Potential prophylactic and treatment use for serotoninergic agents in COVID-19 disease

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Abstract

COVID-19 is a systemic multi-organ disease with short term and long term implications due to the novel Sars-CoV2 coronavirus that emerged end of 2019 in China.

The milder form of the disease typically presents itself with loss of smell, mild fever, cough, fatigue and mild hypoxic distress.

A more severe course of the disease involves respiratory decompensation, severe vascular (hemolysis, clotting) and neurological complications requiring intensive care and potentially leading to death.

A number of people recovering from the illness will likely experience severe organ dysfunction (particularly cardiovascular, neurological as well as psychiatric complications) for an unknown period of time.

Some people are also known to be asymptomatic carriers, making the spread of the virus all the more difficult to control.

Since the month of April it had become apparent that long haul COVID-19 cases (protracted covid) and many other active cases were experiencing psychiatric symptoms as well as the physical ones listed above; and this seemed to often be the case irrespective of apparent disease severity, age or comorbidities.

As such, after interviewing a few COVID-19 patients patterns started emerging. Reported symptoms were fairly reminiscent of EBV or chronic fatigue syndrome; they included anxiety, agitation, fatigue, lethargy, depression, various pains and akathisia. As well as plethora of physical symptoms such as tachycardia, persistent fever, myocarditis, exhaustion, episodes of hypoxic manifestations…

At the time we were made aware of an anecdotal preprint from France [1] stating that patients currently on various types of antidepressants and antipsychotics seemed less likely to progress to a more severe form the illness. Considering the drugs described in that preprint as well as anecdotal case reports regarding the use of famotidine (80mg x 3/day) (an anti-H2 agent) in Wuhan [2], serotonin seemed to play a role.

We also speculated based on self-reports of various patients taking medicine for asthma, that chronic antihistamine and corticosteroids use seemed to play a role in lessening symptoms related to COVID-19.

5-HT itself plays are role in many vascular and neuronal processes. From vasoconstriction, to mood regulation, to clotting…

It is known that platelet serotonin release can lead to worsening of various conditions including thrombosis, asthma and sepsis.

Serotonin (along with GABA) is also a known culprit in lyssavirus-related pathology as described in many and often surprising papers [3]. This led us, initially, to wild speculations regarding similarities between coronaviruses and lyssaviruses.

Following recent and older articles regarding the use of fluvoxamine [4] in intensive care and particularly in infectious illnesses, including, COVID-19, we saw our initial hypothesis regarding serotonin implication being validated to some extent.

Additionally, at this time ASA has been added (at a dose of 162mg) as a potentially promising adjunct to treatment as part of the RECOVERY trial[5].

Also it is worth noting that a relationship between psychiatric illness and severity of COVID-10 illness has recently led to an article published in The Lancet [6]. Further reinforcing our belief that the monoamine status of the host plays a key role in the progression of COVID-19 disease.

Search for potential agents

Based upon the reports regarding fluvoxamine and famotidine, we investigated the binding profiles of various well-known and widespread serotoninergic agents.

We came up with the following list by order of potential potency and tolerability (based on 5-HT2B binding as well as other criteria such as side effects and sigma-1 activation): fluoxetine, fluvoxamine, escitalopram, mianserin, cyproheptadine, hydroxyzine, famotidine. We were unsure about adding TeCAs and tricyclics as some of their profiles were ambiguous, especially in the case of tianeptine, although we suspect they could be of use. The same was true for potentially weaker anti-H1 agents.

Regardless of agent used one must weigh the pros and cons regarding side effects. SSRIs for instance are notorious for being difficult to tolerate in some people, especially considering the infamous initial latency period. This further complicates matters as to when to administer such agents; prophylactically, with a chance of poor tolerability? Or in the early stages of the COVID-19 illness and in higher doses with the risk of lesser effectiveness given latency mentioned above.

In our opinion people currently taking these agents should not stop them without medical advice, nor should anyone initiate any of them as prophylaxis until further research in completed.

We have also speculated that if we could find a way to easily test for serotonin levels in platelets we could either determine patients more at risk of clinical deterioration AND/OR if they are infected with SARS-CoV2.

Conclusion

Considering the urgent need for proper prophylactic and treatment agents for COVID-19 illness it seems urgent at this time to investigate all potential agents active on serotonin receptors, especially in lung endothelium as well as in platelets.

We also would like to insist that the role of GABA be investigated as we suspect GABA depletion could lead to respiratory dysfunction as well as an array of neurological symptoms.

We are now certain that COVID-19 illness is not merely a respiratory illness but a potentially lifelong systemic one with serotonin, dopamine, and GABA involvement.

References

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[5] https://www.recoverytrial.net/news/aspirin-to-be-investigated-as-a-possible-treatment-for-covid-19-in-the-recovery-trial

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Competing interests

We declare no competing interests.