had a significant psychological impact on the general population. Stressors now include fear of becoming infected and infecting others, social distancing and quarantining, and uncertainty regarding the pandemic. A significant portion of the population in China has experienced moderate-to-severe symptoms of depression and anxiety, and female sex has been significantly associated with higher symptom severity.<sup>1</sup> During the pandemic, individuals have reported less positive emotions and life satisfaction, but increased anger, anxiety, and depression, which are associated with more stress and reduced sleep quality.<sup>2,3</sup> Psychiatric manifestations of COVID-19 have seemingly disproportionately impacted women, those with psychiatric illness, and patients with chronic medical comorbidities.

Mechanically ventilated patients in intensive care units (ICUs) have been shown to experience unpleasant feelings of fear, anxiety, and loneliness. These feelings can stem from multiple factors including poor breathing, loss of independence, inability to communicate, sleep disturbance, and the ICU environment itself. A qualitative metasynthesis<sup>4</sup> of interpreted knowledge on patient experiences while mechanically ventilated in the ICU found that dependence on health care professionals without the ability to communicate greatly contributed to anxiety. Furthermore, symptom intensity depended both on the ability of health care professionals to remain present with patients and the presence of family throughout their hospital course.<sup>4</sup> Although it is widely believed that patient comfort increases after tracheostomy, patient anxiety scores have not been observed to decrease significantly compared to baseline.<sup>5</sup> This finding suggests that tracheostomy may contribute to the anxiety experienced by ICU patients.<sup>5</sup>

Current management for anxiety in mechanically ventilated patients remains a combination of nonpharmacologic and pharmacologic interventions. The former typically focuses on patient progression and future well-being via

<sup>a</sup>Stony Brook University Renaissance School of Medicine, Stony Brook, New York

<sup>b</sup>Stony Brook University Hospital, Stony Brook, New York \*Corresponding author: Nidhi Sharoha, DO, Stony Brook University Hospital, Stony Brook, NY 11794 (nsharoha0226@gmail.com). Prim Care Companion CNS Disord 2020;22(6):20102785

*To cite:* Howard TL, Korlipara H, Sharoha N. Prompt use of benzodiazepines for anxiety management in COVID-19–positive patients with tracheostomy. *Prim Care Companion CNS Disord*. 2020;22(6):20102785. *To share:* https://doi.org/10.4088/PCC.20102785 © Copyright 2020 Physicians Postgraduate Press, Inc.

relaxation techniques such as breathing exercises, playing music, distractions, and verbal reassurance.<sup>6</sup> Pharmacologic interventions involve a variety of sedatives and anxiolytics, which are used to quell the physiologic manifestations of anxiety.<sup>6</sup> Currently, there are no protocols for managing anxiety in COVID-19–positive ICU patients with tracheostomy despite the pandemic, mechanical ventilation, and tracheostomy all being sources of anxiety. In this case series, we highlight 3 such patients in an effort to show support for early and consistent use of benzodiazepines for anxiety management.

# **Case Series**

*Case 1.* Ms A is a 65-year-old engaged retired white woman who presented to a university hospital in early April with fever, nausea, shortness of breath, malaise, and sore throat after leaving a subacute rehabilitation facility. She had a complex medical history significant for hypertension, hyperlipidemia, systemic lupus erythematosus, primary adrenal insufficiency from chronic use of corticosteroids, fibromyalgia, and chronic back pain post spinal fusion pump. On arrival, she was febrile, tachycardic, and tachypneic, with oxygen saturation of 68% on room air. Portable chest x-ray showed hazy bilateral opacities concerning for COVID-19 viral pneumonia, which prompted treatment with hydroxychloroquine, azithromycin, remdesivir, intravenous (IV) steroids, and empiric antibiotics to treat superimposed bacterial pneumonia.

The psychiatry department was consulted on hospital day 3 for anxiety management despite improvement of oxygenation on a nonrebreather mask while admitted for acute respiratory failure. Her past psychiatric history was notable for anxiety, depression, and opioid use disorder, with her last rehab stay 10 years prior; there were no suicide attempts or inpatient admissions. She was currently prescribed sertraline 100 mg/d, venlafaxine 75 mg/d, and trazodone 100 mg at bedtime. The psychiatry interview was conducted over the phone, yet the patient was noted as inattentive, tangential, and restless, thus she was unable to reveal much about her symptoms. According to the primary treatment team, Ms A had been fidgety, restless, and tachycardic, indicating that anxiety was present. Anxiety disorder unspecified (DSM-5 criteria) was diagnosed, as the patient's anxiety symptoms did not meet criteria for any other anxiety disorder but did cause significant impairment in functioning. However, delirium from multiple etiologies could not be ruled out given the limited interview. Treatment recommendations included clonazepam 0.5 mg twice/day

It is illegal to post this copy by mouth as needed, trazodone 50 mg at bedtime by mouth as needed, and an increase of venlafaxine to 112.5 mg/day by mouth. Despite these changes, Ms A remained anxious and agitated while receiving oxygen therapy, which led to recurrent desaturations from frequently removing her mask. The psychiatry team was reconsulted on hospital day 11, at which time she reported repeat episodes of panic attacks, so recommendations were adjusted to add quetiapine 12.5 mg by mouth every 8 hours as needed, increase venlafaxine to 150 mg/day by mouth, stop clonazepam due to concern for possible worsening of respiratory function, and follow up with the consult psychologist. Her poor oxygenation, underlying illness, and corticosteroid use were also considered as sources of anxiety. The primary team decided to still prescribe as-needed lorazepam and clonazepam due to increased anxiety and agitation requiring safety watch. Her hospital course was complicated by atrial fibrillation with rapid ventricular response, persistent pneumothoraces post chest tube insertions, secondary multidrug-resistant Klebsiella pneumonia anemia post multiple transfusions, rectus sheath hematoma post embolization, and intubation with subsequent open tracheostomy with 8-mm Portex cuff. As Ms A was ventilator dependent, nonverbal, and no longer receiving standing anxiolytics, the psychiatry team was reconsulted on hospital day 60 for persistent anxiety. Recommendations included restarting venlafaxine, quetiapine, and trazodone. After 2 weeks, lorazepam 0.5 mg IV every 12 hours as needed was also suggested for breakthrough anxiety but was switched to clonazepam 0.5 mg twice/day due to patient preference. With these changes and ultimately being stabilized on standing clonazepam, the patient was less anxious, gradually weaned to room air, received a speaking valve, tolerated food, and participated in physical therapy. Although still COVID-19 positive on hospital day 107, Ms A was accepted and discharged safely to a subacute rehabilitation facility.

Case 2. Mr B is a 54-year-old employed married white man domiciled with family who came to the university hospital in early April for 6 days of fever, chills, dry cough, shortness of breath, pleuritic chest pain, and myalgia. He had COVID-19 exposure via his adult daughter and was known to be positive from testing at an outside hospital. His past medical history was significant for hypertension, hyperlipidemia, and obesity. On arrival, he was febrile, tachycardic, and hypertensive, with 79% oxygen saturation on room air. Portable chest x-ray indicated multifocal pneumonia. He was admitted to the medical floor for hyponatremia and sepsis with acute respiratory failure due to viral pneumonia. He was started on hydroxychloroquine, azithromycin, tocilizumab, IV steroids, and oxygen therapy. Initially fearful, Mr B requested to be intubated on hospital day 3 due to anxiety and exhaustion from increased work of breathing. Midazolam drip was used for sedation, while as-needed IV pushes were given by the primary team for elevated blood pressure and agitation overnight. Restraints were also utilized for 7 days after he pulled at the endotracheal tube. Mr B was successfully extubated after 23

anted PDF on any website. days; however, he required reinfubation for hypoxia during nasogastric tube placement. Subsequent tracheostomy was performed on hospital day 38 using 9.0-mm Portex cuff and Bjork flap. His hospital course was also complicated by acute respiratory distress syndrome, bacteremia with persistent fevers, new-onset atrial fibrillation with rapid ventricular response, and persistent pneumothoraces requiring chest tube insertions. Despite tolerating the tracheostomy collar, he remained restless and expressed frustration with being ventilated. The primary team had managed Mr B's anxiety with clonazepam. The psychiatry department was consulted on hospital day 60 for further anxiety management, with the interview conducted over iPad and utilizing yes/no questions due to limited phonation. Mr B was calm and grossly oriented but reported increased sadness and anxiety causing multiple attacks of palpitations with shortness of breath during the day. Using the iPad to talk with family quelled his symptoms. He denied any symptoms of depression, mania, or psychosis. The patient's family confirmed that he had generalized anxiety disorder, which had worsened in the past 3 years. He had no other psychiatric history. The primary diagnosis was delirium (DSM-5 criteria) due to multiple etiologies, as he had disturbances in attention over a short period and cognition, which was not explained by another neurocognitive disorder, and there was evidence from the chart that he had abnormalities such as hypoxia, prolonged intubation, infection, anemia, and hypoalbuminemia that were likely contributing to the delirium. Treatment recommendations included clonidine 0.1 mg by mouth every 8 hours as needed, olanzapine 2.5 mg intramuscular every 12 hours as needed, and melatonin 3 mg by mouth at bedtime along with continuation of benzodiazepines that the primary team initiated. Tracheostomy was downsized to 7.0-mm Portex cuff for better vocalization. Within 2 weeks, Mr B was reported to be calm, began physical and speech therapy, and tolerated by-mouth intake; he was transferred to the step-down unit. Having received his third negative COVID-19 test and displaying stable blood pressure on metoprolol, he was deemed safe for discharge to a subacute rehabilitation facility on hospital day 80.

Case 3. Ms C is a 47-year-old married white woman who presented to the university hospital in mid-April for 7 days of fever, nausea, dry cough, shortness of breath, and diarrhea. Symptoms were not relieved by acetaminophen or albuterol at home. She had exposure to COVID-19 via her husband and had a confirmed positive test 2 days prior to arrival. Past medical history was notable for allergy-induced asthma, migraines, obesity, and partial hysterectomy, and she was a former smoker. On arrival, Ms C was febrile, tachycardic, and tachypneic, with 92% oxygen saturation on 4-L nasal cannula. Initial laboratory tests showed increased inflammatory markers and anion gap metabolic acidosis, while portable chest x-ray was suggestive for viral pneumonia. The patient was admitted to the medical floor for hypoxic respiratory failure with increased oxygen requirements. Having completed azithromycin at home, Ms C was started on hydroxychloroquine, tocilizumab, remdesivir, and IV

It is illegal to post this cop steroids. She was also given ceftriaxone and doxycycline for potential superimposed bacterial pneumonia. Despite some clinical improvement, the patient experienced recurrent desaturations causing inability to wean off a nonrebreather mask and was intubated on hospital day 22. Midazolam drip was used for sedation, while her home escitalopram along with as-needed IV pushes of alprazolam and midazolam were administered for anxiety. Her hospital course was complicated by acute respiratory distress syndrome, critical illness polymyopathy, multidrug-resistant Klebsiella ventilator-associated pneumonia treated with broadspectrum antibiotics, and persistent hypotension requiring pressor support. Ms C was successfully extubated after 12 days; however, she needed reintubation due to hypercarbic respiratory failure with subsequent open tracheostomy performed on hospital day 55 using 8.0-mm Bivona XLT tubes. Despite tolerating the tracheostomy collar, Ms C became more uncooperative and anxious, with palpitations, tachycardia, diaphoresis, and pupil dilation. She had a desire to see her children, thus talking with family via iPad provided hope. As she was currently managed with clonazepam, alprazolam, midazolam, and quetiapine, the primary team consulted the psychiatry department on hospital day 61 to further evaluate her anxiety. A psychiatry interview was first attempted over iPad; however, Ms C was unable to communicate due to tracheostomy. Her family reported that she had a history of depression and anxiety stemming from worries about her child with special needs. In the past, she trialed venlafaxine and had a psychologist, but no other symptoms of depression, mania, or psychosis or concerns for suicidal or homicidal behavior were evident. Ms C's family thought prolonged hospitalization and underlying infection explained her current symptoms. The primary diagnosis was anxiety disorder unspecified (DSM-5 criteria) most likely due to multiple etiologies including respiratory distress, recent alprazolam use, and anemia. The psychiatry team remained concerned for rebound anxiety with benzodiazepines and recommended quetiapine 25 mg by mouth every 12 hours as needed, melatonin 3 mg by mouth every evening, and continuing her home dose of escitalopram. The patient refused quetiapine due to subjective chest discomfort, so recommendations were changed to gabapentin 300 mg by mouth 3 times/day and hydroxyzine 50 mg by mouth every 8 hours as needed with good effect. Within 1 week, Ms C was comfortable, transferred to the step-down unit, taken off isolation, and had the tracheostomy downsized to a 7.0-mm Portex cuff for better phonation. Being COVID-19 negative and asymptomatic, the patient was safe for discharge to a subacute rehabilitation facility on hospital day 72.

## Discussion

This case series highlights 3 patients with viral pneumonia from COVID-19 that ultimately led to intubation and tracheostomy due to acute respiratory failure. All 3 patients were white with underlying anxiety disorder and depression. Two of the patients were female and 2 were **control PDF on any website**, younger than age 65 years. Each patient also had chronic comorbid medical illnesses. Demographic information is imperative to consider with this case series, as it will help in the identification of individuals who are likely to experience specific psychiatric symptoms.

Although these cases possess many similarities, one uniquely differs from the others. As detailed in case 1, the persistent respiratory instability and subsequent prolonged hospital course of Ms A were directly related to her anxiety. Restlessness and panic drove her unwillingness to properly wear oxygen therapy masks, which led to intubation and then ventilator dependence after obtaining tracheostomy. Although we initially recommended clonazepam, concerns about further complicating her respiratory status caused us to hold off on using any further benzodiazepines. With all the unknowns about COVID-19, the psychiatry team thought it best to err on the side of caution. However, this did not stop members of the primary team from offering various benzodiazepines as needed for most of her hospitalization. Noticing no major adverse effects, our team gained confidence to safely recommend low-dose benzodiazepines for breakthrough anxiety later in the hospital course. Once managed, Ms A was able to be discharged after 3 months, which illustrates how earlier and more consistent control of symptoms with standing benzodiazepines would have psychiatrically and medically benefitted the patient. As this case occurred at the height of the pandemic, turnover of house staff was constant and most likely contributed to inconsistencies in Ms A's treatment plan. Comparatively, the other 2 patients only required 1 consultation to evaluate and manage their symptoms. Once psychotropics were optimized for these 2 middle-aged patients whose symptoms exacerbated after tracheostomy, they responded positively and transitioned to subacute rehabilitation facilities 1 month before Ms A.

Benzodiazepines remain one of the most commonly used agents in ICU patients because of their safety and efficacy.<sup>7</sup> These agents, however, have also been linked to adverse effects such as delirium, respiratory depression, dependence, and withdrawal. Mechanically ventilated patients have typically received higher doses at night, which is associated with failure of spontaneous breathing trials and delayed extubation.<sup>8</sup> At the time of this writing, there has been only 1 other published case report<sup>9</sup> regarding anxiety management in patients with COVID-19. Experiencing worsening generalized anxiety disorder and panic attacks in the setting of hospitalization for hypoxia, the patient was treated with gabapentin titrated up from 100 mg 3 times/day to 300 mg 3 times/day and lorazepam/clonazepam for breakthrough panic.<sup>9</sup> With this treatment, symptoms were noted to decrease significantly, and oxygen saturation remained within normal limits.<sup>9</sup> Our case series extends this finding by focusing on critically ill patients needing tracheostomy, which is crucial since anxiety-induced hyperventilation can further compromise lung function.

Seriously ill COVID-19-positive patients are prone to develop acute respiratory distress syndrome and rapid fluid

#### Howard et el

n in alveoli, which has been shown to cause future development of mental health disorders. Twelve months after discharge from the hospital, 66% of patients with acute respiratory distress syndrome are diagnosed with at least 1 psychiatric disorder-the most likely being anxiety at 42%.<sup>10</sup> Long-term clinical outcomes of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) survivors who required ICU-level care showed elevated rates of anxiety, depression, posttraumatic stress disorder, and low quality of life compared to those for healthy subjects or those with chronic medical illness.<sup>11</sup> Since SARS, MERS, and COVID-19 belong to the same viral family, similar psychiatric sequelae in patients with the latter should be anticipated. Thus, patients with COVID-19 should be considered at risk for anxiety disorders, and benzodiazepines can serve as an adequate and even necessary treatment for patients with tracheostomy.

Along with the inherent limitations of generalizability and causality, this case series would have benefitted from selecting patients of more varied demographic backgrounds. Constant turnover of house staff during the initial phases of the COVID-19 pandemic was another drawback because recommendations from the consult team were likely missed or ignored. However, the prompt use of benzodiazepines in patients with tracheostomy and COVID-19 may decrease suffering and length of hospital stay as evidenced by Ms A in case 1. Additional research is needed to investigate types of benzodiazepines and appropriate dosing that can best treat anxiety in COVID-19–positive patients with tracheostomy.

### Conclusions

Several factors are known to exacerbate the anxiety experienced by patients with tracheostomy. The COVID-19 pandemic itself offers another stressor, which can leave those with past psychiatric history most vulnerable. Currently, there are no guidelines on how to manage anxiety in COVID-19–positive ICU patients with tracheostomy. This case series demonstrates how prompt, constant use of benzodiazepines should be considered to curtail symptoms and long-term psychiatric sequela despite potential risk of respiratory depression. Research should be continued to help establish standard treatment protocols.

*Received:* August 10, 2020.

Published online: December 10, 2020. Potential conflicts of interest: None. Funding/support: None. Additional information: All information has been de-identified to protect anonymity.

#### REFERENCES

- Wang C, Pan R, Wan X, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health. 2020;17(5):1729.
- Li S, Wang Y, Xue J, et al. The impact of COVID-19 epidemic declaration on psychological consequences: a study on active Weibo users. Int J Environ Res Public Health. 2020;17(6):2032.
- 3. Xiao H, Zhang Y, Kong D, et al. Social capital

and sleep quality in individuals who selfisolated for 14 days during the coronavirus disease 2019 (COVID-19) outbreak in January 2020 in China. *Med Sci Monit*. 2020;26:e923921– e923928.

- Baumgarten M, Poulsen I. Patients' experiences of being mechanically ventilated in an ICU: a qualitative metasynthesis. *Scand J Caring Sci.* 2015;29(2):205–214.
- Breckenridge SJ, Chlan L, Savik K. Impact of tracheostomy placement on anxiety in mechanically ventilated adult ICU patients. *Heart Lung.* 2014;43(5):392–398.
- Tate JA, Devito Dabbs A, Hoffman LA, et al. Anxiety and agitation in mechanically ventilated patients. *Qual Health Res.* 2012;22(2):157–173.
- Geller E, Halpern P, Barzelai E, et al. Midazolam infusion and the benzodiazepine antagonist flumazenil for sedation of intensive care patients. *Resuscitation*. 1988;16(suppl):S31–S39.
- 8. Mehta S, Meade M, Burry L, et al; SLEAP

Investigators and the Canadian Critical Care Trials Group. Variation in diurnal sedation in mechanically ventilated patients who are managed with a sedation protocol alone or a sedation protocol and daily interruption. *Crit Care*. 2016;20(1):233.

- Khawam E, Khouli H, Pozuelo L. Treating acute anxiety in patients with COVID-19 [published online ahead of print May 14, 2020]. *Cleve Clin J Med*.
- Pompeo-Fargnoli A, Fargnoli AS. The mental health impact of the COVID-19 crisis: the battle ahead for inpatient survivors [published online ahead of print April 8, 2020]. Psychosomatics. 2020:S0033-3182(20)30064-5.
- Ahmed H, Patel K, Greenwood DC, et al. Longterm clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis. J Rehabil Med. 2020;52(5):jrm00063.