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OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

ADULT CYSTIC FIBROSIS PAIN AND ANXIETY MANAGEMENT GUIDELINE

Epidemiology: Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease among Caucasian populations, with a frequency of one in 2000 to 3000 live births. The median predicted survival for CF patients in the United States is 59 years (95% CI, 56.4-65.1), according to the Cystic Fibrosis Foundation 2020 Registry Report. [1]

Prevalence of Pain: The prevalence of pain in adults with CF is estimated between 77-82%. [2] Patients who report pain and anxiety during exacerbation frequently report a negative impact on quality of life. [3]

Guideline Eligibility Criteria: Adult patients (≥ 18 years of age) with CF in the inpatient or ambulatory setting with acute or chronic pain

Guideline 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
- 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

Clinical Practice Recommendations

Long- Term Opioid Therapy for Chronic Pain

Non-pharmacologic therapy and non-opioid 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 non-pharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. [4]
-Strong Recommendation; Low Quality Evidence

Before starting opioid therapy, clinicians should perform an initial pain assessment which includes not only a physical assessment, but considers social, spiritual and psychological factors which may be influencing the patient's perception of pain.
-Consensus Statement

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. [4]
-Strong Recommendation; Very Low Quality Evidence

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. [4]
-Strong Recommendation; Low Quality Evidence

When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids. **[4]**
-Strong Recommendation; Very Low Quality Evidence

When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day. [4]
(See Appendix A for Morphine Milligram Equivalents (MME) Table)
-Strong Recommendation; Low Quality Evidence

Clinicians should evaluate benefits and harms with patients within one to four 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. [4]
-Strong Recommendation; Very Low Quality

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. At OHSU, clinicians should complete the Opioid Risk Assessment. 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. [4]
(See Appendix A for Morphine Milligram Equivalents (MME) Table)
-Strong Recommendation; Very Low Quality Evidence

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 three months. [4]
-Strong Recommendation; Very Low Quality Evidence

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. [4]
-Weak Recommendation; Very Low Quality Evidence

Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. [4]
-Strong Recommendation; Low Quality Evidence

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. [4]
-Strong Recommendation; Moderate Quality Evidence

Opioid Dosing Strategies for Acute Pain
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. [4]
-Strong Recommendation; Very Low Quality Evidence

Opioid Tapering

When harms of continuing opioid therapy outweigh the benefits, prescribing clinicians should approach the taper plan as an alliance with the patient to ensure its success. There are general approaches to tapering. However, patients and clinicians should be aware this is a rapidly evolving field, and tapering should be done based on evidence-based practice and/or best practice. It is essential that each taper plan is individualized and based on the patient's history, goals, and an objective assessment. Generally, a 5 to 20 percent taper per month can be a helpful guide. When discharge planning, consider taper prior to discharge from inpatient care if consistent opioid use inpatient and stopping opioid at discharge. [5] [6]
-Consensus Statement

Patients on higher doses of opioids may tolerate a more rapid taper. Those on a lower dose or who have been on opioids for a long time may need a slower taper. The most common cause of failed tapers is trying to taper too rapidly. [6]
-Consensus Statement

Referrals
Consider Acute Pain Service consultation if patient's pain is beyond the scope and/or comfort level of the prescriber or if opioid dose ≥ 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.
(See Appendix A for Morphine Milligram Equivalents (MME) Table)
-Consensus Statement

Recommend the CF care team partners with specialists who are consulted to assist with palliative care needs to facilitate the specialists' understanding of CF care and the unique needs of individuals with CF. Team should use the Integrated Palliative Care Outcome Scale (IPOS) annually and at disease milestones for screening and assessing unmet palliative care needs. [7]
-Consensus Statement

Non-Opioid Pain Management Strategies

Alternatives to opioid prescribing should be considered in the management of pain in patients with cystic fibrosis, including: non-opioid pharmacologics, massage therapy, acupuncture, chiropractic, physical therapy, and cognitive behavioral therapy. [8-17]
-Strong Recommendation; Low Quality Evidence

From 2021 American Academy of Family Physicians (AAFP) Pharmacologic Therapy for Acute Pain guidance [18]	
Clinical Recommendation	Evidence rating
Topical nonsteroidal anti-inflammatory drugs are safe and effective for treating acute pain	A
Nonsteroidal anti-inflammatory drugs, acetaminophen, or a combination is an effective initial treatment approach for acute pain syndromes. Medication selection should be based on minimizing risks for the specific patient	A
Gabapentinoids and antidepressant medications used to treat chronic neuropathic pain should not be used to treat acute pain	B
Cannabinoids used to treat chronic neuropathic pain should not be used to treat acute pain	C
Opioids should be used for no more than three days, only for severe or refractory acute pain, and only in combination with other medications	C

Airway Clearance Techniques
ACT is recommended for all patients with CF for clearance of sputum, maintenance of lung function, and improved quality of life. [19, 20]

-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. Positive Expiratory Pressure (PEP) may be superior to vest therapy due to patient preference, and decreased exacerbations and antibiotic use while on PEP. **[19-28]**

-Strong Recommendation; Low Quality Evidence

Consider alternatives to vest therapy in patients requiring pre-treatment analgesia to tolerate treatment as it likely exacerbates chest/back pain. [29]
-Conditional Recommendation; Very Low Quality Evidence

Pain Assessment
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.

Anxiety Assessment
Annual screening for anxiety is recommended for all individuals with CF using the GAD-7. [30]
-Consensus Statement

Anxiety Management
For all individuals reporting elevated symptoms of anxiety, it is recommended that they be referred for treatment to a primary care provider or a mental health provider following the completed assessment with a provider on the CF team. [30]
-Consensus Statement

For individuals with severe anxiety, it is recommended that exposure-based cognitive behavioral therapy (CBT) be provided. If exposure-based CBT is not available or not fully effective, it is recommended that antidepressant medication be considered for treatment. [30]
-Consensus Statement

For most individuals who require antidepressant medication for treatment of depression and/or anxiety, the following first-line selective serotonin reuptake inhibitors (SSRIs) are recommended: citalopram, escitalopram, sertraline, and fluoxetine. It is recommended that each individual who is prescribed an antidepressant for treatment of depression and/or anxiety be closely monitored for appropriate dosing, therapeutic effects, and that any adverse effects or drug-drug interactions be promptly identified. [30]
-Consensus Statement

When a short-term pharmacological intervention is indicated for treatment of moderate to severe symptoms of anxiety related to medical procedures, and the individual has not shown a positive response to behavioral interventions alone, it is recommended that lorazepam be considered for treatment. [30]
-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

Principles of Clinical Management

For patients who are prescribed long term opioids for chronic pain who are hospitalized:

- At admission
  a. Establish if the patient has an opioid agreement with his or her primary care provider or other provider
  b. Check the PDMP to confirm opioid dosing and prior prescriber and to ensure there are not multiple prescribers
- Prior to hospital discharge, should do the following
  a. Clearly identify who will be the primary prescriber of opioids after discharge and communicate with that provider
- Should avoid concomitant prescription of benzodiazepines or sedative hypnotics at discharge
- Should obtain Acute Pain Service Consultation if the patient's pain is beyond the scope and/or comfort level of the prescriber or if opioid dose ≥ 90 MME/day

(See Appendix A for Morphine Milligram Equivalents (MME) Table)

When CONSIDERING long-term opioid therapy for cystic fibrosis patients who are not already prescribed long-term opioids for chronic pain in the ambulatory setting:

- Take into consideration psychological, spiritual, and social factors which may be influencing the perception of pain.

Check that non-opioid therapies tried and optimized

- Prior to prescribing an opioid for long-term, continuous use for pain, a pain focused history and examination should be performed. This evaluation should include the following elements:
  a. Subjective pain evaluation
  b. Functional capacity evaluation
  c. Mental health evaluation and history
  d. Substance abuse history
  e. Opioid Risk evaluation including initial urine drug testing and review of the Oregon PDMP
- Prior to prescribing an opioid for long-term, continuous use for pain, the following must be discussed with the patient and documented in the patient record:
  a. A specific pain diagnosis
  b. Set realistic goals for pain and function based on diagnosis (e.g., walk around block)
  c. Discuss benefits and risks (e.g., addition, overdose) with patient
  d. Provide patient (and patient must read and sign) a Controlled Substance for Intractable Pain Notice and Consent Form (also known as Opioid Treatment Agreement). The document will be part of the patient's medical record and should be renewed every 2 years if opioids are continued
  e. Set criteria for stopping or continuing opioids
- An opioid dose ≥ 90 MME/day must not be prescribed without secondary review by another LIP, a clinic opioid review board, or the OHSU Comprehensive Pain Center

(See Appendix A for Morphine Milligram Equivalents (MME) Table)

- Schedule initial reassessment within 1-4 weeks
- Periodically re-evaluate the patient every 3 months to determine if functional gains have been made
- Discontinue opioids in favor of alternatives if progress toward functional goals have not been met
- Avoid use of high-risk medications or substances with opioids
  a. Should avoid concomitant use of benzodiazepines and opioids. If the patient is already prescribed benzodiazepines, consider tapering benzodiazepines before prescribing opioids or do not start opioids.
  b. Should avoid concomitant use of other sedative hypnotics (e.g. barbiturates, carisoprodol, zolpidem, etc).
  c. Should advise patients against concomitant use of alcohol and opioids

d. Should advise patients against the concomitant use of marijuana (including medical marijuana) and opioids
e. Should provide patient counseling on the risks of combining the above substances with opioids

If RENEWING prescription without patient visit:

- Check that return visit is scheduled </= 3 months from last visit

When REASSESSING at return visit or for patients who are already prescribed long-term opioid therapy for chronic pain in the ambulatory setting:

- Continue opioids only after confirming clinically meaningful improvements in pain and function without significant risks or harm
- In the course of prescribing an opioid for long-term, continuous use for pain, a pain focused history and examination should be performed and periodically updated. This evaluation should include the following elements:
  a. Subjective pain evaluation
  b. Functional capacity evaluation
  c. Mental health evaluation and history
  d. Substance abuse history
  e. Opioid Risk evaluation including initial urine drug testing and review of the Oregon PDMP
- Regularly monitor patients for opioid risks
  a. Should check the Oregon PDMP prior to refilling prescribed opioids at least annually
  b. Should perform a random UDT at least annually and more often for high risk patients
  c. Should assess opioid risk and document at least annually
  d. If methadone is prescribed, an ECG should be obtained at least annually for patients prescribed high doses (>20 mg/day) or with increased cardiovascular risk
- Maintain a comprehensive treatment plan with agreed upon treatment goals.
  a. Should periodically review an informed consent and opioid agreement every 2 years
  b. Should regularly review and discuss mutual treatment goals
  c. Should regularly evaluate effectiveness and safety of opioid treatment
  d. Check that non-opioid therapies optimized
  e. In the absence of functional gains or improved pain control, should taper opioids or seek consultation from another LIP or the OHSU Comprehensive Pain Center
  f. If opioids are prescribed at a high dose (>/=90 MME/day), must document discussion of tapering to a lower, safe and effective dose
  g. Should regularly recommend physical modalities and self-care strategies to manage persistent pain
- If opioid dose greater than or equal to 50 MME/day, increase frequency of follow-up, and consider offering naloxone.

(See Appendix A for Morphine Milligram Equivalents (MME) Table)

- An opioid dose ≥ 90 MME/day in a 24 hour period must not be prescribed without secondary review by another LIP, a clinic opioid review board, or the OHSU Comprehensive Pain Center
  a. If a patient is prescribed ≥ 90 MME/day, an opioid taper must be started and have an estimated completion date unless the dose is otherwise agreed upon or approved by another LIP, a clinic opioid review board, or the OHSU Comprehensive Pain Center

(See Appendix A for Morphine Milligram Equivalents (MME) Table)

- Should re-evaluate the patient to determine if functional gains have been made at regular intervals (</= 3 months)
- Should discontinue opioids in favor of alternatives if progress toward functional goals has not been met
- Avoid use of high-risk medications or substances with opioids
  a. Should avoid concomitant use of benzodiazepines and opioids. If the patient is prescribed benzodiazepines, consider tapering benzodiazepines
  b. Should avoid concomitant use of other sedative hypnotics (e.g. barbiturates, carisoprodol, zolpidem, etc).

c. Should advise patients against concomitant use of alcohol and opioids
d. Should advise patients against the concomitant use of marijuana (including medical marijuana) and opioids
e. Should provide patient counseling on the risks of combining the above substances with opioids

- Patients who develop an opioid use disorder during treatment should be referred to an addiction specialist/appropriate specialist and/or addiction treatment

Acute Pain Management:
- Consider non-medication and non-opioid pain treatment modalities
- If prescribing opioids, 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
- Oral opioids are preferred to IV opioids
- Three days or less of opioids will often be sufficient; more than seven days will rarely be needed

Airway Clearance:
- ACT should be used for all patients with CF
- Choice of ACT should be based on patient preference
- Consider alternatives to vest therapy if it increases pain

Anxiety Management:
- Avoid the use of IV diphenhydramine (Benadryl), IV benzodiazepines and opioids for managing anxiety
- In the hospitalized patient, consider use of oral hydroxyzine 25-50 mg every 6 hours as needed for managing anxiety

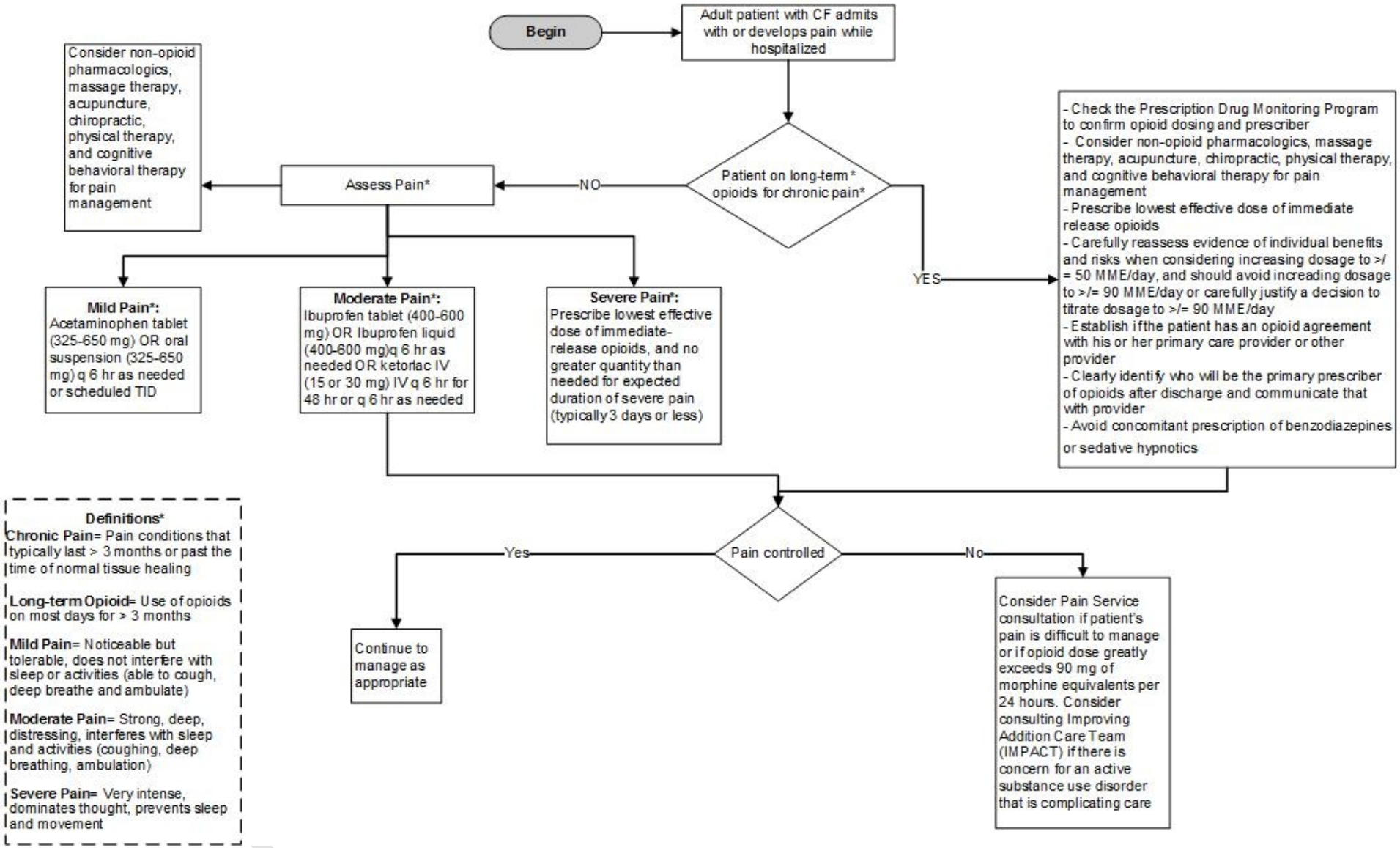
Consults/Referrals:
- When to consider specialty referral:
  - The patient has ongoing severe pain with no significant improvement in pain and/or function despite opioid treatment.
  - Presence of significant psychological and addiction issues
  - Patient requires ≥ 90 mg morphine equivalents per day
  - The provider is considering prescribing opiates in combination with other psychoactive drugs (i.e. benzodiazepines) with potential for abuse
  - There is aberrant drug-related patient behavior

Quality Measures:

Process-
- Utilization of CF IP Order Set
- Utilization of Oregon PDMP reviews on patients admitted with CF
- Prevalence of CF patients treated with opioids and/or schedule II drugs
- Prevalence of IV hydromorphone, benzodiazepine and IV diphenhydramine orders for hospitalized CF patients
- Referrals to IMPACT
- Adherence to airway clearance therapy
- Choice of airway clearance technique

Outcome-
- IP LOS
- Admission Rate

OHSU Office of Clinical Integration and EBP
Inpatient Adult Cystic Fibrosis (CF) Pain Management



Definitions*

Chronic Pain= Pain conditions that typically last > 3 months or past the time of normal tissue healing

Long-term Opioid= Use of opioids on most days for > 3 months

Mild Pain= Noticeable but tolerable, does not interfere with sleep or activities (able to cough, deep breathe and ambulate)

Moderate Pain= Strong, deep, distressing, interferes with sleep and activities (coughing, deep breathing, ambulation)

Severe Pain= Very intense, dominates thought, prevents sleep and movement

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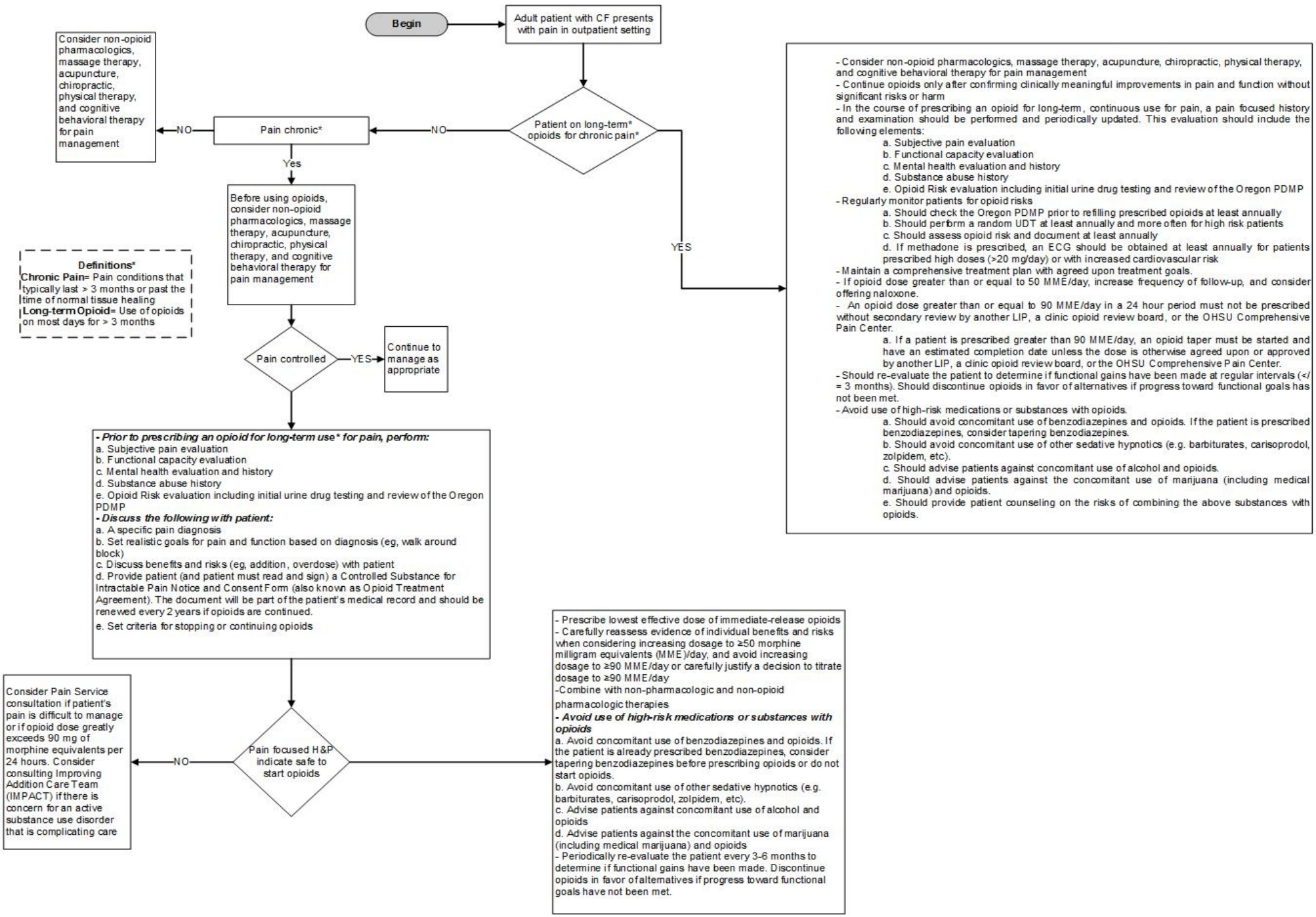
OHSU Office of Clinical Integration and EBP
Outpatient Adult Cystic Fibrosis (CF) Pain Management



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Guideline Preparation

This guideline was prepared by the Office of Clinical Integration (CI) and Evidence-Based Practice (EBP) in collaboration with content experts at Oregon Health and Science University.

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Development Process

This guideline was developed using the process outlined in the CI and EBP Manual (2016). The review summary documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing Internal and External Guidelines
   - Literature Review of Relevant Evidence
3. Critically Analyze the Evidence
4. Summarize the Evidence by preparing the guideline, and order sets
   - Materials used in the development of the guidelines, review summaries and content expert team meeting minutes are maintained in a CF Pain and Anxiety Management EB review manual with the Office of CI and EBP.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **University of Pennsylvania's Trustworthy Guideline Rating Scale**. The summary of these guidelines are included in the evidence summary. The 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. This scale evaluates a guideline's transparency, conflict of interest, development group, systematic review, supporting evidence, recommendations, external review and currency and updates. 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).

The **GRADE (Grading of Recommendations, Assessment, Development and Evaluation)** criteria were utilized to evaluate the body of evidence used to make clinical recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The evidence summary reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong

	evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Recommendations for the guidelines were directed by the existing evidence, content experts, and consensus. Patient and family preference were included when possible. When evidence is lacking, options in care are provided in the guideline and the order sets that accompany the guideline.

Approval Process

Guidelines are reviewed and approved by the Content Expert Team, Office of CI and EBP, Knowledge Management and Therapeutics Committee, Professional Board, and other appropriate hospital committees as deemed appropriate for the guideline's intended use. Guidelines are reviewed and updated as necessary every 2 to 3 years within the Office of CI and EBP at OHSU. Content Expert Teams will be involved with every review and update.

Disclaimer

Guideline recommendations are made from the best evidence, clinical expertise and consensus, in addition to thoughtful consideration for the patients and families cared for within the Integrated Delivery System. When evidence was lacking or inconclusive, content experts made recommendations based on consensus. Expert consensus is implied when a reference is not otherwise indicated.

The guideline is not intended to impose standards of care preventing selective variation in practice that is necessary to meet the unique needs of individual patients. The physician must consider each patient and family's circumstance to make the ultimate judgment regarding best care.

Appendix A: Morphine Milligram Equivalents (MME) Table

MME/day	Hydrocodone	Oxycodone
50 MME/day	50 mg	33 mg
90 MME/day	90 mg	60 mg

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