EDUCATION MODULE

PRESCRIBING OPIOIDS IN PATIENTS WITH NON-MALIGNANT PANCREATIC DISEASE*

*This module provides additional details and risk-reduction guidance specific for this risk factor for serious prescription opioid overdose. It **supplements** but does not replace the general best practices for opioid prescribing presented in the "**Considerations for Safe and Responsible Opioid Prescribing**" module.*

Background

1. Heavy alcohol consumption is the second most common cause of acute pancreatitis in the U.S., and the most common cause of recurrent acute pancreatitis and chronic pancreatitis (~60%).
    a. The risk of disease progression increases with continued alcohol consumption and cigarette smoking.[1]

2. Among patients with chronic pancreatitis, 50% to 85% have abdominal pain, and those with severe and disabling constant pain have some of the worst quality of life scores of any chronic disease.[2,3]

    a. Pain in chronic pancreatitis may arise from inflammatory, mechanical (intraductal pressure or obstruction), malabsorptive, or neurogenic/neuropathic changes in the pancreas and/or surrounding organs.[4]
    b. Chronic inflammation and fibrosis may lead to striking neuropathic changes in structure and function with nociceptive activation that is associated with progressive peripheral and central sensitization to pain as well as aberrant pain processing.[4-6]

3. Opioid analgesics are commonly used to treat pain in chronic pancreatitis: 46% to 51% of patients report opioid use.[7,8]

Pancreatic disease and opioid overdose

1. Opioid-treated patients with chronic pancreatitis have a disproportionately high prevalence of some of the strongest risk factors for opioid overdose, specifically:

    a. Co-occurring mental health disorders such as anxiety or depression[8,9]
    b. Concurrent use of benzodiazepines or other CNS depressants (e.g., gabapentinoid anticonvulsants, alcohol)[8-12]
    c. Co-occurring alcohol use disorder
    d. Increased risk of opioid misuse for uncontrolled pain or for non-pain symptoms (e.g., to treat mood symptoms)[13]

2. Chronic inflammation associated with pancreatitis can lead to impaired hepatic metabolic capacity that is comparable to functional disturbances observed in patients with mild to moderate hepatic cirrhosis.[14-16]

a. Increased plasma levels of some opioids and/or psychotherapeutic medications may result, thus increasing the risk for serious toxicity.[15] (see **"Prescribing opioids for patients treated with antidepressants"** and **"Prescribing opioids for patients treated with benzodiazepines"** modules)

3. Accelerated gastric emptying and/or malabsorption due to pancreatic disease may decrease drug absorption, requiring or resulting in patients taking higher opioid doses.[17-20]

4. Opioids can decrease gut motility. Typical manifestations of opioid-induced bowel dysfunction (diffuse abdominal pain, constipation, nausea, and dyspepsia) can complicate the clinical presentation of patients with pancreatic disease.[17,21]

Risk-mitigating interventions to consider when prescribing opioids to patients with non-malignant pancreatic disease

1. Strongly encourage alcohol abstinence and smoking cessation to reduce risk of recurrence and progression of disease and associated pain.[4,6,8,22]

2. Optimize treatment of co-occurring mental health disorders such as anxiety or depression.

    a. Consider agents that are also effective as adjuvant analgesics for neuropathic pain such as tricyclic antidepressants or serotonin-norepinephrine reuptake inhibitors (SNRIs).[4,22] (see **"Prescribing opioids for patients treated with antidepressants"** and **"Prescribing opioids for patients treated with benzodiazepines"** modules)

3. Treat mild to moderate pain with acetaminophen.
    a. Use nonsteroidal anti-inflammatory drugs cautiously due to their gastrointestinal toxicity (peptic ulcer disease), which can lead to pain.[4,6,22]
    b. Use acetaminophen with caution in persons with hepatic impairment, active hepatic disease, alcohol use disorder, or chronic malnutrition. (FDA- Acetaminophen Information)
        i. Reduce dosage and limit frequency of dosing to protect hepatic function. (FDA-Acetaminophen Information)

4. If pain relief is inadequate:

    a. Consider centrally acting adjuvant analgesics such as gabapentinoid anticonvulsants (pregabalin, gabapentin) or selected antidepressants (SNRIs, certain tricyclics).[4,6,7]
    b. Consider pancreatic enzyme supplementation, antioxidants, or non-pharmacologic treatment such as low-fat elemental diets or, if necessary, nasojejunal enteral feeding.[6,7]
    c. Consider endoscopic or surgical therapy for anatomical abnormalities such as large-duct disease (dilatation) or pseudocysts.

5. For pain that is constant and/or severe enough to require opioid analgesics:

a. Initiate therapy with an immediate-release formulation of a lower potency opioid at the lowest effective dosage. (see 'Treatment' section of the "**Considerations for Safe and Responsible Opioid Prescribing**" module)

b. Some opioids (tramadol, tapentadol, and transdermal fentanyl) *may* have a lower propensity for iatrogenic bowel dysfunction and may thus be useful in this setting.[23-27]
   i. Note: Fentanyl should only be used in patients who are opioid tolerant. (see **"Prescribing Fentanyl"** module)
      Adults are considered opioid-tolerant if they have been receiving a total daily opioid dose equivalent to at least 60 mg of oral morphine (60 MME/day) for one week or longer.[28] (see 'Treatment' section of the **"Considerations for Safe and Responsible Opioid Prescribing"** module)

      This dosage is comparable to:
      • 25 mcg transdermal fentanyl per hour
      • 30 mg oral oxycodone per day
      • 60 mg oral hydrocodone per day
      • 8 mg oral hydromorphone per day
      • 25 mg oral oxymorphone per day

c. Closely monitor patients for respiratory depression and over-sedation, particularly during initiation and after dosage escalations. The risk for overdose is greatest during the first 3 to 7 days after starting an opioid or increasing its dose. This occurs because tolerance to an opioid's respiratory depressant effects is slower to develop and less complete than tolerance to its analgesic or euphoric effects.[29-32]

d. Closely monitor therapeutic adherence and for indicators of opioid misuse or abuse. (see the 'Follow Up' section in the **"Considerations for Safe and Responsible Opioid Prescribing"** module)

6. In patients whose pain is not adequately managed, or worsens with increasing or high total daily opioid dosage in the absence of disease progression, consider the possibility of opioid-induced hyperalgesia[6,22] or opioid-induced bowel dysfunction.[17,21] (see **"Considerations for Safe and Responsible Opioid Prescribing"** module.) Assess for improvement in pain or function with a reduction in opioid dose.

7. Avoid concurrent use of other medications or substances that are central nervous system depressants, such as benzodiazepines, sedatives/hypnotics, and alcohol in opioid-treated patients. The combination can result in profound sedation, respiratory depression, coma, and death and should be restricted to the minimum required dosage and duration in patients for whom alternative treatment options are inadequate.[29,30,33]

8. Consider prescribing take-home naloxone for opioid-treated patients with pancreatic disease to reverse life-threatening respiratory depression if an overdose occurs. Educate the patient, family/household members, and caregivers about signs and symptoms of opioid overdose and train them to properly use naloxone if an opioid-related overdose is suspected.[29,34] (see also: FDA Label; "**Considerations for Safe and Responsible Opioid Prescribing**" module)

9. Consult with or refer to a structured multidisciplinary program, if available, those patients who have poor psychosocial functioning, malnutrition, concurrent mental health disorders (e.g., anxiety, depression), inadequate pain management, or opioid addiction or signs of opioid misuse or abuse, for evaluation and individualized intervention.[4,17]

Additional Resources

**The information presented in this module highlights some fundamental concepts of opioid prescribing for adult outpatients. It excludes certain populations (pediatrics, pregnancy, patients with active cancer or receiving palliative or end-of-life care) and settings (perioperative, emergency, in-patient). The information provided is intended to support safe and effective opioid therapy and minimize serious adverse outcomes, particularly overdose. It is not intended to be exhaustive nor substitute for consulting a medication's full prescribing information for complete details and warnings. Links and references to selected, more comprehensive clinical and prescribing resources are provided to facilitate safe and effective opioid prescribing.*

1. FDA-approved drug label information: FDA Online Label Repository or Daily Med (NIH/National Library of Medicine)
2. Management of acute pancreatitis (UpToDate)
3. Treatment of chronic pancreatitis (UpToDate)
4. Suggested algorithm for pharmacological treatment pain in chronic pancreatitis (From Drewes 2017.[22] Guidelines for the understanding and management of pain in chronic pancreatitis)
5. NIH-LiverTox- detailed information regarding acetaminophen and hepatotoxicity.

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