Fluvoxamine Literature Review: COVID-19 Clinical Advisory Group Update
January 2022

Background:
- Fluvoxamine (Luvox®) is a serotonin reuptake inhibitor and α-1 receptor (S1R) and is FDA-approved for obsessive-compulsive disorder. Other off-label uses include bulimia nervosa, major depressive disorder, panic disorder, post-traumatic stress disorder, and social anxiety disorder. It carries a US Boxed Warning for increased risk of suicidal thinking and behavior in children, adolescents, and young adults aged 18 to 24 years with major depressive disorder and other psychiatric disorders. In addition, fluvoxamine is a substrate of CYP2D6 and inhibits several CYP450 isoenzymes (CYP1A2, CYP2C9, CYP3A4, CYP2C19, CYP2D6).
- Exhibiting rapid intracellular uptake due to its highly lipophilic nature, further investigation of fluvoxamine as a potential COVID-19 therapeutic began during the initial outbreak of COVID-19. The results of one meta-analysis conducted prior to the pandemic showed that antidepressant use in major depressive disorder was associated with reduced plasma levels of several pro-inflammatory mediators (i.e. IL-6, IL-10, TNF-α, and CCL-2), which have been associated with severe COVID-19.
- Preclinical studies suggest that antidepressants such as fluvoxamine may inhibit acid sphingomyelinase activity, which may prevent the infection of epithelial cells with SARS-CoV-2. Other proposed mechanisms include reduction in platelet aggregation, decreased mast cell degranulation, interference with endothelial viral trafficking, regulation of inositol-requiring enzyme 1-driven inflammation and increased melatonin levels, which collectively have thought to have direct antiviral effect, regulate coagulopathy or mitigate cytokine storm. To a lesser extent, other antidepressants agents have also been investigated in COVID-19 (e.g. fluoxetine).
- One observational study showed a possible lower risk of death or hospitalization in intubated patients with COVID-19 taking antidepressants (not specific to fluvoxamine), data from randomized controlled trials in adults are lacking. A recent randomized controlled trial suggests that fluvoxamine may lower risk of emergency room visits or hospitalization due to COVID-19 among symptomatic ambulatory adult patients with mild COVID-19 when initiated early after symptom onset (Low Certainty Evidence). However, fluvoxamine failed to show mortality benefit at 28 days or viral clearance at day 7, a surrogate marker for clinical deterioration.

Data Summary:
- Randomized Controlled Trials
  - Fluvoxamine has been evaluated in three randomized controlled trials, one most recently stopped due to futility (STOP COVID 2). One RCT (TOGETHER) demonstrated a lower risk of composite emergency room visits or hospitalizations due to COVID-19 and was met with multiple study limitations. When evaluating the effect on hospitalizations alone, no statistically significant benefit was observed. Clinical relevance of the >6 hour emergency department observation time endpoint is unclear and applicability to practice settings among different countries.
- Observational Cohorts
  - One observational study showed outcomes treated with fluvoxamine had fewer hospitalizations within 14 days, further randomized controlled trials are needed. A second retrospective analysis suggested a small, statistically significant relative risk reduction in mortality in patients receiving SSRIs, however few patients in this study were treated with fluvoxamine alone.
- Ongoing Clinical Trials

Guideline Recommendations:

- NIH Guidelines
  - There is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of fluvoxamine for the treatment of COVID-19 (Last Updated December 16, 2021).
  - Rationale: Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19.
- IDSA Guidelines
  - Among ambulatory patients with COVID-19, the IDSA guideline panel recommends fluvoxamine only in the context of a clinical trial (Last updated November 8, 2021).
  - Rationale: The panel agreed on the overall low certainty of evidence given the sparseness in mortality data and because upper boundary of the 95% confidence interval failed to exclude the risk of possible harms.

Recommendations:
- Further randomized controlled trials are needed to assess the safety and efficacy of fluvoxamine in ambulatory and hospitalized patients with mild to moderate COVID-19. At this time, there is insufficient evidence to support the use of fluvoxamine as a treatment option for COVID-19 outside of clinical trials. Use in COVID-19 is NOT recommended by the Sutter Health COVID-19 Clinical Advisory Group.
1:1 Randomization to fluvoxamine 100mg TID (n=741) or placebo (n=756) x 10 days

**Primary outcome:**
- Composite endpoint of medical admission to a hospital setting due to COVID-19-related illness or ER observation > 6 hours (11% vs 16%; RR 0.68; [95% CI: 0.52-0.88]); NNT 20 [Time frame = 28 days]
- Patients who reported optimal adherence (greater than 80% for possible days)—per-protocol analysis 74% vs 82% had a greater treatment benefit on primary outcome (RR 0.34; [95% CI: 0.21-0.54]).
  - Majority of events were hospitalizations (87%) and was not significant between groups
  - Emergency setting visit for at least 6 hours (1% vs 5%, p=0.0001)
  - Time to emergency visit 4 vs 5 days (p=0.002)

**Secondary outcome:** **No statistically significant difference**
- No difference in viral clearance at day 7 (p=0.090)
- No difference in all cause hospitalizations (10% vs 13%; RR 0.77 [95% CI: 0.58-1.04]) or hospitalizations for COVID (10% vs 13%; RR 0.77 [95% CI: 0.55-1.05])
- No difference in time to hospitalizations (p=0.11) or LOS (p=0.059)
- No difference in all-cause mortality (p=0.24) or time to death from any cause (p=0.49)
- No difference in mechanical ventilation or time on ventilation (p-values = 0.33 and 0.90, respectively)

**Adverse events:**
- More patients stopped fluvoxamine due to issues with tolerability (11% (n=84) vs 8% (n=64)). However, no difference in treatment emergent adverse events (Grade 1-5) observed between groups

**Patient selection (fluvoxamine vs placebo):**
- Median age 50 years (18-102), female 57%, mixed race 95%, White 1%, Black 1%
- Mean number of days with symptoms before randomization: 3.8 days (SD 1.87)
- BMI ≥ 30 (51% vs 50%), HTN (14% vs 12%), DM2 (14% vs 12%)

**Limitations:**
- Adaptive platform, multiple treatments being evaluated
- Per protocol comparisons are not randomized comparisons
- Adherence self-reported and not verified
- Patient wait times were not contributed to primary outcome
- Rate of hospitalizations was higher compared to historical controls
- Missing primary outcome data
- Not all outcomes reported
- Low statistical power
- No standard of care at the time, usual care variable among sites and over time
- End point not used in other studies of interventions for non-hospitalized patients at high risk for hospitalization and death

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<td>Reis, (TOGETHER) October 2021†</td>
<td>Randomized, placebo-controlled, multicenter, adaptive platform clinical trial of 1497 ambulatory patients with COVID-19 who presented to an outpatient care setting between January 20, 2021 and August 5, 2021 across 11 clinical sites in Brazil</td>
<td></td>
<td>Fluvoxamine was associated with a 5% absolute risk reduction in composite end point of retention in emergency setting &gt;6 hours and hospitalizations</td>
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<td>LOE = 1b, n = 1497</td>
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<td>When evaluating the effect on hospitalizations alone, there was a trend toward less hospitalizations in fluvoxamine treated patients compared to those not receiving fluvoxamine, but this was not statistically significant</td>
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<td>Lenze (STOP COVID), December 2020°</td>
<td>Randomized, double-blind, placebo-controlled, contactless, clinical trial of 152 community-living, adult outpatients with mild COVID between April 10, 2020 and August 5, 2020 in eastern Missouri and southern Illinois</td>
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<td>Outpatients treated with fluvoxamine had a lower likelihood of clinical deterioration over a 15-day period</td>
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<td>LOE 2, n = 152</td>
<td>1:1 Randomization to fluvoxamine 50 mg QHS x1, then 100 mg BID x2 days, then increase to 100mg TID as tolerated or placebo x 15 days</td>
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<td>Study is hypothesis generating only due to study limitations</td>
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### Study (May reduce dose for tolerability reasons) followed by an open-label phase of fluvoxamine 100mg BID x 3 days, 50 mg BID x 3 days then discontinue (could take up to 15 days)

- Included
  - Ambulatory adults ≥ 18 years old with confirmed COVID-19 with one or more of the following symptoms:
    - Fever, cough, myalgia, mild dyspnea, diarrhea, vomiting, loss of smell or taste, sore throat
- Exclusion
  - Illness requiring hospitalization or O2Sat <92% on RA at randomization
  - Severe underlying lung disease (COPD on home oxygen, interstitial lung disease, pulmonary hypertension), decompensated cirrhosis, CHF (stage 3 or 4 per patient report and/or medical records)
  - Immunocompromised (solid organ transplant, BMT, AIDS, on biologics and/or high dose steroids (>20mg prednisone per day)
  - Already enrolled in another COVID 19 trial, or currently taking chloroquine, hydroxychloroquine, azithromycin, or colchicine

### Results
- COVID-19 illness, with the length of stay ranging from 4 to 21 days.
  - One patient required mechanical ventilation for 10 days
    - Adherence: 140 (92%) took the first dose of study medication on the same day they were first contacted by study staff (the rest started it the day after contact). 115 (76%) of participants completed the trial
    - A total of 35 participants opted to take open-label fluvoxamine after the double-blind phase, but no data collection was conducted for this phase

- **Secondary outcome: Not reported**
  - Clinical deterioration on a Likert-type scale
  - Clinical deterioration measured by number of days
  - Total symptomatic severity during the 15 days using a continuous scale

- **Adverse events:**
  - The fluvoxamine group had 1 serious adverse event and 11 other adverse events, whereas the placebo group had 6 serious adverse events and 12 other adverse events

### Observational Cohort Studies

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| Multicenter, retrospective study of 3401 propensity matched COVID-19 patients prescribed SSRIs between January and September 2020 across 87 health care centers in the US | Patient selection (fluvoxamine vs placebo):
  - Median age 46 years (SD 13), female 72%, White, 70%, Black 25%
  - Median number of days with symptoms before randomization: 4 days
  - The most severe presenting COVID-19 symptom varied significantly among groups, with fatigue (23%) and loss of sense of smell (29%) being the most common
  - Median O2Sat 97% for both groups
  - BMI ≥ 30 (54% vs 58%), asthma (21% vs 13%), HTN (19% vs 21%), DM (11% vs 11%)
  - Clinical outcome:
    - Patients treated with any SSRI (14.6% (497/3401) vs 16.3% (1107/6802); p=0.03), fluoxetine (9.8% (46/470) vs 13.3% (937/7050); p=0.03), fluoxetine or fluvoxamine (10.0% (48/481) vs 13.3% (956/7215); p=0.04) was associated with lower mortality compared to propensity matched controls
    - However, patients treated with a SSRI other than fluoxetine or fluvoxamine did not experience mortality benefit (15.4% (447/2898) vs 17.0% (1474/8697); p=0.96)
  - Safety outcome:
    - None assessed
  - Secondary outcomes not reported
| Small sample size within single geographic area
| Study outcomes based on patients self-reported responses
| 20% of patients stopped responding to surveys
| Missing and censored data may have affected outcome of the study
| Small number of end point events
| Differences in clinical deterioration may be due to baseline differences in O2Sat vs treatment effect
| Method of measuring severe baseline symptoms was flawed and did not provide valid data
| Scale used for clinical deterioration not validated
| Short follow-up period
| SSRI was associated with a small, statistically significant 8% relative risk reduction of mortality among patients with COVID-19 compared to propensity matched controls
| It is unknown if morbidity or mortality would have improved because of general improvement in care with other anti-inflammatory regimens or other COVID therapeutics, further reducing the difference attributed to SSRI treatment
| Limitations:
  - Retrospective design
  - No control group
  - Study design cannot identify causal effect
  - Confounding variables and missing data may have affected study outcome
  - In the fluoxetine or fluvoxamine arm (n=481), few patients were treated with fluvoxamine (n=11)

- Patients exposed to SSRIs, specifically fluoxetine (n=470), fluoxetine or fluvoxamine (481), or other SSRIs not fluoxetine or fluvoxamine (n=2898)

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  - Mean age 63.8 years [SD 18.1], female 59.8%, White 76.5%, Black 14.1%
  - Inpatient 73.9%, ED 19.0%, Obs 6.5%, Urgent Care 0.6%
  - Severity of baseline symptoms or day of symptom onset not assessed
  - HTN (70.7% vs 46.4%), DM (42.6% vs 30.5%), mood or anxiety disorder (63.2% vs 18.3%)
  - Mean fluoxetine equivalent dose: any SSRI 30.2 mg/d [22.6], fluoxetine 28.2 mg/d [16.9], fluoxetine or fluvoxamine 29.0 [18.0], SSRI other than fluoxetine or fluvoxamine 30.4 mg/d [23.1]. Dose information was available between 86% and 88% of patients among groups
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- Fluoxetine or fluvoxamine (n=2898)
- Other SSRIs not fluoxetine or fluvoxamine (n=470)

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Study Design
Prospective observational study of 113 congregate living, adult outpatients with mild or asymptomatic COVID-19 between November 2020 and December 2020 in California

Patients exposed in occupational setting at a horse racetrack were serial tested and offered fluvoxamine 50-100 mg x1, then 50 mg daily x 14 days once confirmed positive (n=65) and compared to those opting for observation alone (n=48)

Exclusion
- Evaluated for contraindications or drug-drug interactions, none were excluded

Results
- Clinical outcome:
  - Patients treated with fluvoxamine had lower respiratory rates at day 7 compared to those choosing observation alone (12.9±1.6 vs 15.1±4.1; p=0.001)
  - Fluvoxamine was associated with fewer hospitalizations within 14 days (0 vs 6; p=0.005) and were less likely to have ongoing symptoms at day 14 (0% vs 60%; p<0.001)
    - The most common persisting symptoms were persistent anxiety (n = 19), difficulty concentrating/memory challenges (n = 18), fatigue (n = 16), insomnia (n = 12), myalgia/arthritis (n = 10), and headache (n = 9)
  - Two persons opting for observation required intensive care unit stay with mechanical ventilation, 1 of whom died

- Safety outcome:
  - No serious adverse events occurred with fluvoxamine or led to early discontinuation

Patient selection (fluvoxamine vs observation):
- Median age 42 years [33-56], female 25%, Latino 84%, White 14%
- More patients opting for observation were asymptomatic (58%) vs fluvoxamine (38%)
- Mild (37% vs 19%) or moderate disease (25% vs 23%)
- Mean RR at baseline 17.7 in both groups (p=0.95)
- Mean days for PCR confirmation (3.7 vs 3.4 days)
- HTN (17% vs 35%), DM2 (17% vs 8%)

Conclusions
- Outpatients treated with fluvoxamine had fewer hospitalizations within 14 days, supporting results of Lenze study. Further randomized clinical trial evidence is needed

Limitations:
- Small sample size within single geographic area
- Observational design
- Confounding by indication

References
2. Fluvoxamine. In: Lexicomp Online®, Lexi-Drugs Online®, Hudson, Ohio: Lexi-Comp, Inc. Last assessed: November 2, 2021

FMCP Team December 2021 amd