OHSU Health System
Office of Clinical Integration and Evidence-Based Practice
Adult Cystic Fibrosis Pain and Anxiety Management
Evidence Summary

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Content Expert Team Members:

Gopal Allada, MD, Pulmonology
Rebecca Britton, PharmD, DI/DP Clinical Coordinator
Deanna Eichler, MSN, Nurse Manager
Jeff Gold, MD, Pulmonology
Peter Graven, PhD, Value Analytics
Angie Lee, MSW, Social Work
Susannah Lujan-Bear, MSN, Registered Nurse
Corinne Muirhead, PharmD, CF Ambulatory Care Pharmacist
Sarah Power, MSW, Care Management
Gayle Murphy, BSN, Registered Nurse Wendy Palmrose, MSW, LCSW, Social Work
David Quitmeyer, BHA, Respiratory Therapy
Patricio Riquelme, MD, PhD, Hospital Medicine
Scott Sallay, MD, Hospital Medicine/Clinical Informatics
Virginia Satcher, MSN, Pulmonology
Troy Schmit, MHA, Quality Management
David Sibell, MD, Anesthesiology/Clinical Informatics
Peter Sullivan, MD, Hospital Medicine
Melissa Weimer, DO, General Medicine
Kathy Wunderle, MD, Internal Medicine Resident

Office of Clinical Integration and Evidence-Based Practice Team:

Elizabeth Crabtree, MPH, PhD (c) Director of Clinical Integration and EBP
Andrew Hamilton, MS/MLS, Liaison Librarian
Stephanie Halvorson, MD, Clinical Integration Medical Director/Hospital Medicine

Objective for the Review:

To critically review the evidence on strategies for managing pain and anxiety in adult cystic fibrosis patients in the inpatient and ambulatory settings

Inclusion Criteria:

Adult patients (>/= 18 years of age) with cystic fibrosis in the inpatient or ambulatory setting with acute or chronic pain

Exclusion Criteria:

Pediatric patients (i.e., patients < 18 years of age or patients managed by pediatric pulmonary clinic or admitted to Doernbecher Children's Hospital), end-of-life patients, palliative care patients, cancer patients

Definitions:

Long-term opioid use: use of opioids on most days for > 3 months
Chronic pain: pain conditions that typically last > 3 months or past the time of normal tissue healing

Target Guideline Users:

All clinicians caring for adults with cystic fibrosis in the inpatient or ambulatory setting

Review Preparation:

In adult patients with cystic fibrosis,

1. Is the use of *long-term opioid therapy* compared to placebo, no opioids or non-opioid therapy associated with improved clinical outcomes (i.e., reduction in pain, and improvements in function and QOL) or risks (i.e., abuse, addiction, overdose, other harms)?
2. What opioid dosing strategies for *chronic pain* (methods for initiating and titrating opioids; immediate-release versus ER/LA opioids; different ER/LA opioids; immediate- release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous versus as-needed dosing; dose escalation versus dose maintenance; opioid rotation versus maintenance; different strategies for treating acute exacerbations of chronic pain; decreasing opioid doses or tapering off versus continuation; and different tapering protocols) are associated with improved clinical outcomes (reduction in pain, and improvements in function and QOL)?
3. When is it appropriate to refer paints to the adult pain management service or the IMPACT addiction team?
4. What opioid dosing strategies for *acute pain* (methods for initiating and titrating opioids; immediate-release versus ER/LA opioids; different ER/LA opioids; immediate- release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous versus as-needed dosing; dose escalation versus dose maintenance; opioid rotation versus maintenance; different strategies for treating acute exacerbations; decreasing opioid doses or tapering off versus continuation; and different tapering protocols, also IV vs oral pain medication) are associated with improved clinical outcomes (reduction in pain, and improvements in function and QOL)?
5. What non-opioid pain management strategies (therapy type, dose, frequency) are associated with improved clinical outcomes (reduction in pain, and improvements in function, and QOL) or risks (abuse, overdose, other harms)?
6. Is PEP or vest therapy associated with improved clinical outcomes (i.e., greater lung clearance, fewer painful episodes)?
7. What standardized pain assessment tool is most valid for hospitalized patients with CF vs ambulatory CF patients?
8. What strategies are most effective to help manage anxiety related to painful respiratory treatments?

Quality Measures:

Outcome

- IP LOS
- Admission Rate

Process

- Utilization of CF IP Order Set
- Utilization of Prescription Drug Monitoring Program reviews on patients admitted with CF
- Prevalence of CF patients treated with opioids and/or schedule II drugs
- Prevalence of IV hydromorphone, benzodiazepine and IV diphenhydramine orders for hospitalized CF patients
- Referrals to IMPACT or Acute Pain Service
- Adherence to airway clearance therapy

Cystic Fibrosis Pain and Anxiety Management
Existing External Guidelines/Pathways/Order Sets

Existing External Guidelines

External Guideline	Organization and Author	Last Update
Guideline for Prescribing Opioids for Chronic Pain	Centers for Disease Control and Prevention	2016
Cystic Fibrosis Pulmonary Guidelines: Airway Clearance Therapies	Cystic Fibrosis Foundation	2009
Non-pharmacologic Airway Clearance Therapies Guideline	American College of Chest Physicians	2006

The three published clinical guidelines were evaluated for this review using the **University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale.** The scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

Guideline Issuer	CDC 2016	CFF 2009	ACCP 2006
1. Transparency	A	A	A
2. Conflict of interest	A	NR	NR
3. Development group	A	A	A
4. Systematic Review	A	A	B
5. Supporting evidence	A	A	A
6. Recommendations	A	A	A
7. External Review	A	NR	NR
8. Currency and updates	A	C	C

See appendix B for full description of the Trustworthy Guideline grading system.

Guideline Evidence Evaluation Systems

	Centers for Disease Control and Prevention 2016	Cystic Fibrosis Foundation 2009 and American College of Chest Physicians 2006
Evidence Evaluation	Recommendation Categories: **Category A recommendation:** Applies to all persons; most patients should receive the recommended course of action. **Category B recommendation:** Individual decision making needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations. Evidence Type: **Type 1 evidence:** Randomized clinical trials or overwhelming evidence from observational studies. **Type 2 evidence:** Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies. **Type 3 evidence:** Observational studies or randomized clinical trials with notable limitations. **Type 4 evidence:** Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.	Followed US Preventative Services Task Force methodology **Table 7. Recommendation grid** Quality of evidence / Net benefit: Substantial; Moderate; Small; Zero/negative Good: A; B; C; D Fair: B; B; C; D Poor = I **Table 6. Standard recommendation language** A — The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.) B — The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.) C — The USPSTF makes no recommendation for or against routine provision of [the service]. (The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of the benefits and harms is too close to justify a general recommendation.) D — The USPSTF recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.) I — The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)

		Table 2. Hierarchy of research design I Evidence obtained from at least one properly randomized controlled trial. II–1 Evidence obtained from well-designed controlled trials without randomization. II–2 Evidence obtained from well-designed cohort or case control analytic studies, preferably from more than one center or research group. II–3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence. III Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Review of Relevant Evidence: Search Strategies and Databases Reviewed

Search Strategies	Document Strategies Used
Search Terms/Strategies Used:	**Questions 3 and 8:** *Ovid Search Strategy* 1 Cystic Fibrosis/ (17326) 2 (cystic adj fibro*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (25727) 3 1 or 2 (25727) 4 exp Pain/ (211360) 5 Pain Management/ (14912) 6 exp Pain Measurement/ (61535) 7 exp Pain Perception/ (2515) 8 exp Pain Clinics/ (1174) 9 (pain adj3 (clinic or clinics or servic* or specialist* or specialt* or refer* or consult* or second opinion*)).mp. (5842) 10 4 or 5 or 6 or 7 or 8 or 9 (237979) 11 3 and 10 (146) 12 exp analgesia/ (20325) 13 exp analgesics/tu, ad (115797) 14 12 or 13 (130177) 15 3 and 14 (150) 16 11 or 15 (282) 17 ((cystic fibro* or cf) adj5 (pain* or hurt* or analges* or narcotic* or opioid* or nocicep*)).mp. (96) 18 16 or 17 (333)

	19 limit 18 to humans (310) 20 limit 19 to english language (287) 21 limit 19 to abstracts (259) 22 20 or 21 (303) 24 22 not 23 (243) **Questions 5 and 6:** *Ovid Search Strategy* 1 Cystic Fibrosis/ (17326) 2 (cystic adj fibro*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (25727) 3 1 or 2 (25727) 4 exp Anemia, Sickle Cell/ (9547) 5 Hemoglobin, Sickle/ (1055) 6 4 or 5 (9911) 7 (sickle cell* or hemoglobin s or hgb s).mp. (11664) 8 6 or 7 (11922) 9 3 or 8 (37412) 10 exp Pain/ (211360) 11 Pain Management/ (14912) 12 exp Pain Measurement/ (61535) 13 exp Pain Perception/ (2515) 14 exp Pain Clinics/ (1174) 15 (pain* adj5 (manag* or control* or treat* or therap* or interven* or regimen* or protocol*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (77203) 16 10 or 11 or 12 or 13 or 14 or 15 (256221) 17 exp analgesia/ (20325) 18 exp analgesics/tu, ad (115797) 19 16 or 17 or 18 (342736) 20 9 and 19 (1518) 21 exp Decision Making/ (117097) 22 exp Professional Competence/ (78574) 23 exp "Patient Acceptance of Health Care"/ (156262) 24 ((dose* or dosing or dosag* or administ* or deliver* or prescri* or give or giving or gives or given or gave) adj5 (pharm* or drug* or opioid* or narcotic* or analges* or painkill* or pain kill*) adj7 (effect* or strateg* or decision* or decid* or choic* or choos* or option* or opt or opts or opting or guid* or recommend* or prefer*)).mp. (24505) 25 21 or 22 or 23 (336383)

	26 20 and 25 (68) 27 exp "Quality of Life"/ (122548) 28 quality-adjusted life years/ (8139) 29 (qualit* adj3 (life or living)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (192712) 30 27 or 28 or 29 (192712) 31 20 and 30 (138) 32 exp prognosis/ (1054174) 33 exp "Outcome and Process Assessment (Health Care)"/ (785742) 34 32 or 33 (1115950) 35 20 and 34 (210) 36 exp Risk/ (779679) 37 exp vital statistics/ (598435) 38 exp "Drug-Related Side Effects and Adverse Reactions"/ (49196) 39 ae.fs. (937815) 40 exp Medical Errors/ (71924) 41 (iatrogen* or nosocom*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (35182) 42 36 or 37 or 38 or 39 or 40 or 41 (2018075) 43 20 and 42 (366) 44 26 or 31 or 35 or 43 (632) 45 limit 44 to english language (610) 46 limit 44 to abstracts (561) 47 44 or 45 (632) 48 limit 47 to humans (628) **Question 7:** *Ovid Search Strategy* 1 Cystic Fibrosis/ (17326) 2 (cystic adj fibro*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (25727) 3 1 or 2 (25727) 4 exp Positive-Pressure Respiration/ (13619) 5 3 and 4 (96) 6 (pep adj5 (cf or cystic fibro*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (16)

	7 (positiv* adj3 (expir* or exhal*) adj3 pressur*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3271) 8 3 and 7 (56) 9 (vest* adj5 (treat* or therap* or physiother* or interven* or rehab* or compress* or press*)).mp. (1828) 10 3 and 9 (8) 11 5 or 6 or 8 or 10 (132) 12 limit 11 to english language (121) 13 limit 11 to abstracts (115) 14 12 or 13 (129) 15 limit 14 to humans (128) **Question 9:** *Ovid Search Strategy* 1 exp Respiratory Therapy/ (56025) 2 exp Anxiety/ (41407) 3 exp Anxiety Disorders/ (35594) 4 exp Stress, Psychological/ (71072) 5 exp fear/ (19055) 6 exp anger/ (4550) 7 2 or 3 or 4 or 5 or 6 (152496) 8 1 and 7 (301) 9 exp Lung Diseases/dh, dt, nu, pc, rt, rh, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Radiotherapy, Rehabilitation, Surgery, Therapy] (179496) 10 ((breath* or respir* or exhal* or inspir* or dyspne*) adj3 (treat* or therap* or exercis* or rehab* or interven* or regimen*)).mp. (14807) 11 9 and 10 (4364) 12 7 and 11 (51) 13 8 or 12 (342) 14 limit 13 to english language (293) 15 limit 13 to abstracts (302)
Years Searched - All Questions	1996-May 2016
Language	English
Age of Subjects	Adult and Pediatric Patients (ages >/= 1)

Evidence Found with Searches

Check type of evidence found	Summary of Evidence – All Questions	Number of articles obtained
☒	Systematic reviews/Meta-analysis	14
☒	Randomized controlled trials	21
☒	Non-randomized studies	14
☒	Government/State agency regulations	1
☒	Professional organization guidelines/white papers, etc.	2

Evaluating the Quality of the Evidence

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. For more detailed information, see Appendix A.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Question #1. In adult patients with cystic fibrosis, is the use of long-term opioid therapy compared to placebo, no opioids or non-opioid therapy associated with improved clinical outcomes (i.e., reduction in pain, and improvements in function and QOL) or risks (i.e., abuse, addiction, overdose, other harms)?

OHSU Clinical Practice Recommendation(s): OHSU will defer to and adopt the clinical practice recommendations from the *2016 CDC Guideline for Prescribing Opioids for Chronic Pain.*

Guideline Recommendations:

Determining When to Initiate or Continue Opioids for Chronic Pain

The Centers for Disease Control and Prevention 2016 guideline states that nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate **(recommendation category: A, evidence type: 3).** Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety **(recommendation category: A,**

evidence type: 4). Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy **(recommendation category: A, evidence type: 3).**

References:
Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65:1–49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1

Question #2. What opioid dosing strategies for chronic pain (methods for initiating and titrating opioids; immediate-release versus ER/LA opioids; different ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous versus as-needed dosing; dose escalation versus dose maintenance; opioid rotation versus maintenance; different strategies for treating acute exacerbations of chronic pain; decreasing opioid doses or tapering off versus continuation; and different tapering protocols) are associated with improved clinical outcomes (reduction in pain, and improvements in function and QOL)?

OHSU Clinical Practice Recommendation(s): OHSU will defer to and adopt the clinical practice recommendations from the *2016 CDC Guideline for Prescribing Opioids for Chronic Pain.*

Guideline Recommendations:

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

The Centers for Disease Control and Prevention 2016 guideline states when starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids **(recommendation category: A, evidence type: 4).** When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day **(recommendation category: A, evidence type: 3).** Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids **(recommendation category: A, evidence type: 4).**

Assessing Risk and Addressing Harms of Opioid Use

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present **(recommendation category: A, evidence type: 4).** Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months **(recommendation category: A, evidence type: 4).** When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs **(recommendation category: B, evidence type: 4).** Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible **(recommendation category: A, evidence type: 3).** Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder **(recommendation category: A, evidence type: 2).**

References:
Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65:1–49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1

Question #3. In adult patients with cystic fibrosis, when is it appropriate to refer patients to the adult pain management service or the IMPACT addiction team?

OHSU Clinical Practice Recommendation(s): Consider Acute Pain Service consultation if patient's pain is difficult to manage or if opioid dose greatly exceeds 90 mg of morphine equivalents per 24 hours. Consider consulting Improving Addition Care Team (IMPACT) if there is concern for an active substance use disorder that is complicating care.
-Consensus Statement

Guideline Recommendations:

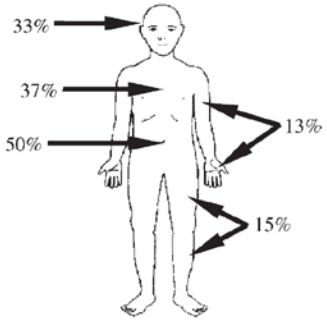
The Centers for Disease Control and Prevention 2016 guideline states that clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder **(recommendation category: A, evidence type: 2).**

Primary Literature:

PICO Question #3: In adult patients with cystic fibrosis, when is it appropriate to refer patients to the adult pain management service or the IMPACT addiction team?						Lower Quality Rating if: ☒ Studies inconsistent (*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)* ☒ Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)* Increase Quality Rating if: ☐ Large Effect Level of evidence for studies as a whole:
Author/Date	*Purpose of Study*	*Study Design*	*Sample*	*Outcomes*	*Design Limitations*	
Festini et al., 2004, *Journal of Cystic Fibrosis*	To evaluate the prevalence of pain symptoms in adult CF patients, if they are noticed and treated, and the influence of pain symptoms on patients' life	Cross-sectional survey	239 Italian adults with CF	In a 2 months period **32.6% of patients experienced episodes of pain described as intense to severe, and 29.7% had more than 10 occurrences of pain in the same location**. Headache, gastric pain and backache were the most frequently reported kind of pain. **59.8% of subjects perceived pain episodes as the cause of unfavorable effects on their life. Only 42.6% of those with pain asked a CF center physician for help and another 3.5% a general practitioner**	Study Limitations = ☒ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☐ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Hayes et al., 2011, *Chest*	To examine the prevalence of pain in CF patients and whether it is associated with psychologic distress, and	Cross-sectional survey Outcomes were assessed for 12 months	83 adults with CF from Johns Hopkins Hospital were surveyed about their pain	**Eighty-two percent of patients reported pain within the past month**, the most common sites being the head, sinuses, back, and chest. Pain frequently interfered with general activities (41.9%), mood (56.8%), and	Study Limitations = ☒ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive,***	

	adversely affects clinical outcomes	following survey completion		work (47.3%). Symptom sof depression and anxiety, as well as lower quality-of-life (QOL) scores, were associated with the presence of pain (P < .05 for each). **The risk of pulmonary exacerbations was increased in patients with higher levels of pain, even after adjusting for FEV 1 and age (OR = 1.65; P = .038; 95% CI, 1.03-2.64). Additionally, the risk of death was higher in patients with higher average pain scores (HR =2.28; P = .008; 95% CI = 1.2-4.2)**	***epidemiologic, case study/series, QI, survey)*** ☐ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	☐ High ☐ Moderate ☐ Low ☒ Very Low
Hubbard et al., 2005, *Pediatric Nursing*	To develop a web-based education program tailored to patients with CF who may be experiencing pain, and to investigate, via the website, the pain experiences of those patients by studying their pain reports, disability, and coping strategies	Cross-sectional survey	18 pediatric CF patients	**Approximately half of the sample reported experiencing daily pain episodes lasting two hours or less. The average intensity of a pain episode was reported to be in the moderate range**. Participants reported pain disability highest in areas of recreation, occupation, and social activities. The most commonly used coping strategies included active and accommodative coping techniques such as problem solving, acceptance, and self-encouragement.	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☒ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition	

					☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Keelman et al., 2012, *Physiother Res Int*	To describe the intensity and location of pain and its relationship with health-related quality of life (HRQOL) and pain catastrophizing in adults with CF	Prospective observational study	73 adult CF patients	**Mild pain was reported by 89% of stable participants and 79% of those with exacerbations.** Severity of lung disease did not affect prevalence or intensity of pain. **Pain interfered with airway clearance therapy during exacerbations (p<0.012) and exercise regimens when participants were clinically stable (p<0.002) and was related to a poorer physical function, regardless of clinical status (p<0.05).** Although pain intensity was associated with reduced HRQOL (p<0.001), only FEV1 and the degree of pain catastrophizing were independent predictors of poorer HRQOL	Study Limitations = ☒ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☐ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Koh et al., 2005, *Pediatric Pulmonology*	Assess acute and chronic pain symptoms as reported by children with CF, and examine the	Cross sectional survey	46 pediatric CF patients	The primary locations of pain reported were the abdominal/pelvic region, chest, and head/neck.	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross***	

	relationship between pain symptoms and disease severity as measured by percentage of forced expired volume in 1 sec (FEV1%)			 **Forty-six percent of the sample described pain occurring at least once per week. Most children reported their pain intensity as mild and of short duration.** However, a small subgroup of children reported longer-lasting and moderately intense pain. **Children with chest pain were found to be particularly at risk for experiencing more functional limitations and a significantly lower FEV1% compared to children without chest pain.** The majority of children reported that rest (63%), medication (41%), relaxation (41%), heat or cold (39%), family/friends (39%), and distracting activities (36%) provided some pain relief. **Twenty-four percent of patients reported taking no medication for pain. Of those taking medication to treat pain, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or a combination of the two were used. None of the patients reported taking opioids for pain management.**	***sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☒ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Palmermo et al., 2006, *Clin J Pain*	To describe the effect of recurrent pain symptoms on the health-related quality of life (HRQOL) of children and adolescents with CF	Cross-sectional survey, retrospective pain interview	46 CF children and adolescents	**Forty-six percent of children (n=21) reported experiencing pain at least once per week. Children with frequent pain had more decrements in their HRQOL compared with children with no pain or less frequent pain (Wilks lambda=0.62, P=0.02)**. Specifically, children with frequent pain (n=21) had	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☒ Insufficient sample size	

				significantly reduced physical functioning (mean difference 14.7; 95% CI 4.3–25.2), more role limitations (mean difference 19.1; 95% CI 6.5–31.6), reduced vitality (mean difference 20.3; 95% CI 9.0–31.6), increased eating disturbances (mean difference 13.3; 95% CI 1.3–25.3), greater perceived treatment burden (mean difference 14.1; 95% CI 1.8–26.4), more respiratory symptoms (mean difference 18.4; 95% CI 6.9–29.9), more digestive symptoms (mean difference 18.0; 95% CI 4.6–31.4), and reduced overall perceptions of their health (mean difference 27.3; 95% CI 5.4–49.2) compared with children with no pain or less frequent pain (n=25).	☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Ravilly et. al., 1996, *Pediatrics*	Examine the incidence and therapy of chronic pain in a group of older patients with CF	Retrospective chart review	55 adult and pediatric CF patients	**46 patients (84%) reported serious pain of some sort**. The most common locations were chest pain (64%) and headache (53%), followed by limb pain (11 %), abdominal pain (11%), and back pain (16%). **A variety of nonpharmacological and pharmacological therapies were reported. 53% had pain severe enough to require opioid treatment, and 10 patients (13%) received opioids for more than 3 months. In eight patients with more severe pain, regional analgesia was found to be particularly effective.**	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☒ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison	

					between index test and gold standard	
Sermet-Gaudelus et al., 2009, *Journal of Pain and Symptom Management*	Assess the prevalence of pain symptoms, their characteristics and treatment, their impact on daily quality of life, and the occurrence of procedural pain.	Cross-sectional survey	73 children (1-18 years) and 110 adults (18-52 years) with CF in France	**59% of the children and 89% of the adults reported at least one episode of pain during the previous month**. Pain was significantly more intense and lasted significantly longer among adults, but its rate and recurrence did not differ significantly between the two populations and were not related to the severity of CF. The most prevalent locations were the abdomen for children, and the back, head, and chest for adults. Although pain significantly limited physical activity, only 15% of patients reported that it caused absenteeism, and 27% reported that it negatively affected their family life. The mean pain intensity rates on a visual analog scale for the episode that had caused the greatest pain during the past month were 4.9 (2) (mean [SD]) for children and 6 (2) for adults; however, **only 40% and 50%, respectively, of those with pain reported the use of analgesic treatment, mainly paracetamol (acetaminophen). At least one episode of procedural pain during the previous month was reported by 85% of children and 78% of adults**	Study Limitations = ☒ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☒ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Stenekes et al., 2009, *Journal of Pain and Symptom Management*	To assess the frequency, severity, and self-management of pain, breathlessness, and cough	Cross-sectional survey	123 adult and pediatric CF patients in Canada	**Eighty-four percent (103 of 123) of participants reported having pain.** They reported an average of 2.1 locations of pain, with headache and abdominal pain most frequently described. Sixty-four percent (76 of 123) of participants reported having breathlessness, and 83% (99 of 123) of participants reported experiencing cough	Study Limitations = ☒ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☐ Insufficient sample size ☐ Sample not representative of patients in the population as a whole	

					☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	

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Question #4. In adult patients with cystic fibrosis, what opioid dosing strategies for acute pain (methods for initiating and titrating opioids; immediate-release versus ER/LA opioids; different ER/LA opioids; immediate- release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous versus as-needed dosing; dose escalation versus dose maintenance; opioid rotation versus maintenance; different strategies for treating acute exacerbations; decreasing opioid doses or tapering off versus continuation; and different tapering protocols, also IV vs oral pain medication) are associated with improved clinical outcomes (reduction in pain, and improvements in function and QOL)?

OHSU Clinical Practice Recommendation(s): Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
-Strong Recommendation; Very Low Quality Evidence

Guideline Recommendations:

The Centers for Disease Control and Prevention 2016 guideline states that long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed (recommendation category: A, evidence type: 4).

References:
Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65:1–49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1

Primary Literature:

PICO Question #4: In adult patients with cystic fibrosis, what opioid dosing strategies for acute pain (methods for initiating and titrating opioids; immediate-release versus ER/LA opioids; different ER/LA opioids; immediate- release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous versus as-needed dosing; dose escalation versus dose maintenance; opioid rotation versus maintenance; different strategies for treating acute exacerbations; decreasing opioid doses or tapering off versus continuation; and different tapering protocols, also IV vs oral pain medication) are associated with improved clinical outcomes (reduction in pain, and improvements in function and QOL)?

Author/Date	*Purpose of Study*	*Study Design*	*Sample*	*Outcomes*	*Design Limitations*
Dampier et al., 2011, *American Journal of Hematology*	To compare two alternative opioid PCA dosing strategies (HDLI—higher demand dose with low constant infusion or LDHI—lower demand dose and higher constant infusion) in SCD patients	Multi-site RCT	38 adult and pediatric patients with SCD who completed randomization prior to trial closure	Total opioid utilization (morphine equivalents, mg/kg) in 22 adults was 11.6 ± 2.6 and 4.7 ± 0.9 in the HDLI and in the LDHI arms, respectively, and in 12 children it was 3.7 ± 1.0 and 5.8 ± 2.2, respectively. Opioid-related symptoms were mild and similar in both PCA arms (mean daily opioid symptom intensity score: HDLI 0.9 ± 0.1, LDHI 0.9 ± 0.2).	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☐ Lack of randomization ☐ Lack of blinding ☒ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U
Krishnamurti et al., 2014, *Pediatric Blood Cancer*	To test hypothesis that pain management plans individualized for each patient can improve pain management and lead to high levels of patient satisfaction of those patients by studying their pain reports, disability, and coping strategies	Pre- post- QI study treated all patients with SCD reporting to Children's Hospital of Pittsburgh ED with VOC using a structured algorithm. Recorded regimens used successfully for each patient as an "individualized pain plan" and implemented it during subsequent VOC visits. Compared rates of hospitalization following an ED visit with VOC and readmission within 1 week after discharge for CHP with that of	All pediatric SCD patients presenting to Children's Hospital of Pittsburgh ED	Between 2002 and 2008 there was a **greater decline in the rate of admission of patients presenting to the ED at CHP (78% to 52%) as compared to PHIS (71% to 68%)**, (P<0.05) **and readmission rates at CHP (7.3% to 3.2%) as compared to PHIS (6.5% to 5.1%)** (P<0.05). **Improvement in pain score during ED management was 2.0 or more on a Wong Baker scale of 0–5 (P<0.01). Participants on average, rated quality of pain management as very good or higher.**	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☐ Insufficient sample size ☒ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U

Lower Quality Rating if:
☒ Studies inconsistent (*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)*

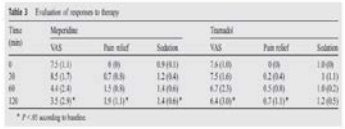
☒ Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)*

Increase Quality Rating if:
☐ Large Effect
Level of evidence for studies as a whole:
☐ High

		four comparable hospitals from Pediatric Health Information database				☐ Moderate ☐ Low ☒ Very Low
Melzer-Lange et al., 2004, *Pediatric Emergency Care*	To determine whether a protocol to start patient controlled analgesia (PCA) in the emergency department (ED-PCA) would shorten the length of time between narcotic bolus doses and PCA initiation as compared with standard inpatient initiation of PCA (IP-PCA). Also, to compare patient satisfaction and inpatient length of stay for the 2 groups.	Quasi-experimental pilot study; comparing patients on protocol to institute ED-PCA after an initial bolus dose of narcotics to those off protocol	69 pediatric SCD patients	**Patients treated using the protocol had initiation of PCA therapy within 35 ± 7 minutes from the last bolus narcotic dose in the emergency department versus 211 ± 17 minutes for nonprotocol patients**. Forty-eight of 50 patient surveys indicated preference for starting ED-PCA; 2 did not have a preference. No complications were identified in either group	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☒ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	
New et al., 2014, *J Pediatr Hematol Oncol*	Present clinical experience in 7 sickle cell patients who received epidural analgesia for persistent refractory pain	Case series	7 pediatric SCD patients	The median duration of epidural catheter placement was 4 days (interquartile range, 3 to 6 d). Mean pain scores changed from 6.8±2.7 to 4.8±2.2, whereas mean daily parenteral opioid requirements changed from 79.7±100.4 to 13.0±13.1mg of morphine equivalents Authors suggest using epidural analgesic techniques may provide an alternative to further escalating IV opioids in the patient with severe pain and problematic opioid-related symptomatology	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☒ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison	

					between index test and gold standard	
Uzan et al., 2009, *American Journal of Emergency Medicine*	To compare meperidine and tramadol with respect to their effects on the hemodynamics and pain relief in patients with sickle cell disease who were admitted to the emergency department with painful crisis	RCT randomly assigned to receive either tramadol 1.5 mg/kg (n = 34) or meperidine 1 mg/kg (n = 34)	68 patients with SCD	Both meperidine and tramadol administration resulted in a significant reduction in systolic and diastolic blood pressure after 2 hours (P < .05). **Additional analgesics were indicated in 38% of the patients within the meperidine group, whereas 73% of the patients within the tramadol group required medication within 2 hours. This difference was statistically significant (P < .05).** **Sedation was more commonly seen in the meperidine arm. None of the patients had experienced neurotoxicity** 	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☐ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	
van Beers et. al., 2007, *American Journal of Hematology*	To compare the efficacy of intravenous morphine administration with PCA to continuous infusion (CI) of morphine in patients with SCD during vaso-occlusive crisis	RCT 12 patients allocated to PCA, 13 patients allocated to continuous infusion	Twenty five consecutive episodes of vaso-occlusive crisis in 19 patients with SCD were included in the study	**Patients in the PCA group had a markedly and significant lower mean and cumulative morphine consumption when compared with the patients in the CI-group (0.5 mg/hr versus 2.4 mg/hr (P < 0.001) and 33 mg versus 260 mg (P = 0.018, respectively).** The mean daily pain scores were comparable (4.9 versus 5.3). **The lower mean and cumulative morphine consumption in the PCA-group led to significant less nausea and constipation during treatment when compared with the CI-group (area under the curve, respectively, 11**	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☐ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	

				versus 18 (P = 0.045) and 30 versus 45 (P = 0.021). Furthermore, a nonsignificant reduction in the duration of hospital admission of 3 days was observed in the PCA-group		

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Question #5. In adult patients with cystic fibrosis, what non-opioid pain management strategies (therapy type, dosing, and frequency) are associated with improved clinical outcomes (reduction in pain, and improvements in function and QOL) or risks (abuse, overdose, other harms)?

5a. what *non-pharmacological* pain management strategies (therapy type, dosing, and frequency) are associated with improved clinical outcomes (reduction in pain, and improvements in function and QOL) or risks (abuse, overdose, other harms)?

OHSU Clinical Practice Recommendation(s): Alternatives to opioid prescribing should be considered in the management of pain in patients with cystic fibrosis, including: massage therapy, acupuncture, chiropractic, physical therapy, and cognitive behavioral therapy.
-Strong Recommendation; Low Quality Evidence

Guideline Recommendations:

There were no guidelines found that addressed this clinical question.

Primary Literature:

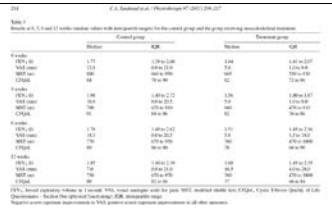
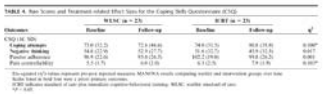
PICO Question #5a: In adult patients with cystic fibrosis, what non-pharmacological pain management strategies (therapy type, dosing, frequency) are associated with improved clinical outcomes (reduction in pain, and improvements in function and QOL) or risks (abuse, overdose, other harms)?						Lower Quality Rating if: ☒ Studies inconsistent (*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)*
Author/Date	*Purpose of Study*	*Study Design*	*Sample*	*Outcomes*	*Design Limitations*	
Anie & Green, 2015, *Cochrane Database of*	To examine the evidence that psychological interventions improve the ability of people with	Systematic Review	5 randomised or quasi-randomised controlled trials (260 participants) comparing psychological interventions with no (psychological)	One study showed that cognitive behaviour therapy significantly reduced the affective component of pain (feelings about pain), mean difference -0.99 (95% confidence	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question	

Systematic Reviews	sickle cell disease to cope with their condition		intervention in people with sickle cell disease	interval -1.62 to -0.36), but not the sensory component (pain intensity), mean difference 0.00 (95% confidence interval -9.39 to 9.39).	☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☒ Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)* <u>Increase Quality Rating if:</u> ☐ Large Effect Level of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low
Eccleston et al., 2014, Cochrane Database of Systematic Reviews	To determine the effectiveness on clinical outcomes of pain severity, disability, depression, and anxiety of psychological therapy delivered face-to-face for chronic and recurrent pain in children and adolescents compared with active treatment, waiting-list, or standard medical care	Systematic Review	37 RCTs (2111 participants) with at least 10 participants in each arm post-treatment comparing psychological therapies with active treatment, standard medical care, or waiting-list control for children or adolescents with episodic, recurrent or persistent pain	**For headache pain, psychological therapies reduced pain post-treatment and at follow-up** respectively (risk ratio (RR) 2.47, 95% confidence interval (CI) 1.97 to 3.09, z = 7.87, p < 0.01, number needed to treat to benefit (NNTB) = 2.94; RR 2.89, 95% CI 1.03 to 8.07, z = 2.02, p < 0.05,NNTB = 3.67). **Analyses revealed beneficial effects of psychological treatment for children with non-headache pain. Pain was found to improve post-treatment** (SMD -0.57, 95% CI -0.86 to -0.27, z = 3.74, p < 0.01), **but not at follow-up** (SMD -0.11, 95% CI -0.41 to 0.19, z =0.73, p > 0.05).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	
Goldbeck et al., 2014, *Cochrane Database of Systematic Reviews*	To determine whether psychological interventions for people with cystic fibrosis provide significant psychosocial and physical benefits in addition to standard medical care	Systematic Review	16 RCTs (556 participants) of a broad range of psychological interventions evaluating subjective and objective health outcomes, such as quality of life or pulmonary function, in individuals of all ages with cystic fibrosis and their immediate family	There is some evidence that behavioural interventions targeting nutrition and growth in children (4 to 12 years) with cystic fibrosis are effective in the short term. Evidence was found that providing a structured decision-making tool for patients considering lung transplantation improves patients' knowledge of and expectations about the transplant, and reduces decisional conflict in the short term. One study about training in biofeedback-assisted breathing demonstrated some evidence that it improved some lung function measurements. **Currently there is insufficient evidence for interventions**	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

				aimed at other aspects of the disease process. No studies evaluated impact on pain.		
Hubert et al., 2014, *PLOS ONE*	To evaluate the impact of osteopathic manipulative treatment (OMT) on pain in adults with CF	multicenter RCT three parallel arms: OMT (group A, 16 patients), sham OMT (sham treatment, group B, 8 patients) and no treatment (group C, 8 patients)	32 adult CF patients seen at CF centers in France	**There was no statistically significant difference between the treatment and control groups in the decrease of chest/back pain** (difference =22.20 IC95% [24.81; 0.42], p = 0.098); also, **group A did not differ from group B**. However, chest/back pain decreased more in groups A (p = 0.002) and B (p = 0.006) than in group C. **Cervical pain, headache and QOL scores did not differ between the treatment and control groups**	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☐ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☐ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	
Kato-Lin et al., 2014, *International Journal of Medical Informatics*	To evaluate the impact of digitization of paper-based individualized pain plans on process efficiency and care quality by examining both objective patient data and subjective clinician insights	Retrospective, before and after, mixed methods evaluation of digitization of paper documents in Children's Hospital of Pittsburgh of UPMC.	1089 ED visits made by 150 SCD patients in VOC	Surveys indicate that **all clinicians perceived the digitization to improve the efficiency and quality of pain management. Physicians overwhelmingly preferred using the digitized plans, but only 44% of the nurses had the same response**. **Analysis of patient records indicated that adjusted time from analgesic order to administration was signifi-cantly reduced from 35.50 to 26.77 min** (p < .05). **However, time to first dose and some of the objective quality measures (time from administration to relief, relief rate, admission rate,and ED re-visit rate) were not significantly affected.**	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☐ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☒ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	

Lee et al., 2009, Journal of Cystic Fibrosis	To examine the effect of a combination of musculoskeletal physiotherapy techniques and massage therapy on musculoskeletal pain and ease of breathing	Quasi-experimental study A single individualized treatment session of up to one hour duration was completed for each patient. A combination of spinal joint and intercostal mobilization was used, together with soft tissue therapy and remedial massage for each patient (66%) participated whilst admitted with an acute exacerbation while 35 (33%) were clinically stable	105 adults with CF, with a mean (SD) age of 30.5 (9.4) years and an FEV1 of 48.1 (18.6) % predicted who accessed musculoskeletal and massage physiotherapy services during the study period	**Overall, there was a significant reduction in pain following treatment (mean difference of 1.8 cm, 95% CI 1.5–2.1 cm, p<0.001), with both subgroups reporting less pain after treatment.** Overall, **the rating of EOB improved significantly following treatment (mean difference 0.5 cm, 95% CI 0.4–0.7 cm, p<0.001), with significant improvements in the acute group, but not the clinically stable group**	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☐ Insufficient sample size ☒ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	
Lin et al., 2005, *American Journal of Chinese Medicine*	To evaluate the effects of acupuncture for pain management in patients with cystic fibrosis	Quasi-experimental study The treatments were based on Traditional Chinese Medical diagnosis. Each patient received weekly acupuncture treatments. The patients 0–10 visual analog pain scales (VAS) were recorded immediately before and after each treatment by a member of the staff, other than the acupuncturist. The patients were asked about the duration of the effectiveness of	30 adult and pediatric patients with cystic fibrosis who were experiencing both acute and chronic pain that underwent acupuncture treatments	**The average VAS pain score were 5.95 ± 1.4 and 2.8 ± 1.0 immediately before and after the treatments, respectively**. **The acupuncture treatments significantly reduced the pain scores by 3.2 ± 1.1 (p < 0.05). The average duration of the acupuncture effect was 3.0 ± 1.1 days.** There was no difference noted in the VAS pain score response between male and female. No side effects or complications were reported.	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☒ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	

		acupuncture therapy at each follow-up visit				
Obideen et al., 2006, *Dig Dis Sci*	To determine whether nocturnal hydration (NH) prevents recurrent abdominal pain and recurrent acute pancreatitis in patients with adult-onset CF	Quasi-experimental study Each patient was encouraged to drink plenty of water during the night and established a 6-month diary (3 months before and 3 months after NH was initiated), recording the frequency and severity of their abdominal pain, the amount of pain medication taken, and the volume of their water intake	9 adult CF patients who were referred to Pancreatic Diseases Clinic for recurrent abdominal pain and pancreatitis	**The frequency and the severity of abdominal pain in this group of patients were significantly reduced. The amount of pain medication and the number of emergency room visits and hospitalizations for abdominal pain and acute pancreatitis were reduced**. Table 2 Patients' symptoms and medical facility utilization before and after NH[a] NH | Episodes of AP[b] | Severity of AP | ER visits[b] | Hospitalizations[b] Before | 6.0 ± 1.75 | 5.0 ± 1.2 | 2.5 ± 1.0 | 2.0 ± 1.1 After | 1.8 ± 1.0 | 1.9 ± 0.8 | 0.7 ± 0.7 | 0.4 ± 0.5 P[c] | 0.0040 | 0.0001 | 0.0050 | 0.0040 P[d] | 0.0001 | 0.0001 | 0.0003 | 0.0002	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☒ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	
Sandsund et. al., 2011, *Physiotherapy*	To assess the sensitivity of selected outcome measures to any change resulting from treatment of adults with cystic fibrosis with physiotherapy musculoskeletal techniques, use the data for sample size calculations for future studies and assess the acceptability of the methods to potential participants	Preliminary, prospective, single-blind, RCT The control group (n=10) received normal optimal physiotherapy care and the intervention group (n=10) received weekly musculoskeletal treatment for 6 weeks in addition to normal optimal physiotherapy care	20 adults recruited from a cystic fibrosis outpatient clinic	Baseline differences between groups in thoracic index and modified shuttle test made any differences difficult to interpret, but the results for thoracic index and chest wall excursion at the third rib in the treatment group showed a trend towards improvement. **At baseline, the VAS pain score in the control group was 12.8 mm; this increased to 18.3mm and reduced again to 7mm at 12 weeks. In the treatment group, the pain levels were 5mm at baseline and 16.5mm at 12 weeks. The VAS pain scores showed greater variability than the error of the measurement (2 mm), but the minimally important clinical difference in VAS pain scores for this group is not known**	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☒ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	

						
Schatz et al., 2015, Clin J Pain	To examine the outcomes of a cognitive-behavioral therapy intervention for pain in pediatric SCD using smartphones as a novel delivery method	Quasi-experimental Children with SCD received CBT coping skills training using a randomized, waitlist control design. The intervention involved a single session of CBT training and home-based practice using smartphones for 8 weeks. Pre-post questionnaires between the randomized groups were used to evaluate changes in active psychological coping and negative thinking	Forty-six children with SCD	**The pre-post group comparison suggested that the youth increased active psychological coping attempts with the intervention. Daily diary data indicated that when children used CBT skills on days with higher pain, there were reductions in next-day pain intensity.** 	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☒ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	

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5b. what *pharmacological* pain management strategies (therapy type, dosing, and frequency) are associated with improved clinical outcomes (reduction in pain, and improvements in function and QOL) or risks (abuse, overdose, other harms)?

Guideline Recommendations:

There were no guidelines found that addressed this clinical question.

Primary Literature:

PICO Question #6b: In adult patients with cystic fibrosis, what pharmacological pain management strategies (therapy type, dosing, frequency) are associated with improved clinical outcomes (reduction in pain, and improvements in function and QOL) or risks (abuse, overdose, other harms)?

Author/Date	*Purpose of Study*	*Study Design*	*Sample*	*Outcomes*	*Design Limitations*
Bartolucci et al., 2009, *Blood*	To evaluate the effectiveness of ketoprofen in treating adults with VOC	Phase III RCT	66 VOC episodes in adults with SCD Patients randomized to either ketoprofen (300 mg/day for 5 days) or placebo	Seven VOCs in each group were excluded from the analysis because of treatment failures, suggesting that the prevention of acute chest syndrome or need for blood transfusions as the result of ketoprofen administration is not supported by evidence **The administration of ketoprofen did not achieve any morphine sparing or pain-intensity relief. Median total morphine consumption during the study was similar for the 2 groups** (P= .64); **pain relief did not differ between the 2 groups, as assessed by the median total VAS** (P =.50) and the median total CPS (P= .46). Among the 52 of 66 VOCs discharged after VOC termination, 4 ketoprofen-group and 5 placebo-group patients were readmitted (P =1)	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☐ Lack of randomization ☐ Lack of blinding ☒ Stopped early for benefit ☐ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U
Brousseau et al., 2015, *Blood*	To test hypothesis that intravenous magnesium would shorten length of stay, decrease opioid use, and improve health-related quality of life (HRQL) for pediatric	RCT of intravenous magnesium vs normal saline placebo Children received 40 mg/kg of magnesium or placebo every 8 hours for up to 6	204 pediatric patients with SCD hospitalized for pain crisis conducted at 8 sites within the Pediatric Emergency Care Applied Research Network (PECARN)	**The median interquartile range (IQR) length of stay was 56.0** (27.0-109.0) **hours for magnesium vs 47.0** (24.0-99.0) **hours for placebo** (P = .24). **Magnesium patients received 1.46 mg/kg morphine equivalents vs 1.28 mg/kg for placebo** (P = .12). **Changes in HRQL before discharge and 1 week**	Study Limitations = ☒ None ***RCT & Quasi-Experimental Studies*** ☐ Insufficient sample size ☐ Lack of randomization ☐ Lack of blinding ☐ Stopped early for benefit ☐ Lack of allocation concealment ☐ Selective reporting of measures

Lower Quality Rating if:

☒ Studies inconsistent (*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)*

☒ Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)*

	patients hospitalized with sickle cell pain crises	doses plus standard therapy		**after discharge were similar** (P > .05 for all comparisons).	☐ Large losses to F/U	Increase Quality Rating if: ☐ Large Effect Level of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low
Gladwin et al., 2011, *JAMA*	To determine whether inhaled nitric oxide gas reduces the duration of painful crisis in patients with SCD who present to the emergency department or hospital for care	RCT Randomized to 72 hours of inhaled nitric oxide gas vs inhaled nitrogen placebo	150 participants presenting with VOC of SCD at 11 centers	**There was no significant change in the primary end point between the nitric oxide and placebo groups, with a median time to resolution of crisis of 73.0 hours** (95% confidence interval [CI], 46.0-91.0) **and 65.5 hours** (95% CI, 48.1-84.0), **respectively** (P=.87). **There were no significant differences in secondary outcome measures, including length of hospitalization, visual analog pain scale scores, cumulative opioid usage, and rate of acute chest syndrome**	Study Limitations = ☒ None ***RCT & Quasi-Experimental Studies*** ☐ Insufficient sample size ☐ Lack of randomization ☐ Lack of blinding ☐ Stopped early for benefit ☐ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	
Goldman et al., 2013, *Pediatrics*	To determine if intravenous (IV) magnesium sulfate (MgSO4) reduces length of stay (LOS) in hospital, pain scores, and cumulative analgesia when compared with placebo in SCD patients	RCT Randomized to IV MgSO4 (100 mg/kg) every 8 hours or placebo in addition to standard therapy	104 children aged 4 to 18 years requiring admission to hospital with a sickle cell disease VOE requiring IV analgesia	**There was no significant difference in the primary outcome measure, LOS in hospital, with a mean of 132.6 and 117.7 hours in the MgSO4 and placebo groups, respectively** (P = .41). **There was no significant difference between groups for the secondary outcomes of mean pain scores** (4.9 6 2.6 vs 4.8 6 2.6, respectively; P = .92) **or analgesic requirements** (continuous morphine infusion [P = .928], boluses of IV morphine [P = .82], acetaminophen [P = .34], ibuprofen [P = .15], naproxen [P = .10])	Study Limitations = ☒ None ***RCT & Quasi-Experimental Studies*** ☐ Insufficient sample size ☐ Lack of randomization ☐ Lack of blinding ☐ Stopped early for benefit ☐ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	
Morris et al., 2013, *Haematologica*	To test hypothesis that arginine may be a beneficial treatment for pain related to sickle cell disease	RCT Patients received L-arginine (100 mg/kg tid) or placebo for 5 days or until discharge	38 children with sickle cell disease hospitalized for 56 episodes of pain	**Significant reduction in total parenteral opioid use by 54%** (1.9±2.0 mg/kg versus 4.1±4.1 mg/kg, P=0.02) **and lower pain scores at discharge** (1.9±2.4 versus 3.9±2.9, P=0.01) **were observed in the treatment arm compared to the placebo one. There was no significant difference in hospital length of stay** (4.1±01.8 versus 4.8±2.5 days, P=0.34), **although a trend favored the arginine arm**, and total opioid use was strongly correlated with the duration of the	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☐ Lack of randomization ☐ Lack of blinding ☐ Stopped early for benefit ☐ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	

				admission (r=0.86, P<0.0001). No drug-related adverse events were observed.		
Okomo & Meremikwu, 2015, *Cochrane Database of Systematic Reviews*	To determine the optimal route, quantity and type of fluid replacement for people with sickle cell disease with acute painful crises	Systematic Review	Randomised and quasi-randomised controlled trials that compared the administration of supplemental fluids adjunctive to analgesics by any route in people with any type of sickle cell disease during an acute painful episode, under medical supervision	No relevant trials identified.	N/A	
Ng & Franchini, 2014, *Cochrane Database of Systematic Reviews*	To assess the effect of drug therapies for reducing gastric acidity in CF patients for: nutritional status; symptoms associated with increased gastric acidity; fat absorption; lung function; quality of life and survival; and to determine if any adverse effects are associated with their use	Systematic Review	17 randomised and quasi-randomised trials (273 participants) involving agents that reduce gastric acidity compared to placebo or a comparator treatment	One trial found that drug therapies that reduce gastric acidity improved gastro-intestinal symptoms such as abdominal pain 1988 study looked at relief from chronic abdominal pain in the treatment group (misoprostol) compared with the control group. There were six participants who reported relief in the treatment group and none in the control group. The symptoms returned in five of the six participants after misoprostol was stopped at the end of the trial period.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	
Thornton & Rangaraj, 2016, *Cochrane Database of Systematic Reviews*	To review the effectiveness and safety of pharmacological agents for the symptomatic management of cystic fibrosis-related arthritis in adults and children with cystic fibrosis	Systematic Review	RCTs which compared the efficacy and safety of anti-inflammatory and analgesic agents (e.g. non-steroidal anti-inflammatory agents, systemic corticosteroids, intra-articular corticosteroids) with each other, with no treatment or with placebo for CFA and HPO	No relevant studies were identified.	N/A	

van Zurren et al., 2013, *Cochrane Database of Systematic Reviews*	To assess the effects of low-molecular-weight heparins for managing vaso-occlusive crises in people with sickle cell disease	Cochrane Systematic Review	1 RCT (included 253 participants) that assessed the effects of low-molecular-weight heparins in the management of VOC in people with sickle cell disease	This study, with limited data, reported that **pain severity at day two and day three was lower in the tinzaparin group than in the placebo group** (P < 0.01, analysis of variance (ANOVA)) **and additionally at day 4** (P < 0.05 (ANOVA)). Thus tinzaparin resulted in more rapid resolution of pain, as measured with a numerical pain scale. The mean difference in duration of painful crises was statistically significant at -1.78 days in favor of the tinzaparin group (95% confidence interval -1.94 to -1.62). Participants treated with tinzaparin had statistically significantly fewer hospitalization days than participants in the group treated with placebo, with a mean difference of -4.98 days (95% confidence interval -5.48 to -4.48). Two minor bleeding events were reported as adverse events in the tinzaparin group, and none were reported in the placebo group	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	
Weiner et al., 2003, *JAMA*	To explore the efficacy and safety of inhaled nitric oxide for treatment of VOC in pediatric SCD patients	RCT Randomized to receive INO (80 ppm with 21% final concentration of inspired oxygen) or placebo (21% inspired oxygen) for four hours	20 SCD pediatric patients in severe VOC	**The decrease in VAS pain scores at 4 hr was 2.0 cm in the INO group and 1.2 cm in the placebo group** (p=0.37). Repeated measures analysis of variance for hourly pain scores showed a 1-cm/hr greater reduction in the INO group (p=0.02). **Morphine use over 6 hr was significantly less in the INO group (mean cumulative use, 0.29 vs. 0.44 mg/kg; p=0.03), but was not different over 4 hours or 24 hours.**	Study Limitations = ☒ None ***RCT & Quasi-Experimental Studies*** ☐ Insufficient sample size ☐ Lack of randomization ☐ Lack of blinding ☐ Stopped early for benefit ☐ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	

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Question # 6. In adult patients with cystic fibrosis, is PEP or vest therapy associated with improved clinical outcomes (i.e., greater lung clearance, fewer painful episodes)?

OHSU Clinical Practice Recommendation(s): ACT is recommended for all patients with CF for clearance of sputum, maintenance of lung function, and improved quality of life.
-Strong Recommendation; Low Quality Evidence

For the individual, one form of ACT may be superior to the others. The prescription of ACT should be individualized based on factors such as age, patient preference, and adverse events, among others. PEP may be superior to vest therapy due to patient preference, and decreased exacerbations and antibiotic use while on PEP.
-Strong Recommendation; Low Quality Evidence

Consider avoiding the use of vest therapy in patients requiring extra pain medication prior to treatment as it likely exacerbates chest/back pain.
-Consensus Statement

Guideline Recommendations:

The 2009 Cystic Fibrosis Pulmonary Guidelines for Airway Clearance Therapies state: ACT is recommended for all patients with cystic fibrosis for clearance of sputum, maintenance of lung function, and improved quality of life. **Level of evidence, fair; net benefit, moderate; grade of recommendation, B** In general, there is no ACT that has been demonstrated to be superior to others. **Level of evidence, fair; grade of recommendation, B** For the individual, one form of ACT may be superior to the others. The prescription of ACT should be individualized based on factors such as age, patient preference, and adverse events, among others. **Level of evidence, fair; grade of recommendation, consensus recommendation, B**

The American College of Chest Physicians 2006 Nonpharmacologic Airway Clearance Therapies Guideline states: In patients with CF, chest physiotherapy is recommended as an effective technique to increase mucus clearance, but the effects of each treatment are relatively modest and the long-term benefits unproven. **Level of evidence, fair; benefit, small; grade of recommendation, C** In patients with expiratory muscle weakness, manually assisted cough should be considered to reduce the incidence of respiratory complications. **Level of evidence, low; benefit, small; grade of recommendation, C** In patients with COPD and CF, huffing should be taught as an adjunct to other methods of sputum clearance**. Level of evidence, low; benefit, small; grade of recommendation, C** In patients with CF, autogenic drainage should be taught as an adjunct to postural drainage as a method to clear sputum because it has the advantage of being performed without assistance and in one position. **Level of evidence, low; benefit, small; grade of recommendation, C** In patients with CF, PEP is recommended over conventional chest physiotherapy because it is approximately as effective as chest physiotherapy, and is inexpensive, safe, and can be self-administered. **Level of evidence, fair; benefit, intermediate; grade of recommendation, B** In patients with CF, devices designed to oscillate gas in the airway, either directly or by compressing the chest wall, can be considered as an alternative to chest physiotherapy. **Level of evidence, low; benefit, conflicting; grade of recommendation, I** The effect of nonpharmacologic airway clearance techniques on long-term outcomes such as health-related quality of life and rates of exacerbations, hospitalizations, and mortality is not known at this time. The committee recommends that future investigations measure these outcomes in patients with CF, and in other populations with bronchiectasis, COPD, and neuromuscular diseases. **Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A**

Primary Literature:

PICO Question #7: In adult patients with cystic fibrosis, is PEP or vest therapy associated with improved clinical outcomes (i.e., greater lung clearance, fewer painful episodes)?						Lower Quality Rating if: ☒ Studies inconsistent (*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)* ☐ Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)* Increase Quality Rating if: ☐ Large Effect
Author/Date	*Purpose of Study*	*Study Design*	*Sample*	*Outcomes*	*Design Limitations*	
Flores et al., 2013, *Respiratory Care*	To determine rates of self-reported adherence to ACT by patients treated in an adult CF program, to identify patient characteristics associated with poor adherence, to typify adherence according to ACT technique, and to indicate reasons for poor adherence	Cross-sectional study	63 CF subjects age 16 years and older	Of the 63 subjects studied, 38 (60%) qualified as high adherence, 12 (19%) as moderate adherence, and 13 (21%) as poor adherence. **Treatment recommendations and self-reported patient adherence were in best agreement when PEP and flutter devices were used. Positive expiratory pressure k= 0.87) and flutter device (k= 0.63) usage both corresponded with a high level of agreement, while active cycle of breathing technique (k=0.40) and autogenic drainage (k=0.39) each showed moderate agreement. Agreement was low for percussion and postural drainage (k=0.23).**	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☒ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	
Lee et al., 2015, *Cochrane Database of Systematic Reviews*	To determine effects of airway clearance techniques on rates of acute exacerbation, incidence of hospitalisation and health-related quality of life (HRQoL) in individuals with acute and stable bronchiectasis	Systematic Review	7 randomised controlled parallel and cross-over trials (105 participants) that compared an ACT versus no treatment, sham ACT or directed coughing in participants with bronchiectasis	One study including 20 adults that compared an airway oscillatory device versus no treatment found no significant difference in the number of exacerbations at 12 weeks (low-quality evidence). The same study reported clinically significant improvements in HRQoL on both disease-specific and cough-related measures. The median difference in the change in total St George's Respiratory Questionnaire (SGRQ) score over three months in this	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

				study was 7.5 units (P value = 0.005 (Wilcoxon)). Treatment consisting of high-frequency chest wall oscillation (HFCWO) or a mix of ACTs prescribed for 15 days significantly improved HRQoL when compared with no treatment (low-quality evidence). Two studies reported mean increases in sputum expectoration with airway oscillatory devices in the short term of 8.4 mL (95% confidence interval (CI) 3.4 to 13.4 mL) and in the long term of 3 mL (P value = 0.02). HFCWO improved forced expiratory volume in one second (FEV1) by 156 mL and forced vital capacity (FVC) by 229.1 mL when applied for 15 days, but other types of ACTs showed no effect on dynamic lung volumes. Two studies reported a reduction in pulmonary hyperinflation among adults with non-positive expiratory pressure (PEP) ACTs (difference in functional residual capacity (FRC) of 19%, P value < 0.05; difference in total lung capacity (TLC) of 703 mL, P value = 0.02) and with airway oscillatory devices (difference in FRC of 30%, P value < 0.05) compared with no ACTs. Low-quality evidence suggests that ACTs (HFCWO, airway oscillatory devices or a mix of ACTs) reduce symptoms of breathlessness and cough and improve ease of sputum expectoration compared with no treatment (P value < 0.05). ACTs had no effect on gas exchange, and no studies reported effects of antibiotic usage. Among studies exploring airway oscillating devices, investigators reported no adverse events **AUTHORS' CONCLUSION: ACTs appear to be safe for individuals (adults and**		Level of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

				children) with stable bronchiectasis and may account for improvements in sputum expectoration, selected measures of lung function, symptoms and HRQoL		
Main et al., 2013, Cochrane Database of Systematic Reviews	To compare conventional chest physiotherapy with other airway clearance techniques in terms of their effects on respiratory function, individual preference, adherence, quality of life and other outcomes	RCT	29 randomised or quasi-randomised clinical trials (475 participants) including those with a cross-over design where CCPT was compared with other airway clearance techniques. Studies of less than seven days duration were excluded	**There was insufficient evidence to confirm or exclude any differences, between CCPT and other airway clearance techniques in terms of respiratory function measured by standard lung function tests. Studies undertaken during acute exacerbations demonstrated relatively large gains in respiratory function irrespective of airway clearance technique. Longer-term studies demonstrated smaller improvements or deterioration over time. Ten studies reported individual preferences for technique, with participants tending to favour self-administered techniques**	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	
McKoy et al., 2012, *Cochrane Database of Systematic Reviews*	To compare the clinical effectiveness of active cycle of breathing technique (ACBT) with other airway clearance therapies in cystic fibrosis	Systematic Review	18 randomised or quasi-randomised controlled clinical studies (375 participants), including cross-over studies, comparing ACBT with other airway clearance therapies in cystic fibrosis Five randomised controlled studies (127 participants) were included in the meta-analysis	**Patient preference varied: more patients preferred autogenic drainage over ACBT; more preferred ACBT over airway oscillating devices; and more were comfortable with ACBT versus high frequency chest compression. No significant difference was seen in sputum weight, lung function, or oxygen saturation between ACBT and autogenic drainage or between ACBT and airway oscillating devices. There was no significant difference in lung function and the number of pulmonary exacerbations between ACBT and ACBT plus conventional chest physiotherapy.** **AUTHORS' CONCLUSION: There is insufficient evidence to support or reject the use of ACBT over any other airway clearance therapy. Five studies, with five different comparators, found that ACBT was**	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

				comparable to other therapies in outcomes such as patient preference, lung function, sputum weight, oxygen saturation, and number of pulmonary exacerbations		
McLlwaine et al., 2015, *Cochrane Database of Systematic Reviews*	To determine the effectiveness and acceptability of PEP devices compared to other forms of physiotherapy as a means of improving mucus clearance and other outcomes in people with cystic fibrosis	Systematic Review	26 randomised controlled studies(733 participants) in which PEP was compared with any other form of physiotherapy in people with cystic fibrosis	Forced expiratory volume in one second was the review's primary outcome and the most frequently reported outcome in the studies. Single interventions or series of treatments that continued for up to three months demonstrated no significant difference in effect between PEP and other methods of airway clearance on this outcome. However, long-term studies had equivocal or conflicting results regarding the effect on this outcome. A second primary outcome was the number of respiratory exacerbations. There was a lower exacerbation rate in participants using PEP compared to other techniques when used with a mask for at least one year. Participant preference was reported in 10 studies; and in all studies with an intervention period of at least one month, this was in favour of PEP **PEP vs. Vest results: In the only one-year study comparing PEP to HFCWO, FEV1 increased by a mean of 0.22L with PEP and 0.23 L with HFCWO (McIlwaine 2013). Data were provided at each study visit and the change in FEV1 % predicted over one year was not significantly different between the two groups, MD -3.59 (95% CI -9.29 to 2.11) One parallel study with 107 participants which ran for one year, reported the number of respiratory exacerbations requiring either oral or IV antibiotics as the primary outcome**	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

				(McIlwaine 2013). In 43 participants performing PEP, 26 had 49 respiratory exacerbations compared with 96 respiratory exacerbations in 40 of the 48 participants performing HFCWO, which showed a statistically significant difference in favour of PEP, RR 0.73 (95% CI 0.55to 0.95) This study by McIlwaine also reported that respiratory exacerbations, which were severe enough to require either IV antibiotics or hospitalisation, occurred six times in the PEP group (six participants) and 19 times in the HFCWO group (13 participants). This represented a mean of 0.12 respiratory exacerbations requiring IV antibiotics per participant in the PEP group and a mean of 0.4 respiratory exacerbations requiring IV antibiotics per participant in the HFCWO group		
Morrison & Agnew, 2014, *Cochrane Database of Systematic Reviews*	To identify whether oscillatory devices, oral or chest wall, are effective for mucociliary clearance and whether they are equivalent or superior to other forms of airway clearance in the successful management of secretions in people with cystic fibrosis	Systematic Review	35 randomised controlled studies and controlled clinical studies (1050 participants) of oscillating devices compared with any other form of physiotherapy in people with cystic fibrosis	**One long-term study (seven months) compared oscillatory devices with either conventional physiotherapy or breathing techniques and found statistically significant differences in some lung function parameters in favour of oscillating devices. One study identified an increase in frequency of exacerbations requiring antibiotics whilst using high frequency chest wall oscillation when compared to positive expiratory pressure.** There **were some small but significant changes in secondary outcome variables such as sputum volume or weight, but not wholly in favour of oscillating devices. Participant satisfaction was reported in 15 studies but this was not specifically in favour of an oscillating device, as some participants preferred breathing techniques or techniques used prior to the study interventions**	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

				AUTHORS' CONCLUSION: There was no clear evidence that oscillation was a more or less effective intervention overall than other forms of physiotherapy; furthermore there was no evidence that one device is superior to another		
Warnock & Gates 2015, *Cochrane Database of Systematic Reviews*	To determine the effectiveness and acceptability of chest physiotherapy compared to no treatment or spontaneous cough alone to improve mucus clearance in cystic fibrosis	Systematic Review	8 randomized or quasi-randomised clinical studies (96 participants) in which a form of chest physiotherapy (airway clearance technique) were taken for consideration in people with cystic fibrosis compared with either no physiotherapy treatment or spontaneous cough alone	Four studies, involving 28 participants, reported a higher amount of expectorated secretions during chest physiotherapy as compared to a control. One study, involving 18 participants, reported no significant differences in sputum weight. In five studies radioactive tracer clearance was used as an outcome variable. In three of these (28 participants) it was reported that chest physiotherapy, including coughing, increased radioactive tracer clearance as compared to the control period. One study (12 participants) reported increased radioactive tracer clearance associated with all interventions compared to control, although this was only reported to have reached significance for postural drainage with percussion and vibrations; and the remaining study (eight participants) reported no significant difference in radioactive tracer clearance between chest physiotherapy, without coughing, compared to the control period. Three studies, involving 42 participants reported no significant effect on pulmonary function variables following intervention; but one further study did report significant improvement in pulmonary function following the intervention in some of the treatment groups **AUTHORS' CONCLUSION: Airway clearance techniques have short-term effects in the terms of increasing mucus transport. No evidence was**	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

				found on which to draw conclusions concerning the long-term effects		

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Morrison, L., & Agnew, J. (2014). Oscillating devices for airway clearance in people with cystic fibrosis. *Cochrane Database of Systematic Reviews, 7*, CD006842.
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Question # 7. In adult patients with cystic fibrosis, what standardized pain assessment tool is most valid for hospitalized patients with cystic fibrosis versus ambulatory cystic fibrosis patients?

OHSU Clinical Practice Recommendation(s): There is insufficient evidence to make a recommendation. Clinicians should use standardized pain assessment scales currently in use at OHSU, and defer to existing OHSU policies.

Guideline Recommendations:

No guidelines were found addressing this clinical question.

Primary Literature:

No primary research studies were found addressing this clinical question.

Question # 8. In adult patients with cystic fibrosis, what strategies are most effective to help manage anxiety related to painful respiratory treatments?

OHSU Clinical Practice Recommendation(s): CF patients should be screened annually for depression and anxiety.
-Consensus Statement

IV diphenhydramine (Benadryl), IV benzodiazepines and opioids are NOT preferred agents for managing anxiety.
-Consensus Statement

Consider using oral hydroxycine for anxiety management.
-Consensus Statement

Guideline Recommendations:

No guidelines were found addressing this clinical question.

Primary Literature:

PICO Question #8. In adult patients with cystic fibrosis, what strategies are most effective to help manage anxiety related to painful respiratory treatments?

Author/Date	*Purpose of Study*	*Study Design*	*Sample*	*Outcomes*	*Design Limitations*
Casier et al., 2013, *Pain Res Manag*	To investigate the occurrence of spirometry-related pain and distress in adolescents and young adults with cystic fibrosis (CF), and to investigate the role of acceptance of illness in spirometry-related pain and distress	Mixed methods study Spirometry-related distress was assessed using self-report (ie, anxiety/worry about the procedure) and physiological outcomes (ie, heart rate and heart rate variability) before spirometry. Spirometry-related pain was assessed using self-report (ie, expected pain and pain-related thoughts). Self-reported distress and pain during spirometry were also assessed	36 adolescents and young adults with CF (12 to 22 years of age)	89% of subjects reported distress before spirometry, 67% experienced distress during spirometry, 28% expected pain during spirometry and 22% actually experienced pain. **Partial correlations revealed that more acceptance was related to less expected pain and pain-related thoughts. Acceptance, however, was unrelated to distress, anxiety and pain during spirometry**	Study Limitations = ☐ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☒ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard
Bradt & Dileo, 2014, *Cochrane Database of Systematic Reviews*	To examine the effects of music therapy or music medicine interventions on anxiety and other outcomes in mechanically ventilated patients	Systematic Review	14 randomized and quasi-randomized controlled trials (805 participants) that compared music interventions and standard care with standard care alone for	Results indicated that music listening may be beneficial for anxiety reduction in mechanically ventilated patients. Specifically**, music listening resulted, on average, in an anxiety reduction that was 1.11 standard deviation units greater (95% CI -1.75 to -0.47, P = 0.0006) than in the standard care**	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not

Lower Quality Rating if:
☒ Studies inconsistent (*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)*

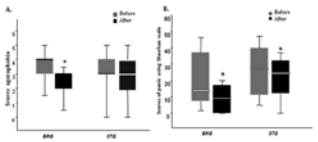
☒ Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

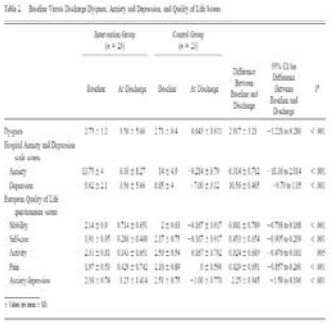
☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)*

Increase Quality Rating if:
☐ Large Effect
Level of evidence for studies as a whole:

			mechanically ventilated patients	**group.** Findings indicated that listening to music consistently reduced respiratory rate and systolic blood pressure, suggesting a relaxation response. **Furthermore, one large-scale study reported greater reductions in sedative and analgesic intake in the music listening group compared to the control group, and two other studies reported trends for reduction in sedative and analgesic intake for the music group.** One study found significantly higher sedation scores in the music listening group compared to the control group	appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☐ High ☐ Moderate ☐ Low ☒ Very Low
Delord et al., 2013, *CHEST*	To evaluate the efficacy of medical hypnosis to reduce anticipatory anxiety and acclimatization time in children who are candidates for long-term non-invasive positive pressure ventilation	Case series	nine children aged 2 to 15 years with high levels of anxiety about NPPV	The hypnosis techniques were based on distraction in the youngest patient and indirect or direct hypnotic suggestions in the older children to obtain a progressive psychocorporal relaxation. All patients accepted the interface and the NPPV after the first hypnosis session. A median of three sessions was needed for overnight (> 6 h) NPPV acceptance. The 6-month compliance with NPPV was excellent, with a median use of 7.5 h per night.	Study Limitations = ☒ None ***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)*** ☐ Insufficient sample size ☐ Sample not representative of patients in the population as a whole ☐ Variables (confounders, exposures, predictors) were not described ☐ Outcome criteria not objective or were not applied in blind fashion ☐ Insufficient follow-up, if applicable ☐ For prognostic study, sample not defined at common point in course of disease/condition ☐ For diagnostic study, gold standard not applied to all patients ☐ For diagnostic study, no independent, blind comparison between index test and gold standard	

Farquhar et al., 2010, *Palliative and Supportive Care*	To evaluate the effectiveness of the Breathlessness Intervention Service (BIS), a multidisciplinary service that uses both pharmacological and non-pharmacological evidence-based interventions to reduce the impact of the symptom of breathlessness in COPD patients **Table 1.** *The Breathlessness Intervention Service* A multidisciplinary service was established in the Department of Palliative Care in a tertiary referral center in 2004, with the aim of improving the palliation of breathlessness. The service model was developed on the basis of the findings of earlier studies (Booth et al., 1996; Booth & Adams, 2001; Booth et al., 2003; Booth et al., 2006) conducted within the MRC framework for the development and evaluation of complex interventions (Medical Research Council, 2000). A specialist respiratory physiotherapist was recruited to join the Macmillan consultant in palliative medicine to offer a number of evidence-based interventions over a period of weeks, working closely with other clinical services already caring for the patient. The service was given the title Breathlessness Intervention Service[1] (BIS) because it uses an active, focused rehabilitative approach in partnership with patient and carer. A detailed initial assessment of the impact of breathlessness on the patient and family is followed by implementation of an individualized treatment program with emphasis on problem-solving and the enhancement of self-management strategies. Evidence-based interventions are both non-pharmacological (modifying central perception by a range of psychological and physical interventions including a palliative care approach to life-threatening disease and psychosocial issues) and pharmacological, as required. Uniquely, care is flexibly located where the patient chooses. Referrals come from hospital and primary care specialists in medicine, nursing, and the allied health profession.	Pre- post- test analysis of non-randomized data	13 patients with severe advanced COPD	**Mean VAS-Distress scores (primary outcome measure) decreased (improved) for the group between baseline and follow up suggesting a clinically significant improvement: 6.88** (SD = 2.50) to 5.25 (SD = 2.99). At an individual level, 11 of the 13 patients showed a decrease in their distress due to breathlessness, and for eight of these this was clinically significant (range of all decreases 0.3–7.1 cm).	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☒ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	
Laurino et al., 2012, *Clinical Science*	To verify the degree of anxiety, respiratory distress, and health-related quality of life in a group of asthmatic patients who have experienced previous panic attacks, and evaluate if a respiratory physiotherapy program (breathing retraining) improved both asthma and panic disorder symptoms, resulting in an improvement in the health-related quality of life of asthmatics	RCT Asthmatic individuals were assigned to a chest physiotherapy group that included a breathing retraining program held once a week for three months or a paired control group that included a Subtle Touch program	Thirty-eight asthmatic patients with a history of panic symptoms in Brazil	Patients from both groups had high levels of agoraphobia and panic disorder at the start of the study. Statistically significant reductions in panic disorder symptoms (according to the DSM-IV-R) (p</=0.05) and agoraphobia (p</=0.05) were observed only in the BRG 	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☒ Insufficient sample size ☐ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☒ Lack of allocation concealment ☐ Selective reporting of measures ☒ Large losses to F/U	

		Breathing retraining consists of six repetitions of each the following physiotherapeutic exercises: 1. pursed-lip breathing associated with a lying relaxed posture; 2. manual expiratory passive therapy maneuvers; 3. diaphragmatic breathing; 4. hiccup inspiratory maneuvers; 5. postural orientation; and 6. twenty repetitions of Pompage (maneuvers performed for the muscle fascia).				
Mularski, 2009, *Journal of Alternative and Complementary Medicine*	To test the efficacy of a mindfulness-based breathing therapy (MBBT) on improving symptoms and health-related quality of life in those with COPD secretions in people with cystic fibrosis	RCT Randomized to 8-week mindfulness-based breathing therapy (MBBT) or support groups	86 patients with COPD at VA hospital	**Found no improvements in dyspnea** (post 6MWT Borg difference between the MBBT and support group was 0.3 (95% confidence interval [CI]:1.1, 1.7). **Found no differences between groups in almost all other outcome measures by either intention-to-treat analysis or within the subset that completed assigned group sessions**. For the physical summary scale of the generic Short Form-36 for Veterans, the difference between outcomes favored the support group (4.3, 95% CI: 0.4, 8.1).	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☐ Insufficient sample size ☐ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☐ Lack of allocation concealment ☐ Selective reporting of measures ☒ Large losses to F/U	
Valenza et al. 2014, *Respiratory Care*	To evaluate if breathing techniques can improve anxiety and depression in patients	RCT Randomized to control group or controlled	46 male subjects, 67–86 years old, hospitalized with acute COPD exacerbation in Spain	**Controlled breathing techniques significantly improved dyspnea, anxiety, and mobility. All the measured variables improved in the intervention group. The control group**	Study Limitations = ☐ None ***RCT & Quasi-Experimental Studies*** ☐ Insufficient sample size	

	hospitalized for COPD exacerbation	breathing intervention group controlled breathing program was delivered by a trained physiotherapist twice a day during hospitalization. The physiotherapy session duration was 30 min, and the subjects were instructed to take a break of 3 min when necessary. The controlled breathing program included relaxation exercises, pursed-lips breathing, and active expiration		**had poorer values in all the variables after the hospitalization period** 	☐ Lack of randomization ☒ Lack of blinding ☐ Stopped early for benefit ☐ Lack of allocation concealment ☐ Selective reporting of measures ☐ Large losses to F/U	

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Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high
Observational study–low
Any other evidence–very low

Criteria for increasing or decreasing level

Reductions
Study quality has serious (–1) or very serious (–2) problems
Important inconsistency in evidence (–1)
Directness is somewhat (–1) or seriously (–2) uncertain
Sparse or imprecise data (–1)
Reporting bias highly probable (–1)
Increases
Evidence of association† strong (+1) or very strong (+2)
Dose-response gradient evident (+1)
All plausible confounders would reduce the effect (+1)
†Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:
Who wrote the initial draft
How the committee voted on or otherwise approved recommendations
Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a

surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:
Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.
Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline

reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers’ stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst’s discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.