# *Opioids and their Role in the Management of Chronic Non-Cancer Pain (CNCP): Initiating Short-Acting Opioids (SAOs)*

**Key Message 2:**

- **Patients with CNCP who continue to experience moderate-to-severe pain despite an adequate trial of non-pharmacologic and non-opioid therapies should be evaluated to determine if a SHORT-TERM trial of an SAO is appropriate.**
- **Prescriptions for a trial of an SAO should be written for the shortest time possible*; 7-day trial per New York State Public Health Law Section 3331, 5. (b), (c).***
- **Patients initiated on opioids should be re-evaluated every 1-4 weeks.**

**Patients started on opioid therapy for CNCP will not achieve total pain relief; studies suggest that pain improvement averages less than 2-3 points on a 0-10 point scale.[1-3]**

**Prior to initiating an SAO, all patients MUST undergo a comprehensive evaluation that includes an assessment of baseline pain severity and any history of substance use or psychiatric disorders.[1-7]**

**Selected Tools for Risk Assessment:[8-12]**

- **Opioid Risk Tool (ORT)**:
  - Screens for aberrant behaviors when patients are prescribed opioids for CNCP
- **Cut down, Annoyed, Guilty, Eye Opener – Questions Adapted to Include Drugs (CAGE-AID):**
  - 4-question survey which screens for alcohol and/or drug dependence
- **Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R):**
  - 24-question assessment tool predicts possible opioid abuse in chronic pain patients
  - Determines amount of monitoring required for each patient
- **Diagnosis, Intractability, Risk, Efficacy (DIRE) Tool**:
  - Assesses the risk of opioid abuse
  - Determines patient suitability for long-term opioid therapy
- **Baseline urine drug testing (UDT) –** 2 types are currently available:
  - Immunoassay - based in a lab or office (point-of-care test):
    - Most common UDT used
    - Detects presence or absence of a drug or drug class according to a predetermined threshold
    - *Important to obtain a list of the drugs/drug classes detected by the immunoassay. It may be helpful to add additional screening tests for benzodiazepines and semi-synthetic or synthetic opioids*
  - High performance chromatography/mass spectrometry - available only through a laboratory (confirmatory drug test or as initial definitive drug test):
    - Typically, only used if verification or identification of a specific drug and/or metabolite(s) is needed

**For patients with CNCP, the decision to initiate opioid therapy must be carefully evaluated.[1-7] Individuals with a history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors should be referred to a mental health professional or other specialist prior to opioid initiation.**

**After Completion of a Complete Baseline Risk Assessment:**

- Discuss and sign a **Patient-Prescriber Controlled Substance Agreement prior to initiating therapy.**[1-7] The purpose is to provide clear descriptions of expectations regarding medication use and abuse, as well as the consequences for violating the agreement. The agreement should:
  - Identify that there should be only 1 prescriber and 1 designated pharmacy.
  - Establish treatment goals regarding improvement of pain.
  - Describe monitoring parameters (e.g., UDTs).
  - Outline that no early refills will be allowed and if medications are lost or stolen, a police report will be required for additional prescriptions.
- Examples of controlled substance agreements are available at https://www.drugabuse.gov/.

## CDC Checklist for Prescribing Opioids for Chronic Pain:[13]

- ☐ Set realistic goals for pain and improvement of function.
- ☐ Ensure non-opioid therapies have been tried and optimized.
- ☐ Discuss benefits and risks of opioid use with patient.
- ☐ Evaluate risks of harm or misuse.
- ☐ Set criteria for stopping or continuing opioids.
- ☐ Assess baseline pain and function.
- ☐ Check prescription monitoring program (PMP) (New York State [NYS] **Internet System for Tracking Over-Prescribing [I-STOP]).**[14]
- ☐ Schedule initial reassessment within 1-4 weeks.
- ☐ Prescribe SAOs using the lowest dosage: match duration to scheduled reassessment.
- ☐ If renewing without patient visit:
  - Check that return visit is scheduled within 3 months from the last visit.
- ☐ When reassessing at return visit:
  - Assess pain and function.
  - Evaluate risks for harm or misuse. If there are signs of over-sedation or overdose risk, taper dose.
  - Check that non-opioid therapies are optimized.
  - Determine whether to continue, adjust, taper, or stop opioids.
  - Calculate opioid dosage in morphine milligram equivalents.
  - Schedule reassessment at regular (≤3 month) intervals.

## Opioid Pharmacologic Overview:

- Opioid receptors are located within the central nervous system (CNS) and throughout the peripheral tissues.[15] The 4 opioid receptors are mu, kappa, delta and sigma. Opioid activity depends on the affinity for opiate receptors and other mechanisms.
- The Food and Drug Administration (FDA) requires all opioid product labels to contain boxed warnings related to:[16]
    - The risks of addiction, abuse, and misuse which can lead to overdose and death.
    - A patient's risk should be assessed before prescribing and the patient should be monitored for development of addictive behavior.
    - Serious, life-threatening or fatal respiratory depression can occur.
    - Accidental ingestion, especially in children, can result in fatal overdose.
    - Prolonged use of opioids during pregnancy can result in neonatal abstinence (opioid withdrawal) syndrome.
    - Combined use with benzodiazepines increases the risk of respiratory depression and death.
- The FDA has approved risk evaluation and mitigation strategies (REMS) for extended-release and long-acting opioids (LAOs). The REMS are continually updated and available at REMS@FDA (https://www.accessdata.fda.gov/scripts/cder/rems/).[16]

**Table 1: Opioid Classification Based on Receptor Activity.[15]**

| Type | Opioids | Clinical Considerations |
|---|---|---|
| **Pure Agonists** | Codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, methadone, oxycodone, oxymorphone, propoxyphene (no longer commercially available) | High binding affinity and high efficacy at the mu receptor<br>No dosage ceiling effect |
| **Partial Agonists** | Buprenorphine | High binding affinity but low efficacy at the mu receptor<br>Ceiling effect for analgesia<br>Beneficial in abuse deterrence and detoxification |
| **Mixed Agonist-Antagonists** | Butorphanol, nalbuphine, pentazocine | High affinity but low efficacy at the mu receptor, yet also have partial kappa agonist activity<br>Partial agonist activity at the kappa receptor |
| **Pure Antagonists** | Naloxone, naltrexone, methlynaltrexone | Antagonists at mu, kappa, and delta receptors<br>High binding affinity to mu receptor with NO efficacy<br>Beneficial in abuse deterrence and detoxification |
| **Other** | Tramadol, tapentadol | Weak agonists at the mu receptor; also inhibit reuptake of norepinephrine and serotonin |

**Pure opioid agonists have no ceiling effect for analgesia.[15] In theory, as the dose is increased, analgesic effects also increase; the degree of analgesia induced is LIMITED ONLY by intolerable dose-related adverse side effects.**

**Table 2A: Special Considerations for SAOs.[15]**

| Opioids | Special Considerations |
|---|---|
| **SHORT-ACTING OPIOIDS** | |
| **Codeine (alone or in combo with APAP)** | Codeine alone is a weak analgesic; more effective in combo with APAP. |
| **Hydrocodone (in combo with APAP/IBU)** | Metabolized to active metabolite hydromorphone. |
| **Hydromorphone** | May require dose adjustment in renal and hepatic impairment. |
| **Morphine** | Active metabolite, M6G, may accumulate in renal impairment. |
| **Oxycodone (alone or in combo with APAP)** | Use conservative dose initiation in renal and hepatic impairment. |
| **Oxymorphone** | Take on an empty stomach at least 1h before or 2h after a meal. DO NOT take with alcohol - can have highly variable effects on peak drug levels. |
| **Tapentadol** | Caution in patients on serotonergic agents. If used in combo with other CNS depressants, reduce dose of 1 or both agents. |
| **Tramadol (alone or in combo with APAP)** | Slower initiation and titration improve tolerability.<br>Use another therapy in patients on serotonergic agents. |

**Table 2B: Special Considerations for LAOs.[15]**

| Opioids | Special Considerations |
|---|---|
| **LONG-ACTING OPIOIDS** | |
| **Fentanyl transdermal system*** | Option in patients with persistent, moderate to severe pain who cannot take oral therapies. |
| **Methadone** | Recommended only for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses, within recommended doses. May prolong QTc interval. |
| **Morphine CR/SR/ER** | Refer to the FDA-approved product label for information for conversion from IR morphine products to CR/SR/ER formulations. |
| **Oxycodone CR** | Initiate at one-third to one-half the usual recommended dose in hepatic impairment and with concomitant use of CNS depressants.<br>Patients receiving oxycodone CR tablets and CYP3A4 inhibitors should be carefully monitored for an extended period of time, and dose adjustment should be made if warranted. |
| **Oxymorphone ER** | Take on an empty stomach at least 1h before or 2h after a meal. DO NOT take with alcohol - can have highly variable effects on peak drug levels. |
| **Tapentadol ER** | Use with caution in patients with a history of seizures. Not recommended in patients with renal/hepatic impairment. Patients should avoid consumption of alcoholic beverages. |
| **Tramadol ER** | Use with caution in patients with a history of seizures. The concomitant use or discontinuation of CYP3A4 inducers, 3A4 inhibitors or 2D6 inhibitors can affect the levels of tramadol and its active metabolite; monitoring is required. |

*Note oral transmucosal fentanyl citrate (OTFC) products are FDA-approved for treatment of cancer pain ONLY (e.g., Abstral®, Actiq®, Fentora®, Lazanda®)

APAP=acetaminophen; CNS=central nervous system; CR=controlled release; CYP=cytochrome P450; ER=extended release; FDA=Food and Drug Administration; h=hours; IBU=ibuprofen; IR=immediate release; M6G=morphine-6-glucuronide; SR=sustained release

**OPIOID SIDE EFFECTS[15]**

Constipation, drowsiness, nausea, pruritus, dizziness, tiredness, dry mouth, sweating, hyperalgesia, sexual dysfunction, sedation, and confusion

**Tips for managing side effects:**

- Nausea and constipation can be minimized by the use of antiemetic and bowel regimens.
- Many adverse effects spontaneously resolve with continued administration and development of tolerance.
    - EXCEPTION is constipation; prophylactic initiation and maintenance of a bowel regimen to prevent constipation is strongly recommended.
- SLOW titration and use of LOW doses can help to minimize side effects.

| Guidelines | Recommendations for the Use of Opioids in CNCP |
|---|---|
| **VA/DoD 2017[6]** | Opioid therapy should be initiated at a low dose and may be increased until limited by adverse effects or clear evidence of lack of efficacy. If a high dose (greater than 200 MME per day) provides no further improvement in function, consider consultation rather than further dose increases. |
| **ASIPP 2017[3]** | Goal of opioid therapy: use lowest possible dose and short-acting agents to provide adequate analgesia with minimal side effects. Initiate with short-acting drugs and use appropriate monitoring. Consider up to 40 MME as low dose, 41 to 90 MME as a moderate dose, and ≥91 MME as high dose. |
| **CDC 2016[2]** | When deciding on an opioid dosing strategy, it is important to administer low doses and titrate slowly using an IR formulation. Reassess the individual's benefits and risks when considering increasing the dose to >50 MME per day and avoid increasing dosage to >90 MME per day. Monitor patients for improvement in pain and function. |
| **WA State AMDG 2015[4]** | Choice of opioid should *not* exceed more than 120 per day MME without first obtaining a consultation from a pain management expert. Providers must routinely monitor and document sustained improvement in function and quality of life. |
| **ACOEM 2014[7]** | Opioid use is only indicated if other evidence-based approaches have been used with inadequate improvement in function. Opioid prescriptions should be patient-specific. A maximum daily oral dose of 50 MME is recommended based on risk of overdose/death. |
| **ICSI 2013[5]** | Opioid doses should be titrated until there is adequate pain relief, but generally should not exceed doses of 100 MME per day. |
| **APS 2009[1]** | Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. |
| **WHO 1990[17]** | Recommends a weak opioid if non-opioid/adjuvant therapy fails. Stronger potency opioids are reserved for patients who continue to experience moderate to severe pain. |
| **SUMMARY**<br>**There is a clear consensus across all current CNCP guidelines that, although there is no preference for 1 opioid over another, the opioid of choice should be: (i) patient-specific; (ii) started at a low dose; and (iii) gradually titrated until satisfactory improvement of pain is observed. Caution is advised once the average daily dose >90 MME.** | |

APS=American Pain Society; ACOEM=American College of Occupational and Environmental Medicine; AMDG=Agency Medical Directors' Group; ASIPP=American Society of the Interventional Pain Physicians; CDC=Centers for Disease Control and Prevention; CNCP=chronic non-cancer pain; ICSI=Institute for Clinical Systems Improvement; IR=immediate release; MME=morphine milligram equivalents dose; VA/DoD=Dept. of Veterans Affairs and Dept. of Defense; WA=Washington; WHO=World Health Organization.

# NYS Legislation:

**TO FURTHER REDUCE OVERPRESCRIBING OF OPIOID MEDICATIONS, EFFECTIVE JULY 22, 2016, INITIAL OPIOID PRESCRIBING FOR ACUTE PAIN IS LIMITED TO A 7-DAY SUPPLY PER NYS PUBLIC HEALTH LAW SECTION 3331, 5. (b), (c).** A practitioner may not initially prescribe more than a 7-day supply of an opioid medication for acute pain. Acute pain is defined as pain, whether resulting from disease, accidental or intentional trauma, or other cause, that the practitioner reasonably expects to last only a short period of time.

**An opioid trial should:**[1-7]

- ☐ **Include an SAO:**
  - *SAOs are safer than LAOs for initial therapy, since they have a shorter half-life and may be associated with a lower risk of inadvertent overdose.*
  - *The opioid selected should be based on each patient's specific needs.*
- ☐ **Start at the lowest possible dose.**
- ☐ **Start with 1 medication at a time.**
- ☐ **Be of short duration (limit quantity, e.g., 7-day supply per NYS Public Health Law Section 3331, 5. (b), (c); with follow-up required).**

**Patient Reassessment:**[1-7]

**Once opioid therapy is initiated, patients should be reassessed within 1-4 weeks to determine if therapy is effective. At each of these assessments, the "4 A's" should be monitored.**

- **ANALGESIA: Has the patient's pain severity decreased?**
- **ACTIVITY: Has there been improvement in the patient's daily functionality?**
- **ABERRANT BEHAVIOR: Has the patient requested early refills or used all medication before a refill is due? Is a random urine test necessary? Has an I-STOP review been conducted?**
- **ADVERSE EFFECTS: Is the patient experiencing constipation, dizziness, tiredness, etc.? Does the patient avoid taking medication at the prescribed time due to side effects?**
  - **If the patient's opioid dose is increased, the patient should also be reassessed with 1-4 weeks.**
  - **For patients who continue therapy, the prescriber should evaluate the benefits and harms every 3 months, or more frequently.**

**Screening Tool For Patient Reassessment for Opioid Use Disorder:[18]**

- **Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Criteria for the Diagnosis of Opioid Use Disorder:** 11-question assessment tool that identifies patients with symptoms of opioid use disorder, which can also be used for reassessment.

**The NYS Office of Alcoholism and Substance Abuse Services (OASAS) operates a toll-free, anonymous and confidential service that offers help to patients with alcoholism, drug abuse, and problem gambling. The HOPELINE contact number is 1-877-8-HOPE-NY or text HOPENY.**

**If the current opioid therapy is not providing satisfactory pain reduction and adherence has been confirmed, the patient should be assessed to determine which of the following is most appropriate:[1-7]**

- ☐ **DOSAGE TITRATION**: dose should be SLOWLY increased to minimize toxicity and to find the lowest effective dose that achieves a satisfactory balance between benefits and harm.
- ☐ **OPIOID SWITCH/ROTATION:** switching to a different opioid may help to improve efficacy, reduce side effects, and reduce dose escalation in patients with intolerable adverse side effects or inadequate benefit despite dose increases.
- ☐ **ADDITION OR OPTIMIZATION OF NON-OPIOID/ADJUNCT AGENT(S):** the addition or dosage increase of a non-opioid/adjunctive agent can help to manage pain through a multimodal approach and allows for potential decrease in current opioid dose.
- ☐ **DISCONTINUATION OF OPIOID:** is the patient experiencing intolerable adverse effects, is non-adherence or aberrant behavior suspected, is there a lack of effectiveness of current opioid to meet treatment goals, or is there a desire from the patient to discontinue therapy?

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