Fluvoxamine for early treatment of COVID-19: the STOP COVID trials

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Washington University School of Medicine, St Louis, MO
Lenze disclosures (past 36 months)

- Grant support (non-federal): COVID Early Treatment Fund, Mercatus Center Emergent Ventures (Fast Grants), the Skoll Foundation, the Taylor Family Institute for Innovative Psychiatric Research, the Center for Brain Research in Mood Disorders, the Patient-Centered Outcomes Research Institute, Janssen, and the Barnes Jewish Foundation.
- Consulting fees: Janssen, Jazz Pharmaceuticals.
- Patent: Lenze & Reiersen have applied for a patent for the use of fluvoxamine in the treatment of COVID-19.
Anatomy of innovations

Pearl Kendrick & Grace Eldering

- Unexpected people/places
- Serendipity + trial & error
- A collective enterprise
- Need freedom
- Need champions
To: Eric Lenze  
From: Angela Reiersen  

“...regarding the possibility of using SSRIs as potential treatment for COVID-19 cytokine storm...especially fluvoxamine”
Observation of patients with Wolfram Syndrome
(Rare genetic disorder with dysregulated Endoplasmic Reticulum (ER) Stress Response)

Review of pharmacology:
Many SSRIs also affect another receptor, the Sigma-1 receptor (S1R):
Many are S1R agonists (activators); sertraline is S1R antagonist.

Poor outcomes with sertraline; better with other SSRIs (including fluvoxamine)

Review of S1R literature:
What do we know about the S1R and ER stress response?
Fluvoxamine prevents death in mice exposed to inflammatory triggers (such as Fecal Induced Peritonitis [FIP])...

...and reduces cytokine production in human blood exposed to Lipopolysaccharide (LPS, another inflammatory trigger)

Rosen…& Gaultier, “Modification of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis.” Science Translational Medicine, 2019
Hypothesis: Fluvoxamine activates S1R and reduces IRE1-mediated inflammation

The S1R modulates the ER stress response, involved with virus-host interactions and cytokine production.

S1R agonist dampens inflammation and interferes with viral functions through inhibition of IRE1.


S1R=sigma-1 receptor; ER=endoplasmic reticulum; IRE1=inositol-requiring 1 enzyme
STOP COVID trial
hypothesis: fluvoxamine, given early in COVID-19, prevents clinical deterioration

Participants:
n=152
age 18+
SARS CoV-2+
Community-dwelling Symptomatic (<7d)

Intervention:
Fluvoxamine x 15d

Control:
Placebo x 15d

Outcomes:
Primary:
clinical deterioration (=SOB and/or hospitalization + O2 <92%)

Secondary:
symptom change

Participants surveyed twice daily x 15 days
O2 saturation Vital signs
Symptoms Reminder to take study medication
1\textsuperscript{st} decision: start fast and be pragmatic

Use EHR to screen for SARS-CoV-2 PCR+ persons, then e-consent

Provide study supplies (pills, pulse ox, BP cuff) and instructions
2nd decision: take the study to the patient
3rd decision: non-contact but high-touch

Patients self-monitor and enter their data.

We call them to check on their status.
Many COVID trials failed. How we succeeded...

April 10
1st patient randomized

May: recruitment, $ drying up

June: $ from COVID Early Treatment Fund

July: finish recruitment

New cases per day in the United States
Baseline characteristics of the 172 STOP COVID in modified Intent to Treat

<table>
<thead>
<tr>
<th></th>
<th>Fluvoxamine (n = 80)</th>
<th>Placebo (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) [range], y</td>
<td>46 (35-58) [20-75]</td>
<td>45 (36-54) [21-69]</td>
</tr>
<tr>
<td>Sex at birth, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>56 (70)</td>
<td>53 (74)</td>
</tr>
<tr>
<td>Male</td>
<td>24 (30)</td>
<td>19 (26)</td>
</tr>
<tr>
<td>Race, No. (%)(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56 (70)</td>
<td>50 (69)</td>
</tr>
<tr>
<td>Black</td>
<td>18 (23)</td>
<td>20 (28)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
<td>0</td>
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<tr>
<td>American Indian/Alaska Native</td>
<td>0</td>
<td>1 (1)</td>
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<tr>
<td>Ethnicity, No. (%)(^a)</td>
<td></td>
<td></td>
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<tr>
<td>Non-Hispanic/Non-Latino</td>
<td>75 (94)</td>
<td>66 (92)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>3 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Unknown/not reported</td>
<td>2 (3)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Coexisting conditions, No. (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Fluvoxamine</td>
<td>Placebo</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>Asthma</td>
<td>17 (21)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (19)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (11)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>7 (9)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>6 (8)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Arthritis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4 (5)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (1)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body mass index category, No. (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Fluvoxamine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Normal (18.5-24.9)</td>
<td>14 (18)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Overweight (25-29.9)</td>
<td>22 (28)</td>
<td>22 (31)</td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>43 (54)</td>
<td>42 (58)</td>
</tr>
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<thead>
<tr>
<th>Duration of COVID-19 symptoms, median (IQR) [range], d&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Fluvoxamine</th>
<th>Placebo</th>
</tr>
</thead>
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<tr>
<td>4 (3-5) [1-7]</td>
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<thead>
<tr>
<th>Oxygen saturation, median (IQR) [range], %</th>
<th>Fluvoxamine</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>97 (96-98) [93-99]</td>
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</table>

93% received first dose study medication on the same day we first screened them!

Lenze et al., JAMA 2020
Primary endpoint: clinical deterioration (dyspnea PLUS hypoxia [O2<92%])

Fluvoxamine group: 0% (0/80) deteriorated

Placebo group: 8.3% (6/72) deteriorated.
- 5/6 to hospital
- 4 hospitalized

Lenze et al., JAMA 2020
Example of clinical deterioration

Black, non-Hispanic male in his late 60s, with 3 days of COVID-19 symptoms.

Study Day 0: O2= 96% and a shortness of breath rating of 0/10.

Day 2: O2= 96%, shortness of breath score=5/10 in the morning, 8/10 in the evening.

Day 3: admitted to the hospital for fever and nausea. He underwent a chest x-ray which showed opacities. He was hospitalized a total of 8 days, and received supplemental oxygen for 3 of those days to keep oxygen at or above 92%.

Lenze et al., JAMA 2020
Other research supported a role of SSRIs for COVID-19

Hoertel et al, “Association between Antidepressant Use and Reduced Risk of Intubation or Death in Hospitalized Patients with COVID-19: Results from an Observational Study”, Molecular Psychiatry 2021; In Press.
Multiple Mechanisms have been suggested

and a replication of our fluvoxamine findings

November: results published...

Scientific community response

Nice...BUT must be confirmed.

ps, better do it QUICKLY!
Champions

Also put out a Request for Proposals for fluvoxamine for COVID-19. This funded TOGETHER and others.
Hi Ed, that's great to hear! We are starting a confirmatory trial (n=880) this week. It will recruit throughout the US and Canada. Just testing fluvoxamine vs placebo like the first study.

When will you start? Happy to share notes.

Eric

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From: Edward Mills <edward.mills@cytel.com>
Sent: Sunday, December 13, 2020 6:27 PM
To: Lenze, Eric <lenzee@wustl.edu>
Subject: COVID

* External Email - Caution *

Hi Eric,
I understand we are both working on COVID and interested in fluvoxamine. I was speaking with Patrick Collison last night and Silvana Konermann who told me about your work.

We are hoping to initiate a 4 arm platform trial in Brazil among early treatment high-risk patients. Patrick will be supporting the trial (huge thanks to him!). We recently completed a 700 person trial in this population (HCQ, lopinavir, placebo, no effect).

I also heard from Steve Kern at Gates Foundation that you have been interacting with and he suggested we connect.

Please do let me know of overlap and I'd be delighted to chat with you about this so we can potentially pool any results.

Best wishes
Ed
How to conduct a large trial quickly?

A decentralized clinical trial

A few investigative sites

National recruitment

Telemedicine intervention and remote monitoring

Ship study supplies and medication

Cummings, “Clinical trials without clinical sites”, *JAMA Internal Med* 2021
STOP COVID 2 team (building a plane while flying)
Hub & spoke recruitment

Recruit from here
Local + national recruitment

Partner sites focus on local/regional recruitment resources and participants

Lead site Washington U recruits nationally
How did we recruit and manage?

• Social media (FB, Twitter) and Google ads for national recruitment via study website
  – Working with experts was essential (but expensive)
    • antidote.me for FB
    • Parsemus Foundation provided Google ads and expertise

• COVID testing sites: opt-out messaging
  – Curative; local connections (eg Univ Utah)

• REDCap e-consent, surveys pushed automatically to participants once enrolled (text/email)

• Overnight shipping (some hiccups)
STOP COVID 2: design summary

Participants:
- n=880 mITT*
- High-risk sample**
- SARS-CoV-2+ community-dwelling symptomatic (<7d)
- Age 30+

Outcomes:

Primary:
- clinical deterioration over 15 days (definition: SOB and/or hospit, plus O2 <92%)

Secondary:
- 15-day and 3 month function (Global Health Scale)

* mITT: modified intent-to-treat (= met criteria and took at least one dose study med)
** based on age >30yo or race/ethnicity; medical comorbidity
Recruitment challenges: a portent?

* External Email - Caution *

The ONLY compensation is $50 are you serious..... that’s a complete joke!!!
And SO ARE YOU!

Sent from my iPhone
Recruitment went ok...until the vaccines caught up

More recruitment effort ($) was able to (partially) offset vaccines…

…until it wasn’t.

DSMB recommended early stop for futility

Why futility?

- Low case rate (only 30/551 = 5.4%)
- No differences between flv and pbo
- Sample size recalculation: would need >3,000
As the study proceeded, more problems engaging patients

“I tried calling the wife of xxx to get info on his hospital stay. She was NOT happy to hear from me. She yelled that she was busy and doesn’t have time for this…and she hung up on me.”

“Participants…are actively dodging my calls. One of them answered and after I introduced myself she said “let me put you on hold for a second” and proceeded to leave me on hold for 6 minutes. I have tried calling her back but she sends me to VM after 1 or 2 rings.”
“After talking with his physician today, it was suggested to stop the medication since he doesn’t know if he is on the real medication or placebo. His PCP prescribed him Ivermectin 21 mg and Fluvoxamine 50 mg”

(at least 14 cases of clinician interference in STOP COVID 2)
Engagement got **harder** as the study went on. Conscientious people vaccinated, which left…

What it’s like to be a server during the pandemic: ‘The things that I loved about my job — they were gone’

“What became abundantly clear is that people were not excited, or really even willing, to put on a mask to interact with the team.”

Now, I would say 80% of them are combative. ... It is a different clientele walking in the door.”

Bar Owner, 2020
Low case rate: why were people not that ill?

- Only 20 COVID hospitalizations (~3.5%). Why?
  - Highest-risk already vaccinated or receiving monoclonal Abs?
  - Healthy User bias in recruitment strategy?
  - Taking concurrent meds? (e.g. steroids in 10%)
  - Catching people too late?
    - Up to 7 days symptoms, 10 days since + test
## Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Fluvoxamine (N=276)</th>
<th>Placebo (N=275)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years, Median(Q1-Q3)</strong></td>
<td>47(40-55)</td>
<td>48(41-56)</td>
</tr>
<tr>
<td><strong>Onset Days, Median(Q1-Q3)</strong></td>
<td>5(4-6)</td>
<td>5(4-6)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>171(62%)</td>
<td>170(62%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>6(2.2%)</td>
<td>8(2.9%)</td>
</tr>
<tr>
<td>Asian</td>
<td>9(3.3%)</td>
<td>5(1.8%)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>23(8.3%)</td>
<td>23(8.4%)</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>198(71.7%)</td>
<td>201(73.1%)</td>
</tr>
<tr>
<td>Native Hawaiian/ Pacific Islander</td>
<td>5(1.8%)</td>
<td>5(1.8%)</td>
</tr>
<tr>
<td>South Asian</td>
<td>3(1.1%)</td>
<td>2(0.7%)</td>
</tr>
<tr>
<td>Unknown/Not reported</td>
<td>17(6.16%)</td>
<td>22(8%)</td>
</tr>
<tr>
<td>Other</td>
<td>29(10.5%)</td>
<td>21(7.6%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>35(12.7%)</td>
<td>37(13.5%)</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/underweight</td>
<td>71(25.7%)</td>
<td>62(13.5%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>87(31.5%)</td>
<td>90(32.7%)</td>
</tr>
<tr>
<td>Obese</td>
<td>118(42.8%)</td>
<td>123(44.7%)</td>
</tr>
<tr>
<td><strong>Coexisting conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td>4(1.5%)</td>
<td>4(1.5%)</td>
</tr>
<tr>
<td>Lung Disease</td>
<td>2(0.7%)</td>
<td>2(0.7%)</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>1(0.4%)</td>
<td>1(0.4%)</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>1(0.4%)</td>
<td>2(0.7%)</td>
</tr>
<tr>
<td>Hepatitis B/C</td>
<td>1(0.4%)</td>
<td>1(0.4%)</td>
</tr>
<tr>
<td>Immune Disorder</td>
<td>14(5.1%)</td>
<td>4(1.5%)</td>
</tr>
<tr>
<td>HIV</td>
<td>1(0.4%)</td>
<td>4(1.5%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>40(14.5%)</td>
<td>33(12%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57(20.7%)</td>
<td>62(22.6%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23(8.3%)</td>
<td>28(10.2%)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>0(0%)</td>
<td>1(0.4%)</td>
</tr>
<tr>
<td>Thyroid problem</td>
<td>20(7.3%)</td>
<td>27(9.8%)</td>
</tr>
<tr>
<td>Other Medical Conditions</td>
<td>42(15.2%)</td>
<td>54(19.6%)</td>
</tr>
</tbody>
</table>
### No treatment effect: was it a case of “too little, too late”?

<table>
<thead>
<tr>
<th>Timing/adherence</th>
<th>Treatment condition among those who deteriorated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>Started drug with &lt;= 4 days of symptoms</td>
<td>20%</td>
</tr>
<tr>
<td>Started drug day 5-7 of symptoms</td>
<td>80%</td>
</tr>
<tr>
<td>Took &lt;10 pills (i.e. 5 days)</td>
<td>53%</td>
</tr>
<tr>
<td>Started late OR took &lt;10 pills</td>
<td>100%</td>
</tr>
<tr>
<td>Deteriorated AFTER stopping blinded study medication</td>
<td>20%</td>
</tr>
</tbody>
</table>
Conclusion (part 1): what we learned

• COVID-19 treatment trials are VERY challenging
  – Need a lot of sites that can recruit locally and engage patients, clinicians

• BUT Decentralized trials are feasible in academia
  – STOP COVID 2 design can be successful
  – Need robust ($) recruitment AND engagement strategy
But meanwhile, the TOGETHER Trial...

### Relative Risk of Emergency Room Observation for > 6 Hours or Hospitalization for Fluvoxamine vs. Placebo

<table>
<thead>
<tr>
<th>Arm</th>
<th>Number of patients</th>
<th>Number of events</th>
<th>Relative risk(^+) [95% CrI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>739</td>
<td>77</td>
<td>0.71[0.54;0.93]</td>
</tr>
<tr>
<td>Placebo</td>
<td>733</td>
<td>108</td>
<td>Reference</td>
</tr>
</tbody>
</table>

\(^+\) Calculated in a Bayesian framework
Conclusion (part 2)

- Clinical trial innovation is possible!
  - Needs persistence, collaboration, champions, and luck.
  - Trial & error: don’t be afraid to fail (but have a back-up plan)
Thanks to...

- STOP COVID 1 team
- STOP COVID 2 team
- Healthy Mind Lab
- Many champions, esp Steve Kirsch & CETF; Patrick Collison & Fast Grants; Taylor Foundation (WU); NIH; WU COVID committee and IRB

...and Ed Mills and the TOGETHER Trial for getting across the finish!
Questions? (here’re mine)

• Should we use it now?
• When will we have more replications?
• What are the best dose & duration?
• Does it work better if started sooner?
• Does fluoxetine work?
• Mechanism(s)?
• What else does it work for?