




A primer on Post-COVID-19 conditions and implications for clinical pharmacists

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and is largely viewed as an acute illness involving multiple organ systems. In the wake of the acute illness, many survivors fully recover and return to baseline, while others suffer from a wide range of lingering symptoms collectively known as “post-COVID conditions”. The recognition of these conditions as a clinical entity represents the first step in developing a targeted plan for recovery and symptom mitigation. While interventions to directly minimize or reduce new, recurrent, or persistent symptoms are currently unknown, pharmacists can play a key role in optimizing management of these patients.

KEYWORDS

COVID-19, patient care, pharmacists, SARS-CoV-2

1 | INTRODUCTION

Coronaviruses are ubiquitous large, single-stranded RNA viruses capable of causing respiratory illness in humans and other mammals. Clinically, these often manifest as the common cold and are self-limiting. Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has significant genomic overlap with severe acute respiratory syndrome (SARS-CoV) and, to a lesser extent, Middle East Respiratory Syndrome (MERS-CoV).¹ Both SARS-CoV and SARS-CoV-2 share genomic similarities providing insight about virulence, short- and long-term disease expression, and consequences for quality of life.² In addition, both viruses also utilize omnipresent angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine protease 2 (TMPRSS2) receptors for cell entry, thereby permitting viral replication and direct tissue damage with resultant widespread organ-specific manifestations.³ The co-expression of these receptors explains the upper airway tissue tropism displayed by SARS-CoV-2 but also allows the virus to infect other locations in the body, possibly contributing to extrapulmonary manifestations, as well as sequelae lasting beyond the acute infection phase.^{1,3}

Unlike the SARS-CoV and MERS-CoV outbreaks, SARS-CoV-2 has persisted largely because humans are the predominant host, transmissibility is highly efficient, and mitigation strategies have been slow to manifest and are only partially effective. The upper airway colonization in conjunction with high viral loads at symptom onset has allowed for accelerated propagation of disease.⁴ While the exact R_0 (the basic reproduction number indicating contagiousness) of SARS-CoV-2 has been difficult to define, early estimates showed a mean of 2.5 with the range being considerably wide.⁵ SARS-CoV-2 has the highest average R_0 when compared with the 1918 and 2009 influenza pandemics and the SARS-CoV and MERS-CoV outbreaks, which accounts for more than 80 million cases, 4 million hospitalizations, and nearly 1 million deaths in the United States.^{5,6}

While much has been learned about SARS-CoV-2 since it first emerged in late 2019 in Wuhan, China, the priority continues to be on combatting the emergence of new variants and their acute management. Long-term effects of the SARS-CoV-2 variants and sequelae of COVID-19 are developing concerns as the incidence of infection and hospitalizations continues to rise.⁷ The lack of return to baseline health following COVID-19 was commonly referred to as “long-COVID” or “long-haul COVID,” but was recently standardized

as “post-COVID conditions” by the World Health Organization (WHO). However, recommendations for optimal management of long-term sequelae are scant. The purpose of this review is to highlight post-COVID conditions and outline how to optimize pharmacist-delivered patient care.

2 | EMERGING FROM THE ACUTE PHASE OF THE ILLNESS

Recovery from COVID-19 is highly variable and depends on manifestations of the acute illness, disease severity, and chronic comorbidities, as well as medical management and complications.^{3,8,9} While most fully recover and return to baseline, certain patients suffer from symptoms and clinical findings despite eradication of the acute infection. Many of these consequences are due to the host response to SARS-CoV-2 infection and COVID-19-related organ dysfunction, while others may be the result of new diagnosis or unmasking of comorbidities, pandemic prevention measures (eg, social isolation, etc.), SARS-CoV-2 reinfection, or secondary infections.^{3,8-10}

Immune protection against COVID-19 is driven by both T and B cell responses against either the virus itself or against the S protein present in the available vaccines.¹¹ Within 2 weeks, immunoglobulin (Ig)M has developed and begins transforming into IgG, which should confer protection against reinfection. Because SARS-CoV-2 is prone to mutation, it is challenging to determine who can mount a sufficient immune response to protect against current and future variants. Immunity appears to depend on the severity of initial infection or receipt of a vaccine, as well as the age of the exposed patient.¹¹

Once patients acquire SARS-CoV-2, there is a transient period where re-infection is highly unlikely.¹² A study performed in the United Kingdom in 11 000 health care workers demonstrated that those who tested positive in the first wave of the pandemic between March and April 2020 did not experience reinfection during the second wave between October and November 13, 2020.¹³ However, reinfection with the same or different variants of SARS-CoV-2 can still occur, as demonstrated with other coronavirus strains, and attempting to define reinfection is extremely challenging.¹⁴ For the purposes of clinical practice, reinfection is defined as the recurrence of symptoms compatible with COVID-19 combined with a positive polymerase chain reaction (PCR) test after a known close-contact exposure more than 90 days after the prior infection.¹⁵ Unfortunately, the risk of reinfection is highly variable and could be attributed to vaccination status and infective lineage.¹⁶ Additionally, the severity of illness upon reinfection is also highly variable, ranging from asymptomatic infection to death, and may depend on the virulence of the new strain and its inoculum.^{14,15} A population-level observational study found previous infection conferred an 80% reduction in likelihood of reinfection.¹⁷ In tandem, previous infection followed by vaccination with a messenger RNA (mRNA) vaccine is likely to result in augmented humoral immunity, as well as cell-mediated immunity.¹⁸ Both types of immunity are necessary to protect against reinfection.¹⁵

When examining the impact of the vaccine on immunity, the immune response generated confirms both humoral and cell-mediated activation, indicating that the currently available vaccines may be able to withstand many mutations and variants that may arise. Preliminary laboratory data from Pfizer and BioNTech indicate that three doses of their mRNA vaccine are able to neutralize most of the SARS-CoV-2 variants significantly better than two doses.¹⁹ However, the companies state that two doses may still provide protection against severe COVID-19 disease. Similarly, Moderna, Inc. also provided laboratory data that indicate that a third dose of their mRNA vaccine also provides sufficient protection against SARS-CoV-2 variants.²⁰ Meanwhile, the Centers for Disease Control and Prevention (CDC) has adopted the Advisory Committee on Immunization Practices (ACIP) recommendation to encourage patients to receive either of the mRNA vaccines over Johnson & Johnson's COVID-19 vaccine due to safety concerns, but that receiving Johnson & Johnson's vaccine is preferred over no COVID-19 vaccine.²¹ The protection the vaccines confer against emerging variants should highlight the need for vaccination regardless of prior infection, especially as cases reached a new pinnacle due to the Omicron variants. Additionally, more contagious, virulent, or vaccine-escape variants have the most potential to cause concern with respect to post-COVID conditions as the number of people who will be infected continue to increase.

2.1 | Post-COVID-19 conditions

The WHO reports that approximately 10% of patients who develop COVID-19 will go on to have health-related consequences.²² While symptoms of acute COVID-19 can occur for up to 4 weeks after the onset of illness, some hospitalized and non-hospitalized survivors experience new, recurrent, or persistent pulmonary, cardiovascular, dermatologic, renal, nervous system, and psychological manifestations 4 or more weeks after SARS-CoV-2 infection preventing return to baseline health.⁷ According to the clinical case definition developed through a Delphi consensus convened by the WHO in October 2021, post-COVID conditions represent a variety of symptoms occurring 3 months from the onset of illness and persisting for at least 2 months, not explained by an alternative diagnosis. Symptoms may persist from the initial illness despite no signs of on-going viral replication or be newly developed following initial recovery.

Prior to the development of the clinical case definition and associated International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) diagnosis code U09.9 for post-COVID conditions by the WHO, numerous terminologies and definitions were used to describe the post-acute infectious consequences of COVID-19.^{7,23} As a result, data describing the prevalence and risk factors of post-COVID conditions are heterogeneous.

The COVID Symptom Study²³ was a prospective, observational cohort study that enrolled more than 4000 patients infected with SARS-CoV-2 across the U.K., Sweden, and the U.S. who self-reported health status and symptoms daily through a mobile app (Table 1).^{8,9,23-30} While the median symptom duration was 11 days,

13.3% reported symptoms lasting at least 4 weeks, 4.5% for at least 8 weeks, and 2.6% for at least 12 weeks. At the 4 week follow-up, symptoms were more common in patients older than 70 years (21.9%).²³ Alternatively, 35% of patients from Southern California reported a mean 1.3 ± 2.4 symptoms 60 days after a positive test for SARS-CoV-2.³⁰ However, patients who had severe/critical or moderate COVID-19 reported a higher frequency of symptoms compared with those who had mild disease or were asymptomatic upon diagnosis (55.5% and 52.6% vs 29% and 3.7%, respectively).

Long-term complications among previously hospitalized patients appear to be more common (Table 1). In a case series that included 143 Italian patients who recovered from acute COVID-19, 87.4% reported at least one symptom, and 55.2% reported at least 3 symptoms 60 days after symptom onset but an average of 36 days after hospital discharge, while 44.1% reported a decreased quality of life.⁸ Almost 75% of patients included in this case series had interstitial pneumonia, 53.8% required supplemental oxygen, 12.6% required intensive care unit (ICU) admission, and 4.9% required mechanical ventilation. Comparable findings were observed in 150 French patients with non-critical COVID-19.²⁵ Notably, 37% of patients at day 60 from symptom onset reported feeling worse than at the onset of COVID-19. New or worsened symptoms were also identified in 18.9% of patients who were previously hospitalized for COVID-19 and completed a 60-day post-discharge follow-up telephone survey.²⁶ Multiple other studies have reported similar findings with most patients having at least one symptom persist for more than 60 days from symptom onset or hospital discharge.^{9,24,29} Though fewer data are available describing the more long-term symptoms of COVID-19, findings remain consistent.

Overall, patients who were female, older, had pre-existing comorbidities, SARS-CoV-2 RNAemia (detectable viral RNA in blood) at presentation, or required prior hospitalization particularly ICU admission for COVID-19 were more likely to experience post-COVID conditions and decreased quality of life (Table 1).^{8,9,23-32} Additionally, the impact of race, ethnicity, and socioeconomic factors on the rate of post-COVID conditions varies between studies.^{9,23} These data are not without limitation as there is very likely underreporting given the protean manifestations of post-COVID conditions, though some patients may inappropriately attribute their symptoms to COVID-19 despite never being infected with SARS-CoV-2.³³

Symptoms of post-COVID conditions can be non-specific, such as fatigue, brain fog, myalgias or arthralgias, or be residual manifestations of acute disease such as dyspnea, chronic cough or taste, and smell disturbance. In some patients, symptoms may persist beyond 6 months despite no signs of on-going viral replication and without a finite end point for cessation. Though the precise pathophysiology of post-COVID conditions remains unknown, it is likely to involve the direct effects of SARS-CoV-2 coupled with the immunologic and inflammatory response to SARS-CoV-2 infection.³ In addition to post-COVID conditions, there is significant overlap with sequelae attributed to post-intensive care syndrome including cognitive and physical deficits which may act synergistically in those developing critical illness secondary to COVID-19.^{7,34} While a high number of COVID-19

survivors may experience post-intensive care syndrome, a comprehensive review is beyond the scope of this paper and the reader is referred to the literature for further details.³⁵⁻³⁸

Most patients infected with SARS-CoV-2 experience mild symptoms followed by disease resolution and viral eradication due to an effective immunologic response.³ Alternatively, in some patients, particularly those who require hospitalization or have severe disease, SARS-CoV-2 may escape the host immune response, thereby allowing unrestrained viral replication and dissemination. Systemic inflammation and overactivation of the host immune response may soon follow, leading to hyperinflammation, immunoparalysis, and organ damage characterized by leukocytosis, lymphopenia, and thrombocytopenia, as well as an increased erythrocyte sedimentation rate, C-reactive protein, ferritin, and cytokine concentrations. Numerous immunomodulatory therapies, such as high-dose corticosteroids, anti-cytokine monoclonal antibodies, anti-interleukin monoclonal antibodies, and Janus kinase (JAK) inhibitors, have been employed to minimize the robust inflammatory response to SARS-CoV-2.³⁹ Widespread use of immunomodulatory therapies may also contribute to the cytopenias, variable immune response, and secondary infections observed in patients with COVID-19.

3 | CHRONICITY OF COVID-19

SARS-CoV-2 may parallel influenza in that it is likely to persist through the evolution of variants which will at least partially evade vaccination efforts; however, little is known with respect to management of chronic disease exclusive of true reinfection. Clinicians may consider re-screening for SARS-CoV-2 initially to differentiate between reinfection and post-COVID conditions.^{40,41} The importance of documenting prior SARS-CoV-2 infection, timeline of symptoms, disease severity, and treatments received is clear and is supported by public health agencies including the WHO.^{40,41} Unlike many other chronic diseases, post-COVID conditions are often disease manifestations with no obvious pharmacologic targets. Moreover, it is possible that post-COVID conditions may prompt recognition of other diagnoses or exacerbate chronic diseases. This is perhaps best exemplified by the loss of glycemic control in many patients without a history of diabetes experience after COVID-19 illness.⁴² In addition to exacerbation of many chronic disease states, these patients are also more likely to have at least one new medical condition added and/or experience changes to their medication regimen at discharge.⁴³ The new diagnoses may also be latent in their manifestation as evidenced by the recent discovery of what is colloquially referred to as “the COVID heart.”⁴⁴ Moreover, a recent study in the U.K. also showed changes in brain structure in patients after SARS-CoV-2 infection when compared with controls.⁴⁵ A systems-based overview of common post-COVID conditions and potential interventions is presented in Table 2.^{40,41,46-51}

The totality of these findings reiterates the importance of documentation in the medical record, as even patients who were not hospitalized secondary to COVID-19 may still have an increased risk of

TABLE 1 Epidemiology of post-COVID conditions stratified by duration of follow-up

Study citation	Location	No. patients enrolled	Age (years)	Female (%)	Comorbidities (%)	Hospitalized during acute COVID-19 (%)	One or more symptoms at follow-up period (%)	Post-COVID-19 symptoms present at follow-up (%)
Sudre et al. ²³	U.K., Sweden, U.S.	4182	42 (32-53)	71.5	<ul style="list-style-type: none"> • Obesity: 26.3 • Pulmonary disease: 13.6 • Asthma: 10 • Diabetes: 2.9 	13.9	<ul style="list-style-type: none"> • At least 4 weeks from symptom onset: 13.3 	<ul style="list-style-type: none"> • Fatigue: 97.7 • Headache: 91.2 • Cardiovascular symptoms: 6.1 • Cognitive impairment: 4.1 • Peripheral neuropathy: 2
Yomogida et al. ³⁰	Southern California, U.S.	366	<ul style="list-style-type: none"> • 18-24:11.5%† • 25-39:39.3%† • 40-54:30.3%† • 55-64:10.7%† • ≥ 65:8.2%‡ 	57	<ul style="list-style-type: none"> • Overall: 46.4 	5.2	<ul style="list-style-type: none"> • 60 days after a positive test for SARS-CoV-2:35 	<ul style="list-style-type: none"> • Fatigue: 16.9 • Ageusia: 12.8 • Dyspnea: 12.8 • Parosmia/anosmia: 12.6 • Myalgia/arthralgia: 10.9
Logue JK et al. ²⁸	Washington, U.S.	177	48 (18-94)‡	57.1	<ul style="list-style-type: none"> • Hypertension: 13 • Diabetes: 5.1 	9	<ul style="list-style-type: none"> • 3-9 months after symptom onset:32.8 	<ul style="list-style-type: none"> • Fatigue: 13.6 • Anosmia or ageusia: 13.6 • Brain fog: 2.3
Halpin ⁹ – ward patients only	U.K.	68	70.5 (20-93)‡	48.5	<ul style="list-style-type: none"> • Hypertension: 39.7 • Diabetes: 27.9 • Obese: 17.6 • Asthma: 13.2 • At least 3 comorbidities: 70.6 	100	<ul style="list-style-type: none"> • 1-2 months after hospital discharge§ 	<ul style="list-style-type: none"> • Fatigue: 60.3 • Dyspnea: 42.6 • PTSD: 23.5
Halpin ⁹ – ICU patients only	U.K.	32	58.5 (34-84)‡	40.6	<ul style="list-style-type: none"> • Hypertension: 43.8 • Diabetes: 28.1 • Obese: 40 • Asthma: 12.5 • At least 3 comorbidities: 56.5 	100	<ul style="list-style-type: none"> • 1-2 months after hospital discharge§ 	<ul style="list-style-type: none"> • Fatigue: 72 • Dyspnea: 65.6 • PTSD: 46.9
Carfi et al. ⁸	Italy	143	56.5 ± 14.6	37.1	<ul style="list-style-type: none"> • Hypertension: 35 • Thyroid disease: 18.2 • Immune disorder: 11.2 • COPD: 9.1 • Diabetes: 7 	100	<ul style="list-style-type: none"> • 60 days after symptom onset: 87.4 	<ul style="list-style-type: none"> • Fatigue: 53.1 • Dyspnea: 43.4 • Arthralgia: 27.3 • Chest pain: 21.7
Carvalho-Schneider et al. ²⁵	France	150	45 ± 15	56	<ul style="list-style-type: none"> • Overall: 54 	100	<ul style="list-style-type: none"> • 60 days after symptom onset: 66 	<ul style="list-style-type: none"> • Anosmia/ageusia: 22.7 • Myalgia, headache and/or asthenia: 21.5 • Weight loss ≥5%: 17.2 • Arthralgia: 16.3

(Continues)

TABLE 1 (Continued)

Study citation	Location	No. patients enrolled	Age (years)	Female (%)	Comorbidities (%)	Hospitalized during acute COVID-19 (%)	One or more symptoms at follow-up period (%)	Post-COVID-19 symptoms present at follow-up (%)
Chopra et al. ²⁶	U.S.	488	62 (50-72)	48.2	<ul style="list-style-type: none"> Hypertension: 64 Diabetes: 34.9 Cardiovascular disease: 24.1 Moderate or severe renal dysfunction: 23 	100	<ul style="list-style-type: none"> 60-day after hospital discharge: 32.6 	<ul style="list-style-type: none"> Dyspnea: 22.9 Cough: 15.4 Anosmia/ageusia: 13.1
Moreno-Pérez et al. ²⁹	Spain	277	56 (42-67.5)	47.3	<ul style="list-style-type: none"> Hypertension: 36.5 Obesity: 30.6 Pulmonary disease: 18.1 Diabetes: 11.6 	NR	<ul style="list-style-type: none"> 2-3 months after symptom onset: 50.9 	<ul style="list-style-type: none"> Fatigue: 34.8 Dyspnea: 34.4 Anosmia/ageusia: 21.4 Cough: 21.3 Headache: 17.8
Arnold et al. ²⁴	U.K.	110	60 (46-73)	44	<ul style="list-style-type: none"> Hypertension: 25 Pulmonary disease: 25 Cardiovascular disease: 18 Diabetes: 15 	100	<ul style="list-style-type: none"> 3 months after symptom onset: 74 	<ul style="list-style-type: none"> Fatigue: 39 Dyspnea: 39 Insomnia: 24 Chest pain: 12.7 Cough: 11.8
Huang et al. ²⁷	Wuhan, China	1733	57 (47-65)	48	<ul style="list-style-type: none"> Hypertension: 29 Diabetes: 12 Cardiovascular disease: 7 COPD: 2 	100	<ul style="list-style-type: none"> 6 months after symptom onset: 76 	<ul style="list-style-type: none"> Fatigue: 63 Sleep difficulties: 26 Anxiety/depression: 23 Hair loss: 22 Anosmia: 11

Note: Data are presented as median (interquartile range) or mean \pm SD, except for †, where data are categorized by age group, and ‡, where data are presented as median (range). § Overall prevalence of one or more symptoms at follow up not reported.

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; NR, not reported; PTSD, post-traumatic stress disorder; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; U.K., United Kingdom; U.S., United States of America.

incident cardiovascular disease or cognitive impairment. Because the potential for attributable sequelae may persist for up to a year or longer after acute infection, a thorough patient history, physical examination, and routine follow-up are needed. Guidance in the evaluation of these patients is available from the CDC and the National Institute for Health and Care Excellence (NICE), but is constantly evolving.^{40,41}

The development of post-COVID care centers (PCCCs) for COVID-19 survivors allow for close in-person or virtual follow-up and foster a holistic approach, in addition to other ancillary services such as rehabilitation services and support groups.⁵² PCCCs, currently in 48 states as of April 13, 2022, were developed to acknowledge post-COVID conditions in those with documented previous infection.⁵³ Because post-COVID conditions are protean in their manifestation, these clinics may also decrease the burden on primary care providers while offering more targeted symptom relief. Moreover, PCCCs may also prevent COVID-19-related readmissions as one retrospective U.K. study found nearly a 30% readmission rate after acute illness. Post-COVID conditions will shift care of this disease from the inpatient to the outpatient realm. As this happens, pharmacists may face a familiar challenge in antimicrobial stewardship as well as long-term management of post-COVID conditions. Use of current antiviral agents such as remdesivir is unlikely to result in arrest of chronic symptoms. Moreover, promising new oral agents such as molnupiravir and nirmatrelavir/ritonavir are unlikely to impact persistent symptoms due to a lack of competent virus in these patients. However, a preprint case report describes a patient with post-COVID conditions who experienced resolution of her symptoms after completing nirmatrelavir/ritonavir. This should not currently be considered the standard of care, and as more data accumulates, the role of new antivirals as it pertains to post-COVID conditions will be better defined.⁵⁴ Previous infection with SARS-CoV-2 may also result in a predisposition for secondary bacterial, parasitic, or fungal infections especially among patients who received immunomodulatory therapies, including corticosteroids. Despite resolution of acute illness, clinicians should remain vigilant for risk of secondary infection.

Pharmacists should also be keenly involved in the transitions of care process as patients are discharged from the hospital and re-enter the community. Medications that may have been utilized for acute COVID-19 may no longer be appropriate at the time of discharge. This is an opportunity for pharmacists to intervene and collaborate with other health care professionals to optimize patient care and prevent possible harm. Further, patients who develop post-COVID conditions may benefit from additional therapies to mitigate their new COVID manifestations; however, these medications must be initiated mindfully, both with regard to drug clearance but also with regard to pharmacokinetic and pharmacodynamic interactions with other drugs or disease states. The reader is referred to existing databases for recommendations to identify and manage potential drug-drug interactions (<https://www.covid19-druginteractions.org/>). Pharmacists are uniquely positioned in the health care system to not only evaluate evolving post-COVID literature, but also to balance these new treatment modalities or old treatment options for new indications with existing chronic disease states.

Pharmacists will continue to be integral to vaccination efforts and reducing vaccine hesitancy. Vaccination is critical in preventing infection but may also be the most valuable tool to reduce post-COVID conditions.⁵⁵ Moreover, vaccinating against COVID-19 may also be an opportunity to vaccinate against other preventable illnesses. Data are mixed as to whether vaccination prevents post-COVID conditions, but those unvaccinated may benefit most from vaccination.⁵⁶ Another consideration highlighting the importance of COVID-19 vaccination should be the complex relationship between viral illness and the subsequent immunomodulation which could lead to the development of chronic conditions, such as multiple sclerosis. While not specifically shown with SARS-CoV-2 infection, the possibility has been recently hypothesized.⁵⁷ Vaccination has been shown to accelerate viral clearance; thus, it is possible that additional vaccination could “turn off” post-COVID conditions, whereas other therapeutic interventions such as monoclonal antibodies rely on viral replication for efficacy and are highly variant-specific.⁵⁸ Non-pharmacologic approaches represent the best starting point in caring for these patients. Indeed, approximately 50% of hospitalized COVID-19 survivors experience muscle deconditioning and impaired performance of activities of daily living.⁵⁹ This finding highlights the value of common modalities such as physical therapy. Further, psychiatric services, such as counseling and therapy, may be helpful for patients suffering from anxiety and depression post-COVID.

4 | EFFECT OF POST-COVID CONDITIONS ON PHARMACISTS

While interventions to treat and prevent post-COVID conditions are currently unclear, it is clear that these conditions will have lasting implications on the workforce and health care system.⁶⁰ It is estimated that between 10% and 20% of patients who contract SARS-CoV-2 will have a new disability after discharge, which may make the return to work difficult and create financial insecurity secondary to loss of income and health care benefits.⁵⁶ While post-COVID conditions are now recognized as a disability under Titles II and III of the Americans with Disabilities Act, and public and private disability insurance benefits may be available to patients, the application and appeals process is often lengthy and may leave the patient without coverage during that time.⁶¹ Ultimately, the management of post-COVID conditions should include not only the physical effects of the disease but also the emotional and socioeconomic impacts.

Further, the degree of burnout amongst health care providers has been well documented, and much of this is attributed to the surges of COVID-19 admissions as new variants emerge. It is estimated that 18% and 12% of health care workers have quit their jobs or been laid off, respectively, during the pandemic. Since February 2020, health care employment is down nearly 500 000 jobs.⁶² What is less well-established is the lasting impact that provider burnout will have on the health care system, both for acute care and for ambulatory care services. Recognizing the psychological burden of the pandemic is critical to implementing interventions at the organizational level, such

TABLE 2 Potential interventions for post-COVID conditions^{40,41,46-51}

Complications and manifestations	Proposed monitoring and management
Fatigue, functional impairment	Adequate rest Good sleep hygiene Energy conservation strategies (eg, pace, plan, and prioritize daily activities)
Pulmonary <ul style="list-style-type: none"> • Dyspnea • Decreased exercise capacity • Hypoxia • Pulmonary fibrosis 	Home pulse oximetry Pulmonary function tests Incentive spirometry Corticosteroids in post-COVID inflammatory lung disease
Hematologic <ul style="list-style-type: none"> • Thromboembolic events 	Consider extended thromboprophylaxis with either a LMWH or DOAC
Cardiovascular <ul style="list-style-type: none"> • Palpitations • Chest pain 	Consider low-dose beta-blocker Evaluate need for continued amiodarone in patients with COVID-associated fibrotic changes
Neuropsychiatric <ul style="list-style-type: none"> • Brain fog • Anxiety • Depression • Sleep disturbance 	Use of depression scales to assess patients coupled with individualized pharmacotherapy For brain fog, consider a trial of cognitive enhancers, such as eugeroics or stimulants Specific agents which may be trialed include modafinil and amphetamine salts For sleep disturbance, evaluate type of disturbance (eg, sleep onset vs interrupted sleep) Non-pharmacologic therapy such as cognitive behavioral therapy Pharmacologic intervention should be limited and dependent on the type of disturbance including zolpidem, zaleplon, or eszopiclone
Renal <ul style="list-style-type: none"> • Persistent decrease in eGFR 	Evaluate need for renal adjustment of chronic medications Consider a nephrology referral
Endocrine <ul style="list-style-type: none"> • New or worsening control of diabetes mellitus • Diabetic ketoacidosis • Subacute thyroiditis 	Evaluate patients for type 1 diabetes mellitus vs type 2 diabetes mellitus Consider endocrine referral for complex cases Thyroiditis can be managed with corticosteroids
Gastrointestinal <ul style="list-style-type: none"> • Alterations in microbiome • Post-infectious irritable bowel syndrome • Dyspepsia 	Consider fecal microbiota transplant in select patients Probiotics may also be beneficial to some patients
Dermatologic <ul style="list-style-type: none"> • Alopecia 	Consider referral to dermatology vs initiating empiric pharmacotherapy
Immunologic <ul style="list-style-type: none"> • Receipt of immunomodulatory agents during acute illness 	In select patients, re-evaluate for chronic diseases such tuberculosis, HIV, HBV, HCV, and HPV Evaluate patients for secondary bacterial, parasitic (eg, Strongyloidiasis, etc.), or fungal infections (eg, Aspergillosis, Mucormycosis, Cryptococcosis, etc.) Assess need for vaccination against HBV, influenza, pneumococcus, HPV, and VZV

Note: COVID, coronavirus disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; LMWH, low-molecular weight heparin; VZV, varicella zoster virus.

as changes in workload and modifying the culture of the workplace.⁶³ Burnout and job turnover aside, health care workers are not immune from the effects of post-COVID conditions, with one study estimating that as many as 45% of health care workers who contracted COVID-19 noted persistent symptoms and 32% struggled to cope with those persistent symptoms.⁶⁴

Finally, tracking of the true impact of post-COVID conditions continues to evolve. While it is relatively simple to track case counts, hospitalizations, and deaths, tracking the financial, quality of life, and employment implications of this disease is paramount to understanding how to best help these patients. Metrics such as quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs) may give

researchers and policy makers a more well-rounded view of the impact post-COVID conditions.⁶⁰

5 | FUTURE DIRECTION

The COVID-19 pandemic has shown that it can galvanize the health care profession as much as it can disrupt it. As burnout continues to rage on during the pandemic, pharmacists may serve as the linchpin in the ability to create avenues for positive patient outcomes and lessen the burden throughout the patient care continuum. As the pandemic evolves in many parts of the world, there will continue to be

opportunity for pharmacists to engage in both management as well as clinical research in patients with post-COVID conditions. This is perhaps best exemplified by the HEAL-COVID platform which will examine therapies targeting post-COVID conditions and is set to begin enrolling in April 2022.⁵⁷ Novel therapeutic agents and repurposed older drugs will continue to be explored in on-going and future clinical trials. Moreover, as old and new agents are introduced, their integration into clinical algorithms will demonstrate the value of clinical pharmacists and will create opportunities to participate in research endeavors. While most of the therapeutic interventions remain for management of acute infections, it is likely that a shift toward managing post-COVID conditions will be heightened during periods of quiescence with respect to variants of concern.

6 | CONCLUSION

Patients with COVID-19 who experience resolution are not necessarily free of a protracted course of illness. While older patients with pre-existing comorbidities who required hospitalization for COVID-19 are at greatest risk, younger patients are also subject to residual effects given the variety of symptoms associated with post-COVID conditions. SARS-CoV-2 infection has the possibility of being an inciting factor, catapulting previously healthy patients into chronic disease, altering how we care for them moving forward. Mortality as an outcome is appropriate for acute infection, but quality of life, represented by QALYs or DALYs, is a long-term marker which should be captured in all previously infected patients. SARS-CoV-2 has drawn many comparisons with other viral illnesses, but the reality is that SARS-CoV-2 is unlike any other viral infection to date. The ultimate regression of the pandemic into an endemic disease will energize the focus on post-COVID conditions.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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