Research Article

Fluoxetine plus lithium for treatment of mental health impairment in Long Covid

Jeffrey Fessel[1]

1. Department of Medicine, University of California, San Francisco, United States

Mental disability is a serious and often disabling symptom of Long Covid, for which currently there is no recommendable pharmacotherapy for those patients whose response to psychotherapy is suboptimal. Treatment could be formulated by using drugs that address the brain cell-types that have been demonstrated as dominantly affected in Long Covid. Those cell-types are astrocytes, oligodendrocytes, endothelial cells/pericytes, and microglia. Lithium and fluoxetine each address all of those four cell-types. They should be administered in combination for both depth of benefit and reduction of dosages. Low dosage of each is likely to be well-tolerated and to cause neither adverse events (AE) nor serious adverse events (SAE).

Corresponding author: Jeffrey Fessel, jeffreyfessel@gmail.com

Introduction

Global extent of mental symptoms in persons with Long Covid: Chen et al synthesized information from 50 studies involving almost 1.7 million people, showing that 43% still had symptoms 28 days after the acute infection with Covid-19[1]. According to the UK Office of National Statistics, there have been 23.6 million cases of COVID-19 infection in the UK, and 1.2 million of those (5.1%) said that they had symptoms lasting for more than 12 weeks, a condition often termed ‘Long Covid’. Groff et al identified 57 studies with 250,351 survivors of Covid-19 infection, in whom 23.8% had difficulty in concentration, at 30 days and beyond after the acute infection[2].In France, the ComPaRe Long Covid prospective cohort showed that ‘brain fog’/difficulty concentrating, had a prevalence at 60 days of 71.8%, and at 360 days of 60.2%[3]. In Italy, symptoms of posttraumatic stress disorder, affected 30% of the 381 persons who had recovered from infection by Covid-19[4]. As a supplement for those

patients whose response to psychotherapy is suboptimal, there is not yet an effective pharmacotherapy for these mental problems.

A rational approach to finding a drug formulation for control of the mental problems associated with Long Covid, would be to ascertain which of the brain cell-types are dominantly affected and to direct therapy toward them because there are several available drugs that address some or all of the five main brain cell-types.. Evidence exists showing that the cognitive impairment in Long Covid is due to reduced numbers of astrocytes, myelinating oligodendrocytes, neurons, and endothelial cells, plus increased numbers of microglia. Treatment with lithium plus fluoxetine, each of which benefits those abnormalities, should alleviate the mental disturbance of Long Covid. Clinical trial would demonstrate the validity or otherwise, of this proposal.

Infection of astrocytes, neurons, oligodendrocytes, and endothelial cells/pericytes by SARS-CoV-2

Receptors for SARS-CoV-2 allowing infection of cells in brain and elsewhere. The major portal of entry into cells by SARS-CoV-2 is mostly via the angiotensin-converting enzyme 2 (ACE2) receptor; however, that receptor has a variable presence in the brain. As will be shown, both Crunfli et al and Andrews et al demonstrated infection of astrocytes but neither of them could demonstrate that astrocytes have ACE2 receptors[5][6]. Crunfli et al found that neuropilin receptor 1 (NRP1) allows entry for SARS-CoV-2[1]; Andrews et al found that astrocytes could be infected by the SARS-CoV-2 virus via receptors for CD147 and DPP4[6]. Despite the above reports showing no ACE2 receptors in astrocytes, Song et al found that neuronal infection of human brain organoids could be prevented by blocking ACE2 with antibodies, demonstrating that, in fact, ACE2 does occur on neurons, perhaps sparsely[7]. Chen et al confirmed this by analyzing data from publicly available brain transcriptome databases, showing no ACE2-expressing nuclei in the prefrontal cortex but it was expressed in other brain locations as well as in excitatory and inhibitory neurons, astrocytes, oligodendrocytes, and endothelial cells[8]. The apparently conflicting data may be either that the brain contains several genetic variants of ACE2, that determine a differential response to SARS-Cov-2 infection[9], or that ACE2 receptors are present in some brain cell-types and not others.

Astrocytes: Crunfli et al used three different antibodies against the spike S1 component of the SARS-CoV-2 virus, in order to demonstrate the presence of that virus[5]. In one of the five brains examined

by Crunfli et al, approximately 70% of astrocytes contained the virus. Crunfli et al also analyzed the proteome of both infected astrocytes and Covid-19 postmortem brain tissue, showing that glycolysis/gluconeogenesis, carbon metabolism, and the pentose phosphate pathways, were the most involved[1]. Collectively, their data demonstrate that in the brain, SARS-CoV-2 affects energy metabolism and modulates proteins associated with neurodegeneration.

Neurons: Apart from in one brain examined by Crunfli et al, showing that approximately 20% of neurons, contained the virus[5], no other direct data are published regarding neurons in Long Covid. Indirect data come from the studies described below, showing impairments in myelinating oligodendrocytes whose consequences affect neuronal function.

Myelinating oligodendrocyte:. During myelination by oligodendrocytes an extension of its plasma membrane, containing myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP), wraps itself around a naked axon and ensheathes it with multiple layers of myelin proteins. Undifferentiated oligodendrocyte precursor cells (OPC) have markers for PGDF and Olig2; both OPC and mature, myelinating oligodendrocytes express chemokine receptors CXCR1, CXCR2, and CXCR3. Mature myelinating oligodendrocytes also express MOG and MBP. Reduced numbers of myelinating oligodendrocytes, causing impaired neuronal myelination, causes abnormal neural tracts and consequent cognitive impairment.

In covid-19 infection, one reason for low numbers of myelination oligodendrocytes, is antibodies directed against them. Young et al saw antibodies against PDGF correlating with the severity of SARS-CoV-2infection[10]; Schwabenland et al found antibodies against Olig-2[11]; Manzano et al saw anti-MOG seropositivity in 6.7%, of patients[12]; and Wang et al documented plasma antibodies against CXCR1, and CXCR3 in 194 infected persons[13]. Ide et al reported one case and reviewed five other reports of single cases; all of them had anti-MOG antibodies with symptoms related to involvement of brain, spinal cord, or optic nerve[14].

Endothelial cells/pericytes: The data reported by Crunfli et al also suggest that SARS-CoV-2 in the brain, by occupying neuropilin receptors (NRPR), might adversely affect the cerebral microcirculation because NRPRs also bind the proangiogenic factors VEGF, PGF, and HGF/SF. In fact, in four of the five brains from persons who had died from SARS-CoV-2 infection examined by Crunfli et al, four had microvascular damage, produced by inflammatory cells invading endothelium in two, capillary damage in one, and perivascular edema in one. Kirschenbaum et al examined the brains from six

persons who had died from SARS-CoV-2 infection; all had thrombus in the cerebral microcirculation which, in one subject showed intra-endothelial lymphocytic infiltration[15]. Taha and Samavati analyzed 21 studies with a total of 1159 patients and found that among patients hospitalized for SARS-CoV-2 infection, 46.8% had one or more antiphospholipid antibodies[16]. Del Papa et al noted a close association between antiphospholipid antibodies and anti-endothelial antibodies[17]; that was confirmed by Shi et al, who found that IgG (presumably containing antibodies) derived from sera of patients hospitalized with COVID-19, induced activation of cultured endothelial cells[18]. These results suggest strongly that antibodies promoted by SARS-CoV-2 infection, affect endothelial cell function. Pericytes are also involved: Bocci et al demonstrated that pericytes have the ACE2 receptor and that cells of cerebral capillaries from a Covid-19 infected patient showed viral RNA, which is a possible source of entry into the brain by SARS-CoV-2[19]. Hirunpattarasilp et al induced capillary constriction by exposing human cortical slices to SARS-CoV-2 spike protein, resulting in decreased conversion of vasoconstricting angiotensin11 to vasodilating angiotensin1; that was shown as caused by the occupation of ACE2 by SARS-CoV-2 because the effect from blocking angiotensin1 mimicked the effect from blocking ACE2[20].

Microglia: Thakur et al assessed 28 such brains, assessing the presence of SARS-CoV-2 and by RT-qPCR, RNAscope, and immunocytochemistry using primers, probes and antibodies directed against the spike and nucleocapsid regions[21]. Low to very low but detectable, viral RNA levels were in the majority of brains; and each had microglial activation, and microglial nodules, most prominently in the brainstem. Andrews et al saw a minimal increase of microglia during infection by SARS-CoV-2[6].

In sum, in Long Covid, reduction in numbers of astrocytes, oligodendrocytes, and endothelial cells, and increase in numbers of microglia, may occur because of infection by SARS-CoV-2. Treatment with lithium plus fluoxetine addresses all of these abnormalities.

Lithium

Astrocytes: Using cultures of optic nerves, Rivera and Butt showed that lithium caused a doubling of astrocyte numbers ($P < .001$)[22].

Oligodendrocytes: Meffre et al found that lithium stimulated maturation of oligodendrocytes, which promoted remyelination after lysolecithin-induced demyelination of organotypic cerebellar slice cultures[23].

Endothelial cells: Ji et al demonstrated that lithium increased the integrity of the blood brain barrier by 46% (P = .006), one mechanism for which was to increase the protein levels of the tight junctions between adjacent endothelial cells, mediated by Claudin 5 and ZO-1[24]. Lithium also induced proliferation and migration of cultured endothelial cells[25].

Microglia: The microglial activation caused by adding LPS to microglial cultures, was inhibited by lithium[26].

Fluoxetine

Astrocytes: Kinoshita et al demonstrated that fluoxetine increased the release of ATP by astrocytes that, in turn, increases astrocytic production of BDNF[27].

Oligodendrocytes: Fluoxetine prevented the apoptosis of oligodendrocytes that is mediated by expression of pro-nerve growth factor and its neurotrophin receptor[28]; and it also prevented the reduction of oligodendrocytes caused in rats by chronic unpredictable stress[29].

Endothelial cells: After cerebral arteriolar thrombosis had been induced, those arterioles as well as the adjacent ones without thrombosis, became dilatated when infused with fluoxetine; this effect was shown to be due to inhibition of the hydrolysis of acetylcholinesterase, thus enhancing cholinergic activity[30]. Interestingly, the induced vasodilatation by fluoxetine was independent of serotonin, as shown by infusion of fluoxetine together with methylsergide, which blocks the serotonin receptor.

Microglia: Fluoxetine prevented microglial activation[28].

Discussion

Mental symptoms, primarily disturbed cognition, are among the most disabling features of Long Covid. Those symptoms result from impaired function of astrocytes, oligodendrocytes, and endothelial cells plus increased activity of microglia. Two drugs, lithium and fluoxetine, each benefit all of those cell-types; for depth of coverage and reduction of dosages, they should be administered together. Lithium should be used in a reduced dosage to target a serum level of 0,25-0.50 mmol/l, which was shown to provide some benefit in Alzheimer's dementia[31]. Fluoxetine should be administered in the low dosage of 10 mg daily.

Evidence shows that low dosages of lithium and fluoxetine, administered in combination, should be well-tolerated and cause few, if any, serious side effects. Bauer et al, identified 110 patients who were

receiving fluoxetine together with lithium[32]. These patients were compared with a group of patients who were not on lithium therapy. ≥90% in both groups used fluoxetine 20 mgs daily. Adverse events (AE) in the two groups were non-significantly different: in 21.8% during fluoxetine treatment and in 30.9% during treatment with the combination of fluoxetine/lithium (P = 0.13). and there were no serious adverse events (SAE). There were no statistically significant differences in any of the AE. Far higher doses than those suggested here, were administered by Fava and Alpert, who reported 34 patients who used fluoxetine 20 mg plus lithium 300 to 600 mg/day[33]. There were no SAE but many AE, including gastrointestinal distress in 50.0%, dry mouth in 38.2%, insomnia in 35.3%, sedation or fatigue in 32.4%, and headache in 26.5%. In brief, high dose fluoxetine with high dose lithium would cause a high drop-out rate due to AE; but the suggested low dosage of these two drugs, administered in combination, should cause no AE and have a low drop-out rate.

Clinical trial is required to validate benefit from the suggested drugs

The benefit of low dosages of fluoxetine and lithium for the mental symptoms of Long Covid, should be tested in a randomized clinical trial. A trial could have four arms: 1) fluoxetine 10 mg/day; 2) lithium 75-150 mg/day targeting a blood level of .25-.5 mmol/l; 3) a combination of fluoxetine and lithium in the above dosages; 4) placebo. No other psychoactive drugs would be permitted. Duration of treatment would be 12 weeks. Symptoms should be followed by use, at baseline then monthly, of appropriate tests of cognition.

Conclusions and summary

1. Mental impairment is a serious symptom of Long Covid.
2. The brain cell-types that underpin those mental symptoms include astrocytes, oligodendrocytes, endothelial cells and microglia.
3. Both lithium and fluoxetine address all of the affected cell-types.
4. A clinical trial using low dosages of both lithium and fluoxetine should test the validity of using the two drugs in combination for treatment of the mental impairment of Long Covid, for those patients with suboptimal response to psychotherapy.

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