Professionals', patients', and families' views on the use of opioids for chronic breathlessness: A systematic review using the framework method and pillar process

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Abstract

Background

In combination with non-pharmacological interventions, opioids may safely reduce chronic breathlessness in patients with severe illness. However, implementation in clinical practice varies.

Aim

To synthesise the published literature regarding health professionals', patients' and families' views on the use of opioids for chronic breathlessness, identifying issues which influence implementation in clinical practice.

Design

Systematic review and synthesis using the five-stage framework synthesis method.

Data sources

Three electronic databases (MEDLINE, Embase *via* OVID, ASSIA *via* Proquest) were searched (March 2020) using a predefined search strategy. Studies were also citation chained from key papers. Papers were screened against *a priori* eligibility criteria. Data were extracted from included studies using the framework synthesis method. Qualitative and quantitative data were synthesised using the pillar process. Included studies were critically appraised using the Mixed-Methods Appraisal Tool.

Results

After de-duplication, 843 papers were identified. Following screening, 22 studies were included. Five themes were developed: i) clinician/patient characteristics, ii) education/knowledge/experience, iii) relationship between clinician/family, iv) clinician/patient fear of opioids and v) regulatory issues.

Conclusions

There are significant barriers and enablers to the use of opioids for the symptomatic reduction of chronic breathlessness based on the knowledge, views and attitudes of clinicians, patients and families. Clinicians' interactions with patients and their families strongly influences adherence with opioid treatment regimens for chronic breathlessness. Clinicians', patients', and families' knowledge about the delicate balance between benefits

and risks is generally poor. Education for all, but particularly clinicians, is likely to be a necessary (but insufficient) factor for improving implementation in practice.

Keywords

Opioids; Breathlessness; Dyspnoea; Barriers; Enablers; Patients; Clinicians; Systematic Review; Pillar Process

Key statements

What is already known about the topic?

-Chronic breathlessness is a prevalent symptom amongst patients with advanced medical conditions

-In combination with disease-modifying therapies and non-pharmacological interventions, regular low dose opioids may safely reduce moderate to severe chronic breathlessness due to advanced medical conditions.

-Implementation of opioids for chronic breathlessness in clinical practice varies widely.

What this paper adds

-Clinicians' and patients' fears of opioids causing respiratory depression, addiction and regulatory scrutiny are significant barriers in the use of opioids for breathlessness.

-Education and information are necessary, but insufficient as a sole strategy, to improve implementation of opioid use for this indication.

-Clinicians' interactions with patients and their families strongly influence acceptance of, and adherence to opioid treatment regimens for chronic breathlessness

Implications for practice, theory or policy

-An agreed protocol for opioid initiation, titration and monitoring for use by clinicians in conjunction with agreed clinical guidelines may improve both their knowledge and confidence around opioid use for the symptomatic reduction of chronic breathlessness

-Additional research on patients' and carers' experiences of opioids for chronic breathlessness is necessary to inform better implementation of opioids into clinical practice.

Introduction

Chronic breathlessness - disabling breathlessness which persists despite optimum disease-treatment -(1) is prevalent amongst people with advanced medical conditions, including cardio-respiratory diseases, neurodegenerative diseases and cancers.(2) Chronic breathlessness is associated with poorer physical and mental health outcomes in people at end of life (3, 4). One of the aims of defining chronic breathlessness as a distinct clinical entity was to help clinicians identify patients who may benefit from interventions which modify the perception of breathlessness itself. Meta-analyses of clinical trials provide evidence that, in combination with usual care including disease-modifying therapies and non-pharmacological interventions, regular low dose opioids may safely reduce moderate to severe chronic breathlessness due to advanced illness; with the majority of evidence relating to morphine. (5, 6) The most recent published trials (7-9) did not show benefit for the study populations as a whole, but a significant number of participants had less severe chronic breathlessness (for whom a response is less likely (10)). However, sub-group analyses of participants with moderate to severe chronic breathlessness in both trials showed reduction in breathlessness compared with placebo, reaching statistical significance in one.(8) Following independent review of all clinical study data one jurisdiction (Australia) has now authorised an extended license for a sustained release morphine formulation for use in chronic breathlessness.(11) However, clinical use and acceptance of morphine for use in chronic breathlessness has been limited,(12) with implementation in clinical practice varying in relation to, i) whether clinicians will prescribe opioids (13); and if so, ii) the formulations and treatment regimens used, and iii) whether patients adhere to, and family members support, prescribed treatment for chronic breathlessness.

Therefore, an understanding of patient, carer and healthcare professionals' knowledge and views on the use of opioids for chronic breathlessness is important to inform clinical practice. Patients and carers co-manage chronic breathlessness, and both experience the impact of it on their daily lives (14). This study's aim is to review the evidence of health professionals', patients' and family's views on the use of opioids for chronic breathlessness, identifying those which influence implementation in clinical practice. The review is reported

in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.(15) The review includes and synthesises qualitative and quantitative data to enrich understanding of the provision of palliative care within complex systems, highlighting multiple factors in the form of barriers and enablers that impact on the use of opioids for chronic breathlessness. For the purposes of study inclusion, analysis, and reporting in this review, we simplify the term 'chronic breathlessness' to 'breathlessness' to refer to the ongoing daily management of chronic breathlessness distinct from its acute management.

Method

Research Question

In relation to the prescription of morphine for chronic breathlessness, what is known about health professionals', patients', and families' knowledge and views about its use at individual, team, and organisational levels?

Research Design

The research design was based on Brunton et al's(17) five-stage framework synthesis method: familiarisation, framework selection, indexing, charting and mapping, alongside the pillar process to jointly display quantitative and qualitative data alongside each other. We did not apply the second (framework selection) stage as the familiarisation stage had enabled us to develop an applied, fit-for-purpose framework. The first stage (familiarisation) involved the scoping of background literature on opioid use for breathlessness to identify a relevant research question and develop a search strategy. This stage was undertaken to develop a conceptual framework. Key papers were identified from colleagues and citation chaining and research questions were developed based on evidence that opioids can safely reduce breathlessness in severe illness. The second stage of synthesis used in this review was indexing which involved the searching, screening and data extraction process as follows.

Search Strategy

Development of the search strategy was guided by search terms, derivatives and related Medical Subject Headings (MeSH) terms for clinicians, patients, morphine, other opioid

medications and qualitative research (Table 1, Supplementary File 1 Search Strategy). The search terms 'survey' and 'questionnaire' were also used to find papers with quantitative results which reported the knowledge and views of patients, clinicians and carers on opioid use for breathlessness. The search strategy was initially organized into participants, concepts and context (PCC) mnemonic as recommended by the Joanna Briggs Institute(16) and was initially developed in OVID Medline before being translated into other databases. Consistent with the Cochrane Handbook for Systematic Reviews of Interventions (17), the minimum of three appropriate databases were searched including MEDLINE and Embase via OVID and ASSIA via the Proquest platform (March 2020). Studies were also citation chained from key papers in the field. Studies were also citation chained from key papers in the field.

Table 1. Search strategy: Participants concepts and context

Type of term	Term	Keywords	MESH Term
Participants	Clinicians	Clinician*, Doctor*, Healthcare provider*, Healthcare Professional*, Nurse*	Health Personnel
	Patients	Patient*, User*, Adult*, Consumer*, Carer*, Caregiver, Client*	Patients
Concept	Opioids	Morphine, Opioid, Opiate, Morfine, Fentanyl, Codeine, Oxycodone, Buprenophine, Hydrocodone, Methadone	Morphine Morphine Derivatives
	Breathlessness	Dyspn*, Breathlessness, dyspnoea*, breathless*, short* adj2 breath*	Dyspnea
Context	Chronic or Palliative Care in any setting	Qualitative, Knowledge, Experience*, View*, Attitude*, Interview*, Feeling*, Emotion*, Perception*, Perspective*, Opinion*, Accept*, Survey, Questionnaire	Qualitative Research

Inclusion/exclusion criteria

Table 2. Inclusion/Exclusion Criteria

Criteria	Inclusion	Exclusion
Language	English	Non-English
Study Type	Empirical studies reporting on knowledge and views relating to opioid use for breathlessness	Clinical trials Non-empirical studies
Participants	Patients Carers Healthcare professionals	
Publication Type	Peer-reviewed publication	Non-peer-reviewed publication Abstract only
Indication	Chronic Breathlessness	
Treatment	Any opioid	

Screening

References were managed, including deduplication, using the Rayyan web application. Reviewers FR and JC independently (using the blind function), double-screened titles and abstracts of all papers against the a priori eligibility criteria. Once this process was completed FR and JC reached a mutual decision about conflicts (n=21) with the support of a third researcher. After resolving conflicts 49 papers remained which were screened as full papers against the a priori eligibility criteria. After this final screening process, 22 studies were included. The PRISMA Flow Diagram is shown in Figure 1.

Data Extraction and critical appraisal

One reviewer (FR) independently read and extracted data from the 22 included studies. Data extracted included characteristics of study and patients, carers and/or clinicians, primary data on knowledge and/or views of clinicians, patients or carers (participant quotations, quantitative survey data) and secondary data on reflections on knowledge and/or views of clinicians, patients or carers from article authors. The recording of data extraction is available as supplementary material (Supplementary File 3 Qualitative Data Extraction).

Reviewers FR, JC and MP critically appraised the included studies using the Mixed Methods Appraisal Tool.(18) The tool has five categories of study; qualitative research, randomized controlled trials, non-randomized studies, quantitative descriptive studies and mixed methods studies. FR initially critically appraised all 22 studies and JC and MP then checked and further developed comments on each study. The results of the critical appraisal are shown in Table 3 and the full results including comments are available as supplementary material (Supplementary File 5 MMAT). In Table 3, each study has a total number which represents the number of positive yes responses to the questions posed in the tool. It is worth nothing that the one study critically appraised as '0' was conducted in a very different cultural context to other included studies (19) and that the included systematic review (20) was not critically appraised as MMAT criteria apply to primary studies only. We used our critical appraisal to inform the synthesis and discussion, which include reflections on the weight of the evidence based on the appraisal.

Analysis

Analysis of the papers continued the five-stage framework synthesis method from Stage 3 (charting). This entailed the coding of qualitative data by FR using the principles of thematic synthesis,(21) starting with line-by-line coding of the primary data and author reflections from each study. These codes were then refined, and both inductively and deductively organized into descriptive enablers or barriers. This process created a total of 59 codes. Five descriptive themes emerged through reflection by FR on the 59 codes and the linking of the codes into categories. For example, enabler codes "knowledge of national guidelines" and "experience with opioids" were placed into the category of education/experience. This grouping process resulted in five descriptive themes, available as supplementary material (Supplementary File 4 Qualitative Theme Development).

The final stage of analysis, mapping and interpretation synthesized quantitative data and qualitative data using the pillar process method to integrate and jointly display qualitative and quantitative data from the included studies.(22) The pillar process provides a rigorous technique for integrating qualitative and quantitative findings in systematic reviews. It

includes four stages: listing, matching, checking and pillar building. Firstly, the raw data from the included studies were listed as quantitative or qualitative on either side of the pillar process table. This listing was selective, in that only particular data were included based on the emerging themes from the previous charting stage of data analysis. Secondly, the matching stage of the pillar process was conducted, which involved matching qualitative with quantitative data together using qualitative and quantitative categories. Categories were separated into enablers and barriers. The categories were matched across the pillars alongside the listed raw data to align similar data from across the qualitative and quantitative columns. This jointly displays quantitative and qualitative data alongside each other to show patterns and similarities across the quantitative and qualitative data from the included papers. Any data from the qualitative and quantitative lists that did not match were given individual categories with the opposite column left blank, visually displaying any gaps in the matched data. The third stage of the pillar process involved checking the accuracy of the matching data. Reviewers FR and MP independently checked and agreed the matched data and reviewed any identified gaps from the previous stage. This involved reflecting on any emerging patterns or lack of patterns for some of the listed data. The final stage of the pillar process was the building of pillar themes in the central column of the pillar process table. These themes were developed by comparing and contrasting the matched data and codes and categorising the patterns and similarities from the matching stage into themes. These themes were also integrated from the previous charting stage of analysis and matched the initial 5 themes that were developed at that stage. Alongside the pillar process, data were synthesized in a narrative outlining each theme and relevant findings which is presented in the following findings section. The full pillar process table is available as supplementary material (Supplementary File 2 Pillar Process).

Table 3. MMAT Critical Appraisal Results

	AuthorD	Bendiane 2005 (23)	Brozek 2019(24)	Butola 2014(19)	Carette 2019(25)	Deollon 2010(26)	Gott 2010(27)	Hu 2004(28)	Janssen 2015(29)	Mori 2019(30)	Pohl 2012(31)	Rocker 2012(32)	Rocker 2013(33)	Stefan 2015(34)	Stenekes 2019(34,	Tsao 2019(36)	Young 2012(37)	Ecenarro 2018(38)	Verberkt 2019(39)	Hadjiphilippou 2014(40)	Oxberry 2012(41)	Smallwood 2018(42)
1. Qualitative	1.1. Appropriate qualitative approach	-	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	✓	-	-	-	✓	-
	1.2. Appropriate data collection methods	-	-	-	-	✓	?	-	-	-	-	-	-	-	-	-	✓	-	-	-	✓	-
	1.3. Findings based on data	-	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	✓	-	-	-	✓	-
	1.4. Interpretation of results	-	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	✓	-	-	-	✓	-
	1.5. Coherence	-	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	✓	-	-	-	✓	-
2. Quantitative randomised controlled (trials)	N/A – no trials included	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3. Quantitative non-randomized	3.1. Appropriate randomization	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	3.2. Appropriate measures	-	-	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	3.3. Complete data	-	-	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	3.4. Confounders accounted for	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	3.5. Intervention as intended	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4. Quantitative descriptive	4.1. Sampling strategy	x	?	?	-	-	-	✓	✓	✓	✓	✓	-	✓	✓	✓	-	?	✓	✓	-	✓
	4.2. Sample representative	x	?	?	-	-	-	?	?	?	✓	✓	-	✓	?	✓	-	?	?	X	-	?
	4.3. Appropriate measures	✓	?	x	-	-	-	✓	?	✓	✓	✓	-	✓	?	✓	-	?	x	X	-	?
	4.4. Risk of nonresponse bias	✓	x	x	-	-	-	✓	x	?	✓	✓	-	x	x	x	-	x	?	x	-	x
	4.5. Statistical analysis appropriate	x	✓	?	-	-	-	✓	✓	✓	✓	✓	-	✓	?	✓	-	✓	✓	?	-	✓
5. Mixed methods	5.1. Rationale for mixed methods	-	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-

	AuthorD	**Bendiane 2005 (23)**	**Brozek 2019(24)**	**Butola 2014(19)**	**Carette 2019(25)**	**Deollon 2010(26)**	**Gott 2010(27)**	**Hu 2004(28)**	**Janssen 2015(29)**	**Mori 2019(30)**	**Pohl 2012(31)**	**Rocker 2012(32)**	**Rocker 2013(33)**	**Stefan 2015/34)**	**Stenekes 2019(34,**	**Tsao 2019(36)**	**Young 2012(37)**	**Ecenarro 2018(38)**	**Verberkt 2019(39)**	**Hadjiphilippou 2014(40)**	**Oxberry 2012(41)**	**Smallwood 2018(42)**
	5.2. Integration of components for research questions	-	-	-	-	-	-	-	-	-	-	-	?	-	-		-	-	-	-	-	-
	5.3. Integration of components for interpretation	-	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-
	5.4. Addressing of divergences	-	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-
	5.5. Quality criteria of different methods involved	-	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-
MMAT Total		**	*	**0**	**	*****	*****	*****	**	**	*****	**	*****	***	*	*****	*****	*	**	*	*****	*

Findings

Characteristics of included studies

The PRISMA Flow Diagram is shown in Figure 1 and the characteristics of included studies in Table 4. A total of 993 papers were identified from electronic database searches and 36 additional papers from citation chaining: 14 included studies contained survey data; 7 interview data; 1 systematic review; 1 case report; and 1 assessment form (total 22 included studies, as some included more than one form of data).

Where stated, participants were patients (N = 482; 46.27% women; mean age 60.98; age range 18-89) in 5 included studies, health professionals (N = 3828; 16.69% women; mean age 44.3; age range 20-70) in 17 studies and carers (N = 27; 85.19% women; mean age 58; age range 32-82) in 1 study. There was an additional study with a mix of patients (N = 8; 37.5% women; mean age 71; age range 52-79), carers (N = 12; 58.33% women; mean age not stated; age range 34-75) and health professionals (N = 28; 39.29% women; mean age 52; age range 29-70).

The medical conditions explored in the included studies were cancer, chronic obstructive pulmonary disease (COPD), motor neurone disease, interstitial lung disease, asthma, COPD-asthma Overlap Syndrome, pulmonary hypertension and heart failure. Health professionals included respiratory physicians (N = 908), residents in respiratory medicine (N = 35), GPs (N = 747), hospital doctors (N = 250), medical students (N = 423), ward nurses (N = 6), practice nurses (N = 5), respiratory nurses (N = 5), palliative care nurses (N = 4), community matrons (N = 2), palliative care physicians (N = 458), midwives (N = 6), oncologists (N = 217), physiotherapists (N = 1), unspecified nurses (N = 130) and unspecified physicians (N = 421). Included studies were from a variety of country contexts spanning 4 continents. More studies were conducted in hospital settings and more studies considered opioids in general.

Just under half of the included studies (9 out of 21 appraised) had high MMAT totals (4s and 5s) and 12 of the studies had lower totals (0s, 1s and 2s) as shown in Table 3. Comparing and contrasting study findings (see Supplementary File 3) in relation to MMAT scores showed

similar findings across the studies, regardless of score. For example, the barrier clinician and patient fear of opioids was identified in several studies with lower MMAT totals (24, 25) and several with higher MMAT totals (26, 27). This was the case across the barrier and enabler findings. The comparisons of the studies with lower and higher MMAT totals informed the findings by confirming that they are appropriately weighted and relevant across multiple studies with differing MMAT totals.

Figure 1. PRISMA Flow Diagram

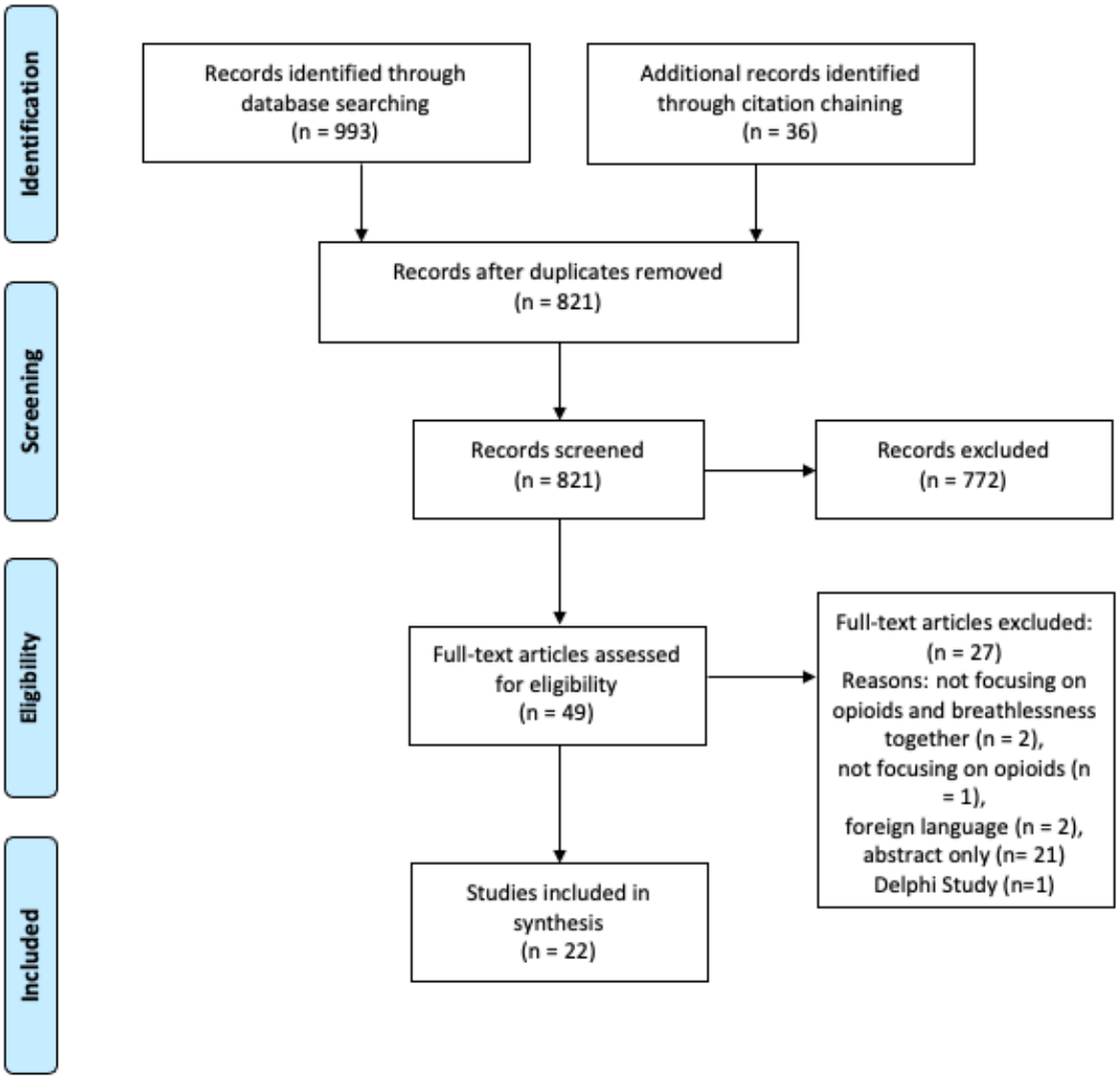

Table 4. Characteristics of included studies

First Author (year)	Participants (N)	Participant Characteristics	Gender	Mean age in years (Range)	Data Collection	Country	Setting	Opioid
Brozek (2019)	174	Health Professionals-Respiratory Physicians	Not stated	Not stated	Survey	Poland	Multiple	Opioids in general
Carette (2019) (25)	46	Health Professionals-Pulmonologists	M: 30 F: 16	45 (Not stated)	Survey	France	Hospital	Opioids in general
Stenekes (2019) (35)	167	Health Professionals-nurses, physicians, midwives	M: 16 F: 149 O: 2	Not stated (26-70)	Survey	Canada	Multiple-(hospitals, children's hospice, health centre)	Opioids in general
Tsao (2019) (36)	392	Health professionals-physicians	M: 211 F: 146	Not stated (20-60)	Survey	Vietnam	Hospitals	Opioids in general
Verberkt (2019) (39)	175	Patients-COPD, asthma, interstitial lung disease, COPD-asthma Overlap Syndrome, pulmonary hypertension	M: 88 F: 87	65 (57-70)	Survey	Netherlands	Hospital	Opioids in general

First Author (year)	Participants (N)	Participant Characteristics	Gender	Mean age in years (Range)	Data Collection	Country	Setting	Opioid
Mori (2019) (30) (31) (31) (30) (30) (30) (29) (32) (31) (31) (30) (30) (30) (30) (30) (30) (30) (31) (30) (31) (30) (31) (30) (30) (30) (30) (30) (30) (30) (30)	189	Palliative care physicians	Not stated	Not stated	Survey	Japan	Multiple	Opioids in general
Ecenarro (2018) (38)	386	Health professionals-pulmonologists	Not stated	Not stated	Survey	Spain	Multiple-(Hospitals, primary care unit)	Opioids in general
Smallwood (2018) (42)	577	Health Professionals-Palliative medicine specialists, respiratory medicine specialists	Not stated	Not stated	Survey	Australia, New Zealand, UK	Hospitals	Opioids in general
Janssen (2015) (29)	146	Doctors-Chest Physicians, residents in respiratory medicine	M: 88 F: 58	43.6 (Not stated)	Survey	Netherlands	Multiple-(University hospital, general hospital, pulmonary rehab centre	Opioids in general
Stefan (2015) (34)	178	Health Professionals-Hospital Doctors	Not stated	Not stated	Survey	USA	Hospitals	Opioids in general
Butola (2014) (19)	210	Health Professionals-GPs	Not stated	Not stated	Survey	India	Border Security Force	Morphine
Hadjiphilippou (2014) (40)	65	Health Professionals-hospital doctors	Not stated	Not stated	Survey	UK	Hospital	Opioids in general

First Author (year)	Participants (N)	Participant Characteristics	Gender	Mean age in years (Range)	Data Collection	Country	Setting	Opioid
Bendiane (2005) (23)	719	Health Professionals-GPs, oncologists	M: 472 F: 247	Not stated	Survey	France	Multiple-(primary care, hospitals)	Morphine
Rocker (2013) (33)	44	Patients-(Advanced COPD)	M: 19 F: 26	74 (51-89)	Semi-structured interviews	Canada	Patient homes	Opioids in general
Oxberry (2012) (41)	10	Patients-male, heart failure	M: 10 F: 0	71 (53-86)	Semi-structured interviews	UK	Heart Failure Clinics	Opioids in general
Rocker (2012) (32)	48	Patients (8), Carers (12), Physicians (28)	Patients: M: 5 F: 3 Carers: M: 5 F: 7 Physicians: M: 17 F: 11	Patients: 71 (52-79) Carers: Not stated (34-75) Physicians: 52 (29-70)	Semi-structured interviews	Canada	Multiple-(hospitals, patient homes)	Opioids in general
Young (2012) (37)	18	Health professionals-family physicians, respiratory therapists	Not stated	Family Physicians: 48 (34-65) Respiratory Therapists: 37.5 (29-54)	Semi-structured interviews	Canada	Primary care	Opioids in general
Dellon (2010) (26)	27	Carers	M: 4 F: 23	58 (32-82)	Semi-structured Interviews	USA	Hospital	Opioids in general

First Author (year)	Participants (N)	Participant Characteristics	Gender	Mean age in years (Range)	Data Collection	Country	Setting	Opioid
Gott (2010) (27)	39	Health Professionals-Mixed-(GPs, Hospital doctors, ward nurse, practice nurse, specialist respiratory nurse, palliative care nurse, community matron, physiotherapist)	M: 27 F: 12	40.2 (Not stated)	Focus Groups	UK	Multiple-(GP practices, hospitals)	Opioids in general
Hu (2004) (28)	136	Patients-Cancer	M: 77 F: 59	27.2 (18-69)	Assessment Form	China	Hospital	Morphine
Pohl (2012) (31)	423	Medical students	Not stated	Not stated	Case Report	Austria	University Medical School	Opioids in general
Mitchell (2018) (20)	46 Papers	Health Professionals-GPs	Not stated	Not stated	Systematic Review	Mixed	Primary Care	Opioids in general

Findings are presented in five themes: clinician/patient characteristics; education/knowledge/experience; relationship between clinician/family; clinician/patient fear of opioids; and regulatory issues.

Clinician and patient characteristics.

High patient need drove a willingness by patients to try opioids, as well as perceived symptom improvement from opioid use. Several studies with high MMAT totals found that those with advanced disease and nearer the end of life were more willing to try opioids, and clinicians who considered their patients to have a poorer prognosis were more inclined to prescribe opioids for them:

"you're grasping for any little thing that comes along, and this morphine I guess it's been the best little thing that I've grasped for" Patient (33)

"Somebody who is in a terminal stage of COPD I would think would have a life expectancy measured in terms of months, whereas advanced could still go on for years depending on how well they're managed. So terminal certainly I have no problems using opiates in them and the advanced ones if that's the only thing that keeps them comfortable I wouldn't hold off in them either but you kind of wonder ... you have to be a little more careful I suppose if somebody's got years of disease in front of them versus a few months." Clinician (37)

However, older patients were less willing and less confident about using opioids for breathlessness than younger patients, although reasons for this were not explored.(39) Furthermore, the study which highlighted this age difference only received an MMAT total of 2 and was found to have little justification for survey questions as well as limited inclusion and exclusion criteria. This may impact the weighting of the relevance of patient age on opioid use.

Palliative care clinicians, younger clinicians and those at an earlier stage of their career were more likely to use opioids for chronic breathlessness in patients with COPD. Positive changes

in attitudes in response to more recent knowledge about the safety and potential benefits of opioids may mean that younger clinicians are more open to using opioids.(24) However, the study which reported this finding only received an MMAT total of 1 and had limitations in terms of response rate and sampling strategy. Support from a palliative care team increased clinician willingness to prescribe opioids, particularly collaboration, communication and information sharing between palliative specialists and non-palliative specialists.(40)

Clinicians' professional characteristics also influenced health providers' knowledge of opioid dosing. One study found that physicians had a more accurate knowledge of opioid dosing than nurses (35) although this study only has a MMAT total of 1.

Education/Knowledge/Experience.

Education and experience with opioids in both clinicians and patients/carers enabled the use of opioids for breathlessness. Clinicians with knowledge of clinical guidelines for opioid use were more willing to prescribe opioids than those without. Several studies, one of which has a MMAT total of 5 (37), highlighted the need to improve clinician knowledge and education on opioid use for breathlessness, particularly regarding prescribing and application.(24, 37, 40)

"I guess the thing is I don't have enough experience in doing that yet [opioid use for advanced COPD] and there hasn't been enough studies out, enough physicians that are on board with it yet." Respiratory Therapist (37)

One study suggested that information about dosing was needed and provision of guidelines.(40) The study also found that clinicians with prior experience prescribing opioids in general (such as for pain) were more knowledgeable and more confident in using them to reduce breathlessness. It is worth noting that this study received a MMAT total of 1 and had limitations with regards to the appropriateness of the questionnaire variables and sampling.

Ethical knowledge and reasoning affected clinicians' willingness to prescribe opioids for breathlessness. One study (MMAT total 5) found that a clinician questioned whether it would be ethical not to give someone opioids for breathlessness if they thought it could lessen their suffering (32). This ethical balance between causing harms and relieving suffering could be both an enabler and barrier to the use of opioids for breathlessness.

Consistent with the above, clinicians' lack of knowledge about national guidelines was identified as a reason for hesitancy to prescribe opioids for breathlessness in one study.(20) Furthermore, clinician lack of knowledge, education and training, in relation to opioid use for breathlessness and lack of experience of the use of opioids for breathlessness was shown to be a barrier across several studies, all of which had high MMAT totals.(30, 37, 41) A perceived lack of evidence for the use of opioids for breathlessness was found to reduce clinician confidence.(37)

Patient lack of knowledge was also shown to affect the use of opioids for breathlessness, in particular the mixed or poor information and communication patients received from clinicians. One study found a large variation of opinions across patients, likely resulting from inconsistent information sharing from clinicians to patients about opioid treatment.(39) This study had limitations in that not all included patients had an indication for opioid treatment as the study has a convenience sampling strategy.

Relationship Between Clinician/Patient and Family.

Effective communication of potential benefits and harms of opioids for breathlessness was important(32) and found to improve patient trust in clinicians and patient approval of clinician recommendation of opioids for breathlessness.(39) Poor communication about the use of opioids and potential harms was found to reduce patient willingness and confidence in using opioids to reduce symptomatic chronic breathlessness.(39) Furthermore, a poor relationship between a clinician and the patient's family was shown to be a potential barrier when there were cultural differences between the clinician and the patient/family. One study (MMAT total 4) found that those from a Chinese cultural background may be less

inclined to accept opioid therapy for pain or breathlessness despite clinicians' recommendations, due to connotations in Chinese culture around the opium wars.(28)

Clinician/Patient Fear of Opioids.

This theme was a major finding across the studies suggesting significant clinician and patient fears relating to opioid use.(25, 32, 39, 41)

Clinicians' fears included opioid-related patient harms, particularly respiratory depression and a concern that opioid use would result in hastening patients' deaths. Fears of opioid use stemmed from previous medical training, as they had been taught that opioids would hasten death in people with respiratory disease:

"I mean when I went to medical school, we were taught to never consider opioids in people with COPD. We were going to kill them. It was like if you gave them one dose of morphine, they would be dead and it would be your fault. That was the teaching." Clinician (32)

One study found that clinicians were particularly fearful of litigation due to the off-label prescription of opioids for the indication of breathlessness.(25) Despite only having a MMAT total of 2, this study's sample was representative of the target population and had clearly defined measures.

Patients feared opioids would hasten death or signified that they were at the final stages of life. Addiction was also a concern for patients. A study found that patient fears related to being unfamiliar with opioids, worries about "getting high" and fear of weight gain.(39) Patients also perceived clinician reluctance in one study, in turn increasing patient fear of opioids, and causing a reluctance to use opioids even when prescribed them:

"He (GP) give me a morphine tablet... and he said "Don't use 'em if you can avoid it" he said "but just keep" he said "have" he said "if you feel really bad" he said "just take one." Patient (41)

Regulatory Issues.

There was a perceived lack of support from regulatory agencies by clinicians, particularly due to delays and concerns about potential censure if adverse effects were caused by opioids. One study (MMAT total 5) found that clinicians were hesitant to use opioids due to fear of criticism from colleagues or regulatory agencies:

"I must admit, I would be leery even at this point, on this date in February 2010, to introduce a narcotic. It would be a hard sell. There has to be some leading edge in this. There will be a delay in using it and there will be people who will go to their deaths that perhaps could have received better comfort. So the long and short of it is, I think, that I would love to start using it. If I start using it, it will come under criticism. That's how blind we are nowadays. And it will be under review. So, it's a sad situation" Clinician (32)

Another study found that clinicians wanted more support from regulatory agencies, particularly in the form of information and guidelines.(40)

Discussion

Main findings

Returning to the issue we identified in the introduction to this paper (acceptance of morphine for use in chronic breathlessness by clinicians, patients, and family members), there is strong evidence from multiple studies highlighting the role of education of clinicians in supporting implementation of clinical guidelines. These studies also showed how improvements in clinicians' knowledge underpinned their confidence in prescribing opioids and how prior experience of effective opioid prescribing increased clinician confidence and likelihood of continuing to prescribe opioids. There is an expressed need for increased information sharing between clinicians and patients, further clinician education and training on the benefits of opioids for chronic breathlessness, dosing, application types, prescribing and upper limits of opioids when seeking to reduce the intensity of chronic breathlessness. Evidence from one high quality study showed how clinicians struggled to

achieve an ethical balance in their opioid prescribing decisions between the risk of causing harm and relieving suffering, feeling unprepared and unsupported to make this judgement.

In regard to formulation and treatment regimens, supportive relationships between clinical teams was helpful. Palliative care specialists, or clinicians supported by palliative care specialists, were more likely to prescribe opioids for chronic breathlessness, although the evidence for this is weaker and comes from a small number of studies. Strong therapeutic relationships between clinicians and patients/families enhanced communication and information sharing, trust in clinician advice and understanding of cultural or personal differences between the clinician and patients/families. This also impacted preparation of opioid prescription, allowing patients to prepare for treatment appropriately, sharing in the decision making process.(44)

Clinician fears regarding prescription of opioids for pain are well documented. In addition, other cancer pain work identify lack of good pain assessment, and, in some countries with restrictive opioid regulations, lack of access to adequate supply of opioids as reasons for inadequate pain management with opioids.(45, 46) In this review, patient and clinician fears around the use of opioids had a big impact on clinicians' willingness to prescribe and patients' adherence to treatment. Fears were similar to the cancer pain literature with the addition of particular fears of respiratory depression and of censure by regulatory bodies and colleagues due to the unlicensed indication (until recently). Interestingly, the more recent pain literature identifies fear of regulatory scrutiny as a significant clinician fear, particularly for opioids for non-cancer chronic pain.(47) Although pain is a licensed indication, current widespread attention to the "opioid crisis" regarding abuse in chronic non-cancer pain, may heighten both clinician and patient fears, and adversely affect appropriate use of opioids for cancer-related pain.(48)

Clinicians' fears were often based on historical teaching about respiratory risks, particularly in lung and heart disease, and hearsay. However, published contemporary evidence regarding the safety of opioids for chronic breathlessness suggests these fears are

unfounded; with appropriate dosing and management adverse events are mild and self-limiting only, with no evidence of excess hospital admission or mortality in low doses.(6, 49) Cultural and social connotations of opioids appear to have a significant impact on the attitudes and perceptions of clinicians and patients.

Despite overall evidence supporting the use of opioids for chronic breathlessness, close assessment and early management of predictable opioid-related harms such as constipation and nausea is crucial. A secondary analysis of one placebo controlled clinical trial found that a fine balance existed for patients' blinded preference for treatment arm when morphine-related adverse events were not optimally addressed.(50-52) This highlights the need for clinicians to actively monitor and manage harms, so patients get maximum benefit. Early work in chronic non-cancer pain opioid management supports the use of a theory driven opioid self-assessment education package to improve knowledge, opioid safety practices and physician perceptions in primary care prescribers.(53) The barriers and enablers outlined in this review provide insights into factors affecting clinician willingness to prescribe opioids, treatment formulation and patient and family adherence to prescribed treatment.

Review strengths and weaknesses

We combined an established systematic review method (framework synthesis) with an emerging tool for synthesizing quantitative and qualitative research (the Pillar Process).(22, 54) The inclusion of both quantitative and qualitative study designs allowed a deeper understanding and exploration of the topic than either approach alone. Direct quotes from study participants were presented in the findings, as well as statistics from included studies and quotes of author reflections and discussions within their studies, through the pillar process presentation method. This remained close to primary data whilst including valuable insights from authors themselves.

Limitations of the review include language, as only publications in the English language were included. However, the paper includes studies from different countries and cultural

contexts. Evidence in the reviewed studies focused more on barriers than positive experiences and enablers, suggesting participants may focus more on negative experiences than positive. Despite this, we aimed to gain insights into the attitudes of clinicians, patients and families and thus finding more negative attitudes provides useful information about the perspectives of the aforementioned groups. None of the studies were published since the recent media interest in the "opioid crisis", which may exacerbate both patient and clinician fears as it had done in the field of cancer-pain.(48) A further limitation is that the majority of participants in included studies were healthcare providers (mainly physicians), although we have taken care to incorporate data about patients' and families' experiences and views wherever this was available in the included studies.

What this study adds

We present an understanding of patient and healthcare professionals' knowledge and views on the use of opioids for chronic breathlessness, important to inform clinical practice. Evidence based education, clinical guidelines and regulatory support are important facilitators for use in clinical practice along with multi-disciplinary collaboration between palliative care and other clinical specialties. A standard protocol for morphine initiation, titration, monitoring and management of harms that clinicians could use in conjunction with clinical guidelines would be useful to improve clinician knowledge and confidence around use for chronic breathlessness. Furthermore, additional research on patient and carer experiences could enhance the findings of this review, offering potential insights into the implementation of opioids in clinical practice with regards to patient acceptance and adherence to opioid treatment.

Conclusion

The knowledge, views and attitudes of clinicians, patients and families regarding opioid medication in the symptomatic management of chronic breathlessness have major impacts on implementation in clinical practice. Clinicians' fears of respiratory depression and of regulatory scrutiny are particular concerns, with the former being based on historical teaching rather than current evidence. Better education is necessary, but both the

complexity of clinician communication and decision-making with patients and families and clinicians' anxieties about prescription and regulation will also need to be addressed.

Authorship

All authors made significant contributions to the paper. FR and MP wrote the first and subsequent drafts of this manuscript, with comments from MJ and DC, and then the remaining authors. FR, MP and MJ conceptualised and designed the study. SG, FR and MP designed the search strategy, with screening conducted by FR, JC and MP. Data extraction and analysis was conducted by FR with input from MP, JC, and MJ. DC, SB, and MF contributed to data interpretation. All authors read and approved the final manuscript.

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The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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