RAPID-C19 Oversight Group

Briefing:

serotonin specific reuptake inhibitors (SSRIs) (fluvoxamine, fluoxetine) (generic) [C19-058]

For administrative purposes only:

Version	Section	Date	Initial
0.1	1-5	18/02/2021	
0.2	1-5	22/02/2021	
0.3	1-5	22/02/2021	
1.0	-	23/02/2021	



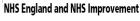


Briefing

1. Key considerations

Question	Response	Section
Where does fluvoxamine and fluoxetine sit in the treatment pathway?	Prevention / mild / moderate / severe / critical / rehabilitation [most studies are being conducted in non-hospitalised patents]	
b) Are there other treatments sitting in this place in the pathway?	Y / N (refer to the pathway diagram that will accompany the papers at the weekly meetings)	
c) What is the mechanism of action of fluvoxamine and fluoxetine that explains why it is being investigated as a potential treatment for COVID-19, and its particular place in the treatment pathway?	Fluvoxamine and fluoxetine are serotonin specific reuptake inhibitors (SSRIs). Antidepressants may be associated with decreases in plasma levels of inflammatory mediators, including IL-10, TNF-α, CCL-2 and IL-6. In addition, it has been proposed that a potential mechanism for fluvoxamine is immune modulation via σ-1 receptor (S1R) agonism (Hoertel 2021).	
d) Are there other treatments in this class (i.e with the same or similar mechanism of action) that have been considered by the Oversight Group and if so, what are these?	A number of other treatments with activity against IL-6 and TNF-α have been considered by the Oversight Group, in moderate/severe and critically ill patients with COVID-19	
e) Are there other treatments in this class that are currently in clinical trials for COVID-19 and if so, what are they?	There are no other SSRIs being investigated for COVID-19.	
2. Is the evidence base sufficient to allow further action to be taken at this stage? Sufficient evidence base should take into account the amount of evidence (number of trials and total number of participants) as well as robustness of the trials.	Y / N Results are available for fluvoxamine from one small placebo-controlled RCT and one observational study. There are no published studies for fluoxetine.	5.1 and appendix 1
3. Is there a positive signal of efficacy across the outcomes?	Y / N In the published RCT, fluvoxamine showed a significant benefit versus placebo for the primary endpoint of clinical deterioration, however the certainty of effect is low given the	5.1 and appendix 1







4. Is there a specific population where there could be significant benefit?	small sample size, short duration of follow up and wide confidence intervals. Results from larger RCTs are required. Y / N / Unknown	
5. Is there a signal of harm (including unfavourable effects and adverse events)?	Y / N In the published RCT the proportion of patients with a serious adverse event was lower for fluvoxamine vs. placebo. The number of non-serious adverse events was similar across treatment arms.	5.1 and appendix 1
6. Are there other relevant issues for consideration (e.g. combination therapies, special populations of interest, regulatory issues, potential supply issues, service delivery or technology delivery challenges)?	Y / N / Unknown There is no information in the trial registry records for the ongoing studies regarding the new variants of SARS-CoV-2.	
Next steps	Stand down / monitor / progress Monitor for results from the larger RC expected to report soon.	CTs

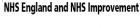
Progress: Oversight Group to take action (e.g. commission an evidence summary, begin regulatory discussions).

Monitor: Oversight Group to reconsider topic at a later date (e.g. after trial results have published). **Stand down**: Oversight Group considers there is not, and is not likely to be, any positive signal that warrants further consideration of this topic.

2. Treatment

Treatment	Fluvoxamine	
	Fluoxetine	
Туре	Anti-depressant (SSRIs)	
Mechanism of action	Antidepressants may be associated with decreases in plasma levels of inflammatory mediators, including IL-10, TNF- α , CCL-2 and IL-6. In addition it has been proposed that a potential mechanism for fluvoxamine is immune modulation via σ -1 receptor (S1R) agonism (<u>Hoertel 2021</u>)	
Administration	Oral	
Dose and schedule	Fluvoxamine, 100mg twice or three times daily, orally	
	Fluoxetine, 20mg to 60mg daily, orally	
Cost	Fluvoxamine 50mg tablets, 60; £17.53 a	
	Fluvoxamine 100mg tablets, 30; £17.70 a	
	Fluoxetine 20mg capsule, 30; £1.12 ^a	





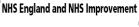


Existing guidance/information	-
Other relevant	-
information	
Source: a BNF	

3. Regulatory status

Commercial sponsor	Fluvoxamine 100mg tablet: Mylan, AAH Pharmaceuticals Ltd, Alliance Healthcare (Distribution) Ltd, DE Pharmaceuticals, Medihealth (Northern) Ltd, Sigma Pharmaceuticals Plc, Tillomed Laboratories, Wockhardt UK Ltd Fluoxetine 20mg capsule: numerous manufacturers hold marketing authorisations
	ACTION (for generics only): NHSE repurposing medicines group to identify commercial sponsors wishing to pursue a license for COVID-19 via the British Generics Manufacturers Association (BGMA) ACTION: MHRA to advise on lead regulator (MHRA/EMA) & likely regulatory process that will be followed
New or repurposed	Repurposed
Branded or generic	Generic
Regulatory status/plans	COVID-19 Not yet licensed for this indication. Regulatory plans still to be confirmed with sponsors. Existing indications in the UK
	Fluvoxamine is indicated for depressive illness and obsessive compulsive disorder. ^a
	Fluoxetine is indicated for major depression, obsessive compulsive disorder, bulimia nervosa and menopausal symptoms, particularly hot flushes, in women with breast cancer. ^a
	ACTION: NICE & MHRA to [consider the appropriate time to] gather additional information on regulatory plans from identified commercial sponsors
Source: a BNF	







4. Supply activities

Supply	Unknown
	ACTION: Once a commercial sponsor is identified, DH Therapeutics Taskforce to [consider the appropriate time to] gather information from companies on supply and scale-up.

5. Evidence

5.1 Published evidence

The table below highlights the signals from the main published evidence and the strength of these signals, taking into account the magnitude of effect shown and the quality of the evidence. Any published studies not reporting key outcomes of interest or case studies are briefly summarised at the end of the table. Detailed information on all published studies are in appendix 1.

Trial	Result	Assessment of evidence	Certainty of effect*		
Mortality					
Lenze 2020 JAMA NCT04342663 US	There were no deaths in either group	Double-blind RCT Risk of bias – low (double-blind) however small sample size limit certainty of effect.	Low		
Adult outpatients with confirmed SARS-CoV-2 and symptomatic within 7 days of first dose of trial medicine Fluvoxamine (n=80) Placebo (n=72)					
Ventilation outcome	es				
-	-	-	-		
Time to recovery					
-	-	-	-		
Clinical deterioration	n				

<u>Lenze 2020</u>	Primary endpoint: clinical	Double-blind RCT	Low
JAMA	deterioration at day 15		
	defined by (1) presence of	Risk of bias – low (double-blind),	
NCT04342663	dyspnoea or	however small sample size, short	
	hospitalisation for	follow-up time and wide	
US	shortness of breath or	confidence intervals limit certainty	
	pneumonia and (2)	of effect.	
Adult outpatients	decrease in oxygen		
with confirmed	saturation (<92%) on		
SARS-CoV-2 and	room air or supplemental		
symptomatic within	oxygen requirement to		
7 days of first dose	maintain oxygen		
of trial medicine	saturation of ≥92%:		
Fluvovom:	00/ (0/90) for flux avairable		
Fluvoxamine (n=80)	0% (0/80) for fluvoxamine		
Placebo (n=72)	vs. 8.3% (6/72) for placebo; absolute		
Placebo (II-72)	difference 8.7% (95% CI		
	1.8% to 16.4%), p=0.009		
Adverse events	1.0 % to 10.4 %), p=0.009		
Auverse events			
Lenze 2020	Serious adverse events	Double-blind RCT	Low
JAMA	occurred in 1.3% (1/80)		
	vs. 6.9% (5/72) of patients	Risk of bias – low (double-blind),	
NCT04342663		however small sample size and	
	Adverse events occurred	short follow-up time limit certainty	
US	in 13.8% (11/80) vs. 8.3%	of effect.	
	(6/72) of patients		
Adult outpatients			
with confirmed	There were patients in		
SARS-CoV-2 and	placebo group who had		
symptomatic within	more than one 'other		
7 days of first dose	adverse event'. Overall		
of trial medicine	the total number of		
	adverse events (other		
	than serious) was 11 for		
Fluvoxamine	,		
(n=80)	fluvoxamine and 11 for		
	,		

*Explanation of the certainty of the effect based on the precision of the estimates and the robustness of the evidence

High certainty: Very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

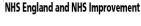
Very low certainty: Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of other published data/trials

• A retrospective observational study (<u>Hoertel 2021</u>) conducted in France reported on 7,230 patients admitted to hospitals with COVID-19 of whom 345 (4.8%) received an antidepressant. Intubation or death was reported as follows: no antidepressant 17.3% (1188/6885); any antidepressant 24.3% (84/345); SSRI 23.1% (45/195) and non-SSRI 26% (39/150). Primary multi-variable analyses with inverse probability weighting showed significant associations between any antidepressant use with reduced risk of intubation or death; see appendix 1









5.2 Ongoing trials

- There are 4 ongoing RCTs of fluvoxamine of phase 2/3 design. Two studies are being conducted in non-hospitalised patients with an expected recruitment of around 3,800 patients and 1 trial, with an estimated enrolment of 400 patients, is in patients admitted to community treatment centres. The 4th study is being conducted in hospitalised patients and has an estimated enrolment of 100 patients
- The non-randomised trial of fluoxetine has an estimated enrolment of 2,000 non-hospitalised patients.
- Two fluvoxamine studies have completed (with published results available for one of these).
- One fluoxetine study was suspended.

5.2.1 Key trials

The table below shows the key trials (in UK and NIHR-prioritised if applicable) that are likely to impact on decision-making (because of robust trial design and reporting of key outcomes):

Fluvoxamine

NCT04668950 (Washington University School of Medicine, RCT of **fluvoxamine**, US) Estimated enrolment: 1100 non-hospitalised patients with mild symptoms of COVID-19 Primary outcome: clinical deterioration

Estimated PCD: July 2020

NCT04727424 TOGETHER2 (Cardresearch, RCT of fluvoxamine, Brazil)

Estimated enrolment: 2724 outpatients with early onset mild symptoms of COVID-19 Primary outcome: emergency visits and observation unit stay >12 hrs; hospitalisation due to COVID-19 progression

Estimated PCD: 01/02/2022

NCT04711863 S2020-3124-0001 (Asan medical Center, RCT of fluvoxamine, South Korea)

Estimated enrolment: 400 patients with mild to moderated COVID-19 in community treatment centres

Primary outcome: clinical deterioration

Estimated PCD: 31/05/2021

ACTION: NICE to contact principle investigators using standard RAPID C-19 template letter to request more information on earliest anticipated reporting dates if possible, and whether key signals/results can be provided in advance of publication.

Further details of these trials are presented in appendix 2.

5.2.2 Trials with the earliest completion dates

The table below shows the trials due to report soon that are reasonably well designed and powered and/or investigating relevant clinical outcomes of interest:

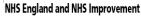
Design	Size	Location	Primary outcome(s)	Estimated PCD
Fluvoxamine				
RCT NCT04711863	400	South Korea	Clinical deterioration	31/05/2021

RCT	1100	US	Clinical	July 2021
NCT04668950			deterioration	

Further details of these trials are presented in appendix 2.









Appendix 1: Published evidence

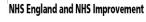
A. Systematic reviews/evidence summaries

Reference	Design of study	Population	Results	
-	-	-	-	
Source: NICE Information Services literature search				
Note: Published evidence has been excluded where [XXX, as applicable] (n=X)				

B. Trials and studies

Reference	Design and location of study	Population	Results
Lenze 2020 JAMA NCT04342663	Double-blind RCT US	Adult outpatients with confirmed SARS-CoV-2 and symptomatic within 7 days of first dose of trial medicine. Fluvoxamine 50mg, then 100mg bd, then 100mg tds up to day 15 (n=80 received fluvoxamine as randomised) Placebo (n=72 received placebo as randomised)	Primary endpoint: clinical deterioration defined by (1) presence of dyspnoea or hospitalisation for shortness of breath or pneumonia and (2) decrease in oxygen saturation (<92%) on room air or supplemental oxygen requirement to maintain oxygen saturation of ≥92%: 0% (0/80) vs. 8.3% (6/72) for the fluvoxamine and placebo groups respectively; absolute difference 8.7% (95% CI: 1.8% to 16.4%), p=0.009 No patients died. SAE occurred in 1.3% (1/80) vs. 6.9% (5/72) of patients AE occurred in 13.8% (11/80) vs. 8.3% (6/72) of patients There were patients in the placebo group who had more than one 'other adverse event'. Overall the total number of adverse events (other than serious) was 11 for fluvoxamine and 11 for placebo. Cochrane living meta-analysis WHO progression score ≥6 day 14 to 28 (all randomised): 0/92 vs. 1/89, RR 0.32, 95% CI 0.01 to 7.82 WHO progression score ≥7 day 14 to 28 (all randomised): 0/92 vs. 1/89, RR 0.32, 95% CI 0.01 to 7.82







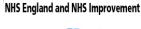
Reference	Design and location of study	Population	Results
Hoertel 2021 Molecular Psychiatry [previously available as a preprint]	Retrospective observational multicentre cohort study 39 hospitals, France 24/1/2020 to 1/4/2020 Antidepressant use defined as receipt of any antidepressant during the first 48 hours of hospital admission and before the end of hospitalisation or intubation or death	7230 patients admitted to hospital with COVID-19 345 (4.8%) received an antidepressant SSRI, n=195 Other, n=150 Mean fluoxetine equivalent dose, 21.6mg	Primary endpoint: time to intubation or death No antidepressant 17.3% (1188/6885) Primary endpoint: composite of intubation or death Any antidepressant 24.3% (84/345) SSRI 23.1% (45/195) Non-SSRI (39/150) Unadjusted hazard ratio age-stratified estimates of the association between antidepressant use and the endpoint were non-significant (all p>0.05) Primary multi-variable analyses with inverse probability weighting showed significant associations between any antidepressant use with reduced risk of intubation or death: Any antidepressant, HR 0.56, 95% CI 0.43 to 0.73, p<0.001 SSRI antidepressant, HR 0.51, 95% CI 0.36 to 0.72, p<0.001 Non-SSRI antidepressant, HR 0.65, 95% CI 0.45 to 0.93,
Source: NICE In	formation Services literature search (15	(02/2021)	SSRI antidepressant, HR 0.51, 95% CI 0.36 to 0.72, p<0.0

Source: NICE Information Services literature search (15/02/2021)

Abbreviations: SAE, serious adverse event. AE, adverse event; RR, risk ratio; HR, hazard ratio; CI, confidence interval; SSRI, serotonin specific reuptake inhibitor









Appendix 2: Ongoing trials

A. Completed trials

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD ³
Fluvoxamine						
IRCT20131115015405N4 Up to 300mg daily	Massih Daneshvari Hospital	Phase 2/3 Open-label Randomised Controlled: Fluvoxamine vs no fluvoxamine	Iran	18 years + Hospitalised (ICU) Estimated enrolment: 40	IL6 level ESR level CRP level	Recruitment complete
NCT04342663** 202004023 STOP COVID Fluvoxamine 100mg three times daily for 15 days	Washington University School of Medicine	Phase 2 Double-blind Randomised Controlled: fluvoxamine vs. placebo	US	18 years+ Non-hospitalised Confirmed SARS-CoV-2 Symptomatic Actual enrolment: 152	Time to clinical worsening	Recruitment complete Published (see appendix 1)

Source: National Institute for Health Research Innovation Observatory (scan 11/2/2021)

Abbreviations: IL6, interleukin 6; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ICU, intensive care unit.

B. Recruiting

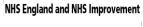
Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
Fluvoxamine NCT04711863 S2020-3124- 0001	Asan Medical Center	Phase 2 Single-blind Randomised	South Korea	18 to 85 years Confirmed SARS-CoV-2 with mild to moderate symptoms	Clinical deterioration	31/05/2021

^{*}PCD (Primary Completion Date) defined on clinicaltrials.gov as the date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. The "estimated" primary completion date is the date that the researchers think will be the primary completion date for the study.

University School of (Stop Covid 2) University School of (University School of (Univ	Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
NCT04668950** 202011101	00mg twice daily for 10 days Mild/moderate		Fluvoxamine vs. placebo		treatment centers Symptom onset ≤7 days		
NCT04718480** SD-COVID19-01 2020-002299-11 Research Ltd. Phase 2 Double-blind Randomised Confirmed SARS-CoV-2 with moderate disease Estimated enrolment: 100 NCT04727424 TOGETHER_2 SigmaDrugs Research Ltd. Phase 2 Double-blind Randomised Confirmed SARS-CoV-2 with moderate disease Estimated enrolment: 100 • Evaluation of emergency visits	CT04668950** 202011101 Stop Covid 2) Early treatment of COVID-19 50mg once then	University School of	Triple blind Randomised Controlled: Fluvoxamine vs.	US	Non-hospitalised Confirmed SARS-CoV-2 Symptomatic (mild) Risk factor for clinical deterioration	Clinical deterioration	July 2021
TOGETHER_2 Quadruple blinded Outpatients emergency visits	NCT04718480** SD-COVID19-01 2020-002299-11		Double-blind Randomised Controlled: Fluvoxamine vs. placebo (both plus	Hungary	Hospitalised Confirmed SARS-CoV-2 with moderate disease	Clinical recovery	August 2021
100mg on day 1 then 100mg twice daily for 9 days Controlled: Fluvoxamine vs. metformin vs. ivermectin vs. placebo Controlled: Fluvoxamine vs. metformin vs. ivermectin vs. placebo Controlled: Fluvoxamine vs. metformin vs. ivermectin vs. placebo Contirmed SARS-CoV2 infection or antigen presence At least one risk factor Estimated enrolment: 2724 progression unit stay >12 hrs thospitalisation due to COVID-19 progression	OGETHER_2 00mg on day 1 hen 100mg wice daily for 9 days Early onset/mild symptoms	Cardresearch	Quadruple blinded Randomised Controlled: Fluvoxamine vs. metformin vs. ivermectin vs.	Brazil	Outpatients Acute flu-like symptoms and confirmed SARS-CoV2 infection or antigen presence At least one risk factor	emergency visits and observation unit stay >12 hrs • Hospitalisation due to COVID-19	01/02/2022









Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
NCT04377308 FRIDA COVID19 20mg up to 60mg (as tolerated) for 2 weeks to 2	University of Toledo Health Science Campus	Phase 4 Open-label Non-randomised: fluoxetine or no fluoxetine	US	18 years + Non-hospitalised patients with confirmed COVID-19 with fever, cough and shortness pf breath Estimated enrolment: 2000	 Hospitalisations Intubation Death	20/04/2021
months depending on symptom duration						

Source: National Institute for Health Research Innovation Observatory (scan 11/02/2021)

Abbreviations: -

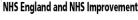
C. Suspended/terminated studies

Reference	Sponsor	Design	Location	Population	Primary endpoints	Status				
Fluoxetine										
NCT04570449 20mg to 60mg for 8 weeks in increasing and reducing schedule	Milton S. Hershey Medical Center	Phase 1 Quadruple-blind Randomised Controlled: fluoxetine vs. placebo	US	18 years+ Confirmed SARS-CoV-2 <10 days since symptoms; persistent fever, other COVID- 19 symptoms Actual enrolment: 0	rate of hospitalisationphysical symptoms	Withdrawn- study timeline is not feasible				
Source: National	Source: National Institute for Health Research Innovation Observatory (scan 11/2/2021)									



Abbreviations: -







^{*}PCD (Primary Completion Date) defined on clinicaltrials.gov as the date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. The "estimated" primary completion date is the date that the researchers think will be the primary completion date for the study.

^{**}Pivotal trials defined as those that are active, phase 2+, randomised with 100+ participants and UK/EU/US/Australia/Canada based.