EDUCATION MODULE

CONSIDERATIONS FOR SAFE AND RESPONSIBLE OPIOID PRESCRIBING

*The information and recommendations provided are intended to support safe and effective opioid therapy for adult outpatients and minimize serious adverse outcomes. They **exclude** certain populations (pediatrics, pregnancy, patients with active cancer or receiving palliative or end-of-life care) and settings (perioperative, emergency, in-patient). The recommendations are selected from published peer-reviewed treatment guidelines and supporting evidence. The current evidence base is limited but is rapidly evolving; accordingly, the information and recommendations provided are based on the best information available at the time of publication.*

All medical decisions must be made by a qualified physician or other appropriately qualified medical professional. The clinical decision support provided does not replace clinical judgment and is not intended as a standard of care for all patients and all clinical situations. Clinicians should be aware of current federal and state (including licensing board) laws, rules and regulations, regulatory guidelines, and policy statements regarding opioid prescribing and medical use.

ASSESSMENT

1. Assess the patient and document one or more recognized medical indications for prescribing an opioid analgesic.[1] Document reasons why non-opioid alternatives are not appropriate or used (e.g., they are not tolerated, not effective, or are contraindicated).[1-3]

2. Assess the patient's pain, function, and quality of life using validated tools such as the Brief Pain Inventory- Short Form (BPIsf), the three-item Pain, Enjoyment of Life and General Activity (PEG) Scale, and the two-item Graded Chronic Pain Scale.[2,4,5] Conduct assessments before starting an opioid, regularly throughout treatment, and following changes in treatment.[4,5]

    a. Function can include emotional and social as well as physical dimensions.[2,4,5]

3. Screen for the major risk factors for developing substance use disorder or overdose, using validated tools as available.

    a. Screen for depression, anxiety, and post-traumatic stress disorders [e.g., Patient Health (PHQ)-4 or-9 Questionnaire, Generalized Anxiety Disorder (GAD)-7 Questionnaire, and Primary Care PTSD Screen (PC-PTSD)].[1,4] (Scoring instructions for PHQ and GAD instruments can be accessed here)

    b. Untreated or undertreated co-occurring mental health disorders frequently interfere with resolution of pain or improvement in function,[2,7] and also increase the risk of substance misuse, substance use disorder, and overdose.[2,4]

    c. Screen for personal history of substance use problems (e.g., NIDA Quick Screen).[1] If positive for illegal or prescription drugs for nonmedical reasons, follow with the NIDA-Modified ASSIST (Alcohol, Smoking and Substance Involvement Screening Test).

d. Screen for family history of substance use disorders.[1]

4. Check the state prescription drug monitoring program (PDMP) data to confirm the history of controlled substances prescribed, and to identify concerns such as multiple prescribers or pharmacies, which raise concern for substance use disorder or diversion.[2,4,7] Check the PDMP before starting an opioid and every three months during ongoing treatment (or at the frequency required by your state regulations).

5. Conduct urine drug testing (Also see: Urine drug test decision support) to check the presence of prescribed controlled medications (adherence) and detect undisclosed use of nonprescribed controlled medications or illicit drugs (misuse/addiction). Oral fluid (saliva) also may be used as a matrix for drug testing.[1,2,4] (see 'Additional Resources')

    a. Do not start opioids if baseline results reveal "red flags" such as the confirmed presence of cocaine, amphetamines, or alcohol, or undisclosed and nonprescribed opioids, benzodiazepines, or other controlled medications.

    b. In most cases, a screening (immunoassay) urine drug test is the appropriate test. Be familiar with the limitations of the tests that you use, including false positives and false negatives, and consult the lab with questions.

    c. Confirmatory testing, such as with gas chromatography/mass spectrometry can be useful and is more sensitive and specific. It may be the only available test for certain opioids such as tramadol, tapentadol, and fentanyl.

TREATMENT

1. A multimodal and multidisciplinary (biopsychosocial) approach to managing pain and functional impairment is the most effective and can minimize the need for opioids.[4,6-8]

    a. Non-pharmacologic interventions include cognitive behavioral therapies, exercise therapy, massage, acupuncture, yoga, and biofeedback.[4,9,10]

    b. Non-opioid analgesics include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX-2) inhibitors, and topical analgesics.

    c. Non-opioid adjuvant analgesics include selected antidepressants [tricyclic (TCA) or serotonin-norepinephrine reuptake inhibitor (SNRIs)] and anticonvulsants (gabapentin and pregabalin).

    d. Interventional therapies include nerve or spinal cord stimulators, nerve blocks, steroid injections, trigger point injections, or surgical procedures.

2. Consider consultation or co-management with, or referral to specialists in pain medicine, addiction medicine, and/or behavioral/mental health, or to an interdisciplinary program* in the following circumstances, if local resources are available (see: For the Primary Care Provider: When to refer to a pain specialist):[4,6,7] (see 'Additional Resources')

    a. The diagnosis or treatment of the pain condition is outside the scope of the clinician's training or comfort.[7]

    b. The patient has an active substance use disorder (by DSM-5 criteria), other mental health disorder, or uncontrolled suicide risk.[4]

    c. There is evidence of or concern about misuse or diversion of controlled medication, or use of an illicit substance use.[7]

    d. The patient appears adherent (including by urine drug testing) but is not responding to opioid treatment as expected at typically effective doses up to 90 MME/day.[4]

    e. Assistance is needed to guide tapering or discontinuation of opioids (e.g., to manage withdrawal symptoms, minimize the risk of adverse outcomes, maximize pain management with non-opioid pharmacologic and non-pharmacologic analgesic modalities).[4]

    **A formal interdisciplinary program or a coordinated multidisciplinary team may include, but not be limited to, primary care, mental/behavioral health, addiction medicine, pain medicine, pharmacy, and physical therapy services.*

3. Discuss the potential risks, realistic benefits, common adverse effects, and alternatives to opioids, and document the discussion in the medical record. For chronic opioid therapy, a signed written treatment agreement (see: American Academy of Pain Medicine, NIDA, Boston Medical Centre Agreement Form) is helpful to set expectations and obligations of the patient and the prescriber.[2,4,7,9,11]

    a. Establish realistic and measurable treatment goals for pain and function that are important to the patient. Emphasize that functional improvement is a primary goal and that function can improve even when pain is still present.[4]

    b. Establish that you will regularly assess progress and will use a combination of pain reduction and functional improvement criteria in deciding whether to continue, modify or discontinue opioids.[4]

    c. Outline the plan to monitor benefits, adverse effects, and harm including aberrant opioid use behavior (e.g., misuse, obtaining opioids from multiple providers, filling at multiple pharmacies, diversion).[4]

    d. Educate patients and caregivers about secure storage, protection from theft, and safe disposal of opioids and other controlled medications, and about safe use (e.g., don't use

more than prescribed, don't use with alcohol or other substances, don't share with others).[4]

4. Opioid initiation: Prescribe an immediate-release formulation at the lowest effective dose, for the shortest expected duration for patients with pain severe enough to require opioid analgesics when alternative non-opioid treatment options have not been or are not expected to be tolerated or adequate to manage pain.[4,12]

    a. For acute pain conditions not related to surgery or trauma, three days or less will often suffice; more than seven days will rarely be needed.[4]

    b. Before considering opioids to manage chronic non-cancer pain:
        i. Stabilize individuals with an active, unstable mental health disorder, uncontrolled suicide risk, or untreated substance use disorder. Consult or co-manage with or refer to a specialist in addiction medicine or behavioral/mental health or refer to an interdisciplinary program.[4,6,7]
        ii. For patients with a history of a psychiatric disorder or suicide attempt, consider consulting or co-management with or referral to a specialist in behavioral/mental health.[4]

5. Opioid formulation: When prescribing opioid analgesics start with an immediate-release opioid.[4] Extended-release/long-acting (ER/LA) opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment when alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (ER/LA information- FDA)

    a. Do not prescribe extended-release or long-acting (ER/LA) analgesics for acute pain or "as needed" for breakthrough pain.[4] Certain ER/LA opioid products, strengths, or daily doses are approved for use only in adults who are considered opioid-tolerant (e.g., *any* strength of transdermal fentanyl or hydromorphone ER).[4]
        i. Adults are considered opioid-tolerant if they are receiving a total daily opioid dose equivalent to at least 60 mg of oral morphine (60 MME/day) for one week or longer.[13] 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
        ii. Tolerance to an opioid's respiratory depressant effects (and thus the risk of an overdose) is slower to develop and less, or never complete compared with tolerance to its analgesic or euphoric effects.[14,15]

    b. Warn patients to swallow extended-release or controlled-release tablets or capsules whole, one tablet at a time, with sufficient water to ensure that they are swallowed completely and without choking. Crushing, chewing, breaking, cutting, or dissolving an ER/LA opioid product to disable its time-release mechanism before ingesting, snorting,

or injecting its contents may result in rapid release and absorption of a potentially fatal dose of opioid.[13]

6. Opioid dosage: There is no completely safe opioid dose. The risks of overdose and other serious harms increase as opioid dosage increases.[2,4,16] (see **"Prescribing Opioids for Patients with Dosage ≥100 MME/Day"** module)

    a. Dosage increases should be by the smallest practical increment based on the product's available dosage formulations.[4]

    b. Carefully reassess the evidence of individual benefits and risks if considering dosage escalation to 50 MME/day or more.[4]

    c. Primary care clinicians should avoid escalating the total opioid dosage to manage chronic non-cancer pain to 90 MME/day or more, or carefully justify a decision to titrate dosage document the rationale for increasing beyond this level. The rationale should be based upon individualized clinical assessment of benefits (pain and function) and risks.[4,6,7]
        i. Interindividual variability in the effectiveness and toxicity of a given opioid dose are also due to differences in important patient-specific characteristics such as age, body surface area, co-occurring organ dysfunction (liver, kidney, lung) or mental health disorders, levels of tolerance to the opioid's respiratory depressant and analgesic effects, pharmacogenetics (cytochrome P450 drug-metabolizing enzymes), and drug-drug interactions.[17]
        ii. Avoid unnecessary opioid dose escalations. If a previously stable patient reports loss of analgesic effectiveness, evaluate for potential causes such as drug interactions, change in the underlying chronic pain condition or health status, a new painful condition, non-adherence, diversion, opioid use disorder, or opioid induced hyperalgesia. If no explanation is found and the pain remains inadequately controlled on the current regimen, consider rotation to a different route of administration (e.g., oral to transdermal), formulation (e.g., immediate-release to ER/LA), or opioid active ingredient rather than increasing the dose (MME/day).[18]

    d. For patients already on high dosage (e.g., above 90 MME/day), primary care clinicians should consider other modalities to manage pain and, in most cases, consult with a pain medicine or other specialist about the need for a high opioid dose. Tapering opioids to a lower dosage is likely to reduce opioid-related risks, but tapering decisions should be based upon individualized clinical assessment of benefits (pain and function) and risks.[4]

    e. These total daily dosage thresholds are based on overdose risk when opioids are prescribed for pain and should *not* guide dosing of medication-assisted treatment for opioid use disorder with methadone or buprenorphine.[19] (see: CDC Daily Opioid Dose Calculator)

7. Switching, converting, or rotating from one opioid to another: Select a safe and reasonably effective starting dose for the new opioid. Use conservative dosing to avoid unintentional overdose of the new opioid due to incomplete cross-tolerance and individual variability in pharmacokinetics between the two opioids.[2,17,20]

    a. First, calculate the approximate equianalgesic dose of the new opioid based on an equianalgesic table. (see 'Opioid MME dose calculators' in 'Additional Resources')

    b. Identify an ''automatic dose reduction window'' lower than the calculated equianalgesic dose.
        i. If switching to methadone, identify this window at 75% to 90% lower than the calculated equianalgesic dose. Use extreme caution when converting to methadone because of its unique pharmacokinetics and large and unpredictable inter-individual variability. Consider consulting a pain medicine specialist if the current total opioid dose is very high (e.g., exceeds 1000 MME/day) or if the provider is not experienced in prescribing methadone.

        ii. If switching to transdermal fentanyl, calculate dose conversions based on the equianalgesic dose ratios included in the full prescribing information for these products. Use particular caution with dose conversions involving fentanyl because it is dosed in mcg/hr instead of mg/day, and its absorption is affected by heat and other factors.[4]

        iii. If switching to any other opioid, identify this window at 25% to 50% lower than the calculated equianalgesic dose.[5,6] Select a dose closer to 50% reduction if the patient is receiving a relatively high dose of the current opioid regimen or is elderly or medically frail.[18] Select a dose closer to 25% reduction if the patient lacks these characteristics or is changing the route of administration of the same opioid active ingredient.[18]

    c. Assess the patient's pain severity and other medical and psychosocial characteristics to determine whether an additional dose increase or decrease of 15% to 30% would enhance the likelihood that the initial dose will be effective for pain, or conversely, less likely to cause withdrawal or opioid-related adverse effects.

    d. Frequently assess the initial clinical response. Slowly titrate the dose of the new opioid regimen if necessary to optimize outcomes (adequate analgesia and tolerability and minimal adverse effects).[5]

        i. If an immediate-release opioid is necessary as a supplemental ''rescue dose'' for titration, begin it at 5% to 15% of the total daily dose of the new opioid and administer at an appropriate interval.

8. Dangerous combinations: Avoid prescribing opioids concurrently with other medications or substances that are central nervous system (CNS) depressants. 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 or contraindicated.[2,4,6,21]

a. Examples of CNS depressants include benzodiazepines, non-benzodiazepine sedatives/hypnotics (e.g., zolpidem, zaleplon, zopiclone, eszopiclone), and others such as alcohol, barbiturates, muscle relaxants, general anesthetics, and certain antipsychotics, antidepressants and anticonvulsants (e.g., gabapentinoids).

FOLLOW UP

1. Opioid duration: Continue an opioid only if there is clinically meaningful improvement in pain and function without serious adverse effects or risks as assessed by validated tools.[2,4]

    a. Clinically meaningful improvement for chronic pain conditions is typically defined as an improvement of 30% or more from baseline in the PEG scale or in other pain and function scores, and/or an improvement in patient's abilities to perform activities of daily living or fulfill social roles.[4]

    b. Evidence supporting the long-term use of opioids (longer than one year) for pain and function is lacking. In contrast, evidence supports dose-dependent risk for serious harms (opioid overdose and misuse, fractures, myocardial infarction, motor vehicle injury, and markers of sexual dysfunction)[4,16]
        i. Monitor patients with elevated risk of adverse effects more frequently.[7]

2. Reassess the patient at each visit where an opioid is prescribed (see 'ASSESSMENT' steps 2, 3, and 4). The risk for overdose is greatest during the first 3 to 7 days after starting an opioid or increasing its dosage.[4]

    a. For acute pain: Follow up within 3 to 5 days of starting opioids. Determine whether dose adjustment or continuation of opioids is appropriate.[7]

    b. For chronic pain: Follow up within 1 to 4 weeks of starting opioids or escalating dose and at least every 3 months during ongoing therapy.[4]

3. Conduct periodic urine drug testing (UDT) during ongoing opioid treatment to monitor therapeutic adherence by the presence of prescribed controlled medications and to detect undisclosed use of non-prescribed controlled medications or illicit drugs.[1,2,4] Evidence of or concern about misuse or diversion of controlled medication or use of an illicit substance use can help determine whether opioids can be discontinued without causing withdrawal.[4] Oral fluid (saliva) also may be used as a matrix for drug testing.

    a. In most cases, a screening (immunoassay) UDT is the appropriate test. Be familiar with the limitations of the tests that you use, including false positives and false negatives, and consult the lab with questions.[4]

b. Confirmatory testing, such as with gas chromatography/mass spectrometry can be useful and is more sensitive and specific. It may be the only available test for certain opioids such as tramadol, tapentadol, and fentanyl.[4]

4. Consider prescribing take-home naloxone to opioid-treated patients to reverse life-threatening respiratory depression if an overdose occurs.[1,4]

    a. Naloxone is most important for opioid-treated patients who are at highest risk for overdose, including those on higher opioid dosages (≥50 MME/day), concurrently using other CNS depressants (such as benzodiazepines, sedatives/hypnotics, or alcohol), with a history of opioid overdose or a substance use disorder, or with signs of opioid use disorder.[1,4]

    b. However, naloxone may be offered to all patients treated with opioids and should be considered when other factors that increase the risk for overdose are present, such as co-occurring mental health disorders; renal, hepatic, or cognitive impairment; heart failure; chronic pulmonary disease or sleep-disordered breathing / sleep apnea; and patients at risk for returning to a high dose to which they are no longer tolerant. For example, patients recently released from a correctional facility or recently completing medically supervised withdrawal (detoxification).[22,23]
        i. Warn patients who have recently discontinued opioid treatment or who are tapering treatment that tolerance to their prior dose may be lost in as little as a week.[4,7]

    c. If naloxone is prescribed, confirm that the patient has filled the prescription.[24]

    d. Educate the patient, family/household members, and caregivers about signs and symptoms of opioid overdose as most fatal overdoses are witnessed by a family member. Train them to properly use naloxone if an opioid-related overdose is suspected.[1,4]

5. Reduce, taper or discontinue opioids if the risks for harm outweigh potential benefits, such as if opioid dosage is high or the patient has a history of overdose or a substance use disorder and improvement in pain or function is small or absent.[4,7]

    a. Optimize non-opioid pharmacologic and non-pharmacologic analgesic modalities and psychosocial support when tapering or discontinuing opioid therapy.[4]

    b. During an opioid taper monitor closely for emergent manifestations of anxiety, depression, suicidality, other underlying mental health disorder, or unmasked opioid use disorder.[4]

    c. Evaluate and consider OUD treatment (methadone or buprenorphine) for all patients with suspected OUD that emerges during opioid tapering.[4] Methadone to treat OUD may be dispensed only by a certified opioid treatment program. However, buprenorphine to treat OUD may be prescribed by trained and certified health care

professionals in most office-based settings after obtaining a waiver from the DEA.[4] (see **"SUD"** and **"Methadone"** modules)

d. Consult with or refer to a structured multidisciplinary program those patients who experience serious challenges in tapering.[4]

Additional Resources

The information presented in this module highlights some fundamental concepts of opioid prescribing for adult outpatients. 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.

- FDA-approved drug label information:
  - FDA Online Label Repository
  - Daily Med (NIH/National Library of Medicine)
  - FDA Required Safety Labeling Language for Immediate-Release Opioids (March 22, 2016)
- Pain Management, Opioid, and Addiction Science Resources. National Institute on Drug Abuse (NIDA)
- Providers Clinical Support System for Opioid Therapies.
- Find Your State's PDMP and Use It Effectively.
- Urine Drug Testing: Decision Support
- For the Primary Care Provider: When to Refer to a Pain Specialist. (American Association of Pain Medicine) 2016
- SCOPE of Pain- Safe and Competent Opioid Prescribing Education (Boston University)
- Safe storage and disposal of opioids and all medications. American Medical Society
- Finding complementary and alternative therapy practitioners. SAMHSA TIP 54 (Appendix D)
- Tapering template. RxFiles Academic Detailing, Saskatoon City Hospital, SK, Canada.
- Opioid Milligram Morphine Equivalent (MME) Calculators (to estimate an equianalgesic dose)
  - New York City Department of Health (online interactive and mobile app)
  - Washington State Agency Medical Directors' Group (online interactive and mobile app)
  - CDC Factsheet: Calculating total daily dose of opioids for safer dosage (manual calculator and mobile app)

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