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

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Potential competing interests: The author(s) declared that no potential competing interests exist.

The submitted paper summarizes comprehensive evidence to support clinical trials to find out how to potentially cope with cognitive and emotional complications of long Covid 19 infection. An intriguing point of view is the extensive review of CNS-related cell types that are affected by the SARS virus and beneficial effects of lithium and fluoxetine on these cells. Relating just to lithium we wish to raise compelling evidence that the approach might be broadened and relate to the possibility to consider lithium treatment for the initial Covid 19 infection rather than just for long Covid. This concept is built on the following beneficial effects of lithium salts (Li) in the CNS. Li's mechanism of its beneficial effect has not yet been unravelled, but we and others robustly reported a myriad of cellular responses induced by Li (see Fig. 4 of reference **1** below) through modulation of homeostatic mechanisms including inflammation, mitochondrial function, oxidative stress, autophagy and apoptosis. Namely, Li is anti-inflammatory[1,2], neuroprotective[3-6], counter-acting oxidative stress[7-9] , hampers apoptosis-induced cell death[10,11] and up-regulates mitochondrial function[12-14] and autophagy[15,16]. All these effects are, possibly, consequences of the drug's inhibition of the key phosphatidylinositol (PI) signalling cascade enzymes inositol monophosphatase (IMPase) and inositol polyphosphate phosphatase (IPPase) and of glycogen synthase kinase-3 (GSK-3)β[6]. In relation with viruses, Li-induced inhibition of IMPase and IPPase results in myo-inositol depletion, dampening of PI signalling and decreased downstream levels of inositol phosphates[17-19]. Specifically, inositol hexaphosphate (IP_6) is apparently a key factor in increasing the stability of the HIV virus, an RNA virus. Hence, Li-induced decreased IP_6 levels would decrease the ability of HIV to replicate effectively[20]. At another level, several DNA and RNA viruses inhibit the infected cell autophagy, thus increasing their survival[21]. Li-induced autophagy enhancement may decrease viruses' survival. Additionally, GSK-3ß inhibition during later infection stages with the RNA virus Dengue virus-2 (DENV-2) resulted in reduced viral titers in cell lines[22]. As for the coronaviridae family, it has been reported that Li inhibits cell infection, viral RNA transcription and progeny production of avian infectious bronchitis virus (IBV), porcine transmissible gastroenteritis virus (TGEV) and porcine epidemic diarrhea virus (PEDV), apparently by exerting an antiapoptotic effect (for extensive review please see Murru et al.[23]). We, therefore, endorse publication of the submitted manuscript following inclusion of the above argumentation.

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