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Long COVID, neuropsychiatric disorders, psychotropics, present and future

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Review Article

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Abstract

Long COVID refers to the lingering symptoms which persist or appear after the acute illness. The dominant long COVID symptoms in the two years since the pandemic began (2020–2021) have been depression, anxiety, fatigue, concentration and cognitive impairments with few reports of psychosis. Whether other symptoms will appear later on is not yet known. For example, dopamine-dependent movement disorders generally take many years before first symptoms are seen. Post-stroke depression and anxiety may explain many of the early long COVID cases. Hemorrhagic, hypoxic and inflammatory damages of the central nervous system, unresolved systematic inflammation, metabolic impairment, cerebral vascular accidents such as stroke, hypoxia from pulmonary damages and fibrotic changes are among the major causes of long COVID. Glucose metabolic and hypoxic brain issues likely predispose subjects with pre-existing diabetes, cardiovascular or lung problems to long COVID as well. Preliminary data suggest that psychotropic medications may not be a danger but could instead be beneficial in combating COVID-19 infection. The same is true for diabetes medications such as metformin. Thus, a focus on sigma-1 receptor ligands and glucose metabolism is expected to be useful for new drug development as well as the repurposing of current drugs. The reported protective effects of psychotropics and antihistamines against COVID-19, the earlier reports of reduced number of sigma-1 receptors in post-mortem schizophrenic brains, with many antidepressant and antipsychotic drugs being antihistamines with significant affinity for the sigma-1 receptor, support the role of sigma and histamine receptors in neuroinflammation and viral infections. Literature and data in all these areas are accumulating at a fast rate. We reviewed and discussed the relevant and important literature.

Summation

- The neuropsychiatric symptoms in long COVID may represent the consequences of acute viral damage of the central nervous system (CNS), stroke and other cerebrovascular incidents.
- Stress from prolonged social isolation and reduced physical activities may also contribute to some of the reported symptoms.
- Safety of psychotropic usage in patients with COVID-19 is always a consideration. Initial reports showed that psychotropics may actually be protective in COVID-19.
- The role of sigma-1 and histamine receptors and glucose metabolism in COVID-19 infection are important areas for further research and possibly raise novel directions for anti-COVID-19 drug development.

Consideration

- Stress from quarantine, social isolation, job loss and fear of infection are confounding factors in the study of long COVID neuropsychiatric disorders.
- The intensity of the prominent symptoms in long COVID, such as depression, anxiety, fatigue, somatic pain, mild memory and cognitive impairments, has to be carefully quantified in future studies of long COVID.
- Differential efficacy of psychotropics in the treatment of long COVID depression and anxiety should be explored in future studies.
- As there are already many reports on long COVID neuropsychiatric symptoms, international collaborative survey of long COVID neuropsychiatric symptoms under stringent and careful design should be the next step.

Introduction

The COVID-19 (SARS-COV-2) pandemic has so far resulted in 276,436,619 confirmed cases and 5,374,744 deaths worldwide as of December 23, 2021, according to the WHO COVID-19 Dashboard (https://covid19.who.int). The appearance of 822,278 new cases just in the 24 hours prior to December 23, 2021 highlights the ominous situation the world is facing and that we are far from passing the peak of devastation in this pandemic. Comparatively, there was a total of 8098 people worldwide who became sick and 774 deaths with the 2003 SARS outbreak (https://www.cdc.gov).

Unlike the 2003 SARS and many common viral infectious diseases, whose impact is largely absent or soon after when the infection ends, there is now increasing clinical and post-mortem pathological evidence that COVID-19 continues to have significant adverse health effects long after the acute phase of the infection.

The scope of COVID-19 impacts on recovering patients was reflected in an online survey (Davis *et al.*, 2021). It covered 3762 participants with confirmed or suspected COVID-19 from 56 countries and estimated the presence of 203 symptoms in 10 organ systems. After month 6, fatigue, post-exertional malaise and cognitive dysfunction were the most frequent symptoms. Almost half of the respondents (45.2%) required a reduced work schedule compared to pre-illness, and about a quarter (22.3%) were still not working. Cognitive dysfunction or memory issues were common across all age groups (~88%).

One of the largest cohort studies with the longest follow-up duration reported very well the health consequences of discharged adult patients recovering from COVID-19 (Huang *et al.*, 2021). Fatigue (Rudroff *et al.*, 2020; Ortelli *et al.*, 2021) or muscle weakness, sleep difficulties and anxiety or depression were common, even at 6 months after symptom onset. It appears that long COVID survivors may follow the same convalescent path of previous Canadian SARS survivors, in that though they had good physical recovery from their illness, a significant number (33%) of them reported a significant decrement in mental health 1 year later (Tansey *et al.*, 2007). Whether this is related to the lingering pulmonary diffusion abnormalities and therefore impaired oxygenation and nutritional supply to the brain (up to 3 months after hospital discharge) (Huang *et al.*, 2019; Zhao *et al.*, 2020) is awaiting further investigation. Evidence from the previous SARS pandemic suggests that reduced lung diffusion capacity could persist in 38% of survived SARS patients 15 years after infection (Zhang *et al.*, 2020).

Similar enduring and debilitating symptoms in COVID-19 patients after recovery also were reported from other countries (Chippa *et al.*, 2021; Dewanjee *et al.*, 2021; Garg *et al.*, 2021; Huang *et al.*, 2021; Sisó-Almirall *et al.*, 2021; Wang *et al.*, 2020). Again, neuropsychiatric symptoms were prominent. Anosmia, the 'Brain fog' syndrome, consisting of confusion and cognitive and attention deficits (Asadi-Pooya *et al.*, 2021; Stefano *et al.*, 2021b), fatigue, headaches, pain syndrome, anxiety and depression were all common. Data from Germany and the United Kingdom showed post-COVID-19 neuropsychiatric symptoms in 20% to 70% of patients, lasting months after respiratory symptoms resolved, suggesting that CNS symptoms persist long after the acute infection (Boldrini *et al.*, 2021). If neurodegeneration and new neuropsychiatric disorders are proven to happen in long COVID, it could become a major public health burden (Serrano-Castro *et al.*, 2020).

The term 'long COVID' is used to refer to the lingering or protracted illness, from 4 (Sisó-Almirall *et al.*, 2021) to 12 weeks (Mohamed-Hussein *et al.*, 2021) after the acute illness and during recovery. Other terms were also used, including 'post-acute COVID-19', 'ongoing symptomatic COVID-19', 'chronic COVID-19', 'post COVID-19 syndrome' and 'long-haul COVID-19'. Long COVID could be the consequence of COVID-19 viral injury, stroke, hypoxia, maladaptive or abnormal inflammation, or the persistent presence of SARS-CoV-2, hypoxia-induced mitochondria dysfunction (Stefano *et al.*, 2021b) and other unknown causes (Viszlayová *et al.*, 2021). There is no consensus so far.

Long-term psychological or adverse mental health consequences of COVID-19 has just begun to be recognised. The episodic, ever-changing, quarantine policies around the world in the last two years have resulted in difficulties in travel, shutdowns of country borders in many countries, decrease in social contacts and also making essential or urgent visits of dependent relatives and families impossible. It is difficult to know how much some of the vague neuropsychiatric symptoms are quarantine/isolation related and psychosomatic or post-traumatic in nature.

We reviewed and discussed the fast-accumulating literature on long COVID.

Method

We searched the English language literature, including foreign-language publications with informative abstracts in English, up to December 28th, 2021, using PubMed (https://pubmed.ncbi.nlm.nih.gov), crossing the keywords "COVID-19", "long COVID", "stress", "quarantine" and "isolation" respectively and in turn with the following words: psychiatry, psychosis, psychiatric disorders, depression, bipolar disorders, anxiety disorders, post-traumatic stress disorder, dementia, neurodegeneration, brain circuits, neurotransmitters, psychotropics, brain areas, serotonin (5HT), dopamine (DA), norepinephrine (NE), histamine, sigma receptor, cortisol, glucose metabolism, brain metabolism, psychological, treatment. Manuscripts identified were included in this review after evaluating the quality of the research and relevancy to the various sections of this review. Health statistics were obtained from the World Health Organization (WHO) and Centers for Disease Control and Prevention, USA (CDC) websites, accessed on December 28 2021.

Results

The renin–angiotensin aldosterone system (RAAS)

The dipeptidyl carboxypeptidase angiotensin-converting enzyme (ACE) and the mono-carboxypeptidase angiotensin-converting enzyme 2 (ACE2)

Regulatory peptides control various physiological processes in the human body. Active peptides are degraded by peptidases after performing their functions. Two amino peptidases enzymes of common ancestry but with opposing actions on the renin–angiotensin aldosterone system (RAAS), the dipeptidyl carboxypeptidase ACE and the mono-carboxypeptidase ACE2, work together to regulate many important physiological processes.

ACE cleaves the decapeptide angiotensin-1 (AngI) into the potent vasoconstrictor angiotensin-2 (AngII). AngII binds to two major receptors, AT1R (angiotensin type 1receptor) and AT2R (angiotensin type 2 receptor) (Carey, 2005). Activation of AT1R produces vasoconstriction, pro-fibrotic and pro-inflammatory

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effects, all of which are important in SARS-CoV-2 infection lung injury (Simões e Silva *et al.*, 2013). The importance of AT1 in the regulation of the cerebrovascular system is also being recognised. The development of biased AT1R agonists has led to new therapeutic strategies to target detrimental effects of AT1R activation (Delaitre *et al.*, 2021).

Activation of the less investigated AT2 receptor may produce opposite actions, antagonising the AT1R effects (Porrello *et al.*, 2009), especially concerning the growth- and differentiation-modulating actions of ANG II. Its effects on the regulation of cell growth, differentiation and apoptosis, may have a role in neurodevelopment and regeneration (Stoll & Unger, 2001).

The other peptidase ACE2 converts AngII into Ang-(1-7). Ang-(1-7) acts on the G protein-coupled Mas receptors (MasR) and produces vasodilatation. It is anti-apoptotic and anti-proliferative and anti-fibrotic. Thus, ACE2 counteracts actions of ACE, being antihypertensive and cardioprotective, and it reduces lung inflammation (Saponaro *et al.*, 2020).

Thus, there are two axes working together: one is the vasoconstrictive axis, renin/ACE/angiotensin II/angiotensin II receptor type 1 (AT1R), and the other is the opposing vasorelaxant axis, ACE2/angiotensin-(1-7)/Mas receptor (MasR) (Povlsen *et al.*, 2020). The two enzymes, ACE and ACE2, work together in concert and maintain homeostasis, not only in maintaining blood pressure, fluid and salt balance, but in many other important physiological processes such as the brain, kidney and heart, many of which are beginning to be discovered. For example, ACE2 may have both positive and negative roles in cancer therapies.

There are two forms of ACE2 (Batlle *et al.*, 2020). The full-length mACE2s are located on human cell membranes and are the binding sites for the spike (S) proteins on the envelope of the virus. These S proteins are cleaved into S1 and S2 subunits. The S1 protein/receptor binding interaction will initiate the infection (Samavati & Uhal, 2020). The other soluble form, sACE2, goes into the circulation (Batlle *et al.,* 2020) in low concentrations. The ratio between the anchored and the soluble forms has been suggested to be related to the severity of symptoms (Scialo *et al.*, 2020). Both membrane-bound and soluble ACE2 degrade angiotensin II to angiotensin-(1-7). Consequently, ACE2 receptors limit several detrimental effects resulting from binding of angiotensin II to AT1 receptors, which include vasoconstriction, enhanced inflammation and thrombosis. The increased generation of angiotensin-(1-7) also triggers counter-regulatory protective effects through binding to G protein-coupled Mas receptors.

As stated, the SARS-CoV-2 virus gains entry to the human body through ACE2 (Beyerstedt *et al.*, 2021; Tai *et al.*, 2020). SARS-CoV-2 has a spike protein (S protein) binding domain that is nearly identical to the earlier SARS virus, but the binding affinity for ACE2 is much higher, explaining its high virulence in comparison (Wrapp *et al.*, 2020). Preclinical data suggest ACE2 might be downregulated after SARS-CoV-2 binding; this ACE2 down-regulation induced by the virus may be especially detrimental in people of old age, suffering from hypertension, diabetes and cardiovascular disease, all of whom already shared baseline ACE2 deficiency. As enhanced and unopposed angiotensin II via the ACE→Angiotensin II→AT1 receptor axis may increase pulmonary inflammation and coagulation (Verdecchia *et al.*, 2020), treatments that increase ACE2 may prevent cardiopulmonary injury. Metformin, by enhancing ACE2 expression, may offer cardiopulmonary protection (Malhotra *et al.*, 2020) and possibly neuroprotection in COVID-19 (Samuel *et al.*, 2021).

Expression of ACE2 also occurred in other organs, highest in the small intestines, high in the salivary glands, testicular, kidney, thyroid and adipose tissues, but lower in the spleen, muscle, pituitary, skin and the brain (Han *et al.*, 2020; Li *et al.*, 2020; Song *et al.*, 2020). High expression of ACE2 was found in the olfactory bulb areas in the mouse (Chen *et al.*, 2021). Though ACE2 is lower in the brain compared to other organs and tissues as described above, it is highly expressed in the choroid plexus and paraventricular nuclei of the thalamus. Nuclear expression of ACE2 was found in neuronal as well as non-neuron cells, including astrocytes, oligodendrocytes and endothelial cells in the human middle temporal gyrus and posterior cingulate cortex.

The high ACE2 expression in the salivary glands and the intestine implies the common infection entry site and the corresponding salivary test for the infection. The high rate of mutations in corona viruses may change their specificity and/or binding affinity to different receptor sites (Scialo *et al.*, 2020). Middle East respiratory syndrome-related coronavirus (MERS-CoV), for example, binds to dipeptidyl peptidase-4 (DPP4) (Letko *et al.*, 2020) which plays an important role in glucose metabolism. Glucose metabolism is known to play an important role in brain functions (see section on brain glucose metabolism below).

The SARS-CoV-2 causes a disruption in ACE/ACE2 balance (Lubbe *et al.*, 2020). A high ACE/ACE2 ratio may be detrimental in the COVID-19 infection (Pagliaro & Penna, 2020), and dysregulation of ACE/ACE2 equilibrium by SARS-CoV-2 is now being investigated for its relationship to long-term neurological complications (Haghighi *et al.*, 2020). RAAS activation may lead to COVID-19 progression, especially in patients with comorbidities, such as hypertension, diabetes mellitus and cardiovascular disease (Beyerstedt *et al.*, 2021).

The COVID-19 virus (SARS-CoV-2) entrance into the brain

High prevalence of neurological symptoms in patients at both the acute stage of COVID-19 and in long COVID suggests the extensive damages of SARS-CoV-2 on CNS tissues (Pezzini and Padovani 2020; Rogers *et al.*, 2021). ^{18}F-FDG PET study of brain metabolism in COVID-19 (Rodríguez-Alfonso *et al.*, 2021) also revealed hypometabolism in areas such as the olfactory/rectus gyrus, amygdala, hippocampus, parahippocampus, cingulate cortex, pre-/post-central gyrus, thalamus/hypothalamus, cerebellum, pons and medulla. Findings reinforce the hypotheses of SARS-CoV-2 neurotropism involving multiple brain structures (Guedj *et al.*, 2021a, b; Sollini *et al.*, 2021).

Loss of smell is prominent in SARS-CoV-2 infection. Using real-time quantitative PCR (rt-qPCR), and in-situ hybridisation to detect the SARS-CoV-2 RNA plus immunohistochemistry and electron microscopy, viral RNA was found in the olfactory mucosa, and then the uvula and the medulla oblongata (Meinhardt *et al.*, 2021). Using this same approach in a mouse model, Bilinska *et al.* (2020) showed that ACE2 is expressed in sustentacular cells of the olfactory epithelium and increased with old age. Thus, SARS-CoV-2 may cross the neural-mucosal interface in the olfactory mucosa, enter the olfactory neurons and then migrate up to the medulla oblongata (Banerjee & Viswanath, 2020; Mahalaxmi *et al.*, 2021). The respiratory and cardiovascular control centres are in the medulla oblongata, and SARS-CoV-2 attack on these neurons may contribute to the respiratory and cardiovascular symptoms. Nasal swab thus is a convenient SARS-CoV-2 detection test (Butowt & Bilinska, 2020). Other possible viral entry points less discussed include the vagal and trigeminal

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nerve and the compromised blood–brain barrier (BBB) with neuroinflammation (Boldrini *et al.*, 2021).

Long COVID psychiatric disorders

Long COVID symptoms of a psychiatric nature have been reported globally. While COVID-19 was regarded as a pulmonary respiratory viral disease in the early stage like SARS, its involvement of other organs like the heart, liver, kidney and the CNS was soon recognised. In Germany and the United Kingdom, post-COVID neuropsychiatric symptoms were reported from 20% to a high of 70% (Woo *et al.*, 2020; Meinhardt *et al.*, 2021).

One of the largest and longest studies was from China (Huang *et al.*, 2021). The study involved 1733 of 2469 discharged patients with COVID-19. Patients had a median age of 57 and 52% were men. The median follow-up time after symptom onset was 186 days. Fatigue or muscle weakness (63%) and sleep difficulties (26%) were common, followed by anxiety or depression (23%). Median 6-min walking distance less than the lower limit of the patient's normal range was 24%. Fatigue or muscle weakness, sleep difficulties and anxiety or depression continued to even 6 months after symptom onset. Being a woman and severity of illness were risk factors for persistent psychological symptoms.

The Chinese findings were echoed by Schou *et al.* (2021). They reviewed 66 studies from Asia, Europe and North America, covering discharged patients up to 7 months. It showed that depression, post-traumatic stress disorder (PTSD), fatigue and sleep disturbances were common. In 47 studies, the incidence of depression and anxiety ranged from no indication of depression or anxiety to >30% at follow-up (up to 199 days after discharge). Risk factors, similar to the Chinese study, were found to be disease severity, duration of symptoms, and the female sex.

The high incidence of insomnia reported by Schou *et al.* (2021) and Huang *et al.* (2021) was confirmed by Li *et al.* (2021b). Their report documented about 37% of patients with COVID-19 had insomnia in the early stage which rose to 41.8% in the later stage.

Taquet *et al.* (2021) analysed US electronic data, covering 62,354 patients from 54 health-care organisations diagnosed with COVID-19. They found that the most common psychiatric diagnosis after COVID-19 diagnosis was anxiety disorder (12.8%), followed by mood disorders (9.9%). Psychotic disorder was rare in the 14–90 days after COVID-19 diagnosis (0.1%). Having a diagnosis of psychiatric disorder in the year before the COVID-19 outbreak was associated with a 65% increased risk of COVID-19. In patients with no previous psychiatric history, a diagnosis of COVID-19 was associated with increased incidence of a first psychiatric diagnosis in the following 14–90 days. The incidence of any psychiatric diagnosis in the 14–90 days after COVID-19 diagnosis was 18.1%, in which 5.8% were a first diagnosis.

A Spanish report (Méndez *et al.*, 2021) covered a total of 179 patients at 2 months and 171 (95.5% retention rate) at 12 months. Screening was by telephone, using questionnaires, self-reporting and screening instruments. At 12 months, the prominent symptoms included fatigue (48.5%), memory complaints (32.2%), arthromyalgia (26.9%), dyspnoea (25.7%), headache (15.8%). Neurocognitive dysfunction and psychiatric morbidity were found in 46.8% and 45% of patients, respectively. Psychiatric morbidity was at a total of 45%, including anxiety (35.1%), depression (32.2%) and PTSD (24.6%).

In summary, psychiatric symptoms are prominent in long COVID and are similar across different countries and cultures. Depression, anxiety, fatigue, insomnia, headache, somatic pain and PTSD were the common neuropsychiatric disorders, while psychosis was rare.

Depression and anxiety are known to be associated with cerebral vascular accidents, but not psychosis. Post-stroke depression (PSD) could occur in up to about 1/3 of the patients (Ahmed *et al.*, 2020; Das & Rajanikant, 2018; Lee *et al.*, 2007, 2008; Medeiros *et al.*, 2020; Robinson & Jorge, 2016; Sharma *et al.*, 2020). Other reports also recorded PSD prevalence at 31.1% (Schöttke & Giabbiconi, 2015) and 36% (Ahmed *et al.*, 2020), with post-stroke anxiety (PSA) at 20.4% and 32%. Lifetime depression could not predict the emergence of PSD but lifetime anxiety was a good predictor of PSA (Schöttke & Giabbiconi, 2015). Thus, a significant percentage of neuropsychiatric symptoms in long COVID could be the result of stroke and other cerebral vascular damages caused by the SARS-CoV-2 in the acute stage.

Controversial infection and mortality rate in COVID-19 patients with pre-existing mental disorders

Data on the mortality of patients with pre-existing mental disorders in COVID-19 have been contradictory. There are reports and data supporting both lower and higher morbidity and mortality rates in this population in COVID-19 and long COVID.

A lower incidence of symptomatic forms of COVID-19 among patients (4%) than among the clinical staff (14%) was observed in Sainte-Anne hospital, a Paris psychiatric hospital (Plaze *et al.*, 2020, 2021). This contradicts another report by Fond *et al.* (2021), who reported that schizophrenic patients admitted to acute care hospitals in Marseille, France, had much higher mortality compared to the non-SCZ patients (26.7% vs. 8.7%). In examining the data in detail, it became obvious that the report by Fond *et al.* (2021) had a highly skewed/sample. There were 15 schizophrenic patients only, out of a total of 1092 patients studied. 100% of the schizophrenic patients who died were institutionalised. Health conditions of the schizophrenic patients versus the other patients were also not comparable, with smokers (33.3% vs. 11.1%), suffering from cancers (20.0% vs. 5.5%) and respiratory comorbidities (26.7% vs. 4.9%).

Higher infection and mortality rate in schizophrenic patients and patients with severe mental disorders in other countries were also reported, including Israel (Tzur Bitan *et al.*, 2021), Spain (Garcia-Ribera *et al.*, 2021), Italy (Barlati *et al.*, 2021), Canada (Zhand & Joober, 2021), the United Kingdom (Hassan *et al.*, 2021) and USA (Teixeira *et al.*, 2021; Wang *et al.*, 2021b).

Karaoulanis and Christodoulou (2021) reviewed the literature, with seven studies meeting their criteria. They found a statistically significant effect for higher infection rates and a strong statistically significant effect for higher mortality rates in patients with schizophrenia.

On the other hand, there are reports contradicting the high infection and mortality rate observations. Apart from the report by Plaze *et al.* (2020, 2021), Rivas-Ramírez *et al.* (2021) from Mexico reported their observation on 198 patients with psychiatric and neurological disorders and hospitalised in Puebla. They found the mortality rate (5.75%) was lower than that reported in Mexico (11.28–13.55%), which was higher than the worldwide average of 2.95–4.98%.

Moga *et al.* (2021) studied 101 schizophrenic patients tested positive for COVID-19 and treated with oral antipsychotics in a long-term facility in Brasov, Romania, between April 2020 and April 2021. They found that schizophrenics on antipsychotic treatment, when compared to 101 individuals without schizophrenia in

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the same hospital, showed a lower risk of SARS-CoV-2 severe infection and a likely better COVID-19 prognosis.

It may be difficult to exclude the confounding factors such as pre-morbid health conditions, comorbidities and availability/accessibility/quality of care for patients with mental disorders, institutionalised versus acute care differences, etc., in different cultures and different countries. This likely will remain controversial until data becomes available from better design studies with ample case numbers. For now, whether patients with severe mental disorders are more vulnerable to COVID-19 or not, further studies will be useful to reveal the neurobiology and interaction between the virus and the CNS.

Neurological complications

The neurological complications/consequences in long COVID can be largely grouped into three major categories:

1. Direct viral invasion of the brain neuronal and vascular structures and its consequences
2. Abnormal immune and inflammatory reaction such as 'cytokine storm' and its long-term consequences
3. Neurological consequences secondary to viral pulmonary and associated systemic disease including systemic inflammation, sepsis and multi-organ failure, resulting in hypoxic brain damage, encephalopathy and stroke, Guillain–Barré syndrome (GBS), acute haemorrhagic necrotising encephalopathy (ANE) and acute disseminated encephalomyelitis (ADEM) (Pezzini & Padovani, 2020; Ryoo *et al.*, 2020).

Pilotto *et al.* (2021) in Italy studied 208 non-neurological patients hospitalised for COVID-19 disease and evaluated 165 survivors at 6 months follow-up, using a structured standardised clinical protocol. They found that these patients displayed a wide array of symptoms, including fatigue (34%), memory/attention (31%) and sleep disorders (30%). Neurological abnormalities were found in 40 % of patients, with hyposmia at 18.0%, cognitive deficits at 17.5%, postural tremor at 13.8% and subtle motor/sensory deficits at 7.6%. Older age, pre-morbid comorbidities and severity of COVID-19 were independent predictors of neurological manifestations. Some motor symptoms however may take longer to develop (Otero-Losada *et al.*, 2020).

A report from Saudi Arabia covered 79 patients infected with SARS-CoV-2 and found a high incidence of stroke. The commonest neurological signs and symptoms were altered level of consciousness (45.9%), dizziness (11.5%) and focal neurological deficit (10.4%). Acute ischaemic stroke was seen in 18 of the 79 patients. Diabetic patients were 4 times more at risk to develop stroke while patients with respiratory failure were 21 times more likely to have a stroke (Tawakul *et al.*, 2021).

A systematic review by Collantes *et al.* (2021) covering 403 articles and 49 studies, with a total of 6,335 confirmed COVID-19 cases, reported headache, dizziness, nausea and vomiting, confusion and myalgia vascular disorders, encephalopathy, encephalitis, oculomotor nerve palsy, isolated sudden-onset anosmia, Guillain–Barré syndrome and Miller-Fisher syndrome. Similar wide spectrum of COVID-19 neurological was also summarised by others (Delorme *et al.*, 2020; Paterson *et al.*, 2020).

Guillain–Barré syndrome (GBS) and its variants, dysfunction of taste and smell, and muscle injury are examples of peripheral nervous system (PNS) involvement. Hemorrhagic and ischaemic stroke, encephalitis, meningitis, encephalopathy (Kas *et al.*, 2021) ADEM, endothelialitis and venous sinus thrombosis are examples of COVID-19 CNS involvement. Thus, COVID-19 poses a large-scale threat to the whole nervous system, acutely and in the long term as well (Jha *et al.*, 2021).

There were other less known long COVID symptoms of neurological nature. For example, strange disturbing internal vibration and tremor sensation was reported in newspaper (Wall Street Journal Dec 21, 2021). It is unknown if they were caused by autonomic nervous system damages as suggested by some.

In summary, about 30% of hospitalised COVID-19 patients developed neurological symptoms, including ataxia, agitation, delirium, headache, cerebrovascular disease, epilepsy, loss of taste and smell and diffuse corticospinal tract signs (Mao *et al.*, 2020; Helms *et al.*, 2020). While the area of the brain first affected by the virus may depend on the distribution of the ACE2 receptors, the neuropsychiatric symptoms in long COVID (Jozuka *et al.*, 2021) are likely secondary to neurological damages from neuroinflammation, stroke, hypoxia and other causes yet to be discovered.

Age effect

Although all patients infected with COVID-19 showed neuroinflammatory changes, those with severe infections and particularly elderly patients seemed more likely to suffer from 'cytokine storm', referring to the excessive release of the pro-inflammatory cytokines (IL) interleukin-1,-6,-10 and tumour necrosis factor-alpha (TNF) (Garber *et al.*, 2018). In the brain, these cytokines activate the microglia and astrocytes to release more inflammatory cytokines in addition to neurotoxins and complement proteins (Vasek *et al.*, 2016; Liddelow *et al.*, 2017; Xu *et al.*, 2016). These changes contribute to excitotoxicity and long-term neuronal damage and may start a neurodegenerative process. Inflammatory neuropsychiatric disorders have been previously reviewed in more detail (Leonard & Wegener, 2020; Myint 2013; Tang *et al.*, 2021).

The expression of the neuropsychiatric symptoms of long COVID differs in different age groups. Delirium from hypoxia and metabolic complications are more likely in the vulnerable aged patients and those with dementia (Butler & Barrientos, 2020; Garg, 2020; Toniolo *et al.*, 2021), whereas encephalopathy and encephalitis, together with acute neuropsychiatric symptoms, were more likely to occur in younger patients (Varatharaj *et al.*, 2020). Severe fatigue is a common feature in most age groups. Elevated creatine kinase indicates severe myopathy which accounts for the debilitating fatigue and myalgia (Garg, 2020; Orsucci *et al.*, 2021).

Long COVID neurodegeneration

Normal CNS neuronal mitochondrial function requires high oxygen levels. SARS-CoV-2 virus can hijack mitochondrial function to cause long-lasting metabolic problems. Coupled with the inflammatory process discussed above, neurodegeneration or exacerbation of pre-existing dementia may begin (ElBini Dhouib, 2021; Ge *et al.*, 2021; Roman *et al.*, 2021; Stefano *et al.*, 2021a, b; Stuckey *et al.*, 2021; Tang *et al.*, 2017, 2021).

COVID-19 neuroinflammation may lead to decreased neurogenesis, as shown in a reduction in the size of the hippocampus, dentate gyrus and fewer granule neurons and neural progenitor cells (Mahajan *et al.*, 2018; Boldrini *et al.*, 2019; Klein *et al.*, 2021). It is already well-established that cognitive dysfunction may persist for many months after patients have apparently recovered from COVID-19 (Troyer *et al.*, 2020; Zhou *et al.*, 2020). This points to the possibility that there is long-term damage to the

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neuronal networks initiated by the virus and extended and sustained by chronic neuroinflammation and the disruption of brain metabolic homeostasis. Stroke, which is common in COVID-19, is also known to be associated with the development of dementia (Kalaria *et al.*, 2016) which could be up to 18.4 %, 1 year after stroke (Craig *et al.*, 2021) or 28.5% mostly at 6 months after stroke (Hénon *et al.*, 2001). Impaired glucose tolerance and asymptomatic hyperglycaemia are common in the elderly (Wargny *et al.*, 2021), and the role of brain glucose metabolism in depression and neurodegeneration has been studied (Leonard & Wegener, 2020).

COVID-19, diabetes and brain energy metabolism

Diabetes and obesity are cofactors which are frequently associated with vulnerability to SARS-CoV-2 infection and death.

A report summarised 9 studies in China, involving a total of 1070 patients with diabetes, out of 8807 COVID-19 case. It showed that comorbid diabetes was associated with an increased risk of disease severity or death (Guo *et al.*, 2020). Another study from China demonstrated that elevated blood glucose levels led to the rapid progression and high death rates, based on data obtained from 2433 COVID-19 patients (Wang *et al.*, 2021). It was reported that in patients of 60 years or older, the elevated blood glucose levels correlated with the respiratory rate, fever, blood CRP, lactic dehydrogenase, low serum albumin and low lymphocyte counts; these were significant factors in the progression and the severity of the disease. In addition, elevated glucose, fibrinogen and creatine kinase levels were significant risk factors for death. The authors concluded that patients with elevated blood glucose were 58% more likely to progress to hospitalisation and 3.22 times more likely to die from the infection.

Another report showed that in 952 patients with pre-existing type 2 diabetes, well-controlled blood glucose was associated with markedly lower mortality compared to individuals with poorly controlled blood glucose (Zhu *et al.*, 2020a, b). Similar findings were reported by others (Aggarwal *et al.*, 2020; Kumar *et al.*, 2020; Singh & Singh, 2020; Wang *et al.*, 2020b, c; Zhang *et al.*, 2020b) and even in non-diabetics (Singh & Singh, 2020b; Lin *et al.*, 2021).

In a study involving 5700 patients hospitalised in the New York City area, the most common comorbidities were hypertension, obesity and diabetes. Of the patients who died, those with diabetes were more likely to have received invasive mechanical ventilation or care in the ICU compared with those who did not have diabetes (Richardson *et al.*, 2020).

This suggests that brain glucose metabolism might be a factor in the spread of the SARS-CoV-2 virus in the brain (Morand *et al.*, 2021).

SARS-CoV-2 infection induces the expression of glucose transporters and enhances the uptake of glucose into the tissues it infects. It also increases the activity of the glycolytic pathway enzymes. These changes in glucose metabolism have been shown to be a feature of other types of viruses such as the influenza virus (Reading *et al.*, 1998) and more recently for SARS-CoV-2 (Codo *et al.*, 2020). There is experimental and clinical evidence that significant change in brain glucose metabolism is a prelude to neurodegenerative changes (Leonard & Wegener, 2020), a situation that is enhanced by the increased energy demands of the activated microglia (Pailla *et al.*, 2001) and, in the case of chronic major depression, by insulin receptor desensitisation, oxidative stress and hypercortisolemia.

One of the consequences of inflammation is insulin and glucocorticoid receptor resistance (Miller *et al.*, 2008; Shelton & Miller, 2010; Leonard, 2018). Functional insulin receptor insensitivity may occur as a consequence of stress-induced cortisol elevation and decrease the insulin-mediated expression of the GLUT 4 glucose transporter. Increase in TNF-alpha also contributes to the desensitisation of the insulin receptors (Solomon *et al.*, 1997). These changes result in a reduction of glucose availability to peripheral tissues and the brain (Weinstein *et al.*, 1995). Such changes would be particularly relevant following the recovery from the acute stage while the inflammation remains.

The brain is a unique organ which requires glucose as the main energy source. The glucose transporters located on the BBB are vital to ensuring that sufficient glucose is available for optimal brain activity. GLUT1 is produced in brain microvasculature and ensures glucose transport across the blood–brain barrier (BBB) (Jurcovicova, 2014). Once it enters the brain, glucose is further transported by GLUT 1 and GLUT 3 to astrocytes and neurons, respectively (Freemerman *et al.*, 2014; Wang *et al.*, 2019).

Glucose, glutamate, lactate, fatty acid and amino acid transporters are involved in the regulation of macrophage polarisation. Metabolite transporters required for the uptake of metabolites (such as glucose, glutamate, fatty acid and amino acids) are important regulators of macrophage polarisation. They may represent novel drug targets for the treatment of disorders in which macrophages play a part, such as seen in long COVID (Cheng *et al.*, 2021).

Logette *et al.* (2021) provided evidence that elevated glucose in the pulmonary airway surface liquid facilitates the major entry point for the virus. This breaks down the primary innate antiviral defence in the lungs and facilitates the viral infection, stimulates the release of pro-inflammatory cytokines and causing the acute respiratory distress syndrome. In diabetes, there is endothelial dysfunction or leaky endothelium, resulting in hypercoagulation, thrombosis and vascular complications. SARS-CoV-2 can gain entry into endothelial cells via the endothelial cell surface ACE2 receptors (Varghese *et al.*, 2021). Cumulative evidence suggests that a glycolytic trait can influence the course of the disease by promoting viral tropism and negatively modulate the immune response and functional integrity of tissues, including endothelium. Finally, elevated blood glucose acts synergistically with COVID-19 to inactivate ACE2 which dysregulates glycaemic control in all those cell types that are infected by the virus.

Once SARS-Cov-2 virus enters the cell, like other viruses, it switches the cellular energy metabolism from the aerobic to the anaerobic state thereby ensuring ATP synthesis provided by glycolysis without the requirement of molecular oxygen. At the same time, glucose transport is increased and coupled with the increased activity of hexokinase and lactate dehydrogenase (Fontaine *et al.*, 2015; Ritter *et al.*, 2010; Sanchez & Lagunoff, 2015). The replication of COVID-19 is entirely dependent on ATP provided by the elevated glucose (Codo *et al.*, 2020). While the data supporting these mechanisms are largely dependent on in vitro studies, there is clinical evidence demonstrating that elevated blood glucose explains the variance and the severity of the COVID-19 infection as discussed above. Epidemiological, clinical and in-depth experimental studies have identified an increase in blood glucose as a key factor in the spread of the virus throughout the body including the brain. Controlling the blood glucose level in infected patients could therefore be a practical way to reduce the severity of the disease and contribute to a reduction in the death rate. It could form the basis for treatment with anti-hyperglycaemic drugs such as

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metformin, supported by a low carbohydrate diet or ketone diet as an alternative energy source to glucose. More extensive and detailed studies are essential to validate, or invalidate, this hypothesis.

Psychotropics, sigma-1 receptor and antihistamines in long COVID

Whether to continue on psychotropics in patients suffering from long COVID is an important clinical decision. In this regard, the sporadic reports on the protective action of antidepressants and antipsychotics on COVID-19 patients suggest that this is an important area for further investigation.

Antidepressant drug's protective effect on long COVID

In Missouri, USA, 115 outpatients completed a randomised trial. Patients treated with fluvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over 15 days. Clinical deterioration occurred in none of the 80 patients in the fluvoxamine group but in 6 of 72 patients in the placebo group (Lenze *et al*., 2020).

In a cell culture model to test small molecule acting on the homeostasis of the endolysosomal host-pathogen interface, fluoxetine impaired endolysosomal acidification and the accumulation of cholesterol within the endosomes. Fluoxetine, an inhibitor of acid sphingomyelinase (FIASMA), was found to inhibit the entry and propagation of SARS-CoV-2. It also showed potent antiviral activity against two influenza A virus subtypes. The FIASMAs amiodarone and imipramine also showed similar effect. Thus, the FIASMA group of small molecules may offer opportunities for the development of host-directed therapy to counteract enveloped viruses, including SARS-CoV-2 (Schloer *et al*., 2020).

There are earlier reports of anti-microbial/anti-parasitic (Hewlett *et al*., 1985) or cytotoxic effect of antidepressant drugs. Tricyclic antidepressant drugs, such as clomipramine and imipramine, were reported to be cytotoxic against human protozoan parasites Leishmania donovani and Leishmania major. The mechanism of action was hypothesised to cause cellular death by non-specific mechanisms, probably involving a general increase in membrane permeability (Zilberstein & Dwyer, 1984; Zilberstein *et al*., 1990).

Amitriptyline was also reported to be antibacterial (against 254 strains, with 72 gram-positive and 181 gram-negative), anti-fungal and anti-virulent strains of Salmonella typhimurium. It inhibited both Cryptococcus and *Candida albicans* as well (Mandal *et al*., 2010). In a pre- and post-infection H5N1-infection mouse model, significant alleviation of acute lung injury by amitriptyline was reported (Huang *et al*., 2020). Imipramine was reported to alter the sterol profile in Leishmania amazonensis and increases its sensitivity to miconazole (Andrade-Neto *et al*., 2016). In Leishmaniasis, clomipramine, in μM concentrations, stimulated nitric oxide production in host macrophages and led to mitochondrial depolarisation in the parasites. Coupled with the inhibition of trypanothione reductase induced strong oxidative stress in the parasites, it induced programmed cell death (da Silva Rodrigues *et al*., 2019).

Microglia detect and subsequently clear microbial pathogens and injured tissue. They adapt their phenotype depending on whether they participate in acute defence against pathogenic organisms ('M1'-phenotype) or in clearing damaged tissues and performing repair activities ('M2'-phenotype). Stimulation of pattern recognition receptors by viruses or vaccines, presence of bacterial membrane components such as bacterial lipopolysaccharides (LPS), promotes M1 polarisation. A less known action of antidepressant treatment and agents, electroconvulsive shock (ECT), and vagus nerve stimulation (VNS), inhibit LPS-induced microglia/macrophage M1 polarisation and inflammation (Kalkman & Feuerbach, 2016). How much the protective effect of antidepressant agents against COVID-19 and long COVID is related to their inhibition of microglial M1 polarisation would require further research.

An important issue which needs to be resolved is that in many of these in vitro experiments, high concentrations of antidepressant drugs (in mM and high μM) were used. A concentration of 30 mg per Kg body weight of amitriptyline (Zilberstein & Dwyer, 1984) is equivalent to 1500 mg dosage. This dosage is fatal in human.

Antipsychotic's protective effect in long COVID

Canal-Rivero *et al*. (2021) found patients with severe mental disorders and good compliance on antipsychotics were less likely to contract COVID-19. They also had better outcomes following infection, than the general population.

In Romania, Moga *et al*. (2021) reported no deaths in their patients with schizophrenia. The patient group had a higher number of cases with pulmonary and metabolic comorbidities but there were fewer severe cases compared to the control group. Some markers of inflammation (CRP and fibrinogen) were significantly lower in the patients also.

These reports led to the hypothesis that psychotropic drugs have a prophylactic action against SARS-CoV-2 or have an antiviral action.

Some psychotropics have indeed been investigated for their anti-microbe properties.

Chlorpromazine (CPZ) was claimed to be antiviral (Hewlett *et al*., 1997; Plaze *et al*., 2020, 2021), maybe via the inhibition of clathrin-mediated endocytosis (Pho *et al*., 2000). Inhibition of HIV infection of H9 cells by chlorpromazine derivatives was also reported (Hewlett *et al*., 1997). Recent in vitro studies have reported that CPZ exhibits anti-MERS-CoV and anti-SARS-CoV-1 activity in monkey VeroE6 cells, with an IC_{50} (half maximal inhibitory concentration) of 8.2 μm, half maximal cytotoxic concentration (CC_{50}) of 13.5 μm. In human A549-ACE2 cells, CPZ was found to have anti-SARS-CoV-2 activity, with IC_{50} of 11.3 μm and CC_{50} of 23.1 μm. However, similar to the case of antidepressant drugs, such high drug concentration in the μM range is unlikely to be achieved clinically. There were arguments that a high chlorpromazine concentration could be achieved in the human saliva and in the brain (Tsuneizumi *et al*., 1992; Wiesel & Alfredsson, 1976), much higher than in the plasma (May *et al*., 1978). However, this requires further validation.

Other studies reported the immunomodulatory effects of CPZ, such as increasing blood levels of IgM (Zucker *et al*., 1990). In the mouse septic shock model, CPZ caused a decrease in IL-2, IL-4, IFN alpha, TNF and GM-CSF pro-inflammatory cytokines, an increase in IL-10 and anti-inflammatory cytokine (Bertini *et al*., 1993; Mengozzi *et al*., 1994; Tarazona *et al*., 1995). In a recent meta-analysis of 12 studies, consisting of 961 patients with schizophrenia *vs* 729 controls, on the impact of antipsychotics on the production of serum interleukin-6 (IL-6) (Kappelmann *et al*., 2021) a pro-inflammatory cytokine, it was found that antipsychotic treatment was associated with a decrease of IL-6 in patients (Zhou *et al*., 2021).

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For other antipsychotics, trifluoperazine was also found to reduce inflammatory response by suppressing pro-inflammatory cytokines in mice (Park *et al.*, 2019) while a transcriptomic analysis revealed that aripiprazole could revert effects induced by COVID-19 on gene expression in patients (Crespo-Facorro *et al.*, 2021; Dratcu & Boland, 2021).

May *et al.* (2020), on the other hand, cautioned the use of antipsychotics in COVID-19, citing the anti-inflammatory action as risky in viral infections.

Sigma-1 receptor

The endoplasmic reticulum (ER) resident multi-functional protein sigma-1 receptor is an essential inhibitor of cytokine production (Rosen *et al.*, 2019). Sigma-1 receptors play crucial roles in cellular signal transduction and interact with receptors, ion channels, lipids and kinases. Changes in their functions and expression may lead to various neuropsychiatric disorders, including affective and cognitive disorders (Salaciak & Pytka, 2021), pain (Gris *et al.*, 2015; Ruiz-Cantero *et al.*, 2021), neurodegeneration and neuro-restoration (Ruscher & Wieloch, 2015), addiction and DA function (Hong *et al.*, 2017), memory impairments (Sałaciak and Pytka 2021). When stimulated by ligands or undergoing prolonged stress, sigma-1 receptors translocate from the mitochondrion-associated ER membrane to the ER reticular network and plasma membrane to regulate a variety of functional proteins such as ion channels, receptors and kinases. Sigma-1 receptors thus serve as inter-organelle signalling modulators and coordinators locally at the mitochondrion-associated ER membrane and remotely at the plasmalemma/plasma membrane (Su *et al.*, 2010, 2016).

Sigma-1 receptors modulate a number of neurotransmitters and neurotransmission processes, including glutamate-NMDA, 5HT, NE and DA and BDNF signalling (Skuza, 2012), pain (Sánchez-Fernández *et al.*, 2017) neuroplasticity, neuroinflammation (Kourrich *et al.*, 2012; Jerčić *et al.*, 2019; Jia *et al.*, 2018) and neurorepair (Lisak *et al.*, 2020).

Some psychoactive drugs show high to moderate affinity for sigma-1 receptors, including haloperidol, fluvoxamine and sertraline, cocaine and methamphetamine, whereas phenytoin allosterically modulates sigma-1 receptors (Cobos *et al.*, 2008). We have previously reported the affinity of DA agents to brain sigma receptors and the decrease of sigma receptors in post-mortem schizophrenia brains, implying that sigma receptors may play a role in psychiatric disorders (Helmeste *et al.*, 1996a, b, 1997, 1999; Tang *et al.*, 1997). The decrease in sigma-1 receptor density in mental disorders has also been observed by other research groups (Reynolds *et al.*, 1991; Weissman *et al.*, 1991). What needs to be determined is whether this is a result of drug treatment or whether reduced sigma receptor numbers are also consistently seen in drug-naïve subjects. Considering that knockdown/knockout of sigma-1 receptors reduces SARS-CoV-2 replication, we also need to know if reduced sigma-1 receptor expression in schizophrenic patients makes these subjects less sensitive to SARS-CoV-2 infection (Brimson *et al.*, 2021; Gordon *et al.*, 2020; Hashimoto, 2021). Note however that sigma-1 receptor agonists stimulate brain-derived neurotrophic factor (BDNF) levels in the brain (Dalwadi *et al.*, 2021; Hashimoto, 2013) and may be useful in treating COVID-19 infection irrespective of their effects on viral replication (Hashimoto, 2021).

Also important is whether the reduced sigma-1 receptor number seen in schizophrenic patient brain is likewise reduced in peripheral body tissues of the same subjects. Besides being expressed in the brain, sigma-1 receptors are widely expressed in the lung, liver, adrenal glands, testis, kidney and heart (Abdullah *et al.*, 2018; Dalwadi *et al.*, 2021; Hashimoto, 2013; Lever *et al.*, 2015; Patone *et al.*, 2021; Shen *et al.*, 2017; Su *et al.*, 2016; Vela, 2020).

As a chaperone protein, the sigma-1 receptor does not appear to exhibit biological functions independent of other protein partners (Jia *et al.*, 2018). However, cardiac dysfunction is seen in sigma-1 receptor knockout mice and is associated with impaired mitochondrial dynamics and bioenergetics (Abdullah *et al.*, 2018). Considering that myocarditis has been reported in a small number of younger patients after COVID-19 vaccination or infection (Patone *et al.*, 2021), would sigma-1 receptor levels in these subjects predict or predispose these subjects to certain types of treatment? Lung tissue also expresses sigma-1 receptors (Lever *et al.*, 2015) but how this affects COVID-19 therapeutics is not known yet.

SARS-CoV-2 enters cells via the spike glycoprotein through a process called endocytosis. Subsequent SARS-CoV-2 replication takes place in an ER-derived intermediate compartment in the ER-Golgi (Harrison *et al.*, 2020). Substantial evidence suggests that the sigma-1 receptor plays a role in the pathophysiology of a number of psychiatric and neurodegenerative disorders. Fluvoxamine's agonistic effects at the sigma-1 receptor (S1R) may reduce damaging effects of the inflammatory response.

In other studies, using the comparative viral-human protein–protein interaction map, it was revealed that the sigma-1 receptor in the ER plays an important role in SARS-CoV-2 replication in cells. Knockout and knockdown of SIGMAR1 (sigma-1 receptor, encoded by SIGMAR1) caused robust reductions in SARS-CoV-2 replication. This indicates that the sigma-1 receptor may be a key therapeutic target for SARS-CoV-2 replication and lead to the proposed repurposing of traditional CNS drugs that have a high affinity at the sigma-1 receptor (i.e. fluvoxamine, donepezil, ifenprodil) for the treatment of SARS-CoV-2-infected patients, and also other agents such as cutamesine and arketamine. (Hashimoto, 2021).

Of the common antidepressant drugs, only fluvoxamine possesses agonist and sertraline antagonist action at the sigma receptor with clinically relevant affinity (Ki) at the receptor. Imipramine, escitalopram and fluoxetine are only agonists at high concentrations as their affinity (Ki) are all in the 200–300 nm range, well above the concentration seen in clinical situation (Narita *et al.*, 1996; Ishima *et al.*, 2014).

Antipsychotics such as haloperidol (Ki = 4 nm), perphenazine (Ki = 12 nm), fluphenazine (Ki = 17 nm), trifluoperazine (Ki = 67 nm), pimozide (Ki = 144 nm), chlorpromazine (Ki = 180 nm) and triflupromazine (Ki = 214 nm) all possess high to moderate affinity at the sigma-1 receptor (Tam & Cook, 1984). These agents given at normal clinical doses would tag on the sigma receptors.

In summary, sigma receptors agents (Brimson *et al.,* 2020) are beginning to emerge as potential modulators of neuroplasticity and the neuroinflammatory process, both of which are important in the development of effective treatment for long COVID.

Antihistamine

Histamine is an important mediator of the immune response to infection. Antihistamines thus play an important role in the management of inflammatory diseases and the cytokine storm of COVID-19 (Eldanasory *et al.*, 2020). Usage of diphenhydramine, hydroxyzine and azelastine was associated with reduced incidence

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of SARS-CoV-2 positivity in subjects greater than age 61. Diphenhydramine, hydroxyzine and azelastine were found to exhibit direct antiviral activity against SARS-CoV-2 in vitro. Mechanisms by which specific antihistamines exert antiviral effects is not clear, but hydroxyzine binds to (ACE2) and the sigma-1 receptor (Reznikov *et al*., 2021).

Unpublished Chinese data claiming that the mortality rate for patients with COVID-19 taking famotidine was 14% compared with 27% for those not taking the drug triggered off the rapid launch of a 21 million study (Borrell, 2020; Ghosh *et al*., 2020). Use of famotidine was associated with a decreased risk of in-hospital mortality (Mather *et al*., 2020). High-dose oral famotidine is associated with improved patient-reported outcomes in non-hospitalised patients with COVID-19 (Janowitz *et al*., 2020). Another cohort study of cetirizine and famotidine found them to be safe and effective in reducing the progression in symptom severity, presumably by minimising the histamine-mediated cytokine storm (Hogan Ii *et al*., 2020).

The use of *Nigella sativa* (black cumin seeds) to treat the patients with COVID-19 was being analysed, as it has been shown to possess antihistaminic action, in addition to being antiviral, antioxidant, anti-inflammatory, anticoagulant, immunomodulatory, bronchodilatory, antipyretic and analgesic (Maideen, 2020).

An Electronic health record (EHR) review suggested that 3 allergy medications (cetirizine, diphenhydramine and hydroxyzine) could prevent SARS-CoV-2 infection. It found that only use of diphenhydramine was associated with a negative SARS-CoV-2 test. Selection bias was cautioned, citing the observation that increasing age and public insurance were associated with a higher adjusted odds of test negativity, while being Black or Hispanic was significantly associated with test positivity. (Thompson *et al*., 2021).

It is important to remember that early psychotropic drugs were derived from the atropine molecule and many, such as the tricyclic antidepressant drugs (TCAs), retain significant antihistamine properties (Tang & Tang, 2019). Some of them, for example, doxepine, is a potent antihistamine, and more potent than the commonly used antihistamine diphenhydramine. ^{11}C-doxepin was a popular ligand used to study histamine H1 receptor occupancy (Tashiro *et al*., 2008).

CYP enzyme

Anderson (2021) argued that fluvoxamine might also exert beneficial effects in COVID patients through its high ability to substantially increase (~ 2–3-fold) night-time plasma levels of melatonin through inhibition of the melatonin-metabolising liver enzymes CYP1A2 and CYP2C19 (von Bahr *et al*., 2000). Many other psychotropic drugs also inhibit CYP enzymes but fluvoxamine, specifically possesses a strong action against CYP2C19 and CYP1A2. Paroxetine and fluoxetine also possess significant inhibition against both CYP1A2 and CYP2C19. Whether only CYP2C19 and CYP1A2, and no other CYP enzyme inhibition (such as CYP2D6) is related to protection against COVID-19 would require further confirmation.

Stress from isolation and the vulnerable

Although depression, anxiety, insomnia and PTSD are observed to be common in long COVID, the mechanism is still unclear. In many of the reports concerning neuropsychiatric symptoms in long COVID, quality of the diagnostic and inclusion criteria were often unclear. Telephone, questionnaires, self-reporting, review of records were often used in time of a pandemic and social distancing. With the quarantine measures imposed in many parts of the world, quarantine/travel ban related economic downturn and job losses, social isolations and many other adversaries, stress-related symptoms and emotional complaints could be difficult to separate from true depression, anxiety and PTSD cases that met strict criteria. This may explain the relative low numbers of psychosis in long COVID.

Health-care professionals are particularly under tremendous stress, especially those caring for COVID-19 patients in the frontline. They suffered heavy mental workload (Ching *et al*., 2021; Pollock *et al*., 2020; Mo *et al*., 2020; Zhan *et al*., 2020; Wu *et al*., 2021; Shan *et al*., 2021), facing shortage of protective equipment, worked long hours and serviced high numbers of critical patients. It is also stressful facing dying COVID-19 patients, feeling helpless and unable to help. There is the fear of carrying virus back to family. Thus, anxiety, depression, burnout, addiction and PTSD could be the outcome of a stressful profession (El-Hage *et al*., 2020; Li *et al*., 2021). A digital learning package developed to mitigate the psychological impact of COVID on frontline health workers was accessed 17,633 times within 7 days of completion (Blake *et al*., 2020). The contents included practical items for health-care workers such as psychological first aid, self-care strategies (e.g. rest, work breaks, sleep, shift work, fatigue, healthy lifestyle behaviours), managing emotions (e.g. moral injury, coping, guilt, grief, fear, anxiety, depression, preventing burnout and psychological trauma) (Blake *et al*., 2020). It is understandable that this is a group that would be highly vulnerable for long COVID neuropsychiatric disorders.

The isolated and quarantined subjects consisted of another group with high stress and vulnerability for long COVID. Apart from isolation stress, there is reduction in physical activity (Burtscher *et al*., 2020; Razai *et al*., 2020; Rivers & Ihle, 2020) producing or accelerating sarcopenia, a deterioration of muscle mass and function and increases in body fat (Kirwan *et al*., 2020; Simpson & Katsanis, 2020). Many also experienced the problem of obtaining accurate and reliable news and associated fear and anxiety (Nowak *et al*., 2021). A stressful life could produce the vague health symptoms in long COVID.

Being a woman and severity of illness were risk factors for persistent psychological symptoms in long COVID. Female COVID or SARS survivors appeared to have higher stress levels and higher levels of depression and anxiety and contributed to the high incidence of depression and anxiety in long COVID (Huang *et al*., 2021).

Long COVID in the young age groups may also be stress-related. Stress could be from prolonged school absence, concerns about loss of the family, isolation/quarantine related loss of friendships, loss of peer supports, domestic violence and child maltreatment. Children and adolescents with disabilities, existing mental health problems, migrant background and poverty are especially vulnerable (Fegert *et al*., 2020).

The elderly and live-alone, with or without dementia, plus their care givers, are definitely a high-risk group for long COVID (Liu *et al*., 2021). Research has shown that people suffering from dementia have a relatively high risk of contracting severe COVID-19. They are also at risk of additional neuropsychiatric disturbances as a result of quarantine/lockdown measures and stringent social isolation (Cations *et al*., 2021; Giebel *et al*., 2021; Numbers & Brodaty, 2021; Ryoo *et al*., 2020). Lack of social engagements with families and friends, cancelled day care centre programmes may worsen the cognitive, physical and neuropsychological condition of the patients with dementia. Being confined at

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home without contact with the outside or without updated news may increase levels of stress, anxiety and a feeling of loneliness and depression (Xu & Liu, 2021). This is critical for dementia patients, as stress is known to be detrimental to patients with cognitive impairments. Maintaining physical activity during isolation is important (Morrison *et al.*, 2020; Oren *et al.*, 2020). In addition to the patients, we must also focus on the well-being of families and caregivers who may be suffering from reduced public health-care support or home care services during the COVID-19 outbreak.

Mohamed-Hussein *et al.* (2021) found that during the acute phase, hospitalised patients had more respiratory symptoms, while non-hospitalised patients had more neuropsychiatric symptoms (84.4% vs. 69.5%). This implies long COVID may not be related to the severity of COVID-19 infection, in contrast to some other studies, which showed that long COVID was related to severity of infection.

Thus, there are specific groups of COVID-19 patients who were living a highly stressful life during COVID. Managing stress in those infected obviously is an urgent public health task (Hagger *et al.*, 2020). It would be interesting to investigate if incidence of long COVID neuropsychiatric disorders (such as depression, anxiety, PTSD, psychosomatic and other stress-related disorders) would be lower in communities which implemented effective stress management programmes (Cheng *et al.,* 2020b).

Areas of further research in long COVID

In the shortage of truly effective agents against the SARS-CoV-2 virus, repurposing/trials of existing drugs are taking place in many parts of the world. These included the controversial animal anti-parasite drug ivermectin (Ortega-Guillén *et al.*, 2021; Rajter *et al.*, 2021), the commonly used antimalarials chloroquine (CQ) and hydroxychloroquine (HCQ) (Abena *et al.*, 2020) and psychotropics described above. These two areas are important for future research in the fight against COVID-19.

Targeting glucose metabolism

There are a number of possible strategies to reverse the changes in brain glucose metabolism particularly in the early stages of the infection. Reducing neuroinflammation, re-sensitising the glucose transporters and increasing brain energy metabolism by dietary manipulations are practical approaches which seem worthy of consideration. A reduction in glucose during the acute infective stage would not only reduce viral replication but also help to restore the innate immune defence mechanisms. However, during the post-infective long COVID stage, the adverse changes in the brain are mainly due to neuroinflammation which has a major impact on brain glucose metabolism. The anti-diabetic agent metformin would appear to have advantages in treating long COVID patients. The mechanisms of action of metformin and its potential advantages make it a viable candidate drug for repurposing against SARS-CoV-2 infection (Ibrahim *et al.*, 2021; Samuel *et al.*, 2021; Malhotra *et al.*, 2020).

Besides its efficacy in regulating blood glucose levels without inducing hypoglycaemia, metformin is an effective anti-inflammatory agent (Dehkordi *et al.,* 2016). Metformin inhibits the formation of advanced glycation products which are required for the formation of the glycan tree structure which are essential for viral pathogenesis. An added advantage is the reduction in mitochondrial synthesis of ROS which would further contribute to the beneficial effects of metformin in treating long COVID patients (Beisswenger & Ruggiero-Lopez, 2003; Bellin *et al.*, 2006).

So far, the clinical benefit of metformin in COVID-19 patients is limited but there is evidence that diabetic patients with COVID infection have benefited (Scheen, 2020); similar results have been recorded in patients with heart failure (Cheng *et al.*, 2020a). Metformin's anti-thrombotic effects, its potential attenuation of endothelial dysfunction, inhibition of viral entry and infection and modulation of inflammatory and immune responses would also be added advantages (Samuel *et al.*, 2021). However, only appropriate controlled and randomised clinical trials will establish if metformin is an effective treatment both at the acute stage and in long COVID.

Regulation of the carbohydrate content of the diet could be a practical approach to limiting the virus. A ketone rich diet, and a low carbohydrate diet, could provide ketones as an alternative energy source for neurons. Unlike other organs, the brain requires acetoacetate and gamma-hydroxybutyrate to compensate for the lack of glucose. In addition, there is evidence that ketones activate the protective gamma-delta T-cell responses involved in antiviral protection against the influenza virus (Goldberg *et al.,* 2019). There are several clinical studies in progress exploring the protective value of low carbohydrate diets in those with COVID-19 infection.

Targeting sigma receptor and histamine receptor

The role of the sigma receptor and histamine in both inflammation and viral infection is an important area for future research in long COVID. The reported decrease in sigma receptor numbers in post-mortem schizophrenic brains, the reported protective role of certain psychotropics against COVID-19 infection and the observed reduction in COVID-19 infection in patients with schizophrenia, taken together, suggests that sigma receptor agents should be tested for their potential anti-COVID-19 effect, in properly designed experiments and clinical trials.

Conclusion

As of this date, there appears to be no well-established or accepted treatment to reduce, or prevent, long COVID. Understandably, clinical attention has been directed primarily at the impact of COVID-19 on the potentially lethal acute infection stage. However, there is now increasing concern regarding the pathological changes and health problems which occur in a significant number of patients following their apparent recovery from the acute infection, the 'long COVID'. The neuropsychiatric symptoms of long COVID are obstacles for returning to a normal life and a potentially heavy burden on the health system of all countries. Whether the long COVID neuropsychiatric symptoms reported are stress-related and psychosomatic, or metabolic and neurodegeneration-related are all important areas for further research. The suspected protective action of some psychotropics against COVID-19, amid contradictory reports on the higher/lower mortality rates of patients with severe mental disorders infected, is also an important area to pursue. The neuropsychopharmacology of continuing neuroinflammation, glucose metabolism, the role of ACE2, sigma and histamine receptors are all important areas for further research and may lead to repurposing or novel therapeutics against COVID-19. Meanwhile, cognitive and neuropsychological function, and signs of neurodegeneration, should be closely monitored in COVID-19 survivors (Serrano-Castro *et al.*, 2020).

In this review, we have reviewed the spectrum of long-term neuropsychiatric and psychological impacts of COVID-19. We have also attempted to identify some areas of long COVID that

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might provide useful paths to research for new treatments of long COVID.

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