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 patients 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:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>- IP LOS</td>
<td>- Utilization of CF IP Order Set</td>
</tr>
<tr>
<td>- Admission Rate</td>
<td>- Utilization of Prescription Drug Monitoring Program reviews on patients admitted with CF</td>
</tr>
<tr>
<td></td>
<td>- Prevalence of CF patients treated with opioids and/or schedule II drugs</td>
</tr>
<tr>
<td></td>
<td>- Prevalence of IV hydromorphone, benzodiazepine and IV diphenhydramine orders for hospitalized CF patients</td>
</tr>
<tr>
<td></td>
<td>- Referrals to IMPACT or Acute Pain Service</td>
</tr>
<tr>
<td></td>
<td>- Adherence to airway clearance therapy</td>
</tr>
</tbody>
</table>
Cystic Fibrosis Pain and Anxiety Management
Existing External Guidelines/Pathways/Order Sets

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

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.

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

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation Categories:</strong></td>
<td>Followed US Preventative Services Task Force methodology</td>
<td></td>
</tr>
<tr>
<td><strong>Category A recommendation:</strong></td>
<td>Table 7. Recommendation grid</td>
<td></td>
</tr>
<tr>
<td>Applies to all persons; most patients should receive the recommended course of action.</td>
<td>Quality of evidence</td>
<td>Substantial</td>
</tr>
<tr>
<td><strong>Category B recommendation:</strong></td>
<td>Good</td>
<td>A</td>
</tr>
<tr>
<td>Individual decision making needed; different choices will be appropriate for different patients.</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td>Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.</td>
<td>Poor = I</td>
<td></td>
</tr>
<tr>
<td><strong>Evidence Type:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type 1 evidence:</strong></td>
<td>Randomized clinical trials or overwhelming evidence from observational studies.</td>
<td></td>
</tr>
<tr>
<td><strong>Type 2 evidence:</strong></td>
<td>Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies.</td>
<td></td>
</tr>
<tr>
<td><strong>Type 3 evidence:</strong></td>
<td>Observational studies or randomized clinical trials with notable limitations.</td>
<td></td>
</tr>
<tr>
<td><strong>Type 4 evidence:</strong></td>
<td>Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Standard recommendation language

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>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.)</td>
</tr>
<tr>
<td>B</td>
<td>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.)</td>
</tr>
<tr>
<td>C</td>
<td>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.)</td>
</tr>
<tr>
<td>D</td>
<td>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.)</td>
</tr>
<tr>
<td>I</td>
<td>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.)</td>
</tr>
</tbody>
</table>
## Review of Relevant Evidence: Search Strategies and Databases Reviewed

<table>
<thead>
<tr>
<th>Search Strategies</th>
<th>Document Strategies Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questions 3 and 8:</td>
<td><strong>Ovid Search Strategy</strong></td>
</tr>
<tr>
<td></td>
<td>1 Cystic Fibrosis/ (17326)</td>
</tr>
<tr>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>3 1 or 2 (25727)</td>
</tr>
<tr>
<td></td>
<td>4 exp Pain/ (211360)</td>
</tr>
<tr>
<td></td>
<td>5 Pain Management/ (14912)</td>
</tr>
<tr>
<td></td>
<td>6 exp Pain Measurement/ (61535)</td>
</tr>
<tr>
<td></td>
<td>7 exp Pain Perception/ (2515)</td>
</tr>
<tr>
<td></td>
<td>8 exp Pain Clinics/ (1174)</td>
</tr>
<tr>
<td></td>
<td>9 (pain adj3 (clinic or clinics or servic* or specialist* or specialt* or refer* or consult* or second opinion*)).mp. (5842)</td>
</tr>
<tr>
<td></td>
<td>10 4 or 5 or 6 or 7 or 8 or 9 (237979)</td>
</tr>
<tr>
<td></td>
<td>11 3 and 10 (146)</td>
</tr>
<tr>
<td></td>
<td>12 exp analgesia/ (20325)</td>
</tr>
<tr>
<td></td>
<td>13 exp analgesics/tu, ad (115797)</td>
</tr>
<tr>
<td></td>
<td>14 12 or 13 (130177)</td>
</tr>
<tr>
<td></td>
<td>15 3 and 14 (150)</td>
</tr>
<tr>
<td></td>
<td>16 11 or 15 (282)</td>
</tr>
<tr>
<td></td>
<td>17 ((cystic fibro* or cf) adj5 (pain* or hurt* or analges* or narcotic* or opioid* or nocicep*)).mp. (96)</td>
</tr>
<tr>
<td></td>
<td>18 16 or 17 (333)</td>
</tr>
</tbody>
</table>
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)
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)
Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

**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 exhali* 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**

<table>
<thead>
<tr>
<th>Check type of evidence found</th>
<th>Summary of Evidence – All Questions</th>
<th>Number of articles obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗</td>
<td>Systematic reviews/Meta-analysis</td>
<td>14</td>
</tr>
<tr>
<td>✗</td>
<td>Randomized controlled trials</td>
<td>21</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRONG</td>
</tr>
<tr>
<td>WEAK</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality</th>
<th>Type of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>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.</td>
</tr>
<tr>
<td>Very Low</td>
<td>Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

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:

September 2016
Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

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 maintenence; 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 (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:

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:

September 2016
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?**

| Author/Date | Purpose of Study | Study Design | Sample | Outcomes | Design Limitations | Study Limitations =
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Festini et al., 2004, <em>Journal of Cystic Fibrosis</em></td>
<td>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</td>
<td>Cross-sectional survey</td>
<td>239 Italian adults with CF</td>
<td>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</td>
<td>None</td>
<td>Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient sample size</td>
<td>Sample not representative of patients in the population as a whole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Variables (confounders, exposures, predictors) were not described</td>
<td>Outcome criteria not objective or were not applied in blind fashion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient follow-up, if applicable</td>
<td>For diagnostic study, gold standard not applied to all patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For diagnostic study, no independent, blind comparison between index test and gold standard</td>
<td></td>
</tr>
<tr>
<td>Hayes et al., 2011, <em>Chest</em></td>
<td>To examine the prevalence of pain in CF patients and whether it is associated with psychologic distress, and Outcomes were assessed for 12 months</td>
<td>Cross-sectional survey</td>
<td>83 adults with CF from Johns Hopkins Hospital were surveyed about their pain</td>
<td>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</td>
<td>None</td>
<td>Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug)</td>
<td></td>
</tr>
</tbody>
</table>

**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)
| 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 | Increase Quality Rating if:

- Large Effect
- Level of evidence for studies as a whole:
  - High
  - Moderate
  - Low
  - Very Low |
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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 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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relationship between pain symptoms and disease severity as measured by percentage of forced expired volume in 1 sec (FEV1%) section, 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

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.

Palermo 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,

Study Limitations =

- None
- Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)
- Insufficient sample size
### Evidence Summary

<table>
<thead>
<tr>
<th>Ravilly et al., 1996, Pediatrics</th>
<th>Examine the incidence and therapy of chronic pain in a group of older patients with CF</th>
<th>Retrospective chart review</th>
<th>55 adult and pediatric CF patients</th>
</tr>
</thead>
</table>

- **46 patients (84%) reported serious pain of some sort.** The most common locations were chest pain (64%) and headache (53%), followed by limb pain (13%), 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
### Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Methodology</th>
<th>Participants</th>
<th>Key Findings</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sermet-Gaudelus et al., 2009, <em>Journal of Pain and Symptom Management</em></td>
<td>Assess the prevalence of pain symptoms, their characteristics and treatment, their impact on daily quality of life, and the occurrence of procedural pain.</td>
<td>Cross-sectional survey</td>
<td>73 children (1-18 years) and 110 adults (18-52 years) with CF in France</td>
<td>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.</td>
<td>- For diagnostic study, no independent, blind comparison between index test and gold standard</td>
</tr>
<tr>
<td>Stenekees et al., 2009, <em>Journal of Pain and Symptom Management</em></td>
<td>To assess the frequency, severity, and self-management of pain.</td>
<td>Cross-sectional survey</td>
<td>123 adult and pediatric CF patients in Canada</td>
<td>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.</td>
<td>- For diagnostic study, gold standard not applied to all patients</td>
</tr>
</tbody>
</table>
**Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary**

<table>
<thead>
<tr>
<th>breathlessness, and cough</th>
<th>described. Sixty-four percent (76 of 123) of participants reported having breathlessness, and 83% (99 of 123) of participants reported experiencing cough</th>
<th>epidemiologic, case study/series, QI, survey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ Insufficient sample size</td>
<td>□ Sample not representative of patients in the population as a whole</td>
</tr>
<tr>
<td></td>
<td>□ Variables (confounders, exposures, predictors) were not described</td>
<td>□ Outcome criteria not objective or were not applied in blind fashion</td>
</tr>
<tr>
<td></td>
<td>□ Insufficient follow-up, if applicable</td>
<td>□ For diagnostic study, gold standard not applied to all patients</td>
</tr>
<tr>
<td></td>
<td>□ For diagnostic study, no independent, blind comparison between index test and gold standard</td>
<td></td>
</tr>
</tbody>
</table>

**References:**


**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*

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**Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary**

**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:**


**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)?

<table>
<thead>
<tr>
<th>Author/Date</th>
<th>Purpose of Study</th>
<th>Study Design</th>
<th>Sample</th>
<th>Outcomes</th>
<th>Design Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dampier et al., 2011, <em>American Journal of Hematology</em></td>
<td>To compare two alternative opioid PCA dosing strategies (LDHI—higher demand dose with low constant infusion or LDHI—lower demand dose and higher constant infusion) in SCD patients</td>
<td>Multi-site RCT</td>
<td>38 adult and pediatric patients with SCD who completed randomization prior to trial closure</td>
<td>Total opioid utilization (morphine equivalents, mg/kg) in 22 adults was 11.6 ± 2.6 and 4.7 ± 0.9 in the LDHI 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).</td>
<td>Study Limitations = None</td>
</tr>
<tr>
<td>Krishnamurti et al., 2014, <em>Pediatric Blood Cancer</em></td>
<td>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</td>
<td>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</td>
<td>All pediatric SCD patients presenting to Children’s Hospital of Pittsburgh ED</td>
<td>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&lt;0.05) and readmission rates at CHP (7.3% to 3.2%) as compared to PHIS (6.5% to 5.1%) (P&lt;0.05). Improvement in pain score during ED management was 2.0 or more on a Wong Baker scale of 0–5 (P&lt;0.01). Participants on</td>
<td>Study Limitations = None</td>
</tr>
</tbody>
</table>

**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

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<table>
<thead>
<tr>
<th>Study Title</th>
<th>Study Design</th>
<th>Study Description</th>
<th>Patients</th>
<th>Key Findings</th>
<th>Study Limitations</th>
<th>Increase Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melzer-Lange et al., 2004, <em>Pediatric Emergency Care</em></td>
<td>Quasi-experimental pilot study; comparing patients on protocol to institute ED-PCA after an initial bolus dose of narcotics to those off protocol</td>
<td>69 pediatric SCD patients</td>
<td>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.</td>
<td>Study Limitations = None</td>
<td>RCT &amp; Quasi-Experimental Studies</td>
<td>Increase Quality Rating if: Large Effect Level of evidence for studies as a whole: High Moderate Low Very Low</td>
</tr>
</tbody>
</table>

<p>| New et al., 2014, <em>Pediatric Hematol Oncol</em> | Present clinical experience in 7 sickle cell patients who received epidural analgesia for persistent refractory pain | 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 |</p>
<table>
<thead>
<tr>
<th>Study Authors and Year, Journal</th>
<th>Objective</th>
<th>Study Design</th>
<th>Sample and Intervention</th>
<th>Main Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uzan et al., 2009, <em>American Journal of Emergency Medicine</em></td>
<td>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</td>
<td>RCT randomly assigned to receive either tramadol 1.5 mg/kg (n = 34) or meperidine 1 mg/kg (n = 34)</td>
<td>68 patients with SCD</td>
<td>Both meperidine and tramadol administration resulted in a significant reduction in systolic and diastolic blood pressure after 2 hours (P &lt; .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 &lt; .05). Sedation was more commonly seen in the meperidine arm. None of the patients had experienced neurotoxicity.</td>
<td>None</td>
</tr>
<tr>
<td>van Beers et al., 2007, <em>American</em></td>
<td>To compare the efficacy of intravenous morphine administration with PCA to continuous infusion</td>
<td>RCT</td>
<td>Twenty five consecutive episodes of vaso-occlusive</td>
<td>Patients in the PCA group had a markedly and significant lower mean and cumulative morphine consumption when compared with</td>
<td>Insufficient sample size</td>
</tr>
</tbody>
</table>
Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

| Journal of Hematology | (CI) of morphine in patients with SCD during vaso-occlusive crisis | allocated to continuous infusion | crisis in 19 patients with SCD were included in the study | 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 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. |

References:

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

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Guideline Recommendations:

There were no guidelines found that addressed this clinical question.

Primary Literature:

<table>
<thead>
<tr>
<th>Author/Date</th>
<th>Purpose of Study</th>
<th>Study Design</th>
<th>Sample</th>
<th>Outcomes</th>
<th>Design Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anie &amp; Green, 2015, Cochrane Database of Systematic Reviews</td>
<td>To examine the evidence that psychological interventions improve the ability of people with sickle cell disease to cope with their condition</td>
<td>Systematic Review</td>
<td>5 randomised or quasi-randomised controlled trials (260 participants) comparing psychological interventions with no (psychological) intervention in people with sickle cell disease</td>
<td>One study showed that cognitive behaviour therapy significantly reduced the affective component of pain (feelings about pain), mean difference -0.99 (95% confidence 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).</td>
<td>Study Limitations = None Systematic Review</td>
</tr>
<tr>
<td>Eccleston et al., 2014, Cochrane Database of Systematic Reviews</td>
<td>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</td>
<td>Systematic Review</td>
<td>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</td>
<td>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 &lt; 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 &lt; 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 &lt; 0.01), but not at follow-up (SMD -0.11, 95% CI -0.41 to 0.19, z = 0.73, p &gt; 0.05).</td>
<td>Study Limitations = None Systematic Review</td>
</tr>
</tbody>
</table>

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)
### Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

<table>
<thead>
<tr>
<th>Study Source</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldbeck et al., 2014, Cochrane Database of Systematic Reviews</td>
<td>To determine whether psychological interventions for people with cystic fibrosis provide significant psychosocial and physical benefits in addition to standard medical care</td>
</tr>
<tr>
<td>Systematic Review</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>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 aimed at other aspects of the disease process. No studies evaluated impact on pain.</td>
</tr>
<tr>
<td>Study Limitations =</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Systematic Review</td>
</tr>
<tr>
<td></td>
<td>Review did not address focused clinical question</td>
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<tr>
<td></td>
<td>Search was not detailed or exhaustive</td>
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<tr>
<td></td>
<td>Quality of the studies was not appraised or studies were of low quality</td>
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<tr>
<td></td>
<td>Methods and/or results were inconsistent across studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Source</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hubert et al., 2014, PLOS ONE</td>
<td>To evaluate the impact of osteopathic manipulative treatment (OMT) on pain in adults with CF</td>
</tr>
<tr>
<td>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)</td>
<td>32 adult CF patients seen at CF centers in France</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Study Limitations =</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>RCT &amp; Quasi-Experimental Studies</td>
</tr>
<tr>
<td></td>
<td>Insufficient sample size</td>
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<td></td>
<td>Lack of randomization</td>
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<td></td>
<td>Lack of blinding</td>
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<td></td>
<td>Stopped early for benefit</td>
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<td></td>
<td>Lack of allocation concealment</td>
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<td></td>
<td>Selective reporting of measures</td>
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<tr>
<td></td>
<td>Large losses to F/U</td>
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</table>

<table>
<thead>
<tr>
<th>Study Source</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Kato-Lin et al., 2014, International Journal of Medical Informatics</td>
<td>To evaluate the impact of digitization of paper-based individualized pain plans on process efficiency and care quality by examining</td>
</tr>
<tr>
<td>Retrospective, before and after, mixed methods evaluation of digitization of paper documents in</td>
<td>1089 ED visits made by 150 SCD patients in VOC</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Study Limitations =</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)</td>
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</table>

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## Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Description</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 2009, Journal of Cystic Fibrosis</td>
<td>To examine the effect of a combination of musculoskeletal physiotherapy techniques and massage therapy on musculoskeletal pain and ease of breathing</td>
<td>Quasi-experimental study&lt;br&gt;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&lt;br&gt;&lt;br&gt;Overall, there was a significant reduction in pain following treatment (mean difference of 1.8 cm, 95% CI 1.5–2.1 cm, p&lt;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&lt;0.001), with significant improvements in the acute group, but not the clinically stable group</td>
</tr>
</tbody>
</table>

Both objective patient data and subjective clinician insights. Analysis of patient records indicated that adjusted time from analgesic order to administration was significantly 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.

Analysis of patient records indicated that adjusted time from analgesic order to administration was significantly 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. Nurses had the same response.

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## Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Overview</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al., 2005, <em>American Journal of Chinese Medicine</em></td>
<td>To evaluate the effects of acupuncture for pain management in patients with cystic fibrosis</td>
<td>Quasi-experimental study</td>
<td>30 adult and pediatric patients with cystic fibrosis who were experiencing both acute and chronic pain that underwent acupuncture treatments</td>
<td>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 &lt; 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.</td>
<td>Study Limitations =</td>
</tr>
<tr>
<td>Obideen et al., 2006, <em>Dig Dis Sci</em></td>
<td>To determine whether nocturnal hydration (NH) prevents recurrent abdominal pain and recurrent acute pancreatitis in patients with adult-onset CF</td>
<td>Quasi-experimental study</td>
<td>9 adult CF patients who were referred to Pancreatic Diseases Clinic for recurrent abdominal pain and pancreatitis</td>
<td>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.</td>
<td>Study Limitations =</td>
</tr>
</tbody>
</table>

### Table 1: Patients’ symptoms and medical facility utilization before and after NH

<table>
<thead>
<tr>
<th></th>
<th>Episodes of AP</th>
<th>Severity of AP</th>
<th>ER visits</th>
<th>Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>1.0 ± 1.0</td>
<td>8.0 ± 1.0</td>
<td>2.0 ± 1.0</td>
<td>3.0 ± 1.0</td>
</tr>
<tr>
<td>After NH</td>
<td>1.0 ± 1.0</td>
<td>8.0 ± 1.0</td>
<td>1.0 ± 1.0</td>
<td>2.0 ± 1.0</td>
</tr>
<tr>
<td>Δ</td>
<td>-</td>
<td>-</td>
<td>1.0 ± 1.0</td>
<td>1.0 ± 1.0</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Note: NH = Nocturnal Hydration; AP = Abdominal Pain; ER = Emergency Room
## Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Sample</th>
<th>Baseline Differences</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandsund et al., 2011, <em>Physiotherapy</em></td>
<td>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</td>
<td>Preliminary, prospective, single-blind, RCT</td>
<td>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 18.3 mm and reduced again to 7 mm at 12 weeks. In the treatment group, the pain levels were 5 mm at baseline and 16.5 mm 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.</td>
<td>Study Limitations = None</td>
</tr>
<tr>
<td>Schatz et al., 2015, <em>Clin J Pain</em></td>
<td>To examine the outcomes of a cognitive-behavioral therapy intervention for pain in pediatric SCD using smartphones as a novel delivery method</td>
<td>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-</td>
<td>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.</td>
<td>Study Limitations = None</td>
</tr>
</tbody>
</table>

---

*OHSU*
Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

References:

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:

Primary Literature:

<table>
<thead>
<tr>
<th>Author/Date</th>
<th>Purpose of Study</th>
<th>Study Design</th>
<th>Sample</th>
<th>Outcomes</th>
<th>Design Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartolucci et al., 2009, Blood</td>
<td>To evaluate the effectiveness of</td>
<td>Phase III RCT</td>
<td>66 VOC episodes in adults with SCD</td>
<td>Seven VOCs in each group were excluded from the analysis because of treatment failures, suggesting that the</td>
<td>Study Limitations = None RCT &amp; Quasi-Experimental Studies</td>
</tr>
</tbody>
</table>

September 2016
### Ketoprofen in Treating Adults with VOC

**Patients randomized to either ketoprofen (300 mg/day for 5 days) or placebo**

- 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** =
- 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

**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)
- 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

**Publication Bias**
- 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

**Increase Quality Rating if:**
- Large Effect
- Level of evidence for studies as a whole:
  - High
  - Moderate
  - Low
  - Very Low

---

### Inhaled Nitric Oxide Gas

**RCT of intravenous magnesium vs normal saline placebo**

- Children received 40 mg/kg of magnesium or placebo every 8 hours for up to 6 doses plus standard therapy.
- 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 after discharge were similar (P > .05 for all comparisons).

**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

**Publication Bias**
- None

**RCT & Quasi-Experimental Studies**
- Insufficient sample size
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---

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**Study Limitations** =
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- Lack of randomization
- Lack of blinding
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- Selective reporting of measures
- Large losses to F/U

**Publication Bias**
- 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

---

### Inhaled Nitric Oxide Gas

**RCT of inhaled nitric oxide vs inhaled nitrogen placebo**

- 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,

**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

**Publication Bias**
- None

**RCT & Quasi-Experimental Studies**
- Insufficient sample size
- Lack of randomization
- Lack of blinding
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- 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 after discharge were similar (P > .05 for all comparisons).

**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

**Publication Bias**
- None

**RCT & Quasi-Experimental Studies**
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### Inhaled Nitric Oxide Gas

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- There were no significant differences in secondary outcome measures, including length of hospitalization, visual analog pain scale scores,
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Objective</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Primary Outcome Measure</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldman et al., 2013, Pediatrics</td>
<td>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</td>
<td>RCT Randomized to IV MgSO4 (100 mg/kg) every 8 hours or placebo in addition to standard therapy</td>
<td>104 children aged 4 to 18 years requiring admission to hospital with a sickle cell disease VOE requiring IV analgesia</td>
<td>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 ± 2.6 vs 4.8 ± 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]).</td>
<td>Study Limitations = None</td>
</tr>
<tr>
<td>Morris et al., 2013, Haematologica</td>
<td>To test hypothesis that arginine may be a beneficial treatment for pain related to sickle cell disease</td>
<td>RCT Patients received L-arginine (100 mg/kg tid) or placebo for 5 days or until discharge</td>
<td>38 children with sickle cell disease hospitalized for 56 episodes of pain</td>
<td>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±0.8 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 admission (r=0.86, P&lt;0.0001). No drug-related adverse events were observed.</td>
<td>Study Limitations = None</td>
</tr>
<tr>
<td>Okomo &amp; Meremikwu, 2015, Cochrane Database of Systematic Reviews</td>
<td>To determine the optimal route, quantity and type of fluid replacement for people with sickle cell disease with acute painful crises</td>
<td>Systematic Review Randomised and quasi-randomised controlled trials that compared the administration of supplemental fluids adjunctive to analgesics by</td>
<td>No relevant trials identified.</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Study Title</td>
<td>Study Design</td>
<td>Study Objective</td>
<td>Study Findings</td>
<td>Study Limitations</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
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<td>----------------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>Ng &amp; Franchini, 2014, Cochrane Database of Systematic Reviews</td>
<td>Systematic Review</td>
<td>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</td>
<td>One trial found that drug therapies that reduce gastric acidity improved gastro-intestinal symptoms such as abdominal pain.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Thornton &amp; Rangaraj, 2016, Cochrane Database of Systematic Reviews</td>
<td>Systematic Review</td>
<td>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</td>
<td>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</td>
<td>No relevant studies were identified.</td>
<td></td>
</tr>
<tr>
<td>van Zurren et al., 2013, Cochrane Database of Systematic Reviews</td>
<td>Cochrane Systematic Review</td>
<td>To assess the effects of low-molecular-weight heparins for managing vaso-occlusive crises in</td>
<td>1 RCT (included 253 participants) that assessed the effects of low-molecular-weight heparins in the</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

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

September 2016
## Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

| 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. | 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 Limitations = None |

### References:


September 2016
Question # 6. In adults 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

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. 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

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.

- Consensus Statement

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

Primary Literature:

<table>
<thead>
<tr>
<th>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)?</th>
<th>Lower Quality Rating if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author/Date</td>
<td>Purpose of Study</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
</tr>
<tr>
<td>Flores et al., 2013, <em>Respiratory Care</em></td>
<td>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</td>
</tr>
<tr>
<td>Lee et al., 2015, <em>Cochrane Database of Systematic Reviews</em></td>
<td>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</td>
</tr>
</tbody>
</table>
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 children) with stable bronchiectasis.
### Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Design</th>
<th>Findings</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main et al., 2013, Cochrane Database of Systematic Reviews</td>
<td>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</td>
<td>RCT</td>
<td>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</td>
<td>None</td>
</tr>
<tr>
<td>McKoy et al., 2012, Cochrane Database of Systematic Reviews</td>
<td>To compare the clinical effectiveness of active cycle of breathing technique (ACBT) with other airway clearance therapies in cystic fibrosis</td>
<td>Systematic Review</td>
<td>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.</td>
<td>None</td>
</tr>
</tbody>
</table>

**AUTHORS’ CONCLUSION:** There is insufficient evidence to support or reject the use of ACBT over any other airway clearance therapy. Five
<table>
<thead>
<tr>
<th>Study Title</th>
<th>Study Type</th>
<th>Study Details</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLlwaine et al., 2015, Cochrane Database of Systematic Reviews</td>
<td>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</td>
<td>26 randomised controlled studies (733 participants) in which PEP was compared with any other form of physiotherapy in people with cystic fibrosis</td>
<td>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 2.12).</td>
</tr>
</tbody>
</table>

**Study Limitations**
- None
- 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

**Systematic Review**

The study included 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 2.12).
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 (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 0.55 to 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

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
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Design</th>
<th>Results</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warnock &amp; Gates 2015, Cochrane Database of Systematic Reviews</td>
<td>To determine the effectiveness and acceptability of chest physiotherapy compared to no treatment or spontaneous cough alone to improve mucus clearance in cystic fibrosis</td>
<td>Systematic Review</td>
<td>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</td>
<td>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</td>
</tr>
</tbody>
</table>

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.

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.
### References:

- MckoyNA, Saldanha II, OdololaOA, Robinson KA. Active cycle of breathing technique for cystic fibrosis. *Cochrane Database of Systematic Reviews 2012*, Issue 12

### 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.

September 2016
**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

**Consensus Statement**

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

- Consensus Statement

Consider using oral hydroxyzine for anxiety management.

- Consensus Statement

**Guideline Recommendations:**

No guidelines were found addressing this clinical question.

**Primary Literature:**

<table>
<thead>
<tr>
<th>Author/Date</th>
<th>Purpose of Study</th>
<th>Study Design</th>
<th>Sample</th>
<th>Outcomes</th>
<th>Design Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casier et al., 2013, Pain Res Manag</td>
<td>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</td>
<td>Mixed methods study</td>
<td>36 adolescents and young adults with CF (12 to 22 years of age)</td>
<td>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</td>
<td>Study Limitations =</td>
</tr>
</tbody>
</table>
### Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradt &amp; Dileo, 2014, Cochrane Database of Systematic Reviews</td>
<td>Systematic Review</td>
<td>14 randomized and quasi-randomized controlled trials (805 participants)</td>
<td>Compared music interventions and standard care with standard care alone in mechanically ventilated patients</td>
<td>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 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.</td>
</tr>
<tr>
<td>Delord et al., 2013, CHEST</td>
<td>Case series</td>
<td>Nine children aged 2 to 15 years with high levels of anxiety about NPPV</td>
<td>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 (&gt; 6 h) NPPV acceptance. The 6-month</td>
<td></td>
</tr>
</tbody>
</table>

**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

### Conclusion

Music listening may be beneficial for anxiety reduction in mechanically ventilated patients. However, the results are uncertain due to sample size and wide confidence intervals. Further research is needed to confirm these findings.

**Publication Bias**

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

- Insufficient sample size
- Sample not representative of patients in the population as a whole
## Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary

<table>
<thead>
<tr>
<th>Study Limitations</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>RCT &amp; Quasi-Experimental Studies</td>
</tr>
<tr>
<td>Insufficient sample size</td>
<td>Lack of randomization</td>
</tr>
<tr>
<td>Lack of blinding</td>
<td>Stopped early for benefit</td>
</tr>
<tr>
<td>Lack of allocation concealment</td>
<td>Selective reporting of measures</td>
</tr>
<tr>
<td>Large losses to F/U</td>
<td></td>
</tr>
</tbody>
</table>

| 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 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). | compliance with NPPV was excellent, with a median use of 7.5 h per night. 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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September 2016
**Adult Cystic Fibrosis Pain and Anxiety Management Evidence Summary**

<table>
<thead>
<tr>
<th>Laurino et al., 2012, Clinical Science</th>
<th>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</th>
<th>RCT</th>
<th>Thirty-eight asthmatic patients with a history of panic symptoms in Brazil</th>
<th>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&lt;=0.05) and agoraphobia (p&lt;0.05) were observed only in the BRG</th>
<th>Study Limitations =</th>
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<tr>
<td>Breathlessness in COPD patients</td>
<td>Table 1. The Breathlessness Intervention Service</td>
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<td>RCT</td>
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<td>A multidisciplinary service was established in the Department of Pulmonary Care in a tertiary referral center in 2004, with the aim of improving the quality of breathlessness. The service model was developed on the basis of the findings of earlier studies (Booth et al., 1996; Booth &amp; Adams, 2001; Booth et al., 2004) conducted within the BRG framework for the development and evaluation of complex interventions (Medical Research Council, 2004). A specialist respiratory physiotherapist was recruited to join the Macaulay respiratory 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 (BIS) because it was an active, focused rehabilitation 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 (mainly attention control techniques) and psychological and physical interventions including a palliative care approach to life-limiting diseases and psychosocial issues and pharmacological, as required. Unique, care is finally decided on when the patient dies. Referrals came from hospital and primary care specialists in medicine, nursing, and the allied health professions.</td>
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<td>Study Limitations =</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Mularski, 2009, *Journal of Alternative and Complementary Medicine*

- **Objective:** 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.
- **Study Design:** RCT
- **Participants:** 86 patients with COPD at VA hospital

<table>
<thead>
<tr>
<th>RCT</th>
<th>Randomized to 8-week mindfulness-based breathing therapy (MBBT) or support groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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).</td>
</tr>
</tbody>
</table>

### Valenza et al. 2014, *Respiratory Care*

- **Objective:** To evaluate if breathing techniques can improve anxiety and depression in patients hospitalized for COPD exacerbation
- **Study Design:** RCT
- **Participants:** 46 male subjects, 67–86 years old, hospitalized with acute COPD exacerbation in Spain

<table>
<thead>
<tr>
<th>RCT</th>
<th>Randomized to control group or controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controlled breathing techniques significantly improved dyspnea, anxiety, and mobility. All the measured variables improved in the intervention group. The control group had poorer values in all the variables after the hospitalization period</td>
</tr>
</tbody>
</table>

#### Study Limitations
- **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 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

<table>
<thead>
<tr>
<th>Month</th>
<th>Day</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sep</td>
<td>2016</td>
<td></td>
</tr>
</tbody>
</table>

Large losses to F/U

References:

September 2016
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**

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>Starting level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trial</td>
<td>high</td>
</tr>
<tr>
<td>Observational study</td>
<td>low</td>
</tr>
<tr>
<td>Any other evidence</td>
<td>very low</td>
</tr>
</tbody>
</table>

**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.

September 2016
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. guideline 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 September 2016
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

<table>
<thead>
<tr>
<th></th>
<th>Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Guideline development group includes one of the above, but not both.</td>
</tr>
<tr>
<td>B</td>
<td>Guideline developers all from one specialty or organization, and no methodologists.</td>
</tr>
<tr>
<td>NR</td>
<td>Affiliations of guideline developers not reported</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Guideline includes a systematic review of the evidence or links to a current review.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Guideline is based on a review which may or may not meet systematic review criteria.</td>
</tr>
<tr>
<td>B</td>
<td>Guideline is not based on a review of the evidence.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Specific supporting evidence (or lack thereof) for each recommendation is cited and graded</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded</td>
</tr>
<tr>
<td>B</td>
<td>Recommendations are not supported by specific evidence.</td>
</tr>
</tbody>
</table>

September 2016
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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>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.</td>
</tr>
<tr>
<td>B</td>
<td>Either one or the other of the above criteria is met.</td>
</tr>
<tr>
<td>C</td>
<td>Neither of the above criteria are met</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Guideline was made available to external groups for review.</td>
</tr>
<tr>
<td>B</td>
<td>Guideline was reviewed by members of the sponsoring body only.</td>
</tr>
<tr>
<td>C</td>
<td>Guideline was not externally reviewed.</td>
</tr>
<tr>
<td>NR</td>
<td>No external review process is described.</td>
</tr>
</tbody>
</table>

8. Updating and currency of guideline

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Guideline is current and an expiration date or update process is specified.</td>
</tr>
<tr>
<td>B</td>
<td>Guideline is current but no expiration date or update process is specified.</td>
</tr>
<tr>
<td>C</td>
<td>Guideline is outdated.</td>
</tr>
</tbody>
</table>

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.

September 2016