Outpatient Therapeutic Management of Adults (≥18 years of age) with Mild COVID-19[1,2]

Mildly ill patients are defined as those who do not require new or additional supplemental oxygen from their baseline status.

Treatments that are RECOMMENDED for High Risk patients

Drug	Criteria	Comments
Sotrovimab 500mg IV x 1 dose over 30 min Monitor x 60 min after infusion	For mildly ill patients presenting within 7 days of symptom onset who meet the following criteria: • Symptomatic residents of LTC facilities, retirement homes or other congregate living conditions • Symptomatic inpatients with nosocomial infections • **High risk patients:** a) ≥70 years AND have at least 1 additional risk factor OR b) ≥50 years AND is First Nations, Inuit or Métis, AND have at least 1 additional risk factor Risk Factors include: Obesity (BMI ≥30), dialysis or stage 5 kidney disease (eGFR <15 ml/min/1.73m^2), diabetes, cerebral palsy, intellectual disability of any severity, sickle cell disease, receiving active cancer treatment, solid organ or stem cell transplant recipients	Previous SARS-CoV2 infection and vaccination status do not need to be considered. Serological testing for IgG antibody does not need to be done. At this time, regional infusion sites are being established. More information will be circulated as it becomes available. Hamilton has an operational infusion site. A direct physician referral can be made here if a patient is outside of catchment area. See here for a summary of the clinical evidence for sotrovimab from the Ontario Science Table.

Please refer to the Ontario Science Table 's Science Briefs for more detailed information on treatment options in this document.

Treatments that are NOT RECOMMENDED

Due to insufficient evidence to support use
- Anticoagulation
- Colchicine
- Vitamin D

Due to lack of benefit, potential for harm, and system implications of overuse
- Antibiotics (e.g. azithromycin)
- Dexamethasone
- Hydroxychloroquine/Chloroquine
- Ivermectin
- Lopinavir-ritonavir (Kaletra®)

Treatments that MAY BE CONSIDERED for High Risk and Other patients at risk of adverse outcomes

Drug	Criteria	Comments
Sotrovimab 500mg IV x 1 dose over 30 min Monitor x 60 min after infusion	For mildly ill patients who DO NOT meet the above criteria BUT who, in the opinion of the physician, have other important **risk factors for disease progression (e.g. immunosuppression, on immunosuppressive therapy)**	Previous SARS-CoV2 infection and vaccination status do not need to be considered. Serological testing for IgG antibody does not need to be done. See comments above for information on infusion sites.
Budesonide (Pulmicort®) 800mcg inhaled BID x 14 days	For mildly ill patients presenting within 7 days of symptom onset who meet the **high risk patient** criteria under sotrovimab above.	See next page for relevant clinical trial data on budesonide in non-hospitalized patients. Cost (based on Ontario Drug Benefit pricing):[3] Pulmicort Turbuhaler 400mcg x 200 doses = $100.29; 200mcg x 200 doses = $68.70 *Note: The 100mcg strength does not provide enough doses for the full 14-day treatment course.*
Fluvoxamine (Luvox® and generics) 50mg PO at bedtime x 1 day, then 100mg BID x 2 days if tolerated, then 100mg TID if tolerated through to day 15 *Note: The above titration is based on the STOP-COVID[7,8] trial. For tolerability reasons, a slower titration may be required. A final dose of 100mg BID may be considered based on the dose used in the TOGETHER[9] trial.*	For mildly ill patients presenting within 7 days of symptom onset. This is based on very low certainty of evidence of reduction in hospitalization, and the need for outpatient treatment options with a reasonable safety profile during an anticipated spike in COVID-19 cases due to Omicron. Please consult your **clinic pharmacist** for consideration of drug interactions and dose titration where appropriate. *Note: In the STOP-COVID[7,8] trials, caffeine intake was limited to no more than 1 cup/day.*	See next page for relevant clinical trial data on fluvoxamine in non-hospitalized patients and postulated mechanism of action of fluvoxamine as an immune modulator. *Note: Other SSRIs may possibly exhibit similar immune modulating activity. Providers should weigh benefits and risks of switching patients currently on other antidepressants to fluvoxamine for the relatively small clinical benefits noted in the trials. Note also that individuals on SSRIs were excluded in the TOGETHER[9] trial but permitted in the STOP-COVID[7,8] trial if the doses were low.* Common side effects:[4] Sedation, headache, insomnia, dizziness, nervousness, weakness, nausea, diarrhea, dry mouth, anorexia. *Note: Preference for larger doses to be given at bedtime for tolerability if required..* Drug interactions (strong inhibitor of CYP1A2, CYP2C19) – *the following is NOT all inclusive*:[4] Buprenorphine**,** caffeine, citalopram, clopidogrel, clozapine, haloperidol, olanzapine, methadone, phenytoin, propranolol, warfarin, verapamil Cost (based on Ontario Drug Benefit pricing):[3] Generic fluvoxamine 50mg tab = $0.21; 100mg tab = $0.38

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Summary of clinical trial data for budesonide and fluvoxamine in non-hospitalized patients[2,5-9]

PRINCIPLE[5] trial - Open label RCT, in non-hospitalized patients
Inclusion: ≥65 years or ≥50 years with comorbidities, PCR-confirmed or suspected COVID-19, ≤14 days of symptoms. Exclusion: On inhaled or systemic corticosteroids, unable to use an inhaler, contraindication to inhaled budesonide
Interventions: Usual care plus **budesonide 800 mcg inhaled twice daily (n = 1,069) vs. Usual care (n = 787) x 14 days**
Primary Endpoints: COVID-19-related hospitalization or death up to 28 days from randomization, Time to reported recovery up to 28 days from randomization
Outcomes: Percentage of patients hospitalized or died within 28 days: 6.8% in budesonide arm vs. 8.8% in usual care arm (OR 0.75; 95% CI, 0.55–1.03). Median time to reported recovery: 11.8 days in budesonide arm vs. 14.7 days in usual care arm (HR 1.21; 95% CI, 1.08–1.36). **In older high-risk adult outpatients, inhaled budesonide reduced time to reported recovery but not hospitalization or death up to 28 days of randomization.**

STOIC[6] trial - Open label, Phase 2 RCT in non-hospitalized patients
Inclusion: ≥18 years, ≤7 days of symptoms. Exclusion: Use of inhaled or systemic glucocorticoids in past 7 days, known allergy or contraindication to budesonide
Interventions: Usual care plus **budesonide 800 mcg inhaled twice daily until symptom resolution (n = 73) vs. Usual care (n = 73)**
Primary Endpoint: COVID-19-related urgent care visit, including ED visit or hospitalization
Outcomes: Percentage of patients with COVID-19-related urgent care visit or hospitalization: 1% in budesonide arm vs.14% in usual care arm (relative risk reduction 91%). Median duration of budesonide use: 7 days. **In adult outpatients with mild COVID-19, inhaled budesonide used until symptom resolution reduced the need for urgent care or ED assessment and/or hospitalization.**

STOP-COVID[7,8] trial - DB, RCT in non-hospitalized patients in the US
Inclusion: ≥18 years, Positive SARS-CoV-2 PCR result, ≤7 days of symptoms. Exclusion: Immunocompromised, unstable medical comorbidities
Intervention**: Fluvoxamine 50 mg PO for 1 dose, then fluvoxamine 100 mg twice daily x 2 days, then fluvoxamine 100 mg 3 times daily through Day 15 (n = 80) vs. placebo (n = 72)**
Primary Endpoint: Clinical deterioration within 15 days of randomization (dyspnea or being hospitalized for dyspnea or pneumonia; and having SpO2 <92% on room air or requiring supplemental oxygen to attain SpO2 ≥92%)
Outcomes: Clinical deterioration: 0% in fluvoxamine arm vs. 8.3% in placebo arm (absolute difference 8.7%; 95% CI, 1.8% to 16.4%). **In adult outpatients with mild COVID-19, fluvoxamine reduced the proportion of patients who experienced clinical deterioration within 15 days of randomization.** *Note: The subsequent STOP COVID 2, a Phase 3 RCT in the US/Canada was stopped early due to lower than expected case rates and treatment effects.*

TOGETHER[9] trial - DB, adaptive RCT in non-hospitalized patients in Brazil
Inclusion: ≥50 years or aged ≥18 years with comorbidities, Laboratory-confirmed SARS-CoV-2 infection, ≤7 days of symptoms. Exclusion: Use of an SSRI, severe mental illness, cirrhosis, recent seizures, severe ventricular cardiac arrhythmia
Interventions: **Fluvoxamine 100 mg PO twice daily (n = 741) vs. placebo (n = 756) x 10 days**
Primary Endpoint: Composite endpoint of emergency setting observation for >6 hours OR hospitalization due to progression of COVID-19 within 28 days after randomization
Outcomes: Proportion of patients who met the primary composite endpoint: 11% in fluvoxamine arm vs. 16% in placebo arm (relative risk 0.68; 95% CI, 0.52–0.88). **In high-risk adult outpatients with mild COVID-19, fluvoxamine reduced the composite endpoint of COVID-19-related hospitalization OR retention in an ED setting for >6 hours within 28 days of randomization. However, fluvoxamine did not impact COVID-19-related hospitalizations alone.**

Postulated mechanism of action for fluvoxamine in setting of COVID-19[8,10,11]

Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), is postulated to have immune modulatory effects through strong agonistic effects on the Sigma-1 receptor (S1R). The S1R is an endoplasmic reticulum chaperone protein with various cellular functions, including regulation of cytokine production through its interaction with the endoplasmic reticulum stress sensor inositol-requiring enzyme 1α (IRE1). Previous studies have shown that fluvoxamine reduced damaging aspects of the inflammatory response during sepsis through the S1R-IRE1 pathway, and decreased shock in animal sepsis models. Pharmacologic agents that act at S1R have demonstrated in-vitro activity against SARS-CoV-2. Furthermore, SSRIs may decrease uptake of serotonin from platelets during thrombosis, resulting in decreased neutrophil recruitment and platelet aggregation, which may be helpful in the early stages of COVID-19. The order of potency for other antidepressants at the S1R has been noted as follows: **fluvoxamine>sertraline>fluoxetine>escitalopram>citalopram>paroxetine>duloxetine**. Venlafaxine, milnacipran, and mirtazapine showed weak affinity while **sertraline also showed antagonist activity**.

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