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

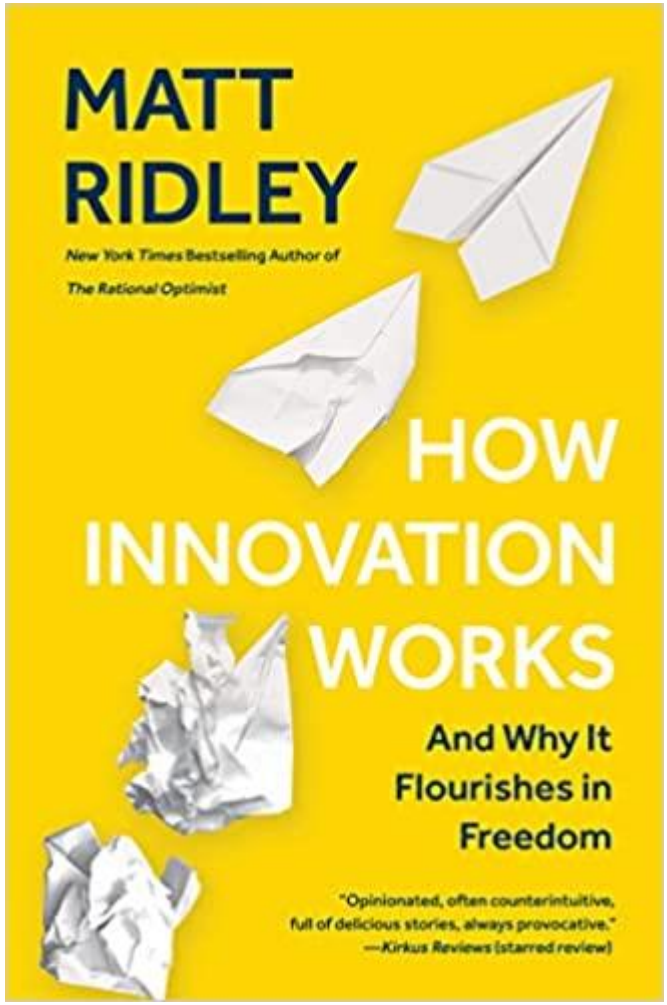
Eric Lenze, M.D.

Wallace & Lucille Renard Professor of Psychiatry & Anesthesiology

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

Rewind…March 25, 2020

To: Eric Lenze
From: Angela Reiersen

"…regarding the possibility of using SSRIs as potential treatment for COVID-19 cytokine storm…especially **fluvoxamine**"

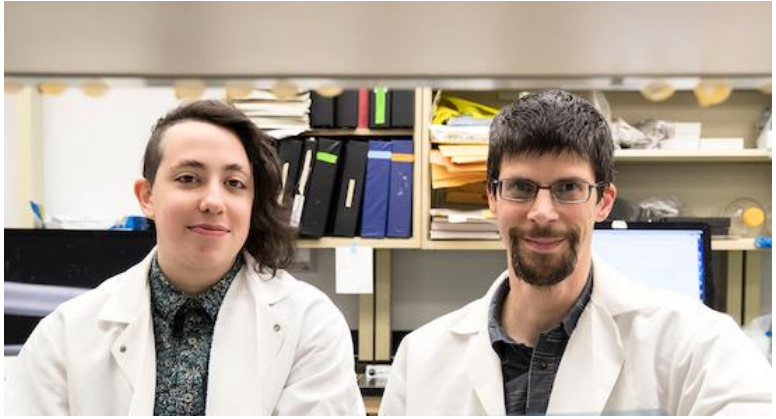
Angela Reiersen, M.D.
(Washington University, St Louis)

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.**

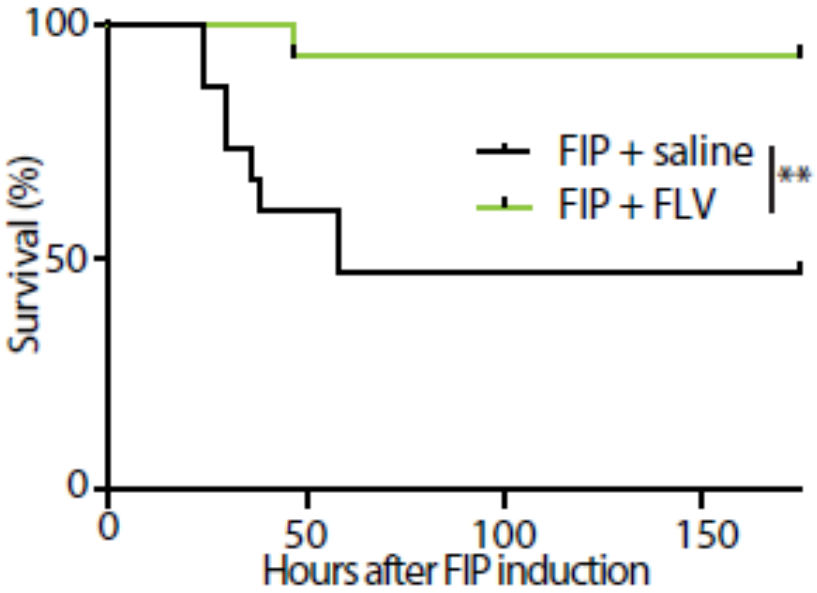
Poor outcomes with sertraline; better with other SSRIs (including fluvoxamine)

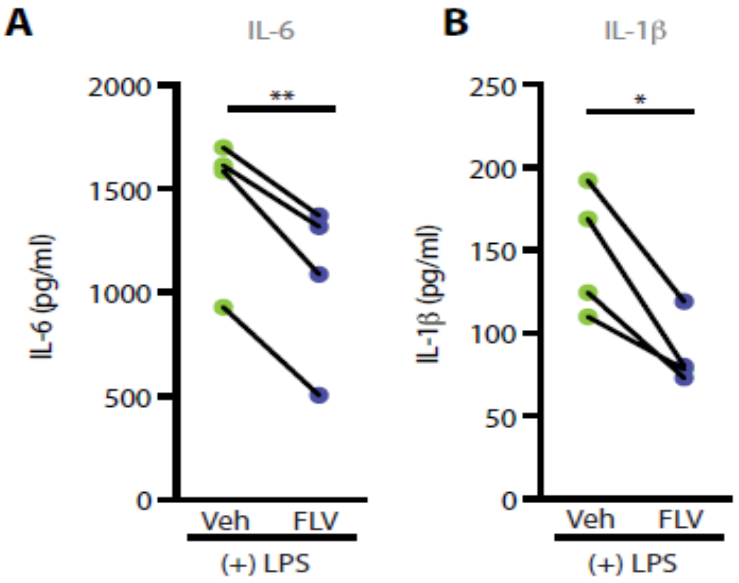
Review of S1R literature:
What do we know about the S1R and ER stress response?



Dorian Rosen and Alban Gaultier
(at University of Virginia)

Fluvoxamine prevents death in mice exposed to inflammatory triggers (such as Fecal Induced Peritonitis [FIP])…

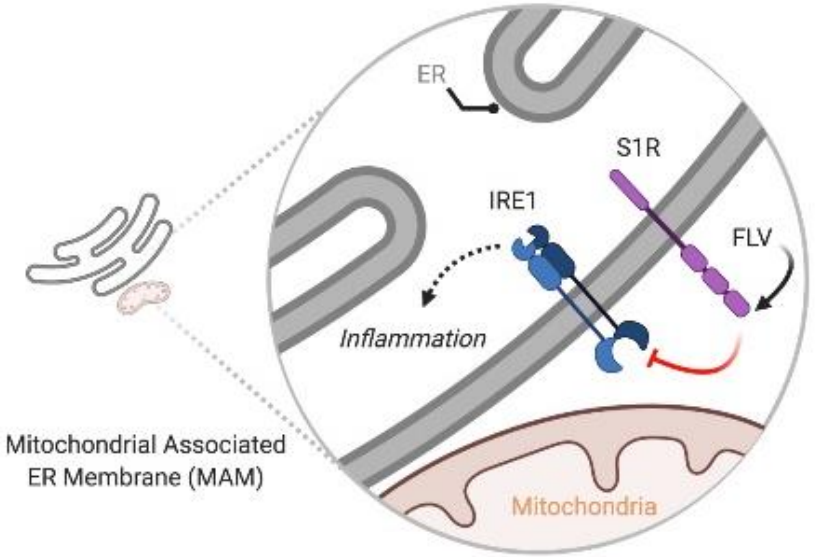




…and reduces cytokine production in human blood exposed to Lipopolysaccharide (LPS, another inflammatory trigger)

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.

From Sukhatme, Reiersen, et al, “Fluvoxamine: A review of its mechanism of action and its role in COVID-19”, Front Pharmacol 2021

S1R=sigma-1 receptor; ER=endoplasmic reticulum; IRE1=inositol-requiring 1 enzyme

Caline Mattar. M.D.

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

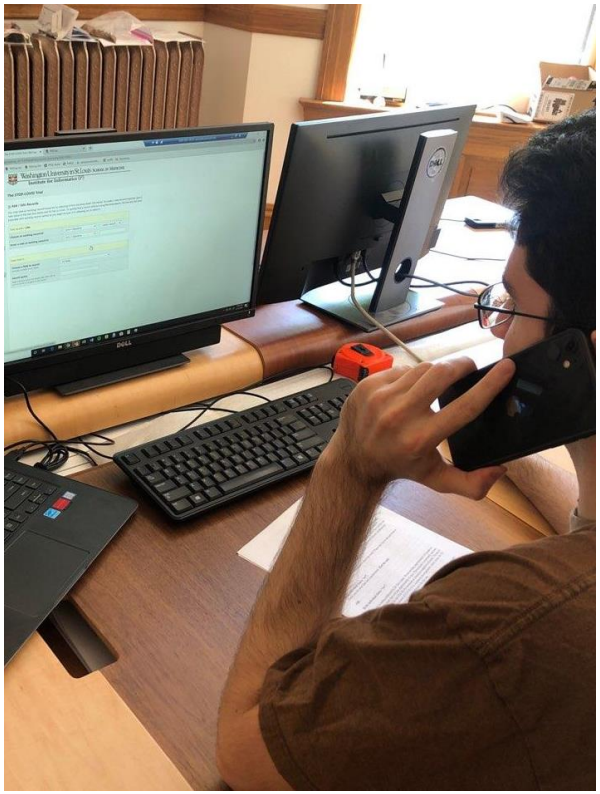
Control:
Placebo x 15d

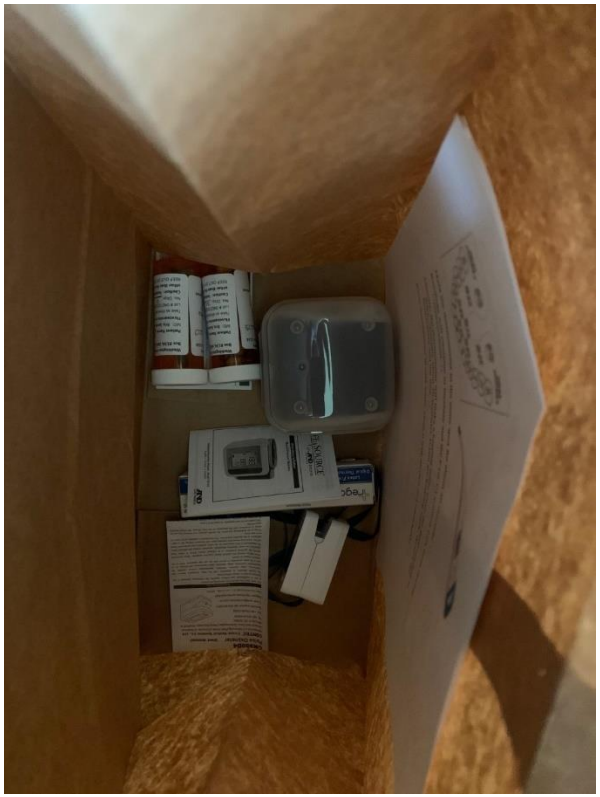
Outcomes:
Primary:
clinical deterioration (=SOB and/or hospitalization + O2 <92%)

Secondary:
-symptom change

Participants surveyed twice daily x 15 days
O2 saturation
Symptoms
Vital signs
Reminder to take study medication

1st decision: start fast and be pragmatic

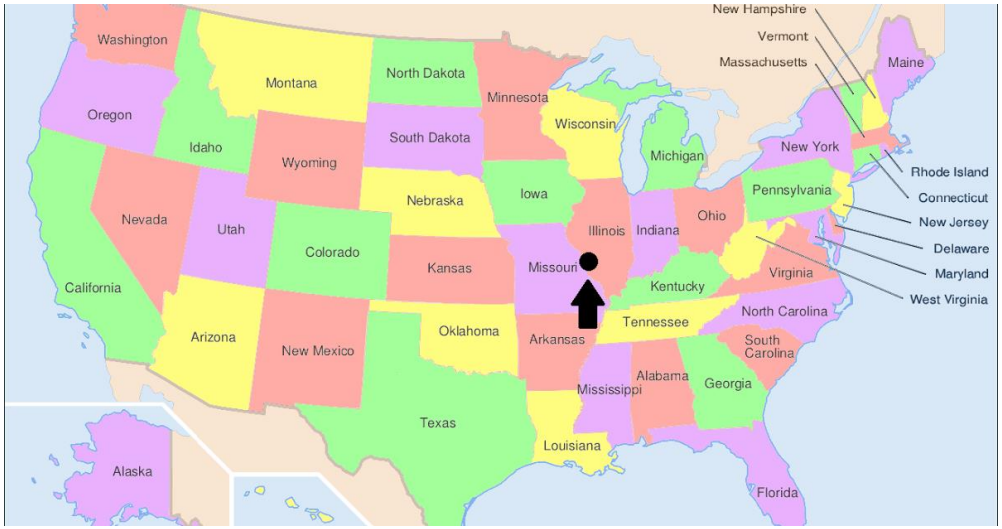


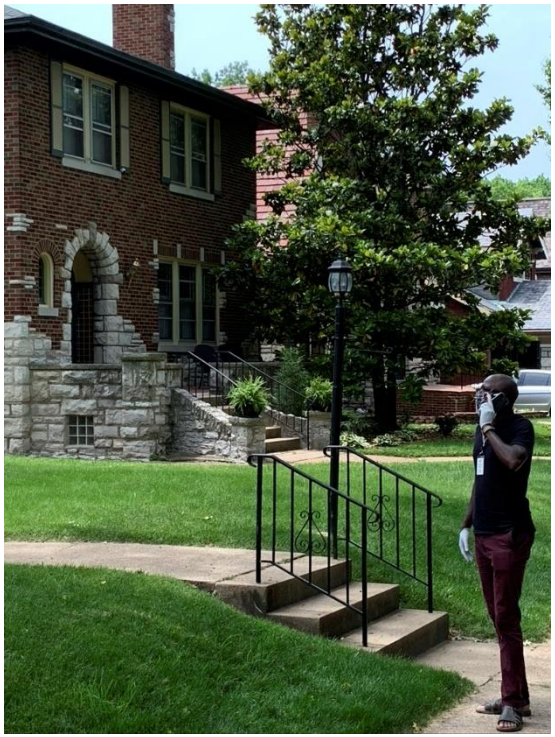


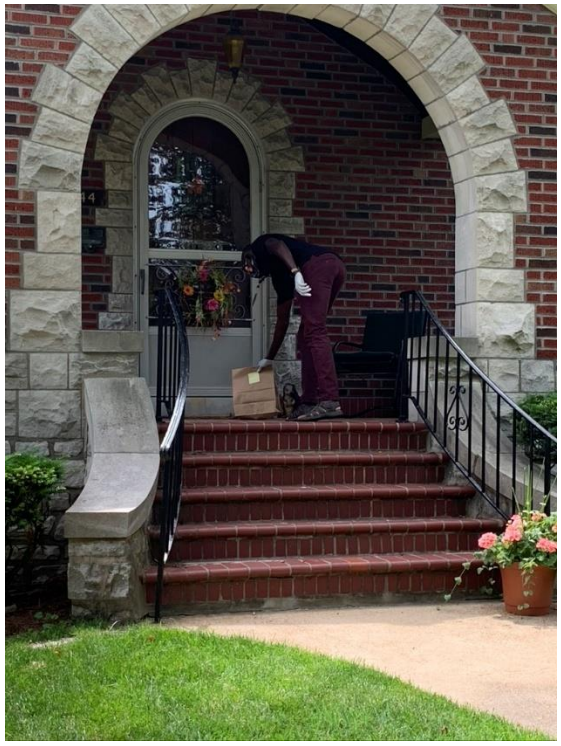
Use EHR to screen for SARS-CoV-2 PCR+ persons, then e-consent

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

2nd decision: take the study to the patient

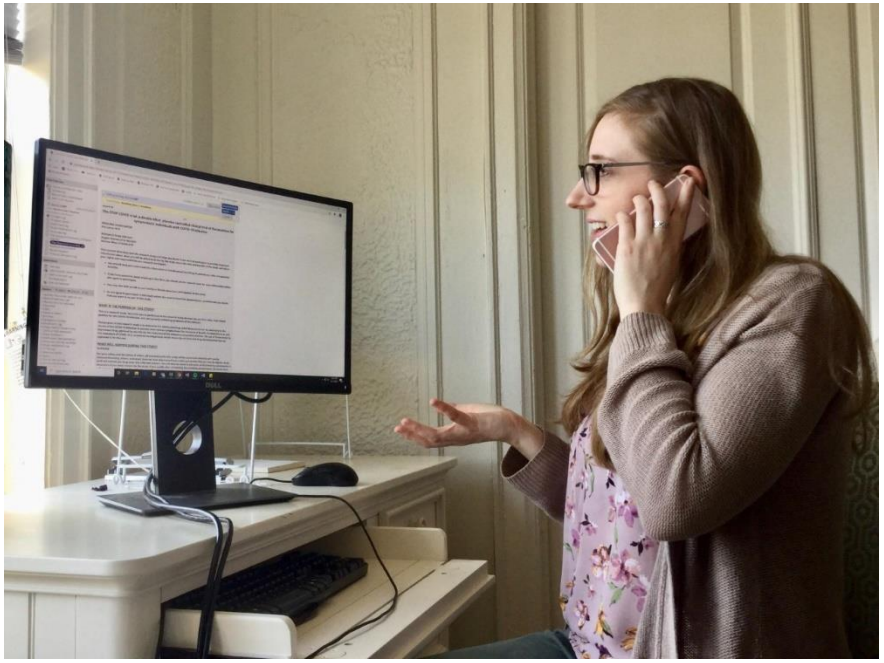






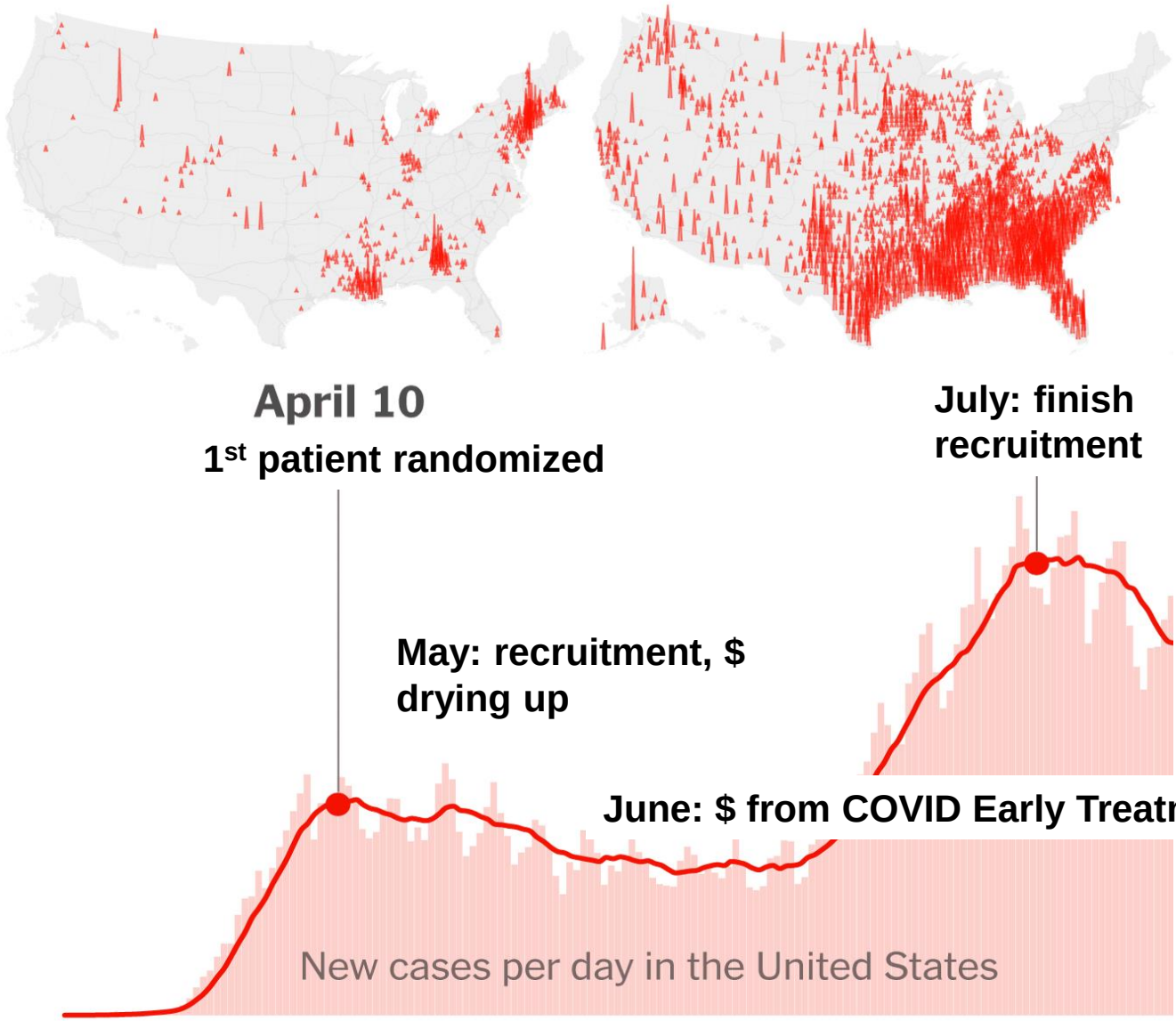
3rd decision: non-contact but high-touch

Patients self-monitor and enter their data.



We call them to check on their status.

Many COVID trials failed. How we succeeded…



Baseline characteristics of the 172 STOP COVID in modified Intent to Treat

	Fluvoxamine (n = 80)	Placebo (n = 72)
Age, median (IQR) [range], y	46 (35-58) [20-75]	45 (36-54) [21-69]
Sex at birth, No. (%)		
Female	56 (70)	53 (74)
Male	24 (30)	19 (26)
Race, No. (%)[a]		
White	56 (70)	50 (69)
Black	18 (23)	20 (28)
Asian	3 (4)	1 (1)
Other	2 (3)	1 (1)
Unknown	1 (1)	0
American Indian/Alaska Native	0	1 (1)
Ethnicity, No. (%)[a]		
Non-Hispanic/Non-Latino	75 (94)	66 (92)
Hispanic/Latino	3 (4)	2 (3)
Unknown/not reported	2 (3)	4 (5)

Lenze et al., JAMA 2020

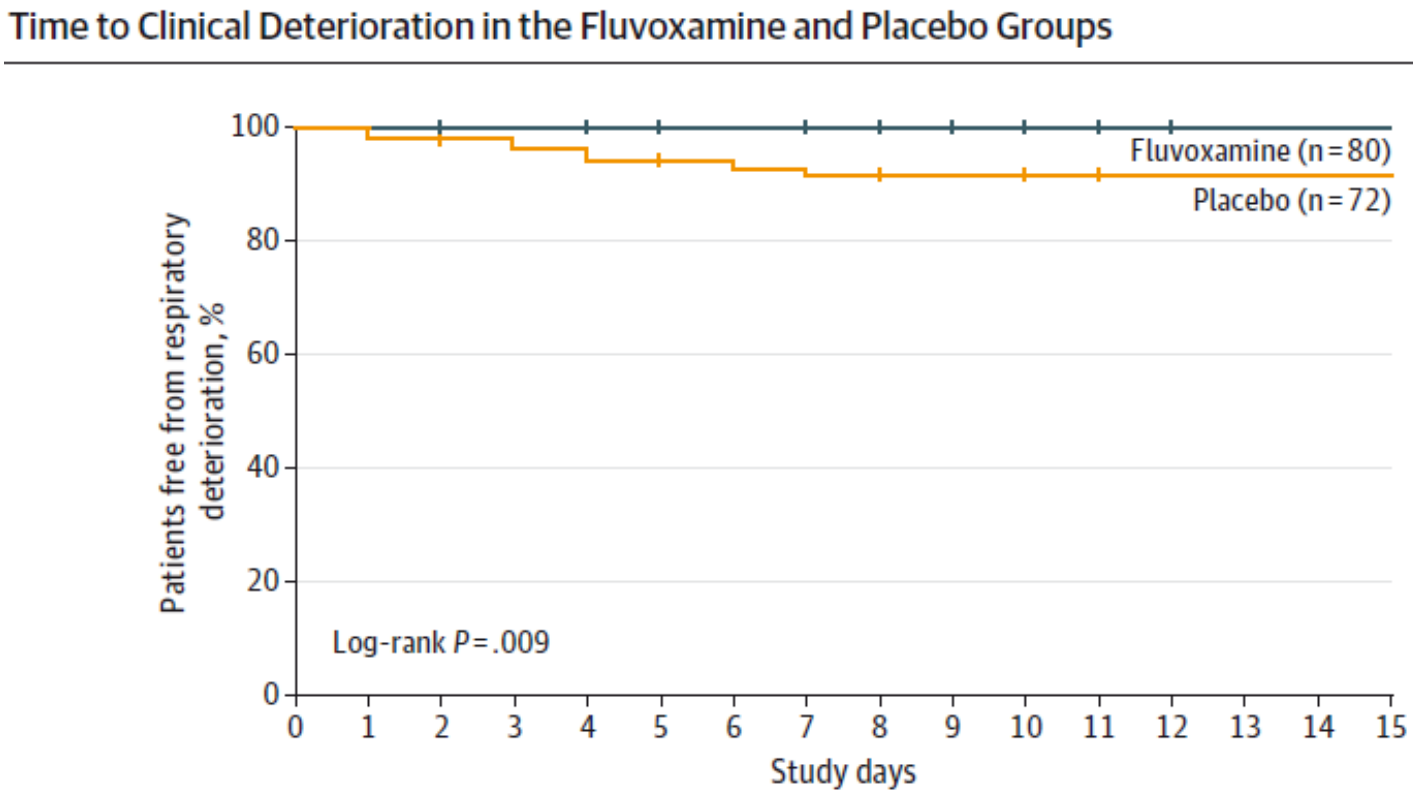
Coexisting conditions, No. (%)[a]	Fluvoxamine	Placebo
Asthma	17 (21)	9 (13)
Hypertension	15 (19)	15 (21)
Diabetes	9 (11)	8 (11)
High cholesterol	7 (9)	7 (10)
Hyperthyroidism	6 (8)	6 (8)
Anxiety	5 (6)	1 (1)
Arthritis[b]	4 (5)	3 (4)
Depression	1 (1)	4 (6)
Body mass index category, No. (%)[c]		
Underweight (<18.5)	1 (1)	1 (1)
Normal (18.5-24.9)	14 (18)	7 (10)
Overweight (25-29.9)	22 (28)	22 (31)
Obese (≥30)	43 (54)	42 (58)
Duration of COVID-19 symptoms, median (IQR) [range], d[a]	4 (3-5) [1-7]	4 (3-5) [1-7]
Oxygen saturation, median (IQR) [range], %	97 (96-98) [93-99]	97 (96-98) [92-99]

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.

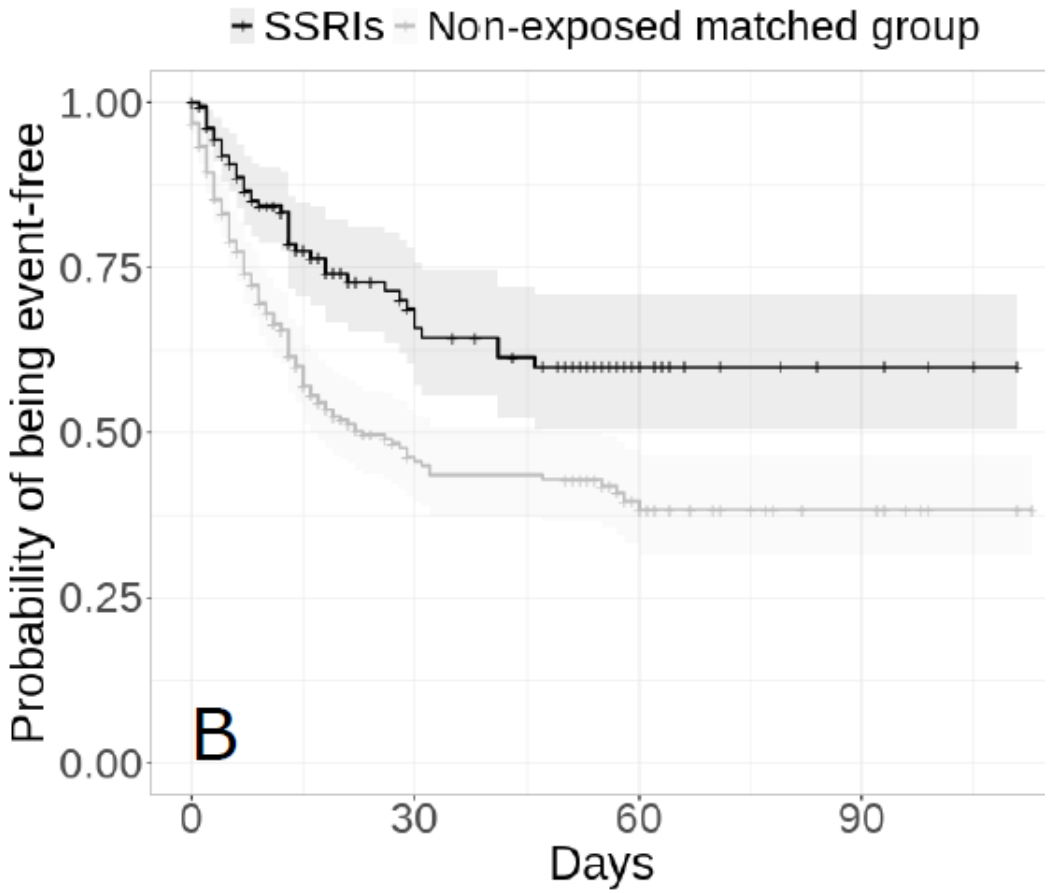
Study Day 0: O2= 96% and a shortness of breath rating of 0/10.

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

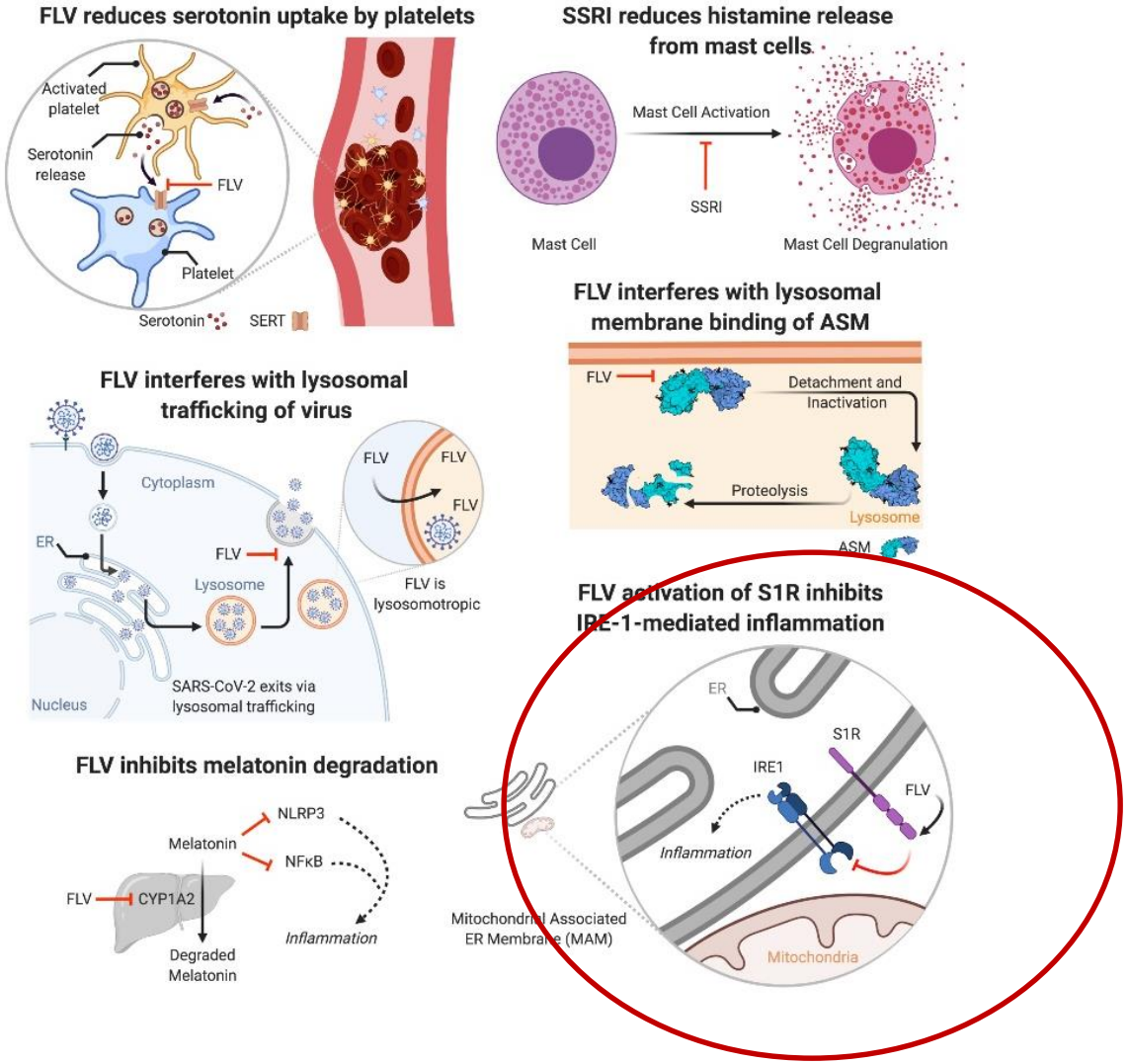
Other research supported a role of SSRIs for COVID-19



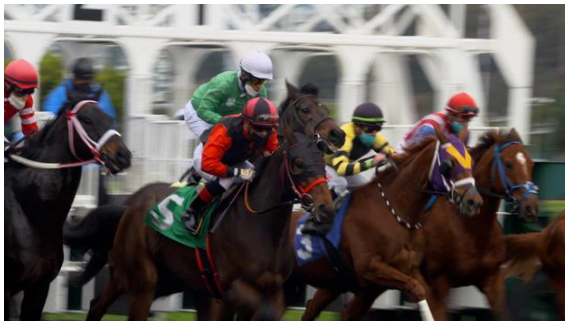
Observational study in Paris: patients hospitalized with COVID-19 had lower likelihood of intubation or death, if taking SSRIs

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



Sukhatme, Reiersen, et al, “Fluvoxamine: A review of its mechanism of action and its role in COVID-19”, *Front Pharmacol* 2021; *In Press*.



….and a replication of our fluvoxamine findings

Mass Occupational Outbreak in California

113 non-hospitalized persons

- Detected by rapid Ag tests
- Confirmed by PCR

All offered Fluvoxamine as an optional therapy

		Hospitalization	Symptoms at 14 days
N = 65	Fluvoxamine 50mg 2x daily for 14 days	0% (0/65)	0% (0/65)
N = 48	Observation Alone	12.5% (6/48)	60% (29/48)

Seftel & Boulware, “Prospective cohort of fluvoxamine for early treatment of Coronavirus disease 19”, *Open Forum Infectious Diseases 2021*.

November: results published…

JAMA | Preliminary Communication

Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19
A Randomized Clinical Trial

Eric J. Lenze, MD; Caline Mattar, MD; Charles F. Zorumski, MD; Angela Stevens, BA; Julie Schweiger; Ginger E. Nicol, MD; J. Philip Miller, AB; Lei Yang, MPH, MSIS; Michael Yingling, MS; Michael S. Avidan, MBBCh; Angela M. Reiersen, MD, MPE

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.

Edward Mills <edward.mills@cytel.com>

Re: COVID

o this message on 4/1/2021 12:10 PM.
roblems with how this message is displayed, click here to view it in a web browser.

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

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

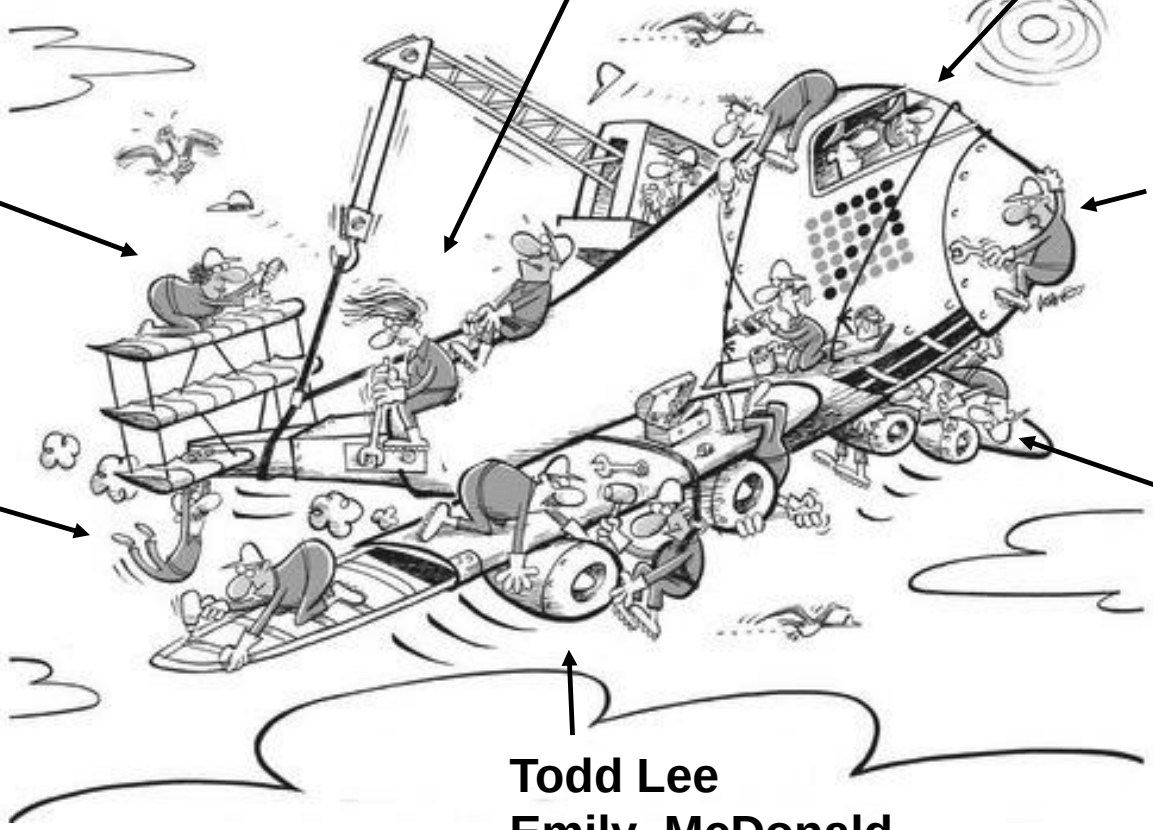
Ship study supplies and medication

FedEx

Telemedicine intervention and remote monitoring

Cummings, “Clinical trials without clinical sites”, *JAMA Internal Med 2021*

STOP COVID 2 team (building a plane while flying)



Rachel Bender Ignacio
Josh Schiffer
Fred Hutch

Eric Lenze
Angela Reiersen
Washington U

Simone Vigod
Payal Agarwal
U Toronto

David Boulware
U Minn
(Consultant)

Jeff Rado
Northwestern

Rachel Hess
Adam Spivak
Univ of Utah

Todd Lee
Emily McDonald
McGill

Hub & spoke recruitment

Recruit from here
Local + national recruitment

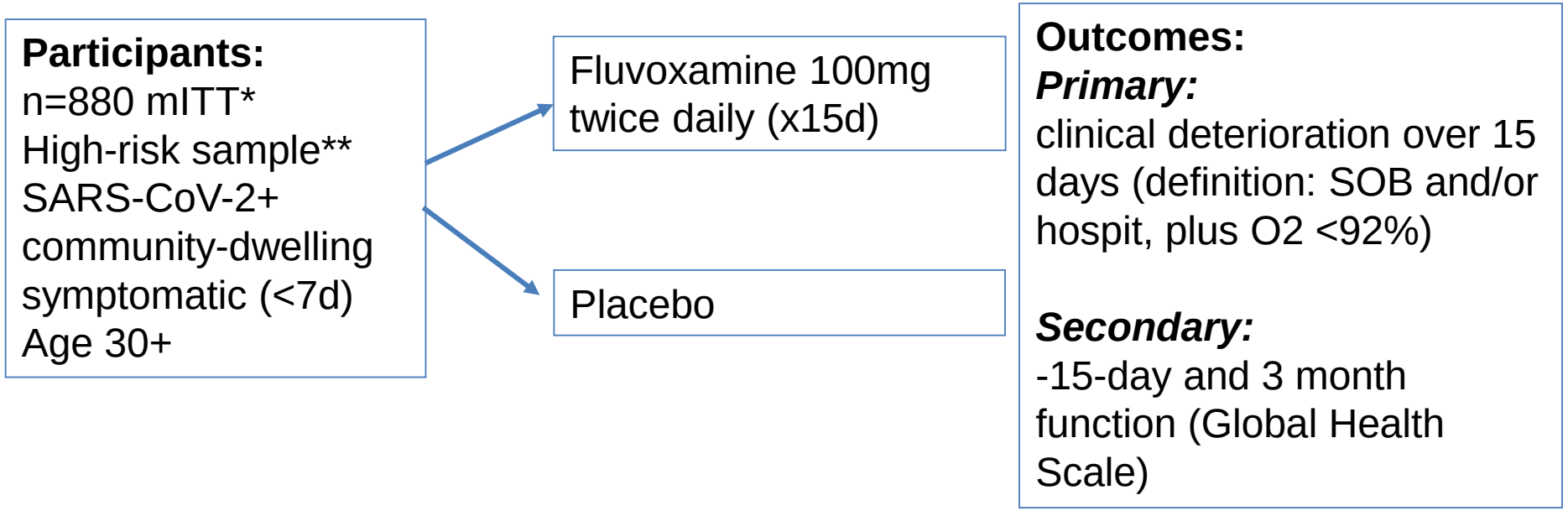
Partner sites focus on local/regional recruitment resources and participants

Lead site
Washington U recruits nationally

How did we recruit and manage?

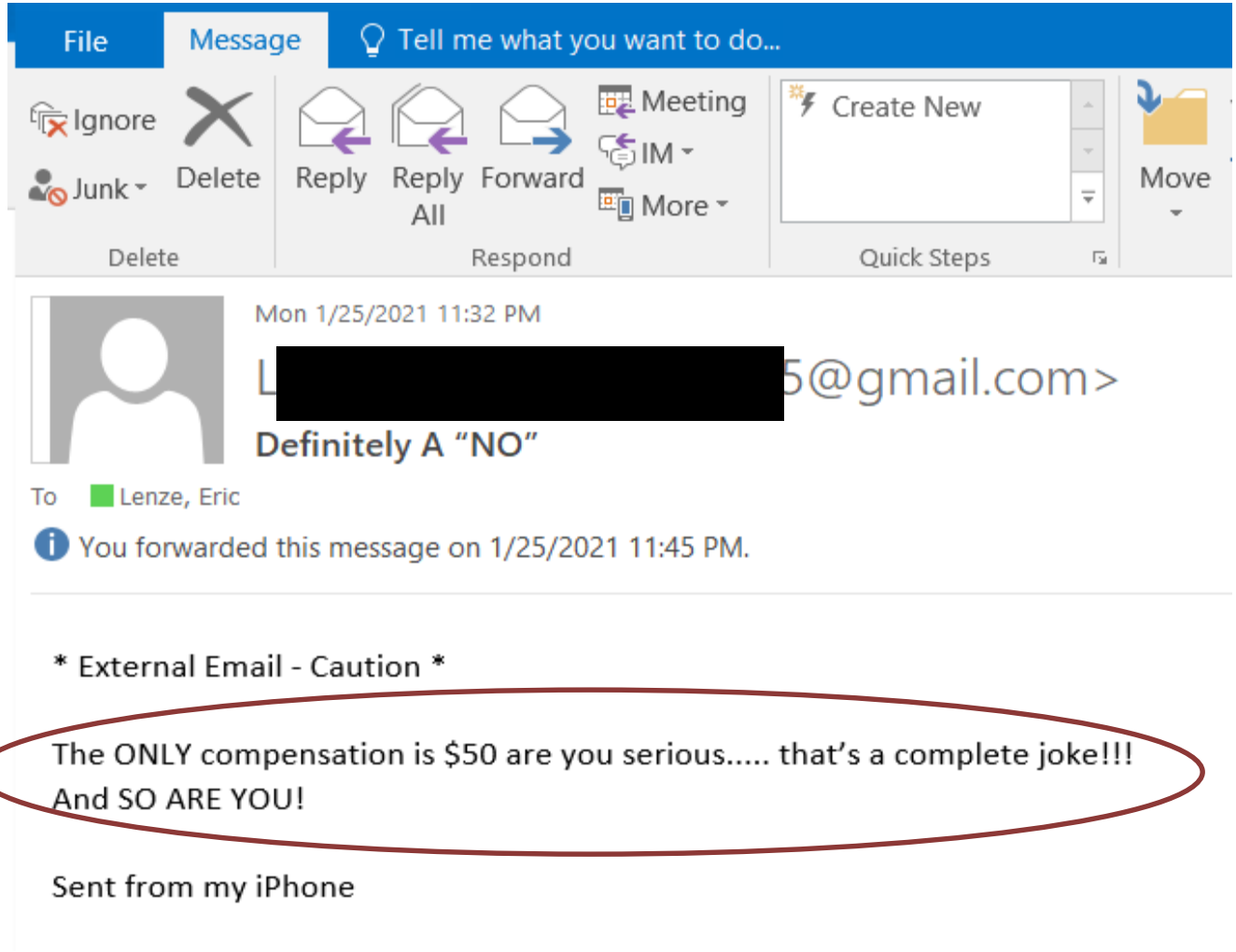
- Social media (FB, Twitter) and Google ads for national recruitment via study website
  - Working with experts was essential (but expensive)
    - antidote.me for FB
    - Parsemus Foundation provided Google ads and expertise
- COVID testing sites: opt-out messaging
  - Curative; local connections (eg Univ Utah)
- REDCap e-consent, surveys pushed automatically to participants once enrolled (text/email)
- Overnight shipping (some hiccups)

STOP COVID 2: design summary

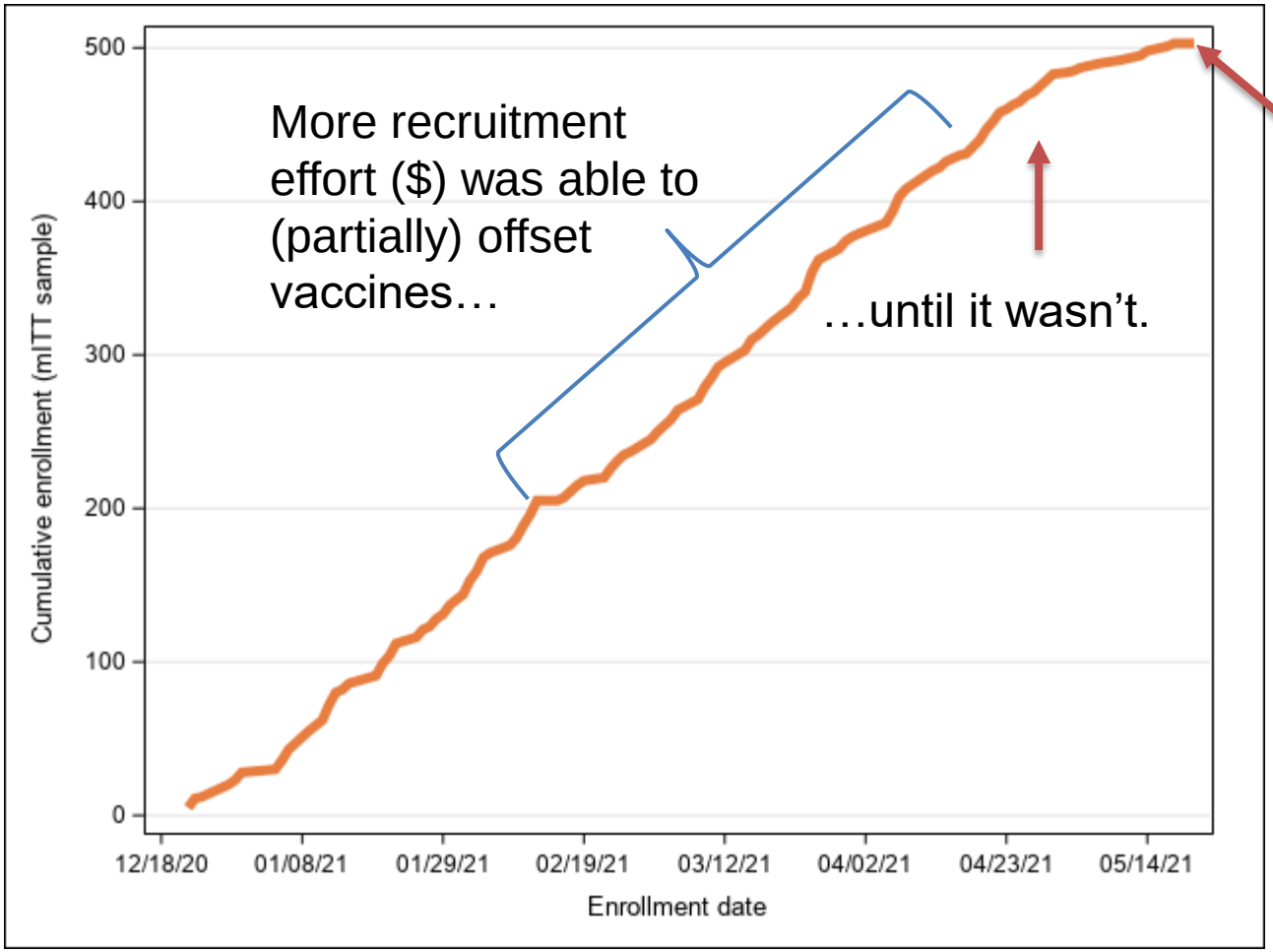


* mITT: modified intent-to-treat (= met criteria and took at least one dose study med)
** based on age >30yo or race/ethnicity; medical comorbidity

Recruitment challenges: a portent?



Recruitment went ok…until the vaccines caught up



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."

…and clinician interference

"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…

The Philadelphia Inquirer

Food

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

Characteristics	Fluvoxamine (N=276)	Placebo(N=275)
Age in years, Median(Q1-Q3)	47(40-55)	48(41-56)
Onset Days, Median(Q1-Q3)	5(4-6)	5(4-6)
Women	171(62%)	170(62%)
Race		
American Indian/Alaska Native	6(2.2%)	8(2.9%)
Asian	9(3.3%)	5(1.8%)
Black/African American	23(8.3%)	23(8.4%)
White/Caucasian	198(71.7%)	201(73.1%)
Native Hawaiian/ Pacific Islander	5(1.8%)	5(1.8%)
South Asian	3(1.1%)	2(0.7%)
Unknown/Not reported	17(6.16%)	22(8%)
Other	29(10.5%)	21(7.6%)
Ethnicity		
Hispanic/Latino	35(12.7%)	37(13.5%)
Obesity		
Normal/underweight	71(25.7%)	62(13.5%)
Overweight	87(31.5%)	90(32.7%)
Obese	118(42.8%)	123(44.7%)
Coexisting conditions		
Heart Disease	4(1.5%)	4(1.5%)
Lung Disease	2(0.7%)	2(0.7%)
Liver Disease	1(0.4%)	1(0.4%)
Kidney Disease	1(0.4%)	2(0.7%)
Hepatitis B/C	1(0.4%)	1(0.4%)
Immune Disorder	14(5.1%)	4(1.5%)
HIV	1(0.4%)	4(1.5%)
Asthma	40(14.5%)	33(12%)
Hypertension	57(20.7%)	62(22.6%)
Diabetes	23(8.3%)	28(10.2%)
Active cancer	0(0%)	1(0.4%)
Thyroid problem	20(7.3%)	27(9.8%)
Other Medical Conditions	42(15.2%)	54(19.6%)

No treatment effect: was it a case of "too little, too late"?

Timing/adherence	Treatment condition among those who deteriorated	
	Fluvoxamine	**Placebo**
Started drug with <= 4 days of symptoms	20%	33%
Started drug day 5-7 of symptoms	80%	67%
Took <10 pills (i.e. 5 days)	53%	47%
Started late OR took <10 pills	**100%**	**93%**
Deteriorated AFTER stopping blinded study medication	20%	7%

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 <u>are</u> feasible in academia
  - STOP COVID 2 design can be successful
  - Need robust ($) recruitment AND engagement strategy

But meanwhile, the TOGETHER Trial…

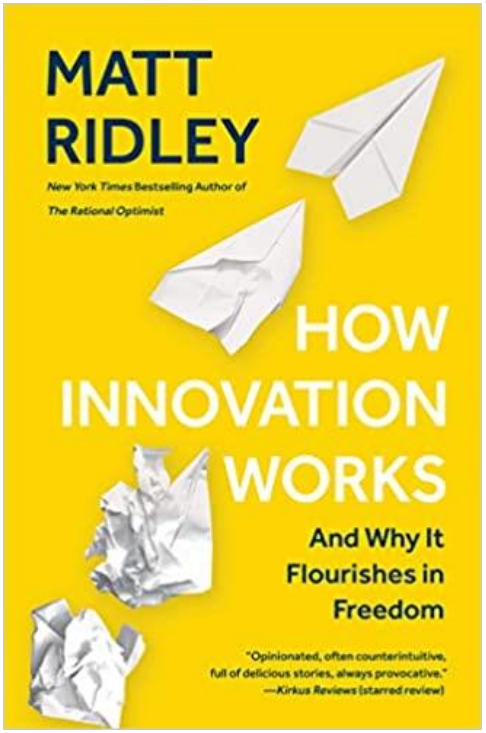
Relative Risk of Emergency Room Observation for > 6 Hours or Hospitalization for Fluvoxamine vs. Placebo

Arm	Number of patients	Number of events	Relative risk⁺ [95% CrI]
Fluvoxamine	739	77	0.71[0.54;0.93]
Placebo	733	108	Reference

⁺ 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)



Reiersen & Lenze

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?