



Approaches to Acute and Chronic Pain and Opioid Use

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Introduction

The Opioid Epidemic is upon us. Every day we hear stories about this problem, and the medical profession is at its epicenter. Knowingly or unknowingly, we have been a part of creating it—as instigators, participants, and victims—and must now take the lead in controlling the epidemic.

The opioid crisis rose from a perfect storm of events and developments. Part of the crisis was due to more emphasis on pain relief as a core element of what was defined as good care for patients. This led to increasingly generous prescriptions of narcotic analgesics in an effort by providers to provide the best care to their patients.

It is well established that there is a wide variation of narcotic prescribing among medical providers for the same medical condition. Excessive numbers of leftover drugs from emergency departments, urgent cares, postoperative cases, and post-discharge have led to predictable problems. Multiple studies show that excess (leftover) narcotics not only increase the duration of opioid ingestion, which increases the propensity for dependence (opioid use disorder) but also leads to unauthorized use by others (family, friends) for recreational use. This has been causally linked to the heroin epidemic in our youth population.

Incomplete knowledge of acute pain, chronic non-cancer pain (CNCP) syndromes, extended release opioids, opioid use disorder, and opioid hyperalgesia have all led to a propagation of the opioid problem. This has also distracted providers from their role as patient advocates, while creating a cognitive bias that clouds their assessments and treatment of patients with CNCP. The bias can then lead to misdiagnosis and treatment of critical medical disorders.

Multiple organizations have been aggressive in the formation of policy and recommendations specific to opioid prescribing. Although several organizations have made recommendations, many states have yet to implement any guidelines. A study published in the *Western Journal of Emergency Medicine* (2017) evaluated and categorized current state-sponsored opioid guidelines for the practice of emergency medicine. The results were that 17 states had emergency specific guidelines, organized into four categories: limiting prescription for opioids; preventing/diverting abuse; addiction-related guidelines; and a community resources section [1]. Many current state guidelines focus on providers limiting opioid prescriptions and vetting patients for possible abuse/diversion. The hope is this study will provide rational basis for similar efforts in other states or on the federal level.

Purpose of the Whitepaper

This whitepaper will concisely address all of the points above by encouraging:

- **Standardization of prescribing habits of opioids.** This includes established recommendations (as bullet points) to reduce variation in our practices.
- **Better understanding and standardizing** the approach to treating chronic non-cancer pain (CNCP).
- **Using alternatives to opioids** in treating acute pain whenever effective and possible.

- **A positive approach to opioid use disorder (OUD)** to increase the knowledge and awareness of OUD in hopes of restoring the compassion of providers for their patients with CNCP. This will lead to minimal, but judicious, use of all available treatment modalities for OUD and CNCP.
- **Elimination of the practice of the cognitive bias** towards patients with OUD and CNCP. This will help providers address the risk inherent in treating patients with these disorders and help prevent:
 - Over-prescription, which often leads to overdose and other complications of opioid overuse. This is a major public health issue and medical boards are targeting providers who fail to follow evidence-based guidelines. Censure of non-compliers might become increasingly common.
 - Under-prescription with unnecessary suffering.
 - Alienation between providers and patients.
 - Missing major complications such as cauda equina syndrome and spinal epidural abscess, which develop most frequently in patients with OUD and CNCP.

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Things to Know

1. There is a wide variation in provider opioid prescribing habits.
2. Excess opioid prescribing leads to longer therapy, and often conversion to non-opioid therapy can occur sooner.
3. Longer therapy creates higher rates of Opioid Use Disorder (OUD).
4. The time period for severe pain after major injuries and surgeries is typically just 3-5 days.
5. Excess opioids might be used by family and friends of patients for recreational use and lead to addiction.
6. Long-acting opioids have a much higher rate of subsequent OUD than short-acting.
7. Opioids are not the most efficacious treatment for chronic pain disorders and can actually lead to worsening of chronic pain.
8. For patients with chronic pain who have OUD, keep in mind the opioid burden in morphine milligram equivalents (MMEs).
9. Alternatives to opioids for both acute and chronic pain are often equally effective.
10. Nociceptive pain calls for different therapy from neuropathic pain, both acute and chronic.
11. OUD is not the same as Narcotic Abuse or Drug Seeking.
12. Patients frequently have three distinct simultaneous conditions and good care requires addressing all three: 1) Chronic Pain, 2) the disorder causing Chronic Pain (which can worsen), and 3) Opioid Use Disorder.
13. There is cognitive bias towards patients with chronic pain, which can lead to missed diagnoses and improper treatment.
14. Opioid prescribing rules vary by state and medical board and it's important for providers to be familiar with the local requirements.

Treatment Guidelines for the Acute Care Setting

These are general guidelines and not a substitute for provider judgment.

1. Do not prescribe more than 24 tablets (3-day supply). If extenuating pain, 36 tablets (4-5 days).
2. Do not prescribe long-acting opioids, such as methadone, transdermal patches, or extended/controlled release opioids.
3. Do not prescribe refills.
4. Do not fill lost or stolen prescriptions.
5. Utilize your state's Prescription Drug Monitoring Database in tracking OUD.
6. Prescribe oral opioids unless there is significant injury or cause for IV or IM administration.
7. Avoid tramadol and codeine in children with acute pain. Acetaminophen, NSAIDs, and hydrocodone/oxycodone (only for very painful acute conditions) for 3 days is preferable.
8. Avoid opioids for chronic pain disorders such as migraines and back pain.
9. For patients with chronic pain who have OUD, discuss weaning options, including but not limited to:
 - a. referrals to pain specialists
 - b. opioid agonist and antagonist prescriptions
 - c. cognitive behavioral therapy and physical therapy for treating OUD
 - d. conversion to non-opioids

Guidelines for Treatment of Acute and Chronic Pain

Treating Acute Pain

Pain is one of the most common symptoms for which patients seek medical care. There are few conditions that we are motivated to treat more aggressively than severe pain. Regardless of our background or specialty, our primary goal as medical professionals is to alleviate pain quickly, safely, effectively and with compassion [1].

When considering which therapeutic approach is most appropriate for patients experiencing (for 0-6 weeks) acute, nociceptive pain, the prescribing provider should consider which medication will provide the appropriate level of analgesia for the patient's condition. In general, the selection of opioids for treatment should be reserved for pain resulting from severe injuries, medical conditions, or surgical procedures in which it is anticipated that non-opioid therapies will unlikely provide adequate pain control for the expected duration of healing (or when alternatives are contraindicated). Providers should emphasize the use of opioids for treating breakthrough pain—as part of a regimen of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, rest, and ice or heat therapy—as opposed to the administration of around-the-clock opioid administration [2].

Examples of conditions severe enough for consideration of opioid medications may include acute fractures, renal colic, cluster headaches, and shingles, among others. Of course, when deciding which pharmacotherapy is most appropriate for any given patient, one should consider the individual patient's needs and circumstances and weigh the risks and benefits of using opioid medications.

If it is determined that an opioid medication is the most appropriate treatment for the patient experiencing acute pain, one should consider the following prescribing guidelines recommended by ACEP as well as several state medical boards to minimize the risk of physical dependence and addiction [3]:

- **Short-acting:** Use short-acting opioid medications only—extended release or long-acting opioids should never be used when treating acute pain.
- **Lowest dose:** Use the lowest dose possible to achieve the necessary analgesic effect for the patient.
- **Shortest duration:** Dispense quantities consistent with the typical duration of the condition. Given that the probability of long-term opioid use increases most sharply in the first days of therapy, particularly after 5 days, dispensing no more than a 3-day supply (1-2 tablets every 6 hours; 12-24 tablets total) and never (under any circumstances), exceeding more than a 5-day supply, is recommended [5].

Whether opioids are ultimately selected to treat a patient's pain or not, education is critically important. Beyond discussing with patients the potential risks and side effects of the medications, it is important to emphasize that healing from any injury or procedure is a gradual process. Talking to patients about the expected symptoms and helping them to set reasonable expectations about their recovery can help them become comfortable with alternate therapeutic options and increase compliance [6].

Treating Chronic Pain

Treatment of chronic pain (duration >3 months) with long-acting opioid medications is a primary driver of the opioid epidemic [1]. One in five patients on chronic opioid analgesic therapy will develop opioid use disorder as defined by DSM-5. If tolerance and withdrawal are considered, the prevalence rises to nearly 1 in 3 [4]. Patients suffering from pain related to chronic conditions, either already taking opioid medications or not, frequently visit the acute care environment seeking treatment for their pain [6].

With the notable exception of pain related to cancer, pain related to most chronic conditions typically does not respond well to opioid treatment but the potential for abuse is significant. Although opioids may be considered the only option for adequate analgesic relief in some patients, this decision is best made by pain management specialists familiar with the patient's condition and psychological health. Therefore, whenever possible, opioid medications should be avoided for the treatment of chronic, non-cancer pain, especially in the acute care setting.

Similar to patients with acute pain, for patients presenting with acute exacerbation of their chronic pain, such as in low back pain, the provider should first maximize the effect of non-opioid therapeutics before considering opioid-based options. Furthermore, the pain must be severe enough to warrant treatment with opioid medications and full consideration of the risks and benefits of opioid therapy must be carefully evaluated with each patient. If the provider determines that opioid therapy is still indicated, we recommend adopting the following guidelines [2,3,6]:

- **Avoid intravenous (IV) and intramuscular (IM) opioids.** The administration of intravenous (IV) and intramuscular (IM) opioids clearly is correlated to euphoria and associated addiction. In addition, IV/IM formulations of these medications are ideal for rapid pain relief, but have a short duration of effectiveness and thus are more suited for new acute pain than for exacerbations of chronic pain.
- **Avoid outpatient prescribing of opioids.** Physicians should avoid the routine prescribing of outpatient opioids for patients with acute exacerbation of chronic non-cancer pain seen in the acute care setting.
- **Lowest dose and limited duration.** If opioids are prescribed on discharge, the prescription should be for the lowest practical dose for a limited duration (e.g., < 1 week) and the prescriber should consider the patient's risk for opioid misuse, abuse, or diversion.
- **Consult Prescription Drug Monitoring Programs (PDMPs):** If prescriptions are written, consider past prescription patterns from information sources such as PDMPs. ACEP suggests that the use of PDMPs may help identify patients who are at high risk for prescription opioid diversion or doctor shopping.

Guidelines for Treatment of Acute and Chronic Pain References

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Non-Opioid Treatments for Common Causes of Acute and Chronic

Low Back Pain

Up to 85% of all people will have low back pain at least once in their lives. Low back pain is the most common presenting symptom of chronic non-cancer pain in emergency departments and urgent care centers. It is the most common cause of disability worldwide. Integral to all of this is the necessity to treat acute back pain with the minimal necessary dosage and duration of opioids before we can begin to get the opioid overuse problem under control.

A helpful guide for the noninvasive treatment of acute (<4 weeks), subacute (4-12 weeks), and chronic (>12 weeks) back pain has been developed by the American College of Physicians (ACP) in 2017. The ACP's process was rigorous, and based on an extensive review of randomized control trials and data from observational studies. For adults with acute (<4 weeks), subacute (4–12 weeks), or chronic (>12 weeks) low back pain, the ACP Consensus guidelines [10] recommend the *following*:

Recommendation 1: *Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select nonpharmacologic treatment with superficial heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). If pharmacologic treatment is desired, clinicians and patients should select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants (moderate-quality evidence). (Grade: strong recommendation)*

Recommendation 2: *For patients with chronic low back pain, clinicians and patients should initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction (moderate-quality evidence), tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation (low-quality evidence). (Grade: strong recommendation)*

Recommendation 3: *In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence)*

With regards to **harms associated with pharmacologic therapy**, the guidelines note the following:

- Increased adverse effects are seen with NSAIDs vs. placebo; COX-2 selective NSAIDs are associated with lower risk for adverse effects vs. traditional NSAIDs; acetaminophen is associated with lower risk of adverse effects than NSAIDs (moderate-quality evidence).
- Short-term use of opioids increased nausea, dizziness, constipation, vomiting, somnolence, and dry mouth compared with placebo (moderate-quality evidence).
- Skeletal muscle relaxants vs. placebo increased risk of any adverse event and CNS events (moderate-quality evidence).

- Antidepressant use was shown to increase the risk for any adverse event vs. placebo although rates of specific events did not differ (moderate-quality evidence).
- Benzodiazepines increased somnolence, fatigue, lightheadedness with vs. placebo (low-quality evidence).

Vitaly important here, and this must be stressed to patients, is that over 95% of those patients who have acute or subacute low back pain will improve and most often recover over the next 2-3 months, regardless of treatment. This further justifies limiting the duration of opioid treatment for low back pain to 3-5 days of treatment.

For patients with **chronic low back pain**, low cost therapies with the least harm should be considered as **there are "no clear comparative advantages for most treatments compared with one another."** Medications with substantial potential harms and those shown to be ineffective (e.g., long-term opioids, tricyclic antidepressants, selective serotonin reuptake inhibitors) should be avoided.

Headaches

Acute and chronic recurrent headaches are a significant cause of multiple visits for recurrent pain. This whitepaper will not deal with the diagnostic approach to acute headaches. Patients with chronic recurrent headaches have the same danger of being considered "Chronic Pain, Drug-Seeking" patients due to cognitive bias. It is therefore vital to treat, especially chronic recurrent headaches, in a systematic method and to avoid opioid therapy whenever possible. Abortive therapy, especially nonnarcotic, should be attempted whenever possible.

Although narcotics remain the most frequently administered medication for patients with migraine and for patients with headache, evidence suggests that they are potentially ineffective, and their use may lead to more prolonged emergency department and urgent care stays.

Muscle Contraction/Mixed Headaches

Most headaches are of the mixed contraction or tension, and vascular types. In the approach to patients presenting with mixed headaches, recognition of associated comorbid illness that may actually either be causative or contributory is essential. Migraine or other vascular headaches are often associated with tension-type headache (TTH), and management overlaps. Other associated conditions may include depression, anxiety, and emotional or adjustment disorders. Management with a combination of tricyclic antidepressant medication and stress management therapy may result in a better outcome than with monotherapy.

Abortive Therapy for Headaches

Abortive therapy is used to stop or reduce severity of the individual attack. **Preventive drugs are the main therapy for chronic muscle contraction or mixed headaches**, but they seldom are needed for episodic TTH.

- TTH generally respond to simple over-the-counter (OTC) analgesics such as acetaminophen, NSAID'S. Caffeine or use of prescription drugs is recommended.
- If possible, avoid use of barbiturates or opioid agonists.

- Discourage overuse of all analgesics which induce other symptoms and/or are addictive because of the risk of dependence, abuse, and development of chronic daily headache.
- Fiorinal with codeine is generally significantly more effective than placebo or Fiorinal alone. The combination is also significantly better than codeine alone in relieving pain and maintaining ability to perform daily activities. However, Fiorinal with codeine should not be first-line therapy and carries a significant risk of abuse.

For migraines, abortive therapy approaches are graded:

- **Moderate:** NSAIDS, Ergotamine, 5-hydroxytryptamine-1agonists (Triptans), DHE
- **Severe:** Triptans, DHE (Nasal or IM), Dopamine Antagonists (prochlorperazine)
- **Extremely Severe:** IV DHE, Opioids, Dopamine Antagonists, Triptans

Note that a severe episode of migraine can also be beneficially treated with high flow oxygen, antiemetics, and IV fluids (if vomiting is a significant component). Intravenous metoclopramide (variable dosage: 10-30 mg IV) has been shown to be effective for moderate to severe migraines. Intravenous diphenhydramine added to dopamine antagonists to prevent akathisia and extrapyramidal symptoms has been shown to be more effective than SC sumatriptan.

Preventive Therapy for Headaches

Preventive therapy is used if the headaches are frequent (>2 attacks per week), of long duration (>3-4 hours), or severe enough to cause significant disability or overuse of abortive medication.

- Amitriptyline (Elavil) and nortriptyline (Pamelor) are the most frequently used tricyclic antidepressants.
- The selective serotonin reuptake inhibitors (SSRIs) fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft) are generally not recommended for migraine prophylaxis.
- Other antidepressants such as doxepin, desipramine, protriptyline, and buspirone also can be used.
- There is limited data that SNRI's (Serotonin/Norepinephrine Reuptake Inhibitors) such as duloxetine (Cymbalta) are effective.

Physical therapy techniques include hot or cold applications, positioning, stretching exercises, traction, massage, ultrasound therapy, transcutaneous electrical nerve stimulation (TENS), and manipulations.

- Heat, massage, and stretching can be used to alleviate excess muscle contraction and pain.
- **Cranial electrotherapy stimulation** is different from TENS, is safe, and may be effective in alleviating the pain intensity of TTH. It may be considered as an alternative to long-term analgesic use.

Psychophysiological therapy includes reassurance, counseling, relaxation therapy, stress management programs, and biofeedback techniques. With these modalities of treatment, both frequency and severity of chronic headache may be reduced.

- **Cognitive Behavioral Therapy:** Benefits from cognitive-behavioral therapy and biofeedback therapy have been reported to reduce pain and disability compared to placebo use.
- **Biofeedback** may be helpful in some patients when combined with medications.

The following various minimally invasive techniques may provide pain relief:

- Trigger point injections

- Greater or lesser occipital nerve blocks
- Auriculotemporal nerve block
- Supraorbital nerve block
- Botulinum toxin injection in the pericranial muscle

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In-Hospital and Discharge Management

This section provides recommendations for in-patient providers for the treatment of pain, as well as medication and discharge management.

Managing Pain

- Perform regular evaluation of pain: on admission, throughout the hospital stay and at discharge
- Perform reassessments of patient responses to treatment including function
- Use non-opioid agents first in as needed or scheduled dosing
- Provide oral instead of intravenous or intramuscular analgesia when possible
- Limit administration of intravenous opioids to acute needs (e.g. painful procedures) and when patients are unable to take oral medications
- Allow opioid dosing in anticipation of painful dressing changes or other events
- Increase (or decrease) opioid doses by 25% of the total dose per day as tolerated. If increasing dose by 50% wait for 48 hours before the next basal dose increase and have sufficient short-acting pain medications available for breakthrough pain
- Order opioids by mouth, and by the hour (i.e. Q 6 hours instead of QID)
- Avoid range orders (i.e. Q 4-6 hours as needed)
- Consult subspecialty services such as Pain Management and Palliative Care when indicated (i.e. pain remaining inadequately controlled)
- Consider interventional pain procedures for patients who have inadequate pain control with maximal systemic medications or who suffer significant side effects (i.e. epidural steroid injections or facet joint injections for acute or acute-on-chronic spinal pain)
- Provide constipation prophylaxis with laxatives (i.e. Senna or Miralax)

Non-opioid Pharmacological Agents

- Opioid tolerant patients might benefit from other therapies. Opioid tolerance is defined as a patient receiving, for one week or longer, at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, or an equianalgesic dose of another opioid
- For acute pain: IV acetaminophen, IV ibuprofen, IM/IV ketorolac
- For chronic pain especially neuropathic: gabapentin, pregabalin, duloxetine, venlafaxine, amitriptyline, desipramine, and nortriptyline
- Topical agents: capsaicin, topical diclofenac and lidocaine patch

Opioid Conversion

- Calculate 24-hour use and convert to morphine milligram equivalents (MME) per day. See the table below from the Centers for Disease Control and Prevention for conversion factors for MMEs [4].

Calculating morphine milligram equivalents (MME)

OPIOID (doses in mg/day except where noted)	CONVERSION FACTOR
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥ 61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

These dose conversions are estimated and cannot account for all individual differences in genetics and pharmacokinetics.

Admission Diagnosis Tracks

	Acute pain admissions	Non-acute pain admissions
Opioid Naive	<ul style="list-style-type: none"> Non-opioids Oral short acting opioids 	<ul style="list-style-type: none"> Non-opioids
Opioid Tolerant	<ul style="list-style-type: none"> PCA 	<ul style="list-style-type: none"> Same chronic dose

PCA Dosing

	Opioid Naive	Opioid Tolerant
Basal Rate	No Basal rate	Calculate 24-hour dose, adjust by 50-75% for incomplete cross tolerance, and divide by 24 hours
Demand Dose	Morphine 1mg IV (or equivalent)	50% of the basal rate
Bolus Dose	x1-2 the demand dose	Equal to basal rate

Side Effects and Dosing Considerations

Monitor the following to minimize side effects:

- Doses of opioids used in the last 24 hours
- Pain scores, sedation scale and vitals
- Allergies and reactions
- Concurrent use of other CNS depressants such as benzodiazepines and anticholinergic medications
- Respiratory or CNS diseases
- Laboratory values, especially renal and liver functions
- In renal and liver failure: Avoid morphine and codeine
- Decreased opioids dose by 25-50% in the elderly
- A pharmacist should be involved in choosing and dosing opioids in patients with significant renal or hepatic impairment.

Converting to a Discharge Regimen

- Transition from IV or PCA therapy to an oral opioid regimen should ideally occur at least 24 hours before discharge
- Overlapping for 8-12 hours allows the oral medication to become effective before the switch
- Preference is to prescribe short term only of immediate release opioids (3-5 days)
- If prescribing extended and immediate release:
- Use same opioid, not different (i.e., Oxy IR + Oxy ER)
- Breakthrough (IR) dosing should be 10-15% of the total daily dose

Special Populations

Certain populations may pose particular challenges in managing their pain and often require higher doses of medications:

- Cancer patients
- Patients with sickle cell disease
- Patients with co-morbid psychiatric or psychological conditions
- Patients with a substance use disorder
- Patients at the end of life
- Geriatric patients with pain: balance CNS effect with pain control needs

In-Hospital and Discharge Management References

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Chronic Pain Syndrome and Opioid Induced Hyperalgesia

Chronic Pain Syndrome (CPS)

Chronic (neuropathic or central) pain results when the damaged end organ continues to send a sensation of pain after the initial damage is no longer present. **Chronic pain is defined differently by different sources but is usually defined as a length of time, such as >3 months or longer than 30 days after tissue healing would be expected to have occurred.** The longer the pain persists, the less effective and more harmful opioids become as they are associated with the loss of function due to side effects such as sedation, lethargy, lack of engagement in physical therapy, and limited exercise. This leads to poor socialization, isolation, and assuming the sick role as pain patients [2].

CPS is common, but has a complex history, unclear etiology and poor response to therapy. Pain persists longer than the reasonably expected healing time for the involved tissues. **CPS symptoms can include depressed mood, poor-quality sleep, fatigue, reduced activity and libido, excessive use of drugs and alcohol, dependent behavior, and disability out of proportion with impairment [1].**

CPS management is complex and may include psychological treatment and physical therapy such as hot or cold applications, positioning, stretching exercises, traction, massage, ultra-sonographic treatment, transcutaneous electrical nerve stimulation (TENS), and manipulations. Other treatments include nerve blocks, intrathecal pumps and spinal cord stimulation [1].

CPS might be a learned behavioral syndrome that begins with a noxious stimulus (can involve any organ system) that causes pain [1]. This pain behavior progresses to become rewarded externally or internally without any noxious stimulus. Internal reinforcers are relief from personal factors associated with many emotions (e.g., guilt, fear of work, sex, responsibilities). External reinforcers include attention from family members & friends, socialization with the physician, medications, compensation, and time off from work.

Lack of or no exercise contributes to CPS. Women who are overweight or obese have a 60-70% greater risk of developing fibromyalgia than do women of normal weight.

Sternbach's 6 D's of CPS are as follows: dramatization of complaints, drug misuse, dysfunction, dependency, depression, and disability [1]. Patients need to be informed with the first prescription of narcotics that the longer they are on the medication, the harder it will be to stop [2]. Tell patients from the outset that the goal is not total elimination of pain, but recovery, and that they are going to have to tolerate some pain to continue to function. In some ways, increased discomfort equals an increased rate of recovery. Patients who decide that they cannot live a life of pain may become a "chemical coper" [2]. They find a substance to numb their experience of life, avoid and escape. At this point, the condition is no longer medical, it is behavioral.

Patients in the acute phase of a painful condition, whether it is 1 week or 2 years from the injury, should be treated the same [2]. The treatment goal is a return to function. Methods of treating chronic nerve dysfunction include exercise, physical therapy, tolerance of discomfort, yoga, and meditation. If present, comorbid anxiety, depression, and substance abuse should be addressed as well. Patients in the chronic phase of pain should move

away as quickly as possible from opioids and muscle relaxants as well as the belief that the pain will ever completely go away [2]. Patients benefit most when starting rehabilitation of chronic pain early, by employing non-pharmacologic methods and setting realistic expectations. When they present several years into a painful condition, the treatment recommendations are the same, but the process is much slower and more difficult.

Antidepressants are the initial treatment of choice [2]. SNRI's duloxetine (Cymbalta) and venlafaxine (Effexor) are the initial drugs of choice. They work well for pain and treat comorbid depression or anxiety. These agents treat depression and anxiety at lower doses, but require higher dosing to achieve neuropathic pain benefit. Tricyclic antidepressants (TCAs; amitriptyline, imipramine, nortriptyline) are effective, but can be hard to tolerate. They are anticholinergic and have alpha blocking properties which can cause orthostasis and a prolonged QT interval. Certain tricyclics have a formal indication for mixed headaches, irritable bowel syndrome (IBS), and fibromyalgia. TCAs have immediate pain benefit at lower doses, and mood and anxiety benefits at higher doses (opposite of SNRIs).

Anticonvulsants [2] almost uniformly benefit neuropathic pain. Certain agents are specifically recommended for neuropathic pain conditions. Carbamazepine (Tegretol) is the drug of choice for trigeminal neuralgia. Gabapentin (Neurontin) is the drug of choice for post herpetic neuralgia. Pregabalin (Lyrica) is formally indicated for fibromyalgia. They can be combined as needed with antidepressants due to their different mechanism of action.

Several other medications are helpful in the treatment of CPS. Lidoderm patches can be good adjuncts as they have a combination of neurologic benefit and placebo effect. Clonidine is a centrally-acting alpha agonist with many uses, e.g. opioid and alcohol withdrawal and complex regional pain syndrome, a.k.a. reflex sympathetic dystrophy. Anti-arrhythmics, like antidepressants and anticonvulsants, block sodium and calcium channels and seem to block the firing of damaged nerves. IV lidocaine has shown benefit in some neuropathic pain conditions. An exhaustive review of pharmacological and non-pharmacological approaches to the treatment of chronic pain may be found at the below reference [4].

Benzodiazepines are not recommended for long-term, chronic pain treatment [2]. Combining benzodiazepines and opioids can lead to profound respiratory depression. Muscle relaxants [2] are also not recommended as they only make patients feel relaxed. Like opioids, their use is specific and limited to acute management of real muscle spasm or muscle injury.

Patients taking large amounts of prescribed opioids for chronic pain should be referred to a pain management specialist who should incorporate non-pharmacologic therapy and taper their opioid use [2]. Use scripting to show compassion for chronic pain and desire to avoid harming the patient [3]. Below are a few examples:

- "I know you are in pain and I want to treat your pain but I think opioids are not only the wrong treatment for your pain but also the cause of your pain."
- "If you could stop taking opioids, your pain and life would improve. Please call (the 24/7, U.S. Government SAM- HSA help line) 1-800-662-HELP to help you stop taking pain medications".

- “I’m going to try to manage your pain without opioids because I am concerned that opioids might harm you.” [3]

Consider using the MDCalc Opioid Risk Tool (ORT) to help make informed management choices.

Opioid Induced Hyperalgesia

Opioid Induced Hyperalgesia (OIH) is a paradoxical increase in pain sensitivity after short- and/or long-term opioid use. It is exemplified by exaggerated pain response to minimal procedures like an IV [1]. Chronic pain occurs not despite opioid therapy, but because of opioid therapy.

Simplistically, the theory identifies with prolonged exposure to opioids, the body develops an immunity to opioid receptors and that this will then lead to the development of more pain receptors. This can lead to tolerance to the opioids and increased sensitivity to pain (hyperalgesia). The patient is then more sensitive to new causes of pain, such as from meningitis or trigeminal neuralgia.

This is perhaps the best way to explain to patients the long-term detriment of opioids in the treatment of chronic pain: with prolonged treatment, the body develops even more pain receptors from opioid use and thus the patient has even more pain and less relief from opioid administration.

The Scientific Explanation of OIH

The neuroimmune hypothesis of OIH asserts that opioid induction of immune mediators in the CNS neutralizes anti-nociception and leads to tolerance and hyperalgesia. Blockade of glial reactivity, their pro-inflammatory products, or stimulating anti-inflammatory mechanisms after morphine attenuates ensuing nociceptive hypersensitivity. For instance, opioids may amplify existing headache-induced neuroimmune signaling at meningeal nociceptors and in the trigeminal ganglia.

Concurrent opioid treatment and peripheral nerve injury may trigger a novel mechanism, distinct from known pathways activated in the spinal cord or in response to opioids or pain. A brief course of morphine prolongs the duration of “chronic constriction injury”-induced allodynia following treatment cessation. It was discovered that they could both prevent and reverse the morphine-induced allodynia by treating animals with clozapine-N-oxide. This suggests that OIH can be disrupted and that pain levels can be reset to normal.

Chronic Pain Syndrome and Opioid Induced Hyperalgesia References

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Opioid Use Disorder (OUD)

Definition

Opioid Use Disorder (OUD) is defined as a repeated manifestation of 2 or more of 11 problems (see Table 1 below) within a 12-month period [1].

Table 1. Diagnostic Criteria for an Opioid-Use Disorder.*

<p>Use of an opioid in increased amounts or longer than intended</p> <p>Persistent wish or unsuccessful effort to cut down or control opioid use</p> <p>Excessive time spent to obtain, use, or recover from opioid use</p> <p>Strong desire or urge to use an opioid</p> <p>Interference of opioid use with important obligations</p> <p>Continued opioid use despite resulting interpersonal problems, social problems (e.g., interference with work), or both</p> <p>Elimination or reduction of important activities because of opioid use</p> <p>Use of an opioid in physically hazardous situations (e.g., while driving)</p> <p>Continued opioid use despite resulting physical problems, psychological problems, or both</p> <p>Need for increased doses of an opioid for effects, diminished effect per dose, or both†</p> <p>Withdrawal when dose of an opioid is decreased, use of drug to relieve withdrawal, or both†</p>
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* If two or three items cluster together in the same 12 months, the disorder is mild; if four or five items cluster, the disorder is moderate; and if six or more items cluster, the disorder is severe. Criteria are from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.⁸

† If the opioid is taken only as prescribed, this item does not count toward a diagnosis of an opioid-use disorder.

Tolerance and dependence are distinct from addiction and opioid abuse disorder. Furthermore, a condition sometimes called “pseudoaddiction” occurs when patients overuse their medication and may request early refills or stronger formulations in order to relieve genuine pain that has not been adequately controlled. These conditions must be distinguished from OUD [1].

Both compliant opioid-treated chronic pain patients and persons with addiction or opioid use disorder will suffer withdrawal upon too-abrupt discontinuation of opioids. Therefore, presence of withdrawal symptoms does not delineate OUD [1].

Risk Factors

Several risk assessment tools in the form of questionnaires have been developed but none have been validated as sufficiently accurate to be recommended. The summary below provides potential OUD risk factors from multiple studies [2-10].

- **Longer duration of use and dosage:** Multiple studies use various duration time cut-offs, but the longer a patient was prescribed opioids, the greater the risk was of developing OUD. Short-term acute pain management (often but not always defined as <7-30 days) does not seem strongly associated with the development of OUD.
- **Chronic pain:** Since the risk of OUD increases with both length of time taking the drug and amount of drug taken, chronic pain patients are at substantially higher risk of developing it. It has been estimated that 20-24% of chronic pain patients also suffer from OUD. Of note, among patients being treated for OUD, 30-50% of patients report experiencing chronic pain.
- **Demographics and comorbidity:** Multiple studies have found correlation with male sex, younger age, back pain, and psychiatric comorbidity with increased risk of developing OUD, but findings have not been consistent.
- **Substance abuse:** Previous or concurrent substance abuse disorder, including alcohol abuse, has been found to be a risk factor for developing OUD.
- **Long-acting formulation type:** Some, but not all, studies have shown that risk is increased with use of long-acting or extended release forms of opioid analgesics.
- **Non-medical use:** One interesting study found that 18-year-olds who used prescribed or illegally obtained opioids for non-medical uses were at increased risk of developing any substance abuse disorder by age 35, whereas 18-year-olds who used short term opioid therapy as medically directed were not at increased risk of developing any substance abuse disorder by age 35.

Treatment

Several classes of drugs are used in the management of OUD, including opioid antagonists (naltrexone), partial agonists (buprenorphine), opioid agonists (methadone), alpha-2 adrenergic agonists (clonidine) and psychosocial interventions. See following sections on Alternatives to Opioids and Outpatient Therapy Approach to OUD for details.

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Outpatient Therapy Approach to Opioid Use Disorder

Roles of Buprenorphine, Suboxone, and Naltrexone

Treating opioid use disorder (OUD) with pharmacological agents has been shown to be more effective in reducing illicit opioid use when compared to psychosocial approaches or abstinence therapy alone [2]. Patients addicted to opioids treated in the acute care setting do better when they receive medication to reduce opioid cravings [1]. Buprenorphine, suboxone, and naltrexone have treatment guidelines that have shown to be useful [5,6,7,9]. Patients benefit when they can receive both pharmacologic treatment and psychosocial support [9].

First line treatment in patients with acute withdrawal should be with an opioid agonist such as buprenorphine vs an opioid antagonist such as naltrexone [9]. Suboxone is a combination of both these opioid agonists and antagonists.

Buprenorphine and suboxone can be used in the emergency department and inpatient setting for management of both pain and opioid dependence. However, in the United States as of 2017, outpatient prescribing of buprenorphine and suboxone for opioid dependence (not pain) is limited to physicians and advanced providers who have received a DEA number specific to prescribing these products, also known as a DEA-X license or DATA waiver [5,6]. This waiver or "X-license" is distinct from the standard DEA license most providers have. Waivers may be obtained by completing an online buprenorphine training course from the Substance Abuse and Mental Health Services Administration (SAMHSA), and further details can be found on their website.

The acute care setting provides a unique opportunity to initiate treatment for OUD and arrange follow up treatments.

Buprenorphine

Buprenorphine is an opioid agonist-antagonist available as oral therapy. Like methadone, it may be used for hospital patients but can only be prescribed as an outpatient for addiction by providers with a DEA-X license. Methadone and buprenorphine are similarly effective at ameliorating opioid withdrawal, although buprenorphine shows less risk of over-sedation and respiratory depression.

Buprenorphine exerts its analgesic effect via high affinity binding to mu opioid receptors in the CNS; displays partial mu agonist and weak kappa antagonist activity displacing opioids [6]. A study of 290 patients with OUD presenting to the ED found after 2 months patients who received buprenorphine after initial counseling were more likely to be in formal addiction treatment and to report reduced opioid use than those in other 2 groups (initial counseling only, and referral for addiction services) [1].

Another study compared SL buprenorphine alone vs with buprenorphine implants on relapse rates. Patients with OUD and no withdrawal and no use in the last 90 days were randomized to either daily sublingual buprenorphine at the same pre-study dosage combined with 4 placebo implants, or to daily placebo tablets combined with 4 active implants. Results were based on abstinence from 3-6 months. This study suggested that buprenorphine

implants could help improve relapse prevention in patients who are currently maintaining abstinence with sublingual buprenorphine [3].

Because of the displacement of opioids with buprenorphine, patients should be in mild to moderate withdrawal to find benefit from the drug. This usually takes at least 6-48 hours depending on the half-life of the opioid the patient is using [9]. The level of withdrawal can be assessed using a scale such as the Clinical Opioid Withdrawal Scale [12].

Suboxone

Suboxone is a combination medication buprenorphine/naloxone. It should only be used for patients addicted to short acting narcotics and when the last use was greater than 6 hrs. Buprenorphine can completely displace opioids from receptors and naloxone is an opioid antagonist which when combined can cause severe withdrawal in patients in the acute phase or on long acting opioids [6].

Suboxone is not recommended for use during the induction period for long-acting opioids or methadone; initial treatment should begin using buprenorphine monotherapy under supervision [6]. Patients should be switched to the combination product for maintenance and unsupervised therapy [6]. An FDA approved patient medication guide exists that should be given to patients with suboxone prescriptions [8].

Naltrexone

Naltrexone is used in highly motivated patients to block opioid effects and help maintain abstinence. It is most effective when combined with a program of psychosocial interventions and often self-help groups. Abstinence therapy has somewhat limited utility, however, as most studies show that approximately 50% of patients discontinue the drug by 6 weeks, with only 15% remaining compliant at 25 weeks.

The opioid antagonist naltrexone is an option for maintenance treatment to prevent relapse in opioid use disorder patients not currently using narcotics [9]. Naltrexone should not be used prior to the completion of a medically supervised withdrawal from opioids because it can cause immediate withdrawal symptoms [9].

A long-acting naltrexone formulation is available for patients with difficulty adhering to daily medication; this extended release form requires a once monthly injection [9].

A Cochrane review showed oral naltrexone was more effective than placebo in sustaining abstinence in three trials where patients were forced to adhere to daily doses of the medication [10]. Another trial compared a once-monthly, injectable depot formulation of naltrexone with placebo in 250 patients with a DSM-IV diagnosis of opioid dependence over 24 weeks, finding that the median proportion of weeks of confirmed abstinence was 90 percent in the actively treated group compared with 35 percent in the placebo group [11].

A naloxone challenge test should be initiated prior to administration of naltrexone to ensure that the patient has completed withdrawal from opioids and is no longer physically dependent. The patient is given up to a total dose of 0.8mg of naloxone and observed for one hour. If symptoms of withdrawal present, initiation of naltrexone should be delayed at least 24hrs [9].

Outpatient Therapy Approach to Opioid Use Disorder References

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Tips for Compassionate Management of Chronic Pain

Stay Patient-Centered, Even When Setting Limits

The key is to do what is right for the patient. We do not say no because of societal addiction issues or to steward resources toward sicker patients. We say no to narcotics in the acute care setting because we do what is right for the patient. Administration of narcotics in the acute care setting for chronic pain is not the best for patient. Opioid hyperalgesia (painful things hurt too much) and allodynia (things that shouldn't hurt are painful) are two of the complications that can result.

Blame the Medicines, Not the Patients

Patients need to hear that their hyperalgesia and allodynia are not their fault. It is largely the inherent limitation of the medications. Opioids are great for acute pain and problematic for chronic pain. Some chronic pain specialists do not use them at all. All chronic pain specialists have to be careful and consistent. The patient may be miserable and think narcotics are the answer but narcotics may be part of the reason for excessive pain.

Medical Directors: Apologize if Narcotics Were Given

If you have a patient who is intermittently getting narcotics from some doctors and not others, it makes for some intense anger as that patient is confused by the inconsistency. These are the angry letters that sometimes go to the CEO. When this happens, apologize to the patient for the doctor who gave them the narcotics and not for the doctor who refused to give narcotics. Explain there are guidelines and processes to limit ED use of narcotics in chronic pain, and the doctor who failed to follow those guidelines is responsible for the complaint. This allows you to not only validate the patient's frustration by the mixed message but at the same time reinforce the limits for future encounters.

Suggestions for Explaining the Treatment of Acute and Chronic Pain with Opioids

For Acute Pain

- Explain non-opioid treatments for acute pain first. This includes RICE (Rest, Ice, Compression, Elevation).
 - "You have a painful condition. We want to treat your pain. There are a lot of things we can do besides using opioids that treat the causes of the pain (inflammation and swelling). We do this by elevating and icing, with rest and compression (ace wrap or splint)."*
- Explain that pain from acute injuries and post-operative conditions will significantly improve after 3-5 days, and that narcotics should only be needed for that time period. Also mention that they should use the lowest dose of narcotic necessary to keep their pain manageable.
 - "Keep in mind that much of your pain will diminish within 3-5 days. After that, your pain should be improved to the point where you can manage it with NSAIDs, Tylenol, or (fill in the blank)."*
- Conversion to non-narcotic medications and modalities should be done as soon as they can, with a maximum treatment period of 5 days, even if they still have pain.
 - If the patient still has significant pain, they need to follow up with a medical provider to assure proper healing without complications.
- Explain that there is definite medical evidence that taking narcotics longer, past the 3-5-day treatment period, increases the likelihood for opioid dependence and does not hasten healing.

"The more of a narcotic you take and the longer you take it, the greater your chances are for becoming addicted to the narcotic. Then you may very well have a worse problem, or at best, another problem, which is Opioid Use Disorder."

- Leftover narcotics should be returned to their physician or clinic for proper disposal.

For Chronic (Non-Cancer) Pain

- Don't let them feel abandoned! Acknowledge that they do have pain and that we do not intend to deny them pain relief. The goal is to utilize any and all non-opioid medications and modalities to relieve their pain.
- Explain that narcotic therapy becomes a problem in and of itself after treatment of chronic pain. This can lead to overdose, addiction, and most importantly a worsening of their pain to the ongoing chronic type of pain but also to new painful stimuli (OIH).
- Explain Opioid Induced Hyperalgesia.

"The long-term use of opioids causes the body to actually develop MORE pain receptors, and you will find less and less pain relief from your existing opioid medications and can actually develop more chronic pain."

- Explain that Narcotic therapy has not been shown to make a difference in long term pain relief, return to function, or everyday living.
- With your Case Managers, develop a bundle of resources to give your patients and their primary care providers non-opioid options for treating their Chronic Pain.
- Don't forget that Opioid Use Disorder requires treatment by itself, as well as their Chronic Pain.

"I'm sorry about your chronic pain. The treatment of chronic pain is much different than the treatment of acute pain. Opioid medications are not the best choice for chronic pain and in fact can cause more problems for you. Your pain will not likely improve much on a long-term basis, and in fact may worsen."

"Then you have to deal with the side effects of the medication and you will be at high risk for a condition we call 'Opioid Use Disorder'. OUD is the name for the condition you contract from chronic opioid use and refers to the reliance and tolerance you develop. It is a complicated type of medical addiction."

"To treat you properly, we need to convert the treatment of your Chronic Pain to other drugs and modalities that are not narcotics."

"We don't want to do you further harm with the narcotics."

"We also have to get you off the narcotics. There are many ways to do that".

For Chronic Pain with Opioid Use Disorder

- Explain that OUD has complicated the treatment of their chronic pain and that they need to have therapy for both to maximize their functional status (optimal living with minimal pain).
- Explain that as long as they are on narcotics, they risk worsening of their chronic pain and that there will be an escalated need for more narcotics in their future, which in turn will lead to more chronic pain and the need for more narcotics (the vicious cycle).
- As above, prepare a bundle of resources for the treatment of their OUD.

"Let's get you started on the right path! We need to get you off the narcotics and also find the right treatment for your chronic pain."

"This may take a little while to find the best combination of treatment for you, but it's definitely worthwhile. You need to stick to it, though, and consider opioid treatment as a last resort"

Under all circumstances, acknowledge their problem, reassure them that they are not alone, that there are many resources and alternatives to narcotics, and that they need to stay with their one provider to guide them through these resources and alternatives. Tell them that you care, and that they are not alone in this!

Useful Websites for Info on Opioid Recommendations and Laws

AMA Website: <https://www.end-opioid-epidemic.org/>

CDC Website: <https://www.cdc.gov/drugoverdose/prescribing/guideline.html>

AHCA: https://www.acha.org/documents/resources/guidelines/ACHA_Opioid_Prescribing_in_College_Health.pdf

Massachusetts Law on Opioid Prescribing: <http://www.mass.gov/governor/press-office/press-releases/fy2016/governor-signs-landmark-opioid-legislation-into-law.html>

JAMA Guidelines: <http://jamanetwork.com/journals/jama/article-abstract/2533488>

California Occupational Health Opioid Guidelines: <https://ohsonline.com/articles/2016/08/17/california-adopts-opioid-treatment-guidelines.aspx>

State Guidelines

State by State summary of Statutes and Regulations on Opioid Prescribing:

<http://www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management>

State Emergency Department Opioid Guidelines-Current Status:

<https://www.ncbi.nlm.nih.gov/pubmed/28435482>

Inter-Agency Guideline (Washington): <http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdfS>

Arizona: <http://www.azdhs.gov/documents/audiences/clinicians/clinical-guidelines-recommendations/prescribing-guidelines/az-opioid-prescribing-guidelines.pdf>

California Medical Board: http://www.mbc.ca.gov/Licensees/Prescribing/Pain_Guidelines.pdf

Georgia: http://www.questdiagnostics.com/dms/Documents/State-Monitors/GA_State_Monitor_External.pdf

Idaho:

<https://bom.idaho.gov/BOMPortal/BOM/PDF%20FORMS/ModelPolicyUseofOpioidAnalgesicsinTreatmentofChronicPain.pdf>

Illinois: <https://www.isms.org/opioids/>

Maryland: <http://mbp.state.md.us/pages/overdose.html>

Missouri: http://www.painpolicy.wisc.edu/sites/www.painpolicy.wisc.edu/files/MO_CSGUIDE_0.pdf

Oregon: <http://wcd.oregon.gov/medical/Pages/opioid-guidelines.aspx>

Washington:

<http://www.doh.wa.gov/ForPublicHealthandHealthcareProviders/HealthcareProfessionsandFacilities/PainManagement>

Washington DC: <https://doh.dc.gov/bome>