Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses

Woo-Jung Song, Christopher K M Hui, James H Hull, Surinder S Birring, Lorcan McGarvey, Stuart B Mazzone, Kian Fan Chung

Cough is one of the most common presenting symptoms of COVID-19, along with fever and loss of taste and smell. Cough can persist for weeks or months after SARS-CoV-2 infection, often accompanied by chronic fatigue, cognitive impairment, dyspnoea, or pain—a collection of long-term effects referred to as the post-COVID syndrome or long COVID. We hypothesise that the pathways of neurotropism, neuroinflammation, and neuroimmunomodulation through the vagal sensory nerves, which are implicated in SARS-CoV-2 infection, lead to a cough hypersensitivity state. The post-COVID syndrome might also result from neuroinflammatory events in the brain. We highlight gaps in understanding of the mechanisms of acute and chronic COVID-19-associated cough and post-COVID syndrome, consider potential ways to reduce the effect of COVID-19 by controlling cough, and suggest future directions for research and clinical practice. Although neuromodulators such as gabapentin or opioids might be considered for acute and chronic COVID-19 cough, we discuss the possible mechanisms of COVID-19-associated cough and the promise of new anti-inflammatory or neuromodulators that might successfully target both the cough of COVID-19 and the post-COVID syndrome.

Introduction

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has had an unprecedented effect on global health since its discovery in Wuhan, China.\(^1\,2\) Even in countries where the first pandemic wave of the virus was controlled, second or third waves are happening or have been predicted to occur. With limited availability of effective vaccines, measures to reduce disease spread—such as physical distancing, wearing masks, and avoiding crowds—remain key strategies to combat the infection. Similar to the more common but less serious infections of the common cold or flu, cough is a key symptom of COVID-19 in the acute phase of the infection, and one that persists in the post-infective phase. Cough is not only distressing to patients, but also increases the risk of community transmission by respiratory droplets.\(^1\) Stigmatisation of patients with cough can occur, leading to social isolation,\(^4\) particularly during the COVID-19 pandemic. Identifying ways to control COVID-19-associated cough could help to prevent community transmission and disease spread, as well as removing the stigma of this symptom.

Evidence-based treatment options for COVID-19 cough are needed because patients with cough caused by common viral infections, including cold and flu, frequently resort to over-the-counter cough medicines. Patients with chronic cough also often seek antitussive therapies, but it is unknown whether such approaches are effective in post-COVID cough patients. We propose that it is important to consider cough as a target of intervention in the management of COVID-19 and post-COVID syndrome. However, we currently have little understanding of the mechanisms underlying COVID-19-associated cough. In this Personal View, we review the knowledge that has accumulated on cough in COVID-19, and discuss neuroinflammatory and neuroimmune mechanisms that could potentially underlie COVID-19-associated cough based on our understanding of the pathogenesis of COVID-19 and of the cough associated with other respiratory viruses. We
Table 1. Details of studies reporting persistent cough.

| Study                          | Persistent Cough (%) | Acute Cough (%) |
|--------------------------------|----------------------|-----------------|
| Cheng et al, 2021              | 20                   | 20              |
| Moradian et al, 2020           | 60                   | 60              |
| Halpin et al, 2021             | 20                   | 20              |
| Mandal et al, 2020             | 10                   | 10              |
| D'Cruz et al, 2021             | 13                   | 13              |
| Chopra et al, 2020             | 9                    | 9               |
| Carfi et al, 2020              | 20                   | 20              |
| Arnold et al, 2021             | 16                   | 16              |
| Xiong et al, 2021              | 17                   | 17              |
| Stavem et al, 2020             | 20                   | 20              |
| Petersen et al, 2020           | 21                   | 21              |
| Sonnweber et al, 2020          | 22                   | 22              |
| Valiente-De Santis et al, 2020 | 23                   | 23              |
| Zhao et al, 2020               | 24                   | 24              |
| Wong et al, 2020               | 25                   | 25              |
| Stavem et al, 2020             | 26                   | 26              |

Figure 1: Follow-up studies reporting persistent cough in patients with post-COVID syndrome

Studies sorted by follow-up duration in ascending order from left to right. Follow-up duration ranges from 6 weeks to 6 months. Data were retrieved from available publications, including peer-reviewed papers and preprints.9–11,13–26

Detailed characteristics of each study are summarised in table 1. Some studies did not report acute cough data.

Conclude by discussing the management of acute and chronic COVID-19 cough and future directions for research and clinical practice.

**Acute COVID-19-associated cough**

Dry cough is one of the most common initial symptoms of COVID-19, reported in about 60–70% of symptomatic patients.1,2 Using an app-based COVID symptom tracker on smartphones, cough was reported in about 50% of patients who tested positive for SARS-CoV-2, and in combination with a loss of smell (anosmia), loss of taste (ageusia), unusual fatigue, and loss of appetite, was highly predictive of SARS-CoV-2 infection.4 A systematic review and meta-analysis5 of 21,682 adults infected with SARS-CoV-2 in nine countries reported that cough was present in 57%. A study in Wuhan, China, found that the median time from illness onset to cough was 1 day and that cough persisted for an average of 19 days; cough lasted for 4 weeks or more in approximately 5% of patients.1

The co-presence of cough, anosmia, and ageusia4 indicates that neuroinflammatory mechanisms might be operative in COVID-19 pathogenesis. As the cough reflex is mediated by the vagus nerve,1 interactions between the virus and the airway vagus nerve, with ensuing neuroinflammation, represent the likely primary events for the initiation of cough.

**Cough in the post-COVID syndrome**

An increasing number of reports describes an array of fluctuating or persistent symptoms experienced by patients for months after recovery from COVID-19. Symptoms include cough, fatigue, dyspnoea, pain, and so-called brain fog (cognitive impairment, including confusion and memory loss), and are associated with a deleterious effect on activities of daily living.6–22 This phenomenon has been termed the post-COVID syndrome or long COVID.23,24 A study by Carfi and colleagues25 was the first to describe persistent symptoms in patients after COVID-19. In a post-COVID cohort of 143 patients from a hospital in Italy, 125 (87.4%) reported struggling with symptoms—76 (53.1%) reported fatigue, 62 (43.4%) dyspnoea, and 23 (16.0%) cough—2 months after discharge.24 Many reports have now described post-COVID symptoms and show that cough can persist for weeks and months after SARS-CoV-2 infection in some patients, with differing severity of acute symptoms (figure 1, table 1).1,25

**What is the prevalence of post-COVID cough?**

In a multicentre observational cohort study done in 1250 COVID-19 survivors in Michigan, USA, 75 (15.4%) of those who responded to the telephone survey reported new or worsening cough at 2 months after discharge.28 Persistent cough was also reported in patients with mild baseline severity;29,30 cohort studies in Norway and the Faroe Islands found that about 10% of their non-hospitalised patients had cough at 4 months after symptom onset.29,30 In a pooled analysis, we found that the estimated prevalence of persistent cough was 18% (95% CI 12–24%; I²=93%) in 14 studies of hospitalised patients (follow-up duration ranged from 6 weeks to 4 months; figure 2).1,2,13–21 However, prevalence varied widely between studies, and is presumably dependent on patient characteristics, treatment, follow-up duration, and outcome definition.

Longitudinal studies in the general population have not been reported so far, but in the UK Office for National Statistics COVID-19 Infection Survey, the proportion of patients who remain symptomatic at 5 weeks after infection was estimated at 21·0% (95% CI 19·9–22·1%), and cough was the second most common persistent symptom (11·4% [10·5–12·2%]), fatigue being the first.31 The estimated prevalence of patients symptomatic at 12 weeks was 9·9% (6·7–14·7%), but a specific rate for cough has not yet been reported.30 In online surveys, cough was reported in 20–30% of still symptomatic patients 2–3 months after the onset of symptoms of COVID-19 (table 1).1,2,13,25

Two studies provided information on the prevalence of burdensome cough after COVID-19 (arbitrarily defined as cough with a numerical rating scale ≥4) and indicated that 7–10% of patients who recovered from COVID-19 pneumonia might suffer from burdensome cough 2 months after discharge.32,33 However, more data are needed on the prevalence, severity, effects, and long-term course of post-COVID cough.

**What are the causes of post-COVID cough?**

It is not known why the post-COVID syndrome develops in some individuals. There is emerging evidence that...
female sex, presence of respiratory comorbidities, and severity of acute COVID-19 presentation might be predictive of post-COVID syndrome. So far, it is unclear whether any factors in the acute phase could specifically determine the persistence of cough. Unlike chronic cough that persists after the common cold or flu, in contrast, cough that accompanies post-COVID syndrome is usually accompanied by other multisystem manifestations, which might indicate either multifactorial pathogenesis or shared mechanisms underlying these symptoms.

| Study design and region | Patients | Follow-up duration | Acute cough (%) | Persistent cough (%) | Other common persistent symptoms |
|-------------------------|----------|--------------------|----------------|---------------------|----------------------------------|
| Clinic-based studies    |          |                    |                |                     |                                  |
| Cheng et al, 2021       | Retrospective, multicentre cohort study, London, UK | 113 patients discharged from the respiratory unit after COVID-19; median age 66 years | 6 weeks after discharge | Not reported | 19 of 113 (17%) | Fatigue (6%), breathlessness (38%) |
| Moradian et al, 2020    | Prospective, single-centre follow-up study, Tehran, Iran | 200 patients (166 [80%] men, 40 [20%] women) discharged from hospital after moderate-to-severe COVID-19; mean age 55.6 years | 6 weeks after discharge | 88 of 200 (44%) | 23 of 200 (11.5%) | Fatigue (19.5%), dyspnoea (18.5%), weakness (18%), anxiety (15.0%), activity intolerance (14.5%) |
| Halpin et al, 2021      | Prospective, single-centre follow-up study, Leeds, UK | 100 patients (56 [56%] men, 44 [44%] women) discharged from hospital after COVID-19; mean age 66.6 years | Mean 48 (SD 10.3) days after discharge | Not reported | 21 of 100 (21%) overall; eight of 32 (25%) ICU patients and eight of 68 (12%) ward patients | Fatigue (64%), breathlessness (50%) |
| Mandal et al, 2020      | Prospective, multicentre follow-up study, London, UK | 384 patients (238 [62%] men, 146 [38%] women) hospitalised with COVID-19; mean age 59.9 years | Median 54 (IQR 47–59) days after discharge | Not reported | 131 of 384 (34%) persistent cough (numerical rating scale ≥1), 38 of 356 (10%), burdensome cough (numerical rating scale ≥4) | Fatigue (69%), breathlessness (53%), depression (14%) |
| D’Cruz et al, 2021     | Prospective, single-centre follow-up study, London, UK | 119 patients (74 [62%] men, 45 [38%] women) hospitalised with severe COVID-19 pneumonia; mean age 58.7 years | Median 61 (IQR 51–67) days after discharge | Not reported | 49 of 115 (42.6%) persistent cough (numerical rating scale ≥1), eight of 115 (7.0%) burdensome cough (numerical rating scale ≥4) | Fatigue (67.8%), sleep disturbance (56.5%), pain (49.6%) |
| Chopra et al, 2020     | Prospective, multicentre follow-up survey, MI, USA | 488 survivors of COVID-19 hospitalisation (253 [51.8%] men, 235 [48.2%] women); mean age 62 years | 60 days after discharge | Not reported | 75 of 488 (15.4%) new or worsened cough | Emotional impact (48.8%), breathlessness walking up stairs (23.0%), shortness of breath or chest tightness or wheezing (16.6%), loss of taste or smell (12.1%) |
| Carfi et al, 2020       | Prospective, single-centre follow-up study, Rome, Italy | 143 patients (80 [56.3%] men, 53 [37%] women) discharged from hospital after COVID-19; mean age 56.5 years | Mean 60.0 (SD 13.6) days after symptom onset | 99 of 143 (69%) | 23 of 143 (16%) | Fatigue (53.1%), dyspnoea (43.4%), joint pain (27.3%), chest pain (21.7%) |
| Arnold et al, 2021      | Prospective, single-centre follow-up study, Bristol, UK | 110 patients (62 [56%] men, 28 [44%] women) hospitalised with laboratory-confirmed SARS-CoV-2 infection; median age 60 years | Median 90 (IQR 80–97) days after symptom onset | 74 of 110 (67%) | 13 of 110 (31.8%) | Excessive fatigue (39%), breathlessness (39%), insomnia (24%) |
| Sonnenweber et al, 2020 | Prospective, multicentre follow-up study, Austria | 145 patients (83 [57%] men, 62 [43%] women) who required hospitalisation (75%) or outpatient care with persisting symptoms; mean age 57 years | Mean 100 (SD 23) days after symptom onset | 102 of 145 (70%) | 25 of 145 (17%) | Dyspnoea (36%), sleep disorder (28%), night sweat (24%), pain (24%), hypoxia or anoxia (19%) |
| Xiong et al, 2021       | Prospective, single-centre follow-up study, Wuhan, China | 538 patients (245 [45.5%] men, 293 [54.5%] women) discharged from hospital after COVID-19; median age 52 years | At least 3 months after discharge | 297 of 538 (55.2%) | 38 of 538 (7.1%) | Alopecia (28.6%), fatigue (28.3%), sweating (23.6%), somnolence (12.7%), chest distress (14.1%) |
| Zhao et al, 2020        | Retrospective, multicentre follow-up study, Zhengzhou, China | 55 patients (32 [58.2%] men, 23 [41.8%] women) discharged from hospital (51 patients had pneumonia); median age 47.7 years | 3 months after discharge | 30 of 55 (54.5%) | 1 of 55 (1.8%) | Gastrointestinal symptoms (30.9%), headache (18.2%), fatigue (16.4%), exertional dyspnoea (14.6%) |

(Table 1 continues on next page)
Studies reporting cough at follow-up in patients with COVID-19

Table 1: Studies reporting cough at follow-up in patients with COVID-19

| Study design and region | Patients | Follow-up duration | Acute cough (%) | Persistent cough (%) | Other common persistent symptoms |
|------------------------|----------|--------------------|-----------------|----------------------|----------------------------------|
| (Continued from previous page) |          |                    |                 |                      |                                  |
| Valente (pre-print) | Prospective, single-centre follow-up study, Malaga, Spain; 108 patients (48 [44.4%] men, 60 [55.6%] women) discharged from admission or emergency service care; mean age 55.5 years | 12 weeks after acute phase | Not reported | 28 of 108 (25.9%) | Dyspnoea (55.6%), asthenia (44.9%), chest pain (25.9%), palpitation (22.2%) |
| Wong et al, 2020 | Prospective, multicentre follow-up study, Vancouver, Canada; 78 patients (50 [64%] men, 28 [36%] women) hospitalised with laboratory-confirmed SARS-CoV-2 infection; mean age 62 years | Median 13 (IQR 11–14) weeks after symptom onset | Not reported | 18 of 78 (23%) | Dyspnoea (50%) |
| Garrigues et al, 2020 | Prospective, single-centre follow-up study, Paris, France; 120 patients (75 [62.5%] men, 45 [37.5%] women) discharged from hospital after COVID-19; mean age 63.2 years | Mean 110.9 days after admission | 87 of 120 (72.5%) overall; 69 of 96 (71.9%) ward patients and 18 of 24 (75.0%) ICU patients | 20 of 120 (16.7%) overall; 14 of 96 (14.6%) ward patients and six of 24 (25.0%) ICU patients | Fatigue (55.0%), dyspnoea (42.0%), loss of memory (34.0%), sleep disorder (30.8%), concentration disorder (28.0%) |
| Stavem et al, 2020 | Prospective geographical cohort study, Norway (areas covering 17% of the population); 451 non-hospitalised patients (198 [44%] men, 253 [56%] women) with positive PCR, mean age 49.8 years | Median 117 (range 41–193) days after symptom onset | 302 of 451 (67%) dry cough; 12 of 451 (28%) productive cough | 27 of 451 (6%) dry cough; 18 of 451 (4%) productive cough | Dyspnoea (16%), loss of smell (12%), loss of taste (10%), arthralgia (9%), myalgia (8%) |
| Petersen et al, 2020 | Prospective geographical cohort study, Faroe Islands; 180 non-hospitalised patients (83 [46%] men, 97 [54%] women) with positive PCR, mean age 39.9 years | Mean 125 days after symptom onset | 73 of 180 (40.5%) dry cough; 46 of 180 (25.5%) productive cough | None of 180 (0%) dry cough; 11 of 180 (6%) productive cough | Fatigue (29%), loss of smell (24%), loss of taste (15%), arthralgia (10%), rhinorrhea (9%) |
| Guler et al, 2021 | Prospective, multicentre follow-up study, Switzerland; 113 patients (67 [59.3%] men, 46 [40.7%] women) who survived acute COVID-19 (66 patients had severe or critical disease; 47 had mild or moderate disease); mean age 57 years | Median 128 (IQR 108–144) days after symptom onset | Not reported | Not reported; cough VAS median 0 (IQR 0–2) | – |
| Klein et al, 2021 | Prospective follow-up study of PCR-positive patients with COVID-19 recruited via social media and word of mouth; Israel; 112 patients (72 [64.3%] men, 40 [35.7%] women; six hospitalised and 106 ambulatory patients) in recovery after COVID-19; mean age 35 years | 6 weeks and 6 months after symptom onset | 68 of 112 (61%) | 29 of 112 (26%) at 6 weeks; one of 112 (1%) at 6 months | At 6 months: fatigue (23%), smell change (25%), breathing difficulty (10%), taste change (8%), memory disorder (6%) |

Online population-based surveys

| Study | Patients | Follow-up duration | Acute cough (%) | Persistent cough (%) | Other common persistent symptoms |
|-------|----------|--------------------|-----------------|----------------------|----------------------------------|
| Assaf et al, 2020 | Patient-led survey through the Body Politic COVID-19 Support Group on Slack (75.4% of participants) or through social media sites such as Facebook, Twitter, and Instagram; 71% from the USA and UK, 12% from the USA and UK; 640 patients (150 [23.4%] men, 490 [76.6%] women) who had previously experienced or were currently experiencing symptoms consistent with COVID-19 and had suspected or confirmed SARS-CoV-2 infection (23% tested positive, 27% tested negative, 47% not tested); 62.7% between the ages of 30 and 49 years | Up to 8 weeks after symptom onset | At week 1: 301 of 640 (47.0%) dry cough; 141 of 640 (22.0%) persistent uncontrollable cough | At week 8: 179 of 640 (28.0%) dry cough; 57 of 640 (8.9%) persistent uncontrollable cough | Mild shortness of breath (39%), mild chest tightness (34%), mild fatigue (33%), moderate fatigue (32%) |
| Sudre et al, 2020 (preprint) | Prospective cohort study of users of the COVID Symptom Study app; 4182 patients (1192 [28.5%] men, 2990 [71.5%] women) who had tested positive for SARS-CoV-2 by PCR swab testing and logged as “feeling physically normal” before the start of illness (up to 14 days before testing); mean age 42.8 years | 56 days after symptom onset | Not reported | 920 of 4182 (22%) persistent cough, defined as symptoms lasting more than 56 days | – |
| Goertz et al, 2020 | Online survey of individuals with persistent complaints related to COVID-19; the Netherlands and Belgium; 2133 members of Facebook groups for COVID-19 patients with persistent complaints and a panel of people who registered at a website of the Lung Foundation Netherlands (309 [14.5%] men, 1824 [85.3%] women); mean age 47 years | Mean 79 (SD 17) days after symptom onset | 1450 of 2133 (68.0%) | 619 of 2133 (29.0%) | Fatigue (94.9%), dyspnoea (89.5%), headache (76.0%), chest tightness (72.2%), muscle pain (64.7%) |

Studies are listed by follow-up duration from 6 weeks to 6 months. ICU=intensive care unit. VAS=visual analogue scale.

Table 1: Studies reporting cough at follow-up in patients with COVID-19
The concomitant presence of fatigue, dyspnoea, pain, and cough could point to a derangement of the CNS. Therefore, documentation of the extent and quality of these co-existing symptoms is an important goal. From the point of view of cough, detailed characterisation—including frequency, severity, urge to cough, hypersensitivity, or cough suppressibility—using clinical tools that are already available could improve our understanding of its clinical implications and relationship to the other post-COVID symptoms.

In the clinical management of post-COVID chronic cough, it is important to exclude any pathological or structural causes, such as fibrotic damage to the lung parenchyma or damage to the airways caused by either SARS-CoV-2 or the treatment provided in critical care. Lung parenchymal changes are commonly found on CT scans of adult patients with COVID-19, and lung fibrotic changes can occur in 10–20% of patients. Lung fibrosis could increase cough reflex sensitivity in response to mechanical stimulation of the chest wall, as reported in patients with idiopathic pulmonary fibrosis.

Neuronal mechanisms of cough

There have been great advances in our understanding of the pathways underlying cough and cough hypersensitivity. Cough is a reflex that requires minimum conscious control, occurring through the activation of peripheral sensory nerves into the vagus nerves, which provide input to the brainstem at the solitary nucleus and peripheral sensory nerves into the vagus nerves, which provide input to the brainstem at the solitary nucleus and the spinal trigeminal nucleus. In chronic cough, the concept of cough hypersensitivity has been developed with the notion that the cough pathways have been sensitised by amplification of the afferent signals to the brainstem. In this Personal View, we postulate that neuronal mechanisms of hypersensitivity are central to the cough of COVID-19. We consider the possibility that SARS-CoV-2 infects the sensory nerves mediating cough, leading to neuroinflammation and neuroimmune interactions as mechanisms of cough hypersensitivity (figure 3). We also examine whether the neurotropism of SARS-CoV-2 could explain the other accompanying symptoms of COVID-19 and post-COVID syndrome.

Does SARS-CoV-2 infect sensory nerves?

Angiotensin-converting enzyme 2 (ACE2) receptors and proteases such as transmembrane serine protease 2 (TMPRSS2) and furin are important for viral entry into host cells for coronaviruses such as SARS-CoV-2. SARS-CoV-2 might interact directly with sensory neurons, given that sensory dysfunction—including cough, and olfactory and taste impairments—are frequent in infected patients. However, it is not known whether human airway vagal sensory neurons express ACE2 or TMPRSS2, or can be infected by SARS-CoV-2. In mice, single-cell sequencing of bronchopulmonary vagal sensory neurons showed no expression of murine ACE2. Additional viral entry factors might also have a role in the interactions of SARS-CoV-2 with neurons, including neuropilin-1, which is expressed by vagal and other sensory neurons. In a sequencing study of human olfactory mucosal cells, ACE2 and TMPRSS2 were not found in olfactory epithelial neurons, but were abundantly expressed in olfactory epithelial support cells and stem cells. The findings were confirmed by cellular histological localisation of ACE2 in the specialised neuroepithelium of supporting cells around neuronal dendritic projections; the neuroepithelium contains odour-sensing cilia. Therefore, anosmia induced by SARS-CoV-2 infection might be caused by the effect of the infected epithelium on neuronal activity. However, the ACE2 gene has been reported in a subset of human dorsal root ganglion sensory neurons in the thoracic ganglia, some of which also innervate the lungs. Notably, expression was reported in a subset of nociceptive neurons co-expressing CALCA (calcitonin related polypeptide alpha) or P2X3 (purinergic receptor P2X3), and comparable neuronal subtypes of the vagal sensory ganglia are important for the induction of coughing. The fact that some vagal sensory neurons, including those involved in cough, have a developmental lineage and molecular phenotype that is very similar to dorsal root ganglion neurons means that ACE2 expression in human vagal sensory neurons might be predicted.

Although the infection of dorsal root ganglion neurons containing nociceptors might provide an explanation for the post-COVID symptoms of joint and chest pain, headache, and dyspnoea, the basis for sustained cough after SARS-CoV-2 infection remains unclear. A

---

**Figure 2: Prevalence of post-COVID cough in 14 studies of patients who required hospitalisation**

Follow-up duration ranges from 6 weeks to 4 months. Detailed characteristics of included studies are summarised in table 1. We conducted a random-effects meta-analysis to estimate the pooled prevalence and standard errors for post-COVID cough in previously hospitalised patients, and quantified the degree of heterogeneity between studies using the I² in the MetaXL 5.3 software (EpiGear International Pty, Sunrise Beach, QLD, Australia).

| Study Reference | Prevalence (95% CI) | Weight (%) |
|-----------------|---------------------|------------|
| Cheng et al, 2021 | 0.17 (0.11–0.25) | 70 |
| Moradian et al, 2020 | 0.12 (0.07–0.16) | 74 |
| Halpin et al, 2021 | 0.21 (0.14–0.30) | 69 |
| Mandal et al, 2020 | 0.14 (0.09–0.19) | 77 |
| D’Cruz et al, 2021 | 0.43 (0.34–0.52) | 71 |
| Chopra et al, 2020 | 0.15 (0.12–0.19) | 77 |
| Carfi et al, 2020 | 0.16 (0.10–0.23) | 72 |
| Arnold et al, 2021 | 0.12 (0.06–0.19) | 70 |
| Sonnweber et al, 2020 | 0.17 (0.11–0.24) | 72 |
| Xiong et al, 2021 | 0.07 (0.05–0.09) | 77 |
| Zhao et al, 2020 | 0.02 (0.00–0.08) | 63 |
| Valiente-De Santis et al, 2020 | 0.26 (0.18–0.35) | 70 |
| Wong et al, 2020 | 0.23 (0.14–0.33) | 67 |
| Garrigues et al, 2020 | 0.17 (0.10–0.24) | 71 |
| **Overall** | **0.18 (0.12–0.24)** | **100** |
Does SARS-CoV-2 alter sensory neuronal function?

Viral infection of neurons, including herpes virus infection of primary sensory neurons, leads to the activation of neuronal antiviral signalling, which can include the production of interferons and other cytokines traditionally involved in cellular defence against viral infection. Additionally, neuronal support cells (such as glial cells) respond to neuronal infection by generating a local inflammatory environment. It is now clear that release of cytokines—the so-called cytokine storm—can occur in severe COVID-19 infection, characterised by increased levels of inflammatory cytokines including tumour necrosis factor (TNF) and interleukin (IL)-6, which are associated with increased mortality.

In the peripheral nervous system, traditional immune cells, including macrophages and dendritic cells, infiltrate nerves and neuronal tissues to assist with inflammatory reactions. Collectively, these neuroinflammatory processes would be expected to dramatically alter sensory neuron activity and potentially underpin cough induction and persistence. Alternatively, as sensory neurons commonly express Toll-like receptors (TLRs) and other receptors for recognition of pathogenic organisms, direct functional interactions between viral particles and nerves might occur in the absence of neuronal infection. Indeed, in dorsal root ganglion neurons, TLR activation leads to gating of transient receptor potential (TRP) channels, offering a mechanism by which pathogens can directly change neuronal activity independent of viral entry.

Further studies are warranted to explore the interactions between SARS-CoV-2 and vagal sensory neurons with their supportive cells.

The very rapid onset of cough after SARS-CoV-2 infection might suggest a mechanism independent of a direct nerve–virus interaction. For example, an initial epithelial-derived mechanism could evolve to be sustained by dysregulated inflammation. In addition to TLRs, cytokines released through dysregulated inflammation caused by SARS-CoV-2 activation of the innate immune response (eg, through inflammasome activation) are likely candidates driving acute cough via neuroimmune interactions. These cytokines include IL-1β, TNF, and interferons, because their receptors are commonly present on immune cells and peripheral neurons. Type I and type II interferons, such as interferon-γ, might cause cough hyper-responsiveness through depolarisation of vagal sensory nerves. Neuropeptides released from sensory nerves through activation of TRPV1, such as substance P, neurokinin A, and calcitonin gene-related peptide, can recruit and activate immune cells (eg, lymphocyte and post-mortem study of individuals who died with COVID-19 has reported the presence of SARS-CoV-2 RNA and protein in the olfactory mucosa, confirming entry of the virus into the CNS at a neural–mucosal surface. In the same study, the trigeminal sensory ganglia, which innervate the corneal, nasal, and oral epithelium, also contained virus, suggesting that sensory neurons can offer an entry point for SARS-CoV-2 to the CNS. SARS-CoV-2 has also been shown to infect brain organoids in vitro, and the brains of human ACE-expressing transgenic mice after in-vivo intranasal inoculation. There is evidence in animals that some respiratory viruses can reach the brainstem and the brain by the retrograde route, through infection of the sensory vagal fibres from the respiratory tract. Alternatively, mechanisms might exist that trigger responses in the
dendritic cells) and inflammatory cells (eg, mast cells and macrophages), and increase vascular permeability, thereby aggravating lung inflammation.26,27 Various ligand–receptor interactions after SARS-CoV-2 infection at the level of the dorsal root ganglion have been proposed to induce a neurogenic inflammation.28 Support cells of peripheral sensory neurons (myelinating and non-myelinating glia) can additionally contribute to viral recognition and inflammation, and alter sensory neuron responsivity.29,30 One product of inflammasome activation is ATP, which might activate or sensitise cough receptors directly.31,32

Is COVID-19 cough the result of sensory hypersensitive pathways?
The mechanisms of cough in the context of other respiratory viruses might provide further insight into the mechanisms of acute COVID-19 cough. Human rhinovirus (HRV)-16, a major pathogen for the common cold and asthma exacerbations, can infect sensory neurons and upregulate TRP channels,33 which could explain the heightened cough reflex and urge-to-cough sensations in patients with common cold.34 In A549 alveolar epithelial cells, HRV-16 infection significantly increased not only intracellular ATP concentrations, but also the extracellular release of ATP,35 which is a highly relevant mediator for chronic refractory cough.36 In guinea pigs, infection with parainfluenza type 3 virus caused phenotypic changes of sensory neuronal hypersensitivity in the tracheal nodose neurons, including de-novo expression of substance P or TRPV1.37,38 Therefore, sensory hypersensitivity is likely to underlie virus-associated cough in general, although specific mechanisms might vary between different respiratory viruses (figure 3).

Urge to cough, frequently seen in subjects with common cold and possibly also in those with acute COVID-19-associated cough, has been linked to altered central processing of sensory input and cough reflex (termed central sensitisation).39 Substance P, which might be upregulated in the nodose ganglionic neurons by viral infection,40 can drive central sensitisation in virus-associated cough. Murine pneumovirus infection induced inflammatory glial cell activation and altered neuronal responsiveness in the brainstem nucleus tractus solitarius of mice, the primary site of vagal sensory inputs.41 Therefore, increased inflammatory activation of sensory neurons could induce altered reflex processing in the brain. In ACE2 transgenic mice infected with SARS-CoV, brain areas that have first-order or second-order connections with the olfactory bulb were heavily infected, including the dorsal vagal complex, area postrema, and dorsal motor nucleus of the vagus, which are also implicated in cough regulation.42 SARS-CoV-2 can be found in the brain and cerebrospinal fluid of patients with COVID-19,43 suggesting that this virus is likely to be detectable by microglia and macrophage-like immune cells, which might orchestrate inflammation in the brain and provide a central basis for hypersensitivity. This response could, in turn, influence peripheral mechanisms of hypersensitivity. A post-mortem analysis of individuals who died of COVID-19 found the pro-inflammatory cytokines IL-6, IL-18, and C-C motif chemokine 2 (CCL2) in the cerebrospinal fluid, and SARS-CoV-2 virus in the brainstem medulla.44 Notably, SARS-CoV-2 was detected in brainstem regions involved in respiratory control, perhaps a neuroanatomical basis for effects on breathing and associated reflexes in COVID-19.

Is the post-COVID syndrome due to a generalised neuronal hypersensitivity?
An important consideration is whether the post-COVID syndrome is the result of a generalised hypersensitivity state that underlies the panoply of symptoms associated with this condition. Key symptoms reported in post-COVID syndrome (dyspnoea, pain, and cough) have similarities in terms of the control and peripheral sensitisation of their respective afferent pathways.45 We have shown that idiopathic chronic cough, now often described as the cough hypersensitivity syndrome, is dominated by the presence of a hypersensitivity with both peripheral and central components.46 The central neurobiology of cough hypersensitivity has been supported by functional brain imaging of airway stimulation with a tussive TRPV1 agonist, capsaicin, which showed elevated neural activity in the midbrain of individuals with this syndrome.47 Chronic fatigue syndrome (also called myalgic encephalomyelitis) and fibromyalgia, in which patients complain of fatigue and musculoskeletal pain, have also been associated with alterations in pain and sensory processing in both peripheral and central neurogenic sensitisation.48,49 Functional MRI studies have shown that the insular and cingulate cortices are key areas in the nociceptive processing of dyspnoea, which are the same areas activated by pain and cough.50,51 Therefore, we need to gather evidence to explore shared or common features in the pathways of central hypersensitivity, encompassing not only post-COVID hypersensitive cough, but also the whole post-COVID syndrome. Indeed, brain MRI imaging of patients with neurological complications of COVID-19 infection have shown cortical signal abnormalities and neuroinflammatory features,52 and brain PET imaging suggests hypometabolism in the olfactory gyrus and connected limbic and paralimbic regions, extending to the brainstem and the cerebellum in patients with long COVID.53

Management of COVID-19-associated cough
The advice for treating the acute and chronic cough of COVID-19 is based on available treatments and guidelines.54,55 Although many drugs are on the market or in development for the relief of cough,56 there is no good evidence for their benefits in the treatment of cough associated with acute viral infection or pneumonia.57,58 In
the UK National Institute for Health and Care Excellence guidelines for managing acute symptoms of COVID-19, only taking honey or opioid-derived antitussives are recommended for cough.25 Opiates (such as codeine or low-dose morphine) could exert antitussive effects by acting on the cough reflex network in the brainstem,61 and might have some effects in suppressing cough, particularly in the early stages. However, opiates are not universally effective and have associated risks of dependence, abuse, or central side-effects.62 Oral corticosteroids are often prescribed for acute lower respiratory tract infection and have been used by many centres to treat patients with post-COVID interstitial lung changes. Oral corticosteroids were no better than placebo in reducing cough duration in non-asthmatic adults with acute lower respiratory tract infection.63 However, the situation with SARS-CoV-2 infection might be different, with the likely presence of an early inflammatory response and neuroimmune interactions underlying the acute cough. The report that dexamethasone reduces the mortality rate of hospital-treated patients with COVID-19 provides some support for the use of corticosteroids.64,66 However, cough was not assessed in these trials,65,66 nor was it measured in any other trials of therapies for COVID-19, such as the study of the antiviral replicating agent remdesivir.67 Cough measurements should be incorporated into future trials.

Table 2: Future research in COVID-19-associated cough

| Unanswered questions | Potential research studies |
|----------------------|---------------------------|
| **Mechanistic studies** | • Investigations of SARS-CoV-2 interaction with vagal bronchopulmonary sensory nerves, including neural expression of ACE2 and other entry factors, involvement of neural innate viral recognition factors, and role of resident and recruited airway and lung cells (and their mediators) in sensory neuronal activation. |
| • How does SARS-CoV-2 infection modify the activity of vagal sensory neurons mediating cough? | • Assessment of bronchopulmonary sensory neuron sensitivity in COVID-19, including use of animal models to evaluate cough response pathways and pathological changes following SARS-CoV-2 infection and treatment. |
| • What are the pathological consequences, within peripheral and central cough processing pathways, of SARS-CoV-2 infection? | • Mechanistic studies in humans to assess peripheral and central processing to cough challenge with functional MRI, particularly with respect to post-COVID syndrome. |
| • What is the inflammatory (neural and airway) profile of individuals with COVID-19-related cough? | • Airway sampling to study inflammatory phenotype or effect of SARS-CoV-2 infection on airway nerve architecture or deformity. |
| • What is the impact of modulating neuroinflammation and neuroimmune processes on cough in COVID-19? | |

**Acute COVID-19-related cough**

| Cough is a key symptom of acute infection and an important mode of SARS-CoV-2 transmission | • Subjective and objective cough evaluation, with sound recording, and studies of relationship with health outcomes, with appropriate prospective comparator groups. |
| What are the characteristics of acute COVID-19-related cough? Can these characteristics aid diagnosis or prognosis? | • Assessment of utility of cough sound analysis based on artificial intelligence algorithm to facilitate early detection of COVID-19. |
| How does acute COVID-19-related cough respond to anti-inflammatory drugs (eg, corticosteroids) or SARS-CoV-2-targeted treatments? | • Initial evaluation and re-evaluation of data from randomised clinical trials with cough documentation; future establishment of robust cough measures to monitor cough outcome and clinical responses. |
| How does the presence of comorbid conditions or diagnoses influence the presence of COVID-19-related cough? | • Randomised controlled trials of existing or emerging antitussive therapies with robust primary outcome measures in patients with COVID-19 and cough. |
| Is antitussive therapy during the acute phase of COVID-19 safe and effective in treating morbidity or reducing SARS-CoV-2 transmission? | • Inclusion of validated cough endpoint measures in future viral inoculation models for optimisation of vaccine development. |

**Chronic or post-COVID cough**

| Cough persists in a subgroup of patients after resolution of acute disease, cough in post-COVID syndrome is usually associated with chronic fatigue and dyspnoea | • Cross-sectional evaluation of prevalence of cough in those with co-existing pulmonary infiltrates, documented reflux, or history of airways disease, or in those taking ACE inhibitors; evaluation of changes with treatment response. |
| What are the prevalence, longitudinal course, clinical features, and effect on quality of life of post-COVID cough? Are they similar to those encountered in cough hypersensitivity syndrome? | • Longitudinal follow-up and robust phenotyping with cough hypersensitivity testing (eg, cough challenge testing) and validated measures of cough (eg, cough-related quality of life), evaluation of sequelae and impact on quality of life (eg, incontinence and social exclusion). |
| Do treatments for cough hypersensitivity help in post-COVID cough management? Are novel treatments (eg, P2X3 antagonists) beneficial? | • Randomised controlled trials of novel cough therapies in patients with post-COVID cough using robust cough outcome measures (eg, ambulatory cough count); response of concomitant symptoms of post-COVID syndrome. |
| Does cough modulation treatment (eg, speech pathology therapy) help? | |
| Should the treatment to post-COVID syndrome be a global approach to tackling all symptoms? | |
Anatomical diagnostic protocols for chronic cough\(^\text{17}\) should be applied for the management of cough in the post-COVID syndrome; such approaches could identify any contributing causes to chronic cough—such as gastro-oesophageal reflux disease, ACE inhibitor therapy, lung fibrosis, or airway inflammation—that might have resulted from COVID-19 infection.

Persistent cough in post-COVID syndrome might be driven by neuroinflammation leading to a state of laryngeal and cough hypersensitivity, which is the basis for chronic refractory or unexplained cough. Gabapentin and pregabalin, which are neuromodulators, have been shown to be effective in controlling chronic refractory cough.\(^\text{26,30}\) This approach could be considered for the post-COVID syndrome, because these drugs might also be useful for other symptoms accompanying cough, such as pain, although they have the potential to worsen any cognitive dysfunction. Antimuscarinic drugs, such as tiotropium, could be used to control COVID-19 cough, because they can decrease cough sensitivity in acute viral upper respiratory tract infection.\(^\text{30}\) Similarly, speech and language therapy\(^\text{30}\) might help patients to recover, delivered as part of a multimodal therapy and recovery model in synergy with other aspects of pulmonary rehabilitation for the post-COVID syndrome.

Investigation of novel therapeutic interventions that interfere with the neuroinflammatory pathways could be advantageous, such as inhibitors of TRP channels, ATP-gated P2X3 receptors, neurokinin-1 receptors (NK1Rs), or sodium channels. A P2X3 receptor antagonist, gefapixant, substantially reduced cough in patients with chronic refractory cough,\(^\text{44,45}\) and its use in COVID-19-associated cough is supported by the report that ACE2 is frequently co-expressed with P2X3 in dorsal root ganglion sensory neurons.\(^\text{46}\) Substance P and NK1R might also be a potential target for intervention, because NK1R antagonists such as aprepitant or orvepitant have shown antitussive potential in patients with lung cancer-associated cough or chronic refractory cough, possibly through blocking of central NK1Rs.\(^\text{46,53}\) Although TRPV1 antagonists have not been shown to reduce cough in patients with refractory cough,\(^\text{46,45}\) they should be tested in COVID-19 cough because TRPV1 in sensory neurons is upregulated by viral infections such as human rhinovirus.\(^\text{46}\) The charged sodium channel blocker NTX-I175, which silences nociceptor neurons, is a new neuromodulator that is being trialled (EuraCT 2020-004715-27) for chronic cough, but could also be considered for acute and chronic COVID-19 cough.

**Conclusions and future directions**

Little is known about the cough associated with COVID-19, apart from details of the frequency, prevalence, and persistence of cough. We need to understand more about the mechanisms by which the vagal sensory neurons are activated by the virus and sensitised through the process of neuroinflammation and neuroimmunity. To better understand the characteristics of COVID-19-associated cough, evidence for both peripheral and central sensitisation should be obtained. Chronic cough should be considered together with the other symptoms of the post-COVID syndrome, and evidence sought to address the question of whether they reflect the process of central sensitisation. Table 2 summarises research studies that could be considered. These studies might lead to the consideration of antiviral or anti-inflammatory drugs or neuromodulators for the treatment of acute and chronic COVID-19-associated cough, in addition to the treatment of the post-COVID syndrome as a whole. Steps need to be taken to identify therapies that target the central sensitisation process.

Practical steps have already been taken to address the range of symptoms associated with the post-COVID syndrome. Clinics are currently being set up to manage the many patients with long COVID, and research efforts are underway to better understand the long-term health effects of COVID-19. In the UK, the National Institute for Health Research and UK Research and Innovation are already focusing on long COVID in hospitalised patients—for example, in the ISARIC 4C (ISARIC Coronavirus Clinical Characterisation Consortium) and PHOSP-COVID (Post-Hospitalisation COVID-19 study) research initiatives—to understand and improve the long-term health outcomes of this challenging condition. In addition, a £20m joint research call has been made to fund research into the longer-term physical and mental effects of COVID-19 in non-hospitalised individuals.

We hope that the questions we have addressed in this Personal View will soon be answered. As we learn more about the mechanisms of acute and chronic cough associated with COVID-19, we hope that strategies for improved management and prevention emerge so that the effects of COVID-19-associated cough on the health and wellbeing of patients and on the transmission of SARS-CoV-2 can be reduced. Moreover, identification of shared mechanisms underlying components of the post-COVID syndrome could point to treatment options for debilitating long-term effects of COVID-19.

**Contributors**

WJS, SSB, SBM, and KFC did the literature search. WJS, SBM, and KFC wrote the first draft, with later contributions by CKMH, JHH, and...
The other authors declare no competing interests. Pharmaceuticals and is a member of the advisory board for Bellus Health, Shionogi, Bayer, Bellus Health, Nocion, Chiesi, and Applied Clinical and NeRRe Therapeutics. SSB reports personal fees from Nocion, Merck, Merck. SBM reports grants from Merck and personal fees from Merck remunerated for speaking engagements by AstraZeneca, Novartis, and GlaxoSmithKline Health Care Consumer Products; and he has been involved in the writing process, and all reviewed the advanced version of the manuscript. All authors discussed the scope and focus of the article at the start of the writing process, and all reviewed the advanced version of the manuscript. All authors discussed the scope and focus of the article at the start of the writing process, and all reviewed the advanced version of the manuscript.
37 Daviès J, Randeva HS, Chattha K, et al. Neuropilin1 as a new potential SARS-CoV-2 infection mediator implicated in the neurologic features and central nervous system involvement of COVID-19. Mol Med Rep 2020; 22: 4221–26.

38 Brann DH, Tsukahara T, Weinre B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv 2020; 6: eabc5801.

39 Chen M, Shen W, Rowan NR, et al. Elevated ACE-2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication. Eur Respir J 2020; 56: 2001948.

40 Shiers S, Ray PR, Wangzhou A, et al. ACE2 and SCARF expression in human dorsal root ganglion nociceptors: implications for SARS-CoV-2 virus neurological effects. Pain 2020; 161: 2494–501.

41 Kupari J, Härting M, Agrie E, Castelo-Branco G, Emrns P. Atlas of vagal sensory neurons and their molecular specialization. Cell Rep 2019; 27: 2508–2523.e4.

42 Meinhardt J, Radke J, Dittmayer C, et al. Olfactory transmucosal SARS-CoV-2 infection as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci 2021; 24: 168–75.

43 Song E, Zhang C, Israelow B, et al. Neuroinvasin of SARS-CoV-2 in human and mouse brain. J Exp Med 2021; 218: e20202135.

44 Driessen AK, Farrell MJ, Mazzone SB, McGovern AE. Multiple neural circuits mediating airway sensations: recent advances in the neurobiology of the urge-to-cough. Respir Physiol Neurobiol 2016; 226: 115–20.

45 Rhea EM, Logsdon AF, Hansen KM, et al. The S1 protein of SARS-CoV-2 crosses the blood-brain barrier in mice. Nat Neurosci 2020; 24: 368–78.

46 Rosato PC, Leib DA. Neuronal interferon signaling is required for protection against herpes simplex virus replication and pathogenesis. PLoS Pathog 2015; 11: e1005028.

47 Undem BJ, Zaccone E, McGarvey L, Mazzone SB. Neural dysfunction following respiratory viral infection as a cause of chronic cough hypersensitivity. Palm Pharmacol Ther 2015; 33: 52–56.

48 Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020; 130: 2620–29.

49 Verzele NAJ, Chua BY, Law CW, et al. The impact of influenza pulmonary infection and inflammation on vagal bronchopulmonary sensory neurons. FASEB J 2021; 35: e12130.

50 Driessen AK, Devlin AC, Lundy FT, et al. Perspectives on multiple neural circuits mediating airway sensations: recent advances in the neurobiology of the urge-to-cough. Respir Physiol Neurobiol 2016; 226: 115–20.

51 Park CK, Xu ZZ, Berta T, et al. Extracellular microRNAs activate nociceptor neurons to elicit pain via TRPL and TRPA1. Neuron 2014; 82: 67–74.

52 Chiu IM, von Hehn CA, Woolf CJ. Neurogenic inflammation and the circuits mediating airway sensations: recent advances in the human and mouse brain. Neurosci Lett 2019; 643: 115–20.

53 Song E, Zhang C, Israelow B, et al. Neuroinvasin of SARS-CoV-2 in human and mouse brain. J Exp Med 2021; 218: e20202135.

54 Driessen AK, Farrell MJ, Mazzone SB, McGovern AE. Multiple neural circuits mediating airway sensations: recent advances in the neurobiology of the urge-to-cough. Respir Physiol Neurobiol 2016; 226: 115–20.

55 Rhea EM, Logsdon AF, Hansen KM, et al. The S1 protein of SARS-CoV-2 crosses the blood-brain barrier in mice. Nat Neurosci 2020; 24: 368–78.

56 Rosato PC, Leib DA. Neuronal interferon signaling is required for protection against herpes simplex virus replication and pathogenesis. PLoS Pathog 2015; 11: e1005028.

57 Undem BJ, Zaccone E, McGarvey L, Mazzone SB. Neural dysfunction following respiratory viral infection as a cause of chronic cough hypersensitivity. Palm Pharmacol Ther 2015; 33: 52–56.

58 Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020; 130: 2620–29.

59 Verzele NAJ, Chua BY, Law CW, et al. The impact of influenza pulmonary infection and inflammation on vagal bronchopulmonary sensory neurons. FASEB J 2021; 35: e12130.

60 Abdullah H, Heaney LG, Cosby SI, McGarvey LP. Rhinovirus upregulates transient receptor potential channels in a human neuronal cell line: implications for respiratory virus-induced cough reflex sensitivity. Thorax 2014; 69: 46–54.

61 Dickpiniagits PV, Bhat R, Rotton WA, Tibib AS, Negassa A. Effect of viral upper respiratory tract infection on the urge-to-cough sensation. Respir Med 2011; 105: 635–18.

62 Atkinson SK, Morice AH, Sadosfsky LR. Rhinovirus-16 increases ATP release in A549 cells without concomitant increase in production. ERJ Open Res 2020; 6: 00159–02020.

63 Smith JA, Kivt MM, Morice AH, et al. Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial. Lancet Respir Med 2020; 8: 775–85.

64 Carr MJ, Hunter DD, Jacoby BD, Undem BJ. Expression of tachykinins in nonnociceptive vagal afferent neurons during respiratory viral infection in guinea pigs. Am J Respir Crit Care Med 2002; 165: 1071–75.

65 Zaccone EJ, Lieu T, Muroi Y, et al. Parainfluenza 3-induced cough hypersensitivity in the guinea pig airways. PLoS One 2016; 11: e0155526.

66 Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. Lancet Respir Med 2013; 1: 414–22.

67 Driessen AK, McGovern AE, Narula M, et al. Central mechanisms of airway sensation and cough hypersensitivity. Palm Pharmacol Ther 2017; 47: 9–15.

68 Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Viral 2008; 82: 7264–75.

69 Ahmed MU, Hanif M, Ali MJ, et al. Neurological manifestations of COVID-19 (SARS-CoV-2): a review. Front Neurol 2020; 11: 518.

70 Gracely RH, Undem BJ, Banzett RB. Cough, pain and dyspnoea: similarities and differences. Palm Pharmacol Ther 2007; 20: 433–37.

71 Ando A, Smallwood D, McMahon M, Irving L, Mazzone SB, Farrell MJ. Neural correlates of cough hypersensitivity in humans: evidence for central sensitisation and dysfunctional inhibitory control. Thorax 2016; 71: 323–29.

72 Fukuda K, Strauss SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994; 121: 953–59.

73 Cortes Rivera M, Mastronardi C, Silva-Aldana CT, Arcos-Burgos M, Lidbury BA. Myalgic encephalomyelitis/chronic fatigue syndrome: a comprehensive review. Diagnostics 2019; 9: 71.

74 Pfeifer C, Costes N, Hervé P, Garcia-Larrea L. Relief of dyspnoea involves a characteristic brain activation and a specific quality of sensation. Am J Respir Crit Care Med 2008; 177: 440–49.

75 Katala S, Gholanrezanezhad A. Neuroimaging findings in COVID-19: a narrative review. Neurosci Lett 2021; 742: 115329.

76 Guedj E, Campion J, Dudouit P, et al. 18 F-FDG brain PET hypermetabolism in patients with long COVID. Eur J Nucl Med Mol Imaging 2021; published online Jan 26. https://doi.org/10.1007/s00259-021-03215-4.

77 Gibson P, Wang G, McGarvey L, et al. Treatment of Unexplained Chronic Cough: CHEST guideline and expert panel report. Chest 2016; 149: 27–44.

78 Morice AH, Millqvist E, Beksien K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J 2020; 55: 1901136.

79 Mazzone SB, McGarvey L, Mechanisms and rationale for targeted therapies in refractory and unexplained chronic cough. Clin Pharmacol Ther 2020; published online Aug 4. https://doi.org/10.1002/cpt.2003.

80 Schroeder K, Fahy T. Systematic review of randomised controlled trials of over the counter cough medicines for acute cough in adults. BMJ 2002; 324: 329–31.

81 Chang CC, Cheng AC, Chang AB. Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. Cochrane Database Syst Rev 2014; 10: CD006088.

82 National Institute for Health and Care Excellence in collaboration with NHS England and NHS Improvement. Managing COVID-19 symptoms (including at the end of life) in the community: summary of NICE guidelines. BMJ 2020; 369: m4161.
83 Song WJ, Chung KF. Pharmacotherapeutic options for chronic refractory cough. Expert Opin Pharmacother 2020; 21: 1345–58.
84 Hay AD, Little P, Harroden A, et al. Effect of oral prednisolone on symptom duration and severity in nonasthmatic adults with acute lower respiratory tract infection: a randomized clinical trial. JAMA 2017; 318: 721–30.
85 Group RC. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med 2020; published online Feb 25. https://doi.org/10.1056/NEJMoa2021436.
86 Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA 2020; 324: 1107–16.
87 Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—preliminary report. N Engl J Med 2020; 383: 1813–26.
88 Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet 2012; 386: 1583–89.
89 Vertigan AE, Kapela SL, Ryan NM, Birring SS, McElduff P, Gibson PG. Pregabalin and speech pathology combination therapy for refractory chronic cough: a randomized controlled trial. Chest 2016; 149: 639–48.
90 Dicpinigaitis PV, Spinner L, Santhyadka G, Negassa A. Effect of tiotropium on cough reflex sensitivity in acute viral cough. Lung 2008; 186: 369–74.
91 Chamberlain Mitchell SA, Garrod R, Clark I, et al. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. Thorax 2017; 72: 129–36.
92 Smith J, Allman D, Badri H, et al. The neurokinin-1 receptor antagonist orvepitant is a novel antitussive therapy for chronic refractory cough: results from a phase 2 pilot study (VOLCANO-I). Chest 2020; 157: 111–38.
93 Smith JA, Hazle A, Dockry R, et al. Aprepitant for cough in lung cancer: a randomised placebo-controlled trial and mechanistic insights. Am J Respir Crit Care Med 2020; published online Sept 23. https://doi.org/10.1164/rccm.202006-2359OC.
94 Khalid S, Murdoch R, Newlands A, et al. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. J Allergy Clin Immunol 2014; 134: 56–62.
95 Belvisi MG, Birrell MA, Wortley MA, et al. XEN-D0501, a novel transient receptor potential vanilloid 1 antagonist, does not reduce cough in patients with refractory cough. Am J Respir Crit Care Med 2017; 196: 1255–63.