EFFECT OF EARLY TREATMENT WITH FLUVOXAMINE ON RISK OF EMERGENCY CARE AND HOSPITALIZATION AMONG PATIENTS WITH COVID-19: THE TOGETHER RANDOMIZED PLATFORM CLINICAL TRIAL

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19 ABSTRACT

20 **Background**

21 Recent evidence indicates a potential therapeutic role of fluvoxamine for COVID-19. In the

22 TOGETHER randomized platform clinical trial for acutely symptomatic patients with COVID-19,

23 we assessed the efficacy of fluvoxamine vs. placebo in preventing either extended emergency

24 room observation or hospitalization due to COVID-19. Herein, we report the preliminary findings.

25 **Methods**

26 This placebo-controlled, randomized, adaptive, platform trial conducted among symptomatic

27 Brazilian adults confirmed positive for SARS-CoV-2 included eligible patients with a known risk

28 factor for progression to severe disease. Patients were randomly assigned to either fluvoxamine

29 (100 mg twice daily for 10 days) or placebo. The primary endpoint was a composite outcome of

30 emergency room observation for >6 hours or hospitalization from COVID-19 up to 28 days post

31 randomization. Secondary outcomes included viral clearance at day 7, time to hospitalization,

32 mortality, and adverse drug reactions. We used a Bayesian analytic framework to determine effects

33 along with probability of success of intervention compared to placebo. The trial is registered at

34 clinicaltrials.gov (NCT04727424) and is ongoing.

35 **Results**

36 The study team screened 9020 potential participants for this trial. The trial was initiated on June

37 2, 2020, with the current protocol reporting randomization from January 15, 2021 to August 6th

38 2021, when the trial arms were stopped for superiority. A total of 3238 patients were allocated to

39 fluvoxamine (n=739), placebo (n=733) and other treatments (n=1766). Herein, we report the

40 effectiveness of fluvoxamine vs. a concurrent placebo control. The average age of participants was

41 50 years (range 18-102 years); 57% were female. The proportion of patients observed in an

42 emergency room for >6 hours or admitted to hospital due to COVID-19 was lower for the

43 fluvoxamine group compared to placebo (77/739 vs 108/733; Relative Risk [RR]: 0.71; 95%

44 Bayesian Credible Interval [95% BCI]: 0.54 - 0.93), with a probability of superiority of 99.4%

45 surpassing the prespecified superiority threshold of 97.6% (risk difference 4.3%). Of the composite

46 primary outcome events, 88% were hospitalizations. We found no significant relative effects

47 between the fluvoxamine and placebo groups on viral clearance at day 7 (Odds ratio [OR]: 0.75;

48 95% Confidence Intervals [95% CI]: 0.53 - 1.07), mortality (OR: 0.70; 95% CI: 0.36 - 1.30), time

49 to death (Hazard ratio [HR]: 0.79; 95% CI: 0.58 - 1.08), days hospitalized (Mean Difference (MD)

50 1.22 days; 95% CI: 0.98 - 1.53), number of days ventilated (MD 1.10; 95% CI: 0.70 - 1.73) or

51 other secondary outcomes. Data capturing all 28 days of follow-up will be reported after August

52 26th, 2021.

53 **Conclusions**

54 Treatment with fluvoxamine (100 mg twice daily for 10 days) among high-risk outpatients with

55 early diagnosed COVID-19, reduced the need for extended emergency room observation or

56 hospitalization.

58

59   BACKGROUND

60   Although safe and effective vaccines for COVID-19 have been developed and distributed, there

61   remain, particularly in low resource settings, major challenges regarding their production,

62   allocation, and affordability.[1] Identifying inexpensive, widely available and effective therapies

63   against COVID-19 is, therefore, of great importance. In particular, repurposing existing medicines

64   that are widely available and with well understood safety profiles, has particular appeal.[2]

65   Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) and a Sigma-1 receptor

66   (S1R) agonist.[3] There are several potential mechanisms for fluvoxamine in treatment of COVID-

67   19 illness, including anti-inflammatory and possible antiviral effects.[4] A small placebo-controlled

68   randomized trial has raised the possibility that fluvoxamine may reduce the risk of clinical

69   deterioration in outpatients with COVID-19, suggesting the need for larger randomized, placebo-

70   controlled studies.[5,6]

71   To evaluate the efficacy of fluvoxamine to prevent progression of COVID-19 and

72   hospitalization among outpatients with laboratory-documented SARS-CoV-2, we conducted a

73   randomized, placebo-controlled adaptive platform trial in Minas Gerais, Brazil. This flexible

74   platform trial design allows for additional agents to be added and tested with standardized

75   operating procedures outlined in a single overarching master protocol.[7,8] Among eight different

76   interventions evaluated in this platform trial, we report here on the clinical evaluation of

77   fluvoxamine using a concurrent placebo control group.

78   METHODS

79   ***Study design and oversight***

80   The TOGETHER Trial is a randomized adaptive platform trial to investigate the efficacy of

81   repurposed treatments for COVID-19 disease among high-risk adult outpatients.[9] The trial was

82   designed and conducted in partnership with local public health authorities from eleven

83   participating cities in Brazil to simultaneously test potential treatments for early disease using a

84   master protocol. A master protocol defines prospective decision criteria for discontinuing

85   interventions for futility, stopping due to superiority against placebo, or adding new interventions.

86   Interventions evaluated in the TOGETHER trial, thus far, include, hydroxychloroquine (protocol

87   1), lopinavir/ritonavir (protocol 1),[10] metformin, ivermectin, fluvoxamine, doxasozin and

88   pegylated interferon lambda versus matching placebos (protocol 2).

89   The trial began on June 2, 2020 and enrollment into the fluvoxamine arm began on January

90   15th 2021. The trial, which complied with the International Conference of Harmonization – Good

91   Clinical Practices, as well as local regulatory requirements, was approved for research ethics by

92   local and national ethics boards in Brazil (CONEP CAAE: 41174620.0.1001.5120, approval letter

93   5.501.284) and the Hamilton Integrated Research Ethics Board (HiREB, approval letter 13390) in

94   Canada. The full protocol, statistical analysis plan, and additional details are appended in the web-

95   appendix. The adaptive designs CONSORT extension (ACE) statement guided this trial report.[16,17]

96   The steering committee made all protocol-related decisions and sponsors had no role in trial

97   conduct, data analysis or decision to submit manuscript for publication. An independent Data

98   Safety Monitoring Committee (DSMC) provided trial oversight.

99

Setting

The appended web-appendix lists the cities and investigators of the eleven clinical sites in Brazil that participated in the trial. Local investigators, in partnership with local public health authorities, recruited participants at community health facilities (emergency settings, flu-symptom referral centers, primary care community centers). We used several community outreach strategies including physical and social media as per local public health authorities, in order to create awareness of the trial.

Participant Screening

Upon presentation to one of the trial outpatient care clinics, local investigators screened potential participants to identify those who met the eligibility criteria.

The key inclusion criteria were: 1) patients over the age of 18, 2) presenting to an outpatient care setting with an acute clinical condition consistent with COVID-19 and symptoms beginning within 7 days of the screening date, 3) positive rapid test for SARS-CoV-2 antigen performed at the time of screening or patient with positive SARS-CoV-2 diagnostic test within 7 days of symptom onset, 4) at least one additional criterion for high-risk: diabetes mellitus; systemic arterial hypertension requiring at least one oral medication for treatment; known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, cardiomyopathies being treated, clinically manifested heart disease and with clinical repercussion); symptomatic lung disease and / or being treated (emphysema, fibrosing diseases); symptomatic asthma patients requiring chronic use of agents to control symptoms; smoking; obesity, defined as BMI>30 kg / m^2 (weight and height information provided by the patient); transplant patients; patient with stage IV chronic kidney disease or on dialysis; immunosuppressed patients / using corticosteroid therapy (equivalent to at least 10 mg of prednisone per day) and / or

123   immunosuppressive therapy; patients with a history of cancer in the last 0.5 years or undergoing

124   current cancer treatment, or age ≥ 50 years; and unvaccinated status.

125   Patients who met any of the following criteria were excluded from the trial: 1) Diagnostic

126   examination for SARS-CoV2 negative associated with acute flu-like symptoms (patient with

127   negative test taken early and becoming positive a few days later were eligible, if he/she was <7

128   days after the onset of flu-like symptoms); 2) Acute respiratory condition compatible with COVID-

129   19 treated in the primary care and previously requiring hospitalization; 3) Acute respiratory

130   condition due to other causes; 4) Received vaccination for SARS-CoV2; 5) Dyspnea secondary to

131   other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute

132   bronchitis, pneumonia, primary pulmonary arterial hypertension); 6) Current use of selective

133   serotonin reuptake inhibitors; uncontrolled psychiatric disorders; or suicidal ideation; 7) Inability

134   or unwillingness to follow research guidelines and procedures. A full list of exclusion criteria are

135   provided in the trial protocol.

136   If a patient met the above eligibility criteria, study personnel obtained written informed

137   consent. After obtaining informed consent a rapid antigen test for COVID-19 (Panbio ®, Abbott

138   laboratories) and a pregnancy test for women of childbearing age were performed. If the COVID-

139   19 test was negative or if the pregnancy test was positive, the participant was not included in the

140   trial. After informed consent, study personnel collected the following data prior to randomization:

141   demographics, medical history concomitant medications, co-morbidities, exposure to Index Case

142   information, WHO clinical worsening scale, and the PROMIS Global Health Scale.

143   ***Randomization and Trial Interventions***

144   Participants were randomized using a centralized core randomization process handled by an

145   independent unblinded pharmacist who was not aware of any protocol-related procedures and

146   contracted specifically for this process. Sites requested randomization by text message to the

147   pharmacist at the coordinating center. This maintained concealment of allocation. Patients were

148   randomly assigned using a block randomization procedure for each participating site, stratified by

149   age (< 50 years /≥ 50 years). The trial team, site staff and patients were blinded to treatment

150   allocation. The active drugs and the placebo pills were packaged in identically shaped bottles and

151   labeled with alphabet letters corresponding to the active arm or placebo arm. Only the third-party

152   pharmacist responsible for releasing the randomization was aware of which letter was associated

153   with which drug and/or placebo. As this is a multi-arm trial and all active interventions have a

154   matching inert placebo, the matching placebo represents the proportion of the control group for

155   the number of arms in the trial at any given time.

156   ***Data Collection and Participant Follow-Up***

157   Our primary outcome is a composite that includes emergency room visits due to the clinical

158   worsening of COVID-19 (defined as participant remaining under observation for > 6 hours) or

159   hospitalization due to the progression of COVID-19 (worsening of clinical status) and/or suspected

160   COVID-19 complications within 28 days of randomization. Key secondary outcomes include: 1)

161   viral clearance, 2) time to clinical improvement, 3) number of days with respiratory symptoms, 4)

162   time to hospitalization for any cause or due to COVID-19 progression, 5) all-cause mortality and

163   time to death from any causes, 7) WHO clinical worsening scale score, 8) days in hospital and on

164   ventilator and 9) adverse events, adverse reactions to the study medications and the proportion of

165   participants who are non-adherent with the study drugs. All secondary outcomes are assessed up

166   to 28 days following randomization.

167   Study personnel collected, via in person, telephone contact and social media applications

168   using video-teleconferencing, outcome data on days 1, 2, 3, 4, 5, 7, 10, 14, and 28. We collected

169 outcome data irrespective of whether participants took study medication. In case of adverse events,

170 unscheduled visits (during the treatment period) outside of clinical care could occur at any time.

171 Considering the transmissible characteristic of SARS-CoV-2 and the isolation

172 recommendations of positive individuals, we collected limited vital sign data. Cardiac safety was

173 assessed using a 6-lead ECG (Kardiamobile, Mountain View, CA) at the baseline visit. The digital

174 recordings were de-identified and transferred to a central facility (Cardresearch, Belo Horizonte,

175 Brazil) for reading. Oxygen status was assessed using a pulse oximeter for non-invasive arterial

176 oxygen saturation (SpO2) and pulse (Jumper Medical Equipment, Shenzhen, China), and

177 temperature using a standard digital oral thermometer administered by research personnel. Mid-

178 turbinate nasal swab kits and sterile recipient storage were provided for collection of

179 nasopharyngeal swab or sputum/saliva. They were performed by the first quarter of participants

180 enrolled in the trial at days 3 and 7. PCR of viral clearance was assessed to determine if active

181 drugs demonstrate any anti-viral effects.

182 All serious and non-serious adverse events were reported to study personnel as per local

183 regulatory requirements. Reportable adverse events included serious adverse events, adverse

184 events resulting in study medication discontinuation, and adverse events assessed as possibly

185 related to study medication.

186 ***Trial interventions***

187 All participants received usual standard care for COVID-19 provided by healthcare professionals

188 workers at public health facilities. Patients were randomized to fluvoxamine (Luvox ®, Abbott) at

189 a dose of 100 mg twice a day for 10 days or corresponding placebo starting right after

190 randomization (day 1). Research personnel provided participants a welcome video with

191 information on trial, study drug, adverse events and follow-up procedures. Clinicians providing

192   usual care in public health facilities typically focus on the management of symptoms and with

193   antipyretics, and recommend antibiotics only if they suspect bacterial pneumonia.

194   ***Statistical Analyses***

195   The Adaptive Design Protocol and the Master Statistical Analysis Plan provide details of sample

196   size calculation and statistical analysis (appended). This trial is adaptive and applies sample size

197   re-estimation approaches. To plan for each arm, we assumed a minimum clinical utility of 37.5%

198   (relative risk reduction) to achieve 80% power with 0.05 two-sided Type 1 error for a pairwise

199   comparison against the placebo (talc) assuming a control event rate (CER) of 15%. This resulted

200   in an initial plan to recruit 681 participants per arm. The statistical team conducted planned interim

201   analyses. Stopping thresholds for futility were established if the posterior probability of superiority

202   was less than 40% at interim analysis. An arm can be stopped for superiority if the posterior

203   probability of superiority meets the threshold of 97.6%

204   Baseline characteristics are reported as count (percent) or median and interquartile range (IQR)for

205   continuous variables. We applied a Bayesian framework for our primary outcome analysis and a

206   frequentist approach for all sensitivity analyses and secondary outcomes. Posterior efficacy of

207   fluvoxamine for the primary outcome is calculated using the beta-binomial model for event rates,

208   assuming informed priors based on the observational data for both placebo and fluvoxamine, for

209   both Intention-to-Treat (ITT), modified ITT (defined as receiving the study drug for at least 24

210   hours before an event) and Per-Protocol (PP) analyses (defined as taking >80% of possible doses).

211   Modified ITT was defined as receiving treatment for at least 24 hours before a primary outcome.

212   We accounted for any temporal changes in events rates by using only the concurrent randomised

213   population. We assessed subgroup effects according to the preplanned statistical analysis plan. We

214   calculated the number needed to treat.

215   Secondary outcomes were assessed using a pre-specified frequentist approach. For viral

216   clearance we fitted a longitudinal, mixed-effect logistic regression model with a treatment and time

217   interaction term for binary patient outcomes (Covid-19 positive/negative) reported on day 3 and 7

218   from randomization, with subject random effect. We assessed time-to-event outcomes using Cox

219   proportional hazard models and binary outcomes using logistic regression. Per protocol analyses

220   were considered sensitivity analyses to assess the robustness of the results. All analyses were

221   performed using R version 4.0.3. Full details of the Statistical Analysis Plan (SAP) are appended.

222   **Data and Safety Monitoring Committee**

223   A Data and Safety Monitoring Committee provided independent oversight for this trial. We

224   planned a 4th interim analysis of the fluvoxamine arm with data collected up to August 2nd, 2021.

225   **Role of the funding source**

226   The funders had no role in the study design, data collection, analysis, interpretation or writing, or

227   decision to submit for publication. The executive committee take responsibility for the integrity of

228   the data and the accuracy of the data analysis. The trial executive committee oversaw all aspects

229   of trial conduct, completeness, data accuracy and adherence of trial conduct to the protocol and

230   the committee vouch for the accuracy and completeness of the data and for fidelity to the protocol.

231

232   RESULTS

233   We screened 9020 potential participants for inclusion in this trial to date. The trial enrolled its first

234   participant on June 2, 2020 and enrolment into the fluvoxamine arm began on January 20, 2021.

235   By August 6, 2021, 1,472 recruited participants were randomized to fluvoxamine (n= 739) or the

236   concurrent placebo (n=733), and 1,766 were randomized to other treatment arms (Figure 1). The

237   median age was 50 years (range 18-102) and 846 (57.5%) were women (Table 1). Most

238   participants self-identified as mixed-race 1,403 (95.3%), 11 (0.7%) as white, 10 (0.7%) as black

239   or African American, the rest self-identified as unknown 48 (3.3%). As the trial is ongoing, herein

240   we provide descriptive summaries of only those randomized to fluvoxamine and its concurrent

241   control. With respect to covariates of age, BMI, and co-morbidities, the groups were generally

242   well balanced (Table 1). The mean number of days with symptoms prior to randomization was 4

243   days (Standard Deviation 1.76). All patients were identified at the end of the study for inclusion

244   in the analysis.

245   ***Primary Outcomes***

246   The Data Safety Monitoring Committee met four times since the protocol initiation and last met

247   on August 5, 2021, recommending that the TOGETHER Trial stop randomizing patients to the

248   fluvoxamine arm, as this comparison had met the pre-specified superiority criterion for the primary

249   endpoint (prespecified superiority threshold 97.6%). Based on the Bayesian beta-binomial model,

250   there was evidence of a benefit of fluvoxamine reducing hospitalization or observation in an

251   emergency room for greater than six hours due to COVID-19 (Relative Risk [RR]: 0.71; 95%

252   Bayesian Credible Interval [BCI]: 0.54 - 0.93) in the Intention-to-Treat (ITT) population (figure

253   2A) and (RR: 0.68; 95% BCI: 0.50 - 0.91) in a modified ITT population (figure 2B). The

254   probability that the event rate was lower in the fluvoxamine group compared to placebo was 99.4%

255   for the ITT population, and 99.6% for the modified ITT population (Figure 2A/B). These posterior

256   efficacy numbers were higher than the pre-specified 97.6% threshold set for the fourth interim

257   analysis. In the fluvoxamine group 77 (10.4%) participants experienced a primary outcome event

13

258   compared to 108 (14.7%) in the placebo group (Table 2). Most events (88%) were hospitalizations.

259   The number needed to treat is 24. Per protocol analysis demonstrated a larger treatment effect

260   (0.34, 95% BCI, 0.20-0.54).

261   ***Secondary Outcomes***

262   Table 3 presents findings from secondary outcome analyses. There were no significant differences

263   between fluvoxamine and placebo for viral clearance at Day 7 (p=0.18) and eFigure3 in web-

264   appendix, hospitalizations due to COVID (p=0.17), all-cause hospitalizations (p=0.12), time to

265   hospitalization (p=0.14, number of days in hospital (p=0.07), mortality (p=0.26), time to death

266   (p=0.26), number of days on mechanical ventilation (p=0.67), time to recovery (p=0.86) or the

267   PROMIS Global Health Scale (p=0.44). With respect to adverse events, there were significantly

268   greater number of Grade 1 (mild) treatment emergent adverse events (TEAE) among patients in

269   the fluvoxamine arm (p<0.01). However, no differences between fluvoxamine and placebo were

270   observed for TEAEs of Grades 2, 3, 4, or 5.

271   ***Sub-group Analyses***

272   In the prespecified subgroup analysis, we found no evidence of moderation of treatment effect for

273   fluvoxamine compared to placebo, for sub-groups of age, sex, days since symptom onset, or co-

274   morbidities (Figure 3 and web-appendix eTable 1).

275

276   DISCUSSION

277   This is the first large randomized controlled trial to test the efficacy of fluvoxamine for acute

278   treatment of COVID-19. We found a clinically important absolute risk reduction of 4.3%, and

279   29% relative risk reduction, on the primary outcome of retention in an emergency setting for

280   COVID-19 disease observation or hospitalization, consequent on the administration of

281   fluvoxamine for 10 days. This study is only the 2nd study to demonstrate an important treatment

282   benefit for a repurposed drug in the early treatment population.[11] Our findings represent the latest

283   interim analysis of the trial resulting in the DSMC recommending stopping the active fluvoxamine

284   arm. The final analysis from the trial, wherein all patients have contributed 28 days of follow-up

285   data, will be made available 28 days after the last randomized patient has completed this period

286   (August 25, 2021). Given fluvoxamine's safety, tolerability, ease of use, low cost, and widespread

287   availability, these findings may have influence on national and international guidelines on the

288   clinical management of COVID-19.

289

290   **Comparison with prior evidence**

291   Our results are consistent with an earlier smaller trial conducted in the United States (led by EJL

292   and AMR).[6] That study used a higher dose of fluvoxamine (100mg tid for 15 days) and included

293   a lower risk group for the primary outcome but found no clinical deterioration among 80 patients

294   receiving fluvoxamine vs. 6 of 72 patients receiving placebo. A large observational study from

295   France involved a different population, 7230 hospitalized COVID-19 patients, and reported a

296   reduction in use of intubation or death with use of SSRIs.[5]

297   The underlying mechanism of fluvoxamine for COVID-19 disease remains uncertain. Although

298   hypotheses include several potential mechanisms,[4] the main reason for the initial study of

299   fluvoxamine as a treatment of COVID-19 was its anti-inflammatory action through activation of

300   the σ-1 receptor (S1R).[12] S1R is an endoplasmic reticulum (ER) chaperone membrane protein

301   involved in many cellular functions,[13] including regulation of ER stress response/unfolded protein

302   response and regulation of cytokine production in response to inflammatory triggers.[14] In the

303   presence of fluvoxamine, S1R may prevent the ER stress sensor Inositol-Requiring Enzyme 1α

304 (IRE1) from splicing and activating the mRNA of X-Box Protein 1 (XBP1), a key regulator of

305 cytokine production including IL-6, IL-8, IL-1β and IL-12. In a 2019 study by Rosen and

306 colleagues, fluvoxamine showed benefit in preclinical models of inflammation and sepsis through

307 this mechanism.[14]

308 Another mechanism may be fluvoxamine's anti-platelet activity.[15] SSRIs can prevent loading of

309 serotonin into platelets and inhibit platelet activation, that may reduce the risk of thrombosis, and

310 these antiplatelet effects can be cardioprotective. In vitro and animal studies are needed to help

311 clarify the most likely mechanism(s). Biomarker studies included as part of future RCTs may also

312 help to clarify mechanisms.

313

314 **Strengths and limitations**

315 Since the start of the COVID-19 pandemic, there have been more than 2800 RCTs registered on

316 clinicaltrials.gov. However, less than 300 have been reported and the vast majority of clinical trials

317 have been small and underpowered, with sample sizes less than 100. In many cases, these trials

318 have been unsuccessful at recruiting as the local epidemics occur in waves and sustainable

319 infrastructure to maintain staff or local interest for recruitment is lacking. The trials that provide

320 the clearest medical understanding tend to be the larger platform trials, such as SOLIDARITY,[16]

321 RECOVERY,[17] PRINCIPLE,[11] and REMAP-CAP.[18] As a result, we actively collaborate with other

322 investigators running trials with overlapping interventions so that they can be aware of our study

323 decisions and determine whether they should influence their respective trials.

324 Major strengths include the rapid recruitment and enrolment of high-risk patients for the

325 development of severe COVID-19. Our recruitment strategy involves the engagement with the

326 local public health system, thus allowing recruitment that frequently exceeds twenty patients per

327   day. We enrolled only participants with diagnosed COVID-19 and less than 7 days of symptom

328   onset using a commercially available COVID-19 AG rapid test (Panbio ®). The concordance of

329   COVID-19 positive tests with RT-PCR was evaluated on the group of participants with PCR

330   evaluations and found a concordance rate of > 99% on both tests collected at baseline.

331   Our understanding of the epidemiology of COVID-19 as well as its disease progression and

332   outcomes have evolved since beginning this platform trial in June 2020. Early studies assessed the

333   effects of interventions of viral load and clearance, while later studies also evaluate more clinical

334   outcomes. We made adjustments to the trial according to prespecified rules and in communication

335   with the appropriate ethics review committees that allowed us to respond to the epidemic waves

336   while maintaining high rates of recruitment. Unlike many outpatient clinical trials, our study

337   involves direct patient contact through the use of medical students, nurses and physicians who do

338   at-home visits as well as follow-up via telecommunications. Given the rapid recruitment of patients

339   in combination with the high event rate of emergency room visits and hospitalizations, we were

340   able to evaluate the effects of interventions when portions of the planned population had been

341   recruited. The period of time between first recruitment of a patient on fluvoxamine and the data

342   cut for our trial was 197 days. Our trial assessed a primary outcome as a binary event having

343   occurred by 28 days post-randomization.

344   One of the major limitations of our fluvoxamine trial is primarily related to the challenges of

345   conducting a trial in a disease that is not well characterized. Currently, there is no standard of care

346   that exists for early treatment of COVID-19 and various advocacy groups promote different

347   interventions, including some of those evaluated in this and our previous trials. Furthermore, there

348   is little understanding of who is at greatest risk of disease progression from this disease as some

349   patients with numerous risk factors do recover quickly while some others with less established risk

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350   factors may not. Our population had a higher rate of hospitalization events than observed in most

351   clinical trials, thus permitting inferences on treatment effects in this higher-risk population.

352

353   **Implications**

354   Our trial has found that fluvoxamine, an inexpensive existing drug, reduces the need for advanced

355   disease care in this high-risk population. A ten-day course of fluvoxamine costs approximately $4

356   even in well-resourced settings.[19] Our study compares favorably and exceeds the treatment effects

357   of more expensive treatments including monoclonal antibodies for outpatient treatment.[20,21] The

358   absolute number of serious adverse events associated with fluvoxamine was lower than our

359   placebo group and this might reflect the modulatory effect of fluvoxamine on systemic

360   inflammation in these participants. Lower respiratory tract infections were reported less frequently

361   in patients in the fluvoxamine group than those in the placebo group. This is concordant with the

362   reduction of hospital admissions in patients with confirmed COVID-19 treated with fluvoxamine,

363   and the numerically lower number of patients requiring mechanical ventilation.

364

365   Fluvoxamine is widely available but is not on the WHO Essential Medicines List,[22] whereas a

366   closely related SSRI fluoxetine is on the list. It is now of critical importance to determine whether

367   a class-effect exists and whether these drugs can be used interchangeably for COVID-19. The

368   recent important findings that inhaled budesonide increased time to recovery among a similar

369   population as our trial and had a trend towards decreased hospitalizations suggests this as an

370   alternative or additional intervention for outpatient care that should be evaluated. The PRINCIPLE

371   trial evaluated time to recovery using self-reported recovery up to 28 days after randomization to

372   budesonide.[11] Our trial differed as we evaluated improvement in the WHO categorization of

373   disease disability up to days 14 and then 28 (web-appendix eFigure 2). Finally, our study was

374   among unvaccinated patients. Further evidence of treatment benefits are needed to determine the

375   effect of fluvoxamine among vaccinated populations.

376   Use of interventions, including fluvoxamine, to prevent progression of illness and hospitalization

377   is critically dependent on identifying higher risk individuals. Unselected populations will have a

378   lower risk. What absolute reduction in risk of clinical deterioration would motivate patients to

379   choose treatment (probably the >4% we observed, but perhaps not much lower) remains uncertain.

380   These considerations raise the importance of the development of a validated prediction rule for

381   deterioration in patients in the early stages of COVID-19 infection.

382   **Conclusion**

383   Administration of fluvoxamine reduced the rate of prolonged observation in an emergency care

384   setting or hospitalization due to COVID-19 in people with a high risk of serious disease.

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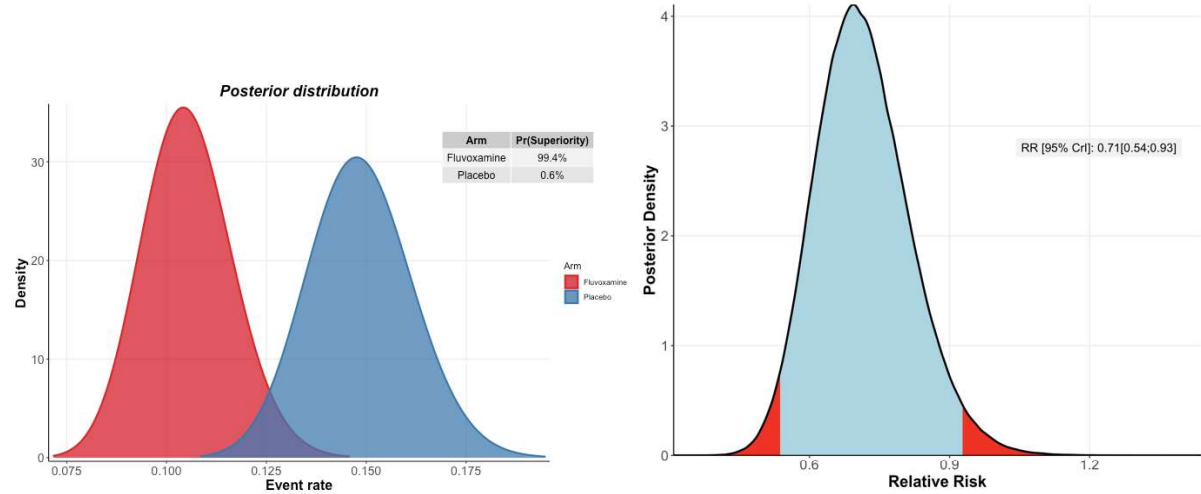
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474 **TABLES & FIGURES**
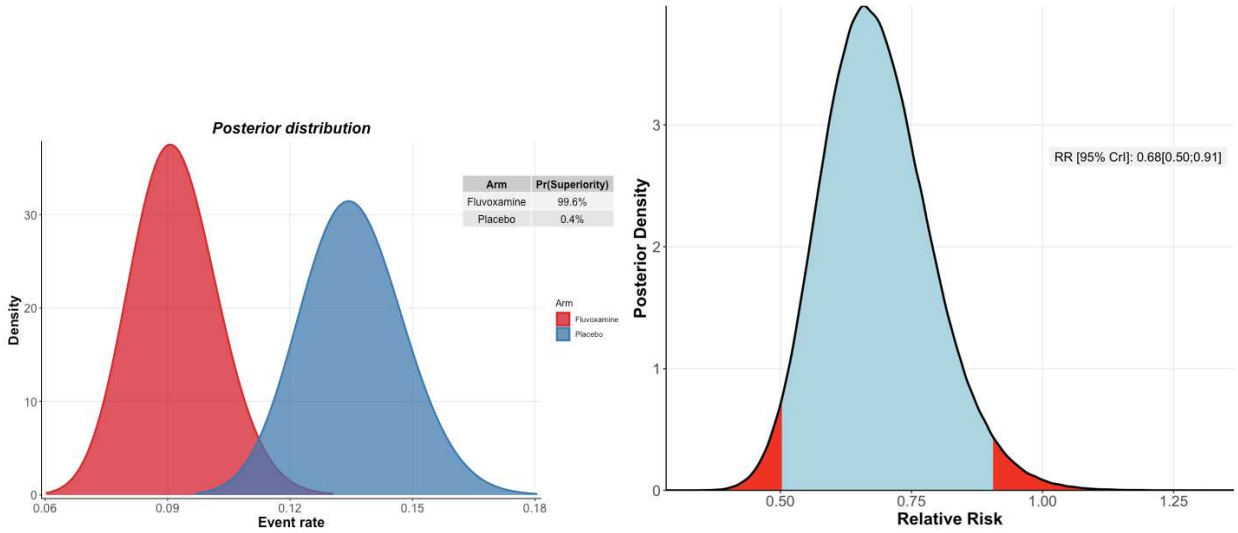
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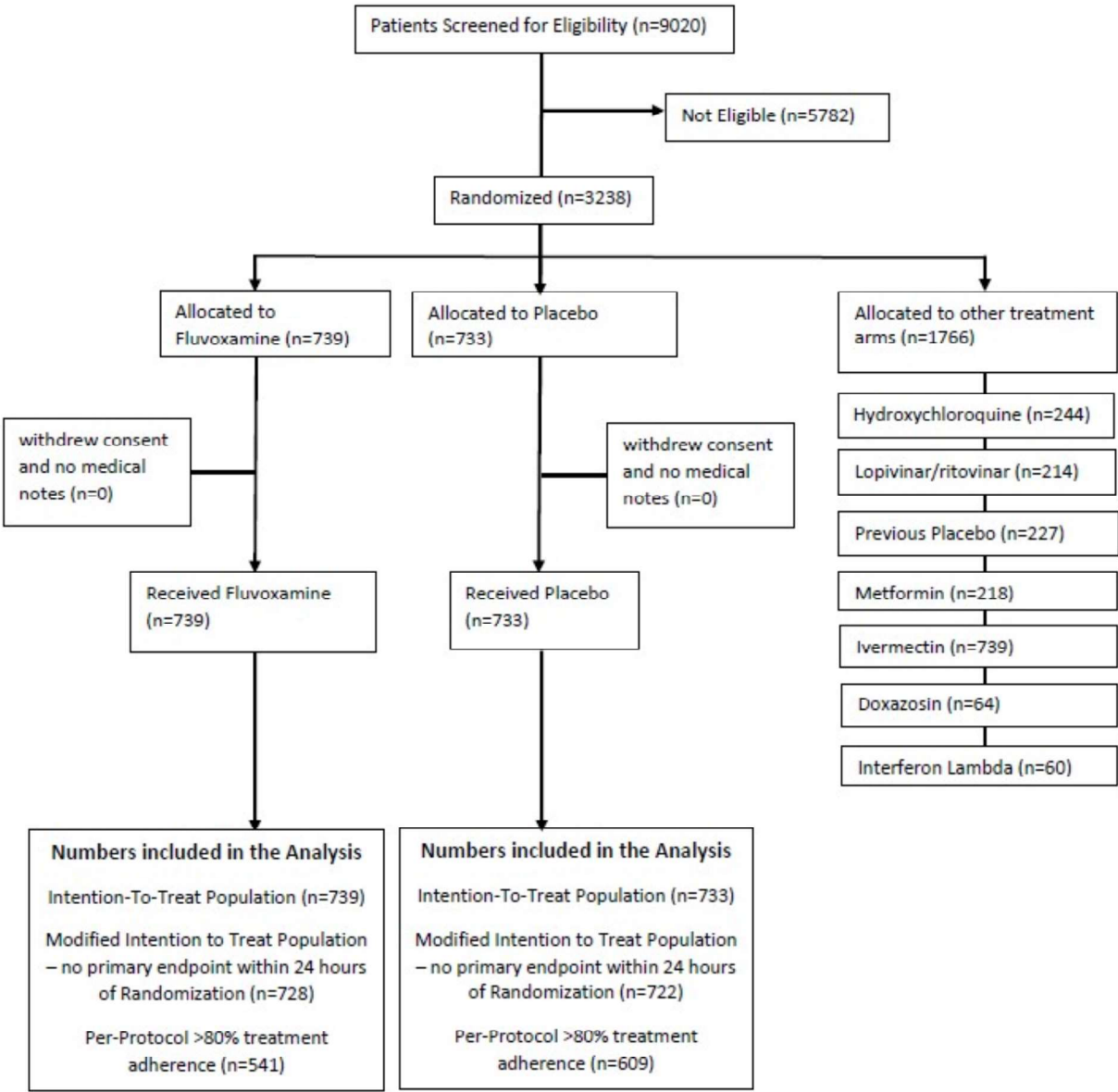
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Figure 2: Probability of efficacy and Bayesian relative risk of extended emergency room observation or hospitalization for fluvoxamine vs. placebo (Panel A: ITT population; Panel B: Modified ITT population)

A) Intention-to-treat analysis

B) Modified intention-to-treat analysis

Figure 3: Sub-group analyses of fluvoxamine vs. placebo in the TOGETHER Trial

Subgroup	N Placebo (N events)	N Treatment (N events)	HR [95% CI]
Age (years)			
<=50	367 (32)	367 (21)	0.65 [0.38; 1.13]
>50	318 (70)	324 (50)	0.67 [0.47; 0.97]
Sex			
Female	438 (53)	407 (27)	0.53 [0.33; 0.84]
Male	295 (55)	330 (50)	0.81 [0.55; 1.18]
BMI (kg/m2)			
<30	360 (49)	354 (34)	0.69 [0.44; 1.07]
>=30	359 (58)	371 (42)	0.69 [0.46; 1.03]
Time from onset of symptoms			
0–3 days	296 (35)	317 (28)	0.73 [0.45; 1.21]
4–7 days	249 (38)	241 (31)	0.83 [0.52; 1.34]
Diabetes mellitus			
N	365 (27)	354 (22)	0.84 [0.48; 1.47]
Y	367 (81)	382 (55)	0.63 [0.44; 0.88]
Cardiovascular disease			
N	444 (54)	442 (39)	0.72 [0.48; 1.08]
Y	289 (54)	295 (38)	0.67 [0.44; 1.01]
Lung disease			
N	711 (102)	716 (73)	0.70 [0.52; 0.94]
Y	21 (6)	20 (4)	0.70 [0.20; 2.47]
Use of corticoid therapy			
N	724 (106)	729 (77)	0.71 [0.53; 0.95]
Y	7 (1)	6 (0)	

0.35 0.50 0.75 1.0 1.5

<————— Fluvoxamine better —— —— Placebo better ———

497   **Table 1.** Patient characteristics by treatment allocation in the TOGETHER Trial

	Fluvoxamine (n=739)	Placebo (n=733)	Total (n=1472)
Sex			
Female	408(55.2)	438(59.8)	846(57.5)
Male	331(44.8)	295(40.2)	626(42.5)
Race			
Mixed Race[+]	708(95.8)	695(94.8)	1403(95.3)
White	5(0.7)	6(0.8)	11(0.7)
Black or African American	5(0.7)	5(0.7)	10(0.7)
Unknown	21(2.8)	27(3.7)	48(3.3)
Age, years			
>= 50 years	325(44.0)	318(43.4)	643(43.7)
Age Descriptive Statistics			
Median	50	49	50
IQR	17	18	18
Body Mass Index (BMI)			
<30 kg/m^2	354(47.9)	360(49.1)	714(48.5)
>=30 kg/m^2	372(50.3)	359(49.0)	731(49.7)
Unspecified	13(1.8)	14(1.9)	27(1.8)
Time since onset of symptoms			
0-3 days	318(43.0)	296(40.4)	614(41.7)
4-7 days	241(32.6)	249(34.0)	490(33.3)
Unspecified	180(24.3)	188(25.7)	368(25.0)
Risk factors			

Chronic cardiac disease	8(1.1)	8(1.1)	16(1.1)
Hypertension	106(14.4)	88(12.0)	194(13.2)
Chronic pulmonary disease	6(0.8)	3(0.4)	9(0.6)
Asthma	11(1.5)	16(2.2)	27(1.8)
Chronic kidney disease	2(0.3)	2(0.3)	4(0.3)
Rheumatologic disorder	1(0.1)	0(0.0)	1(0.1)
Chronic neurological disorder	8(1.1)	6(0.8)	14(1.0)
Diabetes mellitus: Type 1	25(3.4)	22(3.0)	47(3.2)
Diabetes mellitus: Type 2	103(14.0)	93(12.7)	196(13.3)
Obesity	2(0.3)	1(0.1)	3(0.2)
Any other risk factor(s) or co-morbidities	24(3.3)	19(2.6)	43(2.9)

498   **LEGEND:** [+]Self-identified as someone with mixed-race ancestry.

499 **Table 2:** Proportion of primary outcome events and relative risk of extended emergency room

500 observation or hospitalization of fluvoxamine vs. placebo

	Intention-to-treat analysis			Modified intention-to-treat analysis		
	N	n (%)	Relative risk (95% CrI)	N	n (%)	Relative risk (95% CrI)
Fluvoxamine	739	77 (10.4 %)	0.71 [0.54; 0.93]	728	66(9.1 %)	0.68 [0.50; 0.91]
Placebo	733	108 (14.7 %)	1.00 (ref)	722	97(13.4 %)	1.00 (ref)
All	1472	185 (12.6%)	--	1450	163(11.2 %)	--

501 **LEGEND:** 95% CrI – Credible intervals

502

503 **Table 3:** Secondary outcomes of fluvoxamine vs placebo in the TOGETHER Trial

	Fluvoxamine	Placebo	Estimated treatment effect (95% CI)	p-value
Viral clearance (Day 7)	45/218 (21%)	57/217 (26%)	0.73 (0.47, 1.14) *	0.17
Hospitalized for COVID	74/739 (10.0%)	90/733 (12.3%)	0.79 (0.57, 1.10) *	0.17
All-cause hospitalization	74/739 (10.0%)	92/733 (12.6%)	0.77 (0.56, 1.07) *	0.12
Time to hospitalization	5 days [3 to 7]	5 days [3 to 7]	0.79 (0.58, 1.08) †	0.14
Number of days of hospitalization	7 days [5 to 12.5]	6 days [3 to 10.75]	1.22 (0.98, 1.53) ‡	0.07
Emergency room visit for at least 6 hours	6/739 (0.8%)	30/733 (4.1%)	0.19 (0.07, 0.43) *	<0.01
Time to the emergency visit for at least 6 hours	5.5 days [4.25 to 6.75]	6 days [3.25 to 8.75]	0.19 (0.08, 0.47) †	<0.01
Death	17/739 (2.3%)	24/733 (3.3%)	0.70 (0.36 to 1.30) *	0.26
Time to death	17 days [9 to 21]	14 days [8 to 20]	0.79 (0.58 to 1.08)	0.26
Number of days on mechanical ventilator	7 days [3 to 12]	6.5 days [3 to 12]	1.10 (0.70 to 1.73) ‡	0.67
Adherence	541/739 (73.2%)	609/733 (83.1%)	0.48 (0.36, 0.63) *	<0.01
Grade 1 TEAE	17/739 (2.3%)	5/733 (0.7%)	3.43 (1.35 to 10.47) *	0.02
Grade 2 TEAE	62/739 (8.4%)	74/733 (9.4%)	0.82 (0.57 to 1.16) *	0.26
Grade 3 TEAE	34/739 (4.2%)	43/733 (4.6%)	0.77 (0.48 to 1.23) *	0.28
Grade 4 TEAE	18/739 (2.3%)	20/733 (2.2%)	0.89 (0.46 to 1.70) *	0.72
Grade 5 TEAE	18/739 (2.2%)	25/733 (2.3%)	0.71(0.38 to 1.30) *	0.27

504 **LEGEND:** TEAE: Treatment Emergent Adverse Event

505 Summary statistics are presented as n/N or median (IQR) unless otherwise stated.

506 * Unadjusted odd ratio

507 † Unadjusted hazard ratio.

508   ‡ Exponentiated unadjusted estimates from a log-transformed linear regression.

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