

## Appendices

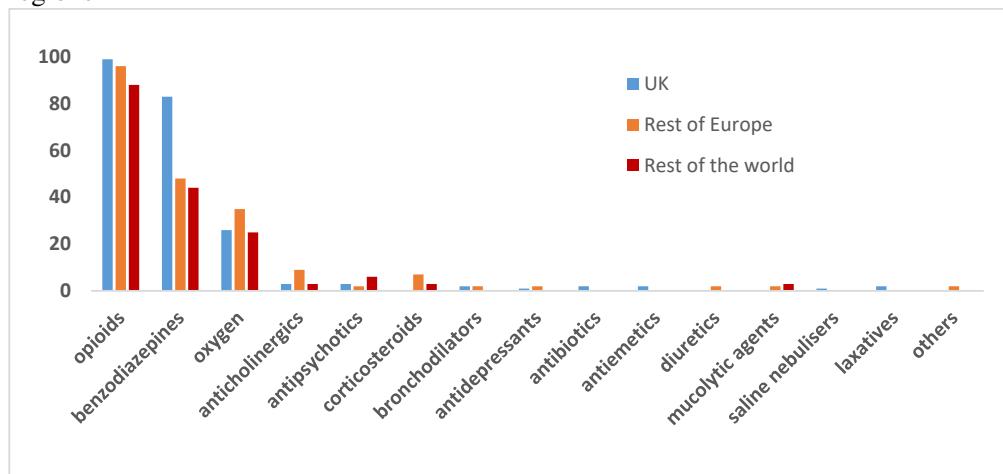
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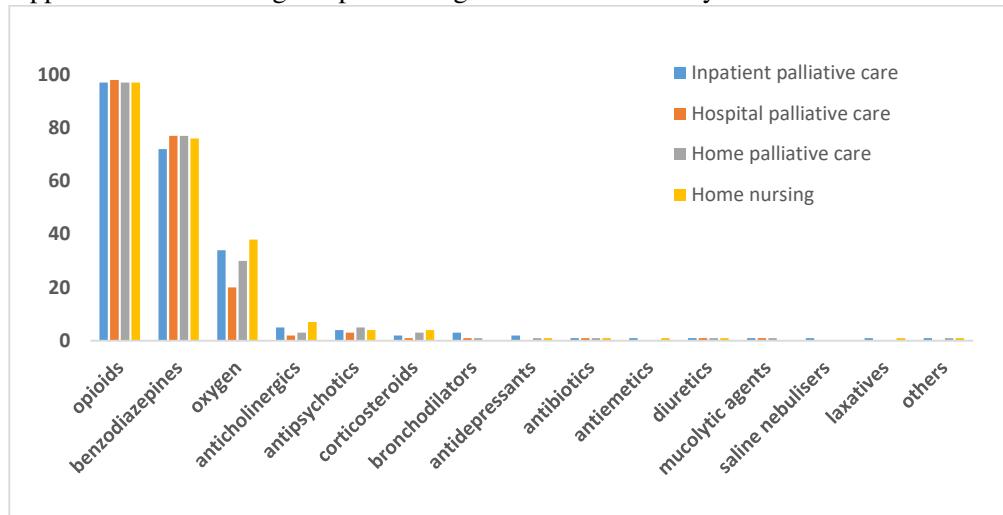
## Appendix 1: Questions analysed in this study

7.4 Do you have protocols for symptom management for COVID-19 patients?	Yes No Unsure
7.4a What sources of information did you use?	Locally developed guidance National Institute for Health and Care Excellence (NICE) National Health Service (NHS) Other
<b>Free text survey questions about management of symptoms in COVID-19</b>	
Breathlessness	
7.5 Which medicines and therapies do you usually prescribe?	
7.6 How effective do you find these? E.g. time to give relief and how well it works	
Agitation	
7.7 Which medicines and therapies do you usually prescribe?	
7.8 How effective do you find these? E.g. time to give relief and how well it works	
Fever/Shivering	
7.9 Which medicines and therapies do you usually prescribe?	
7.10 How effective do you find these? E.g. time to give relief and how well it works	
Cough	
7.11 Which medicines and therapies do you usually prescribe?	
7.12 How effective do you find these? (E.g. time to give relief and how well it works	
Pain	
7.13 Which medicines and therapies do you usually prescribe?	
7.14 How effective do you find these? E.g. time to give relief and how well it works	

### Appendix 2a: Percentage of prescribing for breathlessness by services in different world regions



### Appendix 2b: Percentage of prescribing for breathlessness by services in different settings



## Appendix 2c: Types of medicines prescribed for breathlessness

Opioids	morphine (n = 172), oxycodone (n = 26), fentanyl (n = 9), diamorphine (3), hydromorphone (4), alfentanil (3), buprenorphine (3), sufentanil (1), opioids* (n = 97)
Benzodiazepines	midazolam (n = 126), lorazepam (n = 58), diazepam (n = 3), oxazepam (n = 2), clonazepam (n = 1), anxiolytics/benzodiazepines* (n = 69)
Oxygen	oxygen (n = 76)
Anticholinergics	glycopyrronium (n = 6), hyoscine (n = 5), ipratropium (n = 1)
Antipsychotics	levomepromazine (n = 7), haloperidol (n = 3), antipsychotic* (n = 1)
Corticosteroids	cortisone (n = 3), corticosteroids* (n = 1)
Bronchodilators	salbutamol (n = 2), aminophylline (n = 1), bronchodilator* (n = 1)
Antidepressants	mirtazapine (n = 3), Serotonin-Norepinephrine Reuptake Inhibitor (SNRIs)* (1)
Antibiotics	antibiotics* (n = 4)
Anti-emetics	metoclopramide (n = 1), anti-emetic* (n = 3)
Diuretics	diuretics* (n = 1), furosemide (n = 1)
Mucolytic agents	acetylcysteine (n = 2)
Saline nebulisers	saline nebulisers (n = 2)
Laxatives	laxatives* (n = 3)
Other	paracetamol (n = 1)

Note that the above medicines were reported by services as medicines they prescribed for breathlessness. While some of them are indicated in breathlessness, others do not have an indication but could have been prescribed for other reasons e.g. laxatives and antiemetics for opioid-induced constipation and nausea or vomiting, respectively.

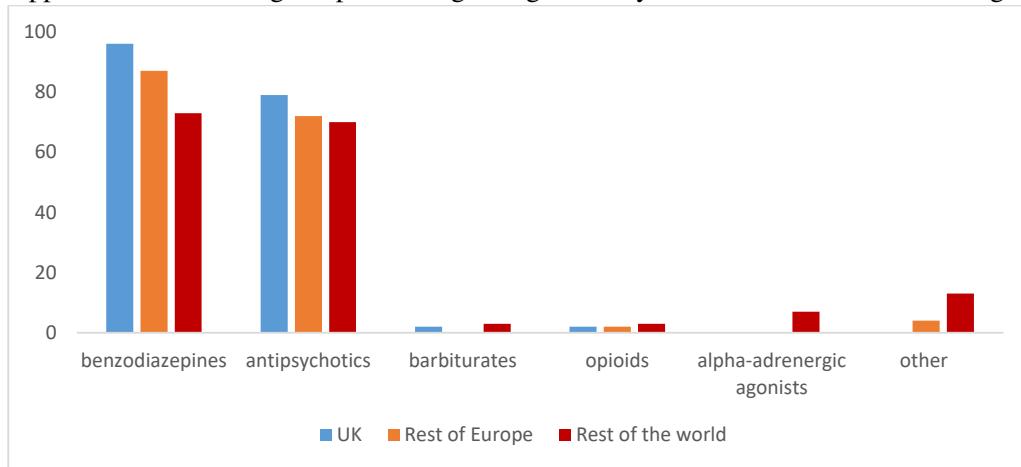
\*Type of medicine prescribed not stated

## Appendix 2d: Examples of quotes on the perceived effectiveness of medicines prescribed for breathlessness

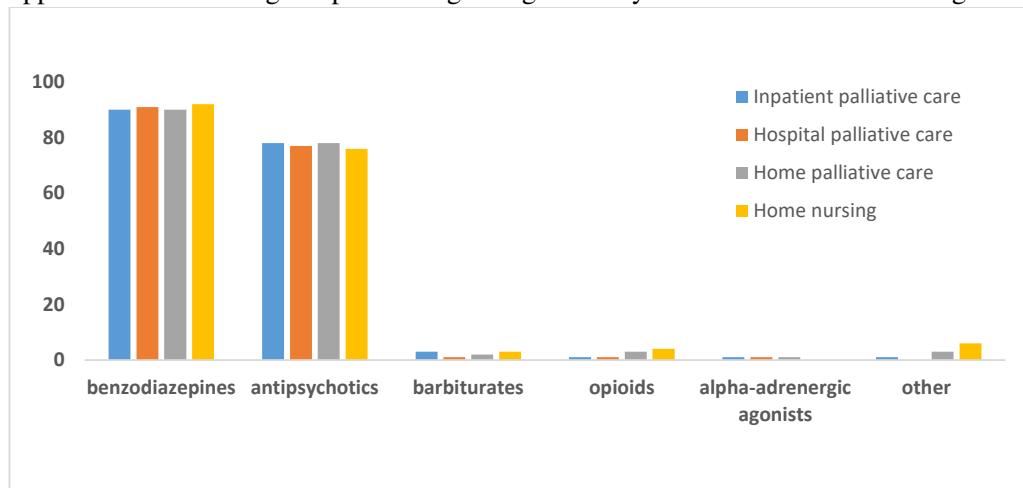
Effective	Some effectiveness
Usual effect, prescription would be usual timings and prns.	Effectiveness depends on overall condition of patients - in rapidly deteriorating patients midazolam has been most effective treatment.
Good effect from opioid and benzodiazepine.	Reasonably effective but obviously limited in people with advanced disease.
Effective. The majority of patients have required sc morphine and midazolam. Time to give relief is as usual. Approx 15-30 mins after sc given. Some patients have required dose escalation in their PRNs' and an increasing number are requiring CSCI's.	(~15minutes). Others seem not to be too breathless and become acutely symptomatic in last hour or two of life at which point oral medication is not obviously helpful and use of the subcut route is vital.
Effective - relief in about 20 mins.	Individual variation and dose dependent.
Effective for most patients many covid patients have been maintained on relatively low doses.	Difficult to predict - some patients get fair benefit in an expected time frame.
Good effect from morphine and benzodiazepine (usually 20-30mins for oral morphine to work), 5-10 mins for injectable or sublingual benzodiazepines...	Variable. Some patients very effective at low doses, others needing larger doses with less effect.

My consultant colleague at the acute trust found that with symptomatic EOLC COVID patient with ARD/pneumonitis she had to use much higher starting PRN doses of morphine 5mg + midazolam 5mg in combination. Then would need to commence CSCl Midazolam 20mg + morphine 20mg.	Variable, some patients with fibrotic lungs are not responding with the normal reduced respiratory rate following a prn you would normally expect to see but they do appear less distressed.
Morphine effective to reduce resp rate and any distress. may need larger doses/ more frequent dosing but only in a small number of patients.	Usually works well but it depends on the patient and their condition.
Morphine seems more effective than midazolam. Many patients too breathless to swallow so sc route more effective. We have seen patients, esp if v hypoxic and on high flow O2, needing higher doses of morphine e.g. 5mg sc repeated 2-3 times over an hour in order to settle, in opioid naive patients.	BZDs not so much, oxygen bringing relief - even when sats 90-92, does seem to help patients feel less breathless.
Drugs effective in usual doses. All patients have been hypoxic and have used Oxygen to maintain sats >90% with good effect.	Varies depending on the patient but usually effective.
In context of COVID 19 we found opioids to be very effective in relieving distressing dyspnoea, particularly when given SC if severe symptoms. In some instances with severe symptoms multiple SC doses were needed to gain symptom control MR Morphine (MST, Zomorph) preparations were helpful for patients to better tolerate CPAP/Venturi masks etc. Addition of Benzodiazepines was helpful where anxiety component. In most instances good relief within 30mins - 1hr if given Midazolam SC or Lorazepam SL.	Morphine sulphate has helped. We have not had success with oxygen as our residents can not tolerate face masks or nasal tubes.
Generally effective within 10-20 minutes and generally not massive doses were needed.	Somewhat effective
Within minutes. However oxygen has a perception of severe illness so patients and relatives are sometimes reluctant to accept its use.	Opiate works best and relieves within 15 minutes. Others variable response and time to relief.
Benzos and opioids tend to work in 10-20 minutes. Most people need small doses, but some need bigger doses.	...not quite effective in some cases, it's difficult due to some senior physicians afraid of opioids.

Appendix 3a: Percentage of prescribing for agitation by services in different world regions



## Appendix 3b: Percentage of prescribing for agitation by services in different settings



## Appendix 3c: Types of medicines prescribed for agitation

Benzodiazepines	midazolam (n = 215), lorazepam (n = 52), diazepam (n = 7), clonazepam (n = 2), oxazepam (n = 3), alprazolam (n = 1), lormetazepam (n = 1), benzodiazepines* (n = 36)
Antipsychotics	levomepromazine (n = 157), haloperidol (n = 132), olanzapine (n = 4), chlorpromazine (n = 3), quetiapine (n = 3), risperidone (n = 2), cyamemazine (n = 1), droperidol (n = 1), promazine (n = 1), antipsychotics* (n = 11)
Barbiturates	phenobarbitone (n = 5)
Opioids	morphine (n = 4), fentanyl (n = 1), hydromorphone (n = 1), oxycodone (n = 1), opioids* (n = 1)
Alpha-adrenergic agonists	dexmedetomidine (n = 2)
Other	anticholinergic (glycopyrrolate, n = 1), antidepressant (trazodone, n = 1), bronchodilator (albuterol, n = 1), diuretics* (n = 1), expectorant (n = 1), non-benzodiazepine sedative (clomethiazole, n = 1)

Note that the above medicines were reported by services as medicines they prescribed for agitation.

\*Type of medicine prescribed was not stated.

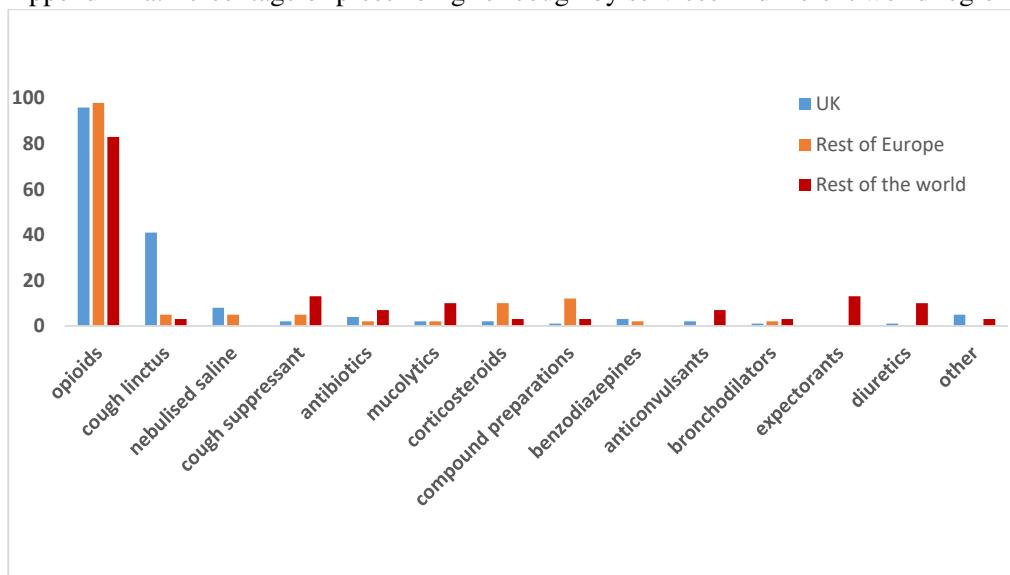
## Appendix 3d: Examples of quotes on the perceived effectiveness of medicines for agitation

Effective	Some effectiveness	Limited effectiveness
Good effect	Depends	Limited effectiveness
We have found that midazolam is usually effective but patients who have had an agitated delirium are needing a combination of midazolam and haloperidol. Takes 15-30 mins usually for effect. The majority of pts dying from COVID in the acute setting are	Midazolam and levomepromazine work the most effectively usually relieving problems within half an (h)our but again some of our covid patients have required larger doses. Haloperidol was said to be the drug of choice but I have not seen this	No(t) so well. especially for ventilated patients with agitation/delirium

requiring CSCI's in view of requiring PRN's with effect for symptom control	as being very helpful during this time when midazolam is not proving to be as helpful as we would like we would move to levomepromazine at larger doses - 12.5mg or 25mg	
Reasonably effective - small doses tending to give reasonable effect within a short time	Variable	Poorly, as in other causes of agitation
Fairly effective, and within < 1 hour	Individual variation and dose dependent	Barely good
20-30 minutes	Varied response, often titration of dose required	
30 mins - 1 hr and usually very effective	Depends on patient	
Generally well. Ward tendency to give low dose and need encouragement with haloperidol or levomepromazine	Midazolam is not always very successful for terminal agitation. Lorazepam for early signs of agitation can be successful	
Midazolam SC effective within 30mins-2hrs. If severe symptoms often needed to give multiple doses before symptom controlled. Levomepromazine was found to be more effective if there was a delirium component to agitation	For most patients about an hour but for some it has taken longer to settle with multiple PRNS. Not always effective at low dose and needing rapid dose escalation although the total dose needed is not always that high	
Good benefit, effective within 30 minutes, if patient not settled we recommend repeat dosing. Patients with terminal agitation due to covid have rarely survived beyond short hours after dosing	Variable in effectiveness. Some patients have required higher doses of levomepromazine for severe delirium/agitation	
Effective similar to normal care of the dying patient	Larger doses required for COVID group compared to usual practice in frail elderly.	
Usual effect, prescription would be usual timings and prns	Depends on each patient, usually has good effects within 20 minutes	
Found Midazolam very effective as long as did not have delirium in which case used Levomepromazine or haloperidol	Effectiveness depends on overall condition of patient - working within pre-existing local guidance frameworks has generally provided adequate symptom relief	
Effective but can need dose adjustment or early consideration of syringe pump	Variable depending on cause, but if effective generally within 45 minutes	
Generally effective within short time frame. Experience helps to be brave enough to use higher doses when indicated	Varies. Some patients have been very difficult to manage and have needed larger doses of levomepromazine	
Effective at the right dose. May need larger doses than usual	Generally good - patient and dose dependent	
Usually very effective within 10-20 mins	Depending on the reason for agitation and interindividual differences. Good	
If subcut 5 to 10 mins some covid patients needed increased and more regular doses as very agitated		
Generally effective. Time to relief - as expected from what is known(n) from existing experience/knowledge of pharmacology of the drug. Most patients who required this medication for symptom control required 10mg or less via syringe driver		
All work well- sometimes levomepromazine can be slower if doses used are not big enough. Phenobarbitone works quickly but we use least as definitely third line. Most commonly midazolam with		

levomepromazine added in if patient remains agitated		
Midazolam SC effective within 30mins-2hrs. If severe symptoms often needed to give multiple doses before symptom controlled. Levomepromazine was found to be more effective if there was a delirium component to agitation		
Usually extremely effective, depending on severity of agitation as to how much and how often it is needed		
Again 15 or so mins and - effective. Work well. If midazolam doesn't at 5mg s/c wd move to trying levomepromazine.		

Appendix 4a: Percentage of prescribing for cough by services in different world regions



Appendix 4b: Types of medicines prescribed for cough

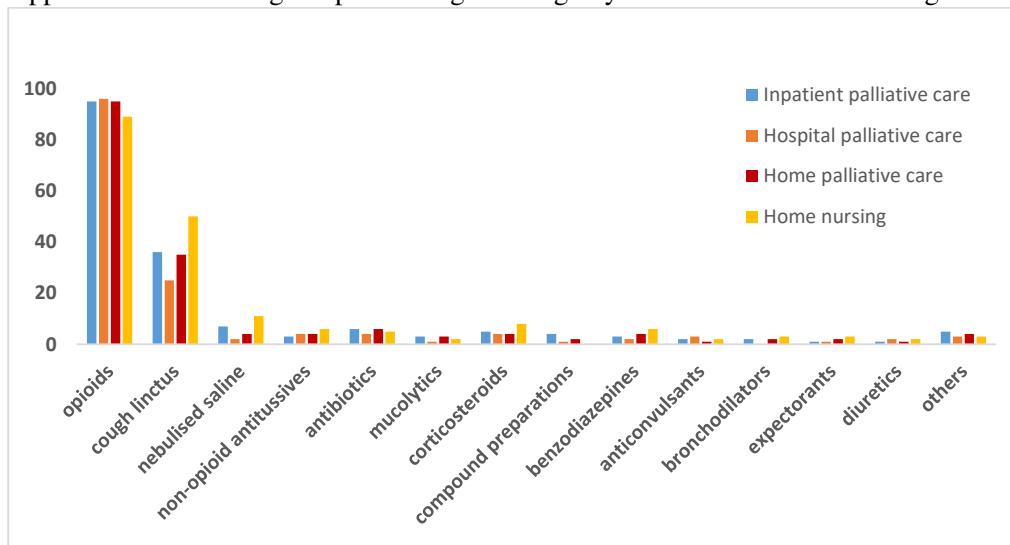
Opioids	morphine (n = 123), codeine (n = 75) <sup>a</sup> , methadone (n = 7), oxycodone (n = 6), paracodeine (n = 4), dihydrocodeine (n = 3), hydrocodone (n = 1), fentanyl (n = 1), sufentanil (n = 1), hydromorphone (1), diamorphine (1), opioids* (n = 79)
Cough linctus	cough linctus (n = 76)
Nebulised saline	nebulised saline (n = 10)
Cough suppressant	dextromethorphan (n = 3), benzonatate (n = 3), cough suppressant (n = 2), antitussives* (n = 2)
Antibiotics	antibiotics* (n = 11)
Mucolytics	acetylcysteine (n = 3), carbocisteine (n = 2), bromhexine (n = 1), mucolytics* (n = 2)
Steroids	cortisone (n = 3), steroids (n = 5)
Compound preparations	codeine and paracetamol (n = 5), cocillana/senega/ethyl morphine (n = 1), guaifenesin and codeine (n = 1)

Benzodiazepines	diazepam (n = 1), lorazepam (n = 3), midazolam (n = 4), benzodiazepine* (n = 2)
Anticonvulsants	gabapentin (n = 5)
Bronchodilators	salbutamol (n = 2), ipratropium (n = 1), terbutaline (n = 1)
Expectorant	ammonium and senega root (n = 1), guaifenesin (n = 2), expectorant (n = 1)
Diuretic	furosemide (n = 1), diuretic* (n = 3)
Others	anti-allergy drugs* (sodium cromoglycate, n = 2), sedatives* (n = 2), anticholinergic agents (hyoscine, n = 1), anti-reflux medicine* (n = 1), anti-secretory drugs* (n = 1), inhalers* (n = 1), local anaesthetics (nebulised bupivacaine, n = 1), menthol (n = 1), stimulant* (n = 1), vitamin (n = 1)

Codeine<sup>a</sup> includes codeine containing compound preparations

\*Type of medicine prescribed not stated

#### Appendix 4c. Percentage of prescribing for cough by services in different settings



#### Appendix 4d: Examples of quotes on the perceived effectiveness of medicines for cough

Effective	Some effectiveness	Limited effectiveness	Unclear effectiveness
Opioids are effective as expected in our experience.	All so-so. Very dependant on type of cough and interacting symptoms.	Limited relief	Not sure how effective
Effective in most cases	Variable depending on condition of patient	Not that good, though not a common Sx in the elderly	Unsure
They usually are effective within 15-20 mins with good results	Variable - I often find low dose methadone works most consistently if hycodan fails. If from pleural mets can be challenging to manage. Roughly 75% of time able to manage cough to acceptable level.	Impression that it didn't work very well, but used it only a few times. So not enough experience to give a valuable comment	
Seems to be effective	Dependent on cause	Not always effective	

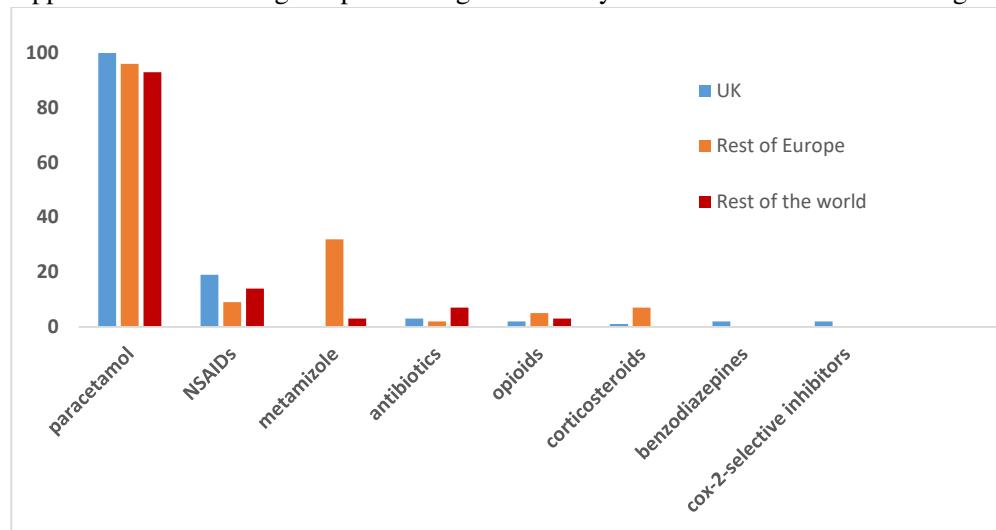
Usual effect, prescription would be usual timings and prns	Partial	Not a lot	
Was effective within 20 mins (NB only one person)	Variabile. Cough not been the major symptoms in our patients	Codeine not particularly morphine a little saline nebs a bit better	
30 mins - 1 hr and reasonably helpful	Sometimes it will work good	Poor response	
Generally effective	Depends on the patient and cause of cough	Not well	
	Linctus sometimes effective Morphine often effective within 30mins Nebs - variable effectiveness within short time (,15mins and sometimes immediately helpful)	Not as many patients have been sig troubled by cough as expected, but when it is a sig feature it has been difficult to stop	
	Individual variation and dose dependent	Not great	
	Variabile depending on individual patients	Not always effective - some cases on ongoing persistent cough	
	Some effectiveness. Dependant on patient.	Minimal change to symptoms	
	Not always effective but helps		

#### Appendix 5a: Types of medicines prescribed for fever

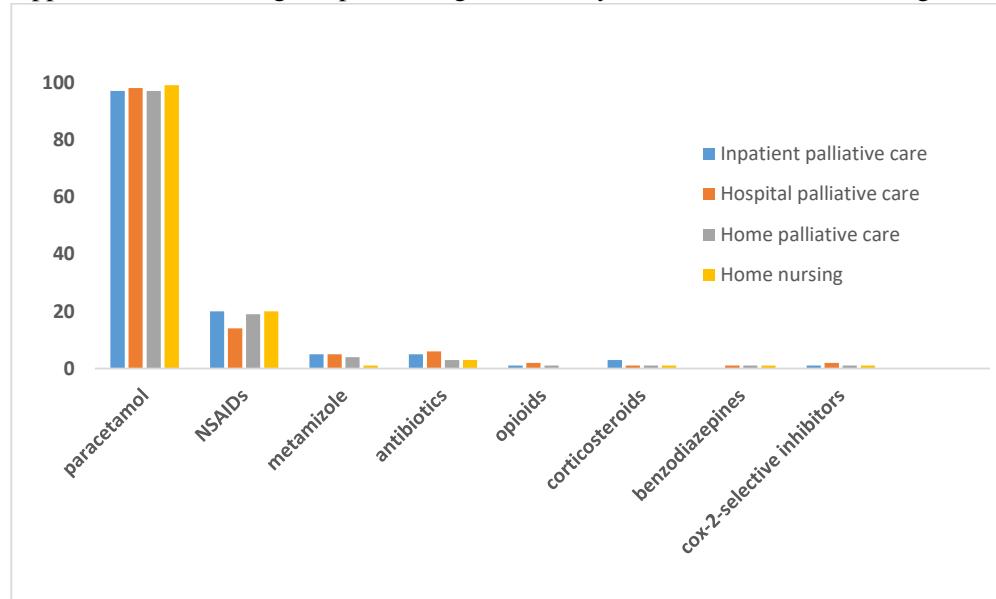
Paracetamol	paracetamol (n = 308)
NSAIDs	ibuprofen (n = 11), diclofenac (n = 7), ketorolac (n = 1), NSAID* (n = 29)
Metamizole	metamizole (n = 20)
Antibiotics	antibiotics* (n = 9)
Opioids	pethidine (n = 3), morphine (n = 1), opioids* (n = 2)
Steroids	cortisone (n = 1), steroids* (n = 4)
Benzodiazepines	midazolam (n = 3)
Cox-2 selective inhibitors	parecoxib (n = 4)

\*Type of medicine prescribed not stated. Note: NSAID = Non-Steroidal Anti-Inflammatory Drugs

Appendix 5b: Percentage of prescribing for fever by services in different world regions



Appendix 5c: Percentage of prescribing for fever by services in different settings



Appendix 5d: Examples of quotes on the perceived effectiveness of medicines for fever

Effective	Some effectiveness	Limited effectiveness	No effect	Unclear effectiveness
Good effect	Variable according to patient condition	Not always effective	Not effective	Unclear as to the benefit
Moderately effective. I am not seeing shivering as a symptom	Depends on patient response	Not particularly effective although can reduce fever a little.	Fever often resistant to anti-pyretics	Uncertain

Usually 1-2 hours	Some relief	Temperatures in COVID +ve patients have not always settled with paracetamol and needed NSAID 2nd line		
Within hour	Somewhat effective	Not always effective		
Appears to work well but patients not usually problematic with fever/rigours	Depends on patient	Limited results initially and long term. We are finding that some residents are responding well when shivering to a staff member holding them and giving lots of reassurance		
Usual effect, prescription would be usual timings and prns	Fair depending on fever	Limited		
Quite effective but NSAIDS might have been more effective - in the French COVID context, they were not recommended because allegedly causing more severe cases	Not usually around to see the outcome. Depends on the patient but paracetamol usually effective	Some sustained and recurrent fever despite regular paracetamol		
Paracetamol was generally for the majority of patients, however, some required NSAID in addition as described above. Time to relief - as expected from what is known(n) from existing experience/knowledge of pharmacology of the drug	Paracetamol slightly more effective than ibuprofen - but sometimes no effect on fever by either in COVID 19. If works, works at about 30 minutes			

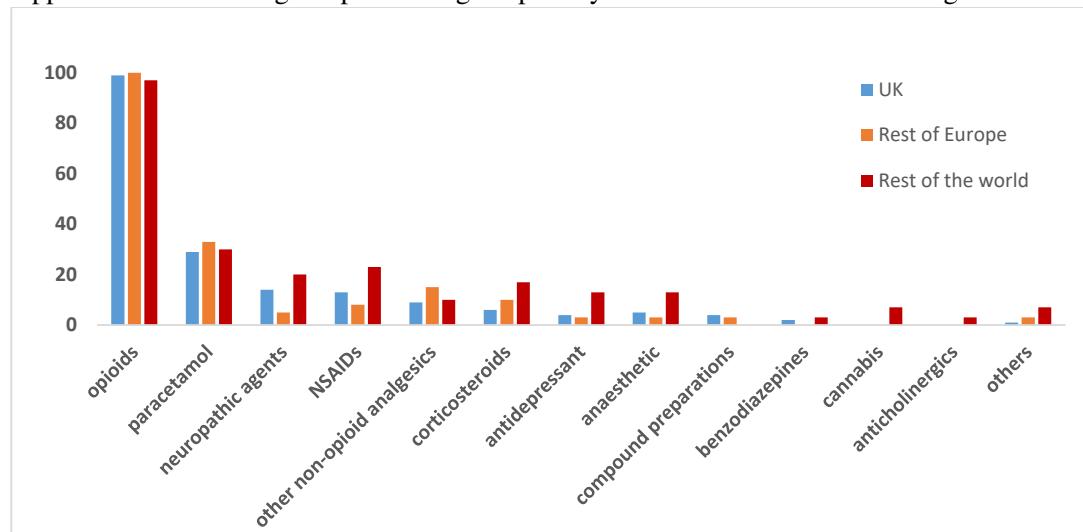
## Appendix 6a: Types of medicines prescribed for pain

Opioids	morphine (n = 119), oxycodone (n = 50), fentanyl (n = 22), alfentanil (n = 12), methadone (n = 12), hydromorphone (n = 11), buprenorphine (n = 8), codeine (n = 3), diamorphine (n = 3), tramadol (n = 2), sufentanil (n = 2), hydrocodone (n = 1), pethidine (n = 1), opioids* (n = 118)
Paracetamol	paracetamol (n = 74)
Neuropathic agents/anticonvulsants	gabapentin (n = 16), pregabalin (n = 8), anticonvulsants (n = 2), neuropathic agents* (n = 14),
NSAIDs	ibuprofen (n = 4), ketorolac (n = 2), naproxen (n = 1), NSAIDs* (n = 26)
Other non-opioid analgesics <sup>a</sup>	non-opioid analgesics* (n = 17), metamizole (n = 7)
Steroids	dexamethasone (n = 2), cortisone (n = 1), steroids* (n = 17)
Antidepressants	amitriptyline (n = 5), duloxetine (n = 4), SSRIs* (n = 1), SNRIs* (n = 1), antidepressants* (n = 2)
Anaesthetic	ketamine (n = 9), lidocaine (n = 4), NMDA receptor antagonist* (n = 1)
Compound preparation	Paracetamol and codeine (n = 7), menthol in aqueous cream (n = 1)
Benzodiazepines	clonazepam (n = 1), lorazepam (n = 1), midazolam (n = 1), benzodiazepine* (n = 1)
Cannabis	cannabis (n = 2)
Anticholinergic agents	antispasmodic* (n = 1)
Others	Stimulants* (n = 1), bisphosphonates (n = 1), antihistamine (loratadine, n = 1), muscle relaxant* (n = 1), selective cyclooxygenase 2 inhibitors* (n = 1)

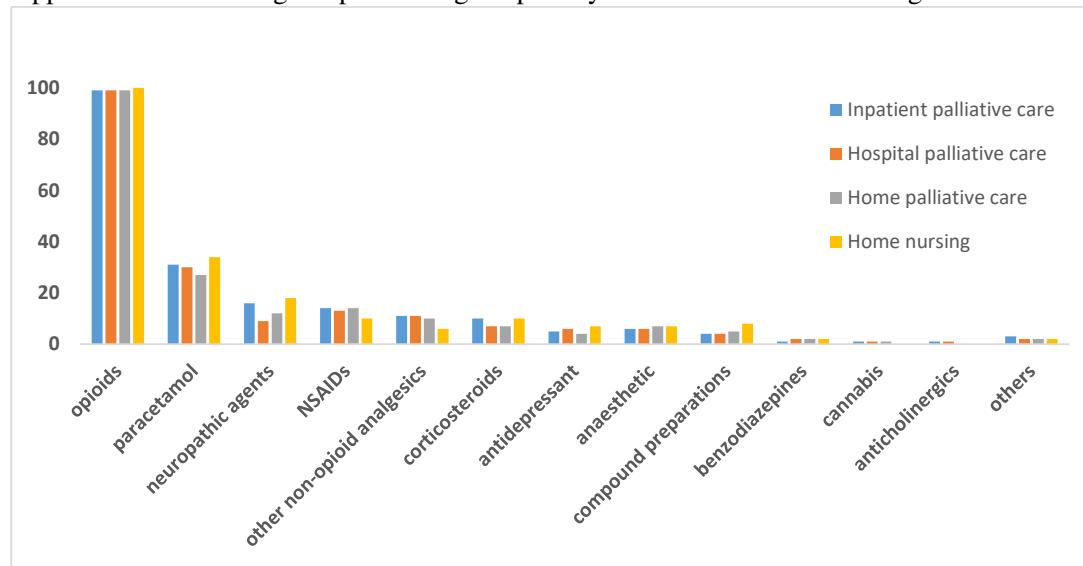
Other non-opioid analgesics<sup>a</sup>: Besides metamizole, it is not clear what the other non-opioid analgesics are as they were not stated. Note: NMDA receptor antagonist = N-methyl-D-aspartate receptor antagonist; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; SSRIs = Selective Serotonin Reuptake Inhibitors; SNRIs = Serotonin and Norepinephrine Reuptake Inhibitors

\*Type of medicine prescribed not stated

Appendix 6b: Percentage of prescribing for pain by services in different world regions



Appendix 6c: Percentage of prescribing for pain by services in different settings



## Appendix 6d: Examples of quotes on the perceived effectiveness of medicines for pain

<b>Effective</b>	<b>Some effectiveness</b>	<b>Unclear effectiveness</b>
30 minutes aprox to become effective. Effectiveness varies but generally good.	Depending on type of analgesic and route of administration	The patients we have had with COVID-19 have usually had an underlying cancer diagnosis that has required a traditional palliative care approach to managing their pain. It is hard to generalise as we have had a limited number of patient and they have all had different underlying conditions.
[Opioids] mostly well. Depends on dose and responsiveness of pain to opioids. Sometimes an NSAID is just better	Depends	
All very effective. I prefer parenteral application overall.	Depends on pain/comorbidities	
It is difficult to know if the pain that we have witnessed has been due to COVID directly or due to other causes because the majority of patients that we are supporting are very unwell and not able to clearly communicate this. So it is difficult to comment. The analgesia that we have used has appeared effective although can need titrating over a 24-48 hour period	Varies depending on patient and cause of pain	
Very effective	Different response depending on cause	
They usually are effective within 15-20 mins with good results	Individual variation and dose dependent	
Typically adequate relief within 15-30min of opioid administration and titrated to a realistic goal comfort level within 24 hours to several days depending on pain. Steroids helpful within 24hours of first dose. Neuropathic agents within short days. Palliative radiation typically within 7-14 days.	Varied response, need for titration	
Effective. In the period before dying we often give Morphine in a continue infusion	Depends on patient	
	This is a huge Q - I think we get better pain control in vast majority - a small percentage we do not despite use of all of above	