PALLIATIVE CARE NETWORK OF WISCONSIN

Care Strategies for Identifying and Managing Aberrant Behaviors with Opioids CME Module

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Care Strategies for Identifying and Managing Aberrant Behaviors with Opioids CME Module
Course Description and Learning Objectives

Course Description: Aberrant behaviors, addiction, involuntary and voluntary diversion, and abuse can occur even among seriously ill patients prescribed opioids under the careful supervision of a treating clinician. In addition to the known public health threats, these behaviors can be damaging to the well-being of the patient and family as they cope with a serious illness. Clinicians who care for patients with illnesses such as advanced cancer, organ failure, dementia, or other serious illnesses need to be able to make informed decisions about the use of opioids for acute and chronic pain management. In order to do this, clinicians must be able to distinguish aberrant drug behaviors identify from expected physiologic responses to opioids such as tolerance and physical dependence. In this module, users can attain 1.0 hours of CME credit after successful completion of the following:

A. Content review of ten *Fast Facts and Concepts* covering the following topics:
    a. Naloxone including inpatient and outpatient use.
    b. Distinguishing pain from addiction
    c. Diagnosis and management of opioid withdrawal
    d. Substance use disorders in the palliative care patient
    e. Screening for opioid misuse and abuse in seriously ill patients
    f. The treatment of pain in patients taking buprenorphine for opioid addiction
    g. Opioids for chronic pain in patients with a history of a substance use disorder
B. Score of 70% or higher on a 10 question quiz covering this content
C. Completion of a course evaluation.

Learning Objectives: At the conclusion of this course learners will be able to:

1. Define addiction, opioid abuse, involuntary diversion and voluntary diversion and be able to distinguish these terms from physical dependence and opioid tolerance.
2. Describe at least two evidence-based screening tools for identifying opioid misuse and abuse in seriously ill patients.
3. Safely manage the symptoms of opioid withdrawal when opioids are discontinued

FAST FACTS AND CONCEPTS #39
USING NALOXNE

Colleen J Dunwoody MS, RN and Robert Arnold MD

Background Naloxone (Narcan®), a semisynthetic opioid antagonist, is indicated for the complete or partial reversal of life-threatening CNS/respiratory depression induced by opioids. Naloxone is often inappropriately used in the hospital setting, administered as a full ampule (0.4 mg) in response to physiologically normal opioid-induced decrease in respiratory rate or mild sedation. This probably comes from application of principles of use in the Emergency Department to other settings. Of note, it is normal to have a lower respiratory rate during sleep, especially on opioids. Mild bradypnea, which is not associated with physiologic consequences like hypoxemia, should be closely monitored.

Depending on the dose administered, naloxone administration to a patient physically dependent on opioids will cause the abrupt return of pain and can precipitate an abstinence (withdrawal) syndrome, with symptoms ranging from mild anxiety, irritability and muscle aches to life-threatening tachycardia and hypertension. Once thought to be devoid of side effects, naloxone can cause cardiovascular collapse and pulmonary edema, probably through abrupt increase in sympathetic nervous system activity associated with opioid reversal.

Key Teaching Points

1. Review treatment goals; naloxone administration is not indicated for patients on opioids who are dying (see *Fast Fact* #3), as all dying patients will at some point have an altered mentation and respiratory changes. It may be necessary to write specific orders **not** to administer naloxone.
2. Patients should meet all of the following criteria before naloxone is administered:
    a) Depressed mental status: difficult to arouse or unarousable (if the patient wakes to voice or light shake, the diagnosis is sleeping, not opioid overdose).
    b) Shallow respirations or rate less than 8/minute, associated with evidence of inadequate ventilation (e.g. low oxygen saturation, hypotension). Note: some people breathe at 6-8 per minute when they sleep yet are well ventilated.
3. Stop opioid administration.
4. Dilute 0.4 mg naloxone (one ampule) with normal saline to a total volume of 10 ml (1 ml = 0.04 mg naloxone).
5. Remind the patient to breathe; though narcotized, patients report hearing concerned staff and being unable to open their eyes or respond. Reminders to “take a deep breath” are often followed.
6. Administer 1 ml IV (0.04 mg) q1min until the patient is responsive. A typical response is noted after 2-4 ml with deeper breathing and greater level of arousal. Gradual naloxone administration should prevent acute opioid withdrawal.
7. If the patient does not respond to a total of 0.8 mg naloxone (2 amps), consider other causes of sedation and respiratory depression (e.g. benzodiazepines, stroke).
8. The duration of action of naloxone is considerably shorter than the duration of action of most short-acting opioids. A repeat dose of naloxone, or even a continuous naloxone infusion, may be needed.
9. Wait until there is sustained improvement in consciousness before restarting opioids at a lower dose.

Final notes: After the patient is stable, review events leading up to the patient requiring naloxone and address oversights and errors which lead to this complication of opioid therapy. Review your institution’s

policy on naloxone administration. Is it appropriate? If not, write one; see (2) for a recommended nursing protocol.

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FAST FACTS AND CONCEPTS #68
IS IT PAIN OR ADDICTION?

David E Weissman MD

Background A very commonly requested educational pain topic by clinicians, surrounds differentiating the patient in pain from the patient with a substance abuse disorder. The key to proper assessment lies in understanding 1) the definitions of tolerance, physical and psychological dependence, 2) the components of an addiction assessment, and 3) the differential diagnosis of the symptom of "pain."

Definitions

- *Tolerance*: the need to increase a drug to achieve the same effect. In clinical practice, significant opioid tolerance is uncommon. Tolerance may be present in the pain patient or the addict; by itself it is not diagnostic of addiction.
- *Physical Dependence*: development of a withdrawal syndrome when a drug is suddenly discontinued or an antagonist is administered. Most patients on chronic opioids will develop physical dependence; its presence cannot be used to differentiate the pain patient from the addict.
- *Psychological Dependence* (Addiction): overwhelming involvement with the acquisition and use of a drug, characterized by: *loss of control, compulsive drug use, and use despite harm.* Research suggests that opioids used to treat pain rarely leads to psychological dependence.

Addiction (Substance Abuse) Assessment Assess for addiction in the domains presented in the list below (see Reference 1). Note: one positive item from the list does not establish a substance abuse disorder. Rather, the diagnosis rests on a pattern of behavior that includes several positive findings (see Reference 4).

- Loss of control of drug use (has no partially filled med bottles; will not bring in bottles for verification).
- Adverse life consequences – use despite harm (legal, work, social, family).
- Indications of drug seeking behavior (reports lost/stolen meds, requests for high-street value meds).
- Drug taking reliability (frequently takes extra doses, does not use meds as prescribed).
- Abuse of other drugs (current/past abuse of prescription or street drugs).
- Contact with drug culture (family or friends with substance abuse disorders).
- Cooperation with treatment plan (does not follow-up with referrals or use of non-drug treatments).

Differential Diagnosis The differential diagnosis for a patient reporting "pain" includes physical causes (broken leg, sciatica, pseudoaddiction – see *Fast Fact* #69); psychological causes (depression, anxiety, hypochondriasis, somatization disorder, etc.); spiritual causes (impending death, grief); substance abuse; and secondary gain/malingering/criminal intent (desire for attention, disability benefit, or financial gain from pain medications).

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FAST FACTS AND CONCEPTS #95
OPIOID WITHDRAWAL

Debra Gordon RN and June Dahl PhD

Background Physical dependence is a normal and predictable neurophysiological response to regular treatment with opioids for more than 1-2 weeks duration. Continuous or near continuous opioid blood levels are required (one oxycodone-acetaminophen tablet per day will not lead to physical dependence). Physical dependence is characterized by a withdrawal syndrome when the opioid is abruptly discontinued, if an opioid antagonist (naloxone) is given, or when drug blood levels fall below a critical level. Withdrawal can also be caused by administration of a mixed agonist-antagonist (e.g., buprenorphine, butorphanol, nalbuphine, pentazocine). Physical dependence is not a defining condition of addiction (see below and *Fast Facts* #68 and #69).

Important definitions

- **Tolerance:** state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug's effects over time.
- **Physical dependence:** state of adaption manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist.
- **Addiction / psychological dependence:** a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors. Characterized by one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Signs and symptoms of the opioid withdrawal syndrome include yawning, sweating, lacrimation, rhinorrhea, anxiety, restlessness, insomnia, dilated pupils, piloerection, chills, tachycardia, hypertension, nausea/vomiting, cramping abdominal pains, diarrhea, and muscle aches and pains. Unlike withdrawal from alcohol or benzodiazepines, opioid withdrawal is not life threatening. Emergence of withdrawal symptoms varies with half-life of the particular opioid; within 6-12 hours after the last dose of a short-acting drug or 72-96 hours following methadone (see *Fast Facts* #75, 86). Duration and intensity of withdrawal are related to clearance of the drug such that withdrawal is shorter (5-10 days) and more intense for opioids like morphine and less severe and more protracted with methadone.

Prevention Opioid withdrawal syndrome should always be prevented. Patients treated with opioids for more than one to two weeks should be instructed to gradually reduce the opioid before discontinuing use. In general, **dose reductions of about 20-25% every day or two** will allow a tapering schedule that will prevent signs and symptoms of withdrawal. An alternative recommendation is to give half the previous dose for the first 2 days and then reduce the dose by 25% every 2 days. When the dose reaches the equivalent of approximately 30 mg/day of oral morphine, this dose is given for 2 days, and then the drug is discontinued. It is important to continue to provide around-the-clock opioids to prevent withdrawal in the patient at end-of-life who is no longer able to communicate or take oral opioids.

Treatment Clonidine 0.1-0.2 mg PO Q 4-6 hours PRN or by transdermal patch (clonidine transdermal 0.1 mg/24hour patch which provides 0.1 mg a day for 7 days) can be used to treat autonomic hyperactivity symptoms. It will not relieve insomnia. The major drawback of clonidine therapy is the tendency to cause hypotension in some patients. Other agents used for control of withdrawal symptoms include: diphenoxylate/atropine (Lomotil), hydroxyzine, trazodone, and dicyclomine hydrochloride (Bentyl). For patients still in pain who have abruptly stopped their opioids (because they ran out, lost their prescription, or stopped because of side effects) reinstituting opioid therapy may be appropriate to treat both their withdrawal symptoms and ongoing pain. Depending on how long a patient has been without opioids it may not be safe to reinstate the full opioid dose immediately (especially for long-acting opioids). In this case patients should go through a dose-titration phase with short-acting opioids to safely achieve analgesia.

This *Fast Fact* was adapted with permission from the University of Wisconsin Hospital & Clinics, Madison, WI Pain Patient Care Team '*Pain Management Fast Facts – 5 Minute Inservice*' series.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #110
URINE DRUG TESTING FOR OPIOIDS AND MARIJAUNA

Marissa Mapa DO and Robert Arnold MD

Background Urine drug testing (UDT) is widely used for testing for opioids and illicit drugs. There are two types of UDT: a screening test and a confirmatory test. The screening test uses an immunoassay to look for the parent drug and/or metabolite. Most UDTs screen for marijuana, cocaine, opiates, PCP, and amphetamines; some also test for benzodiazepines and methadone. The confirmatory urine drug test is done by gas chromatography/mass spectrometry (GC/MS) or high-performance liquid chromatography (HPLC); this test is highly specific and is typically used when testing for the presence of a specific drug is needed.

UDT Interpretation A UDT cannot tell the amount of drug ingested/used or the time of use or the source of drug (intravenous vs. oral vs. inhaled). Detection time of a substance in urine is typically 1-3 days. The rate of excretion varies depending on differences in metabolism/ urinary function. Thus, obtaining history as to when a suspected drug was last used needs to be correlated to the timing of the test. Lipid-soluble drugs (e.g. marijuana) may remain in body fat and be detectable for a week or more.

Typically, the screening immunoassay UDT detects the amount of drug present in urine above a predetermined "cut-off" concentration. Thus, a substance may be present, but if the concentration of that drug is below the cut-off, the result will be negative. If you suspect drug use or desire the confirmation of this substance, ask the urine to be tested with a "no cut-off" or "no threshold testing" or ask for a confirmatory test with GC/MS or HPLC.

If specimen tampering is suspected, ensure the urine is compatible with human physiology. The urine temperature should be 90-100°F; pH between 4.5 – 8.0; and a spot check of urinary creatinine should be greater than 20 mg/dL. A creatinine less than 20 mg/dL is considered dilute; less than 5 mg/dL is not consistent with human urine and the sample should be discarded.

The screening immunoassay test has limited specificity for opiates. The test cannot differentiate morphine from codeine (natural occurring opiates) and will not reliably detect synthetic or semi-synthetic opioids. A confirmatory test is required to test for all opioids.

Knowledge of opiates' metabolism is needed for UDT interpretation. For example, codeine and heroin are both metabolized to morphine, through different pathways and different intermediary metabolites. A prescription for codeine may yield an appropriate positive result for codeine and morphine in the urine. However, if codeine is prescribed and only morphine is found in drug testing, the most consistent interpretation is the unknown use of morphine or heroin. Prescribed morphine will result in only morphine in a sample and not codeine.

The presence of marijuana is detected by the presence of tetrahydrocannabinol (THC), its active ingredient. The screening immunoassay UDT is unable to distinguish between smoked marijuana and the synthetic preparation dronabinol (Marinol).

False positive immunoassays are the result of cross reactivity. Quinolones, specifically levofloxacin and ofloxacin, may give a positive result for opiates.

The cost of a UDT differs from lab to lab and especially in the number of substances tested. The screening test costs between $69 to $148; the confirmatory test ranges from $92 to $165.

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FAST FACTS AND CONCEPTS #127
SUBSTANCE USE DISORDERS IN THE PALLIATIVE CARE PATIENT

Gary M Reisfield MD, Gabriel D Paulian MD, and George R Wilson MD

Background The spectrum of substance use disorders (SUDs) is characterized by increasing degrees of craving, compulsive use, loss of control, and continued use despite harm (see *Fast Fact #68*). Addiction is understood to be a disease with complex genetic, neurobiological, psychosocial, and behavioral determinants. If not properly managed an SUD can: 1) complicate the diagnosis and treatment of psychological (e.g. depression) and physical (e.g. pain) symptoms; 2) compromise compliance with the palliative treatment plan; 3) impair a stressed social support network; 4) weaken trust in patient-physician/nurse relationships; and 5) promote the use of opioids to cope with emotional distress and decision-making – "chemical coping."

Prevalence of SUDs in Palliative Care Patients: Unknown, but it likely reflects that of the general population in which alcoholism and abuse of prescription and non-prescription drugs is common. Bruera reported a prevalence of alcoholism of 27% in patients admitted to a tertiary care palliative medicine unit. Kwon identified an 18% prevalence of chemical coping in a Palliative Medicine clinic. Far from being a source of pleasure, SUDs are more commonly a source of suffering for affected individuals and their loved ones. Addressing addiction may allow for: 1) preservation/restoration of damaged social supports; 2) restoration of self-respect and dignity; 3) accomplishment of end-of-life work through recovery; and 4) improvement in quality of life for patients and families.

Substance Use Disorders and Pain Management Patients with a current or past history of an SUD are particularly challenging. Patients who are in recovery are often fearful of using opioids, even in the setting of severe pain near the end-of-life. Conversely, the ability to complete a pain assessment and use opioids effectively is challenging in patients with an active SUD.

Listed below are suggested management techniques in patients with a past or current SUD.

1. Complete a thorough substance use history. Distinguish between those who have active SUDs from those who are at-risk or in recovery. Validated tools such as the Opioid Risk Tool are available for risk stratification. Explain to patients why your knowledge of this information is important for their care. Be empathic and nonjudgmental.
2. Encourage participation in recovery programs (e.g. 12-step) if the patient is willing and physically able. Consider consultation with an addictions/mental health professional.
3. Formalize a treatment plan and coordinate it with all other involved health professionals.
4. Consider use of a written opioid agreement with carefully defined patient and provider expectations. The need for this agreement to be signed by both the patient and provider is controversial but having an agreement that both patient and provider can refer to can foster clearer expectations for safe opioid use and may foster a sense of control over SUD. Components of an opioid agreement include: establishing a single opioid prescriber and pharmacy, employing regular pill counts and urine drug testing (see *Fast Fact #110*), and utilizing an electronic drug monitoring database.
5. Use non-opioid analgesics and non-pharmacological measures to their full potential; poorly controlled pain can increase substance abuse behaviors (see *Fast Fact* #69).
6. Use opioids at appropriate doses and at appropriate intervals. Titrate long-acting opioids to minimize the need for short-acting opioids.
7. Address anxiety with counseling and antidepressants; this has been shown to reduce illicit drug use in a hospice population (8). Caution with the co-prescription of opioids with benzodiazepines especially in patients with an estimated prognosis longer than a few months. Retrospective analyses have associated their concurrent use with an increased risk of one-year mortality, opioid overdose, respiratory depression, and emergency room visits (11,12).

8. Monitor closely; frequent contact allows for close patient observation and prescription of limited quantities of opioids. Careful monitoring will usually distinguish whether deteriorating function is due to substance abuse or disease progression.
9. Recognize that addiction is a chronic, relapsing illness – and respond with increasing structure and compassion.
10. Develop system policies for identifying and appropriately treating patients with substance abuse.

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FAST FACTS AND CONCEPTS #244
SCREENING FOR OPIOID MISUSE AND ABUSE

Rene Claxton MD and Robert Arnold MD

Background Opioid analgesics are often effective in relieving both cancer and chronic non-malignant pain but can be misused and abused by patients and others (1, 2). Clinicians need to identify patients at risk of misusing prescribed opioids in order to prescribe and monitor opioid therapy safely. This *Fast Fact* discusses how clinicians can screen for risk of misuse. See *Fast Facts* #68, 69, 110, and 127 for further discussions about differentiating pain complaints from abuse, urine drug testing, and substance use disorders in palliative care patients.

Definitions Medication *misuse* is the intentional or unintentional use of a prescribed medication other than as directed. Misuse can include a patient taking more pain medicine than prescribed to control otherwise inadequately controlled pain as well as abusive and addictive behaviors. *Abuse* refers to the intentional self-administration of a medication for non-medical purpose or the use of an illegal drug. *Addiction* is a primary, chronic disease defined by one or more of the following behaviors: impaired control over drug use, compulsive use, continued use despite harm, and craving (4). *Aberrant behavior* is a research term defined differently by various investigators which typically includes activities of misuse and abuse.

Benefits of Screening Opioid therapy is a safe and effective treatment for pain in many patients. However, opioid misuse carries the risk of development of addiction, overdose, and death which require providers to balance individual patient's pain and risk levels. Patients with high risk for opioid misuse should not necessarily be denied opioid therapy but should be followed under closer supervision than those patients with lower risk estimates. In patients with short life expectancies, clinicians may be willing to accept greater risk in prescribing opioids than in patients with chronic non-malignant pain. However, providers should remember that opioids do not improve quality of life for patients who misuse them as a remedy for other symptoms such as anxiety or existential suffering, and that active substance abuse is as devastating to terminally ill patients and families as it is to others (5).

Risk Factors Risk factors for misuse can be grouped into three categories: biological, social and psychological. Biological risk factors include family history of drug abuse and male gender. Social risk factors include poor social support and history of convictions related to drugs or driving while impaired by substances. Psychological risk factors include a personal history of substance abuse (including alcohol or tobacco), pre-adolescent history of sexual abuse, and co-morbid psychiatric illness (i.e. major depression, bipolar disorder, personality disorder) (6).

Screening for Misuse No screening tests have been developed to screen for opioid misuse specifically in cancer patients. However, several screening tests predict the potential for opioid misuse in patients with chronic non-malignant pain. Common instruments include the Screener and Opioid Assessment for Pain Patients (SOAPP) and the Opioid Risk Tool (ORT). While these tools can be applied to patients seen in palliative care settings (such as cancer patients or patients with advanced illnesses), clinicians should be aware they have not been validated in these patient populations. *Clinicians should always keep in mind that these are screening tools used to identify high-risk patients appropriate for close monitoring and further assessment, but are not diagnostic tools to diagnose substance use disorders or to definitively identify patients who should not be prescribed opioids for pain. In addition, they do not assess the risk of diversion of drugs by family or community members.*

- The SOAPP predicts risk potential for aberrant drug behavior via a 14-item self-report. Items included in the SOAPP cluster into categories of: antisocial behavior, substance abuse history, doctor/patient relationship, medication-related behaviors, and psychiatric and neurobiologic need for medicine. Responses are based on a 5 point Likert scale (possible score range 0-56). Using 7 as cut off, this test had a sensitivity of 91%, specificity of 69%, positive predictive value (PPV) of 71%

and negative predictive value (NPV) of 90% (7) to predict aberrant drug behavior. It is important to note that while a score of 7 maximizes this test's sensitivity, i.e. identifies most patients with a risk of opioid misuse, it will also result in a large number of false positive tests given the lower specificity at this cut-off.

- The ORT is a 5-item yes/no tool which predicts the probability of opioid misuse or abuse among patients being considered for opioid therapy for chronic pain. This measure is based on several risk factors including: family history of substance abuse, personal history of substance abuse, age (16-45 years is a risk factor), history of pre-adolescent sexual abuse, and psychological disease. This tool categorizes patients as low, medium or high risk for aberrant behavior. The sensitivity and specificity for the test for patients who score at least 'medium risk' is 99% and 16%, respectively. For those with 'high risk' scores, the test sensitivity is 53% and specificity 96% (8). Because clinicians administering the ORT could be misled by patients with a history of opioid use who downplay past behavior, it is best to apply the tool in lower-risk clinical settings such as primary care rather than in higher risk settings.

Which method is the best way to predict opioid misuse or abuse? In a study of 48 chronic pain patients, the sensitivity of predicting aberrant behavior was compared using three different methods: a trained psychologist's clinical interview, SOAPP and ORT. The clinical interview showed highest sensitivity (77%). SOAPP showed a sensitivity of 73% (score ≥6 as cut-off). ORT showed sensitivity of 45% (score ≥4 as cut-off) (9).

Bottom Line Given the limited number of studies comparing and validating these instruments, it is reasonable to choose a measure based on practicality such as familiarity, ease and time of completion or patient versus provider administration (both the SOAPP and ORT can be completed by patients in less than 10 minutes). Regardless of whether one uses a tool, a thorough history including personal and family history of psychiatric conditions, substance abuse, and sexual abuse is key to identifying patients who need closer assessment and monitoring.

Additional Resources
For an electronic version of the SOAPP, click here: http://www.painedu.org/soapp.asp.
For an electronic version of the ORT, click here: http://www.opioidrisk.com/node/884.

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FAST FACTS AND CONCEPTS #221
TREATMENT OF PAIN IN PATIENTS TAKING BUPRENORPHINE FOR OPIOID ADDICTION

Julie W Childers MD and Robert Arnold MD

Background This *Fast Fact* discusses treating pain in patients using buprenorphine for opioid addiction. Buprenorphine is a mixed opioid agonist/antagonist, available in the United States to treat opioid addiction in the sublingual form as 'Subutex,' and formulated with naloxone as 'Suboxone.' Such use is restricted to qualified physicians who have received training and a waiver to practice medication-assisted opioid addiction therapy. Over the last decade, thousands of physicians have been approved to use buprenorphine for opioid addiction. Given this, clinicians are likely to encounter patients on buprenorphine therapy for opioid addiction who also require treatment for pain. **Note:** buprenorphine is also approved in the US as an analgesic where it is available as an IV solution and a transdermal system (Butrans). When used for analgesia, only proper DEA registration for a controlled III substance is necessary to prescribe buprenorphine. Currently it is more commonly used in Europe than the US as an analgesic. In this *Fast Fact* 'buprenorphine' refers to both sublingual products (Subutex and Suboxone).

Pharmacology Buprenorphine binds to mu-opioid receptors tightly but with low intrinsic activity, providing some analgesic effects but effectively preventing other opioids from binding. This 'blocks' the analgesic and euphoric effects of other opioids, leading to its effectiveness in opioid addiction therapy. Buprenorphine's effect at the mu-opioid receptor lasts 24 to 60 hours, and can lengthen even further with increasing doses. The duration of sublingual buprenorphine's analgesic effects is shorter than its occupation of the receptor – between 6 and 12 hours. When patients on buprenorphine therapy for addiction are in acute pain, the continued interaction of buprenorphine with opioid receptors can limit other opioids' analgesic effectiveness. Naloxone has minimal sublingual bioavailability and is included in Suboxone only to prevent abuse by intravenous injection

Pain Management Strategies While there are no clinical studies addressing how to treat pain in patients taking buprenorphine for opioid addiction, the strategies below are derived from expert opinion, animal studies, federal guidelines, and international experience. As with all patients with pain, non-pharmacologic therapies and non-opioid analgesics should be used when safe and likely to work. The following strategies should be chosen and implemented in close collaboration with the physician treating the patient's opioid addiction.

- If acute pain is anticipated, such as for an elective surgical procedure, adjuvant analgesics and interventional procedures such as nerve blocks should be provided as available.
- For patients with moderate-severe pain who are expected to require opioid analgesic therapy for the short term, federal guidelines recommend holding the buprenorphine and starting short acting opioid agonists. While the buprenorphine's effects diminish (20-60 hours), the patient may require higher opioid doses to compete with the presence of buprenorphine on mu-opioid receptors. The patient should be monitored carefully in the initial period to titrate the opioid agonist dose downward as its effect becomes greater. Before restarting buprenorphine, the patient should be opioid-free for 12-24 hours to avoid precipitating withdrawal. This process should be overseen by an approved buprenorphine provider.
- For patients with mild to moderate acute pain, consider treating the pain with buprenorphine alone. The total daily dose of buprenorphine can be increased (to a maximum of 32 mg sublingual/day); it should be given in divided doses every 6-8 hours.
- Another option is to continue buprenorphine and use short-acting opioid agonists at high enough doses to overcome buprenorphine's partial agonism. Opioids that have a higher intrinsic activity at the mu-opioid receptor, including morphine, fentanyl, or hydromorphone, are reasonable options, while hydrocodone or codeine should be avoided.
- In a patient who is expected to have an ongoing need for pain management, consider replacing buprenorphine with methadone therapy for opioid addiction. For analgesia,

additional methadone or other 'full' mu-opioid receptor agonists can then be added without problems related to use of a partial opioid agonist.

- Patients who have life-limiting illnesses that are expected to cause significant pain are not good candidates for buprenorphine therapy for addiction. A collaborative approach, including patient preference and discussion with both addiction and pain or palliative care specialists, will best identify a therapeutic plan to achieve adequate pain relief and maintain recovery from addiction.

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FAST FACTS AND CONCEPTS #311
OPIOIDS FOR PAIN IN PATIENTS WITH HISTORY OF SUBSTANCE USE DISORDERS
PART 1: ASSESSMENT AND INITIATION
Amy J. Kennedy MD, Robert M. Arnold MD, Julie W. Childers MD.

When is it appropriate to use opioids in the palliative care setting for a patient with a history of a substance use disorder (SUD)? This *Fast Fact* addresses strategies for initiating opioids for patients with a history of SUD; *Fast Fact* #312 will address best practices for monitoring opioids for these patients.

Definitions (1)
SUD**:** a maladaptive pattern of substance use leading to clinically significant impairment or distress.
Aberrant drug behaviors: medication-related behaviors that depart from strict adherence to the prescribed therapeutic plan of care.
Addiction: overwhelming involvement with the acquisition and use of a drug, characterized by: loss of control, compulsive drug use, and use despite harm *(*see *Fast Facts* #68, 69).
Diversion: the illegal transfer of a pharmaceutical controlled substance from the person it was prescribed to another person for use. Patients with SUDs are at higher risk for diversion of opioids.

Risks of opioid therapy in patients with chronic pain and a history of SUD:
- Inability to achieve effective analgesia due to opioid tolerance (2).
- Higher risk of adverse opioid effects when higher doses for extended periods of time are used including unintentional overdose, aberrant drug behaviors, diversion, delirium, and even death (2-5).

Patient selection: The goal is to ensure that opioid prescribing is safe, effective, and does not contribute to worsening of a SUD. Opioids for acute severe pain (such as hospitalization for a broken bone) can be used in a closely monitored setting. Patient selection for moderate-to-severe chronic pain is more complex and involves the interplay of:
- Prognosis of the serious illness
- Status of the SUD: in recovery vs. active substance abuse
- Pain severity, trajectory of tissue injury, and the risk of adverse opioid effects.

Except those with a limited prognosis (e.g. < 2 months) or with an acute pain problem (e.g. bone fracture), we do not recommend starting opioids for patients who are actively using drugs to maintain a SUD (heroin, cocaine, methamphetamine, alcohol, prescription drugs). Marijuana use should be evaluated on a case-by-case basis. Patients with a more distant history of SUD, those who are established in a substance abuse treatment program, and those with aberrant drug behaviors without evidence of a SUD should be evaluated carefully in terms of risk. Long-term opioids for chronic, non-life-threatening conditions are potentially harmful (e.g. chronic headaches, fibromyalgia, chronic lower back pain, osteoarthritis) (2-6). The risks likely outweigh the benefits.

Initial pain assessment: The initial assessment is similar to patients without previously identified SUDs in that a comprehensive identification of the type of pain and its etiology is pivotal. Clinicians should:
- Perform a careful history of past, present, and quantity of tobacco, alcohol, recreational drug use, and prescription drug misuse. Use a validated screening tool to stratify risk of opioid misuse (*FF* #244).
- Differentiate active substance use, at-risk behaviors, recovery, and enrollment in a treatment program.
- Evaluate for potentially treatable psychiatric disorders such as depression and anxiety, which are common both in chronic pain and SUDs (7).
- Assess for current use of sedatives (like muscle relaxants and benzodiazepines (3,4,8).

Initial opioid management
- Describe treatment expectations. Opioids will not completely eradicate pain and their effect on both pain and function may only be short term (6).

- Provide counseling on the associated risks for patients with chronic pain and a history of SUD.
- Though access can be limited, ideally patients with an active SUD and chronic pain are referred to an addiction medicine specialist (6). Multi-disciplinary teams engaging social workers, and mental health professionals can enhance treatment adherence and social support (7,8). See *Fast Fact* #127.
- Use an opioid agreement at initiation of therapy to delineate safe practices and when opioids would be discontinued. Specify the consequences related to the presence of illicit drugs on a urine drug screen (UDS), requests for early refills, or attempts to obtain controlled substances from other clinicians (8).
- For patients on maintenance therapy for opioid addiction such as buprenorphine or methadone, discuss the care plan with the addiction treatment program. If opioids are agreed to be appropriate, be prepared that higher doses may be needed to achieve therapeutic expectations (9,10).
- Published data and expert opinion on the use of long acting opioids in SUDs offer conflicting advice (6,8,10). One study has shown a higher rate of unintentional overdose with long-acting opioids, most pronounced in the first 2 weeks after initiation (11). This may suggest clinicians have a difficult time identifying patients who misuse long-acting opioids.
- A 1-2-week course of short-acting opioids with a follow up date less than 2 weeks may be the safest initial regimen. If available, offer a rescue naloxone prescription and opioid overdose education.
- Combination opioid agonist/antagonist therapy (e.g. oxycodone/naloxone, buprenorphine/naloxone) under the guidance of a pain specialist has shown promise in the treatment of patients with SUD (10).

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FAST FACTS AND CONCEPTS #312
OPIOIDS FOR PAIN IN PATIENTS WITH HISTORY OF SUBSTANCE USE DISORDERS
PART 2: MANAGEMENT AND MONITORING
Amy J. Kennedy MD, Robert M. Arnold MD, Julie W. Childers MD.

Fast Fact #311 discussed the assessment and initiation of opioid therapy in patients with a history of a substance use disorder (SUD). This *Fast Fact* will highlight expert suggested strategies for opioid monitoring in this patient population.

Patient Monitoring: Adherence checklists and individual/group counseling can reduce opioid abuse in high-risk patients (1). Only one clinician and pharmacy should be utilized in providing opioids. Regular follow up visits should be scheduled to assess the "Four A's of Pain" before and after every intervention (2,3): analgesia (pain relief); activities of daily living (functional status); adverse effects; aberrant drug-taking behaviors.

Aberrant Drug Behaviors are not all the same, each behavior should be evaluated based on the specific patient and situation. Clinicians should assess the degree of risk involved with the aberrant drug behavior. Considerations include the extent of the aberrant behavior, including whether it has persisted despite attempts to correct it, if the patient is actively using, the type of substance (opioids, alcohol, methamphetamine, cocaine, cannabis), as well as level of abuse (daily intoxication, binge use).

General Strategies
- Ask patients if they are using other substances or using their opioids to get high or emotionally cope with stressors. Remind patients that these are routine questions asked to all patients.
- Schedule more frequent visits, provide shorter-term prescriptions, and readdress opioid agreements.
- Intensify non-opiate pain strategies.

Patients who are using illegal drugs or abusing alcohol
In addition to the general strategies, consider the type of substance:
- If cannabis or alcohol, perform a patient specific assessment: is there evidence of loss of control or adverse consequences? Taper opioids or intensify monitoring depending on the scenario.
- If cocaine, methamphetamine, or heroin, consider patient's prognosis. Either taper and discontinue opioids, or negotiate use in a highly structured environment and/or ongoing addiction treatment.

Active Substance Abuse: Regardless of the type of aberrant behavior, if the patient is in need of addiction treatment:
- Taper and then discontinue opioid therapy.
- Provide resources for treatment with an addiction specialist.
- Continue to treat pain via non-opioid and non-pharmacologic means -- *"fire the opioid, not the patient".* It is important to maintain a therapeutic relationship with the patient and assure non-abandonment.

Opioid Diversion: Opioid diversion is a serious public health threat with legal ramifications. Patients actively using controlled substances have a higher risk for diversion.

Voluntary diversion occurs when a patient prescribed a controlled substance knowingly transfers it to another person. This can range from "sharing" one or two pills with others to patients selling some or all of the prescribed medications. Treatment teams should inform patients at the beginning of treatment that sharing medication is not permitted, and lost or stolen medications will not be replaced.
- Patients who share medications in small amounts (e.g. giving a pill to a spouse who has acute pain) should be re-educated on the dangers involved and be reminded of opioid agreements/clinic policies.

- Suspected diversion of large amounts of medication should be verified by calling the patient in for a pill count and UDS in the middle of the prescribing period.
- Clinicians should discontinue opioid therapy in patients with whom they have a reasonable degree of suspicion for diversion. Consideration should be given to notification of local police.

Involuntary diversion occurs when a controlled substance is stolen from a patient without their knowledge. This happens more frequently in patients with unstable housing and/or family dynamics.

- Clinicians should discuss safety strategies with patients (e.g. lock boxes) and perform pill counts.
- Clinicians should utilize the help of social workers in determining if exploitation of a vulnerable adult is occurring which could necessitate the involvement of police or adult protective services.
- Consider weaning opioids if involuntary diversion continues given negative public health effects or placing the patient in a more supervised setting such as a nursing home or an inpatient hospice.
- Admission to the hospital to monitor pain management can be a useful management step in situations in which clinicians are suspicious for voluntary or involuntary diversion.

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FAST FACTS AND CONCEPTS #328
NALOXONE FOR OUTPATIENTS AT RISK OF OPIOID OVERDOSE
Marcin Chwistek, MD FAAHPM and Matthew Wolf, RN BSN

Background: In the US, approximately 28,000 opioid overdose deaths occur annually, with at least half of these deaths involving prescription opioids (1). This *Fast Fact* discusses the use of naloxone in the outpatient setting for patients with an advanced illness on opioid therapy who may be at risk for opioid overdose. See *Fast Fact* #39 for further information on naloxone use for inpatient care settings.

Opioid Overdose in Palliative Care Patients: Previous studies have suggested that opioid overdoses are infrequent for patients receiving palliative care (2). In recent years, however, palliative care clinicians have been more routinely involved in the outpatient treatment of cancer pain and, in some instances, may also manage pain in long-term cancer survivors and/or non-cancer pain (2-4). Therefore, there is concern that many palliative care patients may be at risk for opioid overdose given their co-morbidities, relatively high doses of opioids needed to control symptoms, and, in some instances, a history of substance use disorders (see *Fast Facts* #127, 310 and 311) (5). There is also an emerging awareness of inappropriate or excessive use of opioids among patients with cancer-related pain (2).

Naloxone Co-prescribing: In the 1990s, public health and community organizations initiated naloxone distribution programs such as the Overdose Education and Naloxone Distribution (OEND) to prevent opioid overdose fatalities among heroin users (6). Between 1996 and 2010, naloxone was distributed to 50,000 persons, and more than 10,000 overdose reversals were documented (7). In many scenarios, bystanders were able to recognize an overdose from a prescribed opioid and administer naloxone effectively. Federal agencies from the US, Canada, Australia, and many European countries have endorsed the provision of outpatient naloxone as part of a larger strategy to reduce overdose fatalities from prescribed opioids (6). Co-prescribing of naloxone for patients on chronic opioids is currently being implemented through the US Veterans Affairs Medical System (8).

Pharmacology: Naloxone is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. A needle-free formulation which is FDA approved for the emergency treatment of an opioid overdose is available via a pre-filled, single dose intranasal spray. Intranasal administration of naloxone begins to reverse opioid-induced respiratory depression and sedation in 8-13 minutes; peak effect is 20-30 min; and the half-life is about 2 hours (9). The nasal spray is supplied in a box containing two, 4 mg single-use nasal spray devices. A dose can be repeated every 2-3 minutes in alternating nostrils, if necessary (8). In some states, it is available in pharmacies without a prescription. In a study of patients who received naloxone by paramedics, intranasal naloxone was found to be noninferior to intravenous naloxone regarding the reversal of sedation and respiratory rate (10).

Indications For Outpatient Naloxone Prescribing: Co-prescribing of naloxone with prescription opioid medications is still the exception rather than a rule in the palliative care setting. There is a concern that bystanders may administer naloxone inappropriately in seriously ill patients when physiological changes related to disease progression are mistakenly thought to be related to an overdose. The final decision about co-prescribing naloxone should be individualized based on a patient's risk profile, prognosis, care preferences, and the availability of an informed caregiver. Establishing more rigorous evidence-based criteria for co-prescribing is needed, but the following patients may be at risk of an opioid-related fatality when death from their underlying illness is not imminently anticipated (6,11):

- Daily morphine equivalent doses of > 100 mg/day (12,13)
- Methadone as a prescribed analgesic (14)
- Benzodiazepines and/or antidepressants in combination with opioids (15)
- History of unintentional or intentional overdose (16)
- History of a substance use disorder including alcohol or tobacco (17)
- History of chronic pulmonary, renal, or hepatic disease (12)

- A recent history of incarceration (18)

Patient and Caregiver Information: Patients and caregivers should be educated on how to properly identify an opioid overdose and how to administer naloxone. Informational handouts are available for patients and their family members (see reference #19). HIPPA laws allow clinicians to share information to loved one's in the event of a health emergency such as an opioid overdose, specifically when the patient is made incapacitated and/or there is a serious threat to his or her health or safety via opioids (20). Patients and caregivers should be advised to call 911 with any administration of naloxone (19). Naloxone should NOT be administered to patients with comfort goals of care who are imminently dying. This recommendation needs to be clearly communicated to caregivers of patients to avoid inappropriate use. The adverse effects of naloxone administration are primarily opioid-withdrawal related however precipitation of a pain crisis is of serious concern (21). Another concern is the relatively high and raising price of naloxone. As of 2016, estimated costs were $150 for two nasal-spray doses (22).

Gaps in Knowledge: The risks, benefits, safety, and best practices of co-prescribing in the palliative care setting, especially among patients with advanced illness and chronic cancer pain have not been closely examined and require further research.

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