Fluvoxamine for prevention of clinical deterioration in early COVID-19:

Results from a randomized placebo-controlled trial

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Disclosures

Dr. Lenze:

- **Grants for this study:** COVID Early Treatment Fund, Taylor Family Institute for Innovative Psychiatric Research, Center for Brain Research in Mood Disorders
- **Other grant funding:** Patient-Centered Outcomes Research Institute, Takeda, Alkermes, Janssen, Acadia, and the Barnes Jewish Foundation.
- **Consulting fees:** Janssen and Jazz Pharmaceuticals.

Dr. Zorumski

- **Scientific Advisory Board:** Sage Therapeutics
- **Stock and stock options:** Sage Therapeutics.

Prof. Miller

- **Research funding:** Patient-Centered Outcomes Research Institute.

Funding/Support for THIS STUDY:

- COVID-19 Early Treatment Fund
- Taylor Family Institute for Innovative Psychiatric Treatment at Washington University
- Center for Brain Research in Mood Disorders at Washington University
- Bantly Foundation
- NIH grant UL1TR002345.

Background

- Patients with COVID-19 can show deterioration around the second week of illness, which may be due to an excessive inflammatory response (“cytokine storm”).
- Selective serotonin reuptake inhibitors (SSRIs) have varying actions at the Sigma1 receptor, an endoplasmic reticulum (ER) chaperone protein which interacts with the ER stress sensor inositol-requiring enzyme 1α (IRE1).
- The S1R-IRE1 pathway modulates the ER stress response, which is involved with both virus-host interactions and regulation of cytokine production.

Fluvoxamine (SSRI, S1R agonist) has been shown to prevent death in animal models of inflammation and sepsis

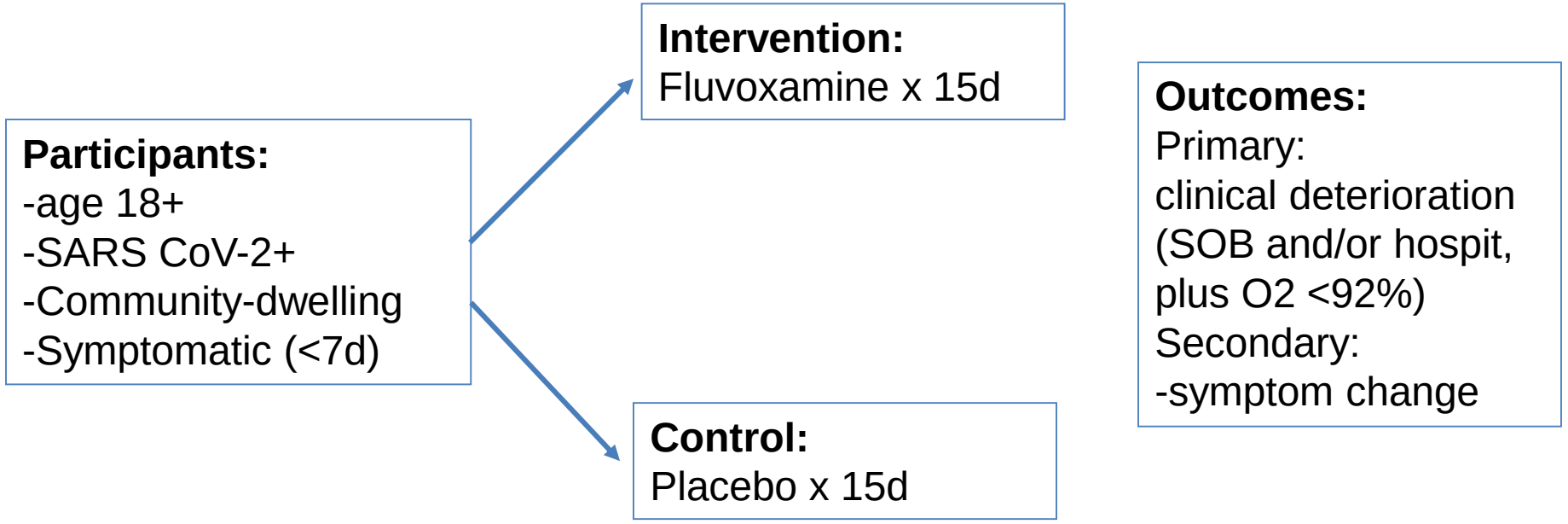
Fluvoxamine prevents death in animal models of inflammation & sepsis…

…and reduces cytokine production in human blood exposed to LPS

Rosen DA, Seki SM, Fernández-Castañeda A, Beiter RM, Eccles JD, Woodfolk JA, Gaultier A. Modulation of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. Sci Transl Med. 2019 Feb 6;11(478):eaau5266.

STOP COVID Trial

hypothesis: fluvoxamine prevents clinical deterioration, if given early in illness



N=152 based on power calculation
(20% clinical deterioration in placebo & 75% reduction of this in fluvoxamine)

Huge challenges to running clinical trials…

-Patients in self-quarantine

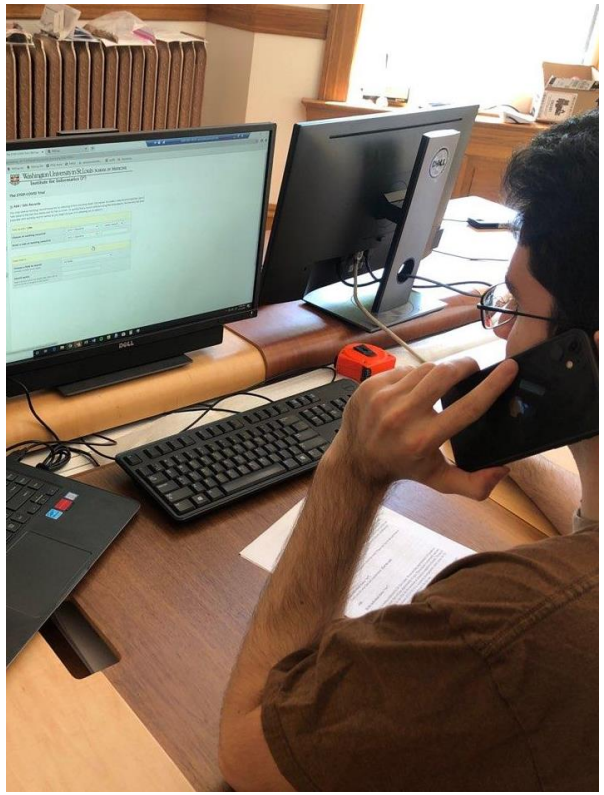
-Need to start treatment fast

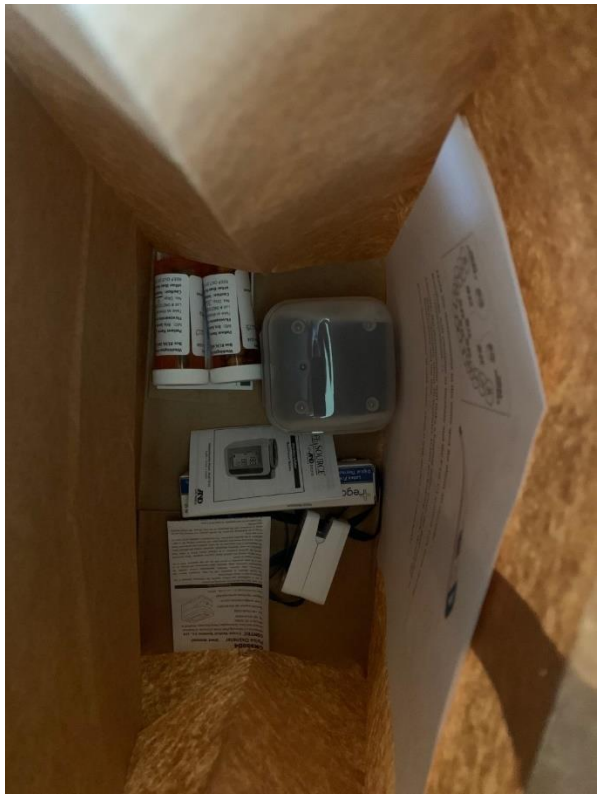
(all this during a pandemic)

SOLUTION: FULLY-REMOTE TRIAL

(take the study to the patient instead of vice versa)

1st decision: be pragmatic

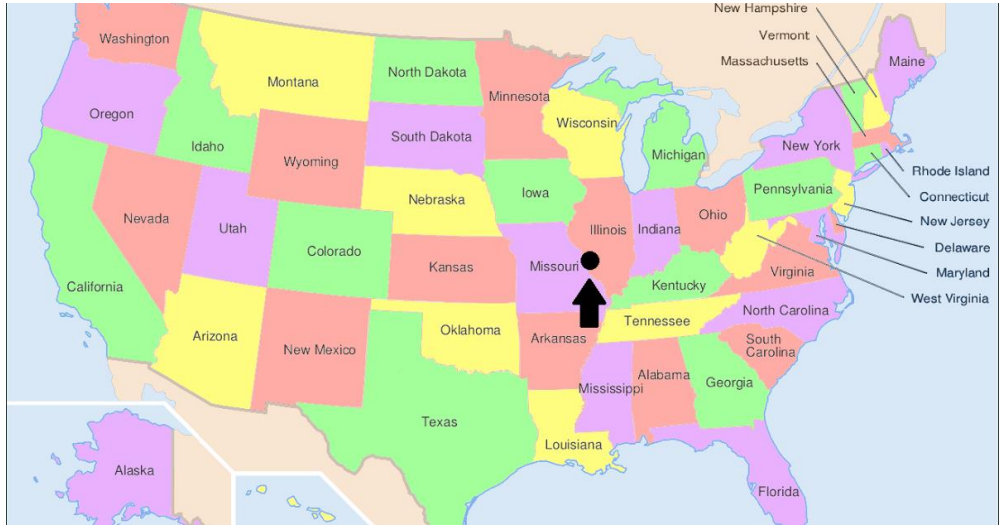


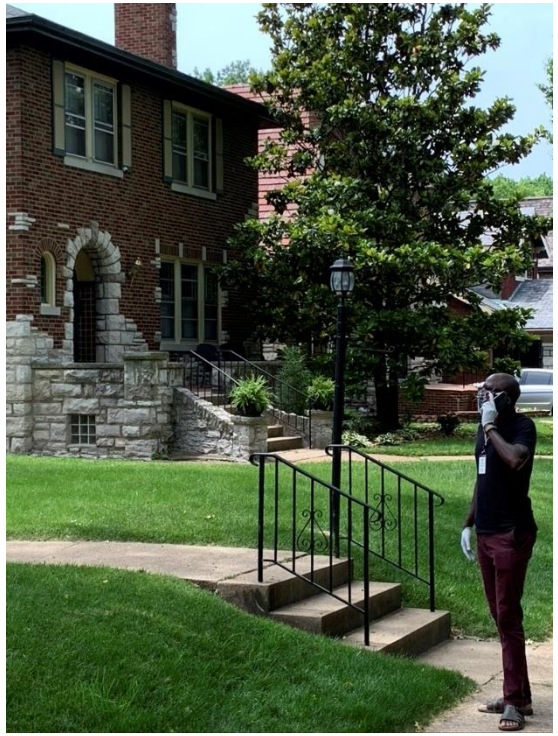


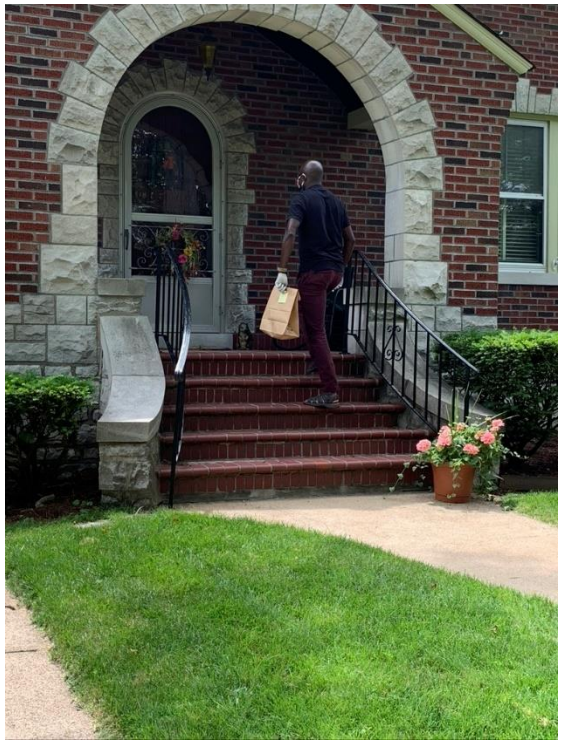
Use EHR to screen for COVID+

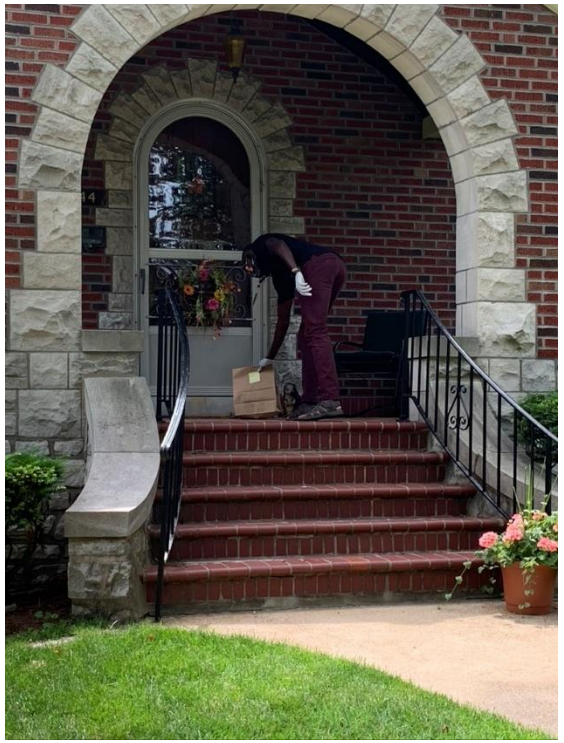
Provide study supples (pills, pulse ox, BP cuff) and instructions

2nd decision: stay local



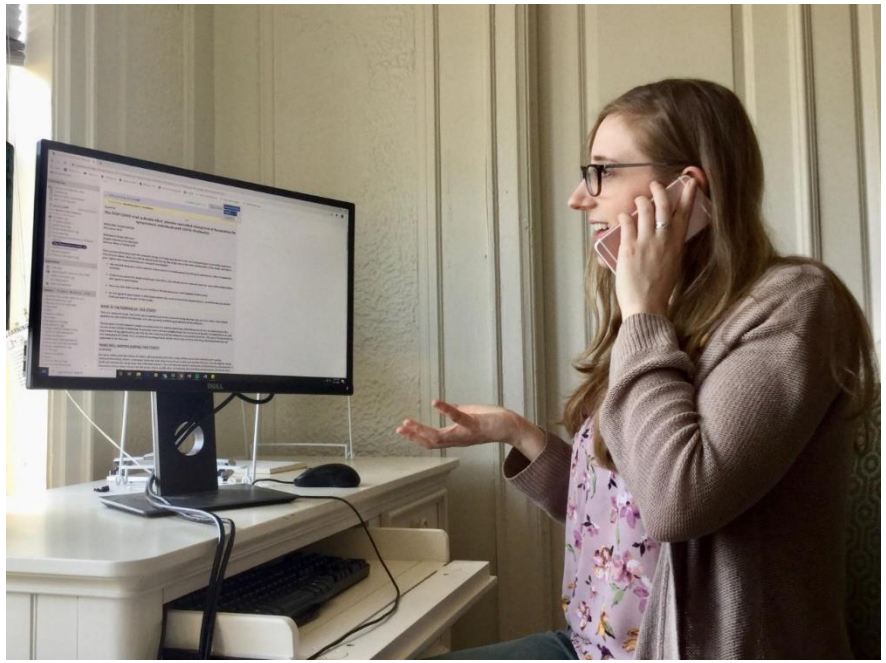






3rd decision: high-touch, not high-tech

Patients self-monitor and enter their data twice daily.



We call them to check on their status.

Methods

- Double-blind, randomized, placebo-controlled, fully-remote (contactless) clinical trial of fluvoxamine.
- 152 adult outpatients with confirmed SARS-CoV-2 infection, with symptom onset within 7 days.
- Randomized to receive fluvoxamine 100mg (n=80), or placebo (n=72), three times daily for 15 days.
- Primary outcome: Clinical deterioration over 15 days, defined by meeting both of the following: (1) shortness of breath and/or hospitalization for shortness of breath or pneumonia; (2) oxygen saturation <92% on room air or need for supplemental oxygen to achieve oxygen saturation ≥92%.

Fully-remote trial success!

- N=152 from one site with minimal resources.
- 92% received 1st dose on same day as first contact.
- Study med started avg 4 days after symptom onset.
- Representative, with 25% African-American.
- Translatable to real-world care.

Results

- 152 participants were randomized in the modified intention to treat group.
- No patients (0/80, 0%) in the fluvoxamine group clinically deteriorated, compared to 8.3% (6/72) in the placebo group (log-rank chi-square 6.8, p=0.009).

Conclusions

- Outpatients treated with fluvoxamine early in the course of symptomatic COVID-19 had a lower likelihood of clinical deterioration over 15 days.

- Larger randomized controlled trials are needed to confirm clinical efficacy.