Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for palliative symptom control in COVID-19 patients (Review)

Andreas M, Piechotta V, Skoetz N, Grummich K, Becker M, Joos L, Becker G, Meissner W, Boehlke C

Andreas M, Piechotta V, Skoetz N, Grummich K, Becker M, Joos L, Becker G, Meissner W, Boehlke C.
Interventions for palliative symptom control in COVID-19 patients.
Cochrane Database of Systematic Reviews 2021, Issue 8. Art. No.: CD015061.
DOI: 10.1002/14651858.CD015061.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for palliative symptom control in COVID-19 patients

Marike Andreas[1], Vanessa Piechotta[1], Nicole Skoetz[2], Kathrin Grummich[3], Marie Becker[4], Lisa Joos[5], Gerhild Becker[5], Winfried Meissner[6], Christopher Boehlke[5]

[1]Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [2]Cochrane Cancer, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [3]Cochrane Germany, Cochrane Germany Foundation, Freiburg, Germany. [4]Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [5]Department of Palliative Care, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany. [6]Department for Anesthesiology and Intensive Care Medicine/ Department of Palliative Care, University Hospital of Jena, Jena, Germany

Contact: Vanessa Piechotta, vanessa.piechotta@uk-koeln.de.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New, published in Issue 8, 2021.

Citation: Andreas M, Piechotta V, Skoetz N, Grummich K, Becker M, Joos L, Becker G, Meissner W, Boehlke C. Interventions for palliative symptom control in COVID-19 patients. *Cochrane Database of Systematic Reviews* 2021, Issue 8. Art. No.: CD015061. DOI: 10.1002/14651858.CD015061.

ABSTRACT

Background

Individuals dying of coronavirus disease 2019 (COVID-19) may experience distressing symptoms such as breathlessness or delirium. Palliative symptom management can alleviate symptoms and improve the quality of life of patients. Various treatment options such as opioids or breathing techniques have been discussed for use in COVID-19 patients. However, guidance on symptom management of COVID-19 patients in palliative care has often been derived from clinical experiences and guidelines for the treatment of patients with other illnesses. An understanding of the effectiveness of pharmacological and non-pharmacological palliative interventions to manage specific symptoms of COVID-19 patients is required.

Objectives

To assess the efficacy and safety of pharmacological and non-pharmacological interventions for palliative symptom control in individuals with COVID-19.

Search methods

We searched the Cochrane COVID-19 Study Register (including Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), Embase, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), medRxiv); Web of Science Core Collection (Science Citation Index Expanded, Emerging Sources); CINAHL; WHO COVID-19 Global literature on coronavirus disease; and COAP Living Evidence on COVID-19 to identify completed and ongoing studies without language restrictions until 23 March 2021.

We screened the reference lists of relevant review articles and current treatment guidelines for further literature.

Selection criteria

We followed standard Cochrane methodology as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.

We included studies evaluating palliative symptom management for individuals with a confirmed diagnosis of COVID-19 receiving interventions for palliative symptom control, with no restrictions regarding comorbidities, age, gender, or ethnicity. Interventions comprised pharmacological as well as non-pharmacological treatment (e.g. acupressure, physical therapy, relaxation, or breathing techniques). We searched for the following types of studies: randomized controlled trials (RCT), quasi-RCTs, controlled clinical trials, controlled before-after studies, interrupted time series (with comparison group), prospective cohort studies, retrospective cohort studies, (nested) case-control studies, and cross-sectional studies.

We searched for studies comparing pharmacological and non-pharmacological interventions for palliative symptom control with standard care.

We excluded studies evaluating palliative interventions for symptoms caused by other terminal illnesses. If studies enrolled populations with or exposed to multiple diseases, we would only include these if the authors provided subgroup data for individuals with COVID-19. We excluded studies investigating interventions for symptom control in a curative setting, for example patients receiving life-prolonging therapies such as invasive ventilation.

Data collection and analysis

We used a modified version of the Newcastle Ottawa Scale for non-randomized studies of interventions (NRSIs) to assess bias in the included studies. We included the following outcomes: symptom relief (primary outcome); quality of life; symptom burden; satisfaction of patients, caregivers, and relatives; serious adverse events; and grade 3 to 4 adverse events.

We rated the certainty of evidence using the GRADE approach.

As meta-analysis was not possible, we used tabulation to synthesize the studies and histograms to display the outcomes.

Main results

Overall, we identified four uncontrolled retrospective cohort studies investigating pharmacological interventions for palliative symptom control in hospitalized patients and patients in nursing homes. None of the studies included a comparator. We rated the risk of bias high across all studies. We rated the certainty of the evidence as very low for the primary outcome symptom relief, downgrading mainly for high risk of bias due to confounding and unblinded outcome assessors.

Pharmacological interventions for palliative symptom control

We identified four uncontrolled retrospective cohort studies (five references) investigating pharmacological interventions for palliative symptom control. Two references used the same register to form their cohorts, and study investigators confirmed a partial overlap of participants. We therefore do not know the exact number of participants, but individual reports included 61 to 2105 participants. Participants received multimodal pharmacological interventions: opioids, neuroleptics, anticholinergics, and benzodiazepines for relieving dyspnea (breathlessness), delirium, anxiety, pain, audible upper airway secretions, respiratory secretions, nausea, cough, and unspecified symptoms.

Primary outcome: symptom relief

All identified studies reported this outcome. For all symptoms (dyspnea, delirium, anxiety, pain, audible upper airway secretions, respiratory secretions, nausea, cough, and unspecified symptoms), a majority of interventions were rated as completely or partially effective by outcome assessors (treating clinicians or nursing staff). Interventions used in the studies were opioids, neuroleptics, anticholinergics, and benzodiazepines.

We are very uncertain about the effect of pharmacological interventions on symptom relief (very low-certainty evidence). The initial rating of the certainty of evidence was low since we only identified uncontrolled NRSIs. Our main reason for downgrading the certainty of evidence was high risk of bias due to confounding and unblinded outcome assessors. We therefore did not find evidence to confidently support or refute whether pharmacological interventions may be effective for palliative symptom relief in COVID-19 patients.

Secondary outcomes

We planned to include the following outcomes: quality of life; symptom burden; satisfaction of patients, caregivers, and relatives; serious adverse events; and grade 3 to 4 adverse events.

We did not find any data for these outcomes, or any other information on the efficacy and safety of used interventions.

Non-pharmacological interventions for palliative symptom control

None of the identified studies used non-pharmacological interventions for palliative symptom control.

Authors' conclusions

We found very low certainty evidence for the efficacy of pharmacological interventions for palliative symptom relief in COVID-19 patients. We found no evidence on the safety of pharmacological interventions or efficacy and safety of non-pharmacological interventions for palliative symptom control in COVID-19 patients. The evidence presented here has no specific implications for palliative symptom control in COVID-19 patients because we cannot draw any conclusions about the effectiveness or safety based on the identified evidence. More evidence is needed to guide clinicians, nursing staff, and caregivers when treating symptoms of COVID-19 patients at the end of life. Specifically, future studies ought to investigate palliative symptom control in prospectively registered studies, using an active-controlled setting, assess patient-reported outcomes, and clearly define interventions.

The publication of the results of ongoing studies will necessitate an update of this review. The conclusions of an updated review could differ from those of the present review and may allow for a better judgement regarding pharmacological and non-pharmacological interventions for palliative symptom control in COVID-19 patients.

PLAIN LANGUAGE SUMMARY

Which treatments are best for symptoms in COVID-19 patients at the end of life?

The burden of symptoms at the end of life of COVID-19 patients and helpful treatments

COVID-19 patients may show symptoms such as breathlessness or delirium at the end of life. The goal of palliative medicine is to relieve such symptoms with specific treatments. Treatments can be drugs, for example opioids, or non-drugs, such as breathing techniques or relaxation.

What was the aim of our review?

To explore how well different interventions (drugs and non-drugs) work for the treatment of palliative symptoms in COVID-19 patients at the end of life. We included patients of all ages and with all comorbidities (additional medical conditions).

What type of studies did we search for?

We searched selected medical databases and trial registries until 23 March 2021. We included studies looking at how well different palliative treatments work to relieve COVID-19-associated symptoms at the end of life. We wanted to compare studies investigating different medicines or therapies, but we only found studies without a comparison group. Only one study reported the specific drugs used for individual symptoms.

Key results

We found four studies that were published in five papers. Individual papers included between 61 and 2105 participants, and two papers partially reported on the same participants. All of the included studies investigated different drug treatments for palliative symptom management in people with COVID-19.

Drugs for symptom control at the end of life

All of the included studies reported on the effectiveness of palliative care for symptom relief. In all studies, clinicians or nursing staff rated symptom relief rather than the patients themselves. Since the quality of the evidence was very low, we do not know the true effect of drug treatments on symptom relief and have very low confidence in the results of the studies. We did not find any data on quality of life; symptom burden; satisfaction of patients, caregivers, and relatives; or safety of the drug treatments.

Non-drug therapies for symptom control at the end of life

We did not find any data on the benefits and harms of non-drug therapies for symptom control of COVID-19 patients at the end of life.

Conclusions

Based on our findings, we could not draw any conclusions on palliative symptom control of people with COVID-19. Future studies need to be designed better so that we can determine which treatments work for symptom control in people with COVID-19.

SUMMARY OF FINDINGS

Summary of findings 1. Pharmacological interventions for palliative symptom control

Pharmacological interventions for palliative symptom control for patients with COVID-19

Patient or population: Patients with COVID-19

Intervention: Pharmacological interventions

Comparison: None

Outcome: Palliative symptom control

Outcome	Number of participants	Results	Certainty of the evidence	Plain text summary
Symptom relief	4 studies (5 references) with 61 to 2105 participants in individual studies[1]	All studies rated a majority of interventions as effective in relieving symptoms of breathlessness, agitation, dyspnea, delirium, pain, and others.	**Very low** Due to study design[2] and high risk of bias[3]	We are very uncertain about the effect of palliative care interventions including opioids, neuroleptics, anticholinergics, and benzodiazepines on symptom relief.
Quality of life	Based on data from 0 participants in 0 studies Follow-up: none	Outcome not reported.	N/A	Outcome not reported in any study.
Symptom burden	Based on data from 0 participants in 0 studies Follow-up: none	Outcome not reported.	N/A	Outcome not reported in any study.
Satisfaction of patients	Based on data from 0 participants in 0 studies Follow-up: none	Outcome not reported.	N/A	Outcome not reported in any study.
Satisfaction of caregivers	Based on data from 0 participants in 0 studies Follow-up: none	Outcome not reported.	N/A	Outcome not reported in any study.
Satisfaction of relatives	Based on data from 0 participants in 0 studies Follow-up: none	Outcome not reported.	N/A	Outcome not reported in any study.
Serious adverse events	Based on data from 0 participants in 0 studies Follow-up: none	Outcome not reported.	N/A	Outcome not reported in any study.
Grade 3 to 4 adverse events	Based on data from 0 participants in 0 studies Follow-up: none	Outcome not reported.	N/A	Outcome not reported in any study.

N/A: Not applicable

[1]Participants of the two cohorts reported on in Strang 2021 partially overlap, therefore we do not know the exact number of participants.
[2] Initial rating of certainty of the evidence: Rated low because all identified studies had a retrospective and uncontrolled design.
[3]Risk of bias: high. Lack of blinding of participants and personnel, resulting in the potential for detection bias in all studies. Lack of blinding of outcome assessors, resulting in the potential for detection bias in all studies. Selective outcome reporting, follow-up not reported, missing intention-to-treat analysis, use of unvalidated outcome measures in Alderman 2020, Lovell 2020, and Hetherington 2020, and use of subjective outcome measures in all studies. Imprecision: none. Publication bias: none. Inconsistency: difficult to assess. Indirectness of evidence: difficult to assess.

BACKGROUND

This work is part of a series of Cochrane Reviews investigating treatments and therapies for COVID-19. Reviews of this series share information in the Background section and methodology based on the first published reviews about monoclonal antibodies, Kreuzberger 2020, and convalescent plasma (Valk 2020a).

Description of the condition

COVID-19 is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; WHO 2020a). On 22 March 2020, the World Health Organization (WHO) declared the current COVID-19 outbreak a pandemic. COVID-19 is unprecedented in comparison to previous coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), with 813 and 858 deaths, respectively (WHO 2007; WHO 2019). Despite intensive international efforts to contain its spread, it has resulted in more than 180 million confirmed cases and more than 4 million deaths worldwide until July 2021 (WHO 2021a; WHO 2021b).

Several vaccines against COVID-19 have been distributed across countries, and an additional hundred vaccine candidates are in development at the time of the writing of this review (WHO 2021d). However, the process is time-consuming, and global access to vaccines differs widely (Wouters 2021). Moreover, the degree to which the vaccines can protect against variants of SARS-CoV-2 was still unclear at the date of publication (Forni 2021).

Specific risk factors for severe disease, hospitalization, and mortality have been identified: individuals aged 65 years or older, smokers, and those with certain underlying medical conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart conditions, immunocompromised state, obesity, sickle cell disease, or diabetes mellitus are more likely to have a severe course of the disease (Huang 2020; Liang 2020; WHO 2020a; Williamson 2020). COVID-19 case fatality varies widely between countries and reporting periods (from 1% to more than 19%; Johns Hopkins 2021). However, these numbers may be misleading due to varying testing frequency, lag in reporting dates, incomplete capturing of all cases, and variations in case definitions since the beginning of the pandemic (WHO 2020b).

Sore throat, cough, fever, headache, fatigue, and myalgia or arthralgia are the most commonly reported symptoms (Struyf 2020). Other symptoms include dyspnea, chills, nausea or vomiting, diarrhea, loss of taste and smell, and nasal congestion (WHO 2020a). The majority of people infected at the beginning of the pandemic had mild symptoms (approximately 80%, Wu 2020), or remained completely asymptomatic (Buitrago-Garcia 2020). Early data from China show that a smaller proportion (approximately 14%) are affected by severe or critical disease with intensive care unit (ICU) admittance due to respiratory failure, septic shock, or multiple organ dysfunction (Wu 2020).

At the time of the writing of this review, treatment consisted of supportive care with extracorporeal membrane oxygenation (ECMO), invasive ventilation, and non-invasive ventilation in severe cases, and oxygen supply in moderately severe cases (WHO 2021c). Few drugs were approved for the treatment of COVID-19, such as corticosteroids, monoclonal antibodies, or convalescent plasma. Recommendations for the use of corticosteroids, Siemieniuk 2020, and tocilizumab, Taskforce NCCE 2021; WHO 2021e, were given in clinical guidelines, but only for patients with severe or critical COVID-19 infection receiving oxygen. Other drugs, such as ivermectin and hydroxychloroquine, were not recommended for the treatment of COVID-19 at the point of review publication (WHO 2021e). Guidelines for symptom control (e.g. dyspnea) were mostly informed by studies of cancer patients and patients with COPD (Barnes 2016). As the course of COVID-19 is quite different from these diseases with respect to the rapid onset of symptoms (e.g. dyspnea) and the underlying cause of symptoms, evidence on interventions in COVID-19 patients is needed.

In light of evolving variants of the virus with increased transmissibility and possibly higher mortality (Challen 2021), the number of COVID-19-associated deaths might increase the need for adequate symptom control in a palliative situation. Moreover, we do not know if the needs of patients with COVID-19 will change with the appearance of new variants. The most prevalent symptoms in hospitalized patients with COVID-19 are dyspnea, cough, fatigue, myalgia (muscle pain), and delirium, with dyspnea being the most significant symptom in the dying (Keeley 2020). Delirium might be more prevalent in patients suffering from COVID-19 when compared to other diseases (Barron 2012; Kennedy 2020). Especially in the dying, multimodal (pharmacological and non-pharmacological) interventions are needed to alleviate symptoms and thus achieve best possible quality of life. If possible, these interventions should be provided by multiprofessional palliative care teams, but also by all other disciplines, such as intensive care or general medicine.

Description of the intervention

According to a recent consensus-based definition, palliative care is "the active holistic care of individuals across all ages with serious health-related suffering due to severe illness and especially of those near the end of life (Radbruch 2020)." Adequate palliative symptom control can significantly improve the quality of life for individuals and their families. This is considered in the WHO 2020c definition of palliative care: "Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." COVID-19 may be incurable or curable, and the treatment goals for these patients may change within hours. Based on the definition of palliative care by Radbruch 2020, we only included studies for patients “near the end of life,” and excluded studies addressing patients with curative treatment goals. We define “palliative symptom control” as palliative (not curative) interventions that aim at amelioration of symptoms in advanced COVID-19.

Palliative symptom control utilizes both pharmacological and non-pharmacological interventions, which are often provided by multiprofessional teams. At present, it is unclear which specific palliative interventions should be used for symptom control for individuals with COVID-19.

Pharmacological interventions might include the use of opioids and second-line benzodiazepines for the relief of dyspnea, or antipsychotics to alleviate symptoms of delirium (Mottiar 2020). Anticholinergics are used in the dying to reduce airway secretions ('death rattle') (Mercadamte 2014). Non-

pharmacological interventions include alternative interventions (e.g. Traditional Chinese Medicine) and psychological support, but also measures such as the discontinuation of interventions (Mottiar 2020). Non-pharmacological interventions can be a prelude to pharmacological interventions or can be used alongside pharmacological treatments. Even though research on symptom control is scarce, the National Institute for Health and Care Excellence (NICE) has published consensus-based guidelines for managing COVID-19-associated symptoms at the end of life (NICE 2020). For example, pharmacological treatments such as codeine linctus, codeine phosphate tablets, or morphine sulfate oral solution are recommended to treat breathlessness and cough; non-pharmacological treatments include controlled breathing techniques.

Palliative care interventions provided by palliative care teams decrease symptom intensity and improve quality of life among individuals with advanced cancer compared to standard cancer care alone (Gaertner 2017; Haun 2017). Similiar positive outcomes can be expected in COVID-19 patients if treated by palliative care teams.

How the intervention might work

The subjective perception of dyspnea, the difficulty to breathe, can appear without hypoxia or hypercapnia, but may be mediated via blood gas abnormalities (increase of partial pressure of carbon dioxide, decrease of oxygen, or both), detected by central chemoreceptors and processed in the respiratory center in the medulla and by cortical structures (Buchanan 2009). Furthermore, the muscular respiratory effort, as well as emotional, social, and psychological factors may significantly contribute to the sensation of dyspnea (Crombeen 2020; von Leupoldt 2007). Endogenous opioids may modulate breathlessness perception to be less unpleasant (Johnson 2020; Mahler 2013). Opioids may alleviate dyspnea via an altered response of the central nervous system to blood gas changes, resulting in a reduction of the respiratory drive (Banzett 2000; Pattinson 2009). Opioid-induced pain reduction and sedation decrease oxygen demand and carbon dioxide production. Benzodiazepines induce anxiolytic, sedative, and anti-agitative effects by gamma-aminobutyric acid (GABA)-receptor modulation (Griffin 2013). Antipsychotics (neuroleptics) for treatment of (terminal) delirium may act through antagonism at the dopamine (D2)-receptor (Hui 2020; Meagher 2018). Anticholinergics may reduce 'death rattle' through reducing airway secretions (Mercadamte 2014). Non-pharmacological interventions include psychological interventions (e.g. relaxation, imagination practices, controlled breathing techniques). They have beneficial effects on dyspnea through the reduction of tachypnea (von Leupoldt 2007).

Why it is important to do this review

There is a clear, urgent need for more information to guide symptom control and end-of-life care in people with COVID-19. Management of the symptoms most frequently encountered in COVID-19 patients, such as dyspnea, cough, fatigue, myalgia and agitation and delirium, is a central component of palliative care and reduces suffering at the end of life. Adequate symptom relief is therefore of utmost importance for patients, but also for relatives, and loved ones. Importantly, palliative care in the context of a pandemic poses new challenges, as the care has to be delivered in a quarantined context and often without families visiting the patient. Various recommendations for the control of these symptoms have been made in expert opinion statements by professional societies (Nehls 2020; NICE 2020). In addition, the first studies investigating symptom control in COVID-19 have been published. A systematic review and subsequent update of the available literature is needed to inform recommendations for action on symptom control of COVID-19 in the palliative setting.

OBJECTIVES

To assess the efficacy and safety of pharmacological and non-pharmacological interventions for palliative symptom control in individuals with COVID-19.

METHODS

Criteria for considering studies for this review

Types of studies

The main description of methods is based on the template for intervention reviews with non-randomized studies of the Cochrane Haematology review group. The protocol for this review was registered with the international prospective register of systematic reviews (PROSPERO) (Andreas 2021).

We planned to include randomized controlled trials (RCTs), and, if these were not available, the following types of studies in a top-down approach: quasi-RCTs, controlled clinical trials, controlled before-after studies, interrupted time series (with comparison group), prospective cohort studies, retrospective cohort studies, (nested) case-control studies, and cross-sectional studies.

As planned at the protocol stage, we included non-comparative study designs because we did not expect any evidence from RCTs. Randomized controlled studies are challenging in the palliative care setting for multiple reasons. For example, using placebo (or other) controls might not be ethically justifiable, as it could lead to unnecessary suffering at the end of life. Furthermore, dying people are often unable to consent to studies, and consent by proxy is complicated by the grief of the relatives. Especially in the field of palliative care, such issues are of major importance, because the vulnerable population and the unstable nature of the underlying diseases are associated with unexpected recruitment and attrition problems that demand the conduction of thoroughly performed feasibility trials (Shelby-James 2012).

We thus do not expect that any RCTs on this topic will be published soon. One controlled study investigating the effectiveness of morphine in the treatment of dyspnea in COVID-19 is currently being conducted (NCT04522037). However, information on the most effective symptom control in individuals with COVID-19 is acutely needed. For this reason, we decided to also include non-controlled studies.

We included studies with one or more participant(s) with COVID-19. We followed the suggestions specified in the *Cochrane Handbook for Systematic Reviews of Interventions* to the greatest degree possible and applied the methodology outlined in the following sections of this review (Higgins 2021). Further information on the methods we had planned should we have identified RCTs or non-randomized studies of interventions (NRSIs) is provided in Appendix 1.

We included full-text publications, preprints, abstract publications, results published in trials registries, and information received from personal communication with investigators if sufficient information was available on study design, characteristics of participants, interventions, and outcomes. We did not apply any limitations with respect to study setting (home-based, hospital, hospices, or nursing homes).

Types of participants

We included individuals with a confirmed diagnosis of COVID-19 receiving interventions for palliative symptom control with no restrictions regarding comorbidities, age, gender, or ethnicity.

We excluded studies evaluating palliative interventions for symptoms caused by other terminal illnesses. If studies enrolled populations with or exposed to diseases, we would only include such studies if the authors provided subgroup data for SARS-CoV-2 infection. We excluded studies investigating interventions for symptom control in a curative setting, for example patients receiving life-prolonging therapies such as invasive ventilation.

Types of interventions

We defined 'palliative symptom control' as palliative (not curative) interventions that aim to ameliorate symptoms in advanced COVID-19. We included the following interventions: palliative symptom control as a multidimensional and holistic approach, including:

- pharmacological interventions (including but not limited to opioids, benzodiazepines, neuroleptics, and anticholinergics);
- non-pharmacological interventions (including but not limited to acupressure, music therapy, physical therapy, distraction, breathing techniques, and relaxation).

In future updates, we plan to include the following comparisons for studies with a control arm:

- pharmacological intervention A (e.g. opioids) versus pharmacological intervention B or placebo for symptom control of dyspnea, cough, agitation/delirium;
- specialized palliative care versus standard care (specialized palliative care is given by specialized palliative care teams (e.g. palliative care consultation services in hospitals) in contrast to general palliative care (e.g. given by general practitioners)).

Types of outcome measures

We planned to evaluate the following outcomes.

Primary outcomes

- Symptom relief, comprising any change of subjective and potentially burdensome symptoms like dyspnea/shortness of breath, cough, anxiety, agitation, fatigue, myalgia, and delirium between baseline measurement before intervention and after intervention, measured with validated patient-reported outcome measures (e.g. visual analogue scale (VAS)), or other standardized instruments reported by patients, family members, or caregivers.

Secondary outcomes

- Quality of life, including fatigue and neurological functions, assessed with standardized scales (e.g. European Organisation for Research and Treatment of Cancer (EORTC), McGill Quality of Life Questionnaire).
- Symptom burden (e.g. distress thermometer, IPOS).
- Satisfaction of patients.
- Satisfaction of caregivers and relatives.
- Serious adverse events, defined as number of participants with event.
- Grade 3 to 4 adverse events, defined as number of participants with event.

Search methods for identification of studies

Electronic searches

For the identification of studies on interventions for palliative symptom control of COVID-19, we designed search strategies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2021). KG developed the search strategy based on input by clinicians. The search strategy was peer-reviewed by two Information Specialists experienced in the terminologies used in COVID-19 research (Ina Monsef and Maria-Inti Metzendorf). Due to the international urgency for research on COVID-19, we assumed that the abstracts of clinical trials would have been published in English. If the full-text publication was published in a language outside the abilities of our team, we would have involved Cochrane Task Exchange to identify people who were able to translate (taskexchange.cochrane.org).

Searches for evidence synthesis

We initially conducted a search for existing or planned evidence synthesis in the following sources.

Manual search

- Evidence Aid Coronavirus (COVID-19) (evidenceaid.org/evidence/coronavirus-covid-19/)
- Coronavirus (COVID-19) (the Cochrane Library) (www.cochranelibrary.com/covid-19) including Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), Embase, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), medRxiv
- Usher Network for COVID-19 Evidence Reviews (www.ed.ac.uk/usher/uncover)
- US Department of Veterans Affairs Evidence Synthesis Program (www.hsrd.research.va.gov/publications/esp/)
- Australian guidelines for the clinical care of people with COVID-19 (https://files.magicapp.org/guideline/8b6f065b-814f-41f0-a1a5-70279b722e19/published_guideline_4346-12_0.pdf)
- Norwegian Institute of Public Health systematic and living map on COVID-19 evidence (www.fhi.no/en/qk/systematic-reviews-hta/map/)
- COVID-19 Evidence Alerts from McMaster PLUS (www.evidencealerts.com/)
- L*OVE (iloveevidence.com/)
- TRIP (www.tripdatabase.com/)

- ECRI COVID-19 Resource Center (www.ecri.org/coronavirus-covid-19-outbreak-preparedness-center/)
- JBI Evidence Synthesis COVID-19 Collection (jbi.global/covid-19)
- NICE Coronavirus (COVID-19) (www.nice.org.uk/guidance/conditions-and-diseases/respiratory-conditions/covid19)

Database search

- MEDLINE (Ovid)

Manual search (planned evidence synthesis)

- Oxford COVID-19 Evidence Service—Current questions under review (www.cebm.net/oxford-covid-19-evidence-service/)
- Cochrane COVID Review Bank (covidreviews.cochrane.org/search/site)
- PROSPERO (www.crd.york.ac.uk/prospero/)

These initial searches were conducted on 27 November 2020. The search strategies are documented in Appendix 2, Appendix 3, and Appendix 4.

Searches for primary studies

We searched the following databases and trials registries for primary studies without any language limits, initially on 8 January 2021 and updated on 23 March 2021.

- Cochrane COVID-19 Study Register (covid-19.cochrane.org/)
- Web of Science (Science Citation Index/Emerging Sources)
- CINAHL (via EBSCO) (Cumulative Index to Nursing and Allied Health Literature)
- World Health Organization COVID-19 Global literature on coronavirus disease (search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/)
- COAP Living Evidence on COVID-19 (zika.ispm.unibe.ch/assets/data/pub/search_beta/)

The search strategies are documented in Appendix 2, Appendix 3, and Appendix 5.

If results were uploaded into trials registries and had not yet been published elsewhere, we integrated these data for the current review, and will add or replace data in future updates of this review in the case of publication.

Searching other resources

We handsearched reference lists of any included articles in order to identify any further relevant studies.

We checked the reference lists of all identified studies and relevant review articles identified by an additional literature search (the initial search) and current treatment guidelines for further literature. Please see Appendix 4 for additional information on our strategy.

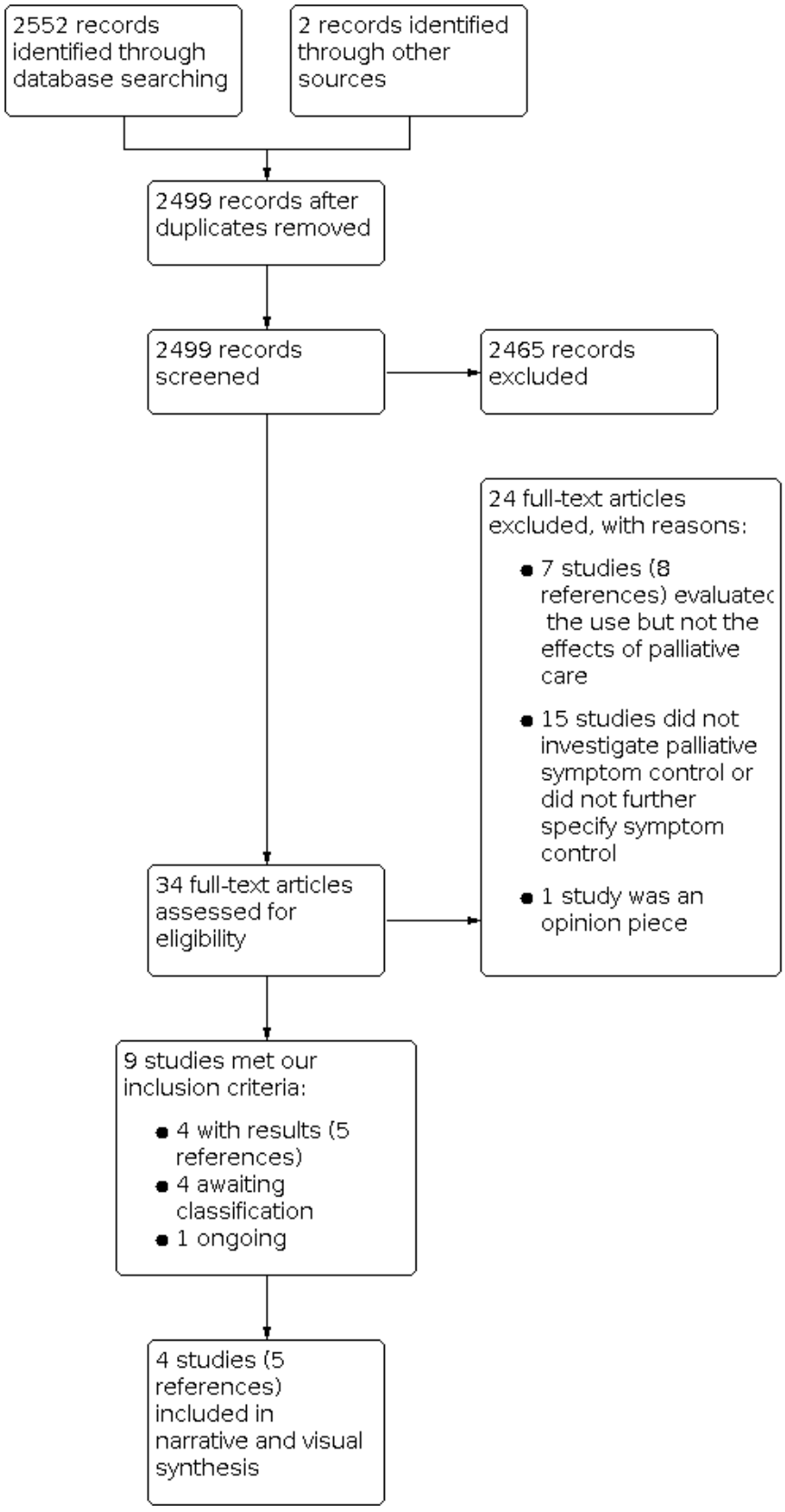
Data collection and analysis

Selection of studies

Three members of the review team (MA, CB, and LJ) independently screened the results of the search for eligibility by reading the abstracts. We coded the abstracts as either 'include' or 'exclude' using the software Rayyan (Ouzzani 2016). In the case of disagreement, or if it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Two review authors (MA and CB) assessed the full-text articles of selected studies. In case of disagreement, a third review author (VP) was consulted to reach a final decision.

We documented the study selection process in a flow chart, as recommended in the PRISMA statement (Moher 2009), and show the total numbers of retrieved references and the numbers of included and excluded studies (see Figure 1). Articles excluded after full-text assessment and the reasons for their exclusions are provided in Characteristics of excluded studies.

Figure 1. Study flow diagram.



Data extraction and management

We conducted data extraction and assessments according to the guidelines proposed by Cochrane (Li 2021). Two out of three review authors (MA, MB, and CB) performed all data extraction and assessments. Two other review authors (VP and WM) verified the accuracy and (where applicable) the plausibility of data extraction and assessments. We collated multiple reports of one study so that each study, rather than each report, was the unit of analysis. We extracted data using a customized data extraction form developed in Microsoft Excel (Microsoft 2018), and extracted the following information.

- General information: author, title, source, publication date, and country.
- Quality assessment and risk of bias: study design, confounding, selection bias, attrition bias, detection bias, and reporting bias.
- Study characteristics: study design, setting, and dates, source of participants, inclusion/exclusion criteria, comparability of groups, compliance with assigned treatment, and length of follow-up.
- Participant characteristics: age, gender, number of participants recruited/allocated/evaluated, disease, severity of disease, comorbidity, prevalence of symptoms and treated symptoms.
- Interventions: pharmacological and non-pharmacological treatment and mode of drug delivery.
- Outcomes: as specified in Types of outcome measures.

Assessment of risk of bias in included studies

We planned that if RCT data were available, we would use the RoB 2 tool to analyze the risk of bias in the underlying study results (Sterne 2019). If NRSI data were available, we would use the Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I) tool (Sterne 2016). Detailed information on how we had planned to assess risk of bias of RCTs and NRSIs is provided in Appendix 1.

To assess risk of bias in uncontrolled studies, we used a modified version of the Newcastle Ottawa Scale, provided by Mulder 2019.

As specified in Types of studies, we included uncontrolled studies only when we were unable to identify controlled studies.

Two review authors (MA and CB) assessed the included studies for methodological quality and risk of bias in accordance with the criteria outlined below and in Table 1. Any disagreements regarding the quality assessments were resolved by discussion, and two review authors (VP and WM) verified the accuracy and the plausibility of assessments. We performed and presented our judgements per outcome per study.

We assessed the following risk of bias domains.

Internal validity

- Unrepresentative study group (selection bias)
- Incomplete outcome assessment/follow-up (attrition bias)
- Outcome assessors unblinded to investigated determinants (detection bias)
- Important prognostic factors or follow-up not taken adequately into account (confounding)

External validity

- Poorly defined study group (reporting bias)
- Poorly defined follow-up (reporting bias)
- Poorly defined outcome (reporting bias)
- Poorly defined risk estimates (analyses)

For every criterion, we made a judgement using one of three response options:

- high risk of bias;
- low risk of bias;
- unclear risk of bias.

We used the highest rating to inform our overall risk of bias judgement per study outcome.

Measures of treatment effect

How we planned to measure the treatment effects of RCTs and NRSIs is discussed in Appendix 1.

For uncontrolled studies, we did not carry out an analysis using quantitative data from indirect controls, as we are aware of the difficulties of indirect comparisons of participant groups with varying baseline characteristics, especially in the absence of individual patient data. We did not meta-analyze the data, but provided information from individual studies per outcome within tables.

Unit of analysis issues

We collated multiple reports of one study so that each study, rather than each report, was the unit of analysis. We did not combine any data from different study designs.

How we planned to resolve unit of analysis issues occurring in RCTs is discussed in Appendix 1.

Dealing with missing data

A number of potential sources of missing data are suggested in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions*, which we took into account: at study level, at outcome level, and at summary data level (Higgins 2021). In the first instance, it is of the utmost importance to differentiate between data 'missing at random' and 'not missing at random.'

We requested missing data from the study authors. The authors of two studies provided us with missing data on interventions used and outcome assessment (Alderman 2020; Strang 2021). Additionally, we requested information on the exact numbers of participants in Strang 2021, as there was an overlap between the two cohorts reported on in the study.

Assessment of heterogeneity

As we identified uncontrolled studies only, meta-analysis was not appropriate. Instead, we described and presented results per study in tables, and discussed potential heterogeneity based on the methodological and clinical components of each included study.

How we planned to assess heterogeneity in meta-analysis is discussed in Appendix 1.

Assessment of reporting biases

As mentioned above, we searched trial registries to identify completed studies not published elsewhere, in order to minimize or determine whether there was publication bias.

How we plan to assess publication bias in future versions of this review is discussed in Appendix 6.

Data synthesis

We planned that if the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we would pool data in meta-analysis. We planned to perform analyses according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). We would not conduct meta-analyses that involved both RCTs and NRSIs. We planned to conduct separate meta-analyses for each comparison. How we planned to synthesize data from RCTs and NRSIs is discussed in Appendix 1.

Meta-analysis was not possible, therefore we synthesized study data without meta-analysis, using the Synthesis Without Meta-analysis (SWiM), Campbell 2020, guideline and Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions*, Reeves 2021, to inform our approach.

We presented outcome data individually per study within tables. For each table, we grouped studies per outcome and collated information on key study characteristics. We included information on study size, treated symptoms, and interventions for each included study. Furthermore, we visualized observed effects for each outcome and per study using histograms to portray the reported effects, so that outcome frequencies (e.g. for symptom relief) can be visually displayed and easily grasped by readers. We also noted risk of bias by color-coding and signs to guide the reader's interpretation of our synthesis.

Subgroup analysis and investigation of heterogeneity

Lack of adequate data precluded subgroup analysis.

How we plan to conduct subgroup analysis in future versions of this review is discussed in Appendix 6.

Sensitivity analysis

Lack of adequate data precluded sensitivity analysis.

How we plan to conduct sensitivity analysis in future versions of this review is discussed in Appendix 6.

Summary of findings and assessment of the certainty of the evidence

We created one summary of findings table and evaluated the certainty of the evidence using the GRADE approach.

Summary of findings

We used the MAGICapp software to create a summary of findings tables (MAGICapp 2020).

According to Chapter 14 of the updated *Cochrane Handbook for Systematic Reviews of Interventions*, the "most critical and/or important health outcomes, both desirable and undesirable, limited to seven or fewer outcomes" should be included in the summary of findings table(s) (Schünemann 2021). We prioritized outcomes most relevant for individuals with terminal illness, as follows.

- Symptom relief.
- Quality of life, including fatigue and neurological functions, assessed with standardized scales (e.g. McGill Quality of Life Questionnaire).
- Symptom burden (e.g. distress thermometer, IPOS).
- Satisfaction of patients.
- Satisfaction of caregivers and relatives.
- Serious adverse events, defined as number of participants with event.
- Grade 3 to 4 adverse events, defined as number of participants with event.

Assessment of the certainty in the evidence

We used the GRADE approach to assess the certainty of the evidence for the outcomes listed above.

The GRADE approach uses five domains (risk of bias, consistency of effect, imprecision, indirectness. and publication bias) to assess the certainty of the body of evidence for each prioritized outcome. According to GRADE guidance 18 (Schünemann 2019), the initial rating for randomized trials and NRSIs (the latter rated with ROBINS-I) is high certainty. As reported in the GRADE guidance 3, uncontrolled studies start from low-certainty evidence (Balshem 2011).

The certainty of the evidence can be downgraded for the following reasons:

- serious (−1) or very serious (−2) study limitations; or moderate (−1), serious (−2), or critical (−3) study limitations for NRSIs;
- serious (−1) or very serious (−2) inconsistency;
- serious (−1) or very serious (−2) indirectness;
- serious (−1) or very serious (−2) imprecise or sparse data;
- serious (−1) or very serious (−2) publication bias.

The certainty of the evidence can be upgraded for uncontrolled studies for:

- large effects;
- dose-response; and
- plausible confounding.

The GRADE system uses the following criteria for assigning grades of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We followed the current GRADE guidance for these assessments in its entirety as recommended in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021). We used our overall risk of bias judgements to inform decisions on downgrading for study limitations. We phrased the findings and certainty of the evidence as suggested in the informative statement guidance of the GRADE guidance (Santesso 2020).

RESULTS

Description of studies

Results of the search

We identified 2554 potentially relevant references (2552 from database searching and 2 from other sources). After removal of duplicates, we screened 2499 references based on their titles and abstracts, excluding 2465 references as irrelevant because they did not meet the prespecified inclusion criteria. We screened the full texts of the remaining 34 references, or, if these were not available, abstract publications or trial registry entries. We identified 9 eligible studies, four of which were assessed as awaiting classification as (complete) results had not yet been published (ChiCTR2000029994; Groninger 2021; Kelly 2020; Okuwoga 2020), and one study as ongoing as participants were still being recruited (NCT04522037).

The process and results of study selection are documented in the PRISMA flow diagram (Figure 1).

Included studies

Design and settings

An overview of the included studies and their characteristics is provided in Table 2.

We included four uncontrolled retrospective cohort studies (five references). Three studies originated from the United Kingdom (Alderman 2020; Hetherington 2020; Lovell 2020), and one from Sweden (Strang 2021). All four studies investigated symptom relief in people with COVID-19 in hospital palliative care. One study also included participants from nursing homes (Strang 2021). No study included a comparator.

Two references from Strang 2021 used the same register to form their cohorts, and study investigators confirmed a partial overlap of participants: the 253 participants who died in nursing homes reported on in the first cohort are a subset of 1903 participants who died in nursing homes included in the second cohort. It is unclear how big the overlap is between patients who died in hospitals in the first cohort (137) and nursing home residents who died in hospitals in the second cohort. However, the study authors estimate the overlap for the second group to be small. Consequently, we do not know the exact number of participants, but individual reports included 61 to 2105 participants.

The authors of two studies provided additional information upon request. Strang 2021 supplied us with information on the drugs prescribed for the study population and the size of the study population, and Alderman 2020 provided additional information on symptom measurement for shortness of breath and delirium.

Participants

Participants in the studies all had diagnosed COVID-19. The age of participants ranged from 30 to 107 years. The studies reported that participants showed symptoms of dyspnea, delirium, agitation, pain, audible upper airway secretions, respiratory secretions, nausea, fatigue, fever, and cough. No study provided information on the severity of symptoms. One study reported that the Australian-modified Karnofsky performance status of participants was 20, meaning that patients were bedfast and required extensive nursing care (Lovell 2020). Three studies reported comorbidities (Alderman 2020; Hetherington 2020; Lovell 2020). The most frequently reported comorbidities were hypertension, diabetes, COPD, respiratory diseases, dementia, and cancer. Strang 2021 did not investigate comorbidities. As older patients with comorbidities were included, we cannot be certain if COVID-19 was the cause of death for participants in the included studies.

Interventions

All studies used pharmacological interventions for palliative symptom control, but the medications used differed between studies. Overall, opioids, benzodiazepines, anticholinergics, neuroleptics, or a combination were given for symptom relief. Two studies specified the dosing of the drugs (Alderman 2020; Lovell 2020). Only one study specified which drugs were prescribed for which symptom (Alderman 2020). Three studies reported the mode of drug delivery. In Lovell 2020, 58 participants were prescribed a continuous subcutaneous infusion. Continuous subcutaneous infusion was also mentioned as one mode of drug delivery in Hetherington 2020. In Alderman 2020 syringe pumps were utilized in 41 (67%) of participants. Strang 2021 did not specify the mode of drug delivery. None of the studies used non-pharmacological interventions for palliative symptom control. None of the studies compared different interventions for palliative symptom control.

Treated symptoms included dyspnea, delirium, anxiety, pain, audible upper airway secretions, respiratory secretions, nausea, cough, and unspecified symptoms.

For details, see Characteristics of included studies.

Outcome measures

All studies assessed symptom relief. In Alderman 2020, symptom relief of shortness of breath was assessed by ward nurses noting whether the symptom was present every four hours. Symptom relief of delirium was assessed through modified Richmond Agitation and Sedation Scale (m-RASS) scores every four hours. In Lovell 2020, symptom relief was assessed via clinical impression of effectiveness based on follow-up documentation of symptoms. Possible answers were "yes," "no," and "unclear." Judgement of clinical effectiveness was made based on medical and nursing case notes. It is unclear who made the judgement. Likewise, in Hetherington 2020 symptom relief was assessed via clinical impression of efficacy. Possible answers were "effective," "partially effective," and "not effective." The judgement of clinical efficacy was made by specialist palliative care clinicians. Strang 2021 used data from the Swedish Register of Palliative Care (SRPC), which is a national quality register that focuses on palliative care in the last week of life. It is built on data assessed with an anonymized end-of-life questionnaire (ELQ). The ELQ is answered retrospectively

by medical staff as soon as possible after a patient dies. The ELQ contains 30 questions and provides information on provided care content and quality during the last week of life, demographics, the occurrence of breakthrough symptoms (regardless of intensity), and, if symptoms occur, the degree of symptom alleviation during the last week of life (Svenska Palliativregistret 2021). Data in all studies were collected retrospectively.

No other predefined outcome was reported in the included studies.

For details, Characteristics of included studies.

Studies awaiting classification

We identified one RCT from a trial registry in China that might be relevant to this review (ChiCTR2000029994). We contacted the authors of the study to request missing information, but received no reply. In addition, we identified three relevant conference abstracts, but data for these studies had not yet been published (Groninger 2021; Kelly 2020; Okuwoga 2020). Data from these three studies would add a further 384 participants. Interventions investigated in these studies are Liu Zi Jue Qigong and acupressure (ChiCTR2000029994); pharmacological interventions such as morphine to manage dyspnea (Kelly 2020); injectable medications for symptom relief of agitation and delirium (Okuwoga 2020); and benzodiazepines and neuroleptics for not further classified symptoms (Groninger 2021).

Ongoing studies

We identified one ongoing study that is still recruiting participants (NCT04522037). This controlled study aims to investigate morphine to manage dyspnea in COVID-19 patients.

Excluded studies

We excluded 23 studies (24 references), as follows.

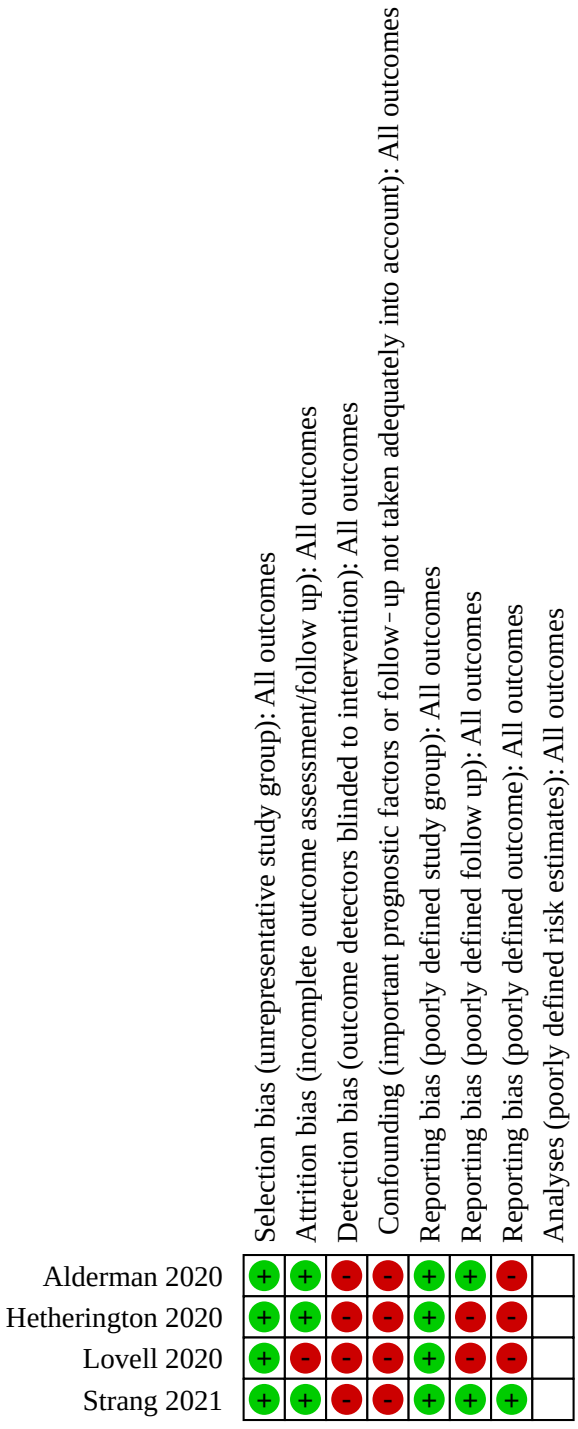
- Seven studies (eight references) evaluated the use but not the effects of palliative care (Haydar 2020; Heath 2020; Pavlu 2020; Rao 2021; Riva 2020; Sun 2020; Turner 2020).
- Fifteen studies did not investigate palliative symptom control or did not further specify symptom control (ACTRN12620000443998p; Allande Cussó 2020; Anneser 2020; Bisson 2020; Cook 2020; Delisle 2020; Galazzi 2020; ISRCTN16561225; Johnston 2020; Lee 2020; Lopez 2020; Martinsson 2021; Mumoli 2021; Paice 2021; Ritchey 2020).
- One study was an opinion piece (Mendoza 2020).

Risk of bias in included studies

Overall judgement

We rated the risk of bias within and across studies overall to be high. In addition to the high risk of bias related to the non-randomised and uncontrolled study design, we assessed the internal and external validity as outlined in the 'risk of bias assessment criteria for observational studies' tool provided by the Cochrane Childhood Cancer Group (Table 1) (Mulder 2019). The full judgement per trial and category is presented in Figure 2, and the support for judgement in the Characteristics of included studies table.

Figure 2. Summary of risk of bias.



Allocation

We considered all studies to be at low risk of selection bias since all studies were retrospective cohort studies that included all patients in palliative care in a certain time frame.

Blinding

All studies were unblinded to interventions and therefore at high risk of detection bias for subjective outcomes. The outcome symptom relief was assessed by physicians or hospital staff, thus all studies were at high risk of detection bias.

Incomplete outcome data

We assessed attrition bias in terms of whether studies (equally) assessed outcomes for all participants. We evaluated attrition bias for the outcome symptom relief. We rated attrition bias as high for one study (Lovell 2020), as 13 participants died before follow-up. We rated attrition bias as low for Alderman 2020, Hetherington 2020, and Strang 2021, as the authors only measured symptom relief in participants that had died or had been discharged retrospectively. We considered outcome assessment to be complete for these three studies.

Selective reporting

We assessed reporting bias in terms of whether the study group and intervention were well defined and whether the outcomes were equally reported for all participants.

We evaluated reporting bias for the outcome symptom relief.

Poorly defined study group and intervention

We judged the risk of reporting bias to be high for all studies. While the study population was well defined in all studies, the interventions were not well described. Only Alderman 2020 specified which pharmacological treatment was used to treat which symptoms. Furthermore, only two studies listed the doses of the pharmacological interventions (Alderman 2020; Lovell 2020).

Poorly defined outcomes

We considered the risk of reporting bias to be high for three studies (Alderman 2020; Hetherington 2020; Lovell 2020), as symptom relief was measured subjectively by physicians and hospital staff responsible for palliative care. Symptom relief was measured on a validated scale in Strang 2021, resulting in a judgement of low risk of reporting bias for this study.

Poorly defined follow-up

We considered the risk of reporting bias for follow-up to be high for Hetherington 2020 and Lovell 2020, as the authors did not clearly define length of follow-up. We judged the risk of reporting bias for follow-up to be low for Alderman 2020 and Strang 2021, as participants were followed up until death.

Other potential sources of bias

Confounding

None of the included studies adjusted for confounding factors such as age, gender, or comorbidities of participants, therefore all studies were at high risk of confounding.

Poorly defined risk estimates

None of the studies performed any statistical analyses.

Effects of interventions

See: **Summary of findings 1** Pharmacological interventions for palliative symptom control

Pharmacological interventions for palliative symptom control

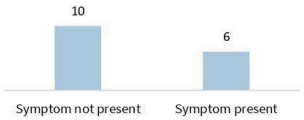
We identified four uncontrolled retrospective cohort studies investigating pharmacological interventions for palliative symptom control in hospitalized patients and patients in nursing homes. None of the studies included a comparator. See Summary of findings 1.

Primary outcome

Symptom relief

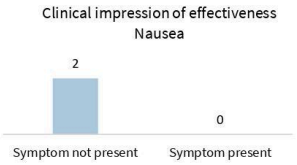
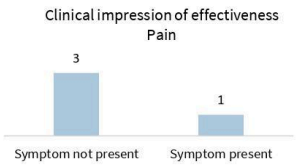
All studies reported symptom relief. Statistical pooling of data was not possible due to heterogenous studies and participant and intervention characteristics. We summarized and visualized data per study in Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8, Figure 9, Figure 10, Figure 11 and below.

Figure 3. Visual synthesis of Alderman 2020

Study	Symptoms [A]	Interventions [B]	Outcome Definition	Symptom relief	Risk of Bias
Alderman, Webber, Davies 2020 N = 91 (61 analyzed)	Shortness of breath (n=35)	Shortness of breath: Opioids (n=14) Shortness of breath + Anxiety: Opioids and Benzodiazepines (n=7)	Effectiveness for symptom control (numbers of patients showing the symptom, evaluated by ward nursing staff every four hours)	Clinical impression of effectiveness shortness of breath (within 4 hours)  	High
	Agitation/Delirium (n=34)	Agitation/Delirium: Neuroleptics (first-line treatment) (n=7) Neuroleptics (second-line treatment) (n=15) Neuroleptics and Benzodiazepines (third-line treatment) (n=1)		m-RASS score of 3 (n=1) for two consecutive assessments, no m-RASS score of 4 during the last 72 h of life. 14 (out of 14) participants who were started on a continuous subcutaneous infusion at the initial assessment had relief of their agitation within 4 h. 7 had no further episodes of agitation.	High
	Audible upper airway secretions (n=11)	Anticholinergics (n=8)		1 participant did not respond to medication	High

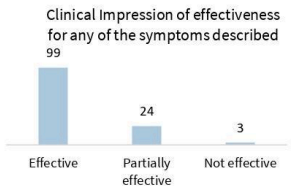
[A] Absolute number of patients showing respective symptoms at baseline.
[B] Absolute number of patients receiving respective interventions.

Figure 4. Visual synthesis for Alderman 2020

Study	Symptoms [A]	Interventions [B]	Outcome Definition	Symptom relief	Risk of Bias
Alderman, Webber, Davies 2020 N = 91 (61 analyzed)	Nausea (n=2)	Neuroleptics (n=1)	Effectiveness for symptom control (numbers of patients showing the symptom, evaluated by ward nursing staff every four hours)		High
	Pain (n=4)	Opioids (n=3)			High

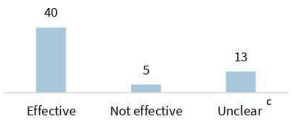
[A] Absolute number of patients showing respective symptoms at baseline.
[B] Absolute number of patients receiving respective interventions.

Figure 5. Visual synthesis for Hetherington 2020

Study	Symptoms [A]	Interventions [B]	Outcome Definition	Symptom relief	Risk of Bias
Hetherington et al. 2020 N = 186	Dyspnea (n=116) Agitation (n=82) Pain (n=35) Delirium (n=18) Cough (n=15) Anxiety (n=12) Fever (n=11) Secretions (n=10) Nausea/Vomiting (n=11) Fatigue (n=6) Drowsiness (4)	Opioids + Benzodiazepines (n=90) Opioids + Benzodiazepines + Anticholinergics (n=19) Opioids alone (n=6) Opioids + Benzodiazepines + Neuroleptics (n=11) Other (n=14)	"Symptoms and clinical impression of efficacy was sought from case note documentation in contemporaneous notes made by specialist Palliative Care clinicians throughout admission." Effective = symptoms improved, and no further titration required Partially effective = improvement in symptoms but further titration advised	 n = 126 (140 patients received infusion) Missing data for 14 patients who received infusion The remaining 46 patients did not receive infusion for symptom control	High

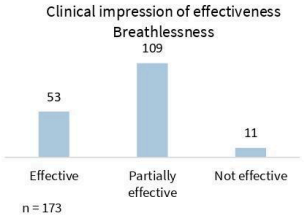
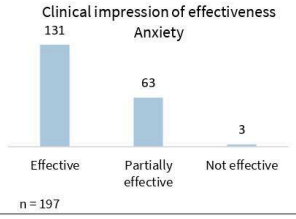
[A] Absolute number of patients showing respective symptoms at baseline.
[B] Absolute number of patients receiving respective interventions.

Figure 6. Visual synthesis for Lovell 2020

Study	Symptoms [A]	Interventions [B]	Outcome Definition	Symptom relief	Risk of Bias
Lovell et al. 2020 N = 101	Breathlessness (n=67) Agitation (n=43) Drowsiness (n=36) Delirium (n=24) Pain (n=23) Secretions (n=11) Fatigue (n=9) Fever (n=9) Cough (n=4) Diarrhea (n=3) Reduced oral intake (n=3) Anxiety (n=2) Seizures (n=1) Ascites (n=1) Incontinence (n=1) Dysuria (n=1)	Opioids + Benzodiazepines (n=36) Opioids + Benzodiazepines + Anticholinergics (n=11) Opioids alone (n=6) Opioids + Benzodiazepines + Neuroleptics (n=2) Benzodiazepines alone (n=1) Opioids + Neuroleptics (n=1) Opioids + Antihistamines (n=1)	"Clinical impressions of effectiveness were determined based on documentation at follow-up (e.g., improved breathing, agitation, comfort). "	Clinical Impression of effectiveness for any of the symptoms described  n = 58 (58 patients received infusion) The remaining 43 patients did not receive infusion for symptom control	High

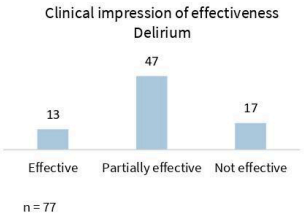
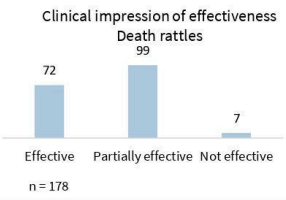
[A] Absolute number of patients showing respective symptoms at baseline.
[B] Absolute number of patients receiving respective interventions.
[C] Unclear refers to patients dying before follow-up.

Figure 7. Visual synthesis for Strang 2021a

Study	Symptoms [A]	Interventions [B]	Outcome Definition	Symptom relief	Risk of Bias
Strang et al. 2021a[C] N = 390	Breathlessness (n=173)	Strong Opioids (n=376) Tranquilizers (n=376) Anticholinergics (n=370) Antiemetics (n=357)	The degree of symptom relief during the last week of life recorded on a 3-grade scale as complete—partial—no relief.		X High
	Anxiety (n=197)				X High

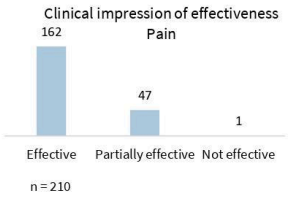
[A] Absolute number of patients showing respective symptoms at baseline.
[B] Absolute number of patients receiving respective interventions.
[C] Participants of Strang 2021a and b partially overlap.

Figure 8. Visual synthesis for Strang 2021a

Study	Symptoms [A]	Interventions [B]	Outcome Definition	Symptom relief	Risk of Bias
Strang et al. 2021a[C] N = 390	Delirium (n=77)		The degree of symptom relief during the last week of life recorded on a 3-grade scale as complete—partial—no relief.		High
	Death rattles (n=178)				High

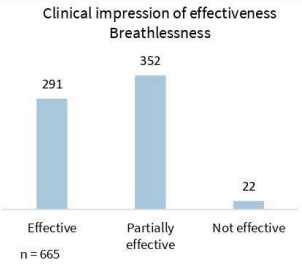
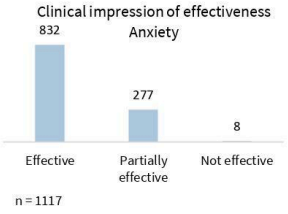
[A] Absolute number of patients showing respective symptoms at baseline.
[B] Absolute number of patients receiving respective interventions.
[C] Participants of Strang 2021a and b partially overlap.

Figure 9. Visual synthesis for Strang 2021a

Study	Symptoms [A]	Interventions [B]	Outcome Definition	Symptom relief	Risk of Bias
Strang et al. 2021a[C] N = 390	Pain (n=210)		The degree of symptom relief during the last week of life recorded on a 3-grade scale as complete—partial—no relief.		High

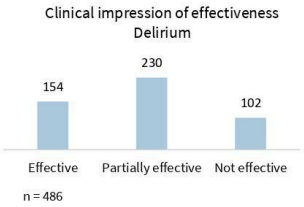
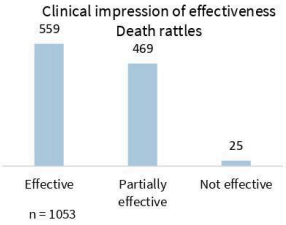
[A] Absolute number of patients showing respective symptoms at baseline.
[B] Absolute number of patients receiving respective interventions.
[C] Participants of Strang 2021a and b partially overlap.

Figure 10. Visual synthesis for Strang 2021b

Study	Symptoms [A]	Interventions [B]	Outcome Definition	Symptom relief	Risk of Bias
Strang et al. 2021b [C] N = 2105	Breathlessness (n=665)	Strong Opioids (n=2019) Tranquilizers (n=2014) Anticholinergics (n=1915) Antiemetics (n=2000)[D]	The degree of symptom relief during the last week of life recorded on a 3-grade scale as complete—partial—no relief.		High
	Anxiety (n=1117)				High

[A] Absolute number of patients showing respective symptoms at baseline.
[B] Absolute number of patients receiving respective interventions.
[C] Participants of Strang 2021a and b partially overlap.
[D] Data were not published in paper, but shared with us by the authors.

Figure 11. Visual synthesis for Strang 2021b

Study	Symptoms [A]	Interventions [B]	Outcome Definition	Symptom relief	Risk of Bias
Strang et al. 2021b [C] N = 2105	Delirium (n=486)		The degree of symptom relief during the last week of life recorded on a 3-grade scale as complete—partial—no relief.		X High
	Respiratory secretions (n=1053)				X High

[A] Absolute number of patients showing respective symptoms at baseline.
[B] Absolute number of patients receiving respective interventions.
[C] Participants of Strang 2021a and b partially overlap.
[D] Data were not published in paper, but shared with us by the authors.

Alderman 2020 reported on 61 participants. Symptom relief for breathlessness was assessed by ward nurses during four-hourly reviews, who indicated through a "yes/no" answer whether the symptom was present or not. A continuous subcutaneous infusion of morphine was applied to relieve shortness of breath. After four hours, the symptom was not present in 10 out of 16 participants. Relief for delirium was assessed by m-RASS scores reported by nursing staff every four hours. Fourteen of 14 participants who were started on a continuous subcutaneous infusion either of haloperidol (first-line treatment; n = 7), levomepromazine (second-line treatment; n = 14), or levomepromazine and midazolam (third-line treatment; n = 1) at the initial assessment had relief of agitation/delirium within four hours. Seven of these participants had no further episodes of agitation. In the last 72 hours of life, only one participant of the cohort had an m-RASS score as high as three (very agitated), and no participant had an m-RASS score of four (combative). One of 11 participants with persistent audible upper airway secretions did not respond to glycopyrronium, and two participants with nausea, one of whom was treated with haloperidol, did not have nausea at final assessment. One of four participants had pain at final assessment. For a visual synthesis, please see Figure 3 and Figure 4.

Hetherington 2020 reported on 186 participants. Symptom relief was not measured on a standardized scale, but assessed by a palliative care specialist in 126 participants to be "effective," "partially effective," or "not effective." The study authors described pharmacological treatment for symptom control as "effective" in 99 of 126 (79%) participants; "partially effective" in 24 of 126 (19%) participants; and "not effective" in 3 of 126 (2%) participants. No further information was provided with regard to the definition or assessment of effectiveness. For a visual synthesis, please see Figure 5.

Lovell 2020 reported on 101 participants. The clinical impression of effectiveness was determined based on documentation at follow-up. Possible answers for the clinical impression of effectiveness were "yes," "no," and "unclear." The study authors described pharmacological treatment for symptom control as effective for 40 of 58 (69%) participants and not effective for 5 of 58 (9%) participants. Treatment effectiveness was rated as unclear for 13 (22%) participants who died before follow-up. Effectiveness was not measured on a standardized scale. For a visual synthesis, please see Figure 6.

Strang 2021 reported on two cohorts extracted from the same registry. We do not know how many participants were reported on twice, and the study investigators were unable to provide this precise information. The first cohort encompassed 390 participants (data retrieved April 2020). Clinical impression of the effectiveness of symptom relief was rated on the ELQ for each participant by the nurse or physician responsible for palliative care. Answer alternatives were "completely relieved," "partly relieved," and "not relieved at all." Complete relief was reached in 53 of 173 (31%) participants with breathlessness, 131 of 197 (66%) participants

with anxiety, 13 of 77 (17%) participants with delirium, 72 of 178 (40%) participants with death rattles, and 162 of 210 (77%) participants with pain. Partial relief was reached in 109 of 173 (63%) participants with breathlessness, 63 of 197 (32%) participants with anxiety, 47 of 77 (61%) participants with delirium, 99 of 178 (56%) of participants with death rattles, and 47 of 210 (22%) participants with pain. No relief was reached in 11 of 173 (6%) participants with breathlessness, 3 of 197 (2%) participants with anxiety, 17 of 47 (36%) participants with delirium, 7 of 178 (4%) participants with death rattles, and 1 of 210 (0.5%) participants with pain.

Additionally, Strang 2021 reported symptom relief separately for the subgroups of nursing home residents who died in nursing homes and those who died in the hospital in this cohort. For 253 participants who died in nursing homes, complete relief was reached in 35 of 84 (42%) participants with breathlessness, 96 of 131 (%) participants with anxiety, 7 of 38 (18%) participants with delirium, 54 of 118 (46%) participants with death rattles, and 122 of 147 (83%) participants with pain. Partial relief in this subgroup was reached in 45 of 84 (54%) participants with breathlessness, 33 of 131 (25%) participants with anxiety, 21 of 38 (55%) participants with delirium, 61 of 118 (52%) participants with death rattles, and 25 of 147 (17%) participants with pain. No relief was reached in 4 of 84 (5%) participants with breathlessness, 2 of 131 (2%) participants with anxiety, 10 of 38 (26%) participants with delirium, 3 of 118 participants (3%) with death rattles, and no participants with pain. For 137 participants who died in the hospital, complete relief was reached in 18 of 89 (20%) participants with breathlessness, 35 of 66 (53%) participants with anxiety, 6 of 39 (15%) participants with delirium, 18 of 60 (30%) participants with death rattles, and 40 of 63 (63%) participants with pain. Partial relief in this subgroup was reached in 64 of 89 (72%) participants with breathlessness, 30 of 66 (45%) participants with anxiety, 26 of 39 (67%) participants with delirium, 38 of 60 (63%) participants with death rattles, and 22 of 63 (35%) participants with pain. No relief was reached in 7 of 89 (8%) participants with breathlessness, 1 of 66 (2%) participants with anxiety, 7 of 39 (18%) participants with delirium, 4 of 60 (7%) participants with death rattles, and 1 of 63 (2%) participants with pain. For a visual synthesis, please see Figure 7, Figure 8 and Figure 9.

The second cohort reported on by Strang 2021 was retrieved in August 2020. The number of participants assessed was 2105. Complete relief was reached in 291 of 665 (44%) participants with breathlessness, 832 of 1117 (74%) participants with anxiety, 154 of 486 (32%) participants with delirium, and 559 of 1053 (53%) participants with respiratory secretions. Partial relief was reached in 352 of 665 (53%) participants with breathlessness, 277 of 1117 (25%) participants with anxiety, 230 of 486 (47%) participants with delirium, and 469 of 1053 (45%) participants with respiratory secretions. No relief was reached in 22 of 665 (3%) participants with breathlessness, 8 of 1117 (0.7%) participants with anxiety, 102 of 486 (21%) participants with delirium, and 25 of 1053 (2%) participants with respiratory secretions.

Additionally, Strang 2021 reported symptom relief separately for the subgroups of nursing home residents who died in nursing homes and those who died in the hospital in this cohort. In 1903 nursing home patients, complete relief was reached in 261 of 556 (47%) participants with breathlessness, 769 of 1015 (76%) participants with anxiety, 148 of 423 (35%) participants with delirium, and 530 of 956 (55%) participants with respiratory secretions. Partial relief was reached in 280 of 556 (50%) participants with breathlessness, 238 of 1015 (23%) participants with anxiety, 198 of 423 (47%) participants with delirium, and 408 of 956 (43%) participants with respiratory secretions. No relief was reached in 15 of 556 (3%) participants with breathlessness, 8 of 1015 (0.8%) participants with anxiety, 77 of 423 (18%) participants with delirium, and 18 of 956 (2%) participants with respiratory secretions. For 202 nursing home patients who died in the hospital, complete relief was reached in 30 of 109 (28%) participants with breathlessness, 63 of 102 (62%) participants with anxiety, 6 of 63 (10%) participants with delirium, and 29 of 97 (30%) participants with respiratory secretions. Partial relief was reached in 72 of 109 (66%) participants with breathlessness, 39 of 102 (38%) participants with anxiety, 32 of 63 (51%) participants with delirium, and 61 of 97 (63%) participants with respiratory secretions. No relief was reached in 7 of 109 (6%) participants with breathlessness, 0 of 102 (0%) participants with anxiety, 25 of 63 (40%) participants with delirium, and 7 of 97 (7%) participants with respiratory secretions. For a visual synthesis, please see Figure 10 and Figure 11.

In summary, all studies rated a majority of interventions as effective to relieve dyspnea, delirium, anxiety, pain, audible upper airway secretions, respiratory secretions, nausea, cough, and unspecified symptoms. We are very uncertain about the effect of opioids, neuroleptics, anticholinergics, and benzodiazepines on symptom relief in individuals with COVID-19. The initial rating of the certainty of the evidence was low due to the non-randomized study design. Additionally, our main reason for downgrading the certainty of the evidence was high risk of bias due to confounding and unblinded outcome assessors.

Secondary outcomes

We planned to assess the following secondary outcomes.

- Quality of life, including fatigue and neurological functions, assessed with standardized scales (e.g. McGill Quality of Life Questionnaire).
- Symptom burden (e.g. distress thermometer, IPOS).
- Satisfaction of patients.
- Satisfaction of caregivers and relatives.
- Serious adverse events, defined as number of participants with event.
- Grade 3 to 4 adverse events, defined as number of participants with event.

However, none of the included studies provided data for these outcomes, or any other information to describe the efficacy and safety of used interventions.

Non-pharmacological interventions for palliative symptom control

None of the included studies used non-pharmacological interventions for palliative symptom control.

DISCUSSION

Summary of main results

The aim of this systematic review was to synthesize all available evidence on pharmacological and non-pharmacological treatment options for palliative symptom control in people with COVID-19.

We identified four retrospective cohort studies from the United Kingdom and Sweden. None of the studies included a comparator.

The identified studies used different pharmacological treatments for symptom control; none of the studies used non-pharmacological interventions. The treatments were opioids, neuroleptics, anticholinergics, and benzodiazepines. Pharmacological interventions were used to control dyspnea, delirium, anxiety, pain, audible upper airway secretions, respiratory secretions, nausea, cough, and unspecified symptoms. The results and the certainty of the evidence for the main outcomes are summarized in the summary of findings table (Summary of findings 1), the evidence synthesis table (Figure 3), and below for the outcome symptom relief.

Effects of interventions

Pharmacological interventions for palliative symptom control

Primary outcome: symptom relief

We identified four retrospective cohort studies (five references) reporting this outcome. Two references used the same register to form their cohorts, and study investigators confirmed a partial overlap of participants. We therefore do not know the exact number of participants, but individual reports included 61 to 2105 participants. For all symptoms (dyspnea, delirium, anxiety, pain, audible upper airway secretions, respiratory secretions, nausea, cough, and unspecified symptoms), a majority of interventions were rated as completely or partially effective by outcome assessors. Interventions were opioids, neuroleptics, anticholinergics, and benzodiazepines.

We are very uncertain about the effect of pharmacological interventions on symptom relief (very low-certainty evidence). Based on the uncontrolled study design, we do not know whether one treatment worked better than other treatments for individuals with COVID-19. The initial rating of the certainty of the evidence was low due to the non-randomized study design. Additionally, our main reason for downgrading the certainty of the evidence was high risk of bias due to confounding and unblinded outcome assessors.

Secondary outcomes

We planned to include the following outcomes: quality of life; symptom burden; satisfaction of patients, caregivers, and relatives; serious adverse events; and grade 3 to 4 adverse events.

We did not find any data on these outcomes, or any other information on the efficacy and safety of used interventions.

Non-pharmacological interventions for palliative symptom control

None of the included studies used non-pharmacological interventions for palliative symptom control.

Overall completeness and applicability of evidence

The included studies reported data for one of our predefined outcomes. We found very low-certainty evidence about the effect of multimodal pharmacological interventions (opioids, neuroleptics, anticholinergics, and benzodiazepines) on relieving dyspnea, delirium, anxiety, pain, audible upper airway secretions, respiratory secretions, nausea, cough, and unspecified symptoms, at the end of life. None of the studies provided information on quality of life; symptom burden; satisfaction of patients, caregivers, and relatives; or adverse events and serious adverse events.

The identified evidence has a limited informative value with regard to our review question because the described pharmacological interventions could not be matched to the reported outcomes, and there was no control for the interventions. Furthermore, outcomes for symptom relief were assessed by clinical staff and not by the patients themselves. Although it is not always possible for palliative patients to report their symptoms themselves, self-reported outcome measures remain the gold standard and should be used whenever possible (Antunes 2014). If this is not feasible, for example for ethical reasons, the perspectives of family members, carers, or clinicians can be assessed. The average age of participants receiving the interventions was rather high, reflecting that COVID-19-related mortality increases with age (Williamson 2020). The pharmacological interventions used in the studies are commonly used in palliative care: opioids for relief of pain and dyspnea, neuroleptics for relief or prophylaxis of nausea and vomiting and relief of agitation/delirium, anticholinergics for relief of cough and death rattle, and benzodiazepines for relief of dyspnea, agitation, delirium, and for palliative sedation when necessary (Bausewein 2020). The included studies were not designed to provide detailed information on the effectiveness and safety of every used medication. We did not identify any study exploring non-pharmacological interventions for palliative symptom control in people with COVID-19. The review question could therefore not be properly answered by the available evidence.

We identified one controlled study investigating the effectiveness of morphine for dyspnea in individuals with COVID-19 in a controlled setting that is still ongoing (NCT04522037), and one RCT investigating the effects of acupressure therapy and Liu Zi Jue Qigong exercises on dyspnea and quality of life in individuals with COVID-19 that has not yet published results (ChiCTR2000029994). We further identified abstracts to three studies that might have relevant information on palliative symptom control once full texts are published (Groninger 2021; Kelly 2020; Okuwoga 2020). Results from these studies might add relevant information to this review and possibly necessitate an update.

Quality of the evidence

Certainty of the evidence

Pharmacological interventions for palliative symptom control

We assessed the certainty of evidence for the outcome symptom relief. None of the other prioritized outcomes of this review were reported in the included studies.

We have very low confidence in the identified evidence on symptom relief. All identified studies had a retrospective and uncontrolled design, thus the initial level of certainty was rated as low. Furthermore, we downgraded the level of certainty once because of study limitations due to risk of bias and confounding, reaching a very low level of certainty. Serious study limitations led to a judgement of high risk of detection and selection bias. Studies were not adjusted for potential confounders (e.g. age or gender of participants). It was difficult to assess imprecision and publication bias for the available studies, as results were not quantifiable.

We did not identify any studies reporting on the effects of pharmacological interventions on quality of life; satisfaction of patients, caregivers, or relatives; and symptom burden in people dying of COVID-19, thus we cannot make a judgement on how to best address these outcomes. We also did not identify any studies reporting on adverse events or serious adverse events, and therefore do not know which adverse events, if any, are associated with pharmacological interventions.

Non-pharmacological interventions for palliative symptom control

We do not know whether non-pharmacological interventions are effective and safe for palliative symptom control in people with endstage COVID-19, because we did not identify any studies investigating non-pharmacological interventions.

Potential biases in the review process

To avoid potential bias in the review process, we were committed at all times to conduct a systematic review that followed published guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

While we published a protocol for this review beforehand (Andreas 2021), we did not publish a peer-reviewed Cochrane Review protocol due to time constraints for this high-priority review in this very critical area of research during the COVID-19 pandemic. This review was based on a peer-reviewed protocol of a series on interventions for COVID-19 (Valk 2020b). However, since PICOs between the reviews differ, this could potentially lead to bias.

As COVID-19 is a novel disease, results from RCTs are not yet available for palliative symptom control. Consequently, we included only data from retrospective cohort studies. As little guidance exists on how to synthesize studies where meta-analysis is not possible, we had to develop an appropriate synthesis method. Our approach was informed by the SWiM (Synthesis Without Meta-analysis) guideline, Campbell 2020, and Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2021). We used a mixed approach of visual and written presentation to provide the reader support in the interpretation of results; however, results without robust data might be misleading or overstated.

An experienced Information Specialist developed a sensitive search strategy to identify all ongoing and completed studies. The search strategy was peer-reviewed by another experienced Information Specialist. We searched all relevant databases and trial registries, and two review authors conducted all review steps independently and in duplicate. In the case of missing data, we contacted study authors for additional data or relevant details as needed. We are confident that we identified all relevant studies, and will monitor ongoing studies as well as studies that have been completed but that are not yet published closely after the publication of this review.

We identified no other potential sources of bias in our review process.

Agreements and disagreements with other studies or reviews

We have identified no other systematic review assessing palliative symptom control in COVID-19 patients. However, we did identify non-systematic reviews addressing palliative symptom control in COVID-19 patients. We agree with the review by Keeley 2020 that more information on palliative care for COVID-19 patients is urgently needed. Symptoms addressed in other reviews and this review seem to be similar: cough, anxiety, pain, and dyspnea are reported to be prevalent among COVID-19 patients (Mottiar 2020; Ting 2020).

Pharmacological interventions found in this review are similar to those that are recommended for the palliative care of cancer patients (Bausewein 2020). Furthermore, the pharmacological interventions used for symptom control found in this review are also recommended by the German Society for Palliative Medicine (Nehls 2020). We did not find any evidence on recommended non-pharmacological interventions, as have been put forward by the National Institute for Health and Care Excellence (NICE) (NICE 2020).

More information is needed to investigate specific challenges for palliative care in the COVID-19 pandemic.

AUTHORS' CONCLUSIONS

Implications for practice

We did not find evidence to confidently support or refute whether pharmacological interventions may be effective for palliative symptom relief in COVID-19 patients, and no evidence on the safety of pharmacological interventions, or effectiveness and safety of non-pharmacological interventions for palliative symptom control in COVID-19 patients. The evidence presented here has no specific implications for palliative symptom control in COVID-19 patients because we cannot draw any conclusions about the effectiveness or safety based on the identified evidence. More evidence is needed to guide clinicians, nursing staff, and caregivers when treating symptoms of COVID-19 patients at the end of life. Specifically, future studies ought to investigate palliative symptom control in prospectively registered studies, using an active-controlled setting, assess patient-reported outcomes, and clearly define interventions. The identified evidence does not rule out current practice for palliative symptom control, for example for cancer.

Implications for research

The results of our systematic review show that randomized controlled trials (RCTs) on the palliative symptom management of COVID-19 patients are needed. However, as RCTs in the palliative setting are complex due to ethical and logistic constraints, well-conducted prospectively registered observational studies would help to fill the current research gap. Specifically, future research ought to investigate treatments in prospectively registered studies, using a controlled setting, assess patient-reported outcomes, and clearly define interventions.

We identified one RCT that may be already completed but for which results are not yet available, investigating the effects of acupressure therapy and Liu Zi Jue Qigong exercises on dyspnea and quality of life in individuals with COVID-19. We further identified abstracts to three studies that might have relevant information on palliative

symptom control once full texts are published. In addition, we found one ongoing study investigating morphine in COVID-19 patients with dyspnea in a controlled setting.

The publication of the results of these studies will necessitate an update of this review. The conclusions of the updated review could differ from those of the present review and may allow for a better judgement regarding pharmacological and non-pharmacological interventions for palliative symptom control in COVID-19 patients.

ACKNOWLEDGEMENTS

This review was published in collaboration with the Cochrane Pain, Palliative and Supportive Care group. We particularly thank Anna Erskine (Managing Editor), Neil O'Connell (Co-ordinating Editor), Peter Tugwell (Sign-off Editor) and Lisa Winer (Copy Editor) for their excellent support, valuable comments on the review, and timely management of the editorial process.

This work is part of a series of reviews investigating treatments and therapies for COVID-19 as part of the project CEOsys. Text passages in the Background section (e.g. Description of the condition and Why it is important to do this review) are shared between reviews of this series. We thank the authors of the first published reviews of this series (Kreuzberger 2020 and Valk 2020a), for providing and sharing this information. Moreover, we thank the Cochrane Haematology working group for using the template for the description of methods.

The research was part of a project supported by the German Federal Ministry of Education and Research (NaFoUniMedCovid19, funding number: 01KX2021; part of the CEOsys project). The contents of this document reflect only the authors' views, and the German Ministry is not responsible for any use that may be made of the information it contains.

We thank the investigator team of Strang 2021 and Alderman 2020 for providing us with all the requested additional information and data.

The authors and editors thank peer reviewers Brian Duncan (Consumer Reviewer), Sarah Mitchell, Jennifer Hilgart, and Sarah Yardley.

Cochrane Review Group funding acknowledgement: this project was funded by the National Institute for Health Research (NIHR) via Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

We thank Ina Monsef and Maria-Inti Mezendorf for peer-reviewing the search strategy.

REFERENCES

References to studies included in this review

Alderman 2020 *{published and unpublished data}*10.1177/0269216320947312

Alderman B, Webber K, Davies A. An audit of end-of-life symptom control in patients with corona virus disease 2019 (COVID-19) dying in a hospital in the United Kingdom. *Palliative Medicine* 2020;**34**(9):1249-55. [DOI: 10.1177/0269216320947312]

Hetherington 2020 *{published data only}*

Hetherington L, Johnston B, Kotronoulas G, Finlay F, Keeley P, McKeown A. COVID-19 and hospital palliative care—a service evaluation exploring the symptoms and outcomes of 186 patients and the impact of the pandemic on specialist hospital palliative care. *Palliative Medicine* 2020;**34**(9):1256-62. [DOI: 10.1177/0269216320949786]

Lovell 2020 *{published data only}*

Lovell N, Maddocks M, Etkind SN, Taylor K, Carey I, Vora V, et al. Characteristics, symptom management, and outcomes of 101 patients with COVID-19 referred for hospital palliative care. *Journal of Pain and Symptom Management* 2020;**60**(1):e77-81. [DOI: 10.1016/j.jpainsymman.2020.04.015]

Strang 2021 *{published data only}*

Strang P, Bergström J, Lundström S. Symptom relief is possible in elderly dying COVID-19 patients: a national register study. *Journal of Palliative Medicine* 2020;**24**(4):514-9. [DOI: 10.1089/jpm.2020.0249]

Strang P, Martinsson L, Bergström J, Lundström S. COVID-19: symptoms in dying residents of nursing homes and in those admitted to hospitals. Journal of Palliative Medicine 2021 Mar 5 [Epub ahead of print]. [DOI: 10.1089/jpm.2020.0688]

References to studies excluded from this review

ACTRN12620000443998p *{published data only}*

ACTRN12620000443998p. Home rehabilitation for people with COVID-19: implementing telehealth approaches to care. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379528&isReview=true (first received 31 March 2020).

Allande Cussó 2020 *{published data only}*

Allande Cussó R, Navarro Navarro C, Porcel Gálvez AM. Humanized care in a death for COVID-19: a case study [El cuidado humanizado en la muerte por COVID-19: a propósito de un caso]. *Enfermería Clínica* 2021;**(31)**:62-7. [DOI: 10.1016/j.enfcli.2020.05.018]

Anneser 2020 *{published data only}*

Anneser J. Dying patients with COVID-19: what should hospital palliative care teams (HPCTs) be prepared for? *Palliative & Supportive Care* 2020;**18**(4):382-4.

Bisson 2020 *{published data only}*

Bisson E, Presswood E, Kenyon J, Shelton F, Hall T. Against the odds: unlikely COVID-19 recovery. BMJ Supportive and Palliative Care 3 July 2020 [Epub ahead of print]. [DOI: 10.1136/bmjspcare-2020-002477]

Cook 2020 *{published data only}*

Cook DJ, Takaoka A, Hoad N, Swinton M, Clarke FJ, Rudkowski JC, et al. Clinician perspectives on caring for dying patients during the pandemic: a mixed-methods study. Annals of Internal Medicine 2020 Dec 8 [Epub ahead of print]. [DOI: 10.7326/M20-6943]

Delisle 2020 *{published data only}*

Delisle S, Heller FE, Blinderman CD. Prolonged critical illness and demoralization: curative factors in hospice care in the age of COVID-19. *Journal of Hospice & Palliative Nursing* 2020;**22**(6):428-31. [DOI: 10.1097/NJH.0000000000000689]

Galazzi 2020 *{published data only}*

Galazzi A, Brioni M, Mistraletti G, Roselli P, Abbruzzese C. The last farewell by video call. *Minerva Anestesiologica* 2020;**86**(11):1254-5. [DOI: 10.23736/S0375-9393.20.14906-X]

Haydar 2020 *{published data only}*

Haydar A, Lo KB, Goyal A, Gul F, Peterson E, Bhargav R, et al. Palliative care utilization among patients with COVID-19 in an underserved population: a single-center retrospective study. *Journal of Pain and Symptom Management* 2020;**60**(2):e18-21. [DOI: 10.1016/j.jpainsymman.2020.05.022]

Pettus K, de Lima L. Update to the fast tracked article entitled: palliative care utilization among patients with COVID-19 in an underserved population: a single-center retrospective study. *Journal of Pain and Symptom Management* 2020;**60**(4):e1. [DOI: 10.1016/j.jpainsymman.2020.07.017]

Heath 2020 *{published data only}*

Heath L, Yates S, Carey M, Miller M. Palliative care during COVID-19: data and visits from loved ones. *Journal of Hospice and Palliative Medicine* 2020;**37**(11):988-91. [DOI: 10.1177/1049909120943577]

ISRCTN16561225 *{unpublished data only}*

ISRCTN16561225. CovPall: Improving palliative care for people affected by the COVID-19 pandemic by sharing learning—the national and international response. www.isrctn.com/ISRCTN16561225 (first received 5 May 2020). [DOI: 10.1186/ISRCTN16561225]

Johnston 2020 *{published data only}*

Johnston B, Blades S. COVID-19: using 'knitted hearts' in end-of-life care to enable continuing bonds and memory making. *International Journal of Palliative Nursing* 2020;**26**(8):391-3.

Lee 2020 *{published data only}*

Lee J, Abrukin L, Flores S, Gavin N, Romney ML, Blinderman CD, et al. Early intervention of palliative care in the emergency department during the COVID-19 pandemic. *JAMA Internal Medicine* 2020;**180**(9):1252-4. [DOI: 10.1001/jamainternmed.2020.2713]

Lopez 2020 *{published data only}*

Lopez S, Finuf KD, Marziliano A, Sinvani L, Burns EA. Palliative care consultation in hospitalized patients with COVID-19: a retrospective study of characteristics, outcomes, and unmet needs. *Journal of Pain and Symptom Management* 2021;**62**(2):276. [DOI: 10.1016/j.jpainsymman.2020.12.015]

Martinsson 2021 *{published data only}*

Martinsson L, Strang P, Bergström J, Lundström S. Were clinical routines for good end-of-life care maintained in hospitals and nursing homes during the first three months of the outbreak of COVID-19? A national register study. *Journal of Pain and Symptom Management* 2021;**61**(1):e11-9. [DOI: 10.1016/j.jpainsymman.2020.09.043]

Mendoza 2020 *{published data only}*

Mendoza A. Palliative care during a pandemic. www.providermagazine.com/Monthly-Issue/2020/September/Pages/Palliative-Care-During-a-Pandemic.aspx.

Mumoli 2021 *{published data only}*

Mumoli N, Florian C, Cei M, Evangelista I, Colombo A, Razionale G, et al. Palliative care in a COVID-19 internal medicine ward: a preliminary report. *International Journal of Infectious Disease* 2021;**105**:141-3. [DOI: 10.1016/j.ijid.2021.02.053]

Paice 2021 *{published data only}*

Paice JA, Wholihan D, Dahlin C, Rosa WE, Mazanec P, Long CO, et al. Palliative nursing: the core of COVID-19 care. *Journal of Hospice & Palliative Nursing* 2021;**23**(1):1-6. [DOI: 10.1097/NJH.0000000000000709]

Pavlu 2020 *{published data only}*

Pavlu D, DeMarco K, Sobrino-Bonilla Y. Field notes from the frontline of a COVID-19 outbreak: dyspnea management for hospitalized patients at end-of-life. *Journal of Hospital & Palliative Nursing* 2020;**23**(2):128-34. [DOI: 10.1097/NJH.0000000000000728]

Rao 2021 *{published data only}*

Rao A, Zaaqoq AM, Kang IG, Vaughan EM, Flores J, Avila-Quintero VJ, et al. Palliative care for patients on extracorporeal membrane oxygenation for COVID-19 infection. American Journal of Hospice and Palliative Medicine 2021 March 9 [Epub ahead of print]. [DOI: 10.1177/10499091211001009]

Ritchey 2020 *{published data only}*

Ritchey KC, Foy A, McArdel E, Gruenewald DA. Reinventing palliative care delivery in the era of COVID-19: how telemedicine can support end of life care. *American Journal of Hospice and Palliative Medicine* 2020;**37**(11):992-7. [DOI: 10.1177/1049909120948235]

Riva 2020 *{published data only}*

Riva L, Caraceni A, Vigorita F, Berti J, Martinelli MP, Crippa M, et al. COVID-19 emergency and palliative medicine: an intervention model. BMJ Supportive & Palliative Care 2020 Nov 23 [Epub ahead of print]. [DOI: 10.1136/bmjspcare-2020-002561]

Sun 2020 *{published data only}*

Sun H, Lee J, Meyer BJ, Myers EL, Nishikawa MS, Tischler JL, et al. Characteristics and palliative care needs of COVID-19 patients receiving comfort-directed care. *Journal of the American Geriatrics Society* 2020;**68**(8):1162-4. [DOI: 10.1111/jgs.16507]

Turner 2020 *{published data only}*

Turner J, Eliot Hodgson L, Leckie T, Eade L, Ford-Dunn S. A dual-center observational review of hospital-based palliative care in patients dying with COVID-19. *Journal of Pain and Symptom Management* 2020;**60**(2):e75-8. [DOI: 10.1016/j.jpainsymman.2020.04.031]

References to studies awaiting assessment

ChiCTR2000029994 *{unpublished data only}*

ChiCTR2000029994. Liu-Zi-Jue qigong and acupressure therapy for pulmonary function and quality of life in patient with severe novel coronavirus pneumonia (COVID-19): A randomized controlled trial. Chinese Clinical Trial Registry 2020. [CHICTR: 2000029994] [URL: https://www.chictr.org.cn/showprojen.aspx?proj=49309]

Zhang S, Zhu Q, Zhan C, Cheng W, Mingfang X, Fang M, et al. Acupressure therapy and Liu Zi Jue Qigong for pulmonary function and quality of life in patients with severe novel coronavirus pneumonia (COVID-19): a study protocol for a randomized controlled trial. *Trials* 2020;**21**(1):751. [DOI: 10.1186/s13063-020-04693-5]

Groninger 2021 *{unpublished data only}*

Groninger H, McPherson A, Vaughan E, Kang IG, Kelemen A. Hospital-based palliative care experiences of patients with COVID-19. *Journal of Pain and Symptom Management* 2021;**61**(3):695. [ABSTRACT NUMBER: SCI947] [DOI: 10.1016/j.jpainsymman.2021.01.108]

Kelly 2020 *{unpublished data only}*

Kelly L, O'Shea N, Azhar M, Beatty S, Brennock J, Mannion E, et al. Symptomatology at the end of life with COVID-19. Abstracts of the 16th International E-Congress of the European Geriatric Medicine Society; 2020 Oct 7-9 2020 Apr 28 [Epub ahead of print]. [ABSTRACT NUMBER: 23] [DOI: 10.1007/s41999-020-00428-6]

Okuwoga 2020 *{unpublished data only}*

Okuwoga O, Picton S, Saber S, O'Sullivan C. Managing delirium in patients with COVID-19—lessons to learn. Abstracts of the 16th International E-Congress of the European Geriatric Medicine Society; 2020 Oct 7-9 2020 Apr 28 [Epub ahead of print]. [ABSTRACT NUMBER: 281] [DOI: 10.1007/s41999-020-00428-6]

References to ongoing studies

NCT04522037 *{published data only}*

NCT04522037. Measurement of the efficacy of morphine in the early management of dyspnea in COVID-19 positive

patients (CODYS). clinicaltrials.gov/ct2/show/NCT04522037 (first received 21 August 2020).

Additional references

Antunes 2014

Antunes B, Harding R, Higginson IJ. Implementing patient-reported outcome measures in palliative care clinical practice: a systematic review of facilitators and barriers. *Palliative Medicine* 2014;**28**(2):158-75. [DOI: 10.1177/0269216313491619]

Balshem 2011

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(4):401-6. [DOI: 10.1016/j.jclinepi.2010.07.015]

Banzett 2000

Banzett RB, Mulnier HE, Murphy K, Rosen SD, Wise RJ, Adams L. Breathlessness in humans activates insular cortex. *Neuroreport* 2000;**11**(10):2117-20. [DOI: 10.1097/00001756-200007140-00012]

Barnes 2016

Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No: CD011008. [DOI: 10.1002/14651858.CD011008]

Barron 2012

Barron EA, Holmes J. Delirium within the emergency care setting, occurrence and detection: a systematic review. *Emergency Medicine Journal* 2013;**30**(4):263-8. [DOI: 10.1136/emermed-2011-200586]

Bausewein 2020

Bausewein C, Voltz R, Steffen S, Radbruch L. Evidence-based guideline: Palliative care for patients with incurable cancer. www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Palliativmedizin/Version_2/LL_Palliativmedizin_Langversion_2.2.pdf (accessed 26 July 2021). [AWMF-REGISTRATION NUMBER: 128/001OL]

Buchanan 2009

Buchanan GF, Richerson GB. Role of chemoreceptors in mediating dyspnea. *Respiratory Physiology and Neurobiology* 2008;**176**(1):9-19. [DOI: 10.1016/j.resp.2008.12.002]

Buitrago-Garcia 2020

Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci Aziz M, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. *PLOS Medicine* 2020;**17**(9):e1003346. [DOI: 10.1371/journal.pmed.1003346]

Campbell 2020

Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;**368**(l6890):1-6. [DOI: 10.1136/bmj.l6890]

Challen 2021

Challen R, Brooks-Pollock E, Read JM, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. *BMJ* 2021;**327**(n579):1-10. [DOI: 10.1136/bmj.n579]

COMET 2020

Core outcome set developers' response to COVID-19 (2nd April 2020). www.comet-initiative.org/Studies/Details/1538 (accessed 9 April 2020).

Crombeen 2020

Crombeen AM, Lilly EJ. Management of dyspnea in palliative care. *Current Oncology* 2020;**27**(3):142-5. [DOI: 10.3747/co.27.6413.]

Deeks 2021

Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

EPOC 2017

Cochrane Effective Practice and Organisation of Care (EPOC). What study designs can be considered for inclusion in an EPOC review and what should they be called? EPOC Resources for review authors. Available from epoc.cochrane.org/resources/epoc-resources-review-authors (accessed 23 April 2019).

Forni 2021

Forni G, Mantovani A. COVID-19 vaccines: where we stand and challenges ahead. *Cell Death & Differentiation* 2021;**28**:626-39. [DOI: 10.1038/s41418-020-00720-9]

Gaertner 2017

Gaertner J, Siemens W, Meerpohl JJ, Antes G, Meffert C, Xander C, et al. Effect of specialist palliative care services on quality of life in adults with advanced incurable illness in hospital, hospice, or community settings: systematic review and meta-analysis. *BMJ* 2017;**375**:1-14. [DOI: 10.1136/bmj.j2925]

Griffin 2013

Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner Journal* 2013;**13**(2):214-23. [PMID: 23789008]

Haun 2017

Haun MW, Estel S, Rücker G, Friederich HC, Villalobos M, Thomas M, et al. Early palliative care for adults with advanced cancer. *Cochrane Database of Systematic Reviews* 2017, Issue 6. Art. No: CD011129. [DOI: 10.1002/14651858.CD011129.pub2]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60. [DOI: 10.1136/bmj.327.7414.557]

Higgins 2021

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Huang 2020

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**(10223):497-506. [DOI: 10.1016/S0140-6736(20)30183-5]

Hui 2020

Hui D, De La Rosa A, Wilson A, Nguyen T, Wu J, Delgado-Guay M, et al. Neuroleptic strategies for terminal agitation in patients with cancer and delirium at an acute palliative care unit: a single-centre, double-blind, parallel-group, randomised trial. *Lancet Oncology* 2020;**21**(7):989-98. [DOI: 10.1016/S1470-2045(20)30307-7]

Johns Hopkins 2021

Johns Hopkins University of Medicine Coronavirus Resource Center. Mortality analyses. coronavirus.jhu.edu/data/mortality (accessed 16 April 2021).

Johnson 2020

Johnson MJ, Currow DC. Opioids for breathlessness: a narrative review. *BMJ Supportive & Palliative Care* 2020;**10**:287-95. [DOI: 10.1136/bmjspcare-2020-002314]

Keeley 2020

Keeley P, Buchanan D, Carolan C, Pivodic L, Tavabie S, Noble S. Symptom burden and clinical profile of COVID-19 deaths: a rapid systematic review and evidence summary. *BMJ Supportive & Palliative Care* 2020;**10**(4):381-4. [DOI: 10.1136/bmjspcare-2020-002368]

Kennedy 2020

Kennedy M, Helfand BKI, Gou RY, Gartaganis SL, Webb M, Moccia JM, et al. Delirium in older patients with COVID-19 presenting to the emergency department. *JAMA Network Open* 2020;**3**(11):e2029540. [DOI: 10.1001/jamanetworkopen]

Kreuzberger 2020

Kreuzberger N, Hirsch C, Chai KL, Piechotta V, Valk SJ, Estcourt LJ, et al. SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No: CD013825. [DOI: 10.1002/14651858.CD013825]

Lefebvre 2021

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Li 2021

Li T, Higgins JPT, Deeks JJ. Chapter 5: Collecting data. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Liang 2020

Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet* 2020;**21**(3):335-7. [DOI: 10.1016/S1470-2045(20)30096-6]

MAGICapp 2020 [Computer program]

MAGIC Evidence Ecosystem Foundation MAGICapp: A digital authoring and publication platform for the evidence ecosystem. MAGIC Evidence Ecosystem Foundation, 2020. Available at app.magicapp.org/.

Mahler 2013

Mahler DA, Gifford AH, Waterman LA, Ward J, Kraemer WJ, Kupchak BR, et al. Effect of increased blood levels of β-endorphin on perception of breathlessness. *Chest* 2013;**143**(5):1378-85. [DOI: 10.1378/chest.12-1541]

McKenzie 2021

McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Meagher 2018

Meagher D, Agar MR, Teodorczuk A. Debate article: Antipsychotic medications are clinically useful for the treatment of delirium. *International Journal of Geriatric Psychiatry* 2018;**33**:1420-7. [DOI: 10.1002/gps.4759]

Mercadamte 2014

Mercadamte S. Death rattle: critical review and research agenda. *Support Care Cancer* 2014;**22**(2):571-5. [DOI: 10.1007/s00520-013-2047-5]

Microsoft 2018 [Computer program]

Excel. Microsoft Corporation. Microsoft Corporation, 2018. Available at office.microsoft.com/excel.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006-12.

Mottiar 2020

Mottiar M, Hendin A, Fischer L, des Ordons AR, Hartwick M. End-of-life care in patients with a highly transmissible respiratory virus: implications for COVID-19. *Canadian Journal of Anaesthesia* 2020;**67**:1-7. [DOI: 10.1007/s12630-020-01699-0]

Mulder 2019

Mulder RL, Bresters D, Van den Hof M, Koot BG, Castellino SM, Loke YK, et al. Hepatic late adverse effects after antineoplastic treatment for childhood cancer. *Cochrane Database of Systematic Reviews* 2019, Issue 4. Art. No: CD008205. [DOI: 10.1002/14651858.CD008205.pub3]

Nehls 2020

Nehls W, Delis S, Haberland B, Maier BO, Sänger K, Tessmer G, et al. Management of patients with COVID-19 —recommendations from a palliative care perspective. *Pneumologie* 2020;**774**(10):652-9. [DOI: 10.1055/a-1156-2759]

NICE 2020

National Institute for Health and Care Excellence (NICE). Managing COVID-19 symptoms (including at the end of life) in the community: summary of NICE guidelines. BMJ 2020;**369**:m1461. [DOI: 10.1136/bmj.m1461]

Ouzzani 2016

Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan —a web and mobile app for systematic reviews. *Systematic Reviews* 2016;**5**(1):210. [DOI: 10.1186/s13643-016-0384-4]

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34. [DOI: 10.1002/(SICI)1097-0258(19981230)]

Pattinson 2009

Pattinson KT, Governo RJ, MacIntosh BJ, Russell EC, Corfield DR, Tracey I, et al. Opioids depress cortical centers responsible for the volitional control of respiration. *Journal of Neuroscience* 2009;**29**(25):8177-86. [DOI: 10.1523/JNEUROSCI.1375-09.2009]

Radbruch 2020

Radbruch L, De Lima L, Knaul F, Wenk R, Ali Z, Bhatnaghar S, et al. Redefining palliative care—a new consensus-based definition. *Journal of Pain and Symptom Management* 2020;**60**(4):754-64. [DOI: 10.1016/j.jpainsymman.2020.04.027]

Reeves 2021

Reeves BC, Deeks JJ, Higgins JPT, Shea B, Tugwell P, Wells GA. Chapter 24: Including non-randomized studies on intervention effects. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

RevMan Web 2021 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 3.6.0. The Cochrane Collaboration, 2021. Available at revman.cochrane.org.

Santesso 2020

Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: Informative statements to communicate the findings of systematic reviews of interventions. *Journal of Clinical Epidemiology* 2020;**1**(119):126-35. [DOI: 10.1016/j.jclinepi.2019.10.014]

Schünemann 2019

Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *Journal of Clinical Epidemiology* 2019;**111**:105-14. [DOI: 10.1016/j.jclinepi.2018.01.012]

Schünemann 2021

Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Shelby-James 2012

Shelby-James TM, Hardy J, Agar M, Yates P, Mitchell G, Sanderson C, et al. Designing and conducting randomized controlled trials in palliative care: a summary of discussions from the 2010 clinical research forum of the Australian Palliative Care Clinical Studies Collaborative. *Palliative Medicine* 2012;**26**(8):1042-7. [DOI: 10.1177/0269216311417036]

Siemieniuk 2020

Siemieniuk R, Rochwerg B, Agoritsas T, Lamontagne F, Leo YS, Macdonald H, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020;**370**:m3379. [DOI: 10.1136/bmj.m3379]

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:1-7. [DOI: 10.1136/bmj.i4919]

Sterne 2019

Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**(l4898):1-8. [DOI: 10.1136/bmj.l4898]

Struyf 2020

Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No: CD013665. [DOI: 10.1002/14651858.CD013665]

Svenska Palliativregistret 2021

The Swedish Register of Palliative Care (SRPC). www.palliativ.se (accessed prior to 9 August 2021).

Taskforce NCCE 2021

Taskforce NCCE. Clinical Care Guidance. covid19evidence.net.au/ (accessed prior to 9 August 2021).

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16. [DOI: 10.1186/1745-6215-8-16]

Ting 2020

Ting R, Edmonds P, Higginson IJ, Sleeman KE. Palliative care for patients with severe covid-19. *BMJ* 2020;**370**:m2710. [DOI: 10.1136/bmj.m2710]

Valk 2020a

Valk SJ, Piechotta V, Chai KL, Doree C, Monsef I, Wood EM, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews* 2021, Issue 5. Art. No: CD013600. [DOI: 10.1002/14651858.CD013600.pub4]

Valk 2020b

Valk SJ, Piechotta V, Kimber C, Chai KL, Monsef I, Doree C, et al. Convalescent plasma and hyperimmune immunoglobulin to prevent infection with SARS-CoV-2. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No: CD013802. [DOI: 10.1002/14651858.CD013802]

von Leupoldt 2007

von Leupoldt A, Dahme B. Psychological aspects in the perception of dyspnea in obstructive pulmonary diseases. *Respiratory Medicine* 2007;**101**(3):411-22. [DOI: 10.1016/j.rmed.2006.06.011]

WHO 2007

World Health Organization (WHO). Cumulative number of reported probable cases of SARS. www.who.int/csr/sars/country/2003_07_11/en/ (accessed 13 April 2020).

WHO 2019

World Health Organization (WHO). Middle East respiratory syndrome coronavirus (MERS-CoV). www.who.int/emergencies/mers-cov/en/ (accessed 13 April 2020).

WHO 2020a

World Health Organization (WHO). Report of the WHO-China Joint Mission on coronavirus disease 2019 (COVID-19). www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report (accessed prior to 9 August 2021).

WHO 2020b

World Health Organization (WHO). Estimating mortality from COVID-19—scientific brief. www.who.int/publications/i/item/WHO-2019-nCoV-Sci-Brief-Mortality-2020.1 (accessed 2 November 2020).

WHO 2020c

World Health Organization (WHO). Palliative care. www.who.int/news-room/fact-sheets/detail/palliative-care (accessed 13 July 2021).

WHO 2021a

World Health Organization (WHO). WHO Coronavirus Disease (COVID-19) Dashboard. covid19.who.int (accessed 14 July 2021).

WHO 2021b

World Health Organization (WHO). Weekly epidemiological update—13 July. www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---13-july-2021 (accessed 14 July 2021).

WHO 2021c

World Health Organization (WHO). COVID-19 Clinical management: living guidance. www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1 (accessed 15 April 2021).

WHO 2021d

World Health Organization (WHO). Draft landscape of COVID-19 candidate vaccines. www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed 15 April 2021).

WHO 2021e

World Health Organization (WHO). Therapeutics and COVID-19: living guideline. Version 6.1. app.magicapp.org/#/guideline/nBkO1E (accessed 15 July 2021).

Williamson 2020

Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**:430-6. [DOI: 10.1038/s41586-020-2521-4]

Wouters 2021

Wouters OJ, Shadlen KC, Salcher-Konrad M, Pollard AJ, Larson HJ, Teerawattananon Y, et al. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. *Lancet* 2021;**10278**:1023-34. [DOI: 10.1016/S0140-6736(21)00306-8]

Wu 2020

Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;**323**(13):1239-42. [DOI: 10.1001/jama.2020.2648]

References to other published versions of this review

Andreas 2021

Andreas M, Piechotta V, Becker G, Metzendorf M-I, Skoetz N, Meissner W, et al. Palliative symptom management in Covid-19 patients: a systematic review. PROSPERO. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021233630. 2021.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alderman 2020

Study characteristics	
Methods	• Study design: retrospective cohort study • Type of publication: journal publication • Setting and dates: general hospital in England, from 16 March to 11 May 2020 • Country: United Kingdom • Language: English • Inclusion/exclusion criteria: inpatients with COVID-19 who had an end-of-life care plan and died
Participants	• Age: median (range): 82 (53 to 98) • Gender: 34 men/27 women • Ethnicity: white British: 58, any other white origin: 3 • Number of participants (recruited/allocated/evaluated): 91 died of COVID-19, 61 with end-of life care plan included in analysis, 60 reviewed by the palliative care team. • Symptoms at baseline: 38 participants had uncontrolled end-of-life symptoms/problems: shortness of breath (20), agitation/delirium (17), anxiety (5), pain (4), audible upper airway secretions (1), nausea (1), myoclonus (1), fever (1), and conjunctivitis (1). 12 participants had more than 1 symptom. • Comorbidities: dementia (8), neurological disease (5), cardiovascular disease (26), hypertension (22), respiratory disease (14), renal disease (11), diabetes mellitus (12), and cancer (15)

Interventions	• Pharmacological intervention(s): drug for symptom: the initial medication in the syringe pump remained unchanged in 23 participants, was altered once in 14 participants, and was altered twice in 4 participants.
	  ◦ Shortness of breath: 14 (34.5%) CSCI morphine; 7 (11.5%) CSCI morphine and midazolam (for shortness of breath-related anxiety). Initial dose morphine: 10 mg/24 h (n = 12); 15 mg/24 h (n = 9). Final dose morphine: 10 mg/24 h (n = 10); 15 mg/24 h (n = 10); 20 mg/24 h (n = 1). Initial dose midazolam: 10 mg/24 h (n = 2); 15 mg/24 h (n = 5). Final dose midazolam: no change
	  ◦ Agitation/delirium: 24 (39.5%) CSCI for agitation/delirium; haloperidol (first-line treatment): final dose: 5 mg/24 h (n = 4; initial dose); 10 mg/24 h (n = 3; dose titrated). Levomepromazine (second-line treatment): final dose: 75 mg/24 h (n = 14; initial dose); 150 mg/24 h (n = 1; dose titrated). Levomepromazine and midazolam (third-line treatment): final dose: 150 mg/24 h and 20 mg/24 h, respectively (n = 1). Midazolam (first-line treatment): final dose: 20 mg/24 h
	• Mode of drug-delivery: syringe pumps were utilized in 41 (67%) participants.
	• Non-pharmacological intervention(s): none

Outcomes	Primary review outcomes • Symptom relief: the presence of symptoms was assessed through clinical assessment of the participant by the ward nursing staff (during their 4-hourly reviews) or a member of the specialist palliative care team. The presence of delirium was assessed through m-RASS scores that were recorded every 4 hours by ward nursing staff. Secondary review outcomes • None reported. Additional outcomes reported in the study • Cumulative number of patients with 1 symptom • Median length of admission • Median time on the end-of-life care

Alderman 2020 *(Continued)*

Notes	Sponsor/funding: the authors received no financial support for the research, authorship, and/or publication of this article. COI: the authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (unrepresentative study group) All outcomes	Low risk	Study group is representative of COVID-19 patient population.
Attrition bias (incomplete outcome assessment/follow up) All outcomes	Low risk	Outcome assessed until participant death.
Detection bias (outcome detectors blinded to intervention) All outcomes	High risk	Not blinded
Confounding (important prognostic factors or follow-up not taken adequately into account) All outcomes	High risk	Not adjusted for confounders
Reporting bias (poorly defined study group) All outcomes	Low risk	Criteria for inclusion is well described.
Reporting bias (poorly defined follow up) All outcomes	Low risk	Assessed until death
Reporting bias (poorly defined outcome) All outcomes	High risk	Effective if not present at subsequent assessments

Hetherington 2020

Study characteristics

Methods	• Study design: retrospective cohort study • Type of publication: journal publication • Setting and dates: hospital palliative care, 30 March to 26 April 2020 • Country: United Kingdom • Language: English • Inclusion/exclusion criteria: COVID-19-positive patients referred to palliative care
Participants	• Age: median age 76 (IQR 71 to 84) years • Gender: 98 men/88 women

Hetherington 2020 *(Continued)*

	• Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 186 evaluated • Symptoms at baseline: dyspnea (116), agitation (82), pain (35), delirium (18), cough (15), anxiety (12), fever (11), secretions (10), nausea and vomiting (11), fatigue (6), and drowsiness (4) • Comorbidities: hypertension 58 (31.2%), diabetes mellitus 52 (28%), chronic obstructive pulmonary disease 50 (26.9%), ischemic heart disease 45 (24.2%), dementia 41 (22%), chronic kidney disease 34 (18.3%), cerebrovascular disease 29 (15.6%), solid tumor—localized 28 (15.1%), congestive heart failure 19 (10.2%), myocardial infarction 17 (9.1%), connective tissue disease 13 (7%), degenerative neurological condition 9 (4.8%), hematological malignancy 8 (4.3%), solid tumor—metastatic 7 (3.8%), peptic ulcer disease 7 (3.8%), and liver disease 6 (3.2%)
Interventions	• Pharmacological intervention(s); median, (range) (IQR) of drug dose in 24 hours: all opiates in sub cut morphine equivalent (n = 133) 15 mg (5 to 90) (10 to 20); morphine (n = 87) 15 mg (5 to 90) (10 to 20); oxycodone (n = 15) 10 mg (5 to 40) (8 to 17.5); alfentanil (n = 33) 900 µg (300 to 4000) (500 to 1000); midazolam (n = 125) 10 mg (2.5 to 60) (10 to 20); haloperidol (n = 4) 1.75 mg (1 to 2); hyoscine butylbromide (n = 21) 60 mg (40 to 120); levomepromazine (n = 16) 15 (100*). • Mode of drug-delivery: CSCI • Non-pharmacological intervention(s): none *IQR not reported
Outcomes	Primary review outcomes • Symptom relief, assessed through clinical impression of efficacy Secondary review outcomes • None reported Additional outcomes reported • Length of hospital stay • Death rate
Notes	Sponsor/funding: the author(s) received no financial support for the research, authorship, and/or publication of this article. COIs: the author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (unrepresentative study group) All outcomes	Low risk	Overall, data from 186 participants were captured. Clear inclusion criteria
Attrition bias (incomplete outcome assessment/follow up) All outcomes	Low risk	Reported until death or discharge
Detection bias (outcome detectors blinded to intervention) All outcomes	High risk	Not blinded
Confounding (important prognostic factors or fol-	High risk	Not adjusted for confounding factors

Hetherington 2020 *(Continued)*

low-up not taken adequately into account) All outcomes		
Reporting bias (poorly defined study group) All outcomes	Low risk	Study population well described, clear inclusion criteria.
Reporting bias (poorly defined follow up) All outcomes	High risk	Follow-up period not defined.
Reporting bias (poorly defined outcome) All outcomes	High risk	Outcome was subjective and was not defined. Data collected retrospectively. Outcome assessment has not been validated.

Lovell 2020

Study characteristics	
Methods	• Study design: retrospective cohort study • Type of publication: journal publication • Setting and dates: hospital palliative care, 4 March to 26 March 2020 • Country: United Kingdom • Language: English • Inclusion/exclusion criteria: COVID-19-positive patients referred to palliative care
Participants	• Age: median age 82 (IQR 72 to 89) years • Gender: 64 men/37 women • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 101 evaluated • Symptoms at baseline: breathlessness (67), agitation (43), drowsiness (36), pain (23), delirium (24), secretions (11), fatigue (9), fever (9), cough (4) • Comorbidities: hypertension (54), diabetes (36), dementia (31), advanced/metastatic cancer (25), chronic pulmonary disease (22), renal failure (21), congestive heart failure (18), stroke/neurological disorder (12), peripheral vascular disorder (4) liver disease (2)
Interventions	• Pharmacological intervention(s): median dose/24 hours (range); alfentanil 500 µg (150 to 1000), midazolam 10 mg (5 to 20), glycopyrronium 1200 µg (600 to 2400), haloperidol 2 mg (1 to 2), cyclizine 50 mg*, morphine 10 mg (5 to 30), fentanyl 100 µg (100 to 200) • Mode of drug-delivery: 58 participants were prescribed a subcutaneous infusion. • Non-pharmacological intervention(s): none *IQR not reported
Outcomes	Primary review outcomes • Symptom relief, assessed through clinical impression of efficacy Secondary review outcomes • None reported Additional outcomes reported • Days of palliative care involvement

Lovell 2020 *(Continued)*

- Palliative care contacts and type of contacts
- Death rate
- Number and type of discharges

Notes	Sponsor/funding: the author(s) received no financial support for the research, authorship, and/or publication of this article. COIs: the author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (unrepresentative study group) All outcomes	Low risk	Clear inclusion criteria
Attrition bias (incomplete outcome assessment/follow up) All outcomes	High risk	Unclear for how long data were collected, 13 participants died before follow-up
Detection bias (outcome detectors blinded to intervention) All outcomes	High risk	Not blinded
Confounding (important prognostic factors or follow-up not taken adequately into account) All outcomes	High risk	Not adjusted for confounding factors
Reporting bias (poorly defined study group) All outcomes	Low risk	Study group well-defined.
Reporting bias (poorly defined follow up) All outcomes	High risk	Follow-up period not defined.
Reporting bias (poorly defined outcome) All outcomes	High risk	Outcome was subjective and was not defined. Data collected retrospectively. Outcome assessment has not been validated.

Strang 2021

Study characteristics

Methods	• Study design: retrospective cohort study
	• Type of publication: journal publication
	• Setting and dates:
	  ○ Strang 2020: hospitals and nursing homes, 1 March 2020 to 24 April 2020
	  ○ Strang 2021: hospitals and nursing homes, data retrieved 24 August 2020
	• Country: Sweden

Strang 2021 *(Continued)*

- Language: English
- Inclusion/exclusion criteria: nursing home residents who died with a COVID-19 diagnosis and an expected death based on their disease trajectory either in the nursing home or in hospital registered in the Swedish Register of Palliative Care

Participants	• Age:
	  ◦ Strang 2020: mean age (range): 84.7 (47 to 104)
	  ◦ Strang 2021: mean age (range): 86.7 (57 to 107) in nursing homes, 83.3 (30 to 107) in hospitals
	• Gender:
	  ◦ Strang 2020: 189 women/201 men
	  ◦ Strang 2021: 947 women/1158 men
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated):
	  ◦ Strang 2020: all deaths in hospitals or nursing homes (n = 490) were analyzed. Deaths in other settings (specialized palliative care wards (n = 11), in palliative homecare (n = 2), or in their own homes (n = 8)) were excluded (n = 21). Only patients with expected deaths (n = 390) were entered in the final analysis. Participants are a partial subset of those reported in Strang 2021.
	  ◦ Strang 2021: 2105 (1903 nursing home deaths and 202 nursing home residents who were admitted to hospital before death)
	• Symptoms at baseline:
	  ◦ Strang 2020: breathlessness (173), anxiety (197), delirium (77), death rattles (178), and pain (210)
	  ◦ Strang 2021: breathlessness (665), anxiety (1117), delirium (486), and respiratory secretions (1053)
	• Comorbidities: NR

Interventions	• Pharmacological intervention(s):
	  ◦ Strang 2020: strong opioid (376), tranquilizer (376), antiemetic (357), anticholinergic (370)
	  ◦ Strang 2021: for all participants (n = 2105), corrected for missing answers:
	  ■ as-needed prescription (during the last week of life) of strong opioids: 2019 of 2095 participants (96%);
	  ■ as-needed prescription (during the last week of life) of tranquillizers: 2014 of 2094 participants (96%);
	  ■ as-needed prescription (during the last week of life) of antiemetics: 1915 of 2082 participants (92%);
	  ■ as-needed prescription (during the last week of life) of anticholinergics: 2000 of 2093 participants (95%).
	• Non-pharmacological intervention(s): none

Outcomes	Primary review outcomes • Symptom relief, retrospectively assessed through the end-of-life questionnaire (ELQ) Secondary review outcomes • None reported Additional outcomes reported • Human presence at death
Notes	Participant data for the 2 cohorts were extracted from the same database, resulting in overlap between cohorts. We do not know how many participants are reported on twice. Sponsor/funding: supported by Region Stockholm (ALF) and the Stockholm Sjukhem Foundation's Jubilee Fund. COI: no competing financial interests exist.

Risk of bias

Strang 2021 *(Continued)*

Bias	Authors' judgement	Support for judgement
Selection bias (unrepresentative study group) All outcomes	Low risk	Clear inclusion criteria
Attrition bias (incomplete outcome assessment/follow up) All outcomes	Low risk	Only assessed when participant was dead
Detection bias (outcome detectors blinded to intervention) All outcomes	High risk	Not blinded
Confounding (important prognostic factors or follow-up not taken adequately into account) All outcomes	High risk	Not controlled for confounders
Reporting bias (poorly defined study group) All outcomes	Low risk	Study group well defined.
Reporting bias (poorly defined follow up) All outcomes	Low risk	Assessed until death
Reporting bias (poorly defined outcome) All outcomes	Low risk	Validated questionnaire (ELQ) used.

CSCI: continuous subcutaneous infusion
m-RASS: modified Richmond Agitation-Sedation Scale
COI: Conflict of Interest
IQR: Interquatile Range
NR: Not reported

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12620000443998p	Does not investigate symptom control
Allande Cussó 2020	Does not investigate symptom control
Anneser 2020	Symptom control not specified.
Bisson 2020	Does not investigate symptom control
Cook 2020	Does not investigate symptom control
Delisle 2020	Symptom control not specified.

Study	Reason for exclusion
Galazzi 2020	No symptom control reported.
Haydar 2020	Evaluated the use but not the effects of palliative care
Heath 2020	Evaluated the use but not the effects of palliative care
ISRCTN16561225	Does not investigate symptom control
Johnston 2020	Does not investigate symptom control
Lee 2020	Does not investigate symptom control
Lopez 2020	Does not investigate symptom control
Martinsson 2021	Does not investigate symptom control
Mendoza 2020	Opinion piece; no data
Mumoli 2021	Does not investigate symptom control
Paice 2021	Symptom control not reported.
Pavlu 2020	Evaluated the use but not the effects of palliative care
Rao 2021	Evaluated the use but not the effects of palliative care
Ritchey 2020	Does not investigate symptom control
Riva 2020	Evaluated the use but not the effects of palliative care
Sun 2020	Evaluated the use but not the effects of palliative care
Turner 2020	Evaluated the use but not the effects of palliative care

Characteristics of studies awaiting classification *[ordered by study ID]*

ChiCTR2000029994

Methods	• Study design: randomized controlled trial • Type of publication: trial registry • Setting and dates: Huangshi Hospital of Traditional Chinese Medicine, dates unknown • Country: China • Language: English • Inclusion/exclusion criteria: (1) meet the critical diagnosis criteria for severe COVID-19; (2) are aged between 20 and 80 years and are male or female; (3) have a stable condition and are conscious and co-operative in the examination; (4) volunteer to join the trial and sign the informed consent form; and (5) promise not to perform other exercise programs. Exclusion: (1) patients with other serious diseases such as lung diseases, cardiovascular and cerebrovascular diseases, hematopoietic diseases, autoimmune diseases, digestive system, or mental illness; (2) pregnant or lactating women; (3) participate in other forms of exercise during the trial
Participants	• Age: median (range): N/A • Gender: N/A

ChiCTR2000029994 *(Continued)*

	• Ethnicity: N/A • Number of participants (recruited/allocated/evaluated): N/A • Symptoms at baseline: N/A • Comorbidities: N/A
Interventions	• Pharmacological interventions: none • Non-pharmacological interventions: standardized program consisting of acupressure therapy and Liu Zi Jue Qigong exercises and standard care versus standard care alone
Outcomes	Primary outcomes • Symptom relief: lung function, ADL, 6-minute walk Secondary outcomes • Modified Medical Research Council (mMRC) Dyspnea Scale, Patient Health Questionnaire-9 (PHQ-9), Respiratory Symptoms (RS) Scale, lung CT, length of hospital stay, immune cells, liver and renal function test
Notes	Sponsor/funding: this study is supported financially by the project of Emergency Scientific Research Project for prevention and control of new coronavirus (COVID-19) by Shanghai University of Traditional Chinese Medicine (first batch) (no fund number) and High-Level Innovation Team of "Peak and Plateau Discipline" in Traditional Chinese Medicine (30304114316). These two projects are funded by the Shanghai University of Traditional Chinese Medicine. The Shanghai further accelerates the 3-year action plan for the development of Chinese medicine (ZY (2018-2020)-CC-CX-2004-02), and the National Key Clinical Difficult Diseases Clinical Collaborative Pilot Construction Project—Osteoarticular Degenerative Disease (ZY (2018-2020)-FWTX-2005) is funded by the Shanghai Government. The funders had no role in the design of the study; analysis, collection, and interpretation of the data; or the writing and decision for publication of the manuscript. This funding relates to a wider group of projects and applies to this study. The trial sponsor is the Shanghai Municipal Government and Shanghai University of Traditional Chinese Medicine. The final fund management is performed by the Yueyang Integrated Traditional Chinese and Western Medicine Hospital affiliated to Shanghai University of Traditional Chinese Medicine. Conflict of interest: none declared. Data have not yet been published. We have contacted the authors for more information.

Groninger 2021

Methods	• Study design: retrospective cohort study • Type of publication: abstract published at conference • Setting and dates: general hospital between March and June 2020 • Country: N/A • Language: English • Inclusion/exclusion criteria: inpatients with COVID-19
Participants	• Age: mean: 70 • Gender: 49% women, 51% men • Ethnicity: 73% African-American • Number of participants (recruited/allocated/evaluated): 227 • Symptoms at baseline: N/A • Comorbidities: N/A
Interventions	• Pharmacological interventions: opioids (77%), benzodiazepines (42%), and antipsychotics (26%)

Groninger 2021 *(Continued)*

	• Non-pharmacological interventions: psychosocial (24%) and spiritual (9%) support, goals-of-care meetings (20%), and bereavement calls (7%)
Outcomes	Primary outcomes • N/A Secondary outcomes • N/A
Notes	Data have not yet been published.

Kelly 2020

Methods	• Study design: retrospective cohort study • Type of publication: abstract • Setting and dates: specialist palliative care, no dates • Country: Ireland • Language: English • Inclusion/exclusion criteria: patients with COVID-19 referred to specialist palliative care
Participants	• Age: median (range): N/A • Gender: N/A • Ethnicity: N/A • Number of participants (recruited/allocated/evaluated): 3 • Symptoms at baseline: agitation and dyspnea • Comorbidities: N/A
Interventions	• Pharmacological interventions: mean of 28 mg morphine sulphate subcutaneous (s/c), as-required (range 12.5 to 42.5 mg) for management of dyspnea, and a mean of 28 mg midazolam s/c, as-required (range 12.5 to 55 mg) for agitation • Non-pharmacological interventions: none
Outcomes	Primary outcomes • N/A Secondary outcomes • N/A
Notes	Full data not yet published.

Okuwoga 2020

Methods	• Study design: retrospective cohort study • Type of publication: abstract • Setting and dates: Homerton University Hospital (London, UK), no dates • Country: United Kingdom • Language: English • Inclusion criteria: inpatients older than 65 with COVID-19 and delirium

Okuwoga 2020 *(Continued)*

Participants	• Age: mean: 84 • Gender: N/A • Ethnicity: N/A • Number of participants (recruited/allocated/evaluated): 104 • Symptoms at baseline: N/A • Comorbidities: N/A
Interventions	• Pharmacological interventions: 58.7% of participants received injectable medications for symptomatic relief of agitation • Non-pharmacological interventions: 39% of all participants received psychosocial support
Outcomes	Primary outcomes • N/A Secondary outcomes • N/A
Notes	Data not yet published.

N/A: Not applicable
ADL: Activities of daily living
CT: Computed tomography

Characteristics of ongoing studies *[ordered by study ID]*

NCT04522037

Study name	Measurement of the efficacy of morphine in the early management of dyspnea in COVID-19 positive patients (CODYS)
Methods	• Study design: retrospective cohort study • Type of publication: trial registry • Setting and dates: first posted 21 August 2020 • Country: France • Language: English • Inclusion/exclusion criteria: patients hospitalized at the hospices civils of Lyon with a level of care 3 or 4
Participants	None yet, still recruiting
Interventions	• Intervention: patients hospitalized at the hospices civils of Lyon with a level of care 3 or 4 receiving morphinic treatment for COVID-19 disease dyspnea • Control: patients hospitalized at the hospices civils of Lyon with a level of care 3 or 4 not receiving morphinic treatment for COVID-19 disease dyspnea
Outcomes	Primary outcomes • Symptom relief: reduction of respiratory rate between hour 0 and hour 12 at initiation of morphine treatment [time frame: hour 0 and hour 12 after initiation of morphinic treatment]. The respiratory rate is analyzed at hour 0 and hour 12 by a scope. Secondary outcomes • N/A

NCT04522037 *(Continued)*

Starting date	
Contact information	
Notes	• Recruitment status: recruiting • Prospective completion date: none given • Sponsor/funding: Hospices Civils de Lyon

ADDITIONAL TABLES

Table 1. Risk of bias assessment criteria for observational studies

Heading	Internal validity	External validity
Study group	**Selection bias** (unrepresentative study group) The study group was considered representative, • if the described study group consisted of > 80% of individuals with COVID-19 treated with palliative symptom control **or** • if it was a random sample with respect to the treatment and important prognostic factors.	**Reporting bias** (poorly defined study group) The study group was considered as well defined, • if the study population is well described (e.g. severity of disease, age, risk factors) **and** • the intervention is well described (e.g. number of doses, volume).
Follow-up	**Attrition bias** (incomplete outcome assessment/follow-up) The outcome assessment and follow-up was considered as complete, • if the outcome was assessed for > 90% of the study group of interest (++) **or** • if the outcome was assessed for 60% to 90% of the study group of interest (+).	**Reporting bias** (poorly defined follow-up) The follow-up was considered as well defined, • if the length of follow-up was mentioned.
Outcome	**Detection bias** (outcome assessors unblinded to investigated determinant) The detection bias was considered as low, • if the outcome assessors were blinded to the investigated determinant.	**Reporting bias** (poorly defined outcome) The outcome definition was considered as well defined, • if the outcome definition was objective and precise, and the method of detection was provided.
Risk estimation	**Confounding** (important prognostic factors or follow-up not adequately taken into account) Risk of confounding was considered as low,	**Analyses** (poorly defined risk estimates) The risk estimates were considered as well defined,

Table 1. Risk of bias assessment criteria for observational studies *(Continued)*

• if important prognostic factors (i.e. age, co-treatment, comorbidities) or follow-up were adequately taken into account.	• if a risk ratio, odds ratio, attributable risk, linear or logistic regression model, mean difference, or Chi^2 was calculated.

Table 2. Overview of included studies

	Alderman 2020	Hetherington 2020	Lovell 2020	Strang 2021
	Study characteristics			
Setting	• Hospital • United Kingdom	• Hospital • United Kingdom	• Hospital • United Kingdom	• Hospitals and nursing homes • Sweden
Design	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Protocol	None published.	None published.	None published.	None published.
Number of participants	61	186	101	Unknown*
Symptoms treated	Shortness of breath, delirium, audible upper airway secretions, cough, pain, nausea	Not specified	Not specified	Cohort 1: breathlessness, anxiety, delirium, audible upper airway secretions, pain Cohort 2: breathlessness, anxiety, delirium, respiratory secretions
Outcome assessed	Symptom relief (assessed by clinicians)	Cinical impression of efficacy	Clinical impression of effectiveness	Symptom relief (assessed by clinicians)
	Participant characteristics			
Age of participants	Median age 82 (IQR 53 to 98) years	Median age 76 (IQR 71 to 84) years	Median age 82 (IQR 72 to 89) years	First cohort: mean age 84.7 (range 47 to 104) Second cohort: • Nursing homes: 86.7 (range 57 to 107) • Hospitals: 83.3 (range 30 to 107)
Gender (male (n (%)))	34 (55.5%)	98 (52.6%)	64 (45.5%)	Cohort 1: 201 (52%) Cohort 2: • Nursing homes: 1084 (57%) • Hospitals: 74 (42%)
Comorbidities (%)	Dementia (13%), neurological disease (8%), cardiovascular disease (42.5%), hypertension (36%), respiratory dis-	Hypertension (31.2%), diabetes mellitus (28%), chronic obstruc-	Hypertension (53%), diabetes (35.6%), dementia (30.6%), advanced/metastatic cancer (24.7%), chronic pul-	None reported.

Table 2. Overview of included studies *(Continued)*

	ease (23%), renal disease (18%), diabetes mellitus (19.5%), cancer (24.5%)	tive pulmonary disease (26.9%)	monary disease (21.7%), renal failure (20.7%), congestive heart failure (17.8%), stroke/neurological disorder (11.8%), peripheral vascular disorder (0.04%), liver disease (0.02%)

Abbreviations: IQR: interquartile range
*We do not know the exact number of participants since the cohorts reported on partially overlap. The first cohort included 390 participants, and the second cohort 2105 participants. It is unclear how big the overlap is between patients who died in hospitals in the first cohort (137) and nursing home residents who died in hospitals in the second cohort.

APPENDICES

Appendix 1. Planned methodology for randomized controlled trials and non-randomized studies of interventions

Types of studies

To assess the benefits and safety of palliative interventions for symptom control, we planned to include randomized controlled trials (RCTs) only, as such studies, if performed appropriately, currently give the best evidence for experimental therapies in highly controlled therapeutic settings. Had RCT data been available, we would have used the methods recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), as specified in the description of the methods.

In the case of insufficient evidence (very low-certainty evidence or no evidence) available from RCTs to answer our review question, we would include prospective controlled non-randomized studies of interventions (NRSIs), including quasi-RCTs (e.g. assignment to treatment by alternation or by date of birth), controlled before-and-after (CBA) studies, and interrupted time series (ITS) studies. In such a case we would use the methods proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* for the inclusion of NRSIs in systematic reviews (Reeves 2021) .

In case of insufficient evidence (very low-certainty evidence or no evidence) available from RCTs and NRSIs, we would include prospective observational studies with a control group and would adapt the methods for the inclusion of NRSIs in systematic reviews as specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2021).

As there was no evidence from RCTs or NRSIs, and only one prospective observational study available, we included prospective non-comparative study designs (e.g. case series) and followed the methodology as specified in the protocol (Andreas 2021).

Data extraction and management

Assessment of risk of bias in included studies

Randomized controlled trials

We planned to use the RoB 2 tool to analyze the risk of bias in the underlying study results (Sterne 2019). Of interest for this review was the effect of the assignment to the intervention (the intention-to-treat (ITT) effect), and we would perform all assessments with RoB 2 on this effect. We would address those outcomes specified for inclusion in Summary of findings 1. Accordingly, the outcomes had been prioritized according to the Core Outcome Measures in Effectiveness Trials Initiative for COVID-19 patients (COMET 2020).

One review author would assess the risk of bias for each study result. A second review author would verify the accuracy and the plausibility. In case of discrepancies among their judgements or inability to reach consensus, a third review author would be consulted to reach a final decision. We would assess the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

- Bias arising from the randomization process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

To address these types of bias we planned to use the signalling questions recommended in RoB 2 and make a judgement using the following options:

- 'yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question);
- 'probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question);
- 'no': if there is firm evidence that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question);
- 'probably no': a judgement has been made that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question);
- 'no information' if the study report does not provide sufficient information to allow any judgement.

We planned to use the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias:

- low risk of bias;
- some concerns;
- high risk of bias.

We subsequently planned to derive a risk of bias rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': the trial is judged to be at low risk of bias for all domains for this result.
- 'Some concerns': the trial is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- 'High risk of bias': the trial is judged to be at high risk of bias in at least one domain for the result, or the trial is judged to have some concerns for multiple domains in such a way that substantially lowers confidence in the results.

Non-randomized controlled studies

As reported above, we planned to include non-randomized studies if there were insufficient evidence from RCTs.

One review author would assess eligible studies for methodological quality and risk of bias (using the Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I) tool) (Sterne 2016). A second review author would verify the accuracy and the plausibility. The quality assessment strongly depends upon information on the design, conduct, and analysis of the trial. The two review authors would resolve any disagreements regarding the quality assessments by consulting a third review author until reaching consensus.

We planned to assess the following risk of bias domains.

- Bias due to confounding
- Bias in selection of participants into the study
- Bias in classification of interventions
- Bias due to deviations from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of the reported result

For every criterion we planned to make a judgement using one of five response options.

- Yes
- Probably yes
- Probably no
- No
- No information

Measures of treatment effect

Randomized controlled trials

For continuous outcomes, we planned to record the mean, standard deviation (SD), and total number of participants in both the treatment and control groups. For dichotomous outcomes, we planned to record the number of events and total number of participants in both the treatment and control groups.

For continuous outcomes using the same scale, we planned to perform analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we planned to perform analyses using the standardized mean difference (SMD). In our interpretation of SMDs, we planned to re-express the SMD in the original units of a particular scale with the most clinical relevance and impact.

We planned to extract and report hazard ratios (HRs) for time-to-event outcomes (overall survival, progression-free survival) if these were available. Had HRs not been available, we would have made every effort to estimate as accurately as possible the HR using the available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007), in an update of this review. In the case of sufficient studies providing HRs, we would use HRs rather than risk ratios (RRs) or MDs in a meta-analysis.

For dichotomous outcomes, we planned to report the pooled RR with a 95% CI (Deeks 2021). If the number of observed events was small (less than 5% of sample per group), and if studies had balanced treatment groups, we would report the Peto odds ratio (OR) with 95% CI (Deeks 2021).

For cluster-randomized trials, we planned to extract and report direct estimates of the effect measure (e.g. RR with a 95% CI) from an analysis that accounts for the clustered design. We planned to obtain statistical advice to ensure the analysis was appropriate. Had appropriate analyses not been available, we would have made every effort to approximate the analysis following the recommendations in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), in an update of this review.

For studies with a control group where meta-analysis is not possible, we planned to perform analyses according to the recommendations in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2021). We will consider summarizing effect estimates when estimates of intervention effect are available, but the variances of the effects are not sufficiently reported. If P values, but no other information, are reported, we will combine P values using Fisher's method to combine P values (see section 12-2-1-2 of McKenzie 2021). We will employ forest plots to visualize results, as they allow a clear depiction of study results when meta-analysis is not possible. In the case that these methods are not feasible, and if the direction of effect is reported, we will use vote counting based on the direction of effect. We will use harvest plots to visualize the effects of vote counting.

Non-randomized controlled studies

For dichotomous outcomes, if available we planned to extract and report the RR with a 95% CI from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the RR postintervention/RR pre-intervention).

For continuous variables, if available we planned to extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models, or hierarchical models), or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute postintervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups/the postintervention level in the control group) (EPOC 2017).

Unit of analysis issues

We followed the methods outlined in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* to identify the unit of analysis (Higgins 2021).

Repeated observations on participants

In case events were observed multiple times, we would consider the number of participants experiencing any event and not the number of experienced events for analysis.

Multiple treatment attempts

Palliative care is a multidimensional concept, and participants usually receive a combination of interventions. We planned to consider the number of participants and not the number of assigned treatments for analysis. In the case of cross-over trials, we would consider results from the first cycle only, unless an appropriate wash-out period had been applied.

Studies with multiple treatment groups

For studies with multiple treatment groups, we planned to combine arms as long as they could be regarded as subtypes of the same intervention. When arms could not be pooled in this way, we would compare each arm with the common comparator separately. For pair-wise meta-analysis, we would split the 'shared' group into two or more groups with smaller sample sizes, and include two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, both the number of events and the total number of participants would have been divided up, and for continuous outcomes, the total number of participants would have been divided up with unchanged means and SDs.

Cluster-randomized trials

For cluster-RCTs that did not make an allowance for the design effect, we planned to calculate the design effect based on a larger assumed intraclass correlation coefficient (ICC) of 0.10. We would follow the methods described in Section 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* for this calculation (Higgins 2021).

Assessment of heterogeneity

We planned to assess heterogeneity of treatment effects between studies using a Chi^2 test with a significance level at $P < 0.1$. We planned to use the I^2 statistic to quantify possible heterogeneity (Higgins 2003), with an $I^2 > 30\%$ signifying moderate heterogeneity and an $I^2 > 75\%$ considerable heterogeneity (Deeks 2021). If heterogeneity was above 80%, we would explore potential causes through sensitivity and subgroup analyses. If we could not find a reason for heterogeneity, we would not perform a meta-analysis, but would comment on results from all studies and present these in tables.

Data synthesis

If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we would pool data in meta-analysis. We planned to perform analyses according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). We would not conduct meta-analyses that involved both RCTs and non-RCTs. We planned to conduct separate meta-analyses for each comparison.

We planned to use Review Manager Web software for analyses (RevMan Web 2021). One review author would enter the data into the software, and a second review author would check the data for accuracy.

We planned to use the random-effects model for all analyses, as we anticipate that true effects will be related but will not be the same for included studies. If we could not perform a meta-analysis, we would comment on the results as a narrative, with the results from all studies presented in tables.

We planned that when meta-analysis for RCTs was feasible, we would use the random-effects model for pooling data. For binary outcomes, we planned to base the estimation of the between-study variance using the Mantel-Haenszel method. We planned to use the inverse-variance method for continuous outcomes, outcomes that include data from cluster-RCTs, or outcomes where HRs are available. We planned to explore heterogeneity above 80% with subgroup analyses. If we could not find a cause for the heterogeneity, then we would not perform a meta-analysis, but comment on the results as a narrative with the results from all studies presented in tables.

Had meta-analysis been feasible for non-RCTs, CBA studies, ITS studies, and cohort studies, we would have analyzed the different types of studies separately. We planned to only analyze outcomes with adjusted effect estimates if these were adjusted for the same factors using the inverse-variance method, as recommended in Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2021).

Appendix 2. Manual searches for evidence synthesis

1) Evidence Aid Coronavirus (COVID-19) (evidenceaid.org/evidence/coronavirus-covid-19/)

search and screen: palliative care; terminal care; end of life care

2) Coronavirus (COVID-19) (the Cochrane Library) (www.cochranelibrary.com/covid-19) – Special Collections“ + New & updated Cochrane Reviews - screen: palliative care; terminal care; end of life care

3) Usher Network for COVID-19 Evidence Reviews (https://www.ed.ac.uk/usher/uncover/register-of-reviews)

search and screen: palliative care; terminal care; end of life care

4) US Department of Veterans Affairs Evidence Synthesis Program (https://www.covid19reviews.org/)

Search Results Covid-19 Reviews /*reviews as of* 11/25/20

search and screen: palliative care; terminal care; end of life care

5) Australian guidelines for the clinical care of people with COVID-19 (https://covid19evidence.net.au/#living-guidelines)

screen: palliative care; terminal care; end of life care

6) Norwegian Institute of Public Health systematic and living map on COVID-19 evidence (https://www.nornesk.no/forskningskart/NIPH_mainMap.html)

(Systematic reviews on COVID-19):

www.fhi.no/en/sys/news/?blockId=90733&ownerPage=45271&language=en

select and screen: palliative (care); terminal (care); (end of life care) + screen reviews

7) COVID-19 Evidence Alerts from McMaster PLUS (https://plus.mcmaster.ca/COVID-19)

search and screen: palliative care; terminal care; end of life care;

in „higher quality studies for clinical attention“

in ”studies currently under review”

8) L*OVE (iloveevidence.com/)

search and screen: *(palliative care OR terminal care OR end of life OR EOL OR endstage)*

+ limit to 1. systematic reviews

9) TRIP (www.tripdatabase.com/)

search and screen: (covid-19 or "novel coronavirus") AND ("palliative care" OR "terminal care" OR "end of life" OR EOL) / + systematic reviews

10) ECRI COVID-19 Resource Center (www.ecri.org/coronavirus-covid-19-outbreak-preparedness-center/)

screen

11) JBI Evidence Synthesis COVID-19 Collection (https://journals.lww.com/jbisrir/pages/collectiondetails.aspx?TopicalCollectionId=15)

screen

12) NICE Coronavirus (COVID-19) (https://www.nice.org.uk/guidance/conditions-and-diseases/respiratory-conditions/covid19)

screen

Appendix 3. Database searches for evidence synthesis

Medline (Ovid)

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 25, 2020

1. (COVID-19 or coronavirus or "Corona virus" or 2019-nCoV or "novel CoV" or "novel coronavirus" or SARS-CoV-2 or sarscov2 or 2019nCoV or nCOV).mp.
2. ((terminal* or end of life or EOL or palliati*) adj5 (care* or cari* or nurs* or surge* or therap* or treat*)).ti,ab.
3. exp "PALLIATIVE CARE"/
4. exp "TERMINAL CARE"/
5. exp "PALLIATIVE MEDICINE"/
6. exp "HOSPICE AND PALLIATIVE CARE NURSING"/
7. or/2-6
8. cochrane database of systematic reviews.jn. or search*.tw. or review.pt. or meta analysis.pt. or medline.tw. or systematic review.tw. *[8. Wong 2006 – systematic reviews filter –modified by adding review.pt]*
9. 1 AND 7
10. 8 and 9

Complementary Search for Evidence Synthesis via PubMed „similar articles“

Export first 20 results, starting from:

Mitchell S, Maynard V, Lyons V, Jones N, Gardiner C. **The role and response of primary healthcare services in the delivery of palliative care in epidemics and pandemics: A rapid review to inform practice and service delivery during the COVID-19 pandemic**. Palliat Med. 2020 Oct;34(9):1182-1192. doi: 10.1177/0269216320947623. Epub 2020 Jul 31. PMID: 32736494; PMCID: PMC7528540.

https://pubmed.ncbi.nlm.nih.gov/32736494/

Appendix 4. Manual searches for planned evidence synthesis

Oxford COVID-19 Evidence Service – Current questions under review (www.cebm.net/oxford-covid-19-evidence-service/)

screen

Cochrane COVID Review Bank (covidreviews.cochrane.org/search/site)

screen

PROSPERO (www.crd.york.ac.uk/prospero/)

search and screen: (*covid* AND (palliative care OR terminal care OR end of life))*

Appendix 5. Database searches for primary studies

1) **CCSR** https://covid-19.cochrane.org

palliati* OR hospice* OR "terminal care" OR "terminal stage" OR "terminal disease" OR "terminally ill" OR "end stage" OR "end of life" OR "supportive care"

+ Filter by "Study design":

- Case Series/Case Control/Cohort
- Parallel/Crossover
- Cross-sectional
- Other
- Unclear

2) **Web of Science** (Science Citation Index / Emerging Sources)

AB=((COVID OR "COVID-19" OR COVID19) OR ("SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2") OR ("2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19") OR ("severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia") OR ("severe acute respiratory syndrome coronavirus 2")) OR TI=((COVID OR "COVID-19" OR COVID19) OR ("SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2") OR ("2019 nCoV" OR 2019nCoV OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19") OR ("severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia") OR ("severe acute respiratory syndrome coronavirus 2")) AND AB=((palliati* OR hospice OR "terminal care" OR "terminal stage" OR "terminal disease" OR "terminally ill" OR "end stage" OR "end of life" OR "supportive care")) OR TI=((palliati* OR hospice OR "terminal care" OR "terminal stage" OR "terminal disease" OR "terminally ill" OR "end stage" OR "end of life" OR "supportive care"))

3) **CINAHL** (via EBSCO)

((TI ("SARS-CoV-2" OR "SARS-CoV2" OR "SARSCoV-2" OR SARSCoV2 OR "SARS-CoV*" OR SARSCoV* OR "severe acute respiratory syndrome 2" OR "severe acute respiratory syndrome cov*" OR "Covid-19" OR Covid19* OR Covid OR nCoV* OR 2019nCoV* OR 19nCoV* OR "HCoV-19" OR coronavirus* OR "corona virus*") OR AB ("SARS-CoV-2" OR "SARS-CoV2" OR "SARSCoV-2" OR SARSCoV2 OR "SARS-CoV*" OR SARSCoV* OR "severe acute respiratory syndrome 2" OR "severe acute respiratory syndrome cov*" OR "Covid-19" OR Covid19* OR Covid OR nCoV* OR 2019nCoV* OR 19nCoV* OR "HCoV-19" OR coronavirus* OR "corona virus*") OR SU ("SARS-CoV-2" OR "SARS-CoV2" OR "SARSCoV-2" OR SARSCoV2 OR "SARS-CoV*" OR SARSCoV* OR "severe acute respiratory syndrome 2" OR "severe acute respiratory syndrome cov*" OR "Covid-19" OR Covid19* OR Covid OR nCoV* OR 2019nCoV* OR 19nCoV* OR "HCoV-19")) AND (DT 20191117-3000)) AND (MH ("Terminal Care" OR "Palliative Care" OR "Hospice Care" OR "Terminally Ill Patients" OR "Hospice Patients") OR TI (palliati* OR hospice OR "terminal care" OR "terminal stage" OR "terminal disease" OR "terminally ill" OR "end stage" OR "end of life" OR "supportive care") OR AB (palliati* OR hospice OR "terminal care" OR "terminal stage" OR "terminal disease" OR "terminally ill" OR "end stage" OR "end of life" OR "supportive care"))

4) **WHO COVID-19** Global literature on coronavirus disease - https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/

tw:((tw:(palliati* OR hospice* OR "terminal care" OR "terminal stage" OR "terminal disease" OR "terminally ill" OR "end stage" OR "end of life" OR "supportive care"))) AND mj:("Palliative Care" OR "Terminal Care" OR "Hospice and Palliative Care Nursing")

5) **COAP Living Evidence on COVID-19** (indexed: PubMed, EMBASE, medRxiv, bioRxiv) - https://zika.ispm.unibe.ch/assets/data/pub/search_beta/

palliative OR hospice OR (terminal care) OR (terminal stage) OR (terminal disease) OR (terminally ill) OR (end stage) OR (end of life) OR (supportive care)

Appendix 6. Planned methodology for updates of this review

Publication bias

In an update of this review, we intend to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test for meta-analyses involving at least 10 studies (Sterne 2019). We will consider $P < 0.1$ as significant for this test.

Subgroup analysis

For future updates, we plan subgroup analyses for the following characteristics:

- different settings (e.g. hospital versus nursing homes versus hospices versus home palliative care);
- different interventions (pharmacological versus non-pharmacological);
- analyses in subgroups of patients (different ages, comorbidities).

Sensitivity analysis

For future updates, we plan sensitivity analyses for the following:

- risk of bias (low risk or some concerns versus high risk for RCTs, low risk or moderate risk versus serious risk for NRSIs (studies at critical risk would be excluded from all analyses));
- influence of completed but not published studies.

CONTRIBUTIONS OF AUTHORS

MA: methodological expertise; study selection; data extraction, assessment, and interpretation; and conception and writing of the review.

VP: methodological expertise, data assessment and interpretation, and conception and writing of the review.

NS: clinical and methodological expertise and advice.

KG: development of the search strategy.

MB: data extraction and assessment.

LJ: study selection.

GB: clinical expertise and advice.

WM: clinical expertise and advice and data assessment and interpretation.

CB: clinical expertise; study selection; data extraction, assessment, and interpretation; and conception and writing of the review.

DECLARATIONS OF INTEREST

MA: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the CEOsys project), which was paid to the institution.

VP: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the CEOsys project), which was paid to the institution.

NS: has declared no conflict of interest.

KG: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the CEOsys project), which was paid to the institution.

MB: has declared no conflict of interest.

LJ: has declared no conflict of interest.

GB: has declared no conflict of interest. GB is a palliative care specialist.

WM: reports consultancy or talks for the following companies: Mundipharma, Grünenthal, Menarini, BioQPharma, Bionorica, Kyowa, TAD, Tilray, Sanofi, Septodont, and Northern Swan. He reports research funding from Pfizer, Mundipharma, and Grünenthal. WM is a palliative care specialist.

CB: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the CEOsys project), which was paid to the institution.

SOURCES OF SUPPORT

Internal sources

- University Hospital of Cologne, Germany

  Evidence-based Oncology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

External sources

- Federal Ministry of Education and Research of Germany, Germany

  This review is part of the CEOsys project funded by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021.
- National Institute for Health Research (NIHR), UK

  Cochrane infrastructure funding for the Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included two further outcomes (adverse events and serious adverse events) after the protocol was published, as these were prioritized by the editorial team of the Cochrane Pain, Palliative and Supportive Care Group. We have also changed the order of the outcomes to reflect the relevance for individuals in palliative care.

Because of time constraints, three and not two review authors, as described in the protocol, screened the results of the search.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; COVID-19 [diagnosis] [*therapy]; *Palliative Care; SARS-CoV-2; Systematic Reviews as Topic

MeSH check words

Aged; Aged, 80 and over; Humans; Male