Opiates and the Law, CURES, State and Kaiser Guidelines

"Pharmacology Update" Symposium on September 24, 2019

Emily Wayshner, PA-C
Mobashshera Jabeen, PA

Financial Disclosures

NO FINANCIAL OR COMMERCIAL AFFILIATIONS TO DISCLOSE

Agenda

- Understanding the prescription opioid epidemic
- Addiction, Iatrogenic opioid dependence
- Are opioids appropriate and safe for chronic non-cancer pain?
- Prescribing/Using Naloxone
- CDC guidelines for opioid prescribing (for acute and CNCP)
- Medical Board of California guidelines
- Kaiser Permanente opioid prescribing guidelines and Opioid Escalation Practice Recommendations

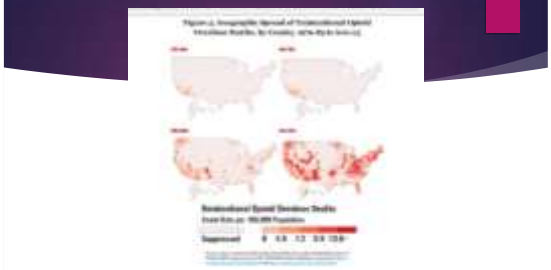
The Opioid Epidemic

- Onset: late 1990s-
- Pharma reassured the medical community that patients would not become addicted to prescription opioids
- Prescriptions increased → widespread misuse (rx and non-rx) before it was clear that these medications could be highly addictive

Drug overdose deaths in the US

- >700,000 deaths from 1999 to 2017
- ~68% of the 70,200 drug overdose deaths in 2017 involved an opioid
- In 2017, the number of drug overdose deaths involving opioids (both rx and illicit) was 6 times higher than in 1999
- On average, 130 Americans die every day from an opioid overdose.

On Average 130 Americans Die Every Day From an Opioid Overdose



The Oversupply and Abuse of Prescription Opioids is at the Heart of the Crisis

- In 1960, four out of five heroin addicts began with heroin, by the 2000's, 3 out of 4 heroin addicts began with prescription opioids (obtained from their own rx or someone else's rx. Drugs freely given by friends and family members accounts for >40%
- In 2016, data analyzed by the CDC shows that 61.8 million Americans received rx opioids, or 19.1% of the US population

The Crisis is Far-Reaching

- Children overwhelming the foster care systems- since 2010 nearly a one-fifth increase in the number of children placed with relatives or foster care- this is especially prevalent in regions hardest hit by the opioid crisis (Appalachia, parts of the Pacific Northwest, parts of the Southwest, Oklahoma and New England)
- Rise in neonatal abstinence syndrome (NAS) – infants with opioid withdrawal syndrome
- From 2004-2014, the rate of US NAS increased 433%
- Rise from 1.5 to 8/ 1000 hospital births, rise from 2.8 to 14.4/1000 births in state Medicaid programs

In the US, One Infant is Born Every 15 Minutes with Withdrawal Symptoms

For the First Time Since 1993, Life Expectancy in the US Has Declined

ONE RESEARCH PAPER ESTIMATING THAT OPIOID OVERDOSE DEATHS ACCOUNTED FOR 2.5 MONTHS OF THE 4 MONTH DECLINE

2017- HHS declares a public health emergency

- 5-Point Strategy to Combat the Opioid Crisis
- Improving access to TX and recovery services;
- Promoting use of overdose-reversing drugs -Narcan
- Strengthening our understanding of the epidemic through improved public health surveillance
- Providing support for cutting edge research on pain and addiction
- Advancing better practices for pain management

- 90% of Americans struggling with addiction are not currently getting treatment

Pain Management

STOPPING THE CRISIS: AVOID CREATING DEPENDENCE IN THE FIRST PLACE

Chronic Pain/Iatrogenic Drug Dependence

- Pain lasting/recurring for >3-6 months
- One of the most common reasons for seeking medical attention in the US, ~50 million Americans suffer with chronic pain, ~20 million high impact chronic pain

Length of Time

Taking opioids for 5 days or more will increase your risk of long term use, which increases your risk of addiction

After just one month, 1 in 3 people will be on opioids chronically

Prescription Drug Misuse

- Any use of a prescription medication that is outside of the manner and intent for which it was prescribed:
  - Overuse
  - Using to get high
  - Diversion
  - Multiple prescribers
  - Concurrent use of ETOH/illicit drugs/non-prescribed controlled substances

Misuse is a necessary but not sufficient criterion for a substance use disorder.

Prevalence of prescribed opioid misuse in the United States (August 2019)

A significant proportion of patients with opioid addiction or fatal opioid overdose were initially prescribed opioid medication for pain.

Misuse — Estimates vary widely, from 12 to 78 percent reflecting differences in the sample populations and definitions of opioid misuse among studies.

Opioid Use Disorder

- Commonly referred to as opioid addiction
- DSM-5 diagnosis, formerly 2 disorders (opioid dependence and opioid abuse)

Symptoms of OUD (at least 2 of the following in a 12-month period)

- Taking more opioid drugs than intended
- Wanting to try to control opioid drug use without success
- Spending a lot of time obtaining, taking, or recovering from the effects of opioid drugs
- Craving opioids
- Failing to carry out important roles at home, work or school because of opioid use
- Continuing to use opioids, despite the use of the drug causing relationship or social problems
- Giving up or reducing other activities because of opioid use
- Using opioids even when it is physically unsafe
- Knowing that opioid use is causing a physical or psychological problem, but continuing to take the drug anyway
- **Tolerance for opioids**
- **Withdrawal symptoms when opioids are not taken**

Does Anyone on Opioids Have Opioid Use Disorder (OUD)?

- While often people will develop a physical tolerance to prescribed opioids and experience a physical withdrawal without the drug, DSM-5 explicitly states that it is not an opioid use disorder if the patient is experiencing these symptoms under appropriate medical supervision.

OUD

- 26% of patients within a large United States health system who were prescribed long-term opioids met criteria for DSM-IV opioid dependence in the past year.

Risk Factors For Opioid Misuse When Prescribed for Chronic Pain

- Substance use disorder (most consistently identified), including tobacco use disorder.
- Family history of a substance use disorder.
- Mental health disorder, including anxiety, depression, posttraumatic stress disorder .
- History of legal problems or incarceration.
- White race (compared with black race), despite studies that have identified greater clinician concern and closer monitoring for black patients.
- Age less than 40 to 45 years old, in most studies

Other Risk Factors for Opioid Use Disorder and Addiction

- Poverty
- Unemployment
- Regular contact with high risk people/environments
- Risk-taking or thrill seeking behavior
- Heavy tobacco use
- Stressful circumstances
- Prior hx of substance use disorder treatment

Women: Unique Set of Risk Factors

Women more likely to have chronic pain than men

Women are more likely to be prescribed opioids, to be given higher doses and to use opioids for longer periods of time

Women may also have biologic tendencies to become dependent on opioids more quickly than men

How Does Opioid Addiction Occur?

- Opioids trigger your brain to release endorphins- muffling pain and boosting feelings of pleasure- creating a temporary but powerful sense of well-being.
- Dose wears off→ you want those good feelings back. This is the first milestone on the path toward addiction

Patient Risk Assessment

CI's to controlled substances include:

- Current untreated substance use disorder
- Poorly controlled psychiatric illness
- Erratic follow-up

Risk Assessment

- Collect both patient-reported data and collateral data from other providers and objective sources.
- Patient-reported : substance use history, mental health history, family and social history, as well as physical examination to assess for signs of substance use (eg, track marks and stigmata of chronic liver disease).
- Collateral data: review medical records, speak with previous or current providers, check the state prescription monitoring program, and conduct drug testing.

Screening Tools (Addiction Risk)

- Several are publicly available
- CAGE
- Opioid Risk Tool

Aberrant Behaviors

- Misuse- use of any medication outside the manner/intent for which it was rx'd
- Opioid Use Disorder- refers to the misuse of opioids, including both abuse and dependence
- Diversion – refers to the redistribution of a drug to an unintended recipient (relative, friend, neighbor) or into the illicit marketplace

Aberrant Behavior Examples

- Unsanctioned dose escalations
- Repeated visits to the office, ED/UC requesting opioids
- Losing prescriptions
- Seeking early refills
- Deterioration in function
- Illicit drug use
- DUI
- Outside fills (CURES)
- UDS abnormalities (including presence of no drug on UDS, drugs not rx'd to pt on UDS, diluted urine sample)

IDENTIFICATION AND MANAGEMENT

- "universal precautions" standard prescribing and monitoring framework for all
- Establishing a clear clinician-patient relationship
- Documentation: Medical hx (including substance use/mental health), PE
- Medical decision-making, including assessment of benefit and harm
- Plan of care
- Regular follow-up with standardized monitoring for benefit and harm
- UDS, CURES

The 5 A's of Follow- Up

- Analgesia
- Activities of daily living (ie, assessment of functional status)
- Addiction
- Adverse effects
- Adherence to the treatment plan

Urine Drug Testing (UDS)

- Confirms patients have taken the prescribed medication
- Identify use of nonprescribed substances.
- Random vs scheduled , (random may be more likely to detect surreptitious drug use).
- Effective at identifying illicit and nonprescribed drug use better than clinician assessment alone
- Among patients whose clinicians believed were not at risk for medication misuse, 60 percent had urine drug tests showing the presence of an illicit drug or the absence of a prescribed medication

Prescription Drug Monitoring Programs (PDMPs)

All US states have operational PDMPs; other countries have similar programs.

Receiving undisclosed controlled substances from other prescribers is a type of prescription drug misuse, could indicate substance use disorder or diversion, and elevates the risk for drug-drug interactions and overdose

May not include all medical sources (i.e., methadone maintenance) Access to dispensing data from neighboring states is variable and increasing.

Data is usually delayed a few days

Addressing Misuse

occurs along a spectrum of severity, from less severe behavior (eg, a single episode of a patient taking more than prescribed) to more severe behavior (eg, undisclosed prescription sources).

Response should be commensurate with the severity and the pattern of the behaviors..

In most cases except diversion, it is appropriate to taper controlled substances to avoid precipitating a severe withdrawal syndrome.

Tapering doesn't work if underlying SUD. Offering /referring for addiction treatment is essential

CURES 2.0 "When Must I Consult CURES?"

- The first time a pt is prescribed/ordered/administered/furnished a controlled substance (unless exemption applies)
- Within 24 hours (or the previous business day) before above
- Before subsequently prescribing a controlled substance, if previously exempt
- At least once every 4 months if the controlled substance remains part of patients treatment plan
- Consider prior to every rx!

CURES Exemptions

- While the patient is admitted to, or during an emergency transfer
- Licensed clinic, outpatient setting, health facility, county medical facility
- In the ED of a general acute care hospital, and the controlled substance does not exceed a non-refillable 7- day supply
- As part of a patient's treatment for a surgical procedure, and the rx does not exceed a non-refillable 5 day supply (procedure must be performed at licensed clinic, outpatient setting, health facility, county medical facility, place of practice)
- The patient is receiving hospice care

Opioid Therapy for the Treatment of Chronic, Non-Cancer Pain (CNCP)?

- Controversial, due to insufficient evidence of long-term efficacy and the risk of serious harm in the context of the ongoing opioid epidemic in the US.
- Inappropriate as a first-line option for CNCP

When to Consider Opioids for CNCP

- Other potentially effective and safer therapies have not provided sufficient pain relief
- Pain is adversely affecting patient's functions
- Potential benefits outweigh potential risks
- Should be combined with non-opioid pharmacotherapy and non-pharma therapy as appropriate.
- **As a last resort!**

Before Initiating Treatment With Opioids

Assess patients for the risk of overdose and opioid use disorder (OUD)

Opioid therapy may not be appropriate for patients who are at risk for misuse

Follow-up and Monitoring During Chronic Opioid Therapy

- Every 3 months for pts on stable doses: in-office visit, PE,
- Assess pain intensity, functional status, adverse effects
- Assess for aberrant behaviors
- Check for changes in health status (respiratory, renal, hepatic, mental illness, substance abuse, OSA)
- If the benefits of opioid therapy do not outweigh the harms- therapy should be modified or d/c'd

Recognition of Opioid Overdose

Inform patients and their family members/caregivers about how to recognize the S&S of an opioid overdose:

- Extreme somnolence- inability to awaken a patient verbally or upon firm sternal rub
- Respiratory depression- this can range from show or shallow respirations to no respirations in a patient who is unarousable.
- Miosis (pinpoint pupils), bradycardia and/or hypotension

Naloxone

- Naloxone HCL (Narcan) Nasal Spray (2.4mg) is the first and only FDA-approved nasal form of naloxone for the emergency TX of a known or suspected opioid overdose
- Also available in injectable form
- Most accidental OD's occur in home setting; Narcan is easy to use with no medical training required.
- Available from your pharmacist, without an rx from your doctor (available to ANYONE who requests it)
- Covered by most major insurance plans

Naloxone and High-Risk Patients

- All patients should be considered for prescribing Naloxone, especially patients at higher risk of overdose
- Hx of substance use disorder, illicit drug use, or previous overdose
- Patient is >64 yo
- concurrent benzodiazepine and/or sedative-hypnotic use
- Pt is exposed to peers with higher potential for misuse, overdose and/or illicit drug use (i.e., teens, college students)

Naloxone Cont.

- Temporarily reverses the effects of opioids. No effect in people who are not taking opioids.
- Opioid antagonist- competes for the same receptor sites as opioids- reversing the effects of opioids, including respiratory depression, sedation and hypotension.
- Can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine
- Not for self –use! Instruct pts to let their friends/family/caregivers know where they keep it- also read all instructions for use at the time they receive the rx
- Naloxone is NOT a substitute for emergency medical care!
- Get emergency help immediately after giving the first dose!

A second dose may be given (in alternate nostril) afar 2-3 minutes if pt does not respond or if symptoms of overdose return (using a new Narcan nasal spray). Additional doses may be given every 2-3 minutes until emergency help arrives (the duration of action of naloxone may be shorter than the opioid duration of action)

Risk of limited Efficacy with Partial Agonists or Mixed Agonists/Antagonists

- Reversal of respiratory depression caused by buprenorphine/pentazocine, may be incomplete. Larger or repeat dosing may be needed

Precipitation of Severe Opioid Withdrawal

- Use in patients who are opioid dependent may precipitate opioid withdrawal. In neonates, this may be life-threatening if not recognized and properly treated.
- Opioid withdrawal: body aches, diarrhea, fast heart rate, fever, runny nose, sneezing, piloerections, sweating, yawning, n/v, nervousness, restlessness/irritability, shivering, stomach cramping, weakness, increased BP

Risk of Cardiovascular Effects

- Abrupt postoperative reversal of opioid depression may result in adverse CV effects. These events have primarily occurred in patients who had pre-existing CV disorders or received other drugs that may have similar adverse CV effects. Monitor these patients closely and in an appropriate healthcare setting after use of Narcan.

Opioids: MOA

- Act on central and peripheral mu-, kappa- and delta-opioid receptors to inhibit the transmission of nociceptive input and the perception of pain.

Opioids vs Opiates

- Opioids
- Semi-synthetic: oxycodone, hydrocodone
- Synthetic: fentanyl, tramadol, methadone

- Opiates
- Compounds that occur naturally in the opium poppy
- Morphine
- codeine

Opioid Formulations

- IR/SA
- ER/LA
- Administration via many routes, most common for CNCP is oral and transdermal
- ER/LA formulations not recommended for opioid naïve patients

Codeine (3-methylmorphine)

- Naturally occurring methylated morphine
- Has no intrinsic analgesic effect- must be metabolized to morphine in the liver via CYP2D6 for analgesia
- This genetics based interpatient variation produces considerable variability in the therapeutic response to recommended codeine dosing- ranging from lack of effect to fatal respiratory failure in ultra-rapid metabolizers

CYP2D6 Activity Variation

- >70 alleles, one from each parent
- Level of enzyme activity ranging from :
- Normal function = 1
- Reduced function= 0.5
- No function= 0
- Poor metabolizers overrepresented in people of northern European/Caucasian decent
- Ultra-rapid metabolizers: ~29% African/Ethiopian heritage
- ~21% Saudi Arabia/Middle Eastern
- ~3.4-6.5% of African-American and white persons
- Poor metabolism less common than intermediate or ultra-rapid

Opioid Selection

- **Following short acting opioid are equally efficacious** when administered for a variety of painful conditions .
- Oxycodone 5 mg,
- Hydrocodone 5 mg,
- Codeine 30 mg, and
- Tramadol 50 mg, each in combination with acetaminophen or ibuprofen.

Avoid Codeine/Tramadol in Adolescents

Codeine/Tramadol Dangers

- Since 1969, codeine has been linked to 64 cases of serious breathing problems, including 24 deaths in children/adolescents
- Tramadol is not approved for pediatric use, but has been tied to nine cases of serious breathing problems, including 3 deaths in children/adolescents
- Reports of breathing problems in breastfed infants whose mothers were taking codeine

Opioids: Pure Agonists and Agonist-Antagonists

- Buprenorphine: agonist with high affinity but low intrinsic activity at the mu opioid receptor, antagonist at the kappa receptor
- Often used as maintenance therapy for OUD, but also FDA approved for severe, refractory chronic pain
- Buccal and transdermal preparations available for chronic pain- formulations do not contain naloxone and doses for chronic pain typically much lower than those used for OUD treatment
- Starting dose for buccal film for chronic pain is 75mcg (compared with 2.1mg/0.3 for OUD therapy starting dose)
- In the US, special license required to rx for OUD, not needed if rx is only for chronic pain

Buprenorphine: Advantages and Concerns

- Less physical dependence and associated with less hyperalgesia compared to pure agonist opioids
- Ceiling effect for respiratory depression, but not for analgesia
- **This benefit is negated if taken along with other CNS depressants!**
- If overdose does occur – very high doses of naloxone may be needed (due to the high affinity for the mu-opioid receptor)
- Does not accumulate in patients with renal failure, and is not removed by dialysis

Methadone and Fentanyl

SHOULD ONLY BE PRESCRIBED BY PROVIDERS FAMILIAR WITH THESE MEDICATIONS

CLOSE MONITORING

QT MONITORING WITH METHADONE

Tramadol : Mixed Mechanism

- Centrally acting analgesic, synthetic codeine analogue
- Pro-drug, metabolized to O-desmethyl tramadol
- MOA based both on mu receptor binding and monoamine reuptake blockade
- Can increase risk of seizures, especially if taken in high doses, with antidepressants, also increased risk of serotonin syndrome
- Reports of seizures even at doses as low 75mg
- Other noted rx factors for seizures on tramadol include: Asian decent, hx of ETOH abuse, CA, renal failure, head injury, stroke, age 24-54

Common Side Effects of Opioids

- Constipation (do not usually develop tolerance to this)
- n/v
- Sedation
- Impaired psychomotor function
- Urinary retention
- Marked interindividual variability- maybe d/t genetic differences, age, comorbidity and interactions with other drugs
- Opioid-induced delirium
- Myoclonus

Adverse Effects of Prolonged Opioid Use

- Hyperalgesia
- Sexual dysfunction
- Fatigue
- Depression
- Arrhythmias (methadone)
- Narcotic bowel syndrome
- Opioid-induced sleep disordered breathing
- Pruritis
- Infection risk (d/t immunosuppressive properties)
- Weight gain and abnormal glycemic control

Opioid Tolerance

Predictable neuro-adaptive process, resulting in the loss of effect over time

Consider opioid rotation

When switching opioids, important to keep in mind equianalgesic dosing and start at half the dose

Avoid increasing the daily MME in the process of opioid rotation

Narcotic Bowel Syndrome (NBS)

- Frequent or longstanding abdominal pain that is associated with long-term use of opioids
- Centrally-mediated, hyperalgesic syndrome caused by opioids
- Pain is often worsened by increasing doses of opioids or with longer duration of use
- Estimated that 1/20 on chronic opioids will develop NBS
- Psychiatric co-morbidity likely worsens NBS
- Pathophysiology is currently unknown, but likely complex
- TX is gradually withdrawing the opioid, TCA's/SNRI/clonidine` help with pain

Opioid-Induced Hyperalgesia

- Characterized by a paradoxical response whereby a patient taking opioids for pain may actually becomes more sensitive to certain painful stimuli
- May experience pain from ordinarily non-painful stimuli (allodynia)
- Improvements in pain following opioid dose reduction
- Consider opioid taper, rotation

Opioid Amnestic Syndrome

- Acute onset of amnesia and hx of prior opioid use
- MRI findings of bilateral hippocampal ischemia
- Fentanyl is implicated
- Approx 19 cases in the US and Canada

Preferred analgesic medications for chronic pain management in CKD stages 4 and 5

TCA- tricyclic antidepressant.

WHO step	Recommended	Use with caution	Do not use
1	Acetaminophen		NSAIDs
2		Tramadol	Codeine
3	Hydromorphone Fentanyl, alfentanil Methadone Buprenorphine	Oxycodone	Morphine Meperidine Propoxyphene
Adjuvant	Gabapentin Pregabalin	TCAs	

Management of Pain in Hepatic Dysfunction

- Mild liver disease: generally can be treated with similar choice of drugs as normal population
- Susceptibility to adverse effects increases with worsening liver function
- Exact cutoff at which drug selection/dosing should be altered is uncertain
- Modification generally for patient's with advanced chronic liver disease or cirrhosis, especially when accompanied by portal HTN or renal insufficiency

Important Exceptions

- Those who are actively consuming ETOH and those on multiple meds, who can develop severe hepatotoxicity from concomitant use of acetaminophen regardless of the severity of liver disease

Hepatic Dysfunction: Non-Opioid

- Acetaminophen generally safe in CLD or cirrhosis up to 2G/day (provided not ETOH use as this further reduces glutathione stores)
- Warn patients about cumulative drug in other meds (i.e., opioid preparations, OTC preparations
- Avoid use in pts with advanced CLD/cirrhosis who are actively consuming ETOH, malnourished, not eating or receiving multiple meds that undergo hepatic bio-transformations, or any co-administered med that is a potent inducer of hepatic enzymes

NSAIDS in Hepatic Dysfunction

- Avoid NSAIDS/ASA in advanced CLD/cirrhosis
- d/t prostaglanding inhibition and increased bioavailability in these pts, NSAIDS can precipitate acute renal failure and GI bleeding, thrombocytopenia, variceal hemorrhage, and development of diuretic-resistant ascites
- This goes for COX-2 as well- pending the availability of additional safety data
- Further research is needed to evaluate safety of topical NSAIDS in this population

Hepatic Dysfunction and Opioids

Use opioid very cautiously, if at all, in patient's with advanced liver disease/cirrhosis

Chronic use of any opioid may lead to tolerance, requiring escalating doses and therefore increasing the risk of hepatic encephalopathy

Fentanyl

- Fentanyl- generally a good choice for pts with CLD or cirrhosis when an opioid is indicated
- Useful option in pts with renal failure in setting of cirrhosis
- No dose adjustment needed for single dose
- Repeated dosing, reduce dose and frequency by 25-50%

Hydrocodone, Oxycodone

- Metabolized to active metabolite by CYP2D6 and CYP3A4- may result in a prolonged time to onset, variable analgesic efficacy, and risk of accumulation in pts with advanced CLD/cirrhosis
- Fentanyl or hydromorphone likely a better option
- If used , reduce dose and frequency , avoid ER formulations (this goes for all opioids)

Hydromorphone

- Generally a good choice for advanced CLD/cirrhosis
- Hepatically metabolized by non-CYP transformations to apparently inactive metabolites, so oral bioavailability increased d/t diminished first-pass extraction
- Reduce dose and frequency by ~50%
- Titrate dose gradually to avoid accumulation of active drug
- First choice opioid in pts with concomitant renal failure; start with 1mg every 6 hours as needed

Meperidine

- Meperidine and Codeine should be avoided in pts with advanced CLD or cirrhosis!

Morphine

- Oral bioavailability in advanced CLD or cirrhosis increased up to 100% relative to normal population (hepatically metabolized by non-CYP transformations (glucuronidation))
- If used, reduce dose and frequency by ~50%, titrate gradually
- AVOID in pts with cirrhosis and renal failure

Naloxone-containing Opioids

- Use in advanced CLD/ cirrhosis is CI'd
- Systemically absorbed in patients with moderate-severe hepatic impairment
- Systematic absorption will reverse analgesic efficacy and can precipitate opioid withdrawal

Remifentanil

- No adjustment needed- does not accumulate in hepatic or renal insufficiency
- Cleared by nonspecific plasma esterases to inactive metabolites
- Prompt reversal of analgesia and sedation upon discontinuation

Tramadol

- Avoid use in decompensated cirrhosis
- Avoid use in patients at risk for seizures
- Based on limited experience, a reduced dose of 25mg tid may be considered for TX of pain in patients with advanced CLD or well-compensated cirrhosis
- Can interact with serotoninergic meds, including SSRI/SNRI

Opiates and the Law

CDC, STATE AND KAISER PERMANENTE GUIDELINES.

CDC Guidelines Opioid Prescribing for Chronic Pain- 12 Recommendations

#1) Determine when to initiate/continue opioids : opioids are NOT first line and should not be the sole treatment strategy for chronic pain treatment.

Non-pharmacologic treatments:

- PT
- CBT
- Exercise/aquatic therapy/Tai Chi/Yoga/Pilates
- Acupuncture
- Topical therapies
- CSI/ESI

2) Establish Realistic Goals for TX of Pain Before Starting Opioids

- Consider you are likely starting TX for chronic pain anytime >30 day supply of opioids is given
- How will effectiveness be evaluated? (validated scale)
- Establish TX goals with patient, including expectations for monitoring, situations for discontinuing or tapering
- Have an exit strategy if therapy is unsuccessful

Assess progress using 3-item validated PEG Assessment Scale

- Pain average (0-10)
- Interference with Enjoyment of life (0-10)
- Interference with General activity (0-10)

*Clinically meaningful improvement defined as 30% improvement in scores for both pain and function

3) Discuss Risks/Potential Benefits of Opioid Therapy Before Starting and Periodically Throughout Treatment

- Be explicit/realistic about benefits: role in short-term management, but no evidence for opioids improving pain/function with long-term use- in fact, many studies showing pts on opioids reporting higher levels of pain with chronic use
- Anticipatory Guidance:
- Serious ADRs (fatal respiratory depression, opioid use disorder)
- Common ADRs: constipation, tolerance, withdrawal symptoms with interruption/cessation, depression, fatigue, sexual dysfunction, hyperalgesia

Overdose Risk

- Risk is 5 fold increased with MEQ of 50 and above
- Risk is at least 10 fold increased with MEQ 90 and above
- Substantially increased risk if combining opioids with other CNS depressants (benzodiazepines, z-drugs, ETOH

4) Immediate-Release

Use immediate release opioids in opioid naïve patients (vs ER formulations)

Avoid using Methadone first line

5) Lowest Effective Dose

- Use caution when prescribing opioids at any dose
- Carefully reassess evidence of individual benefits and risks when considering increasing dosages to 50 MEQ or greater
- Avoid increasing dosage to 90 MEQ or greater (or carefully justify a decision to do so)

6) Prescribe Short Durations for Acute Pain

Long-term opioid use often begins with TX of acute pain

Use the lowest effective dose for the shortest duration of time

3 days or less is often sufficient,
Greater than 7 days should rarely be needed

7) Evaluate Benefits and Harms Frequently

- Within 1-4 weeks after starting or after dose escalation
- Re-evaluate at least every 3 months

8) Use Strategies to Mitigate Risk

- Before starting, periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms.
- Offer Naloxone, educate.
- Avoid starting opioids in **high-risk** populations:
  - hx of substance use disorder (or active SUD)
  - Hx of depression/anxiety
  - Family hx of SUD
  - benzodiazepine use
  - ETOH use

9) Review PDMP Data

CURES-

Monitor this when starting opioid therapy, and at least every 3 months thereafter.

10)Use Urine Drug Testing

Check UDS prior to starting opioid therapy and at least annually thereafter.

Consider more frequent testing for high-risk patients

11) Avoid Concurrent Opioid and Benzodiazepine Prescribing

- **Avoid whenever possible!**

12) Offer Treatment for Opioid Use Disorder

- Offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

2019: KP Updates Opioid Escalation Practice Recommendation (OEPR)

CMS Opioid Care Coordination Edit

- Applies to Medicare Part D members
- If MME >/= to 90, an alert will be triggered
- Prescriber may be contacted by the pharmacist

CMS 7-day supply limit for opioid naïve patients

- Applies to Medicare Part D members
- Applies to a member who has not filled an opioid rx within the past 90 days and presents an rx to the pharmacy that is greater than a 7-day supply

National Permanente Medical Groups 2019 Clinician Practice Recommendations For Opioid Prescribing

Severe, Acute Pain in an Opioid-Naïve Patient

- If opioid needed: non-refillable, 3-day supply
- Rxs of up to 12 pills for non-surgical pain, with a MAX of 20 pills
- Target dose: </= 20MM/day- with MAX 49MME/day
- **Larger amounts should include medical justification**
- Goal is to avoid overprescribing and minimize potential for physical dependence and/or addiction

Post-Procedural and Post-Surgical Pain

- Recommend a quantity sufficient to cover the expected duration of severe pain, which is **typically 2-3 day supply**. Then transition to non-opioid pain management.
- Quantities: up to 20 pills for post procedural/surgical- with a MAX of 50 pills
- Larger amounts should include medical justification.
- Goal is to TX with opioids at the lowest effective dose for the shortest duration of therapy necessary for severe pain management, **maximum of 5 days (including the days post-op in the hospital).**

- Realizing there may be specific situations in which a longer course may be needed, should avoid >14 days total to decrease the risk of serious side effects and long-term dependence.
- Optimizing opioids for post-surgical patients should be in the context of multi-modal pain management

Breaking the Cycle

- Break the cycle of new dependence/addiction
- Studies show increasing rates of drug dependence after just >3-5 days of prescribing with significant long-term consequences.
- Avoid range dosing

LA Opioids?

- Long-Acting Opioid prescriptions should not be prescribed for patients who are opioid-naïve and/or acute pain.
- Long Acting Opioid prescriptions should not be prescribed "PRN"

Additional Recommendations

- Remember: there is no evidence to support the use of ever-increasing doses of opioids for non-cancer pain. There is now evidence that this leads to harm.

Opioid Use with Concomitant Benzodiazepine/Hypnotic-Sedatives

- Avoid at all costs d/t substantially increased risk of morbidity and mortality
- This included benzodiazepines, skeletal muscle relaxants and barbiturates, z drugs
- Due to increased risk of cognitive impairment, one should avoid using opioids for patients who choose to use marijuana.
- Recent 5 year KP review showed significant increased risk of OD in patients taking opioid + benzo or sedative, and the highest risk was observed in patients taking all three (opioid + benzo+ sedative-hypnotic)
- If pt is unable to discontinue the benzo or opioid, the maximum opioid dose should not exceed 20 MME/day

Opioids with Alcohol Use

- Screen patients to identify concurrent use of opioids/ETOH
- Avoid using opioids for patients who choose to consume ETOH
- Hx of ETOH use disorder should be a significant criterion for avoidance of the use of opioids
- Nearly 30% of adults in the US have unhealthy ETOH use; 13% have a diagnosed ETOH use disorder.

Tapering High Dose (90 MME and Above)in Chronic Pain Patients

- Goal is to taper opioids to <50 MME (and definitely LESS than 90 MME/day)
- If on concurrent benzodiazepines- goal is to taper OFF opioids, or less than 20 MME if clinically justifiable.

Strongly Consider Discontinuing Opioid Therapy When:

- Patient does not have clinically meaningful improvement in pain AND function
- Shows signs of SUD
- Experiences overdose or another serious adverse event
- Has or exhibits other risk factors for overdose

Tapering Schedules

- Individualize to minimize symptoms of opioid withdrawal, and maximize pain treatment with non-opioid and non-pharma therapies
- Examples include 5-10% per day
- 5-10% per week
- 5-10% per month
- CDC guidelines of tapering opioids by 10% per week are based on studies on addiction TX
- Patients with chronic pain may benefit from smaller reductions over a much longer period of time

Hx of Illicit Drug Use/ SUD

- Due to the significant risk of triggering relapse, history of illicit drug use and/or substance use disorder should also be a significant criterion for avoidance of the use of opioid medications.

California Law: AB 2760 "Naloxone Prescribing Law"

- Prescribers are required to offer an rx for Naloxone or other FDA approved drug for the complete or partial reversal of opioid depression to a pt when the following conditions are present:
  - MME 90 or greater (at KP we offer at 50 or greater)
  - An opioid is prescribed to a pt with an active rx for a benzodiazepine
  - There is an increased risk of OD (ie. hx of OD, hx of SUD).

Medical Board of California (MBC) Prescriber Guidelines for Substances for Pain

When to Initiate or Continue Opioids for Acute Pain and Chronic (non-cancer)Pain

Acute Pain

- Only use when the severity of the pain warrants it
- Only use after determining that other non-opioid pain medications or therapies likely will not prove adequate pain relief

Long Term

*When considering long-term use of opioids for chronic, non-cancer pain, the physician and patients should develop treatment goals together

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

- Only order enough pills to cover a short duration of time (think usual duration of pain- do not prescribe more than that).
- Do not use LA/ER opioids for acute pain, including post-op pain, except in situations where monitoring and assessments for adverse effects can be conducted
- Methadone is rarely, if ever, indicated for treatment of acute pain
- The use of opioids should be re-evaluated carefully if persistence of pain suggests the need to continue opioids beyond the anticipated time period of acute pain treatment for that condition.
- TX plan and goals should be established as early as possible in the process and revisited regularly.

ED or Urgent Care Clinics

- Avoid the routine prescribing of outpatient opioids for a patient with acute low back pain, or an acute exacerbation of chronic non-cancer pain
- If prescribed on d/c, lowest practical dose for a limited duration (< 1 week)!!
- Consider the patients risk for opioid misuse, abuse or diversion
- Honor existing patient-physician pain contracts/treatment agreements and consider past prescription patterns from CURES

When Considering Long-Term Use of Opioids for Chronic, Non-Cancer pain, Detailed Patient Assessment is Critical

- The nature and extent of clinical assessment depends on pain and the context in which it occurs- including:
- Complete H&P
- Performing a psychological evaluation (also consider screening tools for addiction risk like **ORT, CAGE-AID)**
- Establishing a dx and medical necessity including **Pain Intensity and Interference** (pain scale) and **Sheehan Disability Scale**
- Exploring non-opioid therapeutic options- (**Non-Opioid Pain Management Tool** by Jeremy Biggs MD MSPH)
- Risks vs benefits
- Being aware of aberrant or drug seeking behaviors
- UDS
- CURES

- Consider referring patient to IPMP, Psychiatry, Addiction Med
- Be familiar with the treatment options for opioid addiction and be prepared to make referrals when needed
- If prescribed, pt and family should be counseled on safe ways to store and dispose of medications
- MBC recommends that a patient consent form and pain management agreement be signed
- Educate patients and family/caregivers of signs of respiratory depression
- CURES monitoring, drug testing, periodic pill counting is recommended.

Patient Consent

- Document in chart!
- Typically addresses: Potential risks/anticipated benefits
  Potential short/long term SE's
  Likelihood of tolerance/physical dependence
  Risk of drug interactions and over-sedation
  Risk of respiratory depression
  Risk of impaired motor skills (affecting driving..)
  Risk of misuse/dependence/addiction/overdose
  Limited evidence as to the benefit of long-term opioid therapy

Pain Management Agreement

Recommended when:

- On short acting opioids at the time of the 3rd visit within 2 months
- On long acting opioids
- Expected to be on opioids >3 months
- **In HC, .Narcotics Treatment Agreement (make it your own, and include informed consent so it's all done at the same time- place on patients AVS)**

Primary Differences (CDC vs MBC)

- 1) MBC recommends referral to pain specialist, CDC encourages PCPs to manage their patients pain
- 2) MBC endorses up to 45 days for initiating opioid trial, explaining that there is risk after 90 days; CDC notes risk after 7 days
- 3) CDC cautions when increasing from 50 MME/day and to avoid increasing past 90. MBC recommends a prescriber proceed with caution once 80 MME/day is reached.

What's On the Horizon?

- FDA demands studies of whether opioids do control chronic pain
- Whether there is declining efficacy, and whether that declining efficacy can lead to addiction
- New research will be required for all current and future opioids other than short acting ones used in hospitals
- Negative results could (and should) lead to further restrictions on prescribing
- Recent meta-analysis suggested that opioids have no clear advantage over other analgesics in controlling chronic pain
- FDA will order a second study, to determine whether opioids do induce hyperalgesia

- Push to recognize prescription opioid dependence as a distinct clinical condition
- Recognizing dependence as a distinct condition may contribute to reducing stigma associated with the condition, and allow for the use of management interventions that will lower the risk for morbidity
- Would also allow for buprenorphine indications to be expanded to this population

1. 1.Overdose death rates. National Institute on Drug Abuse website. Dec. 2015. Available at: www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed May. 23, 2019.
2. 2.Society guideline links: Opioid use disorder and withdrawal. https://www.uptodate.com/contents/society-guideline-links-opioid-use-disorder-and-withdrawal?topicRef=7804&source=see_link. Accessed May. 23, 2019.
3. 3.Health and Public Policy to Facilitate Effective Prevention and Treatment of Substance Use Disorders Involving Illicit and Prescription Drugs: An American College of Physicians Position Paper. https://annals.org/aim/fullarticle/2613555/health-public-policy-facilitate-effective-prevention-treatment-substance-use-disorders. Accessed May. 23, 2019.
4. 4. Opioid Overdose Crisis. https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis
5. Accessed May. 24, 2019. Benzodiazepines and Opioids. https://www.drugabuse.gov/drugs-abuse/opioids/benzodiazepines-opioids. Accessed May. 24, 2019.

6. Drug Interactions between benzodiazepines and opioids & back to basics of Pharmacology. | The BMJ.https://www.bmj.com/content/356/bmj.j760/rr. **Accessed June. 1, 2019.**

7. FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use | FDA. **https://www.fda.gov/news-events/press-announcements/fda-requires-strong-warnings-opioid-analgesics-prescription-opioid-cough-products-and-benzodiazepine. Accessed June. 1, 2019.**

8. Prevention of lethal opioid overdose in the community. https://www.uptodate.com/contents/prevention-of-lethal-opioid-overdose-in-the-community?search=cdc%20guidelines%20opioid%20and%20opioid%20antagonists&source=search_result&selectedTitle=6~150&usage_type=default&display_rank=6#H1793708267. Accessed May. 24, 2019.

9. CDC Guideline for Prescribing Opioids for Chronic Pain. https://www.cdc.gov/drugoverdose/prescribing/guideline.html. Accessed May. 24, 2019.

10. 2018 ANNUAL SURVEILLANCE REPORT OF DRUG-RELATED RISKS AND OUTCOMES UNITED STATES Centers for Disease Control and Prevention National Center for Injury Prevention and Control. https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf. Accessed June. 1, 2019.

11. What Healthcare Providers Need to Know about PDMPs. https://www.cdc.gov/drugoverdose/pdmp/providers.html. Accessed June. 1, 2019.

12. Alert: April 2019 Update to Opioid Escalation Practice Recommendation (OEPR). Kaiser Permanente, California Pharmacy Operation. SCAL 2019 Updated edition.
13. Prescription drug misuse: Epidemiology, prevention, identification, and management
https://www.uptodate.com/contents/prescription-drug-misuse-epidemiology-prevention-identification-and-management?csi=ad4e016e-c245-447a-ac5b-ff9f008e02f9&source=contentShare
14. Science Daily: Impact of neonatal abstinence syndrome on state Medicaid programs. March 26, 2018, Vanderbilt University Medical Center
15. Substance use, the opioid epidemic and the child welfare system: Key findings from a mixed methods study, 3/7/2018. The US Department of Health & Human Services
16. CDC Data Show U.S. Life Expectancy Continues to Decline. AAFP December 10, 2018

- Kong EI, Burns B. Narcotic Bowel Syndrome. [Updated 2019 Jan 11].
- Ncbi.nlm.nih.gov
- The Narcotic Bowel Syndrome: Clinical Features, Pathophysiology and Management. David M.S. Grunkemeier, MD, Joseph E. Cassara, MD, and Douglas A. Drossman, MD, FACP. Clin Gastroenterol Hepatol. 2007