



## Letter to Editors

## Noradrenergic and serotonergic drugs may have opposing effects on COVID-19 cytokine storm and associated psychological effects



In previous publications I have suggested that the neurotransmitters norepinephrine (NE) and serotonin (5HT), which are engaged in a wide range of physiological processes outside the brain as well, are largely functionally opposed to one another [1–2]. In addition to its role in various psychiatric, neurologic, and cardiovascular functions, there is increasing evidence that NE plays a role in the symptomatology associated with serious systemic infections such as influenza, including activation of cytokine signaling such as IL-6 as well as the manifestation of psychological effects associated with infection [3].

It has also been suggested that catecholamines, including NE, play a role in producing the potentially lethal “cytokine storm” associated with coronavirus disease 2019 (COVID-19) [4]. I suggest here that this cytokine storm may be counteracted by a range of clinically used drugs that reduce NE transmission (but that may not act through direct effects on viral replication or viral entry into cells) [5]: alpha2 agonists such as clonidine, guanfacine, dexmedetomidine; various beta blockers such as propranolol, nebivolol, carvedilol, atenolol; and various alpha1 antagonists such as prazosin [4]. Since HDAC inhibitors like valproic acid and vorinostat may also decrease NE transmission [6], they may also be therapeutic in COVID-19.

Since 5HT may be functionally opposed to NE, drugs that *facilitate* 5HT transmission may also dampen the cytokine storm associated with COVID-19: SSRIs (fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine; TCA (clomipramine); MAOIs (phenelzine, tranylcypromine); and the 5HT2C agonist lorcaserin.

There are also theoretical underpinnings supporting functional opposition between NE and the neurotransmitter acetylcholine [7], where the latter molecule participates in the cholinergic anti-inflammatory pathway [8]. In this scenario, clinically available cholinesterase inhibitors (pyridostigmine, donepezil, rivastigmine, galantamine, physostigmine) may also counteract the cytokine storm associated with COVID-19.

There are already several ongoing clinical trials, in various countries, testing whether some of the above pharmacological agents reduce morbidity and mortality accompanying COVID-19. I suggest that all of the above compounds are promising candidates for additional prospective clinical trials, and they can also be examined immediately through retrospective epidemiological investigation of the medical records of individuals who were taking these drugs for various indications and were hospitalized and had pneumonia or acute respiratory distress, where their clinical outcomes may be relevant to treating today's ongoing COVID-19 pandemic [4]. If COVID-19 is accompanied by systemically elevated NE signaling, the various drugs listed above may also

counteract deleterious psychological effects associated with this infection [3].

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### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.109985>.

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