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Opioids for Dyspnea End of Life Review

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Abstract

Objective: The objective of this systematic review is to consolidate the existing evidence on opioid use, including administration, dosing and efficacy, for the relief of dyspnea at end-of-life. The overarching goal is to optimize clinical management of dyspnea by identifying patterns in opioid use, improving opioid management of dyspnea, and to prioritize future research.

Background: Opioids are commonly used in the management of dyspnea at end of life; yet specific administration guidelines are limited. A greater understanding of the effectiveness of opioids in relieving end-of-life dyspnea with consideration of study design, patients, and opioids, including dyspnea evaluation tools and outcomes, will leverage development of standardized administration and dosing.

Methods: A PRISMA guided systematic review using six databases identified quality studies of opioid management for patients with dyspnea at end of life.

Results: Twenty-three references met review inclusion criteria which included terminally ill cancer and non-cancer patients with various diagnoses. Studies included two randomized controlled trials, three non-randomized experimental, three prospective observational, one cross-sectional, and one case series. Thirteen retrospective chart reviews were also included due to the limited rigorous studies rendered by the search. Thirteen studies evaluated morphine, followed by fentanyl (6), oxycodone (5), general opioid use (4), and hydromorphone (2). Routes of administration were parenteral, oral, combination, and nebulization. Dyspnea was evaluated using self-reporting and non-self-reporting evaluation tools. Sedation was the most reported opioid related adverse effect.

Discussion: Challenges persist in conducting end of life research preventing consensus on standardization of opioid treatment for dyspnea within this specific palliative timeframe. Future robust prospective trials using specific, accurate assessment with re-assessment of

dyspnea/respiratory distress, and consideration of opioid tolerance, polypharmacy, and comorbidities are required.

Introduction

Dyspnea is defined as "a subjective experience of breathing discomfort", whose presence is a strong predictor of mortality(1) and is documented as the most distressing symptom for Intensive Care Unit (ICU) patients at high risk of dying.(2) Patients near death are often unable to self-report this extremely distressing feeling of breathlessness.(3) Experienced physicians, nurses and respiratory therapists often underestimate breathing discomfort in critically ill patients.(4) Healthcare providers, caregivers, and support persons (family) report insufficient management of respiratory distress in patients.(5) Respiratory distress is the observed corollary to self-reported dyspnea.(6) For patients unable to self-report, respiratory distress requires ongoing evaluation for effective symptom treatment. Similar to the management of pain, self-reported dyspnea and observed respiratory distress have pharmacological and non-pharmacological interventions.(7) While opioid pain management is extensively studied, limited evidence supports the rationale, drug selection, route of administration, dosage initiation and titration, for managing dyspnea.(8) The American Thoracic Society has published initial dosage recommendations for parenteral and oral administration of select opioids for patients with respiratory diseases and critical illness(9, 10) however; recommendations specifically for end of life dyspnea management only include morphine regimens.(11) Recommendations are administration of 5 to 10mg oral morphine or 2 to4mg of intravenous morphine every 30 minutes as needed until respiratory comfort is achieved.(11) For opioid tolerant patients, recommendations are to increase the morphine dose by 25 to 50%.(11) Currently, opioid therapy is administered on an individualized basis for the palliation of dyspnea.(1) The use of opioids in managing end-of-life respiratory distress is understudied, in part due to the inherent fear of further hastening death.(9) While often unable to self-report,

patients receiving palliative care at end-of-life deserve the same comfort and relief as those able to verbalize their symptom experience.

To date, one published review examined opioid use specifically for the treatment of dyspnea in palliative medicine. (12) This study supports ongoing use of oral and parenteral opioids for dyspnea yet found insufficient evidence regarding the effectiveness of nebulized opioids. Other reviews have focused exclusively on dyspnea/breathlessness in cancer patients,(13-15) or generalized palliative treatments without specifically addressing dyspnea.(16, 17) Evidence supports opioid administration for relief of dyspnea in cancer patients,(13-15) (17) with no evidence for opioid management of dyspnea at end of life in advanced heart failure.(17) There is limited evidence regarding the safety and effectiveness of opioid pharmacotherapy for respiratory comfort to guide clinicians caring for patients at the end of life .(16) The previous systematic review of opioids for this population was published in 2002, therefore we aimed to consolidate the current evidence on opioid therapy including dosage, administration and efficacy, for relief of dyspnea at end-of-life.

Methods

The reporting for this systematic review was guided by the five steps to conducting a systematic review and PRISMA 2020 Statement.(18)

Information Sources and Search strategy

Literature searches were conducted in PubMed/MEDLINE, EMBASE, CINAHL Complete, Web of Science, Scopus, and Cochrane Library to identify peer reviewed studies published from January 1, 2000 to December 23, 2021. The publication dates were selected to build upon the existing evidence of the 2002 systemic review investigating the use of opioids for dyspnea management.(12) The research team including a medical librarian harvested a list of search terms on three search concepts: 1) dyspnea, 2) opioids, and 3) end of life. Keywords along with their variants, their associated medical subject headings (MeSH), Emtree terms, and CINAHL

Complete subject headings were used for each database to identify relevant studies. The search query was intended to apply to the title, abstract, and subject headings/keyword fields. The complete search strategy for PubMed is given as an example in figure 1. The reference lists of relevant studies were hand-searched to locate additional studies not captured by our database search. The search resulted in 1831 articles. A total of 925 duplicates were removed using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia).

Inclusion/Exclusion Criteria

Searches were designed to include all studies that might contribute data for the review but exclude case reports, book chapters, conference abstracts and non-English publications using build-in filters. Unpublished clinical trials, qualitative and single case studies, studies with healthy volunteers, pediatric patients, studies not meeting our criteria for terminal stage of life, or studies evaluating palliative sedation were also excluded during screening. Studies included in the review were experimental, quasi-experimental, cross-sectional survey and case-series publications examining opioid use for the relief of dyspnea in adult patients (≥ 18 years) in the last 30 days of life. As rigorous study designs are limited in this specific area of research, retrospective chart reviews were also included in the review. Eligible studies met the following criteria: human, adult, and the use of fentanyl, morphine, hydromorphone or other opioids for the relief of dyspnea at the last 30 days prior to death no matter where the care was provided.

Study selection:

Studies underwent two rounds of screening based on their (1) title and abstract and (2) full text. In each round, studies were screened by two independent reviewers (LO and VTL), with conflicts resolved through discussion and consensus. Both rounds of screening were

conducted using Covidence. Twenty-three studies were selected for data extraction and analysis. The number of included and excluded studies are reported in the PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Figure 2).

Risk of Bias

Studies were assessed individually for risk of bias. The Cochrane Risk of Bias tool (19) was used for randomized studies, and the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) (20) was used for all nonrandomized studies.

Results

A summary of included studies, including purpose/aim, opioid characteristics and dosing, dyspnea measurements and outcomes is presented in Table 1.

Study Characteristics

The search rendered 23 publications for inclusion in the systematic review. Publication dates were 1991 to 2020, with studies conducted in fifteen different countries, with eleven studies from Japan and four from the United States. Studies included thirteen retrospective chart reviews,(21-33) three non-randomized experiments,(34-37) three prospective observational studies,(38-40) two randomized controlled trials (RCT),(41, 42) one cross-sectional observational study,(37) and one case series.(43)   Study sample sizes ranged from a case series of four patients to 901 participants. All studies were conducted within inpatient or long-term facilities, primarily under palliative services or hospice. Generally, study sites included one to three hospital units or locations, with two exceptions, a study with sixteen sites in Japan,(38) and a center in Palliative Care for the Elderly project, conducted in long-term care facilities in six European countries.(37)

Patient Characteristics

Study populations included both terminally ill advanced cancer and non-cancer patients. Specific disease focused studies included patients with lung cancer,(36, 42) interstitial pneumonia,(25, 31, 32) interstitial lung disease,(26) end stage congestive heart failure or chronic obstructive pulmonary disease.(43) Studies included male and female adults up to 99 years of age.(23) Fifteen studies required patients to demonstrate adequate cognitive function per investigator assessment (21, 25, 33, 39-41, 43) while others specified the ability of participants to provide informed consent,(32, 34-36) communicate,(22, 38) or take oral medications.(42)   Study exclusion criteria varied; with some studies excluding patients with chronic obstructive pulmonary disease, congestive heart failure, or renal and/or hepatic failure,(34, 35) renal failure,(40) active or recent chemotherapy or radiation,(26, 39, 40) cancer or focal chest lesions,(29) acute respiratory distress or those receiving codeine or fentanyl for pain relief,(41) and a known cause of interstitial lung disease,.(32) One study enrolled only opioid naïve patients,(33) twelve allowed both opioid tolerant and opioid naïve patients,(22, 23, 25, 30-32, 34, 35, 37-40) eight included only opioid tolerant patients,(21, 24, 27, 29, 36, 41-43) and two studies did not report opioid tolerance.(26, 28)

Opioid Characteristics

Evaluation of Opioids and Medication Combinations

Four studies did not specify the specific types of opioids evaluated,(26-28, 41) with one study excluding patients receiving codeine, codeine derivatives, and fentanyl for pain relief.(41) Thirteen studies evaluated morphine,(23-25, 27, 29-32, 34, 36, 38, 40, 42) six evaluated fentanyl,(21, 24, 30, 37, 39, 43) two evaluated hydromorphone,(34, 35) and five evaluated oxycodone.(22, 24, 29, 33, 37) One study evaluated concomitant opioid and corticosteroid

use.(24) Other investigations focused on opioid administration with consideration to continued

medical treatments potentially affecting dyspnea severity including diuretics, steroids,

antibiotics, benzodiazepines, oxygen delivery, or blood transfusion. Seven studies reported

concurrent oxygen use by varying delivery methods.(21, 22, 25, 31-34)

Routes of Administration and Dosing

The most frequent route of administration was parenteral, followed by oral, a

combination of routes, and nebulization. Routes of administration with specific dosing regimens

are included in Table 1. Four studies did not specify the route(s) of opioid administration.(26, 28,

30, 37) Of the remaining nineteen studies, five evaluated intravenous administration,(23, 31,

33, 36, 39) two used subcutaneous administration,(22, 25) and two included a combination of

these routes.(21, 38) Three studies included solely oral administration,(27, 34, 35) one oral and

intravenous,(32) and two oral and subcutaneous.(41, 42) One study evaluated a nebulized

opioid, (40) and one study evaluated the oral transmucosal route.(43) The remaining two

investigations evaluated a combination of routes, one examining oral, intravenous and

transdermal, with the second examining oral, parenteral, and rectal administration.(24, 29) The

studies evaluated a variety of opioid dosing regimens (Table 1.).

Single opioid dose administration: The efficacy of a single dose of opioid for relief of

dyspnea was evaluated in two studies with initial dosage based on one-quarter or one-half of

the equivalent of a prior four hour analgesic opioid dose(41) or one-twelfth of a prior 24 hour

opioid analgesic dose.(42)

Continuous/multiple-dose opioid administration: Two studies initiated continuous low

dose morphine intravenous infusion for the relief of dyspnea, at 0.25 mg/hr.(25, 38) This initial

morphine dose was used for opioid-naïve patients in both studies with the exception of opioid-

tolerant patients initiated at 0.5mg/hr(38) in one of the investigations.   While the second study

did not report opioid tolerance, four of the twenty-five participants received codeine prior to

hospitalization.(25)   Other parenteral morphine studies based initial dosages on 50% of the

total bolus dose required for respiratory comfort,(36) or a mean starting dose of 3.3mg/hr.(23)

Parenteral fentanyl studies were initiated based on the participants previous opioid treatment

with an addition of 30-50%,(21) or at 5-25mcg/hr for fentanyl responders, and 5-35mcg/hr for

fentanyl non-responders.(39)   Studies with intravenous oxycodone reported an initial median

dose of 6mg/day,(33) and a mean daily basal subcutaneous infusion dose of 25.1mg/day.(22)

One study used transmucosal fentanyl, initiated at 200mcg per dose.(43) Oral

hydromorphone was initiated based on the patient's initial dyspnea intensity as well as

performance status, and titrated every four hours by either 0.5mg (35) or doubled as

needed,(34) and oral morphine was initiated at 3mg every four hours.(44) Nebulized morphine

was initiated at 20mg.(40)

Opioid dosage was not consistently reported for all studies,(24, 26, 28, 30, 37) or was

reported as an initial oral morphine 50 mg equivalent,(27) or equivalent mean daily dose of 7.3

mg intravenous morphine.(32) For studies using opioid titration regimens, dosing titration

occurred every 4 to 48 hours based on the patients' respiratory status, respiratory comfort, and

level of sedation. Seven studies included breakthrough dosing,(21-23, 34-36, 41) calculating

the dose per usual care,(41) as a percentage or fraction of the total daily opioid dose

administered every 15 to30 minutes as needed,(21, 34, 35) or using an unspecified regimen.

Adverse Effects

Ten of the twenty-three studies did not report any opioid associated adverse effects.(23,

24, 26-28, 30, 35, 37, 38, 41) No significant adverse effects e.g. respiratory depression,

excessive sedation, myoclonus, intercostal rigidity, pruritus, or gastrointestinal effects were documented with transmucosal fentanyl use.(43) Morphine oral or subcutaneous administration was without documented adverse effects in one study.(42)

Respiratory depression: Studies using low dose parenteral morphine,(25) oral morphine or hydromorphone reported no decrease in respiratory rate with these opioids.(34) Respiratory depression with continuous morphine infusion resolved after the infusion rate (dose) was reduced by half in one study.(30) *Sedation:* Sedation was reported as a major side effect for intravenous morphine.(31, 36) In one study sedation was managed by temporarily discontinuing the infusion and then restarting at half the dose.(36) In the same study, all patients experienced drowsiness and two patients, both with squamous cell carcinoma (lung) diagnoses, received naloxone for severe sedation.(36) *Other adverse effects:* Delirium,(31, 32) hypercapnia, hypotension, malaise, decreased level of consciousness(32) were reported during continuous morphine infusions. Hemoptysis of uncertain morphine causality, bitter taste, and mask claustrophobia were reported with nebulized morphine;(40). Parenteral oxycodone administration was frequently associated with drowsiness or somnolence,(22, 33) and to a lesser extent, delirium, pruritus, nausea, urinary retention, consciousness disturbance, and respiratory depression.(22)   Parenteral fentanyl administration was well tolerated without serious adverse effects in one study,(18) however a second study documented myoclonic jerks, pruritus (6.3%), nausea, vomiting and nightmares (12.5%).(39)

Dyspnea Measurement

Dyspnea Outcome Reporting

Dyspnea was evaluated in all included studies. Three studies evaluated opioid use for dyspnea along with pain relief in the context of comfort care.(23, 27, 37)   Another study evaluated a combination of symptoms ; dyspnea, loss of consciousness, cough, sputum, fatigue, delirium, insomnia, anorexia and pain.(26) One study evaluated the multidimensional nature of dyspnea, including etiology and concomitant symptoms. (30) The third study was exploratory reporting a range of treatment outcomes which included respiratory rates and Borg scores.(32)

Dyspnea Assessment

Dyspnea measurement tools used in the studies were for self-reporting patients, with few studies including non-self-report or proxy report. Self-report tools included: Visual Analog Scale (VAS),(22, 40-43) four-point scale,(21) Numeric Rating Scale (NRS),(22, 25, 34, 35) zero to two relief scale,(36) Modified Borg Scale,(32) Palliative Care Outcomes Collaboration (PCOC),(30) mild-severe categorical scale,(39) ad hoc symptom rating scale,(31) and the Dyspnoea Assessment Questionnaire (DAQ).(40)

Non-self-reporting or proxy reporting tools/methods included retrospective review of progress notes and clinical care flow sheets,(28, 31) observer three-grade rating,(22) Support Team Assessment Schedule (STAS-J),(24, 29, 33, 38) respiratory rate,(25) and the Comfort Assessment in Dying with Dementia (CAD-EOLD).(37) Three retrospective chart reviews did not report dyspnea measurement tool assessments; they evaluated opioid infusion patterns for treating pain and dyspnea at end of life,(23) signs, symptoms, and treatments before death,(26) and dyspnea, pain and cancer as predictors of increased opioid dosing in the final week of life.(27)

Study Outcomes

Morphine

Morphine was the most studied opioid in thirteen of the twenty-three studies. Morphine showed significant relief of dyspnea intensity when administered alone, (25, 40, 42) and in combination with other opioids.(29, 34) Significant improvement in dyspnea scoring was documented with morphine administration for self-reporting (25, 34, 40, 42) and non-self-reporting patients.(24, 29) Many studies based initial morphine dose and/or dose titration on patients' prior opioid dosing, dyspnea intensity and patient performance, or side effects, instead of a predetermined prescribed or protocol dosage regimen. Additional incremental morphine dosing was documented in only one study of patients undergoing palliative care and was one-sixth of the total daily dose given every fifteen minutes as needed,(34) while two other studies reported the administration of bolus dosing without describing the regimen.(23, 36) Concomitant morphine with a corticosteroid was administered in one study and demonstrated significant dyspnea relief, (24) however the combination was not compared to morphine administration alone.

Non-significant improvement in dyspnea scores was documented in patients with severe Interstitial Pneumonia after oral and intravenous morphine administration,(32) however dyspnea efficacy was evaluated as inadequate.   Positive clinical outcomes were reported in four studies,(30, 31, 36, 38) Parenteral morphine doses for effective dyspnea relief in the studies varied with patients' opioid tolerance.(23, 31, 32, 34, 36, 38, 40, 42)   Studies including both opioid naïve and tolerant patients reported variable initial morphine doses. One study titrated as needed for respiratory comfort, to a median initial dose of 6mg/day (opioid naïve patients) to 12mg/day (opioid tolerant patients).(31) The second study described a two-fold dose increase initiated after 48 hours if comfort not initially achieved.(38)   A study of solely opioid tolerant patients initiated intravenous morphine by administering 1to 2 mg morphine intravenous bolus

doses every 5 to 10 minutes to achieve relief, followed by a mean continuous infusion rate of 5.6 mg/hr.(36)

Hydromorphone

Two investigations demonstrated significant improvement in dyspnea intensity self-reported NRS scores with oral hydromorphone administration.(34, 35) One study evaluated hydromorphone alone(35) and the second also evaluated morphine, using hydromorphone for patients with low performance status,(34) titrating opioid doses every four hours, breakthrough doses as needed (Table 1.). Mean hydromorphone dose administered was 2.5 ± 1.8mg (0.5-6.0mg) for the single agent hydromorphone study.(35) The study examining both hydromorphone and morphine reported the mean opioid dose administered as 10.8mg ± 3.8mg (7.5-15mg) morphine equivalent dose, with a a mean hydromorphone dose of 1.44 mg administered to low performance patients.(34)

Fentanyl

Of the six studies examining fentanyl,(21, 24, 27, 30, 39, 43) only one study where the palliative care team initiated fentanyl infusions reported a significant, positive correlation (r=0.75; p=0.009)) between reduction in categorical dyspnea scores and patient-reported dyspnea severity at 24 hours post initiation of fentanyl intravenous infusion.(39) In another study, patients with reduced dyspnea scores had a median fentanyl cumulative dose of 7.5mcg/hr (5-25mcg), compared with 12mcg/hr (5-25mcg) for non-responders.(45) Median 24-hour fentanyl doses did not differ significantly (p=0.43), between patient responders (167mcg) and non-responders (227.5mcg). Another study reported that 76% of patients responded to intravenous fentanyl, with a higher median dose of 25mcg/hour (12-70mcg).(21) Investigators determined the initial fentanyl dosage using 30% to 50% of the patient's existing opioid

treatment, and titrating by 30% to 50% every 24 hours, with breakthrough doses of 10% administered every 30 minutes as needed.

Concomitant fentanyl and corticosteroid use did not show a significant change in Support Team Assessment Schedule scores in another study.(24) Single dose administration of transmucosal fentanyl 200 to 400mcg as lozenges reduced Visual Analog Scale dyspnea scores by at least 50% within 30 minutes in four patients.(43) During a study of the effect of various opioids on dyspnea, intravenous fentanyl was administered to6.3% of patients evaluated 7 days before death, 15.7% of patients 3 days prior, and 1.9% of patients one day prior .(27) At one day prior to death, 88.7% of patients were receiving morphine. Opioid doses were converted to oral morphine equivalents. The rationale for changing opioids in this retrospective study was not provided.   A palliative care study evaluated intravenous fentanyl and morphine unspecified dosing regimens during hospital admission. Self-reported dyspnea scores were reported for patients discharged alive, however 61.4% of patients died during the admission.(30)

Oxycodone

Concomitant oral or intravenous administration of oxycodone with oral or intravenous corticosteroids did not demonstrate significant decreases in Support Team Assessment Schedule dyspnea scores (P = 0.68).(24)   In a case series describing patients with end of life dyspnea receiving morphine and other opioids, continuous subcutaneous infusion of oxycodone 6 mg/day in one patient with renal dysfunction significantly decreased Support Team Assessment Schedule dyspnea scores (p<.001).(29) Oxycodone administered via continuous intravenous infusion palliated dyspnea assessed by Numeric Rating Scale, Visual Analog Scale, or observer rating, in 88.6% of patients, with an initial mean basal dose of 25.1mg/day (4.8-84.6mg) and a final mean maintenance dose of 61.8mg/day (3.8-192mg).(22) In this study,

bolus doses were also given as needed on an average of 2.1 (0-6.4) times daily, resulting in a mean total oxycodone dose 664.2mg (12-4616.2mg). A lower median initial oxycodone dose (6mg/day; 2-12mg) and maintenance dose equal to 12mg/day (0-24) provided a patient response rate of 68.4%.(33) With this lower oxycodone dosage, two of nineteen patients experienced significant relief of dyspnea. Oxycodone intravenous infusion at an unspecified dose was administered during the study (which converted all administered opioids to oral morphine equivalents) for 8.3% of patients evaluated 7 days before death, 2% of patients 3 days prior, and 1.9% of patients one day prior to death.(27) Overall, oral morphine equivalents increased for younger patients and for those with lowdoses of opioids to relieve dyspnea at 7 days prior to death; there was no evaluation of the specific effect of oxycodone.   Currently, parenteral oxycodone formulations are not available in the U.S.

Discussion

The examined studies contribute to the evidence surrounding opioid use at end of life, however, consensus on standardization for treatment remains to be discovered. In the existing evidence, challenges persist in conducting opioid research for the relief of dyspnea at end of life. The variety of opioids studied, routes of administration, patient populations, end of life timeframes, and dyspnea measurement assessment and re-assessment tools demonstrate a need for further investigation.

To achieve symptom management, the symptom first must be recognized. Dyspnea continues to be underrecognized by hospital staff.(28) As dyspnea at end of life is generally managed in a medical setting, this is the first obstacle in achieving respiratory comfort. Dyspnea under-recognition is subsequently followed by opioid underuse, as undocumented symptoms may go untreated. Opioid underuse in the last three days of life is greater in patients with dyspnea than patients with pain, an additional challenge in conducting dyspnea

research.(37) Inconsistencies in documentation and deficiencies in describing symptoms create limitations for appropriate evaluation and management.(23, 26) Lack of knowledge and experience in treating dyspnea at end of life may play a role in under-recognition and under-treatment.(37) Early palliative care involvement can help educate patients, families and staff, as patients suffering from dyspnea having palliative care consults receive more orders for opioids as a first-line treatment than those without a palliative care team.(28) Palliative care orders contain detailed instructions for symptom specific opioid administration.

As self-report is deemed the "gold standard", numerous studies used self-reporting tools for dyspnea assessment. Self-report evaluation tools are applicable early in palliative care but not feasible when end-of-life approaches.(3) Decreased consciousness is expected with the dying process. Excluding non-self-reporting patients decreases generalization to the end-of-life patient population. Proxy report is often inaccurate and unreliable,(46, 47) therefore the Respiratory Distress Observation Scale (RDOS) or other appropriate tool is needed for evaluation and re-evaluation of dyspnea . Respiratory distress is the observed corollary to self-reported dyspnea (6). The Respiratory Distress Observation Scale, is a reliable and valid tool for measuring the presence and intensity of respiratory distress in adults unable to self-report dyspnea (48-50). Consistent use of the Respiratory Distress Observation Scale assists clinicians in the appropriate identification of this difficult symptom, leading to improved documentation, treatment, and symptom relief. Use of a validated and reliable tool in clinical practice and in research will improve understanding of symptom relief and opioid efficacy to develop treatment consensus end-of-life patients.

The period of "end of life" is poorly defined,(51) complicating end of life research. Palliative care can range from days to several years, depending on the patient and the promptness of initiation. In this highly variable timeframe, symptom severity and patient ability to relay intensity can vary. Dyspnea is a predictor of increased oral morphine equivalent dose

administration in the final seven days of life.(27) Mean dyspnea score two days before death is

significantly higher when compared to scores at admission, even with morphine administration,

indicating refractory dyspnea.(52) Continuous morphine infusion rates at time of death were

demonstrated to be considerably higher when compared to rate at initiation, also supporting the

nature of refractory dyspnea,(23) During this period, consciousness declines limiting the option

of using self-administered or oral opioids. A universally accepted definition of the end-of-life

timeframe will provide greater insight into this specific period of dyspnea management.

The challenges with dyspnea recognition, evaluation and reporting may contribute to the

variability in opioid use and dosing reflected in the end of life literature. A consensus on opioid

selection and dosage regimen has not been established, however dyspnea management

guidelines exist with recommendations on initial dosing and dosing adjustments for

morphine,(11) oxycodone, hydromorphone and fentanyl(1) for oral and intravenous

administration in opioid naïve patients. Recommendations for opioid tolerant patients include an

initial dose increase of 25% to 50%,(11) as these patients often require higher and more

individualized dosing.(1) The studies which described initial dosing of oral and intravenous

opioids generally used dosage regimens recommended by the American Thoracic Society.(1)

Subcutaneous, transmucosal, and nebulized dosage regimens could not be evaluated as there

are no current recommendations for use in dyspnea yet were within the usual dosage ranges for

pain.(53)

Of the included studies, differing opioid dosage regimens were evaluated. One study

found one-quarter of regular opioid dose to be an efficient supplemental dose for dyspnea relief

for up to four hours in patients with low to moderate initial dyspnea intensity.(41) Higher

intensity scoring patients would require increased dosing and careful monitoring. Matsuda et al.

showed that low dose continuous subcutaneous morphine with titration to patient comfort

decreased dyspnea intensity, but numeric rating scale scores remained in a moderate range,

further supporting the requirement to increase/individualize opioid dosages to achieve patient

comfort and manage acute exacerbation.(25) Murakami confirmed a significant decrease in

dyspnea intensity scores with low-dose opioid use with no discussion of increased dosing

requirements for opioid tolerant patients or those with acute exacerbation.(29) Varying degrees

of renal/hepatic insufficiency, CYP metabolizer status, interacting medications, and previous

opioid exposure affect opioid dosage requirements and clinical response.(54) On the contrary,

Maeda and Hayakawa, in a trial of concomitant opioid and corticosteroid use, were unable to

identify a significant relationship between specific morphine and fentanyl dosing and dyspnea

relief.(24) The variation in opioid use, route of administration, dosing, assessments, and the

heterogeneous patient populations, confounding comorbid conditions, and possible effect of

other treatments, limits conclusions for specific opioid dosage regimen recommendations.

Routes of opioid administration varied, but were prominently enteral and parenteral, with

one study, which included nebulized morphine. Studies using nebulized opioids in the specific

end of life population are limited, especially for advanced patients unable to self-report dyspnea

scores. Claustrophobia from the face mask has been reported,(40) resulting in clinician

hesitancy to use this method of opioid administration.(55) Among patients able to provide self-

report, nebulized morphine alleviated dyspnea with little to no systemic side effects.(40, 56-59)

There are no reports of bronchospasm, secondary to local airway irritation in studies of

nebulized morphine for terminal dyspnea. Patients with poorly controlled asthma may be more

susceptible to bronchospasm caused by morphine mediated histamine release into the

airways.(56) Nebulized hydromorphone was shown as safe and effective for dyspnea

management in patients with advanced cancer and hypersensitivity to nebulized morphine,

.(60) Doses of 4mg hydromorphone in 2mL of sterile water,(60) or 5mg hydromorphone in 3mL

of saline(61) administered via nebulization produced rapid improvement in breathlessness in

patients with advanced cancer.(60, 61) Nebulized fentanyl, 25mcg in 2mL of saline,

demonstrated improvements in breathing for cancer patients,(62, 63) and decreased respiratory rate and improved oxygenation, although results were inconclusive when compared to placebo.(62)

In addition, the reviewed studies have other limitations, which decrease generalization of findings. Numerous studies were retrospective reviews, conducted in a single-center with a small sample size. There was limited evaluation of patient age, body composition, opioid metabolism and elimination, renal and hepatic function, which affect the pharmacokinetics and pharmacodynamics of opioids administered for the relief of dyspnea at end of life.(64) Murakami reported respiratory depression in an opioid tolerant patient with low body weight following low-dose opioid administration,(29) emphasizing the need for individualization of opioid dose.

Lin et al. demonstrated a negative association with glomerular filtration rate (GFR) and the number of continuous morphine infusion rate changes (r=-0.18; p,0.01).(23) Patients with glomerular filtration rate greater than 30 ml/min also received more intravenous morphine boluses. Those with glomerular filtration rate less than 30 ml/min did show any difference in length of morphine infusion, 24-hour morphine dosage equivalent, or number of administered IV bolus doses (p>0.05).(23)   Clemens and Klaschik reported that oral hydromorphone relieves dyspnea in patients with renal impairment or morphine intolerance(29, 34, 35). Oral administration of opioids may not be practical during later stages of terminal treatment. However, equianalgesic opioid conversions are readily available for convenient administration via the parenteral route.(65) Hydromorphone undergoes hepatic metabolism to small amounts of active metabolites, presenting an alternative to morphine for patients with renal insufficiency(66) or those experiencing morphine induced cognitive impairment/ drowsiness/nausea.(67) Opioid rotation in palliative care to achieve relief of symptoms or manage opioid adverse effects is well documented.(68)

Yamamoto et al. reported that intravenous oxycodone is a safer option than morphine for dyspnea in cancer patients with renal impairment, however, the investigators reported difficulties recommending use for patients with hepatic impairment (33)   In severe hepatic insufficiency, oxycodone initial doses should be reduced to 30% to 50% of the usual starting dose.(69) As hepatic insufficiency decreases opioid clearance, initial opioid dosages must be low, with extended dosing intervals to avoid accumulation and adverse effects.(69) Changes in the pharmacokinetics, pharmacodynamics and pharmacogenomics of opioids at the end of life, complicated by comorbid conditions require an interprofessional approach.

Risk of Bias

Of the 23 included studies, only two were controlled trials with low to moderate risk of bias (Table 2.). The remaining 21 studies were nonrandomized. Of these, it was determined that eight had a serious risk of bias and eleven had a critical risk (Table 3.)

Conclusion

This systematic review demonstrates a lack of consistent evidence in the current literature regarding end-of-life opioid use and does not permit an overall conclusion on opioid selection, route of administration and dosing, yet supports the limited existing guidelines regarding opioid administration during this critical period.(9) Opioid selection, route of administration and dosing regimens must be individualized, until rigorous studies are available to guide practice. Appropriate dyspnea evaluation and re-evaluation using validated assessment tools is necessary to demonstrate the efficacy of opioids; and establishing a widely accepted definition of the end-of-life period is needed to leverage future investigations.   Robust prospective trials will expand the current limited evidence to improve the respiratory comfort for this extremely vulnerable patient population.