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Australia New Zealand Society of Palliative Medicine

Further Symptom Management in COVID-19:

Treatment Approaches and Alternative Routes

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Summary of Guideline

The diagram and table below are a summary of this guideline, intended for use by non-specialist palliative care clinicians. For detailed symptom management guide (including starting dose), please see relevant sections in the main manuscript. If symptoms persist, please seek specialist palliative care advice. Most palliative care medications such as opioids, benzodiazepines, anti-emetics, anti-psychotics and anti-secretories can be given via oral and/or subcutaneous routes (*preferred parenteral route in palliative care approach*) for symptom management. The table below includes a list of alternative routes to be considered when the conventional treatment approaches are not deemed feasible. The evidence for the alternative routes is relatively limited. However, these alternatives may be the best possible option during the COVID-19 crisis.

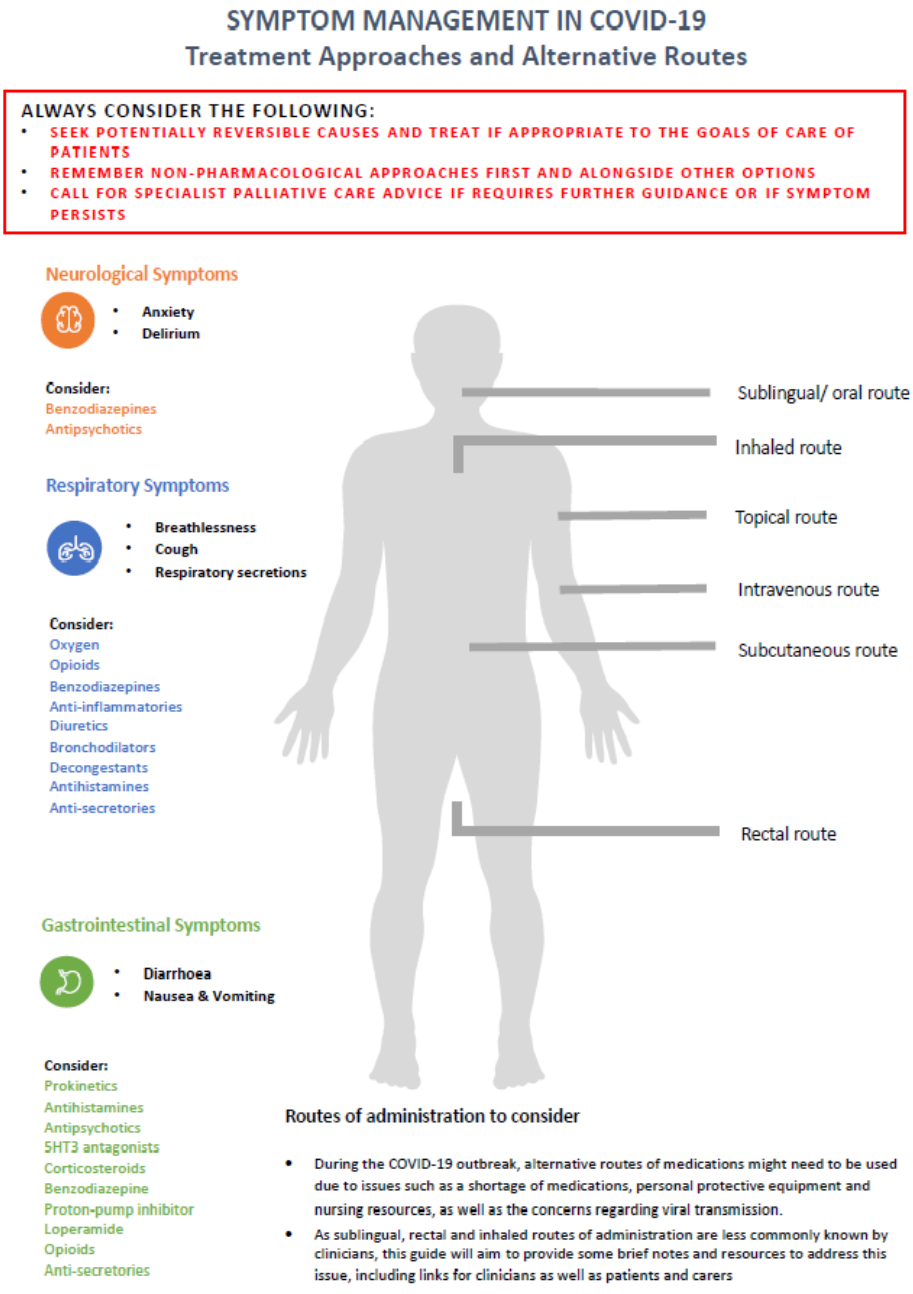

Figure 1. Treatment approaches and alternative routes for consideration in symptom management for COVID-19.

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Summary Table: Available Routes of Medications for Symptom Management for COVID-19

Class		Available routes								Symptoms					
		PO	SL	SC	IV	IM	TOP	PR	Inh	Breathlessness	Cough	Secretions	Anxiety/ Agitation	Nausea/ Vomiting	Diarrhoea
Opioids	Morphine	•	•	•	•	•		•		•	•				•
	Hydromorphone	•	•	•	•	•				•	•				•
	*Fentanyl**		●	●	●	●	●			●	●				●
	*Methadone**	●	●	●				●			●				●
	Codeine	•								•	•				•
	Dextromethorphan	•									•				
	Dihydrocodeine	•									•				
Benzodiazepines	Lorazepam	•	•							•			•	•	
	Clonazepam	•	•	•						•			•		
	Midazolam		•	•	•					•			•		
Anti-psychotics	Haloperidol	•	•	•		•							•	•	
	Olanzapine	•	•	•		•							•	•	
	Risperidone	•	•										•		
	*Levomepromazine**	●	●	●		●							●	●	
Anti-emetics	Metoclopramide	•		•	•	•								•	
	Domperidone	•												•	
	Cyclizine	•	•	•	•	•								•	
	Ondansetron	•	•	•	•	•								•	•
	Prochlorperazine	•				•								•	
Diuretics	Frusemide	•	•	•	•	•				•					
	Bumetamide	•								•					
Anti-inflammatory	Dexamethasone	•	•	•	•					•	•			•	
	Sodium cromoglycate								•	•					
Antihistamine	Promethazine	•			•	•				•				•	
	Loratadine	•									•				
	Diphenhydramine	•									•				
Anti-secretory	Glycopyrrolate			•	•	•						•			
	Hyoscine butylbromide	•	•	•	•	•						•			•
Anti-diarrhoeal	Loperamide	•													•
Decongestants	Phenylephrine	•									•				
	Pseudoephedrine	•									•				
Proton pump inhibitors	Lansoprazole	•	•											•	
Bronchodilators	Salbutamol								•	•					
	Ipratropium								•	•		•			
Oxygen	Oxygen								•	•					

Drugs in red italics* *– seek specialist palliative care advice****. Abbreviations: PO - per oral; SL – sublingual; SC – subcutaneous; IV – intravenous; IM – intramuscular; TOP – topical; PR – per rectal; Inh – inhaled.*

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Introduction

Infection from COVID-19 has become a global pandemic. Subsequently, the provision of care by healthcare services worldwide has been seriously impacted and an inevitable compromise of patient care has ensued.

Palliative care, aimed at optimising comfort and relieving distress, is imperative at this time. Nonetheless, there is a rising concern around the ability to effectively deliver conventional palliative care medications to patients in need due to the possibility of shortages in medication, medical devices (e.g. syringe drivers), protective personal equipment, and staffing resources.

There are currently guidelines targeting the symptom management of patients with COVID-19[1-2]. However, a guideline with an Australian focus, that incorporates alternative routes of treatment options, and considers the potential for scarce conventional treatments is currently lacking.

The aim of this working group, under the Australian and New Zealand Society of Palliative Medicine (ANZSPM) COVID-19 Special Interest Group, is to create a symptom management guideline that assists non-specialist palliative care clinicians in this context.

This guide **does not** replace the clinical judgement involved in the management of people affected by COVID-19. The nuances of caring for individual patients should be considered, as they demand an appreciation of them as a person, their symptom burden, co-morbidities, prognosis and goals of care.

For the ease of referencing by clinicians, the key resources and references are listed according to their relevant sections.

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SECTION 1: Routes of medication

- During the COVID-19 pandemic, alternative routes of medications might be required due to issues such as a shortage of medications and nursing resources, as well as the concerns regarding viral transmission.
- As sublingual, rectal and inhaled routes of administration are less commonly known by clinicians, this guide will aim to provide some brief notes and resources to address this issue:

Sublingual route – general advice

1. Ensure mouth is clean and moist to enhance delivery of medications.
2. If administering a liquid, higher concentration formulations are preferred to aid absorption.
3. If administering a tablet, crush the tablet and mix with 1mL of water, and draw up with a syringe for administration.
4. The patient will need to retain the sublingual medication for around 5 minutes for good effect.
5. The generally acceptable maximal volume for sublingual medication administration is 1ml. If a higher dose of medication is required, it is recommended to either split the required dose and repeat the administration in 10 minute intervals (e.g. to administer 2mL of 20mg morphine, give 1mL of 10mg first, then repeat in 10 minutes) or use another medication formulation with higher potency.
6. Videos for learning how to administer medication under the tongue can be used to teach staff, patients and family members:
    a. Hospice NZ: https://www.youtube.com/watch?v=l1v5F6ep5RM
    b. Canadian Virtual Hospice: https://www.youtube.com/watch?v=6m18xD6Hqs0

Rectal route – general advice

- A number of medications in tablet form can be administered via the rectal route.
- A specially formulated suppository is not required for efficacy – it merely assists in the retention of the medication.
- Ensuring an empty rectum prior to insertion of rectal medications against the rectal wall enhances drug absorption.
- The **rectal route is contraindicated** for neutropenic patients. Other relative contraindications include patients with thrombocytopenia, diarrhoea, anorectal disease, and prior abdominoperineal resection.

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Inhaled routes – general principles

- There are some concerns that the use of nebulisers may facilitate the spread of COVID-19.
- An alternative is the use of inhalers with spacers to deliver medication locally to the lungs.
- In situations where patients may not be able to coordinate the use of spacers (e.g. delirium or terminal phase), consider a face mask attached to a spacer (commonly used in the paediatric setting).

Key Resources

Key resources for sublingual routes

- Canadian Virtual Hospice. *Administering medications: Giving medications under the tongue*. 2012 [cited 2020 8th of Apr]; Available from: https://www.youtube.com/watch?v=6m18xD6Hqs0.
- Reisfield, G.M. and G.R. Wilson, *Rational Use of Sublingual Opioids in Palliative Medicine.* Journal of Palliative Medicine, 2007. **10**(2): p. 465-475
- Hagen, N.A., K. Fisher, and C. Stiles, *Sublingual methadone for the management of cancer-related breakthrough pain: a pilot study.* Journal of palliative medicine, 2007. **10**(2): p. 331-337.
- Hospice New Zealand. *Symptom control for people with COVID-19*. 2020 [cited 2020 8th of Apr]; Available from: https://www.hospice.org.nz/wp-content/uploads/2020/04/Symptom-control-for-COVID-19-patients-V3-17-April-2020.pdf.

Key resources for rectal route

- Samala, R.V. and M. Davis. *Palliative Care Per Rectum*. 2020 [cited 2020 8th of Apr 2020]; Available from: https://www.mypcnow.org/fast-fact/palliative-care-per-rectum/.
- Warren, D.E., *Practical use of rectal medications in palliative care.* Journal of pain and symptom management, 1996. **11**(6): p. 378-387.

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Key resources for inhaler with spacer and mask use

1. **Video of spacer use in competent adults without mask**
   a. National Asthma Council. *How to use a Standard MDI (puffer) and Spacer*. 2020 [cited 2020 27th of Apr]; Available from: https://www.nationalasthma.org.au/living-with-asthma/how-to-videos/how-to-use-a-standard-mdi-and-spacer.
2. **Video of spacer use in other Languages (Mandarin, Nepali, Vietnamese, Korean, Bangla, and Arabic)**
   b. National Asthma Council. *Aiming for asthma improvement in children program*. 2020 [cited 2020 27th of Apr]; Available from: https://www.nationalasthma.org.au/health-professionals/how-to-videos.

3. **Video of spacer and mask use for patients unable to coordinate a spacer (use the same strategies as in the paediatric settings)**
   c. Nationwide Children's Hospital. *Asthma how-to: How to use an inhaler with a spacer and mask*. 2013 [cited 2020 27th of Apr]; Available from: https://www.youtube.com/watch?v=f-O8etEE6kQ.

SECTION 2: Symptom Management of COVID-19

Common Symptoms Observed in COVID-19

- Common symptoms reported for COVID-19 affected patients can be classified into respiratory, neurological and gastrointestinal symptoms, as listed below. The management of COVID-19 related symptoms will be explored using these categories:
  1. Respiratory symptoms
     a. Breathlessness
     b. Cough
     c. Respiratory secretions
  2. Neurological symptoms
     a. Anxiety
     b. Delirium
  3. Gastrointestinal symptoms
     a. Diarrhoea
     b. Nausea and vomiting

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- The sections below are categorised according to the symptoms associated with COVID-19. The broad range of therapeutic approaches are listed to allow for flexibility in symptom management when the usual conventional approach is deemed not feasible.
- As a general principle, the potentially reversible causes for the associated symptoms should be assessed and managed if this is deemed appropriate by the goals of care of the affected patients.
- Non-pharmacological approaches should be considered before and alongside pharmacological approaches.
- First line conventional treatment strategies should be attempted, and when these are not possible, then consider the alternative options as evidence for these are limited.

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Abbreviations used in the Symptom Management Tables Below:

Amp: Ampoule

BD: twice a day

CR: Controlled release

CSCI: Continuous subcutaneous infusion

EPSE: Extrapyramidal side effects

IM: Intramuscular

Inh: Inhaled

IR: Immediate Release

IV: Intravenous

MDI: Metered-Dose Inhaler

N/A: not available

OTC: Over the Counter

PO: Per Oral

PR: Per rectal

QID: four times a day

SC: Subcutaneous

SL: Sublingual

TDS: three times a day

TOP: Topical

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Breathlessness

General Principles of Breathlessness Management:

The general principles of breathlessness management are specified in Figure 1:

- Treat potentially reversible causes and complications of COVID-19 such as pulmonary embolism, cardiac complications and anaemia if deemed appropriate for the patients' goals of care[1].
- Utilise non-pharmacological approaches.
- Utilise opioids ± benzodiazepines as mainstay pharmacological approaches with oxygen if there is hypoxaemia.
- The sole use of pharmacological therapies is unlikely able to eradicate dyspnoea and need to use in adjunct with other non-pharmacological measures - pharmacological interventions can help "take the edge off".

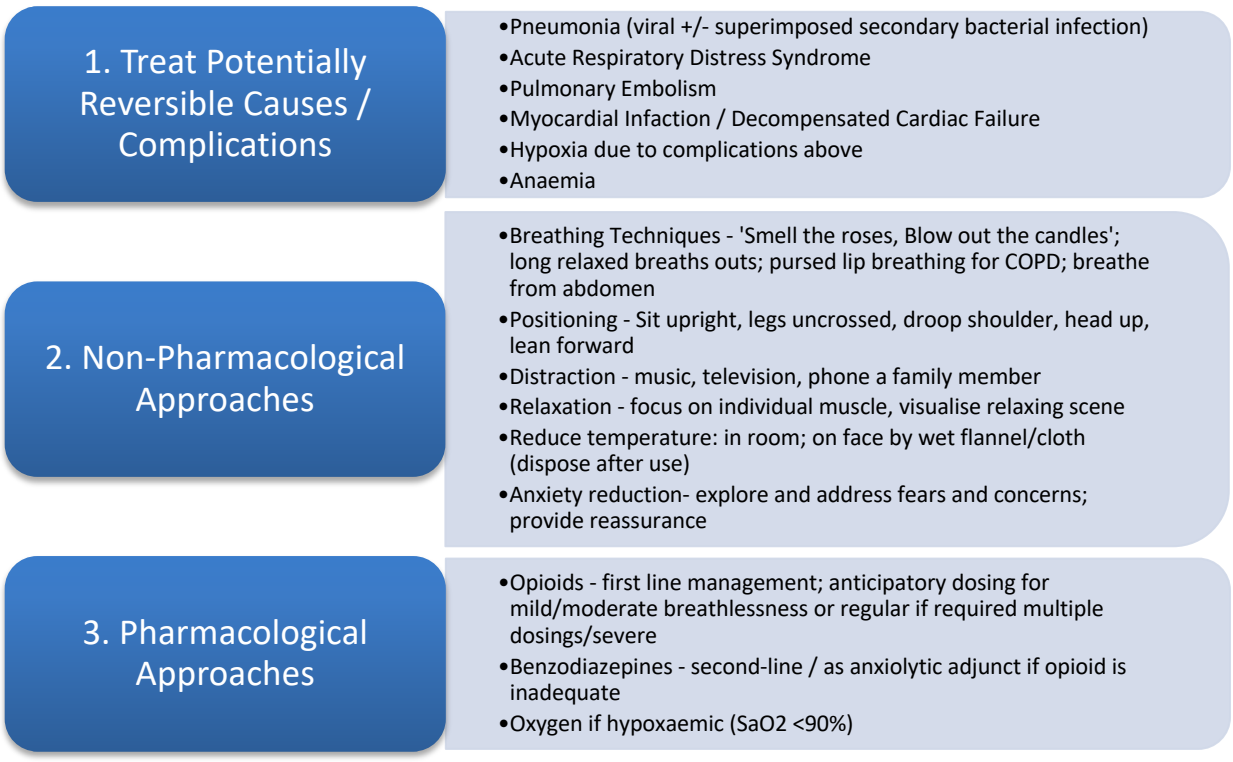

Figure 1. General principles of breathlessness management[1-4].

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Non-Pharmacological Treatments:[1-4]

- Consider use of the 'Breathing, Thinking, Functioning' model to guide a personalised, structured approach[1].
- Breathing techniques - 'Smell the roses, blow out the candles'; long relaxed breaths outs; pursed lip breathing for COPD; breathe from the abdomen
- Positioning - sit upright, legs uncrossed, droop shoulder, head up, lean forward
- Distraction - music, television, phone a family member
- Relaxation - focus on individual muscle, visualise relaxing scene
- Reduce temperature - in room; on face by wet flannel/cloth (dispose after use)
- Anxiety reduction - explore and address fears and concerns; provide reassurance

Pharmacological Treatments:

N.B. IF SYMPTOMS PERSIST SEEK SPECIALIST PALLIATIVE CARE ADVICE

Drug	Route	Preparation	Dosing / Frequency	Notes
Oxygen/Non-invasive Ventilation[1-4]				
Oxygen	Inh	N/A	(As per oxygenation requirement)	• Lack of role for oxygen if patent is not hypoxaemic. • In the setting of CO_2 retention, the target SaO_2 should be lowered (e.g. 88-92%).
Additional notes for oxygen: • Where oxygen provision is scarce, it should not be routinely provided. • For those who are dying and not for further life-prolonging treatment, a careful trial of downward titration can be considered according to subjective dyspnoea while using other pharmacological treatments. Oxygen may be able to be withdrawn completely. • The use of low-flow nasal cannula (compared to the higher flow devices) may allow for closer contact with family members whilst dying.				

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- High flow nasal oxygen or non-invasive positive pressure ventilation poses of a risk of spread, and generally are not recommended.
- If high flow nasal oxygen or non-invasive positive pressure ventilation needs to be considered, decisions should balance the likelihood of patient benefits against the risk of infection for healthcare workers. Single rooms, or negative pressure rooms, need to be used with appropriate contact, droplet and airborne precautions.

Opioids*Δ ǂ[5-23]

Re: opioids safety:

- Generally, the principle of "start low, go slow" of opioid titration to symptom response should be adhered to with regular monitoring – but in the COVID-19 context, rapid titration with regular monitoring taking an early aggressive approach may be required.
- Titrate opioids to effect to 30mg of oral morphine equivalent for opioid naïve patients[9]. When reaching this, consider the use of adjuncts. For opioid tolerant patient, titrate according to response.
- For breathlessness, there is more evidence for titration using slow release opioids (i.e. Kapanol 10mg /day increments) rather than using PRN oral opioids. The slow release formulations are associated with lower peaks and higher troughs and thus less risk of toxicity[5, 9, 23].
- The dosing of PRN opioids for breathlessness is lower than that required for pain.
- The exact opioid dosing required for optimal breathlessness control needs to be titrated separately from that of pain, bearing in mind opioid tolerance for those already on opioids due to other indications such as pain.
- **Both hydromorphone and fentanyl are significantly more potent than morphine**.
- There is evidence that oxycodone does not work for breathlessness[20].
- The administration of IV opioids requires close monitoring and must follow local hospital policies

Morphine	PO	IR Oral liquid (mg/mL): 1, 2, 5, 10 IR Oral tablet (mg): 10, 20, 30	2.5mg Q1h PRN	Strongest evidence of efficacy compared to other opioids[22]. Best evidence/practice is to titrate with slow release morphine (e.g. Kapanol 10mg/day) rather than immediate release to avoid high peaks and low
		CR tablet (12-hr) (MS Contin / Momex) (mg): 5, 10, 15, 30, 60, 100, 200mg	10mg Daily (Kapanol) / MSContin 5mg BD	

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		CR Oral liquid (12-hr) (MS Contin suspension) (mg): 20, 30, 60, 100, 200 CR capsule (12- or 24-hr) (Kapanol) (mg): 10, 20, 50, 100 CR capsule (24-hr) (MS Mono) (mg): 30, 60, 90, 120		troughs and the risk of opioid overdose associated with the titration of PRN oral immediate release opioid given the fast onset and short duration of episodic dyspnoea. In the setting of acute distress, titration using parenteral route is preferable due to its fast onset of action and ability to rapidly titrate[24].
	SC	Amp (mg/mL): 5, 10, 15, 20, 30, 50, 80	1-2.5mg Q1h PRN Or 10mg CSCI (or 5mg CSCI if renally impaired but hydromorphone not available)	In the setting of acute distress, titration using CSCI is preferable compared to PRN or Q4h dosing, as it optimises breathlessness control with the lower peaks and higher troughs while minimising exposure to staffs and medication wastage[24].
	SL	IR Oral liquid: 10mg/mL	1-2.5mg Q1h PRN	Bioavailability: approx. 20-60% [Δ14] .
	PR	CR Oral tablet (MS Contin) (mg): 5, 10, 15, 30, 60, 100, 200	5mg BD	PR = PO dose.

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	SC/ IV/IM	Amp (mg/mL): 5, 10, 15, 20, 30, 50, 80	1mg Q1h PRN	
Hydromorphone **(approximately 5 times more potent than morphine)** -	PO	IR Oral liquid: 1mg/mL IR Oral tablet (mg): 2, 4, 8	1mg Q1h PRN	Useful alternative to morphine in eGFR <30mL/min/m2 and hepatic impairment. In NSW, NSW Health recommends prescription of hydromorphone to be restricted to only pain and palliative care services. Limited evidence of efficacy compared to morphine[21, 22].
		CR Oral tablet (mg): 4, 8, 16, 32, 64	4mg daily PO CR	Use of higher dosage requires opioid tolerance – e.g. patients already on opioids for pain.
	SC/ IV/IM	Amp (mg/mL): 2, 10, 50	0.25-0.5mg Q1h PRN	
	SL	IR Oral liquid: 1mg/mL	0.25-0.5mg Q1h PRN	Bioavailability of SL administration of hydromorphone: approximately 25%[14].
Fentanyl ***(approximately 100 times more potent than morphine)***	*SC / SL / IV/IM / TOP*	***Seek Specialist Palliative Care Advice***		*Limited evidence of efficacy[6, 11, 21, 22].* *Useful in renal/hepatic impairment without*

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				hydromorphone access. *Certain routes /formulation requires significant opioid tolerance (e.g. lozenges).*
Benzodiazepines*[18, 25-28] (See anxiety / agitation section) Adjunct to opioids if suboptimal control, with anxiety component				
Anti-inflammatory				
Sodium Cromoglycate	Inh with spacer +/- mask	5mg/dose	4 puffs inh BD-QID	Steroid-sparing option.
Dexamethasone	PO/SL	Oral tablet (mg): 0.5, 4 (crush for SL)	4-16mg/day	As the evidence for dexamethasone in COVID-19 is evolving, for up-to-date information, please refer to the Australian National COVID-19 Clinical Evidence Taskforce document: Australian Guidelines for the Clinical Care of People with COVID-19[29]
	SC	Amp: 4mg/mL		
Diuretics[30-32]				
Frusemide/ Furosemide	PO	Oral tablet (mg): 20, 40 Oral liquid: 10mg/mL	20-40mg daily, titrate to response	
	IV/IM	Amp: 20mg/2mL	20-60mg PRN Or regularly via CSCI	

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	SC	Amp: 20mg/2mL	20-60mg PRN Or regularly via CSCI	Use IV dose - SC bolus can be given undiluted as a push. If concerned about high volume SC, then give as CSCI.
	SL	Oral liquid: 10mg/mL Or Amp: 20mg/2mL	20-60mg PRN	Bioavailability around 60%.
Bumetanide	PO	Oral tablet: 1mg	1-2mg PRN or regular dosing (like timing for frusemide)	Bioavailability ≥80%. Bumetanide 1mg PO = frusemide 40mg PO.
Bronchodilators				
Salbutamol	Inh with spacer +/- mask	100mcg/dose MDI	2-6 puffs PRN Q20min	**Australian Commission on its position statement late April 2020 advised against nebulisation due to the concern of inducing cough and COVID-19 spread[33].**
Ipratropium	Inh with spacer +/- mask	21mcg/dose MDI	PRN 2-4 puffs Q2h	
Phenothiazines				
Promethazine	PO	Oral tablet (mg): 10, 25 Oral liquid: 1mg/mL	10-25mg TDS PRN	Maybe useful as adjunct to opioids and for sedation/allergic symptoms[34].
	IM/IV	Amp: 25mg/mL	10-25mg TDS PRN	

*If titrated well with regular assessment of patients, respiratory depression and CO^2 retention are unlikely even when using opioids and benzodiazepine combination therapy[8, 15, 25].

†PR opioids dosing are the same as oral opioid dosing due to the bioavailability. Both PR immediate release and sustained release opioids have been used in treatment of palliative care patients with effect[19].

Δ Sublingual opioids administration generally results in a better bioavailability than that of oral, but still have significant fluctuation of bioavailability depend on the type of opioids (lipophilic vs hydrophobic) ranging from 20%-100%[14]. Conversion of sublingual opioids dosage to non-sublingual dosage therefore might be challenging and need to be accounted for on a case-by-case basis.

ŧOpioid conversion calculator: https://www.emrpcc.org.au/uploads/135/Opioid-Conversions-May-2016.pdf

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⚠ Use of Fans in Non-Pharmacological Management of Breathlessness

- The use of fans to relieve breathlessness in people with suspected or confirmed COVID-19 is controversial.
- Several countries and many health services have advised against the use of fans due to theoretical concerns around droplet spread, though the evidence is limited.
- The risks and benefits of the use of fans should be considered on a case-by-case basis in the context of local health and safety regulations.
- If a fan is going to be used, the following precautions are advised:
    - A minimum of 2 metres social distance should be maintained at all times while the fan is running
    - The fan is positioned such that the 'fan draft' is directed back to the person, rather than oscillating side to side. Handheld fans are preferred
    - The fan is switched off once symptoms settle or if close contact is required
    - Wear personal protective equipment for close personal cares
    - Recommend closed door in a single room to reduce the risk of spread

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Cough

Non-Pharmacological Treatments[1]:

- Humidify room air
- Small sips of oral fluids
- Honey & Lemon in warm water (avoid honey if <1yr old)
- Sucking on cough drops or hard sweets
- Avoid patient laying on their back

Pharmacological Treatments[1-2]:

N.B. IF SYMPTOMS PERSIST SEEK SPECIALIST PALLIATIVE CARE ADVICE

Drug	Route	Preparation	Dosing / Frequency	Notes
Opioid-based* opioids for shortness of breath can also be used as first line treatment for cough				
Codeine	PO	Oral tablet: 30mg Oral liquid: 5mg/mL	15-60mg QID PRN (Max 240mg/day)	OTC - Use if traditional opioids not available
Dihydrocodeine	PO	Oral liquid 19mg/10mL	9.5-19mg Q4-6h PRN	OTC – Use if traditional opioids not available
Dextromethorphan	PO	Oral liquid	15-30mg Q4h PRN (Max 120mg/day)	OTC - Use if traditional opioids not available
Methadone	*PO/SC/SL/PR*	*Seek Specialist Palliative Care Advice*		
Decongestants				
Phenylephrine	PO	Oral tablet: 10mg	10mg Q4h PRN	OTC – For post-nasal drip
Pseudoephedrine	PO	Oral tablet: 60mg	60mg Q4-6h PRN (Max 240mg/day)	
Anti-histaminergic				
Loratadine[1]	PO	Oral tablet: 10mg Oral liquid: 5mg/mL	10mg daily	OTC
Diphenhydramine	PO	Oral liquid	25mg Q4h PRN	
Anti-inflammatory - See Breathlessness Section				

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Respiratory Secretions

General Principles:

- Respiratory secretions do not always need treating if they are not distressing for the patient.
- Education for family/friends about secretions may be all that is needed. Careful explanation that secretions are an expected part of the dying process and are usually not distressing for the patient can alleviate family and friends' concerns. Emphasis should be on non-pharmacological approaches and reassurance for family and friends.

Non-Pharmacological Treatments[1]:

- Music/white noise can be used to help reduce distress for family
- Re-positioning patient may help reduce secretion pooling
- Use suction as a last resort due to infection control issues and potential to cause distress

Pharmacological Treatments[1-5]:

- For those being actively treated, anticholinergic agents should be avoided as this may reduce the person's ability to clear secretions from the chest and there is limited evidence of their efficacy in this context.
- The evidence for pharmacological treatments to reduce secretions at end of life is minimal, with systematic reviews showing no treatment better than placebo[4-5].
- The below table is a guide of dosing suggestions to minimise the harm of anticholinergics if they are chosen to be used in the attempt to manage distressing respiratory secretions[4].
- Avoid saline nebulisers (aerosol generating as may induce cough)
- Avoid intravenous or subcutaneous fluids

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N.B. IF SYMPTOMS PERSIST SEEK SPECIALIST PALLIATIVE CARE ADVICE

Drug	Route	Preparation	Dosing / Frequency	Notes
Glycopyrrolate[1]	SC/IM/IV	Amp: 200mcg/mL	0.2mg Q4h PRN (Max 1.2mg daily)[4]	**Lack of benefit against placebo with risk of anti-cholinergic side effects – limit use to distressing secretions[4-5]** OTC
Hyoscine butylbromide	SC/IM/IV[1]	Amp: 20mg/mL	20mg Q1h PRN (Max 120mg daily)[4]	
	PO/SL[3]	Oral tablet (mg): 10, 20 (crush for SL)	20mg Q1h PRN (Max 120mg daily)	

Anxiety

General principles:

- An element of anxiety or panic is almost universal when acute breathlessness is present.
- Anxiety can be further compounded by loss of family support and social isolation during the COVID-19 pandemic.
- Remember psychological, social and existential causes for distress and anxiety.
- Explore and address any underlying concerns, as many patients are fearful of suffocation.
- Remain calm and provide reassurance.
- Utilise non-pharmacological management strategies when the level of anxiety is low enough to allow this. Strategies to consider include controlled breathing exercises, distraction and relaxation therapies (See “Non-pharmacological Treatments” in Breathlessness section above).
- Mainstay of pharmacotherapy is benzodiazepines when prognosis is short – see benzodiazepine section of the “Pharmacological Treatments of Delirium” table below.

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Delirium

General principles:

- Delirium may occur in any patient with acute illness and is a poor prognostic sign. It is highly prevalent in patients who are in the last hours-days of life[1].
- Delirium may be the sole presenting symptom of COVID-19 for some patients, especially in the frail elderly population[2-4].
- Screening for delirium should be part of the regular assessment of a COVID-19 patient[5]. The Confusion Assessment Method and the Nursing Delirium Screening Scale are validated instruments to screen for delirium in the palliative care population[6-7].
- Delirium can be hypoactive (with withdrawal and reduction in activity – more common but often unrecognised), hyperactive (with agitation and hypervigilance) or a combination of both.
- It is important to identify and reverse/manage the possible underlying causes or differential diagnosis of the manifested symptoms such as urinary retention, constipation, pain, hypoxia and withdrawal states (e.g. smoking, alcohol, benzodiazepines).
- In the COVID-19 context, there are other additional factors which can promote fear and agitation of patients, such as the clinicians wearing PPE, isolation and limitation of visitors.
- Non-pharmacological measures should be utilised in all patients with delirium (listed below).
- The use and choice of pharmacological therapy in the setting of delirium needs to be tailored to specific symptoms of delirium individually, not as a "blanket intervention" to all cases of delirium (see "Pharmacological Treatments of Delirium" table below). **When prescribing, the exact indications and intentions should be specified** (e.g. 'distressing hallucinations with risk to self and others with the intent of maintaining alertness' vs 'agitation from breathlessness and anxiety with the intent of sedation')[8].
- Palliative sedation may be indicated in patients with intractable symptoms or where agitation is causing a risk of harm to the patient, their family or staff attending to them. It should only be considered in the terminal stage of the illness with expected prognosis of hours or days at most[9-10]. Appropriate consenting process with patient during lucid period of delirium +/- family members via a shared decision-making process or with proxy decision makers if the patient is not capable of making decision for palliative sedation is strong recommenced if the context allows[6].

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Non-Pharmacological Treatments of Delirium:[1-2]

- If possible, optimise environment (as infection control concerns due to COVID-19 place certain restrictions): Manage in a low stimulus environment where possible; Support with sleep hygiene; Use reorientation strategies (e.g. clock, calendar, radio, room board etc); and avoid unnecessary patient movement between wards/rooms.
- Ensure sensory aids (e.g. glasses and hearing aids) are available and used; ensure adequate lighting.
- Ensure proper hydration and nutrition – make sure patients have their dentures.
- Break down complicated tasks.
- Ensure effective communication, remembering that those with sensory impairments may not be able to hear or use lip reading to assist in understanding if clinicians have masks on. Consider written communication via room boards or paper on clipboards.
- Consider involving family to assist if possible, acknowledging that infection control measures may not allow in person contact. In which case, the use of communication technology (e.g. telephones, video calls via FaceTime, WhatsApp etc.) should be explored.
- Consider side room if available, consider 1:1 nursing & aim for staff continuity.
- Do not confront false beliefs (illusions, delusions) but offer reassurance and foster independence, acknowledge distress, and validate feelings.

Pharmacological Treatments of Delirium:

N.B. IF SYMPTOMS PERSIST SEEK SPECIALIST PALLIATIVE CARE ADVICE

Drug[1-7]	Route	Preparation	Dosing / Frequency	Notes
Anti-psychotics -The indications and intentions should be specified when these medications are prescribed				
Haloperidol	PO	Oral tablet (mg): 0.5, 1.5, 5	0.5mg Q4h PRN	1st line for perceptual disturbance with the intention of non-sedation at low dose. Typical antipsychotic - Higher risk of EPSE than other atypical antipsychotics.
	SL	Oral liquid: 2mg/mL		
	SC / IM	Amp: 5mg/mL		
Risperidone	PO	Oral tablet (mg): 0.5, 1	0.5mg BD PRN Titrate up to 2mg/day if necessary	Alternative to haloperidol if able to use PO or SL routes as less sedating at low dose than
	SL	Oral liquid: 1mg/mL		

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				olanzapine or levomepromazine. Atypical anti-psychotic – less EPSE risk.
Olanzapine	PO/SL	Oral disintegrating tablet or wafer (mg): 5, 10, 15, 20	5mg Q4h PRN	More sedating than haloperidol or risperidone[7]. Atypical anti-psychotic – less EPSE risk.
	SC/ IM	10mg powder	5-10mg PRN* *If necessary, give further doses (up to 10mg) at 2 and 6 hours after initial dose, to maximum 30mg/day	
Levomepromazine	*PO/SL/SC /IM*	***Seek Specialist Palliative Care Advice***		*Special Access Scheme medication.* *Used if above anti-psychotics and benzodiazepines are inadequate to manage agitation (intend for sedation).*
Benzodiazepines				
Lorazepam	PO/SL	Oral tablet: 1mg	0.5mg Q4h PRN	Useful if still conscious Consider for distressing breathlessness /anxiety without the aim of sedation / severe distress with risk of harm / sedation
Midazolam	SL/SC/IV	Amp: 5mg/mL, 15mg/3mL	2.5-5mg Q1h PRN Or CSCI 5-10mg/day as an adjunct to an opioid for distressing dyspnoea at rest	Consider for distressing breathlessness /anxiety / severe distress with risk of harm / palliative sedation (30mg/day CSCI) Large doses may be required for

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			For respiratory CRISIS in a dying patient: 5mg Q15min until comfort achieved	significant respiratory distress. (Consider seeking Specialist Palliative Care advice if > midazolam 30mg/day is required)
Clonazepam	PO	Oral tablet (mg): 0.5, 2	0.5mg Q8h PRN	This medication has a long half-life (30-40 hours) – ongoing frequent doses can cause accumulation and excessive sedation SL drops may be easier for non-professional carers to administer if patients are unable to swallow
	SL	Oral liquid: 2.5mg/mL	2-3 drops (0.2 – 0.3mg) *or* 0.1mL (=2.5 drops) Q8h PRN	
	SC	Amp: 1mg/mL	0.5mg Q8h PRN	

Gastrointestinal

- The below pharmacological interventions are listed in the order of recommendations in the current context.
- COVID-19 may manifest as gastrointestinal symptoms[1-2]. A cross-sectional, multicentred study revealed that nearly 50% of COVID-19 patients had gastrointestinal symptoms, with a majority of patients (84%) being anorexic, and a third having diarrhoea[2]. The presence of gastrointestinal symptoms is associated with poorer prognoses and can occur without the presence of respiratory symptoms[2].

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Pharmacological Treatments:

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Nausea

Drug[3-7]	Route	Preparation	Dosing / Frequency	Notes
Metoclopramide	PO	Oral tablet: 10mg	10mg Q4h PRN If regular: TDS	1st line If need pro-kinetic effect. (e.g. nausea worse with gastric distension)
	SC/IV/IM	Amp: 5mg/mL		
Haloperidol	PO/SL	Oral tablet (mg): 0.5, 1.5, 5 Oral liquid: 2mg/mL	0.25-0.5mg Q4h PRN If regular: BD	2nd line Central nausea – nausea to smell/sights
	SC/IV/IM	Amp: 5mg/mL		
Cyclizine	PO/SL	Oral tablet: 50mg (crush for SL)	12.5-25mg Q4h PRN If regular, TDS	3rd line Central nausea – nausea to smell/sights
	SC/IM/IV	Amp: 50mg/mL		
Olanzapine	PO/SL	Oral disintegrating tablet or wafer (mg): 5, 10, 15, 20	2.5-5mg Q4h PRN or TDS	3rd line Central nausea – nausea to smell/sights
	SC/IM/IV	10mg powder for injection		
Levomepromazine	PO/SL / SC/IM	Seek Specialist Palliative Care Advice	Seek Specialist Palliative Care Advice	Special Access Scheme medication
Ondansetron	PO/SL	Oral disintegrating tablet or wafer (mg): 4, 8	4-8mg Q4h PRN (Max 32mg/day)	Helpful if having diarrhoea
	SC/IV/IM	Amp: 2mg/mL		
Dexamethasone	PO/SL	Oral tablet (mg): 0.5, 4	2-4mg daily, BD	Inflammatory cause
	SC/IV	Amp: 4mg/mL		
Domperidone	PO	Oral tablet: 10mg	10mg Q4h PRN (Max 60mg/day)	Prokinetic with lack of EPSE

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Promethazine	PO	Oral tablet (mg): 10, 25	10-25mg TDS PRN (Max 75mg/day)	
	IV/IM	Amp: 25mg/mL		
Prochlorperazine	PO	Oral tablet: 5mg	5-20mg TDS PRN	Vertiginous nausea
	IM	Amp: 12.5mg/mL	12.5mg TDS PRN	
Lorazepam	PO/SL	Oral tablet: 1mg	0.25-0.5mg Q4h PRN	Anticipatory nausea
Lansoprazole	SL	Wafer: 30mg	30mg Daily-BD	If reflux mediated

Diarrhoea

N.B. IF SYMPTOMS PERSIST SEEK SPECIALIST PALLIATIVE CARE ADVICE

Drug[3-4]	**Route**	**Preparation**	**Dosing / Frequency**	**Notes**
Loperamide	PO	Oral tablet: 2mg	4mg initial, then 2mg after each motion	Comes as orally disintegrating tab
Opioids E.g. Codeine, etc as per cough and breathlessness sections above	PO/ SL/ SC/ TOP			
Hyoscine Butylbromide	PO/SL	Oral tablet: 10mg, 20mg (crush for SL)	10-20mg QID (Max 120mg/day)	Bioavailability of oral hyoscine butylbromide is poor (20%)
	SC/ IV/ IM	Amp: 20mg/mL		
Ondansetron	PO/SL	Oral disintegrating tablet or wafer (mg): 4, 8	4-8mg Q4h PRN (Max 32mg/day)	
	SC/IV/IM	Amp: 2mg/mL		

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THESE GUIDELINES SHOULD BE ADAPTED DEPENDING ON LOCAL PROTOCOL AND DRUG AVAILABILITIES. For further assistance, please contact THE PALLIATIVE CARE TEAM on _____.

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