# STANDARD DEVIATIONS: In Search of the Magic Bullet

Greetings,

Have you ever thrown spaghetti against the wall? You know, just keep tossing until something sticks and then you know it's done? That seems to be a popular method for testing drugs to use in treating Covid-19.

Hydroxychloroquine didn't stick.

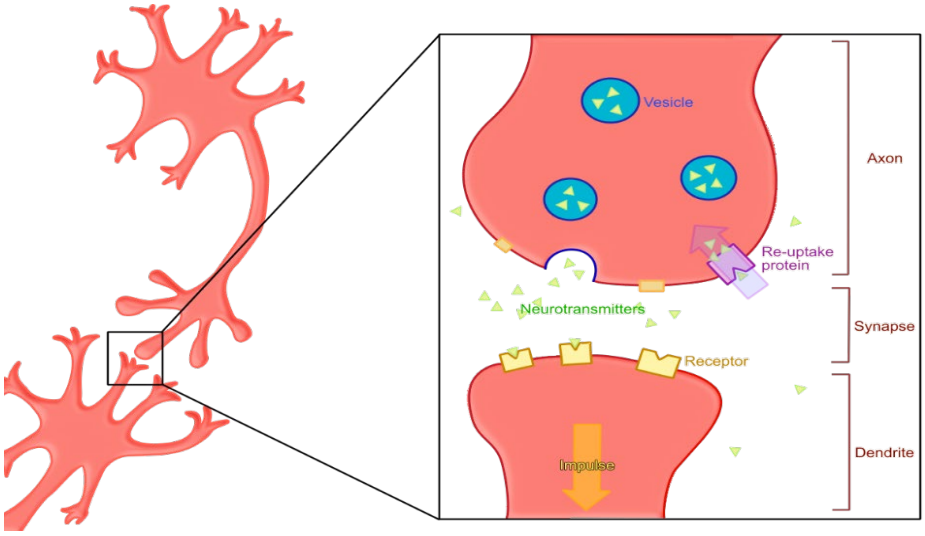
Ivermectin didn't stick.

Fluvoxamine (FLV) seems to be sticking?

This common antidepressant (Luvox) is the new kid on the block for repurposed drugs to treat Covid-19. It has shown some pretty remarkable success in trials and its promise has garnered some serious attention.

So how does an SSRI (selective serotonin reuptake inhibitor) do a better job than an antimalarial or de-wormer fighting a virus?

The mechanisms of SSRIs target **serotonin**, or **5-hydroxytryptamine** (**5-HT**), a tryptophan-derived neurotransmitter. Mostly, it is sequestered in the gut where its notable functions are regulating mood, appetite, and sleep. About 8% of our supply is found in platelets which release it as a vasoconstrictor that modulates hemostasis and clotting. SSRIs block specific re-uptake channels at the neuronal synapse. This leads to more serotonin at the synapse, and that keeps the neuronal signaling firing.




{Fluvoxamine blocks re-uptake.}

The level of serotonin at the synaptic junction is known to be important in mood disorders but how SSRIs act as antidepressants is not understood. SSRIs block uptake *right away* but it's **weeks** before the antidepressant effects kick in. Over a long period of time the receptors get downregulated and it's the eventual tempering of the signal that is thought to alleviate mood disorders. How this all helps is black magic.

But serotonin is a player in inflammation and clotting. The action that serotonin has on the immune system and platelets is the reason this drug holds such promise.

Many different types of immune cells express the machinery to generate, store, respond to and/or transport serotonin, including T cells, macrophages, mast cells, dendritic cells, and platelets (sort of).

The effect of fluvoxamine on clotting reduces thrombosis and neutrophil response. During thrombosis platelets release serotonin, facilitating hemostasis through platelet aggregation and stimulating neutrophils to activate and respond. The resulting coagulopathies and cytokine storms are Covid-19 signatures. BUT platelets don't make serotonin – they just pull it from the plasma. Block the uptake and there's nothing to release. FLV could perhaps inhibit blood clotting more safely than full anticoagulant therapies.

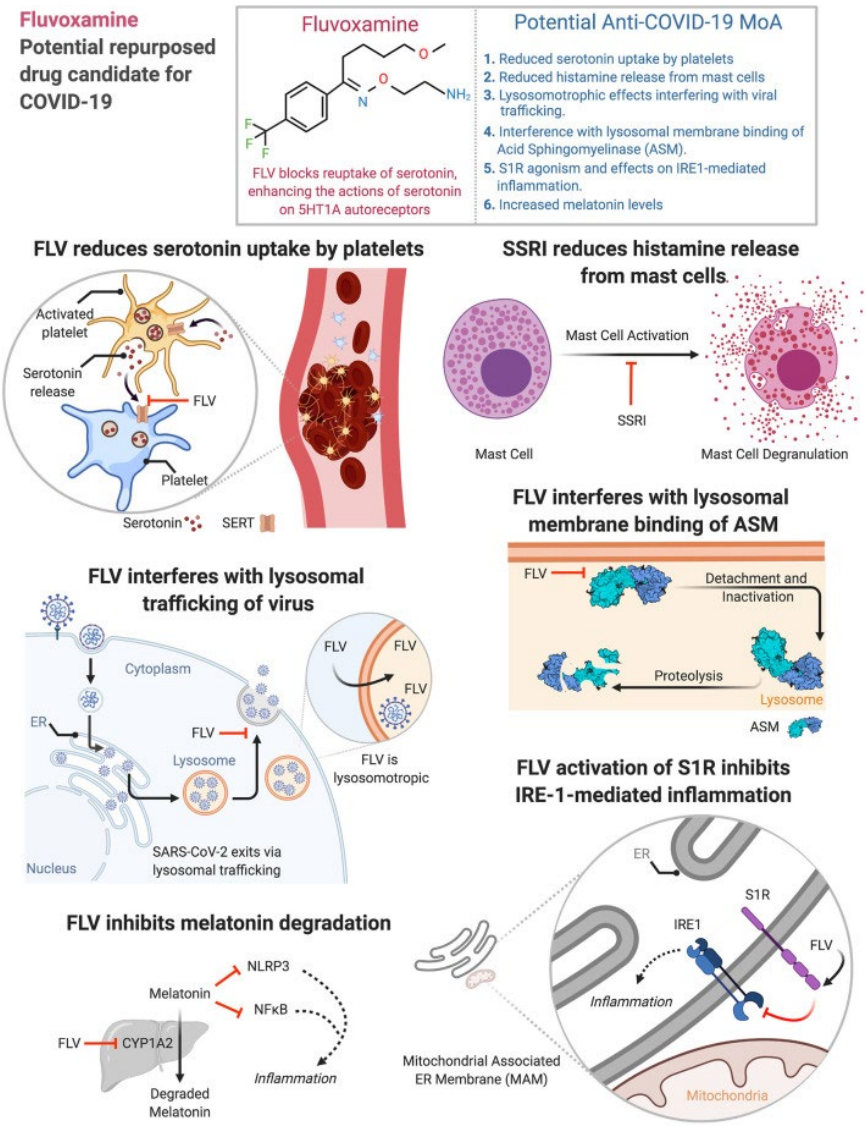
Another route of action is the effect of FLV on Mast Cells. Human mast cells (MCs) are a viral reservoir for RNA viruses and they are flush with ACE2 receptors and histamine. Post-mortem lung biopsies of COVID-19 patients show pulmonary edema and thromboses linked to activated MCs. These cells are kind of amplifiers of messaging in immune response and squelching that bullhorn lessens the cytokine storm. Blocking histamine uptake slows that Mast Cell activity and suppresses the immune response.

Fluvoxamine has other properties that may be at play. They disrupt lysosomes at the Endoplasmic Reticulum. The coronavirus pirates the host's ER to package proteins; and β-coronaviruses, like SARS-CoV-2, use lysosomal trafficking to escape from infected cells. Drugs like FLV could have antiviral effects in the virus laden lysosomes by impeding lysosome function.

Still another mechanism being investigated affects a receptor (Sigma-1-Receptor, S1R) important in proinflammatory interleukins. Simply put, the pro-inflammatory cascade is tempered when FLV acts on S1R to blunt cytokine expression.

So, there are different mechanisms at play in this saga and they involve suppressing inflammation. The evidence is pretty remarkable. In placebo-blinded trials, fluvoxamine has shown efficacy in viral clearance, clinical improvement, number of days with symptoms or hospitalization, time to hospitalization, reduced mortality, reduced ventilator need, less adverse events and fewer adverse reactions to meds.

Upcoming and ongoing studies will evaluate the dosing, whether vaccination matters, and a greater understanding of the effects of fluvoxamine on individual outcomes.




{Potential anti-COVID-19 mechanisms of action of fluvoxamine.}

Fluvoxamine is cheap. It is estimated that dosing would cost about $4-10. Fluvoxamine is pretty safe and has been FDA-approved for a while. Convincingly, FLV has shown a mortality benefit with its anti-inflammatory cytokine inhibition. Maybe, just maybe, we're looking at a drug with potential to help with this pandemic.

Have a great week and be safe,

Bryan