

# New-onset psychosis while being treated for coronavirus

Nathalie Boulos, MD, Brianne M. Newman, MD, and William J. Newman, MD



## How would you handle this case?

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While receiving treatment for COVID-19, Mr. G, age 56, experiences an acute psychotic episode. He has no known psychiatric history. What could be causing his symptoms?

### **CASE** Agitated, psychotic, and COVID-19–positive

Mr. G, age 56, is brought to the emergency department (ED) by emergency medical services (EMS) after his girlfriend reports that he was trying to climb into the “fiery furnace” to “burn the devil within him.” Mr. G had recently tested positive for coronavirus disease 2019 (COVID-19) via polymerase chain reaction and had been receiving treatment for it. In the ED, he is distressed and repeatedly exclaims, “The devil is alive!” He insists on covering himself with blankets, despite diaphoresis and soaking through his clothing within minutes. Because he does not respond to attempted redirection, the ED clinicians administer a single dose of IM haloperidol, 2 mg, for agitation.

### **HISTORY** Multiple ED visits and hospitalizations

Mr. G, who has no known psychiatric history, lives with his girlfriend of 10 years. His medical history includes chronic obstructive pulmonary disease and prostate cancer. In 2015, he had a radical prostatectomy, without chemotherapy. His social history includes childhood neglect, which prompted him to leave home when he was a teenager. Mr. G had earned his general education development certificate and worked at a small retail store.

Mr. G had no previous history of mental health treatment per self-report, collateral information from his girlfriend, and chart review. He reported no known family psychiatric history. He did not endorse past psychiatric admissions or suicide attempts, nor previous periods of mania, depression, or psychosis. He said he used illicit substances as a teen, but denied using alcohol, tobacco products, or illicit substances in the past 20 years.

Mr. G recently had multiple ED visits and hospitalizations due to ongoing signs and symptoms associated with his COVID-19 diagnosis, primarily worsening shortness of breath and cough. Eleven days before EMS brought him to the ED at his girlfriend’s request, Mr. G had presented to the ED with chief complaints of shortness of breath and dry cough (Day 0). He reported that he had been “running a fever” for 2 days. In the ED, his initial vital signs were notable only for a temperature of 100.9°F (38.28°C). He was diagnosed with “acute viral syndrome” and received 1 dose of IV ceftriaxone, 2 g, and

Dr. Boulos is a PGY-4 Psychiatry Resident, Department of Psychiatry, Saint Louis University School of Medicine, St. Louis, Missouri. Dr. Brianne Newman is Associate Professor of Psychiatry, Department of Psychiatry, Saint Louis University School of Medicine, St. Louis, Missouri. Dr. William Newman is Professor of Psychiatry, Department of Psychiatry, Saint Louis University School of Medicine, St. Louis, Missouri.

#### **Disclosures**

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IV azithromycin, 500 mg. On Day 2, the ED clinicians prescribed a 4-day course of oral azithromycin, 250 mg/d, and discharged him home.

On Day 3, Mr. G returned to the ED with similar complaints—congestion and productive cough. He tested positive for COVID-19, and the ED discharged him home with quarantine instructions. Hours later, he returned to the ED via EMS with chief complaints of chest pain, diarrhea, and myalgias. He was prescribed a 5-day course of oseltamivir, 75 mg twice daily, and azithromycin, 250 mg/d. The ED again discharged him home.

On Day 4, Mr. G returned to the ED for a fourth time. His chief complaint was worsening shortness of breath. His oxygen saturation was 94% on room air; it improved to 96% on 2 L of oxygen. His chest X-ray showed diffuse reticulonodular opacities throughout his bilateral lung fields and increased airspace opacification in the bilateral lower lobes. The ED admitted Mr. G to an internal medicine unit, where the primary treatment team enrolled him in a clinical trial. As part of the trial, Mr. G received hydroxychloroquine, 400 mg, on Day 4 and Day 5. The placebo-controlled component of the trial involved Mr. G receiving daily infusions of either remdesivir or placebo on Day 6 through Day 8. On Day 8, Mr. G was discharged home.

On Day 9, Mr. G returned to the ED with a chief complaint that his “thermometer wasn’t working” at home. The ED readmitted him to the internal medicine unit. On Day 9 through Day 11, Mr. G received daily doses of oral levofloxacin, 500 mg, and daily infusions of remdesivir/placebo. Mr. G received 6 total remdesivir/placebo infusions.

During the second hospitalization, nursing staff reported that Mr. G seemed religiously preoccupied and once reported seeing angels and demons. He was observed sitting in a chair praying to Allah that he would “come in on a horse to chop all the workers’ heads off.”

On Day 11, Mr. G was discharged home. Later that evening, the EMS brought him back in the ED due to his girlfriend’s concerns about his mental state.

### EVALUATION Talks to God

On Day 12, psychiatry is consulted to evaluate Mr. G’s new-onset psychosis. Mr. G is alert and oriented to person, place, and time. His speech is loud, though the amount and rate are unremarkable. He displays no psychomotor agitation. His thought process is tangential and focuses on religious themes, specifically referring to Islam. He reports auditory hallucinations of God speaking directly to him. Mr. G states, “I am here because of a miraculous transformation from death back to life. Do you believe in God? Which God do you believe in? There are 2 Gods and only one of them is the true God. He is the God of all the 7 heavens and His true name is Allah, only one God, one faith. Allah is a ball of energy.”

Mr. G’s girlfriend provides collateral information that Mr. G had been raised Christian but was not religious as an adult. She says that he had never spoken about being Muslim. She adds that she had never known him to speak much about religion.

### What is the most likely cause of Mr. G’s new-onset psychosis?

- a primary psychiatric illness
- use of illicit substance(s)
- adverse effect of a prescribed medication
- a general medical condition

### The authors’ observations

The etiology of new-onset psychosis can be related to several factors, including primary psychiatric illnesses, use of illicit substances, sequelae of general medical conditions, or adverse effects of prescribed medications. We considered each of these in the differential diagnosis for Mr. G.

### Clinical Point

Although he had not been religious, Mr. G experiences auditory hallucinations of God speaking directly to him

continued

Table 1

## Inflammation-related biomarker results for Mr. G

Biomarker	Reference range	Result
C-reactive protein	<0.30 mg/dL	8.86 mg/dL
Procalcitonin	<0.10 ng/mL	0.12 ng/mL
Lactic acid dehydrogenase total	125 to 243 units/L	655 units/L
D-dimer	0.27 to 0.5 µg/mL FEU	1.13 µg/mL FEU
Ferritin	22 to 275 ng/mL	5,697 ng/mL

FEU: fibrinogen equivalent units

## Clinical Point

Mr. G is not permitted to leave AMA due to concerns that he is not able to understand or comply with COVID-19 quarantine instructions

**Psychiatric illness or illicit substance use.** Because Mr. G was 56 years old and had no known psychiatric history or family psychiatric history, a primary psychiatric illness seemed less likely. Substance-induced psychosis related to illicit substance use also seemed unlikely because he denied using illicit substances, and an expanded urine drug screen was negative.

**Psychosis due to a general medical condition.** Results from Mr. G's laboratory workup show marked elevation in multiple inflammation-related biomarkers (Table 1), consistent with the inflammatory profile seen with COVID-19 infection. However, results from several laboratory tests for potential etiologies of new-onset psychosis due to a general medical condition were negative (Table 2, page 43). Based on Mr. G's history of prostate cancer, we considered the possibility of metastatic space-occupying lesions of the brain; however, Mr. G's head CT showed no acute intracranial abnormalities. Another possible etiology we considered was COVID-19-induced encephalitis; however, Mr. G's brain MRI with and without contrast showed no evidence of acute or chronic intracranial changes.

**Medication-induced psychosis.** After largely ruling out primary psychiatric illnesses, illicit substances, and sequelae of general medical conditions, we turned our attention to prescribed medications as a potential etiology of Mr. G's new-onset psychosis. During his initial hospitalization, Mr. G had been prescribed 2 doses of hydroxychloroquine, 400 mg, to treat

his diagnosis of COVID-19. Because none of the other medications he received were reported to have neuropsychiatric adverse effects, including psychosis, hydroxychloroquine-induced psychosis was therefore the primary team's working diagnosis.

## EVALUATION Request to leave AMA

On Day 13, Mr. G requests to leave the hospital against medical advice (AMA). Until this point, he had voluntarily remained in the hospital, which he repeatedly referred to as "Heaven." When asked to describe his medical condition, Mr. G replies, "God told me my condition is far beyond man's understanding." He denies that he is positive for COVID-19. He states, "I am cured, and the real fight has just begun."

At the recommendation of the psychiatry consultation-liaison (C-L) service, the primary treatment team determines that Mr. G does not have capacity to leave AMA. The team is concerned that because of his psychotic symptoms, Mr. G would be unable to understand and follow his quarantine instructions. He remains hospitalized on a medical hold.

## The authors' observations

One important consideration this case highlighted was potential third-party responsibility clinicians and hospital systems may face if they discharge a patient with a communicable illness who is unable to follow precautions based on a psychiatric condition.<sup>1</sup>

Table 2

## Mr. G's laboratory test results

	Reference range	Result
<b>Chemistry</b>		
Creatinine	0.6 to 1.2 mg/dL	0.7 mg/dL
Glucose	70 to 115 mg/dL	131 mg/dL
Alkaline phosphatase	40 to 150 units/L	65 units/L
Alanine aminotransferase	0 to 55 units/L	61 units/L
Aspartate aminotransferase	5 to 34 units/L	40 units/L
<b>Complete blood count</b>		
White blood cells	3.5 to 10.5 10 <sup>3</sup> /μL	5.2 10 <sup>3</sup> /μL
<b>Anemia chemistry</b>		
Folate	7.0 to 31.4 ng/mL	12.3 ng/mL
Vitamin B12	213 to 816 pg/mL	675 pg/mL
<b>Thyroid</b>		
Thyroid-stimulating hormone	0.350 to 4.940 uIU/mL	0.845 uIU/mL
<b>Bacterial/viral/parasite</b>		
<i>Chlamydia trachomatis</i> amplified probe	Negative	Negative
<i>Neisseria gonorrhoeae</i> amplified probe	Negative	Negative
<i>Trichomonas vaginalis</i> amplified probe	Negative	Negative
<i>Treponema pallidum</i> antibody	Non-reactive	Non-reactive
Human immunodeficiency virus antigen/antibody 1 & 2	Non-reactive	Non-reactive

**Clinical Point**

Mr. G's sleep, speech, and understanding of his COVID-19 diagnosis gradually improve after starting haloperidol

That concern was based on Mr. G's reported desire to pursue missions "beyond man's understanding," which he felt compelled to complete, and which could unnecessarily place the public at risk. The psychiatry C-L service consulted the local health department and conferred with the hospital's legal representatives, who agreed with the plan to keep Mr. G in the hospital for his safety as well as for the public's safety.

**TREATMENT Oral haloperidol**

The psychiatry C-L service recommends initiating an antipsychotic. On Day 13, Mr. G starts oral haloperidol, 2.5 mg twice a day, to address his ongoing psychotic symptoms. On Day 14, the treatment team increases the dosage to 5 mg twice a day. Mr. G tolerates

the haloperidol and gradually begins to improve. He demonstrates improved sleep, normal speech volume, less religious pre-occupation, and a considerably improved understanding of his medical condition.

**The authors' observations**

Mr. G's initial psychiatric evaluation demonstrated an acute onset of psychotic symptoms, without evidence of delirium. Psychosis secondary to a general medical condition (such as COVID-19) and hydroxychloroquine-induced psychotic disorder topped our initial considerations in the differential diagnosis of this case. While the exact neuropsychiatric sequelae of COVID-19 are not yet clear, previous experiences with viral pandemics and case studies from

**Clinical Point**

**Neuropsychiatric adverse events due to hydroxychloroquine have been reported in the literature**

the current pandemic demonstrate a wide variety of possible neuropsychiatric manifestations. Mood symptoms, psychosis, and encephalopathy represent some of the neuropsychiatric complications observed with past viral pandemics.<sup>2</sup> Neuropsychiatric symptoms may be triggered by the virus itself, or from the host’s immune response to the infection.<sup>3</sup> To further complicate matters, neuropsychiatric symptoms may manifest during the acute viral infection, or may surface later, as subacute or chronic neuropsychiatric illness.

Neuropsychiatric adverse events due to chloroquine or hydroxychloroquine have been reported in the medical literature.<sup>4,5</sup> A recent retrospective pharmacovigilance study reported 520 cases of neuropsychiatric events after chloroquine treatment, from a total of 2,389,474 reports to the FDA Adverse Event Reporting System from 2012 to 2019.<sup>6</sup> Statistically significant neuropsychiatric symptoms included amnesia, delirium, hallucinations, depression, and loss of consciousness. It is not yet clear how patients with COVID-19 illness will respond to the various experimental treatments currently in use.<sup>7</sup>

Mr. G developed psychotic symptoms within the first few days of receiving hydroxychloroquine, which is consistent with the scant literature on this topic.<sup>8</sup> Based on the available information, hydroxychloroquine remains the most likely etiology of his new-onset psychotic symptoms. Mr. G’s case is one example of the possible neuropsychiatric presentations clinicians may face while treating a novel viral illness.

**Bottom Line**

The coronavirus disease 2019 pandemic provides multiple clinical challenges pertinent to psychiatry. Neuropsychiatric symptoms may manifest from delirium, viral infection, host immune response, or adverse reactions to experimental treatments. These potential neuropsychiatric symptoms may complicate medical treatment. They can also raise important ethical and legal considerations, such as weighing patient autonomy vs third-party responsibility to the public at large.

**Related Resources**

- Ferrando SJ, Klepacz L, Lynch S, et al. COVID-19 psychosis: a potential new neuropsychiatric condition triggered by novel coronavirus infection and the inflammatory response? [published online May 19, 2020]. *Psychosomatics*. 2020. doi: 10.1016/j.psych.2020.05.012.
- Vlessides M. COVID-19 and psychosis: is there a link? *Medscape Medical News*. <https://www.medscape.com/viewarticle/930224>. Published May 8, 2020.

**Drug Brand Names**

Azithromycin • Zithromax	Hydroxychloroquine
Ceftriaxone • Rocephin	• Plaquenil
Chloroquine • Aralen	Levofloxacin • Levaquin
Haloperidol • Haldol	Oseltamivir • Tamiflu

**OUTCOME Homeward-bound**

By Day 18, Mr. G’s psychotic symptoms have significantly improved. He is able to rationally process information about his COVID-19 diagnosis and the recommended quarantine instructions he needs to follow after discharge. He is cleared by infection control and discharged home to return to living with his girlfriend.

Mr. G attends his follow-up psychiatric appointment remotely 2 weeks after discharge. He reports that since discharge, he has continued taking his prescribed haloperidol, 5 mg twice a day. He demonstrates improved insight into his medical condition, acknowledging his COVID-19–positive status, and confirms that he has been following quarantine instructions. He does not report ongoing auditory or visual hallucinations, and is no longer religiously preoccupied. He says he is looking forward to being medically cleared to return to work.

### The authors' observations

This case highlights the need for prospective, longitudinal screening and monitoring of neuropsychiatric symptoms as part of the public health response to COVID-19. The case also highlights the importance of careful monitoring for adverse events, including neuropsychiatric symptoms, during clinical trials that involve experimental treatments. The long-term prognosis for individuals such as Mr. G who develop neuropsychiatric symptoms during acute COVID-19 infection remains unknown. Similarly, subacute and chronic neuropsychiatric manifestations that may develop after resolution of acute COVID-19 infection are unknown at this time. However, we can learn from past viral pandemics and anticipate that neuropsychiatric sequelae are likely to occur and should

be part of the public health response to the pandemic.

### References

1. Ghossoub E, Newman WJ. COVID-19 and the duty to protect from communicable diseases. [published online ahead of print, May 8, 2020]. *J Am Acad Psychiatry Law*.
2. Menninger Ka. Psychoses associated with influenza: I. general data: statistical analysis. *JAMA*. 1919;72(4):235-241.
3. Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain, Behavior, and Immunity*. 2020. doi:10.1016/j.bbi.2020.04.027.
4. Alkadi HO. Antimalarial drug toxicity: a review. *Chemotherapy*. 2007;53(6):385-391.
5. Bogaczewicz A, Sobów T. Psychiatric adverse effects of chloroquine. *Psychiatria i Psychologia Kliniczna*. 2017; 17(2):111-114.
6. Sato K, Mano T, Iwata A, et al. Neuropsychiatric adverse events of chloroquine: a real-world pharmacovigilance study using the FDA Adverse Event Reporting System (FAERS) database. *Biosci Trends*. 2020;14(2):139-143.
7. Cortegiani A, Ingoglia G, Ippolito M, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care*. 2020;57:279-283.
8. Das P, Rai A, Chopra A, et al. Psychosis likely induced by hydroxychloroquine in a patient with chronic Q fever: a case report and clinically relevant review of pharmacology. *Psychosomatics*. 2014;55(4):409-413.

### Clinical Point

**We can anticipate that neuropsychiatric sequelae are likely to occur and should be part of the public health response to the COVID-19 pandemic**