

Fluvoxamine reduces COVID-19 risk: real-time meta analysis of 21 studies

@CovidAnalysis, June 2025, Version 37
<https://c19early.org/fmeta.html>

Abstract

Significantly lower risk is seen for mortality, hospitalization, progression, recovery, and cases. 14 studies from 14 independent teams in 8 countries show significant benefit.

Meta analysis using the most serious outcome reported shows 39% [21-52%] lower risk. Results are similar for Randomized Controlled Trials.

Results are very robust — in exclusion sensitivity analysis 12 of 21 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Other treatments are more effective. All data and sources to reproduce this analysis are in the appendix.

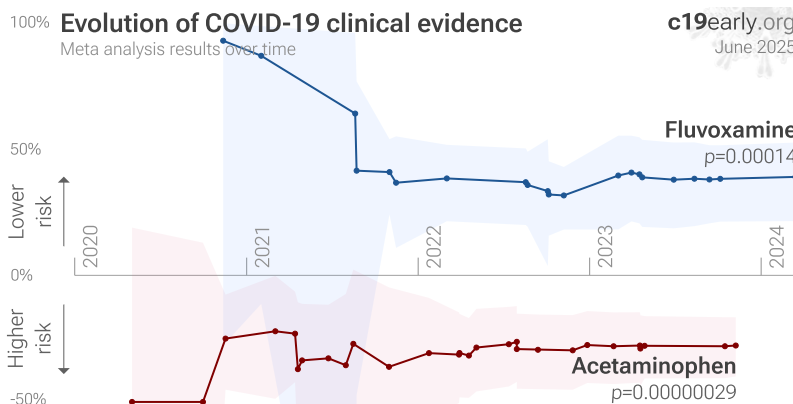
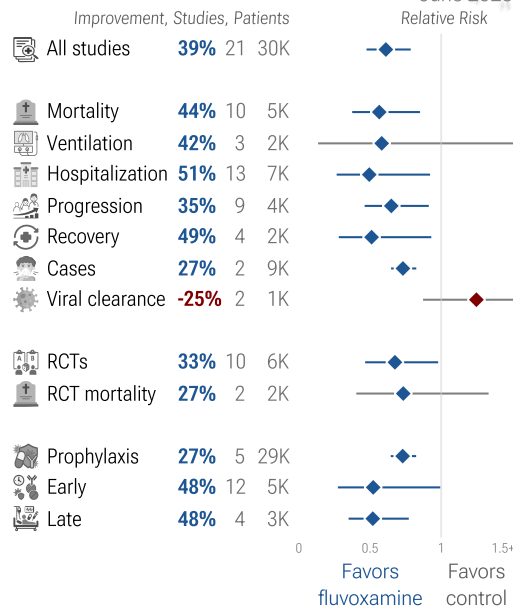
8 other meta analyses show significant improvements with fluvoxamine for mortality^{1,2}, hospitalization^{1,3-7}, progression^{2,7}, and severity⁸.

Serious Outcome Risk



Fluvoxamine for COVID-19

c19early.org
June 2025



FLUVOXAMINE FOR COVID-19 — HIGHLIGHTS

Fluvoxamine reduces risk with very high confidence for mortality and in pooled analysis, high confidence for hospitalization, progression, and recovery, and low confidence for cases, however increased risk is seen with very low confidence for viral clearance.

29th treatment shown effective in November 2021, now with $p = 0.00014$ from 21 studies, recognized in 2 countries.

Real-time updates and corrections with a consistent protocol for 169 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.

21 fluvoxamine COVID-19 studies

c19early.org
June 2025



Timeline of COVID-19 fluvoxamine studies (pooled effects)

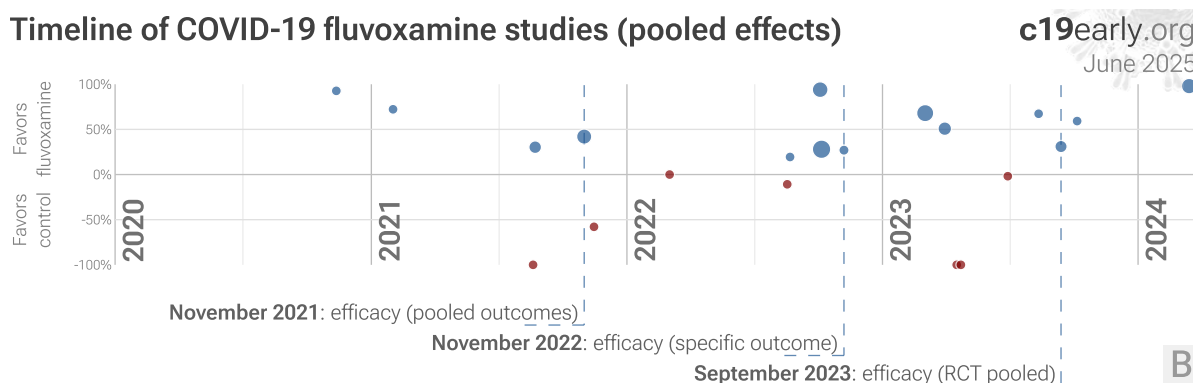


Figure 1. A. Random effects meta-analysis. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found [below](#). Effect extraction is pre-specified, using the most serious outcome reported. For details see the [appendix](#). **B. Timeline of results in fluvoxamine studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of $\geq 10\%$ from ≥ 3 studies for pooled outcomes, one or more specific outcome, and pooled outcomes in RCTs. Efficacy based on RCTs only was delayed by 22.4 months, compared to using all studies. Efficacy based on specific outcomes was delayed by 12.2 months, compared to using pooled outcomes.

Introduction

Immediate treatment recommended

SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury¹⁰⁻²² and cognitive deficits^{13,18}, cardiovascular complications²³⁻²⁷, organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits²⁸—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

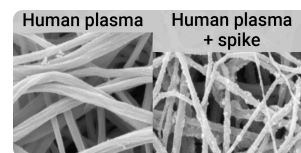


Figure 2. SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from ⁹.

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors^{A,29-36}, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk³⁷, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Supporting research

Fluvoxamine may inhibit SARS-CoV-2 cell entry by preventing the formation of ceramide platforms that facilitates viral uptake³⁸ and may help restore autophagic processes disrupted by NSP6, thereby reducing SARS-CoV-2 replication and improving host cellular defenses³⁹.

Analysis

We analyze all significant controlled studies of fluvoxamine for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, studies within each treatment stage, individual outcomes, and Randomized Controlled Trials (RCTs).

Treatment timing

Figure 3 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

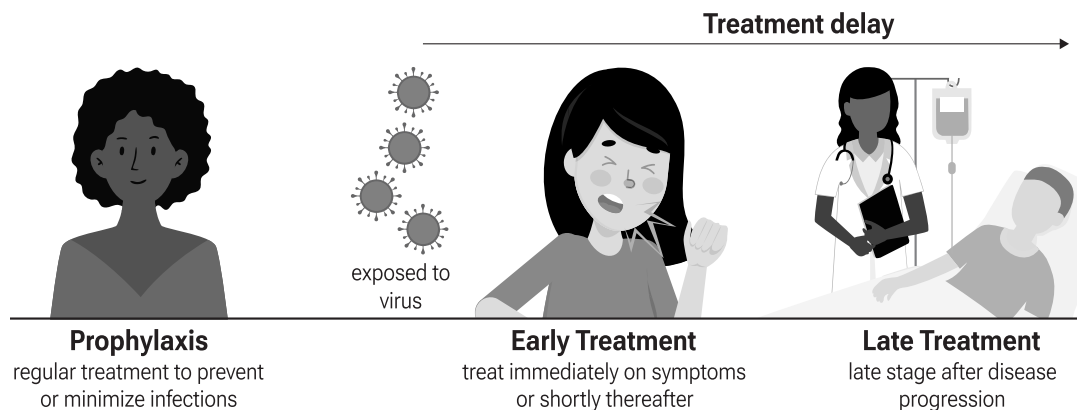


Figure 3. Treatment stages.

Mechanisms of Action

Table 1 shows potential mechanisms of action for the treatment of COVID-19 using fluvoxamine.

FIASMA	Fluvoxamine is a functional inhibitor of acid sphingomyelinase (FIASMA). SARS-CoV-2 activates the ASM/ceramide system which may facilitate viral entry. ASM inhibition may reduce the concentration of ceramides and inhibit viral entry ⁴⁰⁻⁴³ .
Sigma-1 activation	Fluvoxamine may reduce clinical deterioration via σ -1 (S1R) receptor activation, which regulates cytokine production ⁴³⁻⁴⁵ .
Platelet activation	Platelet activation may contribute to COVID-19 severity. Fluvoxamine inhibits platelet activation ^{44,46} .
Lysosomal trafficking	SARS-CoV-2 uses lysosomal trafficking to escape from infected cells. Fluvoxamine is lysosomotropic and interferes with endolysosomal viral trafficking ^{43,44,47} .
Heme oxygenase	COVID-19 risk may be related to low intracellular heme oxygenase (HO-1). Fluvoxamine increases HO-1 and HO-1 has cytoprotective and anti-inflammatory properties ⁴⁸⁻⁵⁰ .
Mast cell degranulation	Fluvoxamine may reduce cytokine storm due to decreased mast cell degranulation ⁴⁴ .
Melatonin	Melatonin may be beneficial for COVID-19, and fluvoxamine may elevate melatonin levels via CYP1A2 and CYP2C19 inhibition ^{43,44,51-53} .

Table 1. Fluvoxamine mechanisms of action.

Preclinical Research

Fluvoxamine may inhibit SARS-CoV-2 cell entry by preventing the formation of ceramide platforms that facilitates viral uptake³⁸ and may help restore autophagic processes disrupted by NSP6, thereby reducing SARS-CoV-2 replication and improving host cellular defenses³⁹.

2 *In Silico* studies support the efficacy of fluvoxamine^{38,54}.

2 *In Vitro* studies support the efficacy of fluvoxamine^{39,54}.

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Table 2 summarizes the results for all stages combined, for Randomized Controlled Trials, and for specific outcomes. Table 3 shows results by treatment stage. Figure 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, 9, 10, 11, 12, and 13 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, and viral clearance.

	Improvement	Studies	Patients	Authors
All studies	39% [21-52%] ***	21	38,283	307
Randomized Controlled Trials	33% [2-53%] *	10	6,462	221
Mortality	44% [15-63%] **	10	5,101	136
Ventilation	42% [-151-86%]	3	2,747	60
ICU admission	-10% [-326-72%]	3	855	17
Hospitalization	51% [8-73%] *	13	7,210	245
Recovery	49% [7-72%] *	4	2,368	57
Cases	27% [18-35%] ****	2	9,116	10
Viral	-25% [-78-13%]	2	1,003	31
RCT mortality	27% [-33-60%]	2	2,973	62
RCT hospitalization	49% [-27-79%]	8	6,325	204

Table 2. Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, and for specific outcomes. Results show the percentage improvement with treatment and the 95% confidence interval. * $p < 0.05$ ** $p < 0.01$ **** $p < 0.0001$.

	Early treatment	Late treatment	Prophylaxis
All studies	48% [1-73%] *	48% [23-65%] **	27% [18-35%] ****
Randomized Controlled Trials	33% [-37-67%]	31% [-9-56%]	
Mortality	71% [-52-95%]	51% [22-69%] **	5% [-76-49%]
Ventilation	77% [-1354-100%]	22% [-28-54%]	
ICU admission	37% [-160-85%]		-395% [-7042-66%]
Hospitalization	62% [5-85%] *	22% [-3-41%]	1% [-118-55%]
Recovery	88% [-446-100%]	45% [6-68%] *	
Cases			27% [18-35%] ****
Viral	-4% [-19-9%]	-49% [-138-6%]	
RCT mortality	-200% [-7253-88%]	30% [-26-63%]	
RCT hospitalization	53% [-69-87%]	22% [-3-41%]	

Table 3. Random effects meta-analysis results by treatment stage. Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage.

* $p < 0.05$ ** $p < 0.01$ **** $p < 0.0001$.

Efficacy in COVID-19 fluvoxamine studies (pooled effects)

c19early.org
June 2025

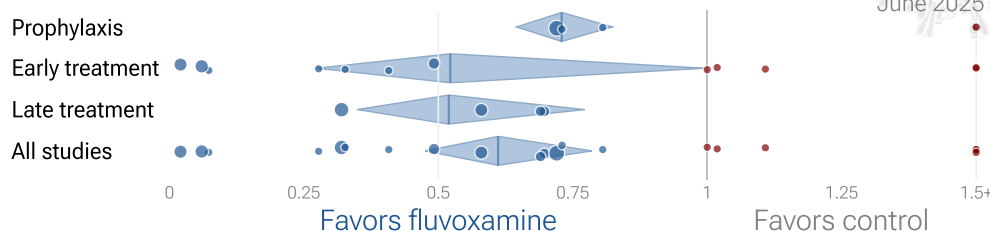


Figure 4. Scatter plot showing the most serious outcome in all studies, and for studies within each stage. Diamonds shows the results of random effects meta-analysis.

21 fluvoxamine COVID-19 studies

c19early.org

June 2025



Figure 5. Random effects meta-analysis for all studies. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

10 fluvoxamine COVID-19 mortality results

c19early.org

June 2025

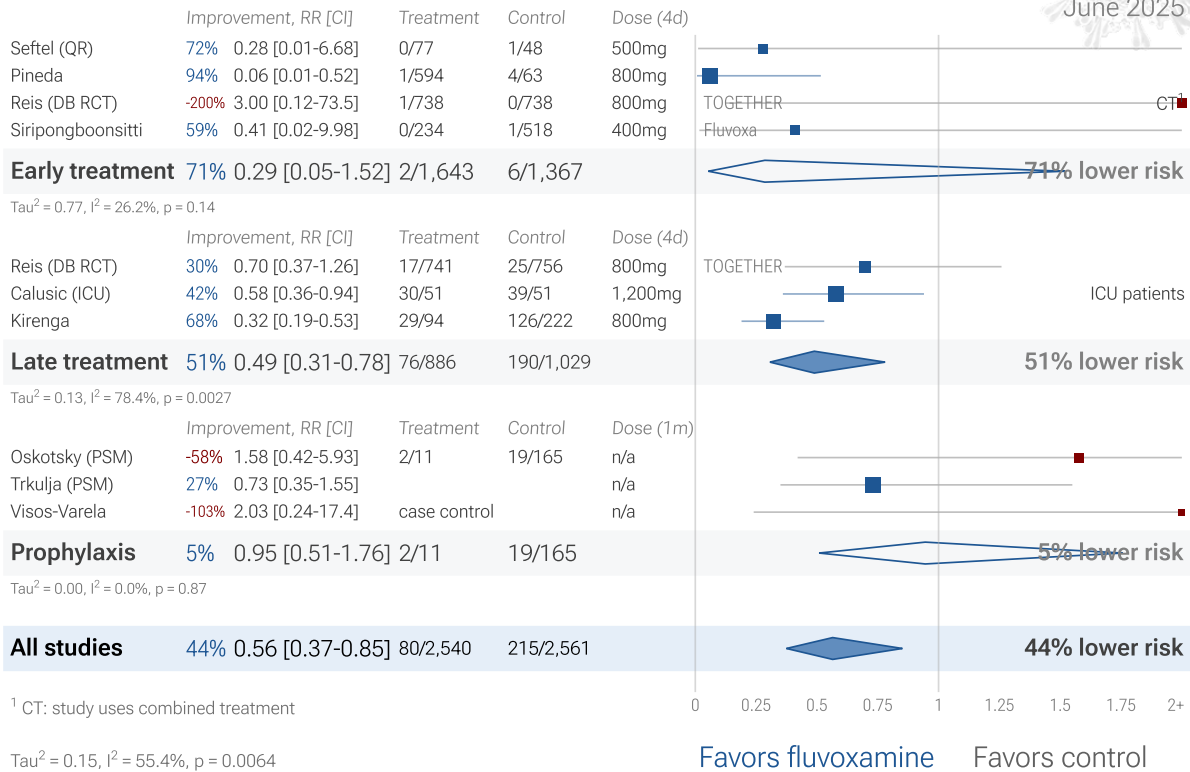


Figure 6. Random effects meta-analysis for mortality results.

3 fluvoxamine COVID-19 mechanical ventilation results

c19early.org

June 2025

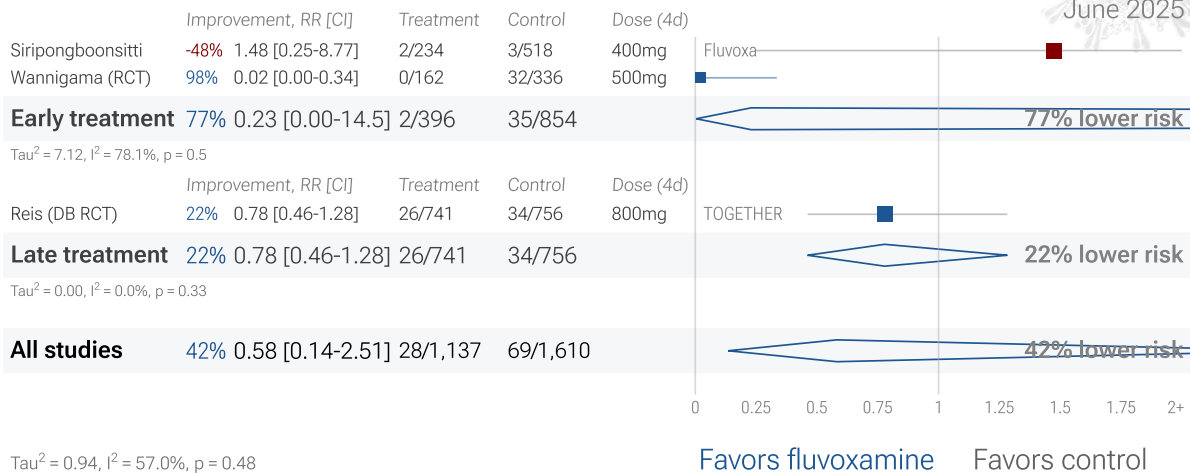


Figure 7. Random effects meta-analysis for ventilation.

3 fluvoxamine COVID-19 ICU results

c19early.org
June 2025

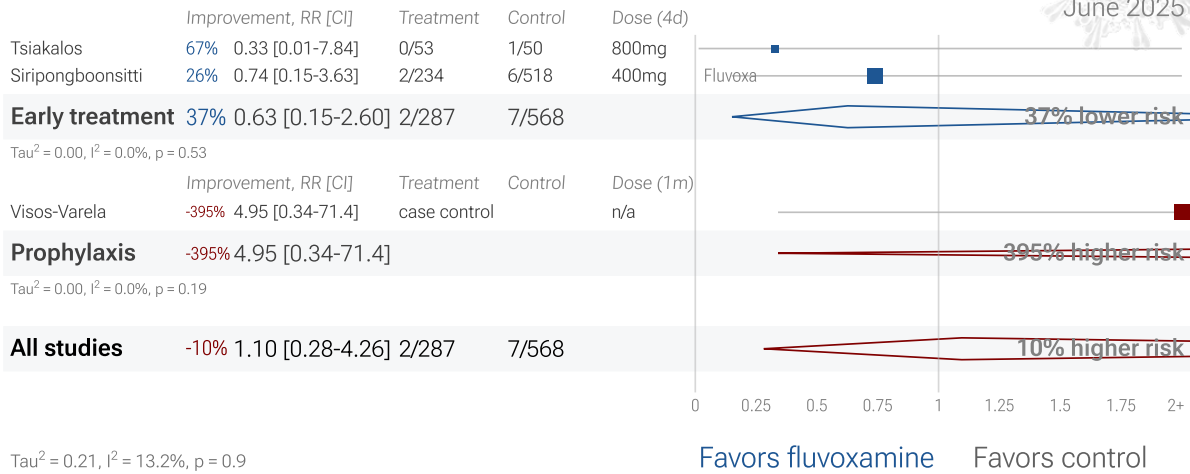


Figure 8. Random effects meta-analysis for ICU admission.

13 fluvoxamine COVID-19 hospitalization results

c19early.org
June 2025

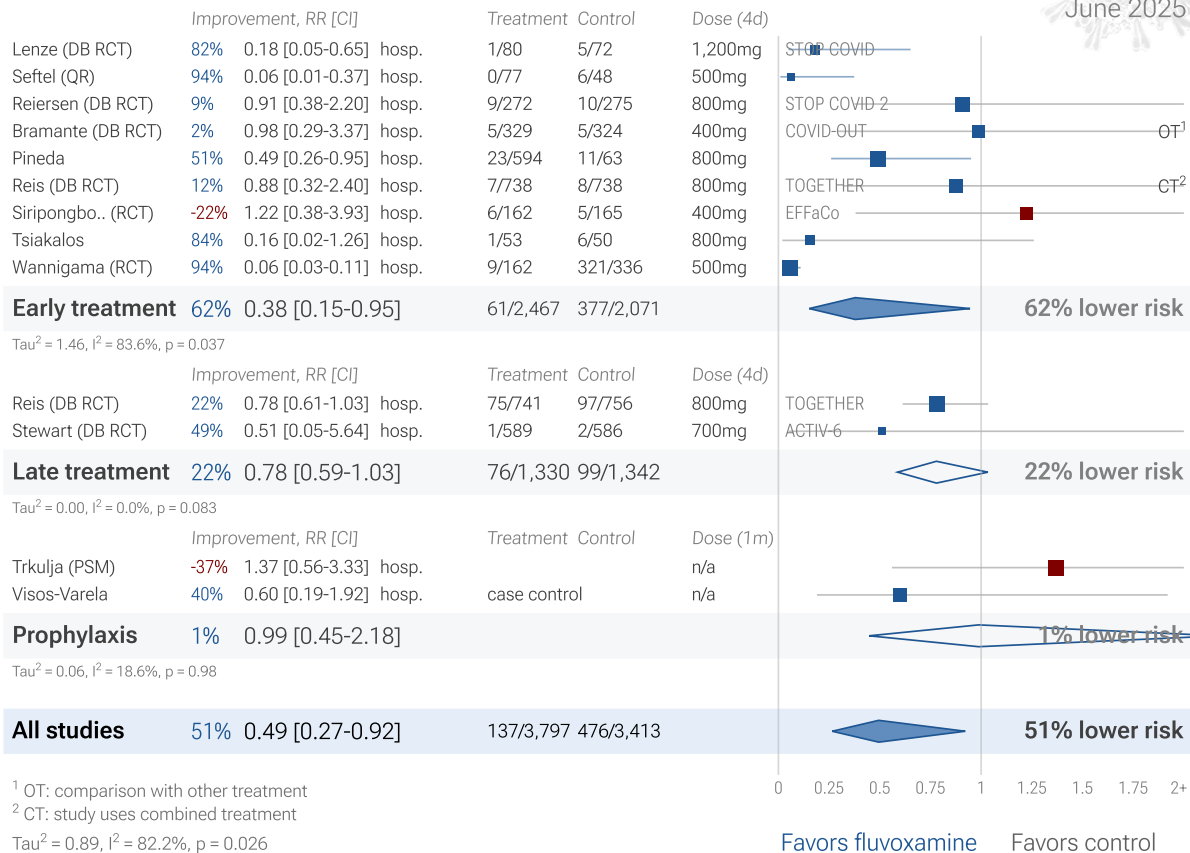


Figure 9. Random effects meta-analysis for hospitalization.

9 fluvoxamine COVID-19 progression results

c19early.org

June 2025

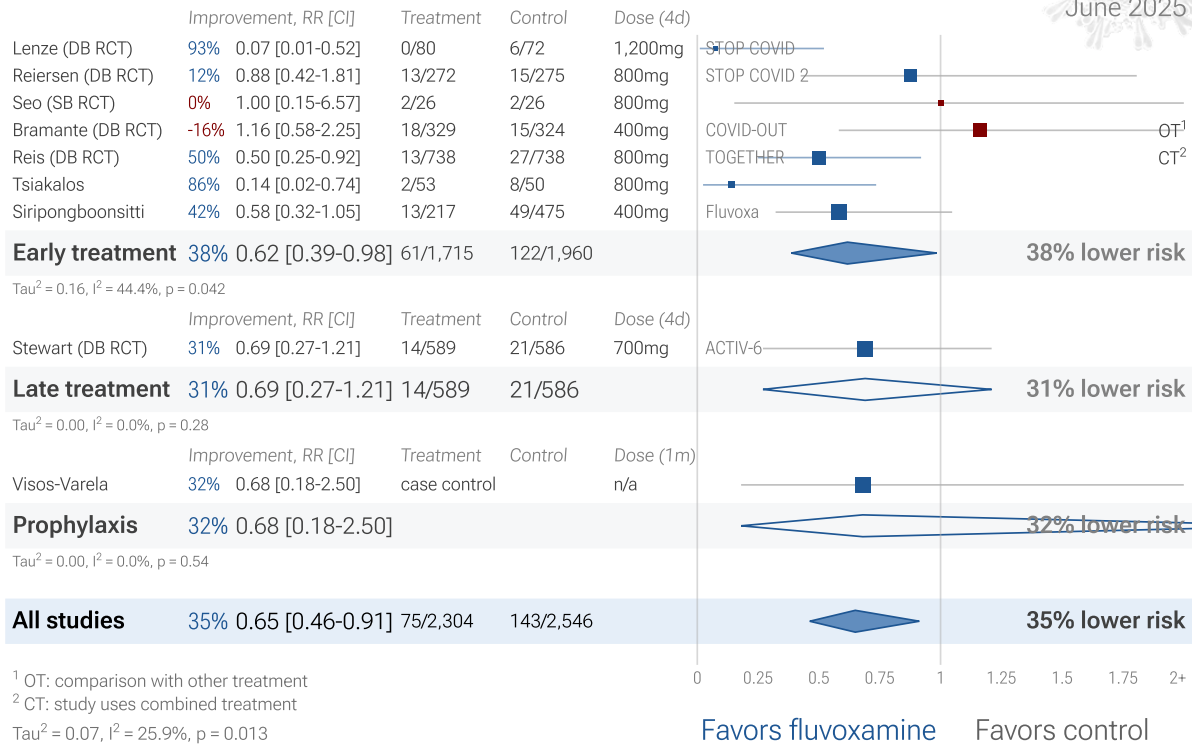


Figure 10. Random effects meta-analysis for progression.

4 fluvoxamine COVID-19 recovery results

c19early.org

June 2025

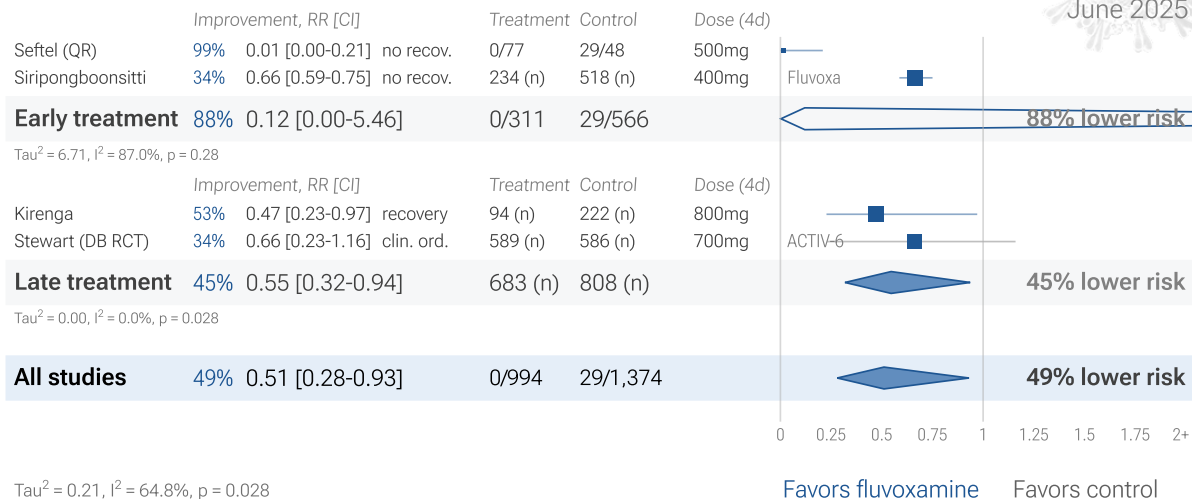


Figure 11. Random effects meta-analysis for recovery.

2 fluvoxamine COVID-19 case results

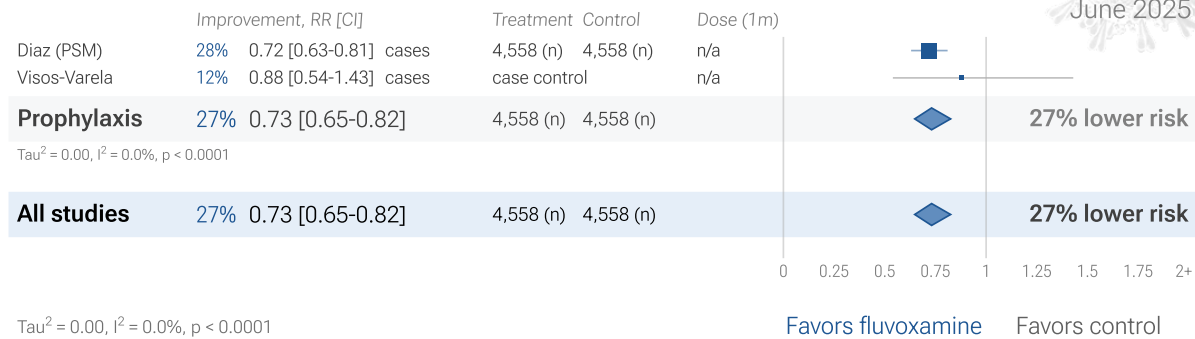


Figure 12. Random effects meta-analysis for cases.

2 fluvoxamine COVID-19 viral clearance results

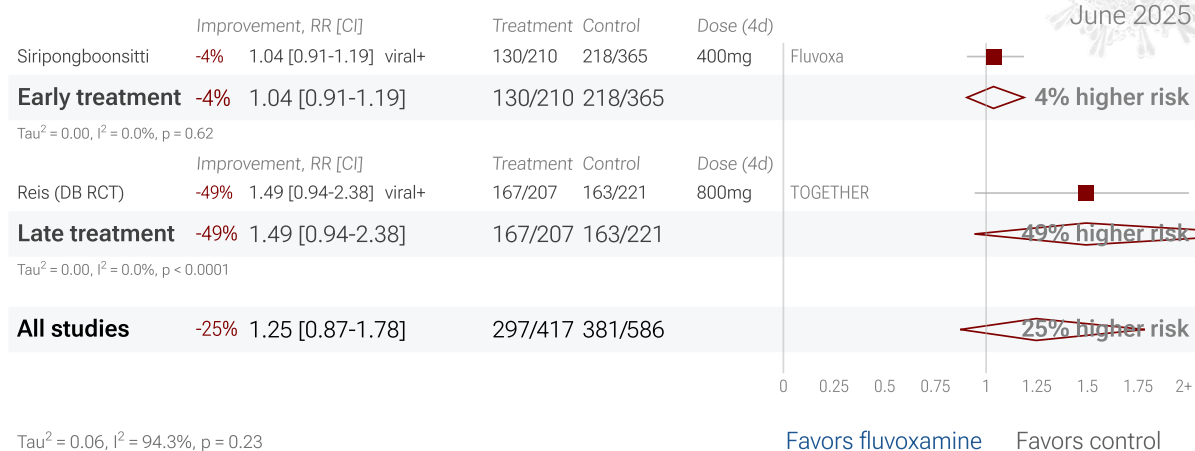


Figure 13. Random effects meta-analysis for viral clearance.

Randomized Controlled Trials (RCTs)

Figure 14 shows a comparison of results for RCTs and non-RCT studies. Figure 15, 16, and 17 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 2 and Table 3.

Efficacy in COVID-19 fluvoxamine studies (pooled effects)

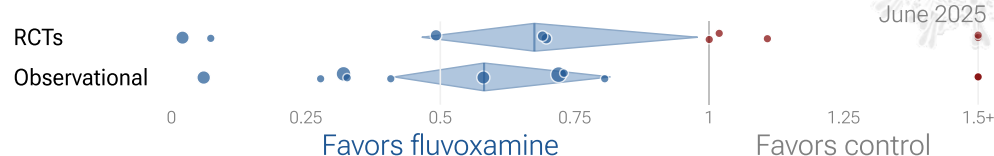


Figure 14. Results for RCTs and non-RCT studies.

10 fluvoxamine COVID-19 Randomized Controlled Trials

c19early.org

June 2025

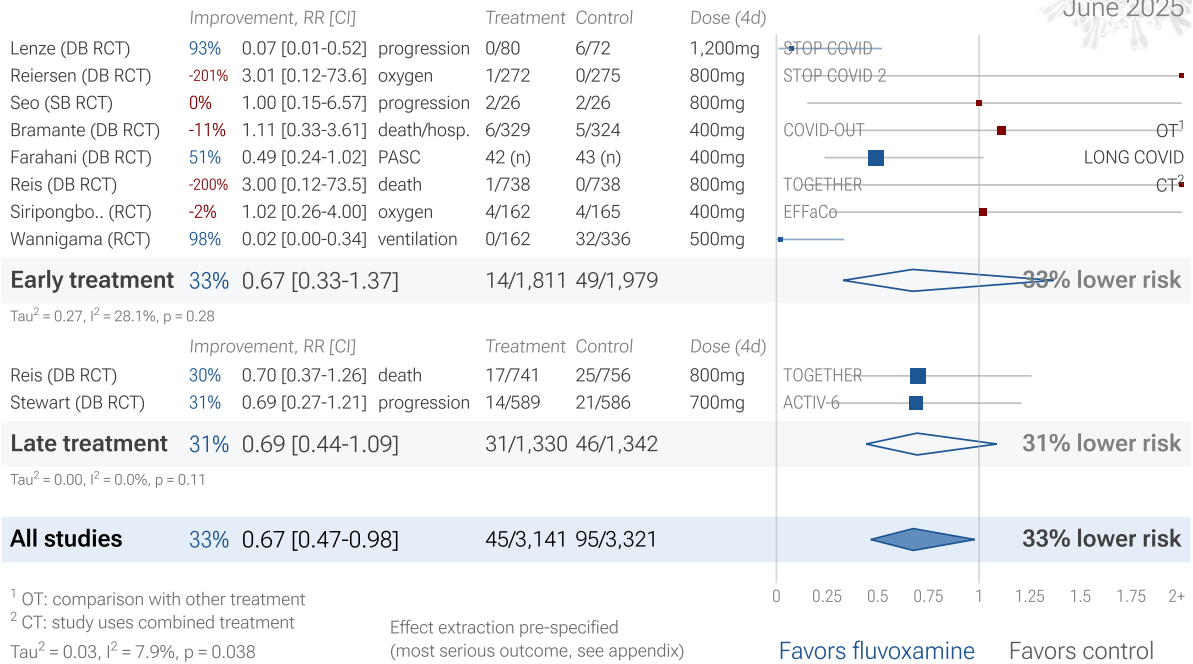


Figure 15. Random effects meta-analysis for all Randomized Controlled Trials. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

2 fluvoxamine COVID-19 RCT mortality results

c19early.org

June 2025

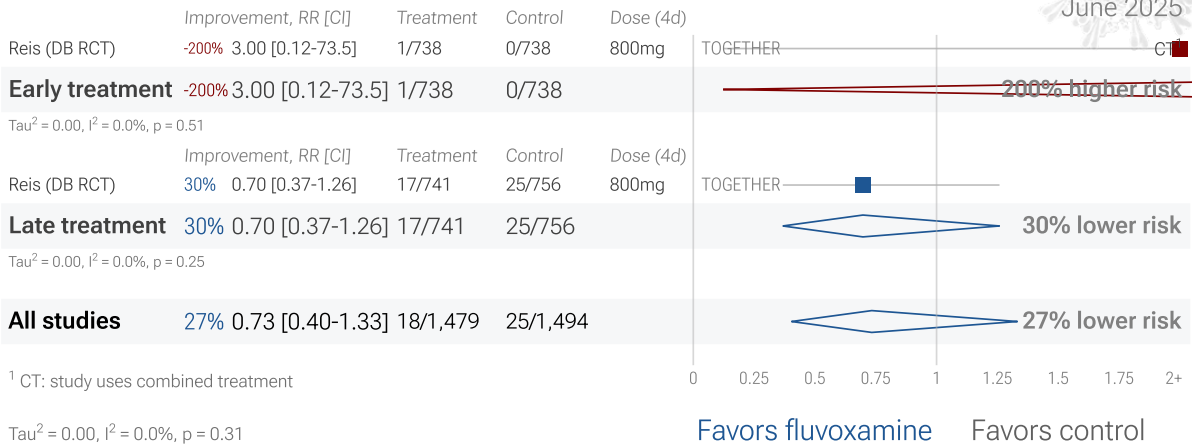


Figure 16. Random effects meta-analysis for RCT mortality results.

8 fluvoxamine COVID-19 RCT hospitalization results

c19early.org

June 2025

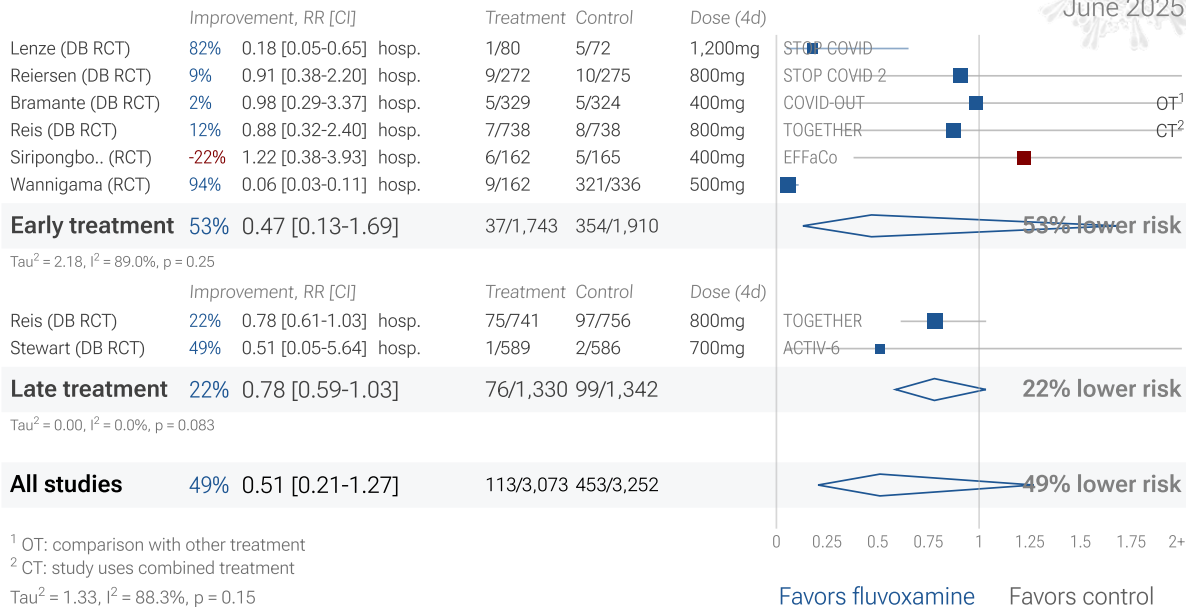


Figure 17. Random effects meta-analysis for RCT hospitalization results.

RCTs have many potential biases

RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases⁵⁵, and analysis of double-blind RCTs has identified extreme levels of bias⁵⁶. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs

RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment

High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 169 treatments we have analyzed, 66% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

RCT bias for widely available treatments

RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for fluvoxamine are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Observational studies have been shown to be reliable

Evidence shows that observational studies can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* analyzed reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. We performed a similar analysis across the 169 treatments we cover, showing no significant difference in the results of RCTs compared to observational studies, RR 0.99 [0.93-1.06]⁶¹. Similar results are found for all low-cost treatments, RR 1.01 [0.92-1.11]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.83-1.03]. Details can be found in the [supplementary data](#). *Lee (B) et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or remote survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see^{63,64}.

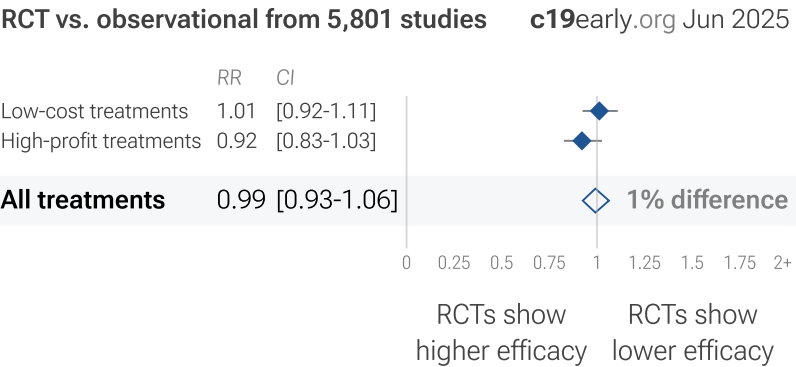


Figure 18. For COVID-19, observational study results do not systematically differ from RCTs, RR 0.99 [0.93-1.06] across 169 treatments⁵⁸.

Using all studies identifies efficacy 8+ months faster (9+ months for low-cost treatments)

Currently, 53 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of these, 58% have been confirmed in RCTs, with a mean delay of 7.8 months (66% with 8.9 months delay for low-cost treatments). The remaining treatments either have no RCTs, or the point estimate is consistent.

Summary

We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.

NIH

NIH provides an analysis of fluvoxamine for COVID-19⁶⁵, recommending against use. However, they appear to have only examined a fraction of the evidence. For example, considering RCTs providing clinical results for COVID-19 and fluvoxamine, they reference only⁶⁶⁻⁷¹, and appear not to know about 4 other RCTs⁷²⁻⁷⁵ as shown in Figure 19. Authors do not reference any of the 11 observational studies. For COVID-19, observational study results do not systematically differ from RCTs, RR 0.99 [0.93-1.06] across 169 treatments⁵⁸.

Fluvoxamine RCTs missing in NIH analysis

c19early.org

June 2025

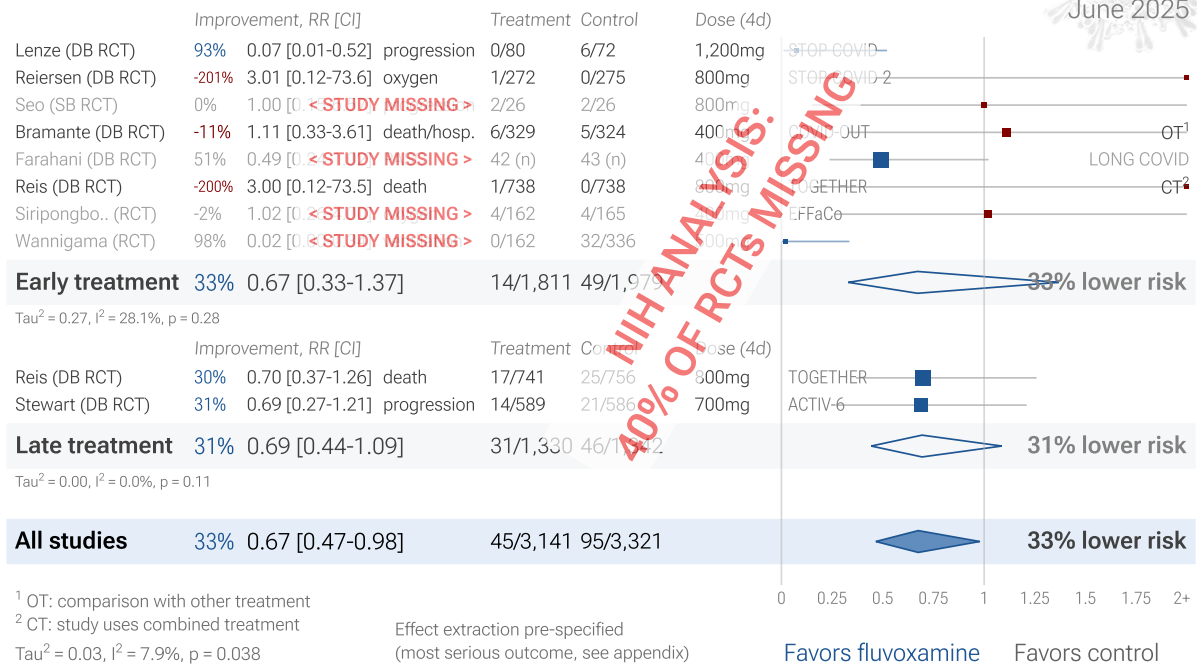


Figure 19. Analysis by NIH is missing 4 RCTs.

Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay

The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours^{76,77}. Baloxavir marboxil studies for influenza also show that treatment delay is critical — Ikematsu *et al.* report an 86% reduction in cases for post-exposure prophylaxis, Hayden *et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and Kumar *et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	Result
Post-exposure prophylaxis	86% fewer cases ⁷⁸
<24 hours	-33 hours symptoms ⁷⁹
24-48 hours	-13 hours symptoms ⁷⁹
Inpatients	-2.5 hours to improvement ⁸⁰

Table 4. Studies of baloxavir marboxil for influenza show that early treatment is more effective.

Figure 20 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 169 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

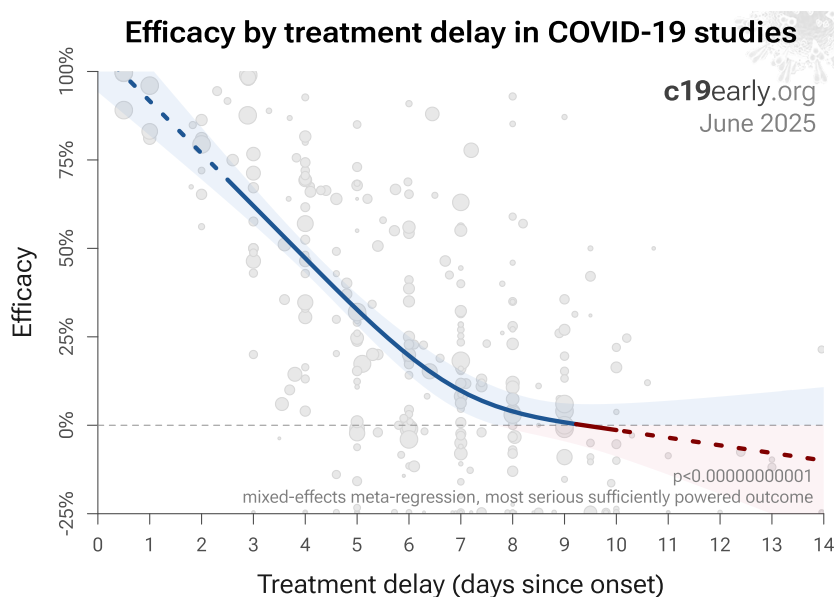


Figure 20. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 169 treatments.

Patient demographics

Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results, for example as in *López-Medina et al.*

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants⁸², for example the Gamma variant shows significantly different characteristics⁸³⁻⁸⁶. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants^{87,88}.

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

Medication quality

The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams et al.* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu et al.* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic⁹¹⁻¹⁰⁷, therefore efficacy may depend strongly on combined treatments.

Effect measured

Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treatment may be more effective against secondary complications and have minimal effect on viral clearance.

Meta analysis

The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Pooled Effects

Pooled effects are no longer required to show efficacy as of November 2022

This section validates the use of pooled effects for COVID-19, which enables earlier detection of efficacy, however pooled effects are no longer required for fluvoxamine as of November 2022. Efficacy is now known based on specific outcomes. Efficacy based on specific outcomes was delayed by 12.2 months compared to using pooled outcomes.

Combining studies is required

For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. *"The studies reported different outcomes"* is not a good reason for disregarding results. Pooling the results of studies reporting different outcomes allows us to use more of the available information. Logically we should, and do, use additional information when evaluating treatments—for example dose-response and treatment delay-response relationships provide additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

Specific outcome and pooled analyses

We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Ethical and practical issues limit high-risk trials

Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster and safer collection of evidence.

Validating pooled outcome analysis for COVID-19

For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.

Analysis of the the association between different outcomes across studies from all 169 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 21 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 22 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 23 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.00000009$ to $p = 0.0000000039$.

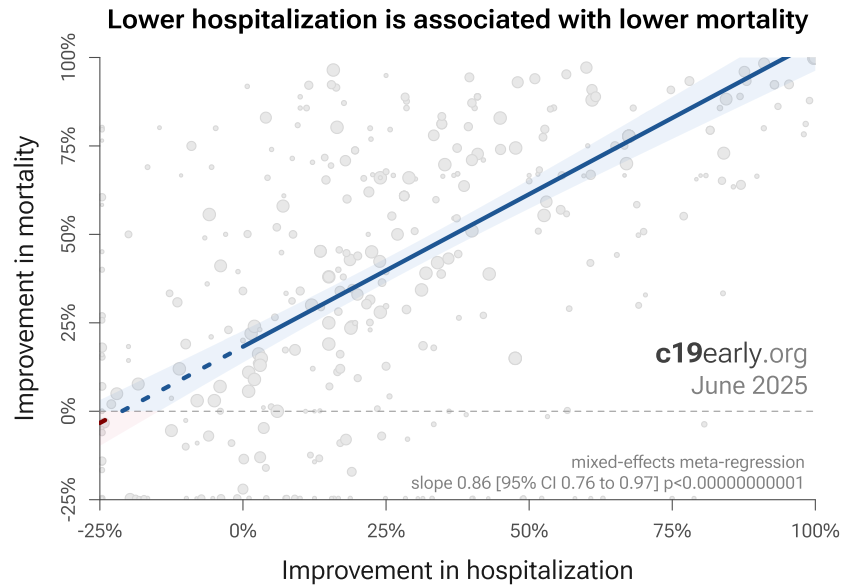


Figure 21. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

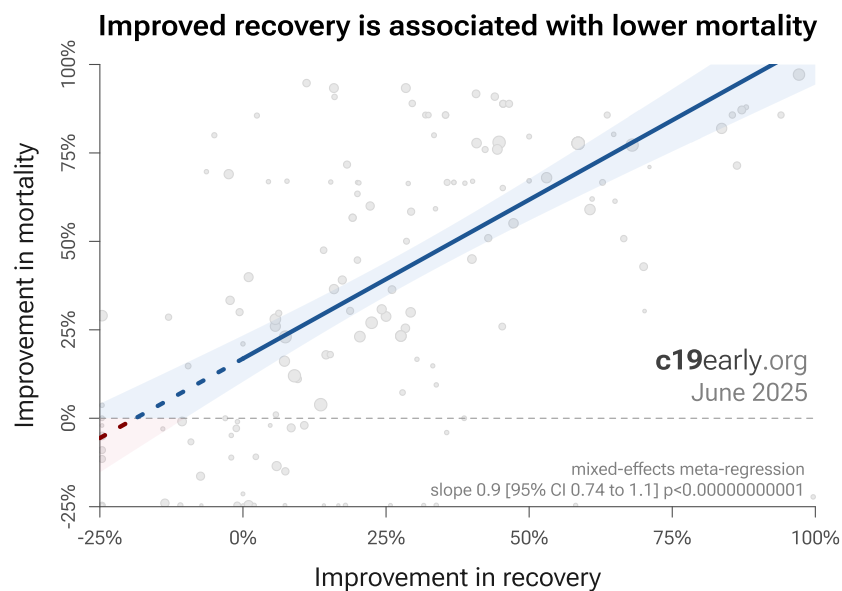


Figure 22. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

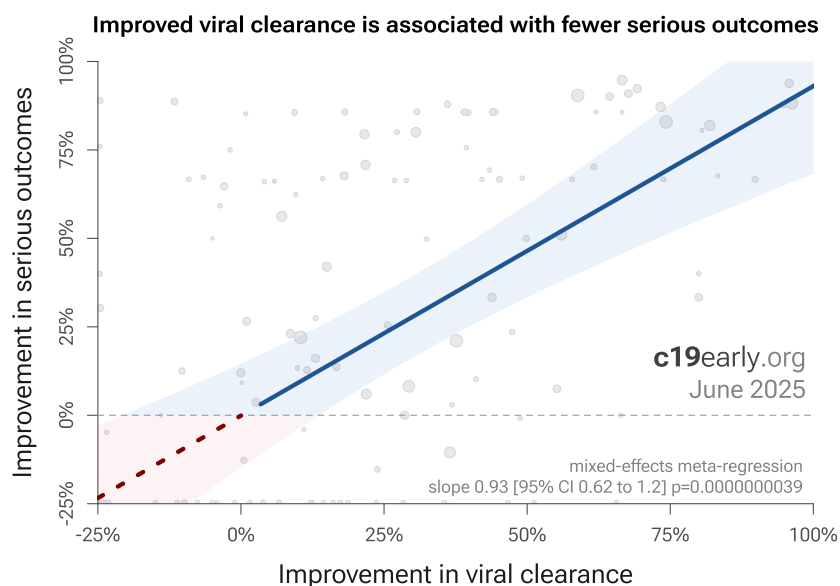


Figure 21. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

Pooled outcomes identify efficacy 5 months faster (7 months for RCTs)

Currently, 53 of the treatments we analyze show statistically significant efficacy or harm, defined as $\geq 10\%$ decreased risk or $>0\%$ increased risk from ≥ 3 studies. 90% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.9 months. When restricting to RCTs only, 55% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.3 months. Figure 24 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

Time when COVID-19 studies showed efficacy

c19early.org
June 2025

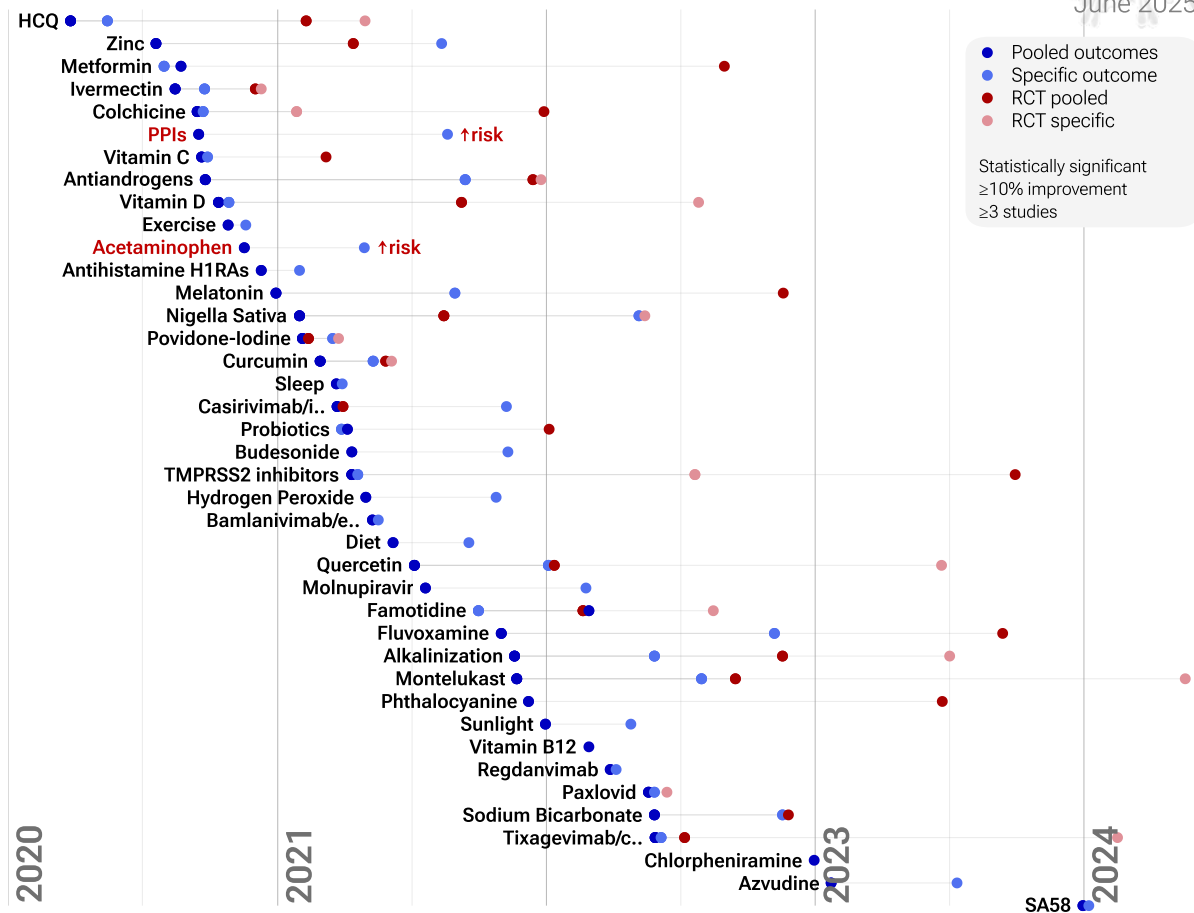


Figure 24. The time when studies showed that treatments were effective, defined as statistically significant improvement of $\geq 10\%$ from ≥ 3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations

Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

Summary

Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

Discussion

Publication bias

Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results¹⁰⁹⁻¹¹². For fluvoxamine, there is currently not enough data to evaluate publication bias with high confidence.

One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 25 shows a scatter plot of results for prospective and retrospective studies. 71% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 64% of prospective studies, consistent with a bias toward publishing positive results. The median effect size for retrospective studies is 27% improvement, compared to 36% for prospective studies, suggesting a potential bias towards publishing results showing lower efficacy.

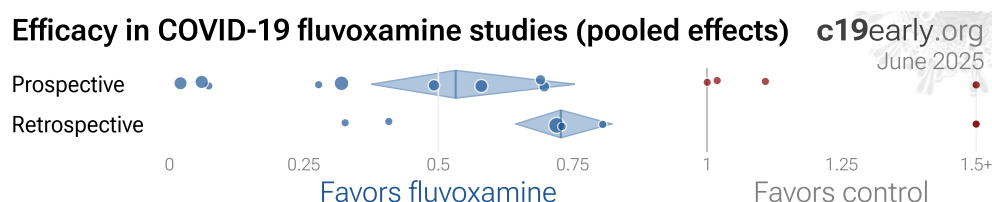


Figure 25. Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.

Funnel plot analysis

Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 26 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ ¹¹³⁻¹²⁰. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

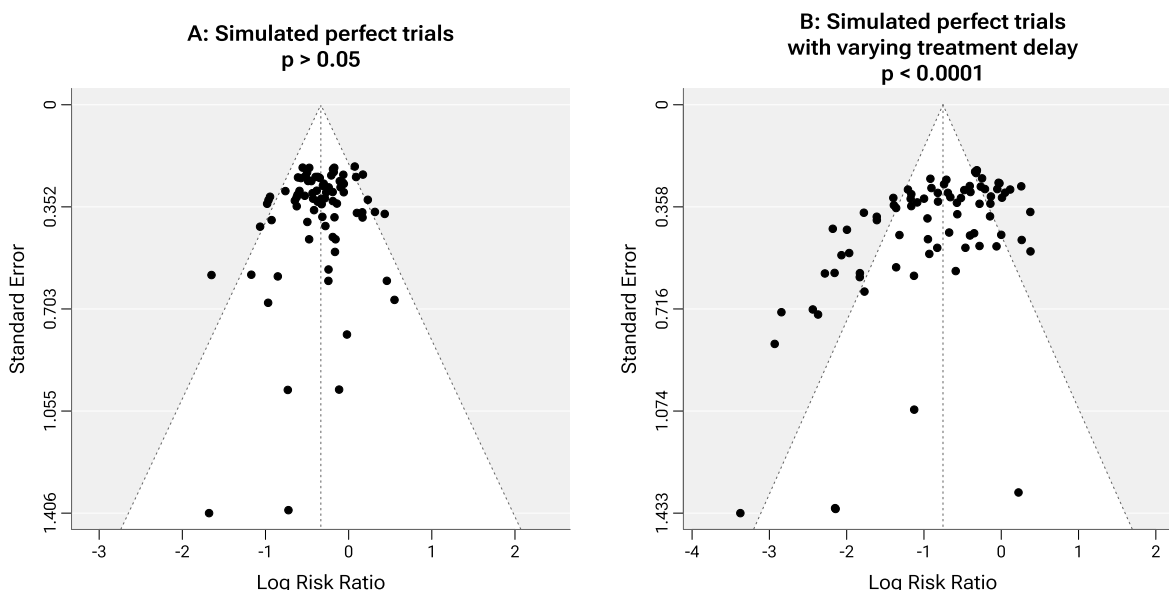


Figure 26. Example funnel plot analysis for simulated perfect trials.

Conflicts of interest

Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Fluvoxamine for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 fluvoxamine trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all fluvoxamine trials represent the optimal conditions for efficacy.

Limitations

Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses for specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

Some analyses classify treatment based on early or late administration, as done here, while others distinguish between mild, moderate, and severe cases. Viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials with conflicts of interest may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone⁹¹⁻¹⁰⁷. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes

1 of the 21 studies compare against other treatments, which may reduce the effect seen. 1 of 21 studies combine treatments. The results of fluvoxamine alone may differ. 1 of 10 RCTs use combined treatment. Currently all studies are peer-reviewed. 8 other meta analyses show significant improvements with fluvoxamine for mortality^{1,2}, hospitalization^{1,3-7}, progression^{2,7}, and severity⁸.

Reviews

Many reviews cover fluvoxamine for COVID-19, presenting additional background on mechanisms and related results, including^{43-45,121-124}.

Other studies

Additional preclinical or review papers suggesting potential benefits of fluvoxamine for COVID-19 include¹³⁶⁻¹⁵³. We have not reviewed these studies in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 100+ host and viral proteins and other factors²⁹⁻³⁶, providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk³⁷, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 27 shows an overview of the results for fluvoxamine in the context of multiple COVID-19 treatments, and Figure 28 shows a plot of efficacy vs. cost for COVID-19 treatments.

Efficacy in COVID-19 studies (pooled effects)

c19early.org

June 2025

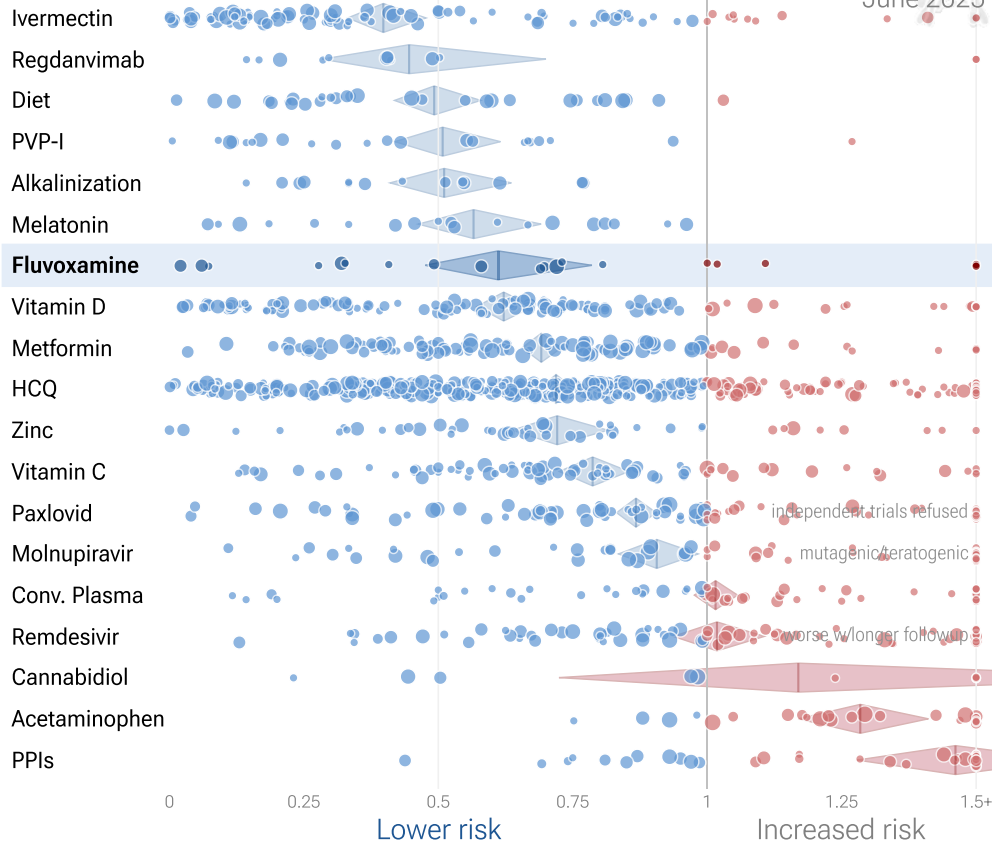


Figure 27. Scatter plot showing results within the context of multiple COVID-19 treatments. Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy¹⁵⁴.

Efficacy vs. cost for COVID-19 treatments

c19early.org

June 2025

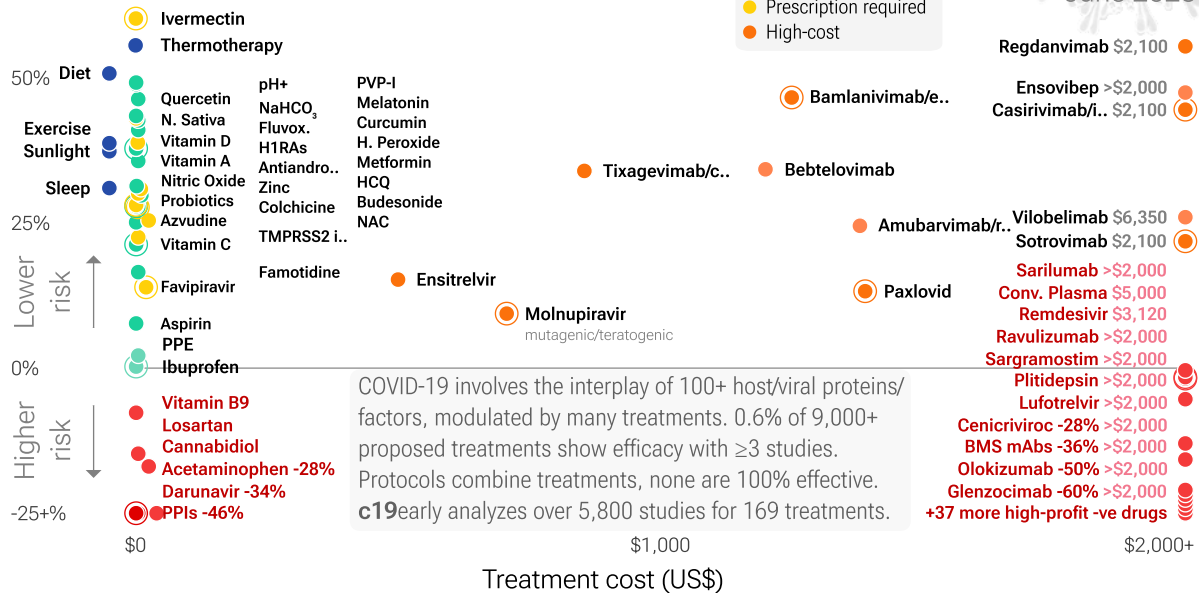


Figure 28. Efficacy vs. cost for COVID-19 treatments.

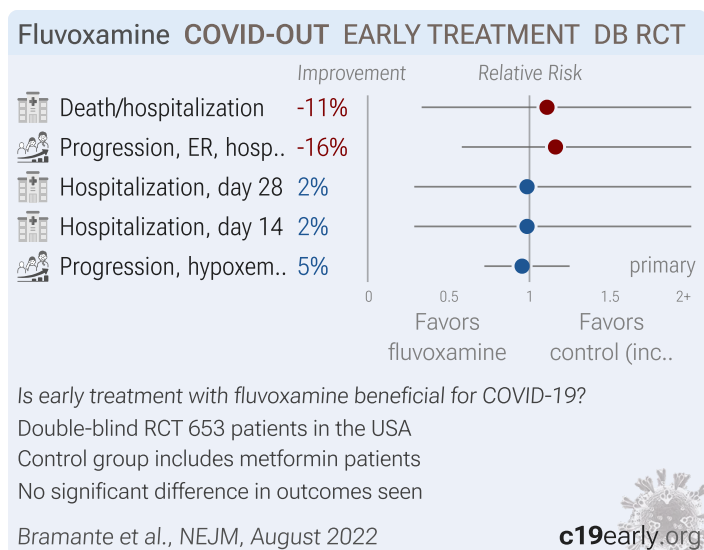
Conclusion

Fluvoxamine is an effective treatment for COVID-19. Significantly lower risk is seen for mortality, hospitalization, progression, recovery, and cases. 14 studies from 14 independent teams in 8 countries show significant benefit. Meta analysis using the most serious outcome reported shows 39% [21-52%] lower risk. Results are similar for Randomized Controlled Trials. Results are very robust — in exclusion sensitivity analysis 12 of 21 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

8 other meta analyses show significant improvements with fluvoxamine for mortality^{1,2}, hospitalization^{1,3-7}, progression^{2,7}, and severity⁸.

Study Notes

Bramante



COVID-OUT remotely operated RCT, showing no significant difference in outcomes. Results for other treatments are listed separately - metformin, ivermectin.

The "control" group includes patients receiving metformin, which is known to be beneficial for COVID-19¹⁵⁵.

Authors note that the dosage used in the trial is lower than that of other trials¹⁵⁶.

Control arm results are very different between treatments, for example considering hospitalization/death, this was 1.0% for ivermectin vs. 2.7% for overall control, however it was 1.3% for the ivermectin-specific control. 394 control patients are shared. The rate for the non-shared 261 metformin control patients is 5%, compared to 1.3% for ivermectin control patients. The metformin arm started earlier, however it is unclear why the difference in outcomes is so large.

Results were delayed for 6 months with no explanation, with followup ending Feb 14, 2022.

Multiple outcomes are missing, for example time to recovery (where ACTIV-6 showed superiority of ivermectin).

Adherence was very low, with 77% overall reporting 70+% adherence. Numbers for 100% adherence are not provided.

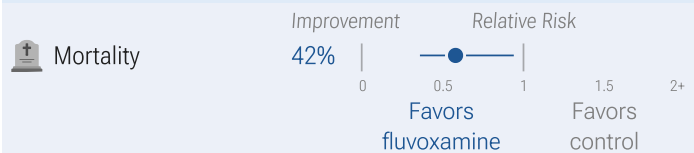
Treatment was 14 days for metformin and fluvoxamine, but only 3 days for ivermectin.

Trial outcomes were changed on January 20, 2022¹⁵⁷, and again on March 2, 2022¹⁵⁸. COVIDOUT.

Medication delivery varied significantly over the trial. In this presentation¹⁵⁹, author indicates that delivery was initially local, later via FedEx, was much slower in August, there were delays due to team bandwidth issues, and they only realized they could use FedEx same day delivery in September.

Calusic

Fluvoxamine for COVID-19 Calusic et al. ICU PATIENTS



Is **very late** treatment with fluvoxamine beneficial for COVID-19?
 PSM prospective study of 102 patients in Croatia (Apr - May 2021)
Lower mortality with fluvoxamine ($p=0.027$)

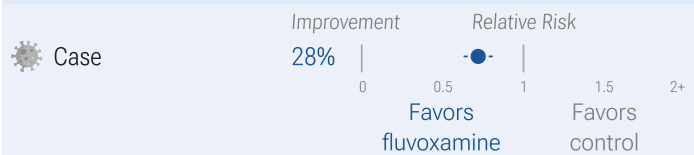
Calusic et al., British J. Clinical Ph., Nov 2021

c19early.org

Prospective PSM study of 51 COVID-19 ICU patients in Croatia and 51 matched controls, showing significantly lower mortality with treatment.

Diaz

Fluvoxamine for COVID-19 Diaz et al. Prophylaxis



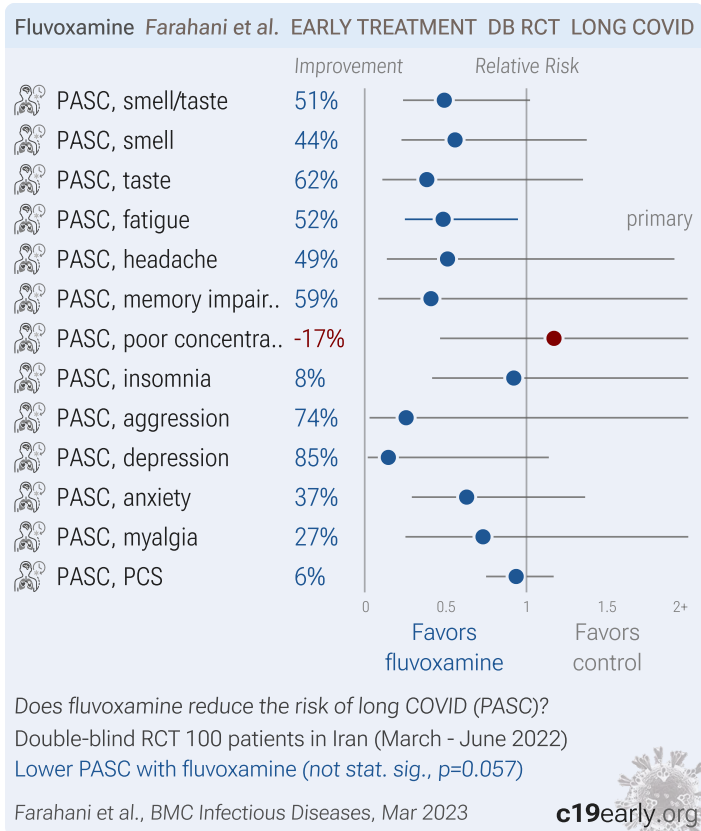
Does fluvoxamine reduce COVID-19 infections?
 PSM retrospective 82,069 patients in the USA
Fewer cases with fluvoxamine ($p<0.000001$)

Diaz et al., The Primary Care Companio., Oct 2022

c19early.org

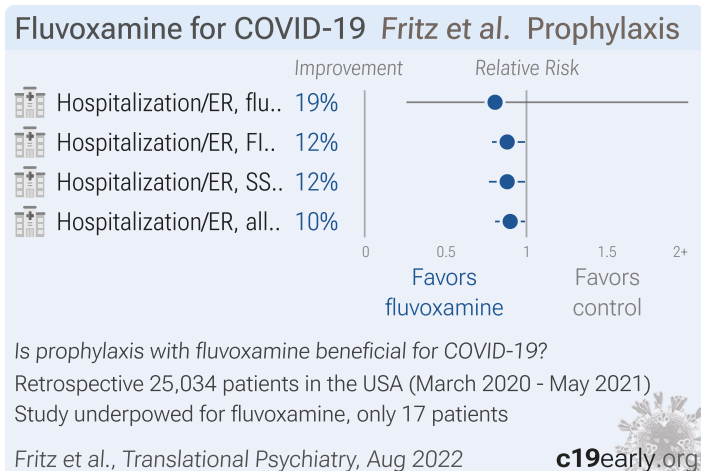
TriNetX PSM retrospective 82,069 OCD patients, showing lower risk of COVID-19 with fluvoxamine use.

Farahani



RCT 100 mild/moderate COVID-19 outpatients in Iran, showing lower post COVID symptoms 12 weeks after infection, statistically significant only for fatigue with the small sample size. All symptoms may occur for non-COVID-19 reasons, smell/taste disorder may be the most likely to be related to COVID-19 infection. Fluvoxamine 100mg daily for 10 days.

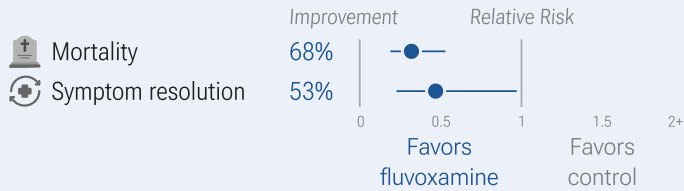
Fritz



Retrospective 25,034 COVID+ outpatients showing significantly lower ER/hospitalization with antidepressants and FIASMA antidepressants, and a dose-dependent response.

Kirenga

Fluvoxamine Kirenga et al. LATE TREATMENT



Is **late** treatment with fluvoxamine beneficial for COVID-19?

Prospective study of 316 patients in Uganda (Dec 2021 - Feb 2022)

Lower mortality ($p<0.0001$) and improved recovery ($p=0.04$)

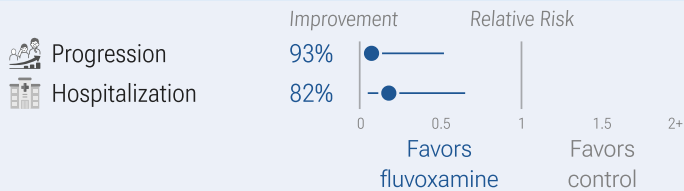
Kirenga et al., *Molecular Psychiatry*, Mar 2023

c19early.org

Prospective study of 316 hospitalized patients in Uganda, 94 receiving fluvoxamine, showing significantly lower mortality and improved recovery with treatment.

Lenze

Fluvoxamine STOP COVID EARLY TREATMENT DB RCT



Is early treatment with fluvoxamine beneficial for COVID-19?

Double-blind RCT 152 patients in the USA (April - August 2020)

Lower progression ($p=0.009$) and hospitalization ($p=0.009$)

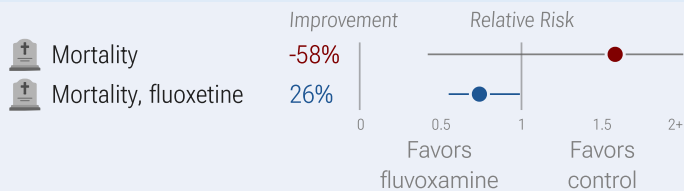
Lenze et al., *JAMA*, November 2020

c19early.org

RCT 152 outpatients, 80 treated with fluvoxamine showing lower progression with treatment (0 of 80 versus 6 of 72 control).

Oskotsky

Fluvoxamine for COVID-19 Oskotsky et al. Prophylaxis



Is prophylaxis with fluvoxamine beneficial for COVID-19?

PSM retrospective 7,696 patients in the USA

Study underpowered for fluvoxamine, only 11 patients

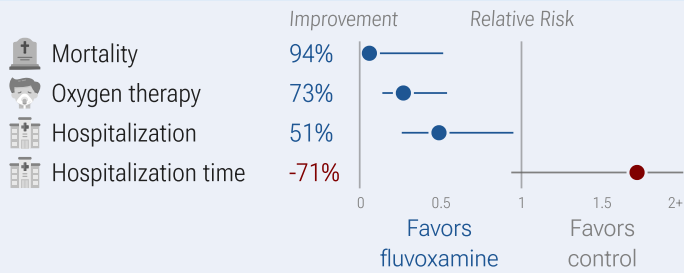
Oskotsky et al., *JAMA Network Open*, Nov 2021

c19early.org

Retrospective database analysis of 83,584 patients in the USA, showing lower mortality with existing fluoxetine use in PSM analysis. There were 11 fluvoxamine patients, showing non-statistically significant higher mortality.

Pineda

Fluvoxamine Pineda et al. EARLY TREATMENT



Is early treatment with fluvoxamine beneficial for COVID-19?

Prospective study of 657 patients in Honduras (Nov 2020 - Jan 2022)

Lower mortality ($p=0.011$) and lower oxygen therapy ($p=0.00016$)

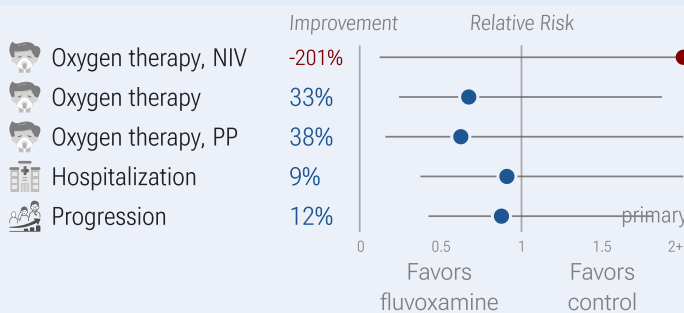
Pineda et al., *Frontiers in Pharmacology*, Oct 2022

c19early.org

Prospective study of 657 COVID+ outpatients in Honduras, 594 accepting fluvoxamine treatment, showing significantly lower mortality and hospitalization with treatment.

Reiersen

Fluvoxamine STOP COVID 2 EARLY TREATMENT DB RCT



Is early treatment with fluvoxamine beneficial for COVID-19?

Double-blind RCT 547 patients in the USA (December 2020 - May 2021)

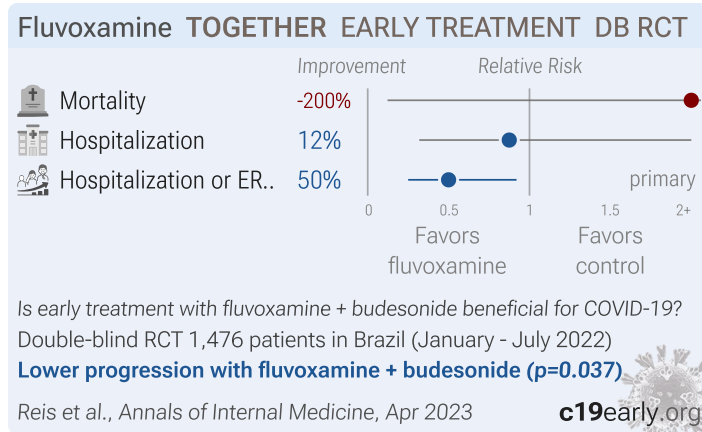
Trial underpowered to detect differences

Reiersen et al., *Open Forum Infectious Diseases*, Aug 2021

c19early.org

Remote RCT 547 outpatients a median of 5 days from onset, showing no significant differences with fluvoxamine. The trial was stopped early and underpowered due to low event rates. The trial does not report outcomes that may not be underpowered like time to recovery. Authors note that treatment may have been too late.

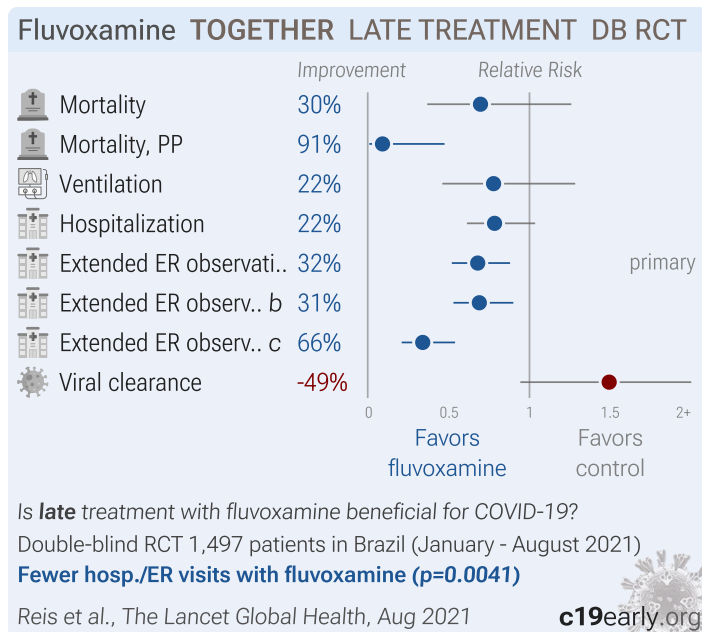
Reis



Low-risk (1% hospitalization) outpatient RCT with 738 fluvoxamine + budesonide patients and 738 placebo patients, showing significantly lower hospitalization/ER visits with treatment.

The TOGETHER trial has extreme COI, impossible data, blinding failure, randomization failure, uncorrected errors, and many protocol violations. Authors do not respond to these issues and they have refused to release the data as promised. Some issues may apply only to specific arms. For more details see ^{66,160-163}.

Reis



Together Trial showing significantly lower hospitalization/extended ER visits with fluvoxamine treatment. Adherence was only 73.2%. Symptom onset was unspecified or ≥ 4 days for 57% of patients. The schedule of study activities specifies treatment administration only one day after randomization, adding an additional day delay. Overall mortality is high for the patient population. Results may be impacted by late treatment, poor SOC, and may be specific to local variants ^{164 165}. Per-protocol analysis shows significantly improved results in this trial, however this may be subject to bias - the probability of adherence may be related to the probability of the outcome.

Regarding the combined hospitalization/extended ER observation outcome, authors have noted that at the study sites, extended medical observation was essentially equivalent to being hospitalized. "These were not standard emergency rooms but instead were COVID-19 emergency centers that were set up due to hospitals being overloaded," Reiersen noted in an email to The Scientist. "A stay in these centers >6 hours was an indication that the patient was receiving care equivalent to hospitalization."

Authors state "this study is only the second study to show an important treatment benefit for a repurposed drug in the early treatment population", however the actual number is at least 66 based on our database at the time of publication, using a conservative definition of at least 10% benefit (with statistical significance).

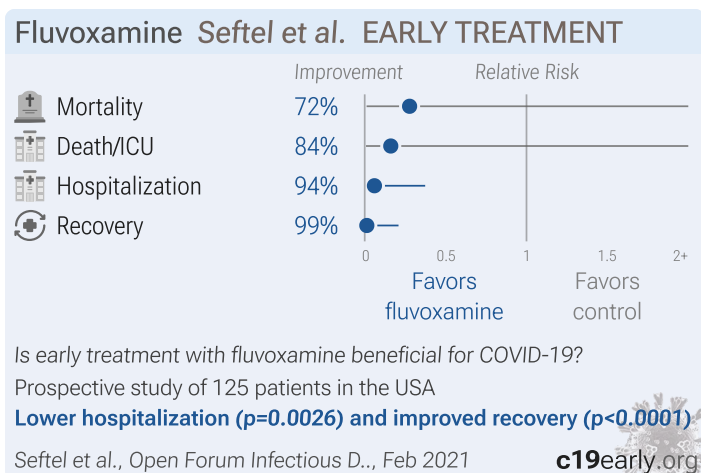
The total dose used is less than half of that in Lenze et al. There is an unusual amount of missing data - age is unknown for 6.5% of patients according to the sub-group analysis. Both age ≤ 50 and >50 show better results on the primary outcome than the overall result. The number of placebo patients changed significantly between the preprint and journal version. The number of treatment patients with viral clearance results reduced significantly between the preprint and journal version. Also see ¹⁶⁶. NCT04727424.

Authors do not specify if the placebo looks identical to the film-coated Luvox tablets. Reportedly there is no registration of manufacturing for matching tablets by Abbott in Brazil, and no import license for identical placebo tablets abroad. This would be an additional reason for blinding failure if the placebo tablets are not identical in appearance.

For other issues with this trial see: ^{167 168 169}.

The TOGETHER trial has extreme COI, impossible data, blinding failure, randomization failure, uncorrected errors, and many protocol violations. Authors do not respond to these issues and they have refused to release the data as promised. Some issues may apply only to specific arms. For more details see ^{67,160-163}.

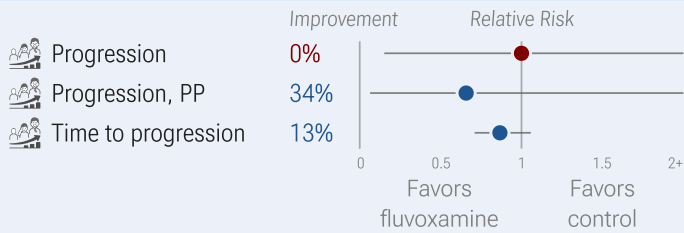
Seftel



Prospective quasi-randomized (patient choice) study with 125 outpatients, 77 treated with fluvoxamine, showing lower death/ICU admission (0 of 77 vs. 2 of 48), lower hospitalization (0 of 77 vs. 6 of 48), and faster recovery with treatment. Note that 12 treatment patients were added but are not reflected in the table in the paper (because the numbers had been previously published and the IRB did not allow updating the table).

Seo

Fluvoxamine Seo et al. EARLY TREATMENT RCT



Is early treatment with fluvoxamine beneficial for COVID-19?

RCT 52 patients in South Korea (January - February 2021)

Trial underpowered to detect differences

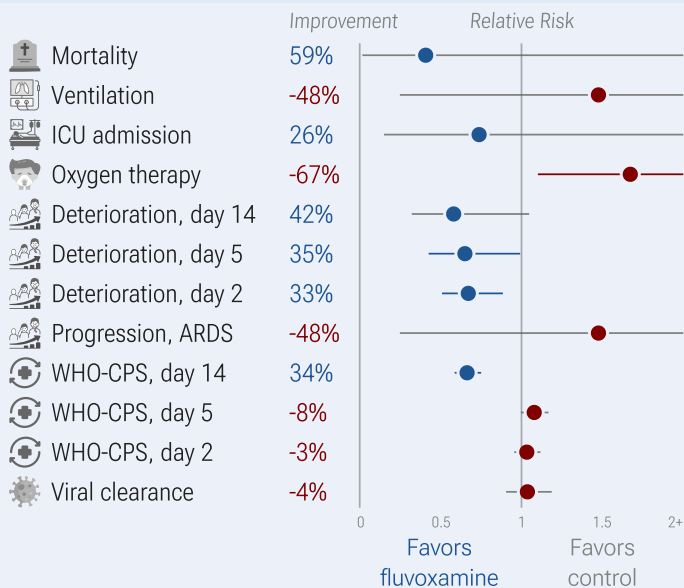
Seo et al., *Infection & Chemotherapy*, Mar 2022

c19early.org

Early terminated RCT with 52 COVID+ patients in South Korea, showing no significant difference in progression with fluvoxamine treatment. There were only 2 events in each arm, and only one event for fluvoxamine in PP analysis. The trial was terminated early because the treatment center closed. 100mg fluvoxamine bid for 10 days.

Siripongboonsitti

Fluvoxamine for COVID-19 Fluvoxam EARLY TREATMENT



Is early treatment with fluvoxamine beneficial for COVID-19?

Retrospective 752 patients in Thailand (April - July 2021)

Higher need for oxygen therapy ($p=0.02$) and improved recovery ($p<0.0001$)

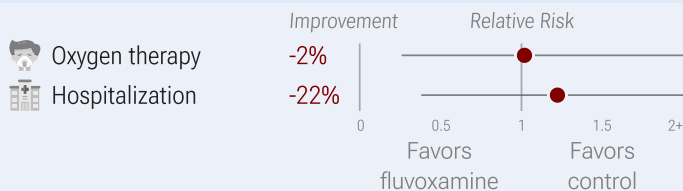
Siripongboonsitti et al., *J. Infection*., Oct 2023

c19early.org

Retrospective 752 patients in Thailand showing mixed results with 50mg fluvoxamine bid. Authors note that trials showing benefit mostly used 100mg bid.

Siripongboonsitti

Fluvoxamine EFFaCo EARLY TREATMENT RCT



Is early treatment with fluvoxamine beneficial for COVID-19?

RCT 327 patients in Thailand (June 2021 - February 2022)

Trial underpowered to detect differences

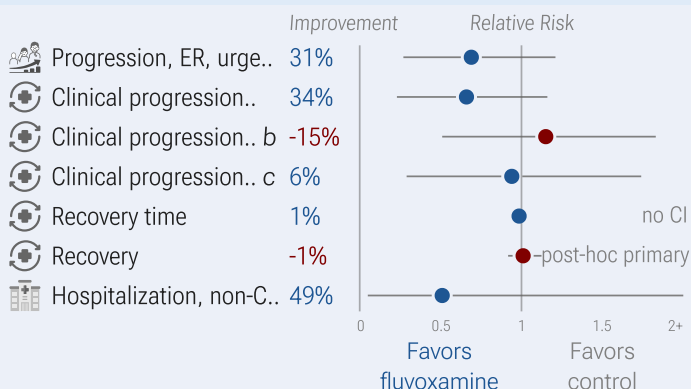
Siripongboonsitti et al., Int. J. Inf., Jun 2023

c19early.org

RCT 327 outpatients in Thailand, showing no significant difference with 50mg fluvoxamine bid added to favipiravir. Authors note that trials showing benefit mostly used 100mg bid.

Stewart

Fluvoxamine ACTIV-6 LATE TREATMENT DB RCT



Is late treatment with fluvoxamine beneficial for COVID-19?

Double-blind RCT 1,175 patients in the USA (August 2022 - January 2023)

Lower progression ($p=0.34$) and improved recovery ($p=0.32$), not sig.

Multiple major issues with trial, see notes

Stewart et al., JAMA, September 2023

c19early.org

Late treatment low risk population RCT showing lower progression to hospitalization or urgent care/ER visits with fluvoxamine, without statistical significance.

There was no mortality and only three hospitalizations. Authors provide no details on the cause of hospitalization, but they appear to be unrelated to COVID-19. eFigure 5 shows no COVID-19 clinical progression to hospitalization (note that a hospitalization can be seen in the equivalent plot for the low dose arm), and the text indicates that the "COVID clinical progression scale simplified into a self-reported evaluation of home levels (limited vs not)".

Note that the urgent care/ER visit outcome is also likely diluted due to inclusion of all-cause events, and could be statistically significant for only COVID-19 events.

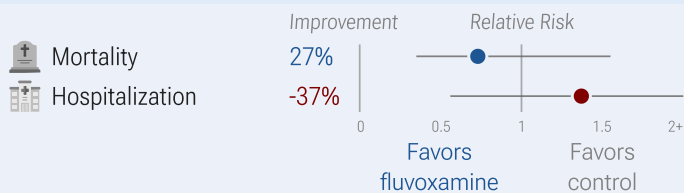
The sustained recovery outcome, which shows no difference, was a post-hoc creation used to hide efficacy for ivermectin, and is not logical for evaluating efficacy in this trial. The definition includes any minor symptom within a three day period - e.g., any minor cough, headache, body ache, or fatigue that occurs in a three day period, regardless of cause, results in the treatment being considered a failure. For example, late treatment that is effective at minimizing progression, but has no improvement in resolution of cough, would not be detected. (Authors even use the end of the three day period to further minimize efficacy).

Late treatment - median 5 days, 75% 4+ days, 25% 7+ days, up to 12 days.

Also see *Naggie* for many issues with this trial, and *McCarthy* for the lower dose arm.

Trkulja

Fluvoxamine for COVID-19 Trkulja et al. Prophylaxis



Is prophylaxis with fluvoxamine beneficial for COVID-19?

PSM retrospective 32,085 patients in Croatia

Lower mortality ($p=0.41$) and higher hospitalization ($p=0.5$), not sig.

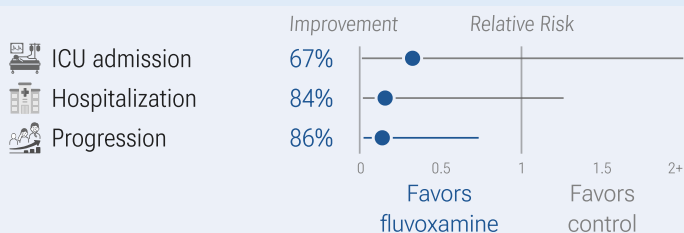
Trkulja et al., *European J. Clinical P.*, Nov 2022

c19early.org

Retrospective COVID+ patients in Croatia, showing no significant difference in outcomes with fluvoxamine prophylaxis.

Tsiakalos

Fluvoxamine Tsiakalos et al. EARLY TREATMENT



Is early treatment with fluvoxamine beneficial for COVID-19?

Retrospective 103 patients in Greece (September - December 2021)

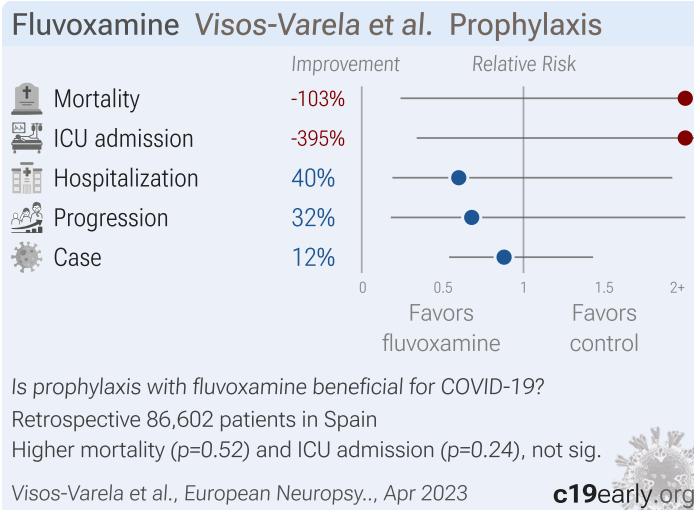
Lower progression with fluvoxamine ($p=0.02$)

Tsiakalos et al., *Microorganisms*, August 2023

c19early.org

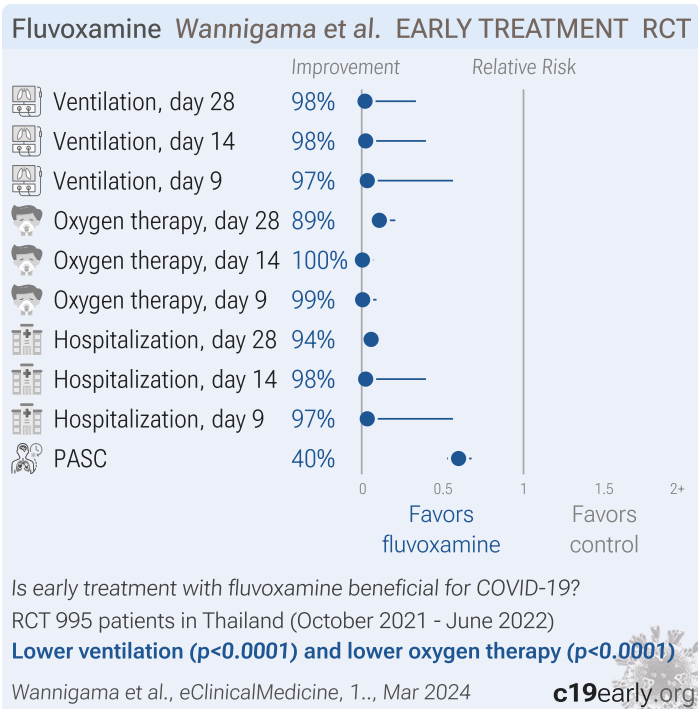
Retrospective 103 outpatients in Greece, showing lower risk of progression with fluvoxamine 100mg bid for 10 days. 2 patients (4%) in the fluvoxamine group had clinical deterioration compared to 8 patients (16%) in the standard care group ($p<0.05$). After adjusting for confounders, fluvoxamine was associated with a lower risk of clinical deterioration (adjusted OR 0.12, $p=0.02$). Fluvoxamine was also associated with improved lymphocyte count. Control patients were during Sep-Nov 2021, and treatment patients Nov-Dec 2021, introducing potential confounding by time due to changes in variants, although the change in risk during this period is expected to be relatively low.

Visos-Varela



Retrospective 86,602 patients in Spain, showing lower COVID-19 risk SSRIs citalopram and paroxetine. There were no significant difference for fluvoxamine, which few patients were taking.

Wannigama



RCT 995 outpatients showing significantly lower progression with early treatment within 48 hours using fluvoxamine, fluvoxamine+bromhexine, fluvoxamine+cyproheptadine, and niclosamide+bromhexine.

70% of patients received treatment within 12 hours of symptom onset.

Treatments groups showed significantly lower long COVID (PASC). The combined treatment groups showed significantly lower viral load as early as day 3. The 3 combination arms were superior to fluvoxamine alone.

The study was open-label. 593 out of 1,900 randomized participants did not receive the treatment, mostly due to inability to confirm eligibility, however baseline characteristics were similar for these patients.

There was a very high hospitalization rate in the control arm. Authors note that the majority of cases were mild - the threshold for hospitalization may have been very low (in some places/times all cases were hospitalized). Authors also note that the patients requiring high flow oxygen all had the delta/alpha variants, and that the population has many health disparities.

Publication was over 500 days after the 90 day followup.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are fluvoxamine and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of fluvoxamine for COVID-19 that report a comparison with a control group are included in the main analysis. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO₂ is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to¹⁷². Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1¹⁷⁵. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.13.3) with scipy (1.15.3), pythonmeta (1.26), numpy (2.2.6), statsmodels (0.14.4), and plotly (6.0.1).

Forest plots are computed using PythonMeta¹⁷⁶ with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I² statistic. Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.2 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but

late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective^{76,77}.

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

A summary of study results is below. Please submit updates and corrections at <https://c19early.org/fmeta.html>.

Early treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

<p><i>Bramante</i>, 8/18/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 37 authors, average treatment delay 5.0 days, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04510194 (history) (COVID-OUT).</p>	<p>risk of death/hospitalization, 10.8% higher, RR 1.11, $p = 0.88$, treatment 6 of 329 (1.8%), control 5 of 324 (1.5%), odds ratio converted to relative risk.</p>
	<p>risk of progression, 16.1% higher, RR 1.16, $p = 0.68$, treatment 18 of 329 (5.5%), control 15 of 324 (4.6%), odds ratio converted to relative risk, combined ER, hospitalization, death.</p>
	<p>risk of hospitalization, 1.5% lower, RR 0.98, $p = 1.00$, treatment 5 of 329 (1.5%), control 5 of 324 (1.5%), NNT 4264, Figure S8, day 28.</p>
	<p>risk of hospitalization, 1.5% lower, RR 0.98, $p = 1.00$, treatment 5 of 329 (1.5%), control 5 of 324 (1.5%), NNT 4264, Figure S7, day 14.</p>
	<p>risk of progression, 4.6% lower, RR 0.95, $p = 0.75$, treatment 79 of 329 (24.0%), control 80 of 321 (24.9%), NNT 110, odds ratio converted to relative risk, combined hypoxemia, ER, hospitalization, death, primary outcome.</p>
<p><i>Farahani</i>, 3/31/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, mean age 38.5, 3 authors, study period March 2022 - June 2022.</p>	<p>risk of PASC, 50.8% lower, RR 0.49, $p = 0.06$, treatment 42, control 43, smell and taste disturbance combined.</p>
	<p>risk of PASC, 44.2% lower, RR 0.56, $p = 0.28$, treatment 6 of 42 (14.3%), control 11 of 43 (25.6%), NNT 8.9, smell.</p>
	<p>risk of PASC, 61.6% lower, RR 0.38, $p = 0.20$, treatment 3 of 42 (7.1%), control 8 of 43 (18.6%), NNT 8.7, taste.</p>
	<p>risk of PASC, 51.5% lower, RR 0.48, $p = 0.04$, treatment 9 of 42 (21.4%), control 19 of 43 (44.2%), NNT 4.4, fatigue, primary outcome.</p>
	<p>risk of PASC, 48.8% lower, RR 0.51, $p = 0.48$, treatment 3 of 42 (7.1%), control 6 of 43 (14.0%), NNT 15, headache.</p>
	<p>risk of PASC, 59.0% lower, RR 0.41, $p = 0.43$, treatment 2 of 42 (4.8%), control 5 of 43 (11.6%), NNT 15, memory impairment.</p>
	<p>risk of PASC, 17.0% higher, RR 1.17, $p = 0.78$, treatment 8 of 42 (19.0%), control 7 of 43 (16.3%), poor concentration.</p>
	<p>risk of PASC, 7.9% lower, RR 0.92, $p = 1.00$, treatment 9 of 42 (21.4%), control 10 of 43 (23.3%), NNT 55, insomnia.</p>

	<p>risk of PASC, 74.4% lower, RR 0.26, $p = 0.36$, treatment 1 of 42 (2.4%), control 4 of 43 (9.3%), NNT 14, aggression.</p> <p>risk of PASC, 85.4% lower, RR 0.15, $p = 0.06$, treatment 1 of 42 (2.4%), control 7 of 43 (16.3%), NNT 7.2, depression.</p> <p>risk of PASC, 37.0% lower, RR 0.63, $p = 0.32$, treatment 8 of 42 (19.0%), control 13 of 43 (30.2%), NNT 8.9, anxiety.</p> <p>risk of PASC, 26.9% lower, RR 0.73, $p = 0.76$, treatment 5 of 42 (11.9%), control 7 of 43 (16.3%), NNT 23, myalgia.</p> <p>risk of PASC, 6.4% lower, RR 0.94, $p = 0.60$, treatment 32 of 42 (76.2%), control 35 of 43 (81.4%), NNT 19, PCS.</p>
Lenze, 11/12/2020, Double Blind Randomized Controlled Trial, USA, peer-reviewed, 11 authors, study period 10 April, 2020 - 5 August, 2020, average treatment delay 4.0 days, trial NCT04342663 (history) (STOP COVID).	<p>risk of progression, 92.7% lower, RR 0.07, $p = 0.009$, treatment 0 of 80 (0.0%), control 6 of 72 (8.3%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), clinical deterioration over 15 days.</p> <p>risk of hospitalization, 82.0% lower, RR 0.18, $p = 0.009$, treatment 1 of 80 (1.2%), control 5 of 72 (6.9%), NNT 18, COVID-19 hospitalization within 15 days, see supplemental appendix for details.</p>
Pineda, 10/4/2022, prospective, Honduras, peer-reviewed, mean age 48.1, 24 authors, study period November 2020 - January 2022.	<p>risk of death, 94.0% lower, RR 0.06, $p = 0.01$, treatment 1 of 594 (0.2%), control 4 of 63 (6.3%), NNT 16, adjusted per study.</p> <p>risk of oxygen therapy, 73.0% lower, RR 0.27, $p < 0.001$, treatment 15 of 594 (2.5%), control 13 of 63 (20.6%), NNT 5.5, adjusted per study.</p> <p>risk of hospitalization, 51.0% lower, RR 0.49, $p = 0.04$, treatment 23 of 594 (3.9%), control 11 of 63 (17.5%), NNT 7.4, adjusted per study.</p> <p>hospitalization time, 71.4% higher, relative time 1.71, $p = 0.08$, treatment 23, control 11.</p>
Reiersen, 8/20/2021, Double Blind Randomized Controlled Trial, USA, peer-reviewed, median age 47.0 (treatment) 48.0 (control), 24 authors, study period 22 December, 2020 - 21 May, 2021, average treatment delay 5.0 days, trial NCT04668950 (history) (STOP COVID 2).	<p>risk of oxygen therapy, 201.1% higher, RR 3.01, $p = 0.50$, treatment 1 of 272 (0.4%), control 0 of 275 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), non-invasive ventilation.</p> <p>risk of oxygen therapy, 32.6% lower, RR 0.67, $p = 0.60$, treatment 6 of 272 (2.2%), control 9 of 275 (3.3%), NNT 94.</p> <p>risk of oxygen therapy, 37.5% lower, RR 0.62, $p = 0.74$, treatment 3 of 164 (1.8%), control 6 of 205 (2.9%), NNT 91, per-protocol.</p> <p>risk of hospitalization, 9.0% lower, RR 0.91, $p = 1.00$, treatment 9 of 272 (3.3%), control 10 of 275 (3.6%), NNT 305.</p> <p>risk of progression, 12.4% lower, RR 0.88, $p = 0.85$, treatment 13 of 272 (4.8%), control 15 of 275 (5.5%), NNT 148, primary outcome.</p>
Reis (B), 4/17/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Brazil, peer-reviewed, 35 authors, study period 15 January, 2022 - 6 July, 2022, average treatment delay 3.0 days, this trial uses multiple treatments in the	<p>risk of death, 200.0% higher, RR 3.00, $p = 1.00$, treatment 1 of 738 (0.1%), control 0 of 738 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).</p>

treatment arm (combined with budesonide) - results of individual treatments may vary, trial NCT04727424 (history) (TOGETHER).	risk of hospitalization, 12.5% lower, RR 0.88, $p = 1.00$, treatment 7 of 738 (0.9%), control 8 of 738 (1.1%), NNT 738.
	hospitalization or ER >6hrs, 50.0% lower, RR 0.50, $p = 0.04$, treatment 13 of 738 (1.8%), control 27 of 738 (3.7%), NNT 53, adjusted per study, day 28, primary outcome.
Seftel, 2/1/2021, prospective quasi-randomized (patient choice), USA, peer-reviewed, 2 authors.	risk of death, 72.3% lower, RR 0.28, $p = 0.38$, treatment 0 of 77 (0.0%), control 1 of 48 (2.1%), NNT 48, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of death/ICU, 83.9% lower, RR 0.16, $p = 0.15$, treatment 0 of 77 (0.0%), control 2 of 48 (4.2%), NNT 24, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 94.0% lower, RR 0.06, $p = 0.003$, treatment 0 of 77 (0.0%), control 6 of 48 (12.5%), NNT 8.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no recovery, 98.7% lower, RR 0.01, $p < 0.001$, treatment 0 of 77 (0.0%), control 29 of 48 (60.4%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
Seo, 3/3/2022, Single Blind Randomized Controlled Trial, placebo-controlled, South Korea, peer-reviewed, median age 53.5, 14 authors, study period 15 January, 2021 - 19 February, 2021.	risk of progression, no change, RR 1.00, $p = 1.00$, treatment 2 of 26 (7.7%), control 2 of 26 (7.7%).
	risk of progression, 34.2% lower, RR 0.66, $p = 1.00$, treatment 1 of 19 (5.3%), control 2 of 25 (8.0%), NNT 37, PP.
	time to progression, 13.3% lower, relative time 0.87, $p = 0.16$, treatment mean 6.5 (± 0.7) $n=26$, control mean 7.5 (± 3.5) $n=26$.
Siripongboonsitti (B), 10/6/2023, retrospective, Thailand, peer-reviewed, 4 authors, study period 16 April, 2021 - 24 July, 2021, trial TCTR20230401001 (Fluvox).	risk of death, 59.2% lower, RR 0.41, $p = 1.00$, treatment 0 of 234 (0.0%), control 1 of 518 (0.2%), NNT 518, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
	risk of mechanical ventilation, 47.6% higher, RR 1.48, $p = 0.65$, treatment 2 of 234 (0.9%), control 3 of 518 (0.6%).
	risk of ICU admission, 26.2% lower, RR 0.74, $p = 1.00$, treatment 2 of 234 (0.9%), control 6 of 518 (1.2%), NNT 329.
	risk of oxygen therapy, 67.3% higher, RR 1.67, $p = 0.02$, treatment 34 of 234 (14.5%), control 45 of 518 (8.7%).
	risk of deterioration, 41.9% lower, RR 0.58, $p = 0.08$, treatment 13 of 217 (6.0%), control 49 of 475 (10.3%), NNT 23, day 14.
	risk of deterioration, 35.0% lower, RR 0.65, $p = 0.047$, treatment 23 of 166 (13.9%), control 88 of 413 (21.3%), NNT 13, day 5.
	risk of deterioration, 32.9% lower, RR 0.67, $p = 0.004$, treatment 51 of 217 (23.5%), control 132 of 377 (35.0%), NNT 8.7, day 2.
	risk of progression, 47.6% higher, RR 1.48, $p = 0.65$, treatment 2 of 234 (0.9%), control 3 of 518 (0.6%), ARDS.

	WHO-CPS, 33.6% lower, RR 0.66, $p < 0.001$, treatment mean 0.73 (± 0.67) $n=234$, control mean 1.1 (± 0.75) $n=518$, WHO-CPS score, day 14.
	WHO-CPS, 7.9% higher, RR 1.08, $p = 0.06$, treatment mean 2.06 (± 1.07) $n=234$, control mean 1.91 (± 0.98) $n=518$, WHO-CPS score, day 5.
	WHO-CPS, 3.3% higher, RR 1.03, $p = 0.43$, treatment mean 2.21 (± 1.25) $n=234$, control mean 2.14 (± 1.06) $n=518$, WHO-CPS score, day 2.
	risk of no viral clearance, 3.6% higher, RR 1.04, $p = 0.66$, treatment 130 of 210 (61.9%), control 218 of 365 (59.7%), day 14.
<i>Siripongboonsitti</i> , 6/29/2023, Randomized Controlled Trial, Thailand, peer-reviewed, 9 authors, study period 26 June, 2021 - 22 February, 2022, trial TCTR20210615002 (EFFaCo).	risk of oxygen therapy, 1.9% higher, RR 1.02, $p = 1.00$, treatment 4 of 162 (2.5%), control 4 of 165 (2.4%).
	risk of hospitalization, 22.2% higher, RR 1.22, $p = 0.77$, treatment 6 of 162 (3.7%), control 5 of 165 (3.0%), day 28.
<i>Tsiakalos</i> , 8/12/2023, retrospective, Greece, peer-reviewed, 5 authors, study period 1 September, 2021 - 31 December, 2021.	risk of ICU admission, 67.3% lower, RR 0.33, $p = 0.49$, treatment 0 of 53 (0.0%), control 1 of 50 (2.0%), NNT 50, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 84.3% lower, RR 0.16, $p = 0.06$, treatment 1 of 53 (1.9%), control 6 of 50 (12.0%), NNT 9.9.
	risk of progression, 86.0% lower, RR 0.14, $p = 0.02$, treatment 2 of 53 (3.8%), control 8 of 50 (16.0%), NNT 8.2, adjusted per study, odds ratio converted to relative risk, multivariable.
<i>Wannigama</i> , 3/14/2024, Randomized Controlled Trial, Thailand, peer-reviewed, 29 authors, study period 1 October, 2021 - 21 June, 2022, average treatment delay 0.5 days, trial NCT05087381 (history).	risk of mechanical ventilation, 97.9% lower, RR 0.02, $p < 0.001$, treatment 0 of 162 (0.0%), control 32 of 336 (9.5%), NNT 10, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
	risk of mechanical ventilation, 97.6% lower, RR 0.02, $p < 0.001$, treatment 0 of 162 (0.0%), control 27 of 336 (8.0%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of mechanical ventilation, 96.6% lower, RR 0.03, $p < 0.001$, treatment 0 of 162 (0.0%), control 19 of 336 (5.7%), NNT 18, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 9.
	risk of oxygen therapy, 89.1% lower, RR 0.11, $p < 0.001$, treatment 9 of 162 (5.6%), control 171 of 336 (50.9%), NNT 2.2, day 28.
	risk of oxygen therapy, 99.6% lower, RR 0.004, $p < 0.001$, treatment 0 of 162 (0.0%), control 150 of 336 (44.6%), NNT 2.2, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of oxygen therapy, 99.4% lower, RR 0.006, $p < 0.001$, treatment 0 of 162 (0.0%), control 117 of 336 (34.8%), NNT 2.9, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 9.

	risk of hospitalization, 94.2% lower, RR 0.06, $p < 0.001$, treatment 9 of 162 (5.6%), control 321 of 336 (95.5%), NNT 1.1, day 28.
	risk of hospitalization, 97.6% lower, RR 0.02, $p < 0.001$, treatment 0 of 162 (0.0%), control 27 of 336 (8.0%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of hospitalization, 96.6% lower, RR 0.03, $p < 0.001$, treatment 0 of 162 (0.0%), control 19 of 336 (5.7%), NNT 18, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 9.
	risk of PASC, 40.1% lower, RR 0.60, $p < 0.001$, treatment 97 of 162 (59.9%), control 336 of 336 (100.0%), NNT 2.5, day 90.

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

<i>Calusic</i> , 11/1/2021, prospective, propensity score matching, Croatia, peer-reviewed, 7 authors, study period 1 April, 2021 - 31 May, 2021.	risk of death, 42.0% lower, HR 0.58, $p = 0.03$, treatment 30 of 51 (58.8%), control 39 of 51 (76.5%), NNT 5.7, adjusted per study, propensity score matching.
<i>Kirenga</i> , 3/3/2023, prospective, Uganda, peer-reviewed, 19 authors, study period December 2021 - February 2022.	risk of death, 68.0% lower, HR 0.32, $p < 0.001$, treatment 29 of 94 (30.9%), control 126 of 222 (56.8%), NNT 3.9, adjusted for unbalanced covariates, propensity score weighting, Cox proportional hazards.
	symptom resolution, 53.1% lower, HR 0.47, $p = 0.04$, treatment 94, control 222, inverted to make $HR < 1$ favor treatment, propensity score weighting, Cox proportional hazards, RR approximated with OR.
<i>Reis</i> , 8/23/2021, Double Blind Randomized Controlled Trial, Brazil, peer-reviewed, 27 authors, study period 20 January, 2021 - 5 August, 2021, trial NCT04727424 (history) (TOGETHER).	risk of death, 30.3% lower, RR 0.70, $p = 0.24$, treatment 17 of 741 (2.3%), control 25 of 756 (3.3%), NNT 99, odds ratio converted to relative risk, ITT.
	risk of death, 90.8% lower, RR 0.09, $p = 0.02$, treatment 1 of 548 (0.2%), control 12 of 618 (1.9%), NNT 57, odds ratio converted to relative risk, per protocol.
	risk of mechanical ventilation, 22.2% lower, RR 0.78, $p = 0.33$, treatment 26 of 741 (3.5%), control 34 of 756 (4.5%), NNT 101, odds ratio converted to relative risk, ITT.
	risk of hospitalization, 21.6% lower, RR 0.78, $p = 0.10$, treatment 75 of 741 (10.1%), control 97 of 756 (12.8%), NNT 37, odds ratio converted to relative risk, ITT.
	extended ER observation or hospitalization, 32.0% lower, RR 0.68, $p = 0.004$, treatment 79 of 741 (10.7%), control 119 of 756 (15.7%), NNT 20, ITT, primary outcome.
	extended ER observation or hospitalization, 31.0% lower, RR 0.69, $p = 0.006$, treatment 78 of 740 (10.5%), control 115 of 752 (15.3%), NNT 21, mITT.

<p>Stewart, 9/13/2023, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 32 authors, study period 5 August, 2022 - 20 January, 2023, average treatment delay 5.0 days, trial NCT04885530 (history) (ACTIV-6).</p>	<p>extended ER observation or hospitalization, 66.0% lower, RR 0.34, $p < 0.001$, treatment 541, control 609, per protocol.</p>
	<p>risk of no viral clearance, 49.3% higher, RR 1.49, $p = 0.09$, treatment 167 of 207 (80.7%), control 163 of 221 (73.8%), adjusted per study, inverted to make $RR < 1$ favor treatment.</p>
	<p>risk of progression, 31.0% lower, RR 0.69, $p = 0.34$, treatment 14 of 589 (2.4%), control 21 of 586 (3.6%), NNT 83, adjusted per study, urgent or emergency care visits, hospitalizations, or death.</p>
	<p>clinical progression, 34.0% lower, OR 0.66, $p = 0.32$, treatment 589, control 586, mid-recovery, day 14, RR approximated with OR.</p>
	<p>clinical progression, 15.0% higher, OR 1.15, $p = 0.68$, treatment 589, control 586, day 7, RR approximated with OR.</p>
	<p>clinical progression, 6.0% lower, OR 0.94, $p = 0.90$, treatment 589, control 586, day 28, RR approximated with OR.</p>
	<p>risk of no recovery, 1.0% higher, HR 1.01, $p = 0.86$, treatment 589, control 586, inverted to make $HR < 1$ favor treatment, post-hoc primary outcome.</p>
	<p>risk of hospitalization, 49.0% lower, RR 0.51, $p = 0.59$, treatment 1 of 589 (0.2%), control 2 of 586 (0.3%), NNT 583, non-COVID-19 hospitalization, day 28.</p>

Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

<p>Diaz, 10/6/2022, retrospective, USA, peer-reviewed, 2 authors.</p>	<p>risk of case, 28.0% lower, OR 0.72, $p < 0.001$, treatment 4,558, control 4,558, propensity score matching, RR approximated with OR.</p>
<p>Fritz, 8/22/2022, retrospective, USA, peer-reviewed, 5 authors, study period 1 March, 2020 - 16 May, 2021.</p>	<p>risk of hospitalization/ER, 19.4% lower, RR 0.81, $p = 0.69$, treatment 4 of 17 (23.5%), control 1,896 of 20,457 (9.3%), adjusted per study, odds ratio converted to relative risk, fluvoxamine, multivariable.</p>
	<p>risk of hospitalization/ER, 11.9% lower, RR 0.88, $p = 0.03$, treatment 707 of 3,414 (20.7%), control 1,896 of 20,457 (9.3%), adjusted per study, odds ratio converted to relative risk, FIASMA, multivariable.</p>
	<p>risk of hospitalization/ER, 11.9% lower, RR 0.88, $p = 0.04$, treatment 559 of 2,744 (20.4%), control 1,896 of 20,457 (9.3%), adjusted per study, odds ratio converted to relative risk, SSRI, multivariable.</p>
	<p>risk of hospitalization/ER, 10.1% lower, RR 0.90, $p = 0.04$, treatment 971 of 4,577 (21.2%), control 1,896 of 20,457 (9.3%), adjusted per study, odds ratio converted to relative risk, all antidepressants, multivariable.</p>

Oskotsky, 11/15/2021, retrospective, propensity score matching, USA, peer-reviewed, 8 authors.	risk of death, 57.9% higher, RR 1.58, $p = 0.62$, treatment 2 of 11 (18.2%), control 19 of 165 (11.5%), fluvoxamine.
	risk of death, 26.0% lower, RR 0.74, $p = 0.04$, treatment 48 of 481 (10.0%), control 956 of 7,215 (13.3%), NNT 31, fluoxetine.
Trkulja, 11/7/2022, retrospective, Croatia, peer-reviewed, 2 authors.	risk of death, 27.0% lower, RR 0.73, $p = 0.41$, treatment 749, control 31,336, cohort A vs. B, propensity score matching.
	risk of hospitalization, 37.0% higher, RR 1.37, $p = 0.50$, treatment 749, control 31,336, cohort A vs. B, COVID-related, propensity score matching.
Visos-Varela, 4/23/2023, retrospective, Spain, peer-reviewed, 8 authors.	risk of death, 103.0% higher, OR 2.03, $p = 0.52$, treatment 1 of 413 (0.2%) cases, 7 of 7,408 (0.1%) controls, adjusted per study, case control OR.
	risk of ICU admission, 395.0% higher, OR 4.95, $p = 0.24$, treatment 1 of 228 (0.4%) cases, 2 of 4,398 (0.0%) controls, adjusted per study, case control OR.
	risk of hospitalization, 40.0% lower, OR 0.60, $p = 0.39$, treatment 3 of 3,060 (0.1%) cases, 69 of 56,785 (0.1%) controls, adjusted per study, case control OR.
	risk of progression, 32.0% lower, OR 0.68, $p = 0.56$, treatment 3 of 3,060 (0.1%) cases, 25 of 26,757 (0.1%) controls, adjusted per study, case control OR.
	risk of case, 12.0% lower, OR 0.88, $p = 0.60$, treatment 28 of 29,817 (0.1%) cases, 69 of 56,785 (0.1%) controls, adjusted per study, case control OR.

Supplementary Data

Supplementary Data

Footnotes

- a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

References

1. **Deng** et al., *Efficacy and safety of selective serotonin reuptake inhibitors in COVID-19 management: A systematic review and meta-analysis*, Clinical Microbiology and Infection, doi:10.1016/j.cmi.2023.01.010.
2. **Prasanth** et al., *A systematic review and meta-analysis, investigating dose and time of fluvoxamine treatment efficacy for COVID-19 clinical deterioration, death, and Long-COVID complications*, Scientific Reports, doi:10.1038/s41598-024-64260-9.
3. **Lee** et al., *Fluvoxamine for Outpatient Management of COVID-19 to Prevent Hospitalization: A Systematic Review and Meta-analysis*, JAMA Network Open, doi:10.1001/jamanetworkopen.2022.6269.
4. **Lu** et al., *Effect of fluvoxamine on outcomes of nonhospitalized patients with COVID-19: A systematic review and meta-analysis*, Journal of Infection and Public Health, doi:10.1016/j.jiph.2022.10.010.

5. **Marcec** et al., A meta-analysis regarding fluvoxamine and hospitalization risk of COVID-19 patients: TOGETHER making a difference, *Journal of Infection*, doi:10.1016/j.jinf.2022.11.011.
6. **Deng (B)** et al., Evaluating fluvoxamine for the outpatient treatment of COVID-19: A systematic review and meta-analysis, *Reviews in Medical Virology*, doi:10.1002/rmv.2501.
7. **Zhou** et al., The efficacy and safety of fluvoxamine in patients with COVID-19: A systematic review and meta-analysis from randomized controlled trials, *PLOS ONE*, doi:10.1371/journal.pone.0300512.
8. **Nakhaee** et al., The effect of antidepressants on the severity of COVID-19 in hospitalized patients: A systematic review and meta-analysis, *PLOS ONE*, doi:10.1371/journal.pone.0267423.
9. **Ryu** et al., Fibrin drives thromboinflammation and neuropathology in COVID-19, *Nature*, doi:10.1038/s41586-024-07873-4.
10. **Rong** et al., Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19, *Cell Host & Microbe*, doi:10.1016/j.chom.2024.11.007.
11. **Yang** et al., SARS-CoV-2 infection causes dopaminergic neuron senescence, *Cell Stem Cell*, doi:10.1016/j.stem.2023.12.012.
12. **Scardua-Silva** et al., Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19, *Scientific Reports*, doi:10.1038/s41598-024-52005-7.
13. **Hampshire** et al., Cognition and Memory after Covid-19 in a Large Community Sample, *New England Journal of Medicine*, doi:10.1056/NEJMoa2311330.
14. **Duloquin** et al., Is COVID-19 Infection a Multiorganic Disease? Focus on Extrapulmonary Involvement of SARS-CoV-2, *Journal of Clinical Medicine*, doi:10.3390/jcm13051397.
15. **Sodagar** et al., Pathological Features and Neuroinflammatory Mechanisms of SARS-CoV-2 in the Brain and Potential Therapeutic Approaches, *Biomolecules*, doi:10.3390/biom12070971.
16. **Sagar** et al., COVID-19-associated cerebral microbleeds in the general population, *Brain Communications*, doi:10.1093/braincomms/fcae127.
17. **Verma** et al., Persistent Neurological Deficits in Mouse PASC Reveal Antiviral Drug Limitations, *bioRxiv*, doi:10.1101/2024.06.02.596989.
18. **Panagea** et al., Neurocognitive Impairment in Long COVID: A Systematic Review, *Archives of Clinical Neuropsychology*, doi:10.1093/arclin/aca042.
19. **Ariza** et al., COVID-19: Unveiling the Neuropsychiatric Maze —From Acute to Long-Term Manifestations, *Biomedicines*, doi:10.3390/biomedicines12061147.
20. **Vashisht** et al., Neurological Complications of COVID-19: Unraveling the Pathophysiological Underpinnings and Therapeutic Implications, *Viruses*, doi:10.3390/v16081183.
21. **Ahmad** et al., Neurological Complications and Outcomes in Critically Ill Patients With COVID-19: Results From International Neurological Study Group From the COVID-19 Critical Care Consortium, *The Neurohospitalist*, doi:10.1177/19418744241292487.
22. **Wang** et al., SARS-CoV-2 membrane protein induces neurodegeneration via affecting Golgi-mitochondria interaction, *Translational Neurodegeneration*, doi:10.1186/s40035-024-00458-1.
23. **Eberhardt** et al., SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels, *Nature Cardiovascular Research*, doi:10.1038/s44161-023-00336-5.
24. **Van Tin** et al., Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF- κ B Signaling, *Cells*, doi:10.3390/cells13161331.
25. **Borka Balas** et al., COVID-19 and Cardiac Implications—Still a Mystery in Clinical Practice, *Reviews in Cardiovascular Medicine*, doi:10.31083/j.rcm2405125.
26. **AlTaweel** et al., An In-Depth Insight into Clinical, Cellular and Molecular Factors in COVID19-Associated Cardiovascular Ailments for Identifying Novel Disease Biomarkers, Drug Targets and Clinical Management Strategies, *Archives of Microbiology & Immunology*, doi:10.26502/ami.936500177.
27. **Saha** et al., COVID-19 beyond the lungs: Unraveling its vascular impact and cardiovascular complications—mechanisms and therapeutic implications, *Science Progress*, doi:10.1177/00368504251322069.
28. **Trender** et al., Changes in memory and cognition during the SARS-CoV-2 human challenge study, *eClinicalMedicine*, doi:10.1016/j.eclinm.2024.102842.
29. **Dugied** et al., Multimodal SARS-CoV-2 interactome sketches the virus-host spatial organization, *Communications Biology*, doi:10.1038/s42003-025-07933-z.
30. **Malone** et al., Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design, *Nature Reviews Molecular Cell Biology*, doi:10.1038/s41580-021-00432-z.
31. **Murigneux** et al., Proteomic analysis of SARS-CoV-2 particles unveils a key role of G3BP proteins in viral assembly, *Nature Communications*, doi:10.1038/s41467-024-44958-0.
32. **Lv** et al., Host proviral and antiviral factors for SARS-CoV-2, *Virus Genes*, doi:10.1007/s11262-021-01869-2.
33. **Lui** et al., Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling, *Virology*, doi:10.1128/mbio.00392-24.
34. **Niarakis** et al., Drug-target identification in COVID-19 disease mechanisms using computational systems biology approaches, *Frontiers in Immunology*, doi:10.3389/fimmu.2023.1282859.
35. **Katiyar** et al., SARS-CoV-2 Assembly: Gaining Infectivity and Beyond, *Viruses*, doi:10.3390/v16111648.
36. **Wu** et al., Decoding the genome of SARS-CoV-2: a pathway to drug development through translation inhibition, *RNA Biology*, doi:10.1080/15476286.2024.2433830.
37. **c19early.org**, c19early.org/treatments.html.
38. **Alkafaas** et al., Molecular docking as a tool for the discovery of novel insight about the role of acid sphingomyelinase inhibitors in SARS- CoV-2 infectivity, *BMC Public Health*, doi:10.1186/s12889-024-17747-z.

39. **Zhang** et al., SARS-CoV-2 NSP6 reduces autophagosome size and affects viral replication via sigma-1 receptor, *Journal of Virology*, doi:10.1128/jvi.00754-24.
40. **Hoertel** et al., Repurposing antidepressants inhibiting the sphingomyelinase acid/ceramide system against COVID-19: current evidence and potential mechanisms, *Molecular Psychiatry*, doi:10.1038/s41380-021-01254-3.
41. **Carpinteiro** et al., Inhibition of acid sphingomyelinase by ambroxol prevents SARS-CoV-2 entry into epithelial cells, *Journal of Biological Chemistry*, doi:10.1016/j.jbc.2021.100701.
42. **Carpinteiro (B)** et al., Pharmacological Inhibition of Acid Sphingomyelinase Prevents Uptake of SARS-CoV-2 by Epithelial Cells, *Cell Reports Medicine*, doi:10.1016/j.xcrm.2020.100142.
43. **Hashimoto** et al., Mechanisms of action of fluvoxamine for COVID-19: a historical review, *Molecular Psychiatry*, doi:10.1038/s41380-021-01432-3.
44. **Sukhatme** et al., Fluvoxamine: A Review of Its Mechanism of Action and Its Role in COVID-19, *Front. Pharmacol.*, doi:10.3389/fphar.2021.652688.
45. **Hashimoto (B)** et al., Old drug fluvoxamine, new hope for COVID-19, *European Archives of Psychiatry and Clinical Neuroscience*, doi:10.1007/s00406-021-01326-z.
46. **Battinelli**, E., COVID-19 concerns aggregate around platelets, *Blood*, doi:10.1182/blood.2020007805.
47. **Norinder** et al., Existing highly accumulating lysosomotropic drugs with potential for repurposing to target COVID-19, *Biomedicine & Pharmacotherapy*, doi:10.1016/j.biopha.2020.110582.
48. **Hooper**, P., COVID-19 and heme oxygenase: novel insight into the disease and potential therapies, *Cell Stress and Chaperones*, doi:10.1007/s12192-020-01126-9.
49. **Almási** et al., Lessons on the Sigma-1 Receptor in TNBS-Induced Rat Colitis: Modulation of the UCHL-1, IL-6 Pathway, *International Journal of Molecular Sciences*, doi:10.3390/ijms21114046.
50. **Hooper (B)**, P., Heme oxygenase agonists—fluvoxamine, melatonin—are efficacious therapy for Covid-19, *Cell Stress and Chaperones*, doi:10.1007/s12192-021-01246-w.
51. **Anderson**, G., Fluvoxamine, melatonin and COVID-19, *Psychopharmacology*, doi:10.1007/s00213-020-05753-z.
52. **Ramos** et al., The Coronavirus Disease 2019 (COVID-19): Key Emphasis on Melatonin Safety and Therapeutic Efficacy, Antioxidants, doi:10.3390/antiox10071152.
53. **Camp** et al., Melatonin interferes with COVID-19 at several distinct ROS-related steps, *Journal of Inorganic Biochemistry*, doi:10.1016/j.jinorgbio.2021.111546.
54. **Abatematteo** et al., A conformational rearrangement of the SARS-CoV-2 host protein sigma-1 is required for antiviral activity: insights from a combined in-silico/in-vitro approach, *Scientific Reports*, doi:10.1038/s41598-023-39662-w.
55. **Jadad** et al., *Randomized Controlled Trials: Questions, Answers, and Musings*, Second Edition, doi:10.1002/9780470691922.
56. **Göttsche**, P., Bias in double-blind trials, Doctoral Thesis, University of Copenhagen, www.scientificfreedom.dk/2023/05/16/bias-in-double-blind-trial-s-doctoral-thesis/.
57. **Als-Nielsen** et al., Association of Funding and Conclusions in Randomized Drug Trials, *JAMA*, doi:10.1001/jama.290.7.921.
58. **c19early.org (B)**, c19early.org/fsupp.html#fig_rctobs.
59. **Concato** et al., *NEJM*, 342:1887-1892, doi:10.1056/NEJM200006223422507.
60. **Anglemyer** et al., Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials, *Cochrane Database of Systematic Reviews* 2014, Issue 4, doi:10.1002/14651858.MR000034.pub2.
61. **c19early.org (C)**, c19early.org/rctobs.html.
62. **Lee (B)** et al., Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines, *Arch Intern Med.*, 2011, 171:1, 18-22, doi:10.1001/archinternmed.2010.482.
63. **Deaton** et al., Understanding and misunderstanding randomized controlled trials, *Social Science & Medicine*, 210, doi:10.1016/j.socscimed.2017.12.005.
64. **Nichol** et al., Challenging issues in randomised controlled trials, *Injury*, 2010, doi: 10.1016/j.injury.2010.03.033, [www.injuryjournal.com/article/S0020-1383\(10\)00233-0/fulltext](http://www.injuryjournal.com/article/S0020-1383(10)00233-0/fulltext).
65. **ncbi.nlm.nih.gov**, www.ncbi.nlm.nih.gov/books/NBK570371/pdf/Bookshelf_NBK570371.pdf#page=357.
66. **Reis** et al., Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial, *The Lancet Global Health*, doi:10.1016/S2214-109X(21)00448-4.
67. **Reis (B)** et al., Oral Fluvoxamine With Inhaled Budesonide for Treatment of Early-Onset COVID-19, *Annals of Internal Medicine*, doi:10.7326/M22-3305.
68. **Stewart** et al., Higher-Dose Fluvoxamine and Time to Sustained Recovery in Outpatients With COVID-19, *JAMA*, doi:10.1001/jama.2023.23363.
69. **Bramante** et al., Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19, *NEJM*, doi:10.1056/NEJMoa2201662.
70. **Lenze** et al., Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial, *JAMA*, doi:10.1001/jama.2020.22760.
71. **Reiersen** et al., The STOP COVID 2 study: Fluvoxamine vs placebo for outpatients with symptomatic COVID-19, a fully-remote randomized controlled trial, *Open Forum Infectious Diseases*, doi:10.1093/ofid/ofad419.
72. **Farahani** et al., Effect of fluvoxamine on preventing neuropsychiatric symptoms of post COVID syndrome in mild to moderate patients, a randomized placebo-controlled double-blind clinical trial, *BMC Infectious Diseases*, doi:10.1186/s12879-023-08172-5.

73. **Seo** et al., *Fluvoxamine Treatment of Patients with Symptomatic COVID-19 in a Community Treatment Center: A Preliminary Result of Randomized Controlled Trial*, *Infection & Chemotherapy*, doi:10.3947/ic.2021.0142.
74. **Siripongboonsitti** et al., *Efficacy of Combination Therapy of Fluvoxamine and Favipiravir versus Favipiravir Monotherapy to Prevent Severe COVID-19 among Mild to Moderate COVID-19 Patients: Open-label Randomized Controlled Trial (EFFaCo Study)*, *International Journal of Infectious Diseases*, doi:10.1016/j.ijid.2023.06.018.
75. **Wannigama** et al., *Early treatment with fluvoxamine, bromhexine, cyproheptadine, and niclosamide to prevent clinical deterioration in patients with symptomatic COVID-19: a randomized clinical trial*, *eClinicalMedicine*, 10.1016/j.eclinm.2024.102517, www.thelancet.com/journals/eclinm/article/PIIS2589-5370(24)00096-8/fulltext.
76. **Treanor** et al., *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, *JAMA*, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016.
77. **McLean** et al., *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, *Open Forum Infect. Dis.* September 2015, 2:3, doi:10.1093/ofid/ofv100.
78. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, *New England Journal of Medicine*, doi:10.1056/NEJMoa1915341.
79. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, *New England Journal of Medicine*, doi:10.1056/NEJMoa1716197.
80. **Kumar** et al., *Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial*, *The Lancet Infectious Diseases*, doi:10.1016/S1473-3099(21)00469-2.
81. **López-Medina** et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial*, *JAMA*, doi:10.1001/jama.2021.3071.
82. **Korves** et al., *SARS-CoV-2 Genetic Variants and Patient Factors Associated with Hospitalization Risk*, *medRxiv*, doi:10.1101/2024.03.08.24303818.
83. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, *Science*, doi:10.1126/science.abh2644.
84. **Nonaka** et al., *SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021*, *International Journal of Infectious Diseases*, doi:10.1016/j.ijid.2021.08.003.
85. **Karita** et al., *Trajectory of viral load in a prospective population-based cohort with incident SARS-CoV-2 G614 infection*, *medRxiv*, doi:10.1101/2021.08.27.21262754.
86. **Zavascki** et al., *Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil*, *Research Square*, doi:10.21203/rs.3.rs-910467/v1.
87. **Willett** et al., *The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism*, *medRxiv*, doi:10.1101/2022.01.03.21268111.
88. **Peacock** et al., *The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry*, *bioRxiv*, doi:10.1101/2021.12.31.474653.
89. **Williams**, T., *Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources*, *Do Your Own Research*, doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal.
90. **Xu** et al., *A study of impurities in the repurposed COVID-19 drug hydroxychloroquine sulfate by UHPLC-Q/TOF-MS and LC-SPE-NMR*, *Rapid Communications in Mass Spectrometry*, doi:10.1002/rcm.9358.
91. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, *Research Square*, doi:10.21203/rs.3.rs-941811/v1.
92. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, *BMC Pharmacology and Toxicology*, doi:10.1186/s40360-022-00580-8.
93. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, *International Journal of Antimicrobial Agents*, doi:10.1016/j.ijantimicag.2022.106542.
94. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, *Pathogens*, doi:10.3390/pathogens10111514.
95. **Alsaïdi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, *Marine Drugs*, doi:10.3390/md19080418.
96. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, *Microbial Pathogenesis*, doi:10.1016/j.micpath.2020.104228.
97. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, *PLoS ONE*, doi:10.1371/journal.pone.0276751.
98. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, *Scientific Reports*, doi:10.1038/s41598-024-54722-5.
99. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, *Frontiers in Pharmacology*, doi:10.3389/fphar.2022.1011522.
100. **Fiaschi** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, *Viruses*, doi:10.3390/v16020168.

101. **Xing** et al., Published anti-SARS-CoV-2 in vitro hits share common mechanisms of action that synergize with antivirals, *Briefings in Bioinformatics*, doi:10.1093/bib/bbab249.
102. **Chen** et al., Synergistic Inhibition of SARS-CoV-2 Replication Using Disulfiram/Ebselen and Remdesivir, *ACS Pharmacology & Translational Science*, doi:10.1021/acspsci.1c00022.
103. **Hempel** et al., Synergistic inhibition of SARS-CoV-2 cell entry by otamixaban and covalent protease inhibitors: pre-clinical assessment of pharmacological and molecular properties, *Chemical Science*, doi:10.1039/D1SC01494C.
104. **Schultz** et al., Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2, *Nature*, doi:10.1038/s41586-022-04482-x.
105. **Ohashi** et al., Potential anti-COVID-19 agents, cepharanthine and nelfinavir, and their usage for combination treatment, *iScience*, doi:10.1016/j.isci.2021.102367.
106. **Al Krad** et al., The protease inhibitor Nirmatrelvir synergizes with inhibitors of GRP78 to suppress SARS-CoV-2 replication, *bioRxiv*, doi:10.1101/2025.03.09.642200.
107. **Thairu** et al., A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality, *Journal of Pharmaceutical Research International*, doi:10.9734/jpri/2022/v34i44A36328.
108. **Singh** et al., The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis, *Journal of Antimicrobial Chemotherapy*, doi:10.1093/jac/dkae045.
109. **Meneguesso**, A., Médica defende tratamento precoce da Covid-19, www.youtube.com/watch?v=X5FCrIm_19U.
110. **Boulware**, D., Comments regarding paper rejection, twitter.com/boulware_dr/status/1311331372884205570.
111. **Meeus**, G., Online Comment, twitter.com/gertmeeus_MD/status/1386636373889781761.
112. **twitter.com**, twitter.com/KashPrime/status/1768487878454124914.
113. **Rothstein**, H., Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments, www.wiley.com/en-ae/Publication+Bias+in+Meta+Analysis:+Prevention,+Assessment+and+Adjustments-p-9780470870143.
114. **Stanley** et al., Meta-regression approximations to reduce publication selection bias, *Research Synthesis Methods*, doi:10.1002/jrsm.1095.
115. **Rücker** et al., Arcsine test for publication bias in meta-analyses with binary outcomes, *Statistics in Medicine*, doi:10.1002/sim.2971.
116. **Peters**, J., Comparison of Two Methods to Detect Publication Bias in Meta-analysis, *JAMA*, doi:10.1001/jama.295.6.676.
117. **Moreno** et al., Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study, *BMC Medical Research Methodology*, doi:10.1186/1471-2288-9-2.
118. **Macaskill** et al., A comparison of methods to detect publication bias in meta-analysis, *Statistics in Medicine*, doi:10.1002/sim.698.
119. **Egger** et al., Bias in meta-analysis detected by a simple, graphical test, *BMJ*, doi:10.1136/bmj.315.7109.629.
120. **Harbord** et al., A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints, *Statistics in Medicine*, doi:10.1002/sim.2380.
121. **Scheim** et al., Back to the Basics of SARS-CoV-2 Biochemistry: Microvascular Occlusive Glycan Bindings Govern Its Morbidities and Inform Therapeutic Responses, *Viruses*, doi:10.3390/v16040647.
122. **Hashimoto (C)**, K., Overview of the potential use of fluvoxamine for COVID-19 and long COVID, *Discover Mental Health*, doi:10.1007/s44192-023-00036-3.
123. **Hoertel (B)** et al., Repurposing antidepressants inhibiting the sphingomyelinase acid/ceramide system against COVID-19: current evidence and potential mechanisms, *Molecular Psychiatry*, doi:10.1038/s41380-021-01254-3.
124. **Kirsch**, S., COVID FAQ, www.skirsch.com/covid/COVID_FAQ.pdf.
125. **Siripongboonsitti (B)** et al., The Real-World Effectiveness of Fluvoxamine Therapy in Mild to Moderate COVID-19 Patients; a Historical Cohort Study (Fluvox Trial), *Journal of Infection and Public Health*, doi:10.1016/j.jiph.2023.10.010.
126. **Tsiakalos** et al., Early Fluvoxamine Reduces the Risk for Clinical Deterioration in Symptomatic Outpatients with COVID-19: A Real-World, Retrospective, before-after Analysis, *Microorganisms*, doi:10.3390/microorganisms11082073.
127. **Pineda** et al., Impact of fluvoxamine on outpatient treatment of COVID-19 in Honduras in a prospective observational real-world study, *Frontiers in Pharmacology*, doi:10.3389/fphar.2022.1054644.
128. **Seftel** et al., Prospective cohort of fluvoxamine for early treatment of COVID-19, *Open Forum Infectious Diseases*, doi:10.1093/ofid/ofab050.
129. **Kirenga** et al., Association of fluvoxamine with mortality and symptom resolution among inpatients with COVID-19 in Uganda: a prospective interventional open-label cohort study, *Molecular Psychiatry*, doi:10.1038/s41380-023-02004-3.
130. **Calusic** et al., Safety and efficacy of fluvoxamine in COVID-19 ICU patients: an open label, prospective cohort trial with matched controls, *British Journal of Clinical Pharmacology*, doi:10.1111/bcp.15126.
131. **Visos-Varela** et al., Repurposing selective serotonin reuptake inhibitors for severity of COVID-19: A population-based study, *European Neuropsychopharmacology*, doi:10.1016/j.euroneuro.2023.03.011.
132. **Trkulja** et al., Outpatients prescribed with fluvoxamine around the time of COVID-19 diagnosis are not at a reduced risk of subsequent hospitalization and death compared to their non-prescribed peers: population-based matched cohort study, *European Journal of Clinical Pharmacology*, doi:10.1007/s00228-023-03479-3.

133. **Diaz** et al., Protective Effect of Fluvoxamine for COVID-19 in Obsessive-Compulsive Disorder, The Primary Care Companion For CNS Disorders, doi:10.4088/PCC.22br03337.
134. **Fritz** et al., Association between antidepressant use and ED or hospital visits in outpatients with SARS-CoV-2, Translational Psychiatry, doi:10.1038/s41398-022-02109-3.
135. **Oskotsky** et al., Mortality Risk Among Patients With COVID-19 Prescribed Selective Serotonin Reuptake Inhibitor Antidepressants, JAMA Network Open, doi:10.1001/jamanetworkopen.2021.33090.
136. **Kumar (B)** et al., Advancements in the development of antivirals against SARS-Coronavirus, Frontiers in Cellular and Infection Microbiology, doi:10.3389/fcimb.2025.1520811.
137. **Grewal** et al., Cholesterol and COVID-19—therapeutic opportunities at the host/virus interface during cell entry, Life Science Alliance, doi:10.26508/lsa.202302453.
138. **Saranya** et al., Systems medicine framework for repurposable drug combinations for COVID-19 comorbidities, Medicine in Omics, doi:10.1016/j.meomic.2024.100038.
139. **Jaimes-Castelán** et al., Drugs and natural products for the treatment of COVID-19 during 2020, the first year of the pandemic, Boletín Médico del Hospital Infantil de México, doi:10.24875/bmhim.23000016.
140. **Choi** et al., Review of COVID-19 Therapeutics by Mechanism: From Discovery to Approval, Journal of Korean Medical Science, doi:10.3346/jkms.2024.39.e134.
141. **Loucera** et al., Drug repurposing for COVID-19 using machine learning and mechanistic models of signal transduction circuits related to SARS-CoV-2 infection, Signal Transduction and Targeted Therapy, doi:10.1038/s41392-020-00417-y.
142. **Behboudi** et al., SARS-CoV-2 mechanisms of cell tropism in various organs considering host factors, Heliyon, doi:10.1016/j.heliyon.2024.e26577.
143. **Cesar-Silva** et al., Lipid compartments and lipid metabolism as therapeutic targets against coronavirus, Frontiers in Immunology, doi:10.3389/fimmu.2023.1268854.
144. **Augustin** et al., Drug repurposing for COVID-19: current evidence from randomized controlled adaptive platform trials and living systematic reviews, British Medical Bulletin, doi:10.1093/bmb/ldac037.
145. **Kushwaha** et al., A comprehensive review on the global efforts on vaccines and repurposed drugs for combating COVID-19, European Journal of Medicinal Chemistry, doi:10.1016/j.ejmech.2023.115719.
146. **Pandit** et al., e-Pharmacophore modeling and in silico study of CD147 receptor against SARS-CoV-2 drugs, Genomics & Informatics, doi:10.5808/gi.23005.
147. **Chen (B)** et al., Metabolic alterations upon SARS-CoV-2 infection and potential therapeutic targets against coronavirus infection, Signal Transduction and Targeted Therapy, doi:10.1038/s41392-023-01510-8.
148. **Oliver** et al., Different drug approaches to COVID-19 treatment worldwide: an update of new drugs and drugs repositioning to fight against the novel coronavirus, Therapeutic Advances in Vaccines and Immunotherapy, doi:10.1177/25151355221144845.
149. **Pati** et al., Drug discovery through Covid-19 genome sequencing with siamese graph convolutional neural network, Multimedia Tools and Applications, doi:10.1007/s11042-023-15270-8.
150. **Ceja-Gálvez** et al., Severe COVID-19: Drugs and Clinical Trials, Journal of Clinical Medicine, doi:10.3390/jcm12082893.
151. **McAuley** et al., Use of Human Lung Tissue Models for Screening of Drugs against SARS-CoV-2 Infection, Viruses, doi:10.3390/v14112417.
152. **Lenze (B)** et al., Beyond “Psychotropic”, The Journal of Clinical Psychiatry, doi:10.4088/jcp.22r14494.
153. **Homolak** et al., Widely available lysosome targeting agents should be considered as potential therapy for COVID-19, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2020.106044.
154. **c19early.org (D)**, c19early.org/timeline.html.
155. **c19early.org (E)**, c19early.org/mfmeta.html.
156. **twitter.com (B)**, twitter.com/boulware_dr/status/1560018343146360832.
157. **clinicaltrials.gov**, clinicaltrials.gov/ct2/history/NCT04510194?A=15&B=16&C=merged#StudyPageTop.
158. **clinicaltrials.gov (B)**, clinicaltrials.gov/ct2/history/NCT04510194?A=16&B=17&C=merged#StudyPageTop.
159. **vimeo.com**, vimeo.com/622665410.
160. **Reis (C)** et al., Effect of Early Treatment with Ivermectin among Patients with Covid-19, New England Journal of Medicine, doi:10.1056/NEJMoa2115869.
161. **Reis (D)** et al., Effect of early treatment with metformin on risk of emergency care and hospitalization among patients with COVID-19: The TOGETHER randomized platform clinical trial, The Lancet Regional Health - Americas, doi:10.1016/j.lana.2021.100142.
162. **Reis (E)** et al., Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19 The TOGETHER Randomized Clinical Trial, JAMA Network Open, doi:10.1001/jamanetworkopen.2021.6468.
163. **Reis (F)** et al., Early Treatment with Pegylated Interferon Lambda for Covid-19, New England Journal of Medicine, doi:10.1056/NEJMoa2209760.
164. **science.sciencemag.org**, science.sciencemag.org/content/372/6544/815.
165. **thelancet.com**, www.thelancet.com/article/S0140-6736(21)00183-5/fulltext.
166. **web.archive.org**, web.archive.org/web/*/https://twitter.com/Covid19Crusher/status/1430170252575395843.

167. **web.archive.org (B)**,
web.archive.org/web/*/<https://twitter.com/Covid19Crusher/status/1453726471499894787>.
168. **web.archive.org (C)**,
web.archive.org/web/*/<https://twitter.com/Covid19Crusher/status/1453803654608269318>.
169. **twitter.com (C)**,
twitter.com/alexandrosM/status/1526586118438670336.
170. **Naggie** et al., *Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19: A Randomized Clinical Trial*, JAMA, doi:10.1001/jama.2022.18590.
171. **McCarthy** et al., *Effect of Fluvoxamine vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19*, JAMA, doi:10.1001/jama.2022.24100.
172. **Zhang (B)** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690.
173. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.
174. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.
175. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, Statistics in Medicine, doi:10.1002/sim.1761.
176. **Deng (C)**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.