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Symptom management in people dying with COVID-19: multinational observational study

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ABSTRACT

Objectives To describe multinational prescribing practices by palliative care services for symptom management in patients dying with COVID-19 and the perceived effectiveness of medicines.

Methods We surveyed specialist palliative care services, contacted via relevant organisations between April and July 2020. Descriptive statistics for categorical variables were expressed as counts and percentages. Content analysis explored free text responses about symptom management in COVID-19. Medicines were classified using British National Formulary categories. Perceptions on effectiveness of medicines were grouped into five categories; effective, some, limited or unclear effectiveness, no effect.

Results 458 services responded; 277 UK, 85 rest of Europe, 95 rest of the world, 1 missing country. 358 services had managed patients with confirmed or suspected COVID-19. 289 services had protocols for symptom management in COVID-19. Services tended to prescribe medicines for symptom control comparable to medicines used in people without COVID-19; mainly opioids and benzodiazepines for breathlessness, benzodiazepines and antipsychotics for agitation, opioids and cough linctus for cough, paracetamol and non-steroidal anti-inflammatory drugs for fever, and opioids and paracetamol for pain. Medicines were considered to be mostly effective but varied by patient's condition, route of administration and dose.

Conclusions Services were largely consistent in prescribing for symptom management in people dying with COVID-19. Medicines used prior to COVID-19 were mostly considered effective in controlling common symptoms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Multinational data on medicines prescribed for symptom control in people dying with COVID-19 are lacking.

WHAT THIS STUDY ADDS

⇒ Multinational specialist palliative care services prescribed similar medicines to those used in other conditions for people dying with COVID-19.
⇒ Medicines were perceived to be effective in symptom management.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Medicines used for symptom control in non-COVID-19 conditions were considered effective in COVID-19.

INTRODUCTION

Specialist palliative care services have been critical in managing people dying with COVID-19 and ensuring symptom control towards the end of life.^{1,2} Frequent symptoms in severe COVID-19 include breathlessness and agitation.^{3,4} Cough, fever, fatigue, pain and respiratory secretions are also common.^{3,5}

A recent rapid review on the pharmacological strategies used for symptom management in patients dying of COVID-19 found seven studies (n=493 patients), and concluded that modest doses of morphine and midazolam are required for symptom control.⁶ There is very limited evidence on international practice and service-level perspectives regarding pharmacological management of symptoms and the perceived effectiveness of medicines in patients dying with COVID-19.

Opioids and benzodiazepines are recommended in guidelines for breathlessness in severe COVID-19.^{2,7} Opioids are generally used in palliative care and are the first line treatment for refractory breathlessness.^{8,9} Benzodiazepines have been recommended in patients dying from severe COVID-19, but there is mixed evidence in other advanced illnesses on benefits and harms,¹⁰ and no evidence in COVID-19.

Before the COVID-19 pandemic, benzodiazepine prescribing had been reported to differ between the UK and European countries. Huerta *et al*¹¹ reported higher benzodiazepine prescribing in UK and Spanish electronic healthcare databases, but lower prescribing in Dutch, German and Danish databases. Possible reasons for differences included variation in help-seeking habits of patients and the diseases for which benzodiazepines are indicated by country as well as prescribing habits. Despite the adverse effects associated with benzodiazepines, the majority of hospice clinicians view them as beneficial treatments for breathlessness and agitation.¹²

While pain, agitation, fever and cough are severe symptoms in COVID-19,^{3,5} there have been limited information about their clinical management.⁴ Given the lack of clarity on benzodiazepine benefit for breathlessness, concerns around safety and variation in its prescribing by country,¹¹ and the dearth of information around prescribing for pain, agitation, fever and cough in COVID-19, it is important to understand what is being prescribed for symptom control in patients dying with COVID-19 and whether prescribed medicines are considered to be effective by specialist palliative care services. We therefore aimed to describe multinational prescribing practices of specialist palliative care services for symptom management in patients dying with COVID-19 and the perceived effectiveness of medicines.

METHODS

Study design and participants

This paper reports results from the CovPall study that aimed to understand the multinational specialist palliative care response to COVID-19.¹ A survey was a fundamental part of the first work package for this study. The survey opened on 23 April 2020 and closed on 31 July 2020.

Services providing hospice and specialist palliative care were eligible for participation and were recruited through palliative care and hospice organisations (Hospice UK, Marie Curie, Sue Ryder, Together for Short Lives, European Association of Palliative Care, palliativedrugs.com and the www.pos-pal.org network). They were provided with a link to the online survey, and service leads (medical or nurse directors/clinicians) or their selected nominees were invited to complete the survey. The CovPall protocol is registered (ISRCTN16561225) and these results are reported according to Strengthening the Reporting

of Observational Studies in Epidemiology,¹³ CHERRIES¹⁴ and MORECARE¹⁵ statements.

Survey and data collection

The questionnaire was developed building on an earlier survey of Italian hospices and has been reported in the main CovPall paper.¹ The Research Electronic Data Capture¹⁶ was used to build a secure, web-based survey which had 72 closed text and 94 free text responses.

This paper focuses on prescribing practices for symptom management and how effective services found prescribed medicines (eg, time to give relief and how well it worked) (see online supplemental appendix 1). For the quantitative data items, we analysed the following variables by world region: protocols and protocol sources for symptom management, prescribing for breathlessness, agitation, cough, fever and pain. From the free text comments, we analysed 10 open-ended questions (see online supplemental appendix 1). Open free text comments were summarised and explored to understand how service leads (or their nominees) perceived the effectiveness of medicines prescribed for symptom management in patients dying with COVID-19.

DATA ANALYSIS

For the quantitative data items, descriptive statistics for categorical variables were expressed as counts and percentages. We used contingency tables, χ^2 tests and Fisher's exact test to explore relationships between variables (using SPSS V.26). Free text comments describing the types of medicines prescribed were summarised in Excel using content analysis; the British National Formulary¹⁷ categories were used. Responses to questions on the effectiveness of prescribed medicines were categorised into 'effective', 'some effectiveness', 'limited effectiveness', 'unclear effectiveness' and 'no effect' based on comments provided by respondents. For example, if medicines were described as generally effective within 10–20 min by respondents, this was classified as 'effective'. Time to effect was also grouped based on respondents' comments into effect within 30 min, effect over 31 min and varied effect.

RESULTS

In the original CovPall survey,¹ 489 questionnaires were commenced and 477 completed (completion rate 97.5%). Nineteen were invalid because they were duplicates, triplicates or were from researchers without a palliative care service, leaving 458 valid responses: 277 UK, 85 rest of Europe, 95 rest of the world, 1 missing country.

In total, 358 services had managed patients with confirmed or suspected COVID-19: 248 UK, 60 rest of Europe, 49 rest of the world and 1 missing country. Of these, services were usually publicly (165, 47%), or charity managed (150, 42.7%); 15 (4.3%) were privately managed, 21 (6%) other; 7 missing. In total,

203 services provided inpatient palliative care units, 204 home care teams, 182 hospital palliative care teams and 94 home nursing teams. Over half of services (56.4%) provided care in more than one setting.

Two hundred and eighty-nine services had protocols for symptom management in COVID-19. Protocols for symptom management were available for 216 of 231 (93.5%) UK services, 44 of 52 (84.6%) services in the rest of Europe and 29 of 41 (70.7%) services in the rest of the world. Of 289 services with symptom management protocols, 238 (82.4%) services reported using locally developed guidelines: 181 UK, 34 rest of Europe and 23 rest of the world. Locally developed guidelines were used by 181 of 216 (83.8%) UK services, 34 of 44 (77.3%) services in the rest of Europe and 23 of 29 (79.3%) services in the rest of the world.

Prescribing for symptoms

Breathlessness

The three most common prescribed medicines for breathlessness were opioids (n=273 of 282 (96.8%) services), benzodiazepines (n=205 of 282 (72.7%) services) and oxygen (n=76 of 282 (27%) services) (table 1, online supplemental appendix 2a).

The level of opioid prescribing by services in different world regions and palliative care settings were similar (figure 1A and B, online supplemental appendix 2a, 2b). Morphine was the most prescribed opioid, representing 172 (54.1%) of the 318 prescribed opioids. Others included oxycodone (n=26 (8.2%)), fentanyl (n=9 (2.8%)), hydromorphone (n=4 (1.3%)), diamorphine (n=3 (0.9%)), alfentanil (n=3 (0.9%)), buprenorphine (n=3 (0.9%)) and sufentanil (n=1 (0.3%)) (online supplemental appendix 2c). Some services reported prescribing opioids but did not state the type of opioid (n=97 (30.5%)).

Prescribing of benzodiazepines for breathlessness was significantly higher in the UK (83%) than the rest of Europe (48%) and the world (44%) (figure 1A, online supplemental appendix 2a) ($\chi^2=38.42$, $p<0.001$). Among benzodiazepines, midazolam (n=126 (48.6%) of 259) was the most prescribed. Others included lorazepam (n=58 (22.4%)), diazepam (n=3 (1.2%)), oxazepam (n=2 (0.8%)), clonazepam (n=1 (0.4%)). The type of benzodiazepines prescribed was not stated in 69 (26.6%) cases (online supplemental appendix 2c).

Palliative care services that prescribed oxygen were less likely to have hospital palliative care teams ($\chi^2=9.16$, $p=0.002$).

Fifty seven services indicated how quickly medicines worked, with 43 (75.4%) responding that they worked within 30 min and 13 (22.8%) over 31 min (table 1).

All respondents on the perceived effectiveness of these medicines considered them to be either effective or as having some effect. Perceived effectiveness

depended on the patient's condition and route of drug administration (online supplemental appendix 2d).

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 (hospital palliative care team, UK).

Although medicines tended to be effective, this was challenging to predict with an acknowledgement that patients sometimes required high doses.

Benzos and opioids tend to work in 10-20 minutes. Most people need small doses, but some need bigger doses (*inpatient palliative care unit/hospital palliative care team/home palliative care team, UK*).

Further, services reported reluctance to prescribe opioids.

...Not quite effective in some cases, it's difficult due to some senior physicians afraid of opioids. (*hospital palliative care team/home palliative care team, rest of the world*).

Agitation

The most common prescribed medicines for agitation were benzodiazepines (n=255 of 277 (92.1%) services) and antipsychotics (n=213 of 277 (76.9%) services) (figure 1c; online supplemental appendix 3a). Prescribing of benzodiazepines was higher in the UK (96%) than the rest of Europe (87%) and the world (73.3%) (Fisher's exact test=16.82, $p\leq 0.001$), but did not differ by setting (figure 1D; online supplemental appendix 3b).

Midazolam was the most prescribed benzodiazepine for agitation, making up 215 of 317 (67.8%) prescribed benzodiazepines. Other benzodiazepines prescribed included lorazepam (n=52 (16.4%)), diazepam (n=7 (2.2%)), clonazepam (n=2 (0.6%)), oxazepam (n=3 (0.9%)), alprazolam (n=1 (0.3%)) and lormetazepam (n=1 (0.3%)) (online supplemental appendix 3c). Some services did not state the type of benzodiazepine prescribed (n=36 (11.4%)).

Among antipsychotics, levomepromazine was most commonly prescribed for agitation: 157 of 315 (49.8%) prescribed antipsychotics. Haloperidol (n=132 (41.9%)), olanzapine (n=4 (1.3%)), chlorpromazine (n=3 (1%)), quetiapine (n=3 (1%)), risperidone (n=2 (0.6%)), cyamemazine (n=1 (0.3%)), droperidol (n=1 (0.3%)) and promazine (n=1 (0.3%)) were also prescribed (online supplemental appendix 3c). In 11 (3.5%) cases, the type of antipsychotic prescribed was not stated.

Table 1 Characteristics of palliative care and hospice services that managed patients with suspected or confirmed COVID-19 by region

	UK (n=248)	Rest of Europe (n=60)	Rest of the world (n=49)	Total
Protocols for symptom management (n/N, %)				
No	14/231 (6.1)	8/52 (15.4)	10/41 (24.4)	32/324 (9.9)
Yes	216/231 (93.5)	44/52 (84.6)	29/41 (70.7)	289/324 (89.2)
Not sure	1/231 (0.4)	0/52	2/41 (4.9)	3/324 (0.9)
Missing	17	8	8	34*
Protocol sources for symptom management (n/N, %)				
Locally developed guidance	181/216 (83.8)	34/44 (77.3)	23/29 (79.3)	238/289 (82.4)
National Institute for Health and Care Excellence	123/216 (56.9)	6/44 (13.6)	0/29	129/289 (44.6)
National Health Service	125/216 (57.9)	9/44 (20.5)	2/29 (6.9)	136/289 (47.1)
Other	86/216 (39.8)	21/44 (47.7)	9/29 (31)	116/289 (40.1)
Opioid prescribing for breathlessness (n/N, %)				
Yes	201/204 (98.5)	44/46 (95.7)	28/32 (87.5)	273/282 (96.8)
Missing	44	14	17	76*
Benzodiazepine prescribing for breathlessness (n/N, %)				
Yes	169/204 (82.8)	22/46 (47.8)	14/32 (43.8)	205/282 (72.7)
Missing	44	14	17	76*
Oxygen prescribing for breathlessness (n/N, %)				
Yes	52/204 (25.5)	16/46 (34.8)	8/32 (25)	76/282 (27)
Missing	44	14	17	76*
How quickly medicines for breathlessness worked (n/N, %)				
≤30 min	29/42 (69)	8/8 (100)	6/7 (85.7)	43/57 (75.4)
>31min†	12/42 (28.6)	0/8	1/7 (14.3)	13/57 (22.8)
Varies	1/42 (2.4)	0/8	0/7	1/57 (1.8)
Benzodiazepine prescribing for agitation (n/N, %)				
Yes	193/201 (96)	40/46 (87)	22/30 (73.3)	255/277 (92.1)
Missing	47	14	19	81*
Antipsychotic prescribing for agitation (n/N, %)				
Yes	159/201 (79.1)	33/46 (71.7)	21/30 (70)	213/277 (76.9)
Missing	47	14	19	81*
Barbiturate prescribing for agitation (n/N, %)				
Yes	4/201 (2)	0/46	1/30 (3.3)	5/277 (1.8)
Missing	47	14	19	81*
How quickly medicines for agitation worked (n/N, %)				
≤30 min	23/31 (74.2)	3/6 (50)	2/5 (40)	28/42 (66.7)
>31min†	7/31 (22.6)	2/6 (33.3)	2/5 (40)	11/42 (26.2)
Varies	1/31 (3.2)	1/6 (16.7)	1/5 (20)	3/42 (7.1)
	UK (n=248)	Rest of Europe (n=60)	Rest of the world (n=49)	Total
Opioid prescribing for cough (n/N, %)				
Yes	173/180 (96.1)	40/41 (97.6)	25/30 (83.3)	238/251 (94.8)
Missing	68	19	19	107*
Cough linctus prescribing for cough (n/N, %)				
Yes	73/180 (40.6)	2/41 (4.9)	1/30 (3.3)	76/251 (30.3)
Missing	68	19	19	107*
Nebulised saline prescribing for cough (n/N, %)				
Yes	8/180 (4.4)	2/41 (4.9)	0/30	10/251 (4)
Missing	68	19	19	107*
How quickly medicines for cough worked (n/N, %)				
≤30 min	10/14 (71.4)	3/4 (75)	0/3	13/21 (61.9)
>31min†	4/14 (28.6)	1/4 (25)	2/3 (66.7)	7/21 (33.3)
Varies	0/14	0/4	1/3 (33.3)	1/21 (4.8)
Paracetamol prescribing for fever (n/N, %)				
Yes	198/199 (99.5)	42/44 (95.5)	27/29 (93.1)	267/272 (98.2)
Missing	49	16	20	86*
NSAID prescribing for fever (n/N, %)				
Yes	38/199 (19.1)	4/44 (9.1)	4/29 (13.8)	46/272 (16.9)
Missing	49	16	20	86*

Continued

Table 1 Continued

	UK (n=248)	Rest of Europe (n=60)	Rest of the world (n=49)	Total
Metamizole prescribing for fever (n/N, %)				
Yes	0/199	14/44 (31.8)	1/29 (3.4)	15/272 (5.5)
Missing	49	16	20	86*
How quickly medicines for fever worked (n/N, %)				
≤30 min	11/26 (42.3)	3/4 (75)	3/7 (42.9)	17/37 (45.9)
>31 min†	14/26 (53.8)	1/4 (25)	4/7 (57.1)	19/37 (51.4)
Varies	1/26 (3.8)	0/4	0/7	1/37 (2.7)
Opioid prescribing for pain (n/N, %)				
Yes	175/177 (98.9)	40/40 (100)	29/30 (96.7)	244/247 (98.8)
Missing	71	20	19	110
Paracetamol prescribing for pain (n/N, %)				
Yes	52/177 (29.4)	13/40 (32.5)	9/30 (30)	74/247 (30)
Missing	71	20	19	110
Neuropathic agent prescribing for pain (n/N, %)				
Yes	25/177 (14.1)	2/40 (5)	6/30 (20)	33/247 (13.4)
Missing	71	20	19	110
How quickly medicines for pain worked (n/N, %)				
≤30 min	12/22 (54.5)	4/4 (100)	1/4 (25)	17/30 (56.7)
>31 min†	9/22 (40.9)	0/4	2/4 (50)	11/30 (36.7)
Varies	1/22 (4.5)	0/4	1/4 (25)	2/30 (6.7)

*Includes data from the one missing country.
†Where time to effect was reported to be between 20 and 45 min or less than 1 hour or 30–60 min, this was grouped under effect over 31 min.
NSAID, non-steroidal anti-inflammatory drug.

Out of 234, 189 (80.3%) respondents considered prescribed medicines to be effective, while 42 (17.9%) and 4 (1.7%) reported some effect and limited effect respectively (online supplemental appendix 3d).

Forty-two services indicated how quickly medicines worked, and 28 (66.7%) responded that they worked within 30 min (table 1). Medicines tended to be effective depending on symptom severity, type of medicine,

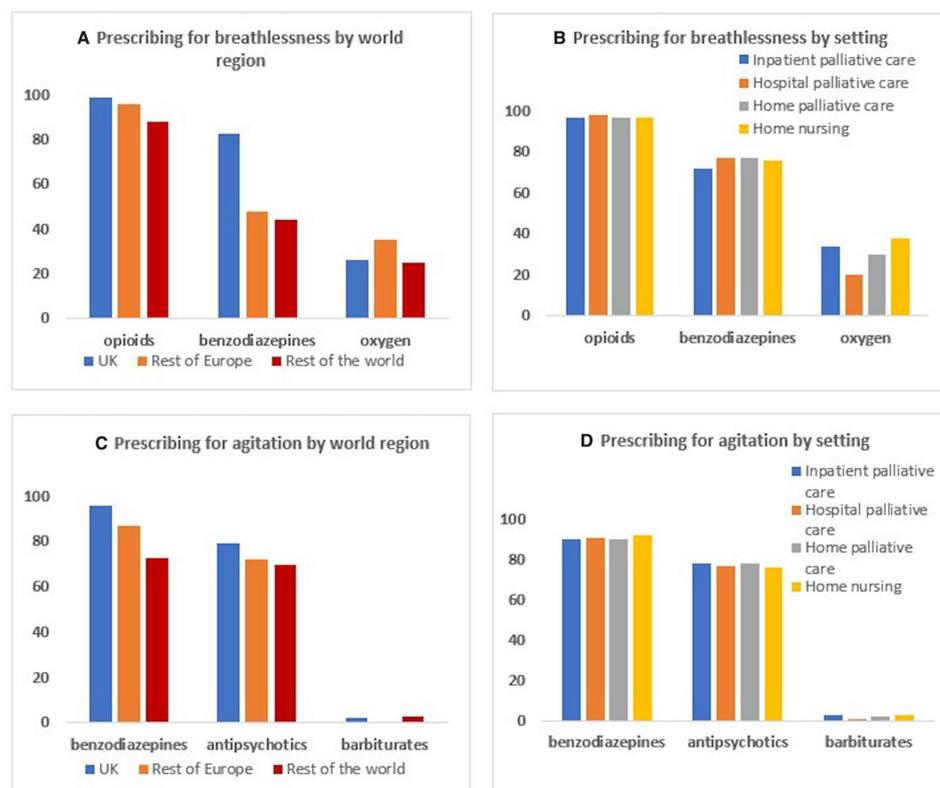


Figure 1 Percentage of prescribing by services in different settings and world regions.

route of administration and dosage. One service highlighted that

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 (hospital palliative care team, UK).

Another service highlighted limited effectiveness

...no(t) so well. Especially for ventilated patients with agitation/delirium (inpatient palliative care team, rest of Europe).

Cough

The three most prescribed medicines for cough were opioids (n=238 of 251 (94.8%) services), cough linctus (n=76 of 251 (30.3%) services) and nebulised saline (n=10 of 251 (4%) services) (table 1; online supplemental appendix 4a).

Opioids prescribed were morphine, representing 123 of 299 (41.1%) prescribed opioids; codeine (n=75 (25.1%)); methadone (n=7 (2.3%)); oxycodone (n=6 (2%)); paracodone (n=4 (1.3%)); dihydrocodeine (n=3 (1%)); hydrocodone (n=1 (0.3%)); fentanyl (n=1 (0.3%)); sufentanil (n=1 (0.3%)); hydromorphone (n=1 (0.3%)); diamorphine (n=1 (0.3%)) (online supplemental appendix 4b). In 79 (26%) cases, the type of opioid prescribed was not stated.

Across settings, opioids were prescribed by 89% to 96% of services; cough linctus by 25% to 50% of services; nebulised saline by 2%–11% of services (online supplemental appendix 4c). Cough linctus prescribing was higher in the UK (41%) than Europe (5%) and the rest of the world (3%) ($\chi^2=31.85$, $p<0.001$); opioid prescribing differed across world regions (83%–98%) (online supplemental appendix 4a) (Fisher's exact test=6.92, $p=0.026$).

Twenty-one services indicated how quickly medicines worked; 13 (61.9%) stated that they worked within 30 min and 7 (33.3%) highlighted effect over 31 min (table 1). The remaining service indicated that the onset of effect varied.

Out of 177, 151 (85.3%) respondents considered prescribed medicines to be effective or somewhat effective, while the remaining reported limited (13.6%) or unclear effects (1.1%) (online supplemental appendix 4d).

not that good, though not a common Sx (symptoms) in the elderly (home palliative care team, UK).

There was an indication that cough was sometimes challenging to treat.

in combination with other medications to support end of life care then I would say that cough can be reduced within a short period of time. Difficult to achieve no cough (hospital palliative care team, UK).

Fever

The most prescribed medicines for fever were paracetamol (n=267 of 272 (98.2%) services), non-steroidal anti-inflammatory drugs (NSAIDs) (n=46 of 272 (16.9%) services) and metamizole (n=15 of 272 (5.5%) services) (table 1). NSAIDs prescribed were ibuprofen, representing 11 of 48 (22.9%) prescribed NSAIDs, diclofenac (n=7 (14.6%)) and ketorolac (n=1 (2.1%)). In 29 (60.4%) cases, the type of NSAID prescribed was not stated (online supplemental appendix 5a).

Prescribing for fever tended to be similar across world regions except for metamizole. Metamizole was not prescribed in the UK, while 32% and 3.4% of services in the rest of Europe and the world respectively prescribed it (online supplemental appendix 5b). Prescribing for fever was similar across settings (online supplemental appendix 5c).

Thirty-seven services indicated how quickly medicines worked; 17 (45.9%) responded that they worked within 30 min and 19 (51.4%) within over 31 min. One (2.7%) service said this varied.

Out of 201, 188 (93.5%) respondents on the effectiveness of these medicines considered them to be effective or to have some effect, while the remaining reported limited effect (10, 5%), no effect (1, 0.5%) or unclear effect (2, 1%) (online supplemental appendix 5d). There was an indication of variation in recommendations across countries regarding what to prescribe for fever.

[paracetamol] quite effective but NSAIDS might have been more effective - in the French COVID context, they were not recommended because allegedly causing more severe cases (inpatient palliative care unit/hospital palliative care team, rest of Europe).

Services also described limited effect.

Temperatures in COVID-19 +ve patients have not always settled with paracetamol and needed NSAID 2nd line (inpatient palliative care unit/home palliative care team/home nursing services, UK).

Pain

Opioids (n=244 of 247 (98.8%) services), paracetamol (n=74 of 247 (30%) services) and neuropathic agents (n=33 of 247 (13.4%) services) were mostly prescribed for pain (table 1). Opioids prescribed included morphine, representing 119 of 364 (32.7%) prescribed opioids, oxycodone (n=50 (13.7%)), fentanyl (n=22 (6%)), alfentanil (n=12 (3.3%)), methadone (n=12 (3.3%)), hydromorphone (n=11 (3%)), buprenorphine (n=8 (2.2%)), codeine (n=3 (0.8%)), diamorphine (n=3 (0.8%)), tramadol (n=2 (0.6%)), sufentanil (n=2 (0.6%)), hydrocodone (n=1 (0.3%)) and pethidine (n=1 (0.3%)) (online supplemental appendix 6a). In 118 (32.4%) cases, the type of opioids was not described.

Neuropathic agents prescribed for pain included gabapentin (n=16 (40%)), pregabalin (n=8 (20%)) and anticonvulsants (n=2 (5%)) (online supplemental appendix 6a). The type of neuropathic agent prescribed was not stated in 14 (35%) cases. Prescribing of neuropathic agents was higher in the rest of the world (20%) compared with the UK (14%) and the rest of the Europe (5%). Other medicines in which there was variation in prescribing across world regions include antidepressants, anaesthetics, NSAIDs and other non-opioid analgesics (online supplemental appendix 6b). Prescribing across settings was broadly similar (online supplemental appendix 6c).

Thirty services indicated how quickly medicines worked; 17 (56.7%) responded that they worked within 30 min and 11 (36.7%) within over 31 min. Two (6.7%) services responded that how quickly medicines worked varied.

Out of 199, 198 (99.5%) respondents considered the medicines to be effective or somewhat effective, while the remaining service reported unclear effects (0.5%). Medicines tended to be effective depending on the route of administration, drug, dose and type of pain (online supplemental appendix 6d):

[Opioids] mostly well. Depends on dose and responsiveness of pain to opioids. Sometimes an NSAID is just better (inpatient hospice palliative care team, UK).

DISCUSSION

We report a multinational service-level perspective on prescribing to manage the symptoms of patients dying with COVID-19. With the exception of benzodiazepines prescribed for breathlessness and agitation, services within world regions tended to prescribe similar medicines for symptom control. This included mainly opioids and benzodiazepines for breathlessness, benzodiazepines and antipsychotics for agitation, opioids and cough linctus for cough, paracetamol and NSAIDs for fever, and opioids and paracetamol for pain. Medicines were considered to be effective as 45.9%–75.4% of prescribed medicines were reported to work within 30 min.

Evidence suggests that breathlessness and agitation are common in severe COVID-19.^{3 18} A recent review⁶ suggests these symptoms in terminal COVID-19 can be alleviated with modest opioid and benzodiazepine doses (eg, 15 mg morphine CSCI and 10 mg midazolam CSCI). This is similar to our findings and is in line with national and international guidelines.^{2 7 19} It is however not clear when benzodiazepines are being used for agitation related to breathlessness or agitation from other causes. Prior evidence from a Cochrane review showed no evidence of effect when benzodiazepines are used for breathlessness in other advanced diseases.¹⁰ Medicines prescribed were typical for similar symptoms in people without COVID-19,

implying that services consider them to be effective. However, it might also represent a dependence on clinical guideline recommendations prevalent at the time, with limited evidence and understanding of the disease.²⁰

We found low levels of prescribing of oxygen and corticosteroids. This may be because this survey was carried out early in the pandemic when little was known about their benefits. In patients with COVID-19, there is scant evidence to support oxygen use in the absence of hypoxaemia. Also, patients may have been in the dying phase and prevented from dying with a mask on which could worsen agitation. There is evidence that corticosteroids are beneficial in reducing the risk of breathlessness, the cytokine storm and mortality in COVID-19 patients who require oxygen and ventilation^{21 22}; the need for mechanical ventilation is also reduced.

Some of the variation by world regions may be due to medicines availability and regulations around prescribing. For instance, metamizole was prescribed for fever in the rest of Europe and the world, but not in the UK. Metamizole is banned in the UK due to the associated risk of agranulocytosis.²³ Furthermore, services sometimes reported the use of medicines that are outside guideline recommendations. For instance, prescribing of antipsychotics for breathlessness. However, we did not explore the reasons for such prescribing in this study.

Over 80% of services with symptom management protocols used locally developed guidelines. While it is unclear whether the locally developed guidelines are adaptations of national guidelines, it does imply duplication of effort by services. For an effective and coordinated response, processes are needed for better translation of learnings from the pandemic into policies and guidelines that are easily accessible and usable.

LIMITATIONS

This study is limited by its cross-sectional design. Given that services sometimes did not state the type of medicine they prescribed in a particular class, we could not make comparisons between different types of medicines (eg, comparing use of different types of benzodiazepines). Assessment of treatment benefit by service leads was a subjective impression of effectiveness, including reports from team members. These responses were then categorised into different levels of effectiveness by our team.

As randomised controlled trials may be impractical, further research, involving observational studies are needed to understand from patient level data whether these medicines, including doses, duration and route, are effective in improving patient outcomes.

Furthermore, there may be non-response, sample and other biases. We cannot tell if the prescribing practices of services that did not respond are different to those of respondents. The survey was distributed through

organisations that were mainly based in the UK and Europe, and most respondents were UK services. The survey was offered only in English and some countries were not represented. When we carried out the survey, countries were at varying stages in the pandemic, which may have affected responses. These limit the interpretation of our international comparisons.

CONCLUSION

Overall, similar medicines to those used in symptom management in other conditions were prescribed for people dying with COVID-19. Our data suggest that medicines used in non-COVID-19 conditions appear to be effective for symptom control. Prescribing was largely consistent across countries and palliative care settings. Further research is needed to clarify which medicines are most effective in improving patient outcomes.

Correction notice This article has been corrected since it was first published. The open access licence has been updated to CC BY.

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Data availability statement Data are available on reasonable request. Applications for use of the survey data can be made for up to 10 years, and will be considered on a case-by-case basis on receipt of a methodological sound proposal to achieve aims in line with the original protocol. The study protocol is available on request. All requests for data access should be addressed to the chief investigator via the details on the CovPall website (<https://www.kcl.ac.uk/cicelysaunders/research/evaluating/covpall-study> and palliativecare@kcl.ac.uk) and will be reviewed by the Study Steering Group.

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Appendices

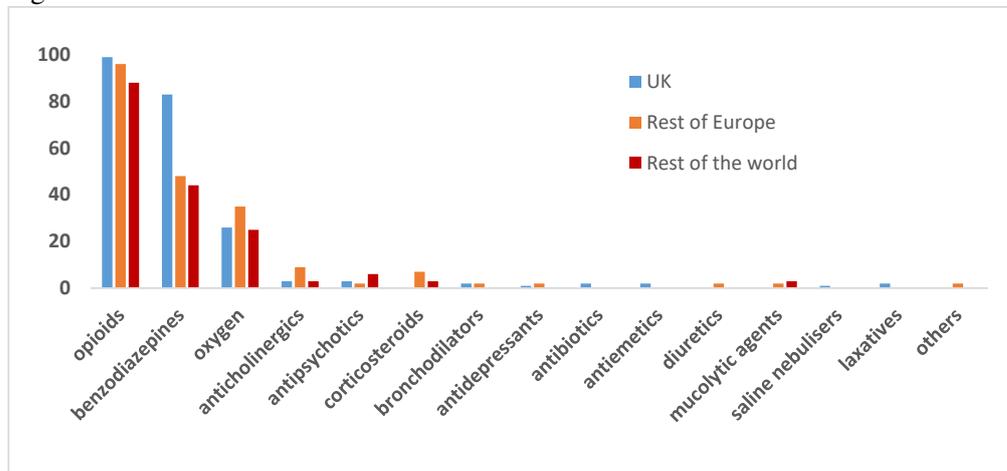
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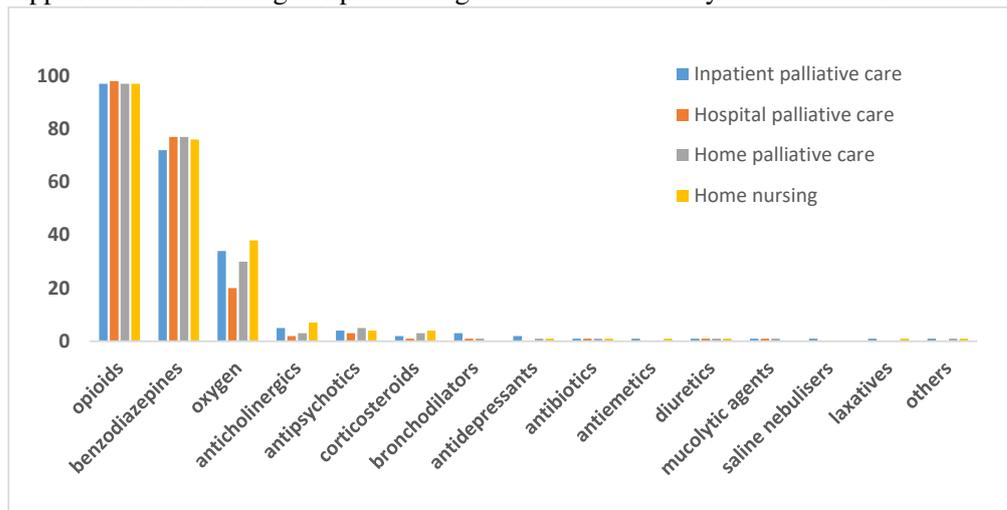
Appendix 1: Questions analysed in this study

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
Free text survey questions about management of symptoms in COVID-19	
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.

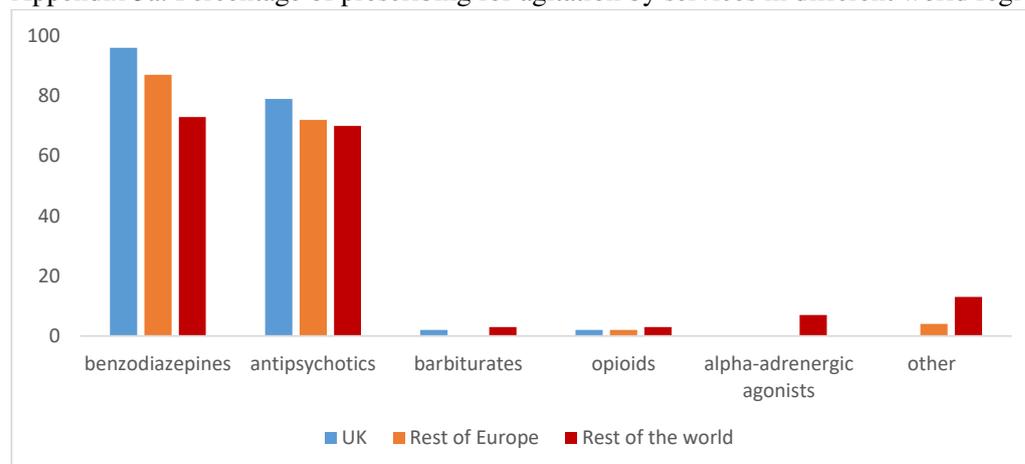
*Type of medicine prescribed not stated

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

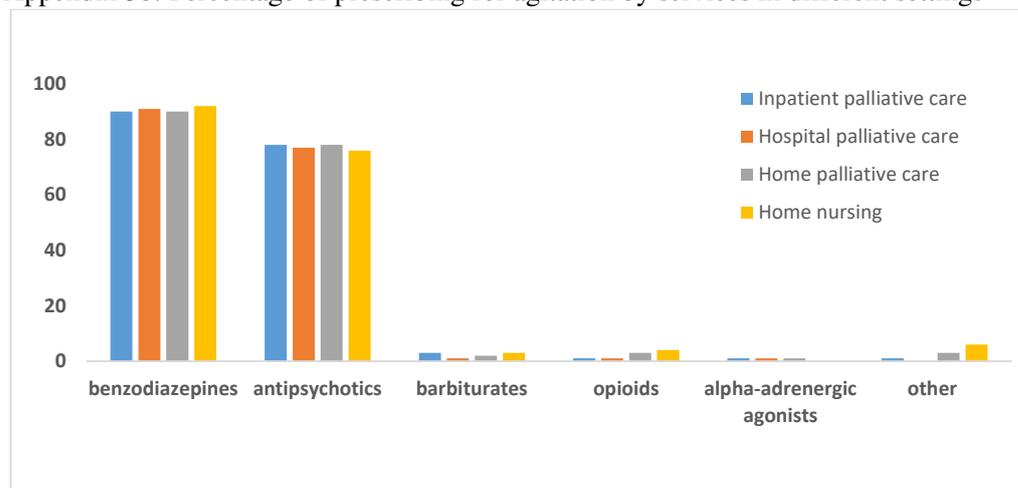
Effective	Some effectiveness
Usual effect, prescription would be usual timings and prns.	Effectiveness depends on overall condition of patients - in rapidly deteriorating patients midazolam has been most effective treatment.
Good effect from opioid and benzodiazepine.	Reasonably effective but obviously 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 CSCIs.	(~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 CSCI 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.

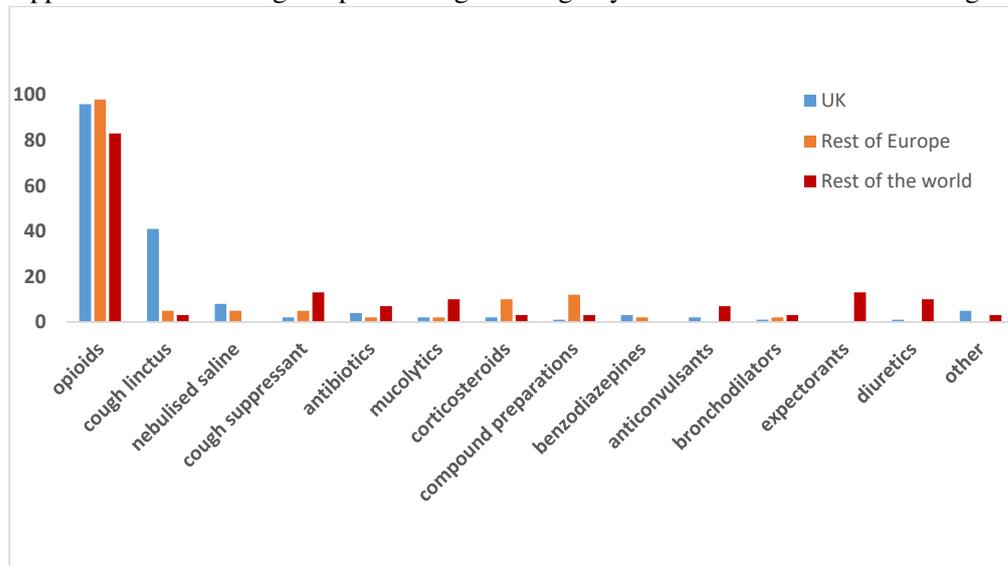
Appendix 3d: Examples of quotes on the perceived effectiveness of medicines for agitation

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 know(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

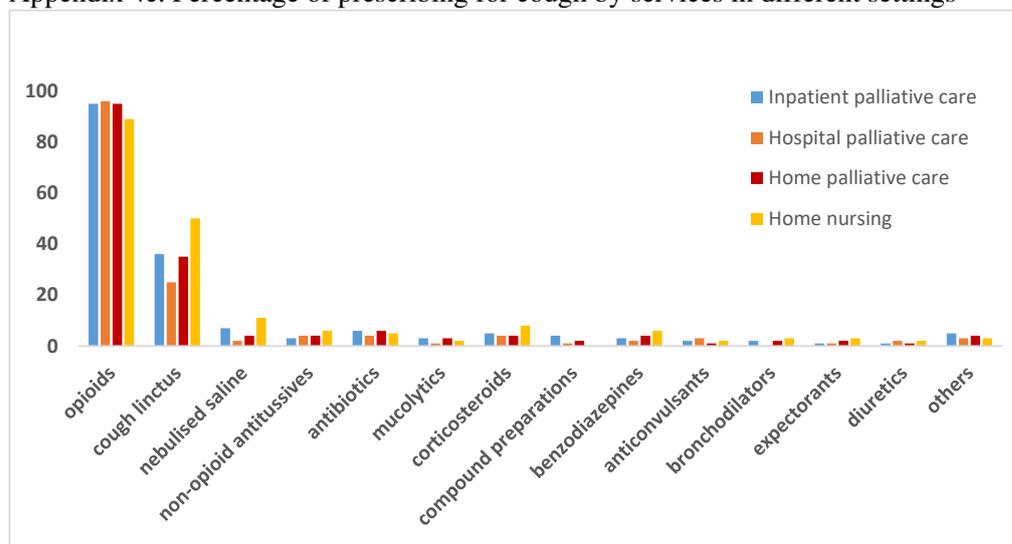
Opioids	morphine (n = 123), codeine (n = 75) ^a , methadone (n = 7), oxycodone (n = 6), paracetamol (n = 4), dihydrocodeine (n = 3), hydrocodone (n = 1), fentanyl (n = 1), sufentanil (n = 1), hydromorphone (1), diamorphine (1), opioids* (n = 79)
Cough linctus	cough linctus (n = 76)
Nebulised saline	nebulised 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), carbocysteine (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^a 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 this. So not enough experience to give a valuable comment	
Seems to be effective	Dependent on cause	Not always effective	

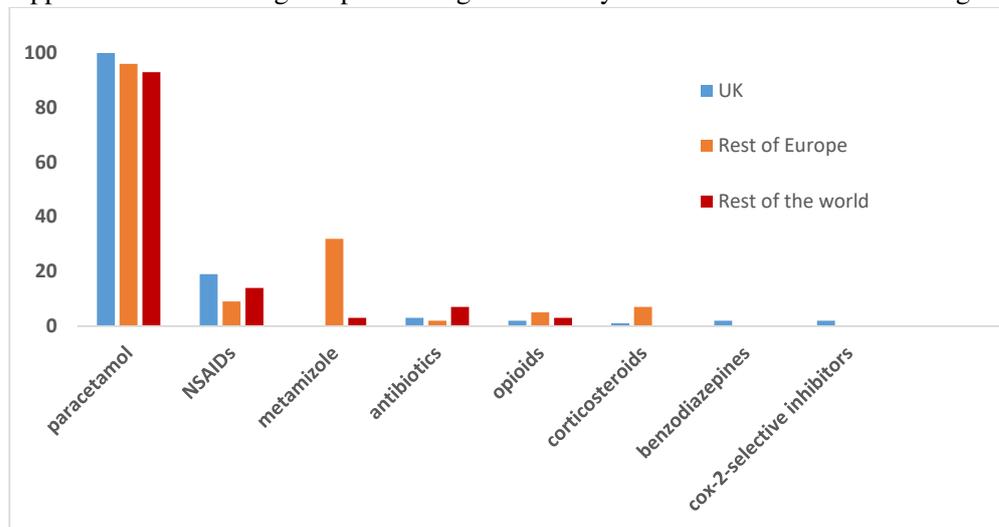
Usual effect, prescription would be usual timings and prns	Partial	Not a lot	
Was effective within 20 mins (NB only one person)	Variable. Cough not been the major symptoms in our patients	Codeine not particularly morphine a little saline nebs a bit better	
30 mins - 1 hr and reasonably helpful	Sometimes 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	
	Variable 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

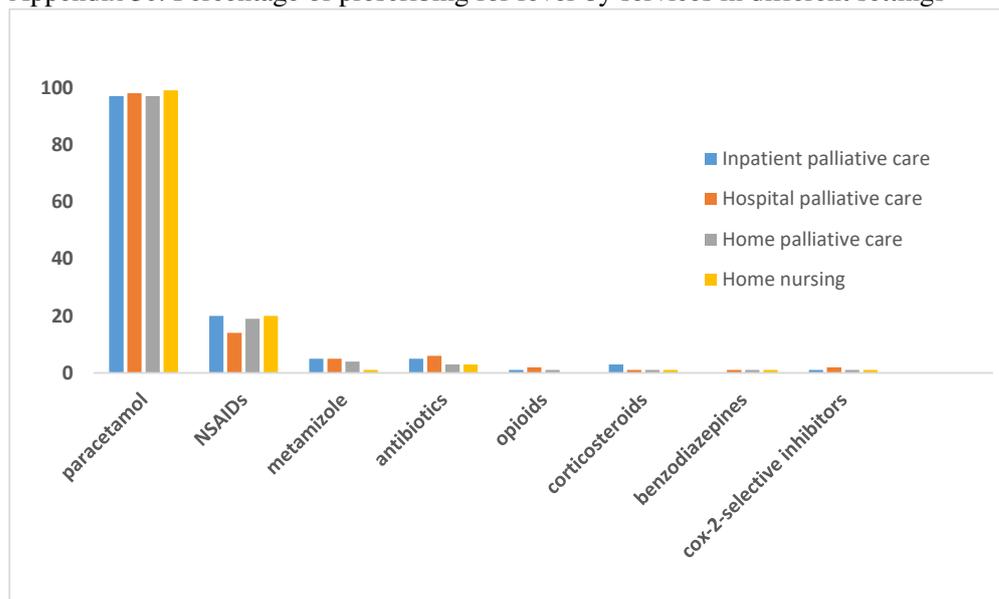
Paracetamol	paracetamol (n = 308)
NSAIDs	ibuprofen (n = 11), diclofenac (n = 7), ketorolac (n = 1), NSAID* (n = 29)
Metamizole	metamizole (n = 20)
Antibiotics	antibiotics* (n = 9)
Opioids	pethidine (n = 3), morphine (n = 1), opioids* (n = 2)
Steroids	cortisone (n = 1), steroids* (n = 4)
Benzodiazepines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

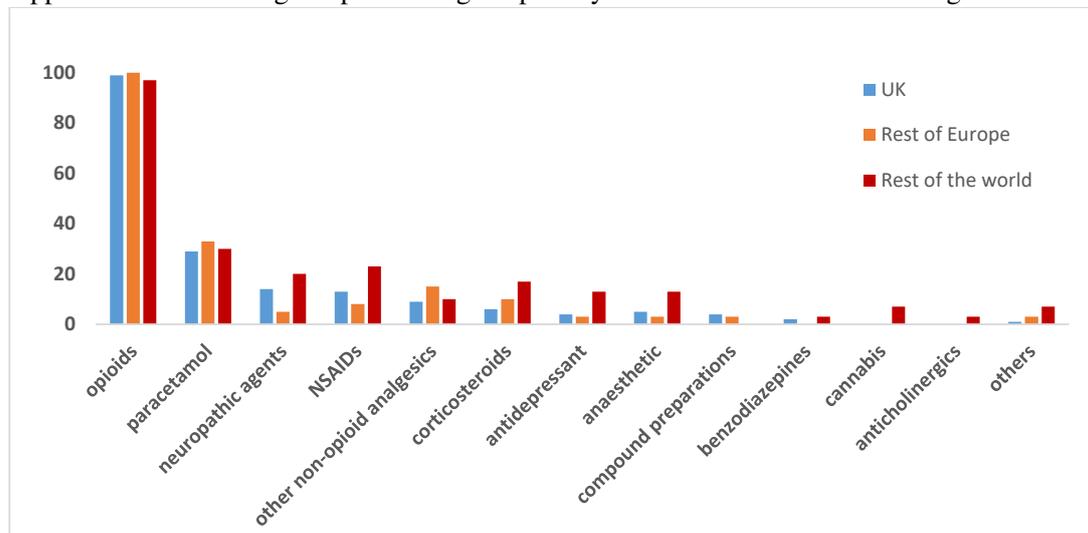
Appendix 6a: Types of medicines prescribed for pain

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 ^a	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)

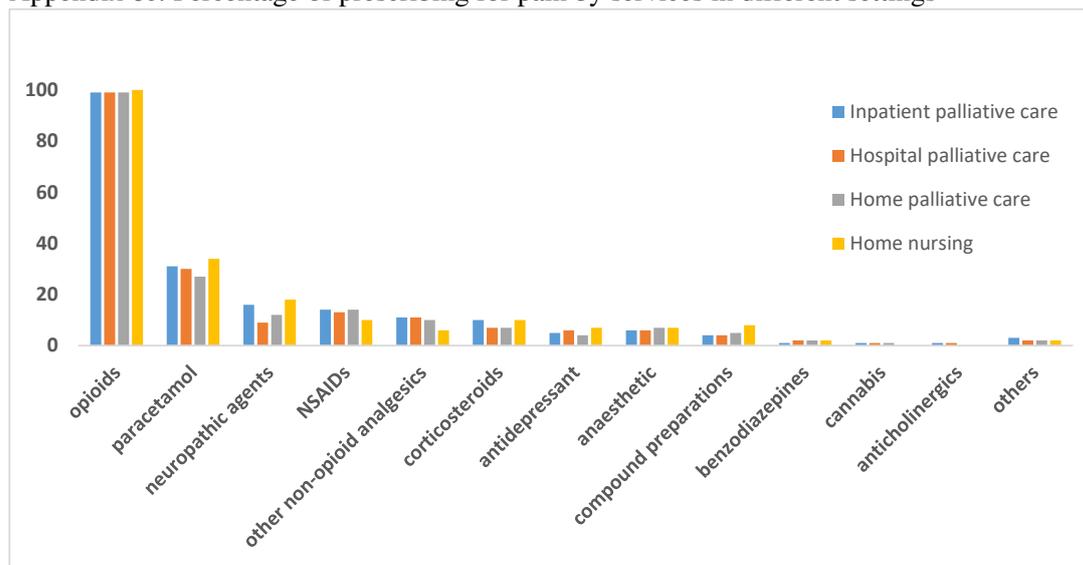
Other non-opioid analgesics^a: Besides metamizole, it is not clear what the other non-opioid analgesics are as they were not stated. Note: NMDA receptor antagonist = N-methyl-D-aspartate receptor antagonist; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; SSRIs = Selective Serotonin Reuptake Inhibitors;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

Effective	Some effectiveness	Unclear effectiveness
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 sue 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	