Exploring the Use of Chronic Opioid Therapy for Chronic Pain: When, How, and for Whom?

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KEYWORDS

• Chronic opioid therapy • Chronic noncancer pain • Pain management
• Opioid risk management • Opioid induced respiratory depression

KEY POINTS

- Chronic opioid therapy (COT) for the treatment of chronic noncancer pain (CNCP) should be individualized based on a comprehensive evaluation and assessment.
- COT should be initiated on a trial basis; phases of the trial include initiation, titration, and maintenance.
- Prescribers of COT must ensure that appropriate monitoring (eg, urine drug tests, prescription drug monitoring programs) and follow-up is done at regular intervals.
- COT, if deemed appropriate, is just one piece of a complete treatment plan for patients with CNCP.

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INTRODUCTION

Prescribed chronic opioid therapy (COT) has dramatically increased over the past decade with resultant startling increased mortality.[1] No doubt, a large portion of associated morbidity and mortality arise from inadequate education, lack of specialty providers, and ineffective support systems for excellent opioid pharmacotherapeutic management. Nevertheless, at the expense of legitimate patient access, media sensationalism has run amok collaterally with various political agendas[2,3] irrespective of potential harm to patients requiring opioids.[4,5]

A 2014 Agency for Healthcare Research and Quality report identified 16,917 fatal prescription opioid overdoses occurred in 2011.[6] Risks increase with higher daily opioid doses, concomitant benzodiazepine or sedative hypnotics, and in patients with mental health comorbidities. Patients receiving 100 or more morphine equivalents per day (MED) are at a 9-fold higher risk for opioid overdose. Moreover, the combination of prescription opioids and benzodiazepines is the most common cause of polysubstance overdose deaths nationwide.[7–10] Nevertheless, correlation of MED to opioid risk should be interpreted carefully because there are no universally accepted morphine equivalents.[11] Long-term efficacy data related to functional improvement on COT has come under great scrutiny with multiple review articles and position statements published in the last 12 months.[12]

INITIAL EVALUATION AND ASSESSMENT

Appropriate treatment considerations for chronic noncancer pain (CNCP) start with a comprehensive physical examination and assessment to determine which treatment modalities are most suitable.[13] Before starting any medication, it is important to obtain the patient's medical and psychiatric history and a family history, including various risk factors for substance abuse disorder, and to perform a psychosocial assessment. All of these elements are components of risk stratification that become critical in determining whether or not COT is appropriate.

Components of a comprehensive assessment are similar to those identified as the "universal precautions" in pain management related to diagnosis and treatment selection: (1) make a diagnosis with appropriate differential, (2) psychological assessment including risk of addictive disorders, and (3) periodically review pain diagnosis and comorbid conditions, including addictive disorders.[14] It is suggested to triage patients based on results and findings in the initial assessment into one of several treatment level categories: primary care patients (those with the lowest risk; no past/current history of substance abuse and absence of major mental health comorbidity), primary care patients with specialist support (moderate risk patients; may have past or remote history of substance use or significant family history but are not actively addicted), and specialty pain management (those with the highest risk; active substance abuse or addiction and/or presence of major mental health comorbidities).[14] Validated risk tools as outlined in **Tables 1** and **2** are available for assessing opioid abuse and misuse; at least one from each category should be used before initiating COT.

Pharmacologic Strategies: Opioid Trial

Before considering COT, appropriate nonopioid medications should be trialed after initial and ongoing attempts of lifestyle changes, diet and exercise, stretching, physical therapy, behavior modification, yoga, and/or other nonmedical modalities, particularly where there is supportive evidence.[15]

Opioids may be considered when a patient has moderate to severe pain that is affecting their function or quality of life, documented failure of alternative therapies,

Table 1
Comparison of risk stratification tools

Risk Tool	Indication	Question Format	Scoring	Advantages	Disadvantages
DIRE	Risk of opioid abuse and suitability of candidate for long-term opioid therapy	7 via patient interview	Numeric, simple to interpret	2 min to complete Correlates well with patient's compliance and efficacy of long-term opioids therapy	Prospective validation needed
ORT	Categorizes patients as low, medium, high risk	5	Numeric, simple to interpret	<1 min to complete Simple scoring High sensitivity and specificity for stratifying patients Validated	1 question based on patient's knowledge of family history of substance abuse
PDUQ	Assess for presence of addiction in chronic pain patients	42 items via patient interview	Numeric, simple to interpret	3 items correctly predicted addiction or no addiction in 92% of patients	20 min to administer
SOAPP-R	Primary care	24	Numeric, simple to interpret	5 min to complete Cross-validated Easy to interpret results	

Abbreviations: DIRE, Diagnosis; Intractability, Risk; Efficacy Score; ORT, opioid risk tool; PDUQ, prescription drug use questionnaire; SOAPP-R, Screener and Opioid Assessment for Patients with Pain-Revised.

Adapted from Fudin J. Opioid risk stratification tools summarized. Available at: http://paindr.com/wp-content/uploads/2012/05/Risk-stratification-tools-summarized_tables.pdf. Accessed May 5, 2015, with permission; and *Data from* Compton P, Darakjian J, Miotto K. Screening for addiction in patients with chronic pain and "problematic" substance use: evaluation of a pilot assessment tool. J Pain Symptom Manage 1998;16(6):355–63.

Table 2
Comparison of opioid misuse assessment tools

Tool	Indication	Question Format	Scoring	Advantages	Disadvantages
ABC	Ongoing assessment of patients on COT	20	≥3 indicates possible inappropriate opioid	Concise Easy to score Studied at VA	Need validation outside VA
COMM	Assess aberrant medications related behaviors in chronic pain	17	Numeric	10 min to complete Useful for adherence assessment	Unknown reliability long term
PADT	Streamline assessment of chronic pain outcomes using the 4 As	N/A	N/A	5 min to complete Documents progress Complements	Not intended to predict drug-seeking behavior or positive/negative outcomes

Abbreviations: ABC, Addiction Behaviors Checklist; COMM, Current Opioid Misuses Measure; PADT, Pain Assessment and Documentation Tool.

Adapted from Fudin J. Opioid risk stratification tools summarized. Available at: http://paindr.com/wp-content/uploads/2012/05/Risk-stratification-tools-summarized_tables.pdf. Accessed May 5, 2015; with permission.

and when the benefits of therapy are expected to outweigh the potential risks. Implementing opioids should be considered a therapeutic trial of short-term duration to determine suitability for continued use based on assessment of risks versus benefits. When discussing an opioid trial with the patient and significant others, it is important to establish realistic therapeutic goals with the patient that will help to determine whether the trial was successful. These goals should be individualized to the patient and include components of reduction in pain, improvements in functioning and/or quality of life, and minimization of side effects or risk. Opioids should be just one piece of a patient's pain management plan.[16–18]

Informed consent and opioid treatment agreements

Before COT is initiated, it is essential to obtain informed consent, which is intended to ensure that the patient has all the necessary information to make a knowledgeable and informed decision commensurate with personal goals and preferences. Acknowledgment of benefits, risks, and alternatives to opioid therapy are essential components. Common and serious risks should be reviewed carefully with the patient and caregiver.[16,18] Throughout therapy, there should be ongoing reevaluation of patient risks and benefits of therapy to ensure COT remains appropriate.[16,18] Patients should understand the differences between addiction, tolerance, and physical dependence (**Table 3**).[19]

Multiple guidelines advocate for the use of opioid treatment agreements in patients on COT. These may be implemented before initiating opioids and continually revisited throughout therapy.[16–18] Generally, opioid treatment agreements (**Box 1**) are used to foster the exchange of information, improve adherence, and develop treatment goals.[20] Opioid treatment agreements outline the responsibilities of both the patient

Table 3
Definitions of addiction, tolerance, and physical dependence

Term	Addiction
Addiction (Association 2013)	"A problematic pattern of opioid use leading to clinically significant impairment or distress."
Tolerance (VA/DoD 2010)	"A form of neuroadaptation to the effects of chronically administered opioids, which is manifested by the need for increasing or more frequent doses of the medication to achieve the initial effects of the drug."
Physical dependence (VA/DoD 2010)	"A physiologic state in which abrupt cessation of the opioid, rapid tapering, or administration of an opioid antagonist, results in a withdrawal syndrome."

Data from American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition. Washington, DC: Author; 2013; and VA/DoD. Clinical practice guidelines for management of opioid therapy for chronic pain. Available at: http://www.healthquality.va.gov/guidelines/Pain/cot/COT_312_Full-er.pdf. Accessed December 17, 2014.

and provider and the conditions for continuation or discontinuation of COT.[20] See other important practice considerations outlined in **Box 1**.

Adverse effects and risks associated with opioids

Common adverse opioid effects include constipation, nausea/vomiting, dizziness, sedation, respiratory depression, and pruritus. Tolerance often develops to these side effects in time with the exception of constipation. To mitigate opioid-induced constipation, patients are often started on prophylactic bowel regimens including a stool softener and stimulant laxative(s). More recently we have seen an introduction of

Box 1
Characteristics of an opioid treatment agreement

- Goals of therapy
- Discussion of risks and benefits
- Expectations about prescribing and taking opioids
  - Considered a trial
  - Use of one prescriber and one pharmacy
  - Avoiding abruptly stopping opioids
  - No early refills
  - No replacement of lost, stolen, or destroyed medication
  - Patients must inform providers of all medications being taken
- Avoidance of alcohol and illicit substances while on opioids
- Prohibition of sharing, selling, or providing others access to opioids
- Follow-up and monitoring parameters
  - Office visits
  - Urine drug screening[a]
  - Prescription drug monitoring programs
  - Pill counts[b]
- Reasons for continuing or discontinuing opioids
- Secure storage of medications

[a] Discussed in further detail elsewhere in this article.
[b] Pill counts are flawed because patients can borrow or rent medications from others.
Data from Refs.[16,18,20]

peripherally acting mu receptor opioid antagonists as an alternative to traditional therapies for opioid-induced constipation. Slow dose titration, opioid dose reduction, opioid rotation, extended release formulations, and symptom treatment are ways to prevent and manage opioid adverse effects.[17] To date, there are no established consensus guidelines for the treatment of opioid-induced constipation.

Despite the use of opioids with the intent to reduce pain, high-dose opioids may lead to increased pain by what some believe to be opioid-induced hyperalgesia. Recently, Eisenberg and colleagues[21] provided a comprehensive overview of opioid-induced hyperalgesia, which demonstrates limited evidence supporting opioid-induced hyperalgesia.

A major concern with opioid therapy is diminished respiration. Opioids contribute to sleep-disordered breathing. Opioid-induced respiratory depression may contribute to overdose and death. Opioid-induced respiratory depression is dose related and increased when combined with central nervous system depressants like alcohol, benzodiazepines, and/or other sedative–hypnotics such as carisoprodol.[12,16–18,22] Opioid overdose risk increases 4-fold at 50 to 100 mg (MED).[12,22]

Endocrine and immune system effects can occur with COT. By interacting with the hypothalamic–pituitary axis, opioids have been shown to decrease testosterone levels, leading to hypogonadism, sexual dysfunction, infertility, and a host of other medical anomalies associated with hypotestosteronemia.[12,16–18,22,23] Other associated morbidities include falls and fractures, neonatal abstinence syndrome, cardiovascular effects including increased risk for myocardial infarction and QT prolongation (methadone), depression, and increased motor vehicle accidents.[12,22]

Contraindications to opioids

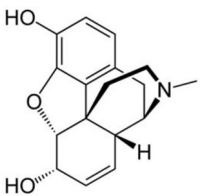
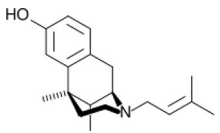
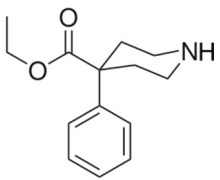
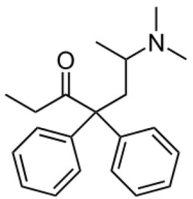
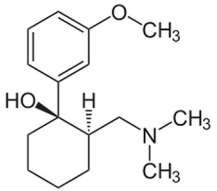
Absolute contraindications to opioid therapy are listed in **Box 2**. Opioid allergies are often incorrectly assigned and are specifically owing to histamine release, which is the most common cause of opioid-induced pruritus, but not a true allergy. Even anaphylaxis to one opioid does not preclude use of opioids from other structural classes. **Table 4** outlines the chemistries of these various agents with relative cross-sensitivities.

Box 2
Contraindications to opioids

- Respiratory instability
- Acute psychiatric instability
- Uncontrolled suicide risk
- Active, untreated alcohol or substance use disorder
- True opioid allergy
- Concomitant medications with potential to cause life-limiting drug interactions
- Prolonged QTc (≥500 ms) with methadone
- Active diversion

Data from Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2–guidance. Pain Physician 2012;15(Suppl 3):S67–116; and VA/DoD. Clinical Practice Guidelines for Management of Opioid Therapy for Chronic Pain. Available at: http://www.healthquality.va.gov/guidelines/Pain/cot/COT_312_Full-er.pdf. Accessed August 25, 2015.

Table 4
Chemical classes of opioids

Phenanthrenes	Benzomorphans	Phenylpiperidines	Diphenylheptanes	Phenylpropyl Amines
				
Morphine	Pentazocine	Meperidine	Methadone	Tramadol
Buprenorphine[a]	Diphenoxylate	Alfentanil	Methadone	Tapentadol
Butorphanol[a]	Loperamide	Fentanyl	Propoxyphene	Tramadol
Codiene	Pentazocine	Meperidine		
Heroin (diacetyl-morphine)		Remifentanil		
Hydrocodone[a]		Sufentanil		
Hydromorphone[a]				
Levorphanol[a]				
Morphine				
Nalbuphine				
Naloxone[a]				
Oxycodone[a]				
Oxymorphone[a]				
Cross-sensitivity risk				
Probable	Possible	Low risk	Low risk	Low risk

[a] Agents lacking the 6-OH group of morphine, possibly decreases cross-sensitivity within the phenanthrene group.
Adapted from Fudin J. Chemical classes of opioids. Available at: http://paindr.com/wp-content/uploads/2012/05/Opioid-Chemistry-09-2011.pdf. Accessed May 5, 2015; with permission.

Codeine is contraindicated for use in pediatric patients undergoing tonsillectomy or adenoidectomy. A Black Box Warning has been issued for this indication owing to potential mortality among pediatric patients, including nursing infants. Several deaths occurred in children who were found to be ultrarapid metabolizers of the CYP2D6 enzyme, which is the enzyme that converts codeine into morphine.[24]

TREATMENT INITIATION, TITRATION, AND MAINTENANCE

Initiation

An opioid trial consists of initiation, titration, and maintenance phases.[17] The initial selection of an opioid medication and dose is patient individualized. For opioid-naïve patients, low doses should be initiated to ensure safety and tolerability. Patient preference, health status, dosing schedule, route of administration, patient's prior experience, and tolerance level (**Box 3**) should be considered.[25,26] Most guidelines prefer long-acting opioids in chronic pain for more consistent pain relief and uninterrupted sleep, adherence, and a possible lesser risk of addiction or abuse; however, this is not evidence based.[18]

Titration

The titration phase involves gradual dose increases to achieve the lowest effective dose that meets patient goals. Caution must be exercised to slowly titrate doses, because rapid escalation may lead to unintentional overdose. Opioid doses should not be adjusted until steady state has been reached, which is typically 5 half-lives (**Table 5**). During this phase, patients should be monitored closely with follow-up every 2 to 4 weeks until stable.[17]

Breakthrough Pain

Breakthrough pain is defined as a period of increased pain in patients with cancer-related pain with otherwise stable well-controlled pain; however, many have expanded the concept to include non–cancer-related pain. Different types of breakthrough pain include spontaneous, incidental, and end-of-dose failure.[27] Ultimately, the use of breakthrough pain medications should be minimized in chronic pain patients through titration of the baseline opioid dose or use of adjunctive agents.[17] A reasonable dose for breakthrough pain medication is 10% to 15% of the total daily opioid dose.[27]

Box 3
Criteria for opioid tolerance

Patients receiving opioids on a daily basis for at least 1 week of

- 60 mg oral morphine/d
- 25 μg transdermal fentanyl/h
- 30 mg oral oxycodone/d
- 8 mg oral hydromorphone/d
- 25 mg oral oxymorphone/d
- Or an equianalgesic dose of any other opioid combination

From FDA. FDA blueprint for prescriber education for extended release and long-acting opioid analgesics. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf. Accessed August 24, 2015.

Table 5
Comparison of extended-release (ER) opioid analgesics (or immediate release with *$T_{1/2}$>12 h)

Opioid	Brand	Extended-Release Technology	FDA-Approved Abuse Deterrent Technology	Initial Dose	Opioid Tolerant Only Doses/Dosage Forms	Half-life (h)
Buprenorphine[a]	Butrans	Matrix	No	5 μg/h patch Q7days	≥5 μg/h patch	26
Fentanyl	Duragesic	Matrix	No	12 μg/h patch Q72H	≥25 μg/h patch	20–27 after removal
Hydrocodone	Hysingla ER	Film-coated	Yes	20 mg PO Q24H	Single dose ≥80 mg daily dose	7–9
	Zohydro ER	Beadtek	Yes (not yet available)	10 mg PO Q12H	Single dose ≥40 mg or ≥80 mg daily dose	8
Hydromorphone	Exalgo	OROS	Yes	8 mg PO Q24H	All tablets	10–11
Levorphanol*	—	—	—	2 mg PO Q8H	—	11–16
Methadone*	Dolophine	—	—	5 mg PO Q8H	—	8–60
Morphine	Avinza	SODAS	No	30 mg PO Q24H	90, 120 mg capsules	24
	Embeda	Pellets	Yes	30 mg PO Q24H	100/4 mg capsules	29
	Kadian	Polymer-coated pellets	No	10 mg PO Q24H	100, 130, 150, 200 mg capsules	11–13
	MS Contin	Film coated	No	15 mg PO Q12H	100, 200 mg tablets	Not listed
Oxycodone	Oxycontin	Film coated	Yes	10 mg PO Q12H	Single dose ≥40 mg or ≥80 mg daily dose	4.5
	Targiniq ER	Film coated	No	10 mg/5 mg PO Q12H	Single dose ≥40/20 mg or ≥80/40 mg daily dose	3.9–5.3
	Xartemis XR	PolyOx	No	(2) 7.5–325 mg PO Q12H	None	4.5
Oxymorphone	Opana ER	INTAC	No	5 mg PO Q12H	None	9.4–11.3
Tapentadol[b]	Nucynta ER	Film-coated	No	50 mg PO Q12H	None	5

Abbreviation: FDA, US Food and Drug Administration.
[a] Buprenorphine is a partial mu opioid agonist, kappa-opioid antagonist, delta-opioid receptor agonist, and a partial ORL-1 (nociceptin) agonist.
[b] Tapentadol is a centrally-acting synthetic analgesic with mu-opioid receptor agonist and norepinephrine reuptake inhibitor activity.
Data from Refs.[57–72]

Opioid Rotation

When patients fail to achieve analgesic and functional benefits with escalating doses of opioids, the potential cause for this must be evaluated, for example, adherence, drug–drug interactions, polymorphism, or worsening of the condition. If there is no identifiable reason, rotation to another opioid may be considered.[16–18] Opioid rotation can be defined as a therapeutic strategy that involves switching from 1 opioid to another in an effort to improve patient outcomes. Opioid rotations may be within the same opioid chemical class or between opioid chemical classes. Opioid alternatives could be considered in the cases of poor tolerability owing to side effects. Other considerations for opioid rotation include changes in patient status (consider buprenorphine transdermal once weekly), as well as availability, cost, and patient preference. Conversion tables are available but are not standardized. These tables list the doses of different opioids that presumably result in similar analgesic benefits. **Table 6** provides one example.[27]

Frequently, a 25% to 50% decrease in dose is used in opioid rotations to account for incomplete cross-tolerance.[16–18] Conversions may be completed via 2 strategies: stepwise or single step. In single-step rotations, the previous opioid is discontinued and the new opioid is initiated. When switching between large doses of opioids, the authors recommend a stepwise conversion be used. This involves reducing the initial opioid MED by 25% to 50% and converting that to an equianalgesic dose of an alternate opioid.[17]

Equianalgesic charts are subject to several flaws. Limited equianalgesic dosing data are available from the chronic pain population. Conversion tables are notoriously flawed and none consider patient specific factors like age, weight, body surface area, pharmacogenetics, drug interactions, organ dysfunction, or comorbid conditions. When using equianalgesic dosing tables or online calculators, it is often assumed the data are bidirectional when they may only be unidirectional and conservative only in one direction.[27] Given all of these concerns, equianalgesic dosing tables are only guides and patient-specific factors should be incorporated into the ultimate dose with a monitoring plan to ensure safety and efficacy.[28]

REASSESSMENT AND FOLLOW-UP

When pain regimens are reviewed for appropriateness, the popularized 4 *A*s—analgesia, adverse effects, activities, and adherence—should be evaluated.[16,17,29] It is

Table 6
Equianalgesic opioid dosing

Opioid	Parenteral (mg)	Oral (mg)
Buprenorphine	0.3	0.4 (SL)
Codeine	100	200
Fentanyl	0.1	N/A
Hydrocodone	N/A	30
Hydromorphone	1.5	7.5
Methadone	Multiple strategies*	N/A
Morphine	10	30
Oxycodone	10	20
Oxymorphone	1	10

Abbreviation: N/A, not applicable.

* Methadone dosing is highly variable and conversion to/from other opioids is NOT linear.

Data from McPherson ML. Demystifiying opioid conversion calculations: a guide for effective dosing. Bethesda (MD): American Society of Health-System Pharmacists; 2010.

prudent to follow-up with patients within 2 to 4 weeks depending on stratified risk level, concomitant therapy, and comorbid conditions. High-risk patients should be seen more frequently and include patients with a history of substance use disorder, older patients, patients with comorbid physical or psychological conditions, and those with an unstable or dysfunctional social milieu.[17,18] For patients with an increased risk of substance abuse or misuse, if they can be safely and reasonably maintained on opioids with strict compliance monitoring and have limited other therapeutic options, abuse deterrent formulations may be considered. Long-acting opioids with US Food and Drug Administration (FDA)–approved indications are listed in **Table 5**. And finally, stable lower risk patients may be seen in clinic every 3 to 6 months.[18]

MONITORING PARAMETERS

Appropriate and timely COT monitoring is vital in the management of chronic pain. Urine drug tests (UDT) generally by immunoassay (IA), prescription drug monitoring programs, behavioral assessments, and "pill counts" have been used in the monitoring of COT.[16] In the authors' experience, the latter is a futile exercise serving only to promulgate inconvenience and hardship for legitimate patients, because it is quite easy for substance abusers to borrow medications from others. Patients on methadone should have baseline electrocardiograms and be monitored closely for electrolyte abnormalities (eg, hypokalemia and hypomagnesemia) and liver function impairment.[30] Guidelines for methadone electrocardiogram monitoring are summarized in **Table 7**.[30]

Table 7
Guidelines for methadone electrocardiogram (ECG) monitoring

Frequency	Recommendations	Considerations
Baseline	Before initiation of methadone: Risk factors for QTc interval prolongation[a] Any record of previous ECG with QTc >450 ms Past medical history of ventricular arrhythmia An ECG with a QTc <450 ms within the past 3 mo with no new risk factors is acceptable	Any patient with no known risk factors for QTc interval prolongation An ECG within the past year with QTc <450 ms with no new risk factors QTc interval prolongation
Follow-up	Pending baseline ECG results, methadone dose changes, and risk factors for QTc prolongation: Performed 2–4 wk after initiation of methadone therapy After significant dose increases in patients with risk factors for QTc interval prolongation Any prior ECG demonstrating a QTc > 450 ms Have a history of syncope	For all patients: Methadone doses titrated up to 30–40 mg/d Methadone doses titrated up to 100 mg/d New risk factors for QTc interval prolongation Signs or symptoms signifying arrhythmia

Abbreviations: ECG, electrocardiogram; QTc, corrected QT interval.

[a] Risk factors for QTc interval prolongation: electrolyte abnormalities (eg, hypokalemia, hypomagnesemia), impaired liver function, structural heart disease (eg, congenital heart disease, history of endocarditis, congestive heart failure), genetic predisposition, QTc-prolonging drugs.

Data from Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain 2014;15(4):321–37.

Urine Drug Tests

UDTs have become a standard of care tool to monitor patients for treatment adherence, detecting nonprescribed drugs, and use of illicit substances. The use of IA UDT poses several advantages in providing clinicians at the point of care with objective, noninvasive, low-cost results to assess patient adherence and possible diversion.[31] Notwithstanding, IA UDT comes with a high risk of false negatives and positives. However, IA UDT could be performed initially and as clinically indicated as part of the COT monitoring.[14,16–18,32] The typical IA UDT primarily screens for morphine, but will detect semisynthetic and synthetic opioids at high doses.[33–35] The detection time on a UDT varies based on the type of opioid, dose, frequency of use, and time of collected specimen in relation to the last dose.[32] **Table 8** provides window of detection times. Nonphenanthrene opioids such as methadone and fentanyl will not be detected on an IA UDT screen, and therefore require a specific qualitative IA test or separate definitive test by chromatography.[36] Published data indicate deficiencies in clinicians' abilities to accurately interpret UDT results, because accurate interpretation requires an understanding of IA limitations, clinical chemistry, and opioid metabolism.[31,33,35,36]

Prescription Drug Monitoring Program

State prescription drug monitoring programs are vital tools developed to assist with combatting prescription drug abuse, doctor shopping, and diversion. Unfortunately, prescribers have encountered several barriers with using these programs, which has prompted states to consider implementing legal mandates to access and use of these programs.[37–39] These can provide a powerful tool for clinicians and should be routinely used in practice.

HIGH-RISK PATIENTS AND SPECIAL POPULATIONS

High-Dose Opioids and the Morphine-Equivalent Dose

According to the American Pain Society and the International Association for the Study of Pain, chronic pain is defined as "daily or near-daily use of opioids for at least 90 days, often indefinitely" and "pain that persists beyond normal tissue healing time, which is assumed to be 3 months."[18,40] High-dose opioid therapy is defined as more than 200 mg of oral morphine or opioid equivalent per day.[17,18] In addition, a 120-mg dose threshold and greater was recommended by the Centers for Disease Control and Prevention to seek pain specialty consultation owing to the increased risk of opioid-related overdoses.[1]

Extended-Release or Long-Acting Opioids

"Improper use of any opioid can result in serious side effects including overdose and death, and this risk can be greater with ER/LA opioid analgesics."[41] The FDA recommends that extended-release/long-acting opioid analgesics should only be prescribed by clinicians who are experienced in the use of opioids for the management of pain and it is their responsibility to ensure safe and effective use of these potent drug products (see **Table 5**).[41] Clinicians should be aware that by FDA guidelines, extended-release/long-acting opioid analgesic formulations and doses are only "indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate," as defined in the product labeling.[41]

Table 8
Opioid metabolism and detection times

Opioid	Metabolism	PGT Impact from Phenotype for CYP450	Active Metabolites	Inactive Metabolites	Detection Time (h)
Buprenorphine TM	CYP3A4	Y	Norbuprenorphine	Buprenorphine-3-glucuronide	9–76
Buprenorphine TD	CYP3A4				—
Codeine	CYP2D6	Y	Morphine Hydrocodone	Norcodeine	48
Fentanyl TD	CYP3A4	Y	None	Norfentanyl	—
Heroin (diacetyl morphine)	Glucuronidation via UGT2B7	Y	Morphine 6-Monoacetylmorphine	Normorphine	24–72
Hydrocodone	CYP2D6	Y	Hydromorphone	Norhydrocodone	20–25
Hydromorphone	Glucuronidation via UGT2B7	N	Hydromorphone-3-glucuronide	Minor metabolites	48–96
Levorphanol	Glucironidation via UGT2B7	N	Levorphanol-3-glucuronide	None	—
Meperidine	CYP3A4 CYP2B6 CYP2C19	Y	Normeperidine	Meperidinic acid	15–20
Methadone	CYP3A4 CYP2B6 CYP2D6 CYP2C19 CYP2C9	Y	None	2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine 2-Ethyl-5-methyl-3,3-diphenylpyrroline	72
Morphine	Glucuronidation via UGT2B7	N	Hydromorphone Morphone-3-G glucuronide Morphone-6-G glucuronide	Normorphine	48–72
Oxycodone	CYP3A4 CYP2D6	Y	Noroxycodone Oxymorphone	None	48–96
Oxymorphone	Glucironidation via UGT2B7	N	6-Hydroxy-oxymorphone	Oxymorphone-3-glucuronide	—

Abbreviations: CYP, cytochrome P450; PGT, pharmacogenetics; TD, transdermal; TM, transmucosal; UGT2B7, uridine diphosphate glucuronosyltransferase 2B7.
Data from Refs.[33–35,46,57–75]

Neuropathy

Opioids such as methadone, levorphanol, tapentadol, and tramadol may offer superiority for neuropathic pain syndromes.[42] However, when using these unique opioids in conjunction with antiretroviral therapy, methadone and tramadol may be especially problematic with respect to its CYP450 drug interactions that can result in decreased efficacy and increased toxicity.[42,43] Careful consideration for patients actively being treated for hepatitis C is in order owing to potential dangerous drug interaction risks associated with p-glycoprotein inhibitors like telaprevir or boceprevir used concomitantly with methadone or morphine.[44] For this reason, levorphanol or tapentadol may be the best options because both avoid CYP450 metabolisms and neither has proven problematic with p-glycoprotein.[45]

Pharmacogenetics in Pain Management

Genetic variability to opioid analgesics in chronic pain management can be complex and involves various genes and phenotypes.[46] Several studied genes have been identified that can alter the perception of pain, affect analgesic activity and drug metabolism, and increase risk for toxicity when polymorphisms occur. These important variations and their applicability are outlined in **Table 9**.

Discontinuation of Therapy

Whenever opioid risks outweigh benefits and functional improvement is limited, adjustments to the treatment plan must be made and may include discontinuation of

Table 9
Pharmacogenetics in pain management

Site of Activity	Genes of Interest	Function
Cytochrome P450 (CYP)	CYP2D6	Involved in the metabolism of several opioids analgesics such as codeine to morphine, oxycodone to oxymorphone, tramadol to O-desmethyltramadol, and hydrocodone to hydromorphone
P-glycoprotein (P-gp)	ABCB1/MDR1	Decreased P-gp expression and activity can affect opioid concentrations and increase patient's risk for toxicity
Catechol-O-methyltransferase (COMT) enzyme	COMT Val158Met variant	May produce an increase of dopaminergic stimulation owing to dysfunctional COMT activity, upregulating expression of MORs, resulting in increased morphine efficacy
Mu opioid receptor (MOR)	OPRM1	Codes for the expression of MOR higher binding affinity of β-endorphin to the opioid-μ receptor
Kappa opioid receptor (KOR)	melanocortin 1 receptor (MC1R)	Associated with sex-specific increased analgesic response via the KOR

Abbreviations: ABCB1, ATP-binding cassette, sub-family B, member 1; MDR1, multidrug resistance protein 1.
Data from Refs.[46,74,76,77]

Table 10
Naloxone

Route	Dose and Administration	Time to "Response"	Advantages	Disadvantages	Approved for In-home Use?
IN naloxone	Spray 1 mg in 1 mL in each nostril using atomizer device (each syringe contains 2 mg in 2 mL). May repeat dose in 3–5 min if no response. Dose may be repeated if apnea or hypopnea recurs.	Mean 4.2 ± 2.7 min; median 3 min. Range 2–13 min.	Decreases risk of bloodborne virus transmission. Decreases risk of needlestick injuries. Obviates need for needle disposal. Easy access to nares. May be preferred by people with an aversion to needles or injections.	May have lower bioavailability vs IM route. Similar or slower onset vs IM route. Similar or slightly lower responder rates vs IM naloxone. May be more likely to require supplemental doses of naloxone. Not manufactured in a formulation for this route (the injectable form is aerosolized). Nasal abnormalities and prior intranasal drug use may reduce effectiveness. Involves more steps to assemble. Inconvenience and bulkiness of carrying the product and necessary supplies.	Yes
IM naloxone	Inject 0.4 mg in 1 mL IM (using vials), through clothing if necessary. May repeat dose in 3–5 min if no response. Dose may be repeated if apnea or hypopnea recurs.	Mean 6–8 min.	Formulation manufactured for this route. Similar responder rates vs IV naloxone in prehospital settings. Fewer steps to assemble. Simpler for some people (eg, those familiar with using injections).	Risk of bloodborne virus transmission (eg, HIV, HBV, HCV). Risk of needlestick injuries. Risk of injury from improper injection technique. Proper use requires training. Requires adequate muscle mass. Inconvenience and bulkiness of carrying the product and necessary supplies.	Yes

(*continued on next page*)

Table 10
(*continued*)

Route	Dose and Administration	Time to "Response"	Advantages	Disadvantages	Approved for In-home Use?
Autoinjector naloxone	Administer 0.4 mg in 0.4 mL into the anterolateral aspect of the thigh, through clothing if necessary. May repeat doses every 2–3 min (each carton contains 2 doses).	Mean 6–8 min (IM). Mean 9.6 ± 4.6 min (subcutaneous or SC).	Pocket-size; convenient; portable. Shown to be relatively easy to use even without prior training (adults took on average about 60 s [range, 30–160]) to administer simulated injections. Retractable needle may reduce accidental needle sticks and risk of bloodborne virus transmission. The needle is not seen before, during, or after the injection; this may be a desirable feature for persons who have an aversion to the sight of needles. Discourages reuse of the device by injection drug users. The autoinjector cannot be opened by hand and modified; opening it by using a tool is difficult and renders it nonfunctional.	If the voice instructions fail, persons with poor vision may have difficulty reading the label instructions because of the small font size. Restriction to IM or SC route of administration. Needle length in children <1 y old; the skin should be pinched to prevent the needle from contacting bone. If the needle strikes bone, the needle may be broken or damaged and delivery of drug may be obstructed. Lack of field testing by OEND programs.	Yes

IV naloxone	May be diluted for IV infusion in 0.9% sodium chloride injection or 5% dextrose injection (2 mg naloxone in 500 mL solution provides concentration of 0.004 mg/mL). Initial dose of 0.4 mg to 2 mg and may be repeated at 2–3 min intervals. If no response after administration of 10 mg of naloxone, diagnosis should be questioned.	Within 2 min.	Rate of administration can be titrated to the patient's response. More rapid onset of action compared with IM or SC routes. May be more effective in the setting of ER or LA opioid formulations.	Administered in a hospital setting. Requires IV access. Mixture should be used within 24 h.	No

Abbreviations: ER, extended release; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IM, intramuscular; IN, intranasal; LA, long acting; OEND, Overdose Education and Naloxone Distribution; SC, subcutaneous.

Note: Naloxone administration in the home using a rescue kit does not preclude the need to activate the emergency response system (calling "911") or perform the "ABCs" (airway, breathing, circulation) of emergency response while waiting for help to arrive.

Data from Naloxone Kits and Naloxone Autoinjectors: recommendations for Issuing Naloxone Kits and Naloxone Autoinjectors for the VA Overdose Education and Naloxone Distribution (OEND) Program. Washington, DC: Veterans Affairs Pharmacy Benefits Management, Medical Advisory Panel and VISN Pharmacist Executives in collaboration with the VA OEND National Support and Development Work Group, Veterans Health Administration, Department of Veterans Affairs; 2015; and Naloxone [package insert]. Lake Forest, IL: Hospira, Inc; 2007.

opioid therapy. Patient individualized goals are established at the outset of the opioid trial, throughout therapy, and progress toward all of these goals requires close and ongoing monitoring. When patients fail to achieve the desired outcomes, opioid therapy should be discontinued. In situations where there are severe, unmanageable adverse effects, misuse or abuse of opioids, or significant nonadherence to the treatment plan, the risks of continuing opioid therapy outweigh the benefits.[17]

If opioids are being tapered owing to aberrant behaviors or safety concerns, a more rapid opioid taper schedule is indicated. For less urgent reasons, a taper can be completed over the course of weeks to months. Typically, the goal in designing a taper is to minimize the potential for opioid withdrawal and maximize the patient's comfort during the taper. The Veteran's Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines for COT recommend tapering by 20% to 50% per week of the original dose for nonaddicted patients.[17] Other suggestions for opioid taper include reduction by 10% each day, reduction by 20% every 3 to 5 days, or reduction by 25% each week.[47] The VA/DoD practice guidelines indicate that 20% of the previous day's dose is required to prevent withdrawal symptoms.[17]

Opioid Reversal: Naloxone

Risks for opioid overdose exist outside of the substance abuse population, some of which include high-daily MED, age, gender, concomitant use of benzodiazepines and/or alcohol with or without other sedative–hypnotics, chronic lung disease, chronic kidney and/or liver impairment, sleep apnea, and accidental exposure to young children in the home.[48–50] Patients on lower doses of opioids (eg, 20 MED/d)[6] and even those on COT for several years remain at risk for opioid overdose as their coprescribed medications and medical status changes.

During an opioid overdose, basic life support is provided and naloxone, a mu-opioid receptor antagonist, is administered to reverse opioid-induced respiratory depression. Possible routes of administration include subcutaneous, intramuscular (traditional or by autoinjector), intravenous, or intranasally. Naloxone administration, routes of administration, advantages, and disadvantages are outlined in **Table 10**.

Use in Obstetrics, Gynecology, and Neonatology

The use of buprenorphine versus methadone during gestation, delivery, post partum, and in the neonate has historic and emerging new evidence suggesting that buprenorphine is the safer, more practical alternative for opioid-dependent mothers and neonatal abstinence syndrome treatment.[51–56] This exciting therapeutic area requires more evidence-based research, requires experienced clinical teams, and is beyond the scope of this article.

SUMMARY

COT is a viable analgesic option for the management of chronic pain in select patient populations to help improve function and overall quality of life. Clinicians should optimize nonpharmacologic and nonopioid modalities for pain management where possible before considering COT. The risks and benefits must be discussed thoroughly and documented with the patient, including a realistic understanding of expectations for functional improvement and ongoing level of pain. This is a conversation that should be revisited periodically while patients are prescribed COT and the risks versus benefits should be continuously evaluated by the treating clinician and treatment team. Universal precautions should be observed in accordance with current published clinical practice guidelines, including regular and intermittent examination

with urine testing. It is crucial that clinicians stress the importance of communication, routine monitoring for efficacy and safety, appropriate and timely follow-up, and patient engagement with the treatment plan and goals while receiving COT.

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