Expanded Skills: Minimizing Opioid Diversion and Overdose Risk

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EXPANDED SKILLS: MINIMIZING OPIOID DIVERSION AND OVERDOSE RISK

Goal

The learner will be able to take steps to limit diversion from the practice and minimize the risk of overdose, educate patients about proper use and storage of pain medications, assess for signs of diversion of pain medications and risk of overdose.

After completing this module participants will be able to:

- Identify patients who are diverting medication, whose medications are being diverted, or who at high risk for diversion or overdose
- Follow clinical protocols that reduce risk of diversion of medications by patients or their family members
- Follow practice management protocols that reduce risk of diversion of medications by patients or their family members
- Follow clinical and practice management protocols that reduce risk of prescription pain medication overdose
- Follow government regulations when prescribing narcotics

Professional Practice Gaps

Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain, developed by the American Pain Society and the American Academy of Pain Medicinechou[1] and more recent guidelines from the CDC on prescribing opioids[2], based on an extensive review of the literature, include recommendations designed to reduce the risk of prescriptions drug overdose and diversion. The need for prescribers to do more to prevent diversion can be inferred from studies showing that a majority of patients do not take their pain medication as prescribed[3] and that the source for the majority of non-medically used prescription drugs is a friend or relative[4]. Research shows that physicians do not follow key recommendations in evidence-based guidelines for avoiding diversion and overdose[5,6]. The need for education/training in the guidelines to avoid diversion and overdose is also evident in results of national physician surveys of physicians[5] and research linking "doctor shopping" to increased risk for overdose[7]. Based on the overall results of their physician survey on the problem of drug diversion, CASA concluded that physicians should receive more continuing medical education related to prescribing and administering controlled substances and identifying, diagnosing, and treating substance abuse and addiction[5].

INTRODUCTION

Contents for this module:

- Recognize diversion
    - Recognize high risk of diversion of prescription medications for substance misuse

    - Recognize signs of diversion
- Practice to prevent diversion
    - Use prescription drug monitoring programs
    - Use clinical protocols that reduce diversion by staff and patients
    - Teach patients to avoid diversion of their medications by others
    - Use practice management protocols that comply with federal and state regulations and reduce the risk of diversion
    - Employ proper safeguards to prevent diversion if opioids are dispensed in the office
    - Work with pharmacists and law enforcement to detect and prevent diversion
- Understand government regulations for prescribing practices
- Be aware of factors that are correlated with opioid overdose
- Take practice steps to avoid overdose
    - Educate patients on how to avoid overdose
    - Use appropriate caution/consultation when converting between opioids
    - Use appropriate precautions when prescribing methadone for pain

At the end of this module, we will ask you to set some goals for your practice based on what you learn in this module.

Case Introduction

The following case is presented throughout this module, providing you an opportunity to practice clinical applications:

Patient: Mr. Sam Burton, 27 years old

Brief History: Requests prescription for a high dose of opioids for phantom limb pain.

DIVERSION: HOW?

How Are Prescription Drugs Diverted?

Diversion of prescription drugs occurs at every point in the manufacturing and distribution chain. Doctor shopping, the method of going to multiple prescribing providers for prescription drugs, is the most common source of prescription diversion followed closely by prescription theft or forgery[8,9]. Other mechanisms of diversion are displayed in the table on the right.

How Are Opioids Diverted from Healthcare Providers?

Healthcare providers may inadvertently or knowingly participate in diversion by being[10]:

- Deceived by patients
- Susceptible to patient pressure
- Poorly informed
- Careless
- Dishonest
- Addicted themselves

Types of fraudulent prescriptions[10]:

- Legitimate prescription pads are stolen from providers' offices and prescriptions are written for fictitious patients
- Altered legitimate provider's prescription
- Prescription pads printed with a phone number that is not a real provider's office
- Diverter phone numbers on prescriptions. When called, the individual pretends to be a provider's office.
- Computer-generated prescriptions for non-existent providers
- Copies of legitimate prescriptions

Diversion by Teens and Young Adults

- stealing medicine from bathroom cabinets of family and friends
- stealing from pharmacies
- buying from drug dealers
- buying from patients who exit clinics with prescriptions
- forging prescriptions
- feigning illness to get medicine
- doctor shopping

PRACTICE TIP

Educate patients in the proper storage and disposal of their opioid medications:

- Any visitor can steal from their medicine cabinet and so this is not a good storage place.
- Individuals who are not tolerant of opioids can overdose on a relatively low dose.

DIVERSION: WHAT?

Which Drugs Are Diverted Most Often?

All prescription opioids are involved in diversion and misused[8.]

The most widely misused opioids in the U.S. are[11]:

1. Hydrocodone and hydrocodone combination medications (e.g., Vicodin, Lortab). These were changed to Schedule II in October 2014 because of their misuse potential.
2. Oxycodone (immediate and extended release)

For **college students**, hydrocodone and oxycodone are the most widely diverted or misused drugs, followed by morphine, tramadol, and methadone[8].

Partly due to its misuse potential, tramadol was made a Schedule IV controlled substance in 2014 (DEA).

Most common routes of administration are[8,11]:

- injection
- ingestion
- inhalation

DIVERSION: WHY?

Why Are Prescription Drugs Diverted?

Common reasons given for the increase in prescription opioid misuse include[12]:

1. Prescription drugs may be more easily obtained compared to the difficulty and danger of obtaining illegal "street drugs," such as heroin.
2. Law enforcement closely monitors illegal drugs, making arrests in such purchases much more likely than for opioid analgesics.
3. The inappropriate use of prescription drugs is viewed as more socially acceptable than heroin or cocaine.
4. Because the purity and dosage of prescription medications are highly monitored, they are seen as "safer" than illicit street drugs.
5. Opioid analgesics may act as substitutes for illicit drugs, such as heroin.

Street value of prescription opioids

Street value is high for opioids. For example, in one informal survey, patients reported a rate of $1 per milligram for hydrocodone with acetaminophen and more for long-acting opioids without additives[13]. Street value of an 80 mg oxycodone prescription taken 3 times per day, was estimated at $12,000 per month.

Comparison of street drugs to prescription opioids

Heroin and prescription opioids have very similar mechanisms of action, so it is not surprising that some substance misusers switch between the two, depending on which is more advantageous to them at the time[14–16]. For example, prescription opioid misusers may switch to heroin if they lose their medical insurance[14] or if prescription opioids simply aren't available[17]. As they age, heroin users may switch to prescription opioids, which are often easier to take orally.

Comparison of the "Advantages" of Heroin and Prescription Opioids

Heroin	Prescription Opioids
Often more widely available than potent prescription opioids [14,15]	Standardized potency[14]
Often cheaper on the street than potent prescription opioids[14,15]	Medical insurance may pay for it[14]
Aura of legitimacy/cleanliness due to association with medical community[17]	
Generally easier to take orally[14])	

FYI

Heroin and prescription opioid users often switch between the 2 drugs, depending upon their circumstances.

DIVERSION: WHO?

Who Is Diverting Prescription Opioids and for Use by Whom?

While some opioid diversion from the doctor's office is by chronic pain patients who may sell excess drugs or trade for other drugs, other diverters visiting a doctor pretend they have pain and may or may not be addicted themselves. Street and recreational drug use, as well as use by individuals with co-morbid psychiatric conditions, accounts for much of prescription drug misuse[9].

How Common is Diversion or Use of Diverted Drugs?

- 1.9 million people over the age of 12 had initiated misuse of prescription pain relievers within the past year in a 2012 survey.
- In 2012, an estimated 22.4 percent of young adults had misused pain relievers at some point in their lifetime[4].
- Nearly 2.5 million emergency department (ED) visits in 2011 were associated with drug misuse - an increase from about 1.3 million in 2004. Misuse of pharmaceuticals was involved in over half of these ED visits[18].
- Opioid analgesics (pain killers), such as hydrocodone, oxycodone, and methadone, and benzodiazepines, such as alprazolam and clonazepam, were present in more than 100,000 ED visits associated with the misuse of pharmaceuticals in 2004[19].

Diversion by Age

The largest percentage of drug misusers are in their 20s, which includes college students. However, all ages are involved. While many drug misusers are engaged directly in drug diversion, some buy their drugs from another party.

Age group	***Percent of Drug Misuse Cases***
6-12	0.25%
13-19	6.5%
20-29	**22.25%**
30-39	17.5%
40-49	21%
50+	16%

Data from RADARS System Poison Centers[8], a monitoring program to detect misuse of Oxycontin and other commonly prescribed opioids by surveying drug abuse experts, law enforcement agencies, and poison control center reports[11].

Prescription opioids and children

The toll of prescription opioid misuse on young children must be recognized; **a single dose of a prescription drug in a child may be fatal.**According to a study compiled by poison centers[8]:

- Most exposure of drugs with children (newborn to <6 yrs) is through ingestion
- More than 99% of drug exposure with children is unintentional
- Most incidences occur in the child's home

IDENTIFY RISK OF DIVERSION

Factors Associated With Risk of Diversion

- Age (18-25)
- Male sex
- Level of education
- History of binge drinking or heavy alcohol use
- Rural community setting
- Low socioeconomic status
- Employment status
- History of criminal behavior
- Single marital status
- Failure to keep medications secure
- Type of medications obtained (Oxycodone, Hydrocodone, and Methadone)
- Family history of drug abuse or illicit drug use

[20]

FYI

- Women who abuse drugs are more likely to abuse prescription drugs than other illegal drugs[21]
- Some diverters may feign symptoms, going so far as to alter urine samples with their own blood in order to corroborate complaints of renal pain[22].

SIGNS OF DIVERSION

Suspicious behavior related to appointments

- Missed follow-up visits
- Frequent extra appointments at the clinic or office
- Seek appointments toward the end of the day or may show up just after regular office hours.

Suspicious stories

- Claim to be passing through town or visiting relatives.
- Insist on being seen or given a prescription immediately because they are on their way out of town or are late for something.
- Claim they cannot remember where they were last treated.
- Claim that the previous clinic, hospital or provider is no longer in business.
- Claim they forgot to pack their medication.
- Frequently reported loss of prescriptions or medications
- Claim their medication was stolen.

Problems related to lab testing

- Unexpected results on toxicologic screening
- Alter urine samples by pricking a finger and putting a drop of blood in the specimen to corroborate complaints of renal problems.

Suspicious behavior related to prescriptions

- Frequent requests for dose increases
- Request specific medication brands and resist generic forms and substitutes, claiming to be "allergic."
- Concurrent use of nonprescribed psychoactive substances
- Prescriptions obtained from a second provider

Uncooperative or non-compliant

- Refuse a physical exam.
- Be unwilling to give permission to access past medical records or allow contact with previous providers.
- Failure to follow the dosage schedule
- Failure to adhere to concurrently recommended treatments

Other suspicious interactions with doctor or staff

- Be unusually complimentary about the office, your appearance, or your reputation.
- Be unusually well-informed about specific medications, have a familiarity that comes straight from text books, rather than real life experiences.
- Try to seem naive by mispronouncing medication names or seeming uninformed about their underlying medical condition.
- Feign symptoms, e.g., back pain, kidney stones, migraine headaches, toothaches, or post-herpetic neuralgia.
- Abruptly leave the office if things are not going their way.

Behaviors outside of the clinic visit

- Frequent visits to the emergency room for opioid therapy
- Tampering with medications

[22–24].

STEPS TO IDENTIFY DIVERSION

Believing what your patients tell you about their pain should be balanced by a degree of skepticism. Behaviors and stories are often better indicators of diversion than appearances, which can be misleading. Also keep in mind that colleagues, friends, and family members may be diverting opioid analgesics.

To identify patients who are diverting medication or whose medication is being diverted[10,25]:

1. Contact the patient's prior treatment providers to determine dosing and duration of past treatment
2. Use sensitive and thorough interviewing techniques to inquire about patient's use of medications and determine history and course of treatment
3. Identify signs that suggest illicit drug-seeking behavior
4. Review records of chronic pain patients for patterns suggestive of diversion before prescribing refills

5. Use random urine drug testing and medication reconciliation, including pill counts, where indicated. UDT can detect when most prescribed drugs are not present as would be expected if the drug was being taken. Note, however, that current urine drug tests are qualitative and not quantitative and do not detect some synthetic opioids such as fentanyl[13]. Note also, that someone who is abusing a drug may be able to temporarily obtain the right amount of drug to bring to the pill count appointment.
6. Continue to check prescription drug monitoring programs
7. Bring special attention to patients taking short-acting drugs due to their greater risk for misuse

MR. BURTON - DIVERSION

Provider: *Hello there Mr. Burton, how are you doing?*

Mr. Burton: *I'm doing all right.*

Provider: *So I understand that you would like some medication for limb pain you are experiencing?*

Mr. Burton: *Yes, that's right. The only thing that helps me since I lost my leg is hydrocodone.*

Provider: *I take it you've been prescribed hydrocodone in the past?*

Mr. Burton: *Yes, yes it has helped me a lot. I just moved recently so I'm trying to get back with it, finding a new doctor, and all of that.*

Provider: *I see. Did your last provider give you a referral?*

Mr. Burton: *No, I didn't even think about that. I was too busy moving.*

Provider: I see. I'd like to obtain your past medical records, or at least contact your previous care provider.

Mr. Burton: *I didn't bring my medical records with me.*

Provider: That is all right, do you have a phone number?

Mr. Burton: *I'm afraid I don't have that either...I didn't really have a regular doctor, just one that I was seeing kind of temporarily while in between moves.*

Question 1: Based on what you know about Mr. Burton so far, what factors and patient characteristics, if any, does he appear to have that may signal a higher risk of diversion? (Check all that apply)

1. High-dose opioid use
    - Feedback: Correct. Mr. Burton came in requesting a prescription for a high dose of an opioid.
2. History of legal problems
    - Feedback: To be determined. Many questions about risk remain to be asked.
3. Comorbid psychiatric problems, current or history, especially those with impulsivity, e.g., ADHD
    - Feedback: Correct. Mr. Burton has a history of ADHD. He should be screened specifically about depression and anxiety.
4. Poor family support
    - Feedback: Correct. Mr. Burton said he is not close to his family and is single.
5. Substance use disorder

- Feedback: To be determined. Mr. Burton should be screened for substance use disorder.

6. Age group
   - Feedback: Correct. Mr. Burton is 27 which is in the age group (20 to 29 years-old) with the highest diversion rate.
7. Smoking
   - Feedback: Correct. Smoking is one of Mr. Burton's risk factors for diversion, along with several others.
8. Family history of addiction
   - Feedback: Correct. Mr. Burton's father was an alcoholic.
9. History of sexual abuse
   - Feedback: Associated with risk for females. Many questions about risk remain to be asked. History of sexual abuse in females is associated with greater risk of opioid misuse.
10. Strange stories
    - Feedback: Correct. His vagueness about where he has been obtaining his prescriptions suggests risk for diversion.
11. Strange symptoms
    - Feedback: Incorrect. Phantom limb pain is a known pain syndrome.
12. Lack of cooperation
    - Feedback: Correct. His lack of cooperation regarding contacting his last provider suggests risk for diversion.

Question 2: What type of diversion does Mr. Burton's behavior suggest the most?

1. Doctor shopping
   - Feedback: Correct. Mr. Burton's avoidance of providing contact information may be as simple as he describes or it may be because he does not want you to contact that provider due to substance abuse or diversion problems.
2. Prescription theft or forgery
   - Feedback: This seems less likely, although he may be trying to hide something by not providing information on his past provider.
3. Residential burglary
   - Feedback: Incorrect. There is no evidence that this is the way Mr. Burton is trying to obtain medication currently.
4. Going to "pill mills"
   - Feedback: Incorrect. This seems less likely, although he may be trying to hide something by not giving information on his past providers.

CLINICAL PROTOCOL TO MINIMIZE DIVERSION

Clinical protocol should be followed to reduce diversion of medications by patients or their family members, within reason. Although this is not reimbursed time, one might consider that time spent with new patients may prevent time consuming problems later. Such a clinical protocol includes the following[25]:

1. Verify patient identity and information:

- Consider requesting official photo identification from patients to photocopy and include in the chart.
- Check the prescription drug monitoring program that is available in your state. For now, this task can be assigned to a staff member, but eventually, the opportunity to access this information while prescribing may become part of the electronic health record.
- A more time-consuming method that provides even more data would be to verify past provider information by contacting former health care providers and pharmacists for each new patient. Written consent from the patient must be obtained.Obtain the previous providers' contact information from official sources instead of from the patients to better spot patients seeing multiple providers and to assure that real providers are being contacted.
- Note: Some patients seeing multiple providers may be attempting to better control their pain; it is not always a sign of addiction.

2. Obtain a thorough medical history:

Acquire information on the type and intensity of the pain, current, and past pain related treatments, co-existing and other medical conditions, the efficacy of past pain treatment, level of function, and any substance abuse or psychiatric history.

3. Conduct a thorough physical exam:

Look for potential signs of drug abuse, including:

- inflamed nasal mucosa
- nasal septum perforation
- unusual jitteriness or sedation
- pupillary changes
- needle puncture sites

4. Educate patients about residential theft/diversion by family:

Explain proper medication storage and monitoring techniques that should occur in their homes. Theft from medicine cabinets is a major source of abused opioids[1], whether from a break-in or someone known to the patient. Thus, it is essential that medications be locked up in a secure cabinet or safe. Discuss the importance of proper medication storage and security with the patient as part of the patient treatment agreement.

5. Use patient treatment agreements

Treatment agreements explain privacy and confidentiality and outline the patient's responsibilities in treatment as well as the consequences for breaking the agreement. When creating and using treatment agreements:

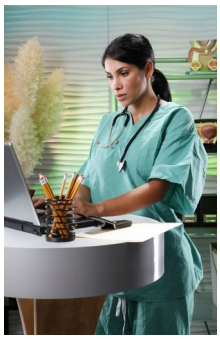
- Spell out the offenses that are allowable to some extent (e.g., a patient who misses one appointment can continue in treatment) and those that are not allowable (e.g., a patient who steals from or vandalizes the office will be discharged from treatment).
- Describe use of periodic random urine screening for illicit substances or medication adherence, and serum medication levels

- Require all prescriptions be filled at one pharmacy[26].
- Require that the patient obtain opioid analgesic prescriptions from only one provider[26].
- Require immediate notification when another prescriber becomes involved.
- State actions which may prompt discontinuation of treatment, including:
    - violations of the agreement
    - evidence of illicit street drug use or prescription medication abuse or outright diversion
- Follow through with these agreements if violations do occur. Doing so will help prevent allegations of enabling drug abuse or prescribing for non-therapeutic purposes.

Patients at high risk. Treatment agreements are important with patients at high risk for misusing medications (i.e. those with a current or past history of substance abuse, co-morbid psychological disorders, or those with chaotic living arrangements susceptible to theft). Extra monitoring and perhaps referral to a pain or addiction specialist are highly recommended. Treatment agreements may request that patients bring all current medications, in the appropriate pharmacy containers, to appointments for periodic pill counts.

CLINICAL PROTOCOL TO MINIMIZE DIVERSION (CONTINUED)

6. Document carefully:



Document all information that is relevant to the patient's treatment, including a legitimate medical purpose for the patient to be prescribed the controlled substance and the results of a thorough physical exam. Document physical exam findings, such as needle wounds, a perforated septum, or other signs of past drug abuse[25]. Document the prescription given to the patient, including the number of pills, and directions. Some states require that clinicians make copies of all prescriptions for controlled medications and include these copies in the patient chart.

7. Use careful patient monitoring:

- **Random callbacks, pill counts, and observed dosing:** For a callback, have the patient suspected of diversion bring their remaining supply of medication in for you to inspect. This policy should be outlined in the patient contract and should state how much notice the patient will be given beforehand. Pill counts should be taken to verify that the proper number of pills is remaining, according to the patient's prescription. For observed dosing, medication is administered under observation in the clinic, rather than prescribed to take at home. This ensures that the patient is ingesting the proper dose, and is not diverting medication outside of the clinic.
- **Urine drug testing:** Conduct periodic but random urine toxicology screening for controlled substances.
- **Prescription drug monitoring programs:** These programs provide databases of prescriptions of certain classes of drugs (schedule II-IV, varies depending on the state) issued and can help to identify forgery, improper prescribing, and drug-seeking, or doctor-shopping patients. As of December 2016, all states other than Missouri have implemented prescription drug monitoring programs.

8. Observe patterns of patient prescription requests:

Paying attention to patterns of prescriptions will help you recognize when diversion is occurring. Prescribing opioids only as part of an ongoing relationship with a chronic pain patient will help limit diversion.

- Provide refill prescriptions only with verification of continuation of pain diagnosis.
- Decrease the size of prescriptions and increase the frequency of follow-up visits according to severity of addiction, suspected diversion, or risk for abuse or diversion.
- Limit the prescription quantity and number of refills that you provide.
- Write prescriptions in pen.
- Do not pre-print your DEA registration number on prescriptions.
- Consider using prescription forms with preprinted numbers for the quantity of refills. Circle the prescribed number and strike through the other numbers to make the quantity very clear to pharmacists[27].

9. Observe other aberrant behavior, such as non-compliance:

Diversion, in addition to inadequate analgesia and addiction, may drive abnormal opioid-seeking behavior. Noncompliance should alert the physician to the possibility of addiction or diversion, and careful control and monitoring of opioid therapy should be initiated, with discontinuation if the behavior persists[28]. Switching to an opioid that is less frequently abused in the community might also be considered.

10. Consider the following guidelines before discharging a patient from your practice:

- When a patient violates a treatment agreement, you have the right to discontinue treatment but you should NOT release him/her from your practice without a plan in place.
- Such patients are often in need of more intensive treatment and you should arrange for another physician (such as a psychiatrist and/or addiction specialist) to take over treatment.
- Work with the patient's psychosocial treatment providers to assure that there is continuity of care after the patient is discharged from your practice[28].

WORK WITH PATIENTS TO DECREASE DIVERSION

Educate Patients: Risk of Diversion by Family and Friends

A rising method of diversion is to use prescribed medication from family, relatives, friends and classmates. Teens may abuse controlled prescription drugs because they are often more easily accessible than illicit drugs, alcohol or tobacco[25]. Younger people are more likely to obtain drugs from family and friends, whereas older people are more likely to obtain them from thefts and dealers[8].

<u>Medicine cabinets: A rising threat</u>

The abundance of prescription opioids and drugs has made the medicine cabinet a great threat to children. Parents need to play an essential role in preventing diversion. Parents must safeguard their

medications (e.g., locking a medicine cabinet) because easily accessible medicine cabinets are inviting to children and teens. Moreover, parents who do not understand the dangers of the medications in their possession can put children at risk. Children and teens may steal their parents' controlled medication to sell or use themselves. Even if their own children can be trusted, the medication should be kept away from visitors who might take it. Counsel patients on these potential dangers and tell them to store opioids in a safe and secure place away from children and pets.

Patients should read any product-specific disposal information included, for example, with extended-release/long-acting opioid products. Additionally, controlled prescription drugs used by terminal patients or from a recently deceased person can be diverted by family and friends[29].

Educate Patients: Proper Disposal of Medications

Proper disposal is also important. Educate patients on systems of drug disposal, for example, sponsored by the FDA. To reduce diversion by family members, medications should be properly disposed of so that their recovery is made difficult. To dispose of medications safely:

- Do not flush or rinse the drug down the drain unless the label or patient information sheet instructs you to do so.
- Find a community drug take-back program or hazardous waste collection program by calling your local government or looking on the FDA website for a take-back program.
- If a drug take-back program is not available, you should[30]:
    - Remove the drugs from their containers.
    - Mix the drugs with an undesirable substance such as cat litter.
    - Put the mixture in a disposable container with a lid or resealable bag.
    - Remove or conceal personal information and Rx number from the container.
    - Dispose all of the above in the trash.

Use Patient/Provider Treatment Agreements

A written treatment agreement should include the provision that the patient will refrain from obtaining or sharing medication with others[28]. Methods for storing and disposing of the medication also should be described.

DRUGS WITH REDUCED DIVERSION POTENTIAL

Drug Formulations May Help Prevent Hazardous Use and Diversion

New formulations of opioids may help prevent hazardous use and diversion[31]. The challenge is to minimize diversion but maintain effectiveness. Some opioids with limited diversion potential already exist, and many others are being considered or are in development.

- **Physical alterations.** Drugs may be physically altered to interfere with use by snorting or injection, for example, by increasing the viscosity of liquids or crush resistance of capsules. These alterations may discourage tampering but are not foolproof.
- **Opioid agonist with antagonist.** An opioid agonist and an antagonist are combined in a single product. Tampering with the medication to snort or inject releases the antagonist, blocking the effects of the opioid. For example, one formula to help reduce misuse of oxycodone combines it with the antagonist naloxone. This combination counteracts the euphoric effects of oxycodone and produces withdrawal symptoms if the tablets are dissolved

and injected[31].

- **Prodrugs.** Prodrugs are medications that are inactive but are converted into active ingredients by metabolic pathways or absorption, which delays euphoria[32]. Moreover, conversion into active ingredients cannot occur after a particular dose[8]. In one example of a prodrug, codeine transforms into morphine once ingested.
- **Drugs that halt release of active opioid ingredients.** This approach prevents the release of active opioid ingredients when tablets are crushed or when chemical extraction of the opioid is attempted. For example, to make extraction more arduous, the opioid could be encapsulated within microparticles that are water insoluble[32].

Drugs Used in Treatment of Opioid Addiction

1. **Methadone.** Methadone is inexpensive and has relatively low street value[33]. It is diverted and misused commonly and has significant risk associated with misuse.
2. **Buprenorphine.** Buprenorphine misuse and diversion are increasing[34,35]. Pure buprenorphine is diverted more often than the combination with naloxone.

PRACTICE MANAGEMENT TO REDUCE RISK OF DIVERSION

This section discusses the following practice management guidelines to reduce risk of diversion:

1. Keeping careful prescribing records for all pain medicine prescribed
2. Following an office protocol that safeguards prescription pads and sample medications
3. Using prescription drug monitoring programs and verifying patient identities
4. Working with pharmacists and law enforcement to detect and prevent diversion
5. Complying with DEA regulations and state regulations

A detailed overview of prescription requirements and regulations on different classes of controlled substances can be found in our Key Info guide, *Government Regulations*.

KEEPING CAREFUL PRESCRIBING RECORDS

Current medical records, including prescribing records, need to be maintained completely and accurately, and be ready for review. According to the Federation of State Medical Boards, the following should be included in medical records[26]:

- Nature and intensity of the pain
- Current and past treatments for pain
- Underlying or coexisting diseases or conditions
- Effect of the pain on physical and psychological function
- History of substance abuse
- Presence of one or more recognized medical indications for the use of a controlled substance

The following should also be recorded:

- treatment objectives, including the objectives that will be used to determine success
- discussion of benefits versus risks
- informed consent
- treatments and medications (date, dosage, type, quantity prescribed)

  - controlled substance prescriptions - must be documented in the patient chart in a specific location
  - reasons for changes in prescribing (e.g., disease progression, physical injury)
  - prescriptions for other co-occurring problems such as depression, anxiety, or insomnia
- agreements and instructions
- discussions with and about the patient

Regulations for prescription records may vary based on the drug's schedule in different states.

FOLLOWING AN OFFICE PROTOCOL

Prevent Prescription Pad Theft

Diverters may try to steal prescription pads or scan blank prescription pads in order to write their own prescriptions. To prevent this[22]:

- minimize the number of prescription pads in use
- keep all prescription blanks in a safe, locked place
- never use prescription blanks to write memos
- never pre-sign prescription blanks

Physicians should contact the company that prints prescription pads to learn about available prescription-safety options. Physicians can also utilize prescription pad features to reduce diversion, including:

- sequential numbering, to make it easier to detect missing forms
- printing on different colors of paper, to try to avoid duplication
- copy-resistant features, such as saying VOID when photocopied
- various ink colors, which makes it more difficult to reproduce than standard white paper with black ink

Prevent Prescription Alteration

Diverters may try to alter physicians' written prescriptions, for example, by transforming certain numbers involved in dosing, e.g., changing 10 into a 70 or 100. To prevent alteration of prescriptions [22]:

- consider writing the strength, dose and quantity of medications in letters and numerals
- always indicate whether or not the prescription may be refilled and include the number of refills
- use ink that cannot be rinsed with solvents, e.g., acetone

Involve Staff

Because diverters may try to appear the most composed when in your direct presence, asking your staff to pay attention to how patients act and what they say may help in identifying any suspicious activity[36].

WORKING WITH PHARMACISTS

Patients who are practicing diversion may try to call in their own prescriptions by claiming to be from a provider's office. Patients that are practicing such maneuvers are often first detected by

pharmacists. Many drug abusers gravitate toward treatment areas having low communication and cooperation between health care professionals. If your local pharmacists know you and are familiar with your office, these attempts will be less likely to succeed. Thus, providers should[22]:

- collaborate and foster a good relationship with local pharmacies, so that problems with patients, such as substance abuse, can be discussed.
- write the name of the patient's pharmacy on the prescription and consider sending prescription faxes instead of calling in prescriptions.
- encourage pharmacies to call if they have any questions regarding the prescription or need prescription verification.
- avoid calling in prescriptions of opioid medications that can be faxed in. This will alert the pharmacist's suspicion when someone tries to do so.

A provider's office should:

- have a system to respond to pharmacy calls.
- document all pharmacy calls in the patient record.

If possible, prescriptions for a patient should be written by one prescriber and filled by a sole pharmacy[37].

WORKING WITH LAW ENFORCEMENT

Taking an Active Role to Identify and Prevent Diversion

Work with law enforcement to detect and prevent diversion and understand responsibilities with respect to law enforcement vs patient confidentiality. If a patient is suspected of diversion, local police should be notified[36]. If a theft of controlled drugs is discovered, the nearest DEA office and local police should be identified[5]. While providers and pharmacists report suspected drug seeking patients to law enforcement, law enforcement officials do not notify or warn providers of suspicious behaviors by people who may try to take advantage of prescribers or pharmacies (AAPS).

- Notify local police when office staff or providers suspect a patient of diverting their own medication or diversion maneuvers, such as attempting to steal prescription pads[36].
- If a theft of controlled drugs is discovered, providers should notify the nearest DEA office and local police[5].
- Do not prescribe controlled substances to patients unless clinically indicated. Inform the patient that it would be illegal for you to prescribe opioid analgesics before performing a meaningful history and physical examination[22].
- Although not realistic for most practices, one pain specialist noted that routinely checking court dockets for new cases of drug diversion can alert you if a patient of yours may be diverting[38].

Reporting a Crime and Privileged Information

Information communicated to a provider in an effort to procure unlawfully a prescription drug or the administration of a prescription drug is not privileged communication

- The provider no longer is bound by the provider-patient relationship.
- However, the provider is *not obligated* to report the criminal behavior.

Health Insurance Portability and Accountability Act (HIPAA)

There is an exception to HIPAA for reporting crimes against a provider limited to the information needed to report the necessary facts.

- It permits a full report, sufficient to enable identification of the perpetrator and prove all elements of the crime.
- It does not authorize turning over the patient's entire chart, including unrelated materials, to the police.

COMPLYING WITH REGULATIONS

DEA Oversight

The two primary responsibilities of the Drug Enforcement Administration (DEA) are:

1. To prevent and investigate diversion and abuse of controlled substances.
2. To ensure an appropriate and timely supply of these substances to meet the legitimate medical and commercial needs in the United States.

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Prescribers must comply with applicable state or federal law[26]. However, the vast majority of providers who legitimately prescribe controlled substances will never warrant scrutiny by Federal or State law enforcement officials. Despite some beliefs to the contrary, the DEA has not changed its criteria regarding investigating providers or increased emphasis on providers.

- Less than 0.01 percent of prescribing providers lose their controlled substance registrations following an investigation into prescribing practices.
- The DEA does not overly scrutinize the prescribing of opioid analgesics as compared to other controlled substances[19].

Patterns of Prescribing Suggesting Illegal Activity

Law enforcement agencies are using the term "over-prescribing" less and less to avoid the implication that there is a predetermined maximum amount that the practitioner should be prescribing, above which they are doing something illegal. Cases in which prescribing violations by providers occurred are associated with the following patterns of abuse:

- An unnecessarily large quantity of controlled substances was prescribed.
- Many prescriptions were issued in a short period of time.
- A physical exam was not performed.
- The provider gave instructions to the patient to fill prescriptions at different pharmacies.
- The provider wrote prescriptions despite knowing that the patient was diverting them.
- Controlled drugs were prescribed at intervals that did not match that of legitimate medical treatment.
- The provider used street slang rather than proper medical terminology.
- The drugs prescribed did not coincide with treatment of the condition allegedly existing[19].

Practitioners should not be inhibited by fear of law enforcement when prescribing appropriately for their patients, and patients with legitimate medical reasons for pain treatment should not unduly suffer due to any such hesitations. Providers can take steps to help safeguard themselves from suspicion by federal and state regulatory authorities by following their guidelines.

GOVERNMENT REGULATIONS

Regulations on Controlled Substances

This website provides a summary of the main Federal regulations regarding the prescription of controlled substances as well as complete access to state regulations in the Key Info Guides section. Substantial changes in policy have occurred over the years[1]. Topics include federal requirements for prescriptions and refills, federal and state regulatory overlap, regulations concerned with unique situations, such as emergencies or narcotic dependent patients. See the Key Info Guide in the Related Resources section for more information.

Sample federal regulation:

21 CFR 1306.05

Prescriptions for controlled substances *must*:

- be dated as of, and signed on, the day when issued and *never* be post dated
- include full name and address of patient, drug name, dosage form, strength, quantity, and directions for use
- include the name, address, and registration number of practitioner
- be written with ink, indelible pencil, or typewriter and manually signed by the practitioner

REQUIREMENTS OF A LEGAL PRESCRIPTION

The federal Comprehensive Drug Abuse Prevention and Control Act of 1970, or the Controlled Substances Act, describes the legalities of prescription drugs. The controlled substance regulations state that:

- *"All prescriptions for controlled substances shall be dated as of, and signed on, the date when issued, and shall bear the full name, address of the patient, the drug name, the strength, dosage form, quantity prescribed, directions for use and the name, address and registration number of the practitioner."*
- *"A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice."*

Further guidelines state that medical records should accurately reveal the conditions which resulted in the prescription.

Furthermore, prescriptions for controlled substances may not be phoned in unless it is a true emergency, in which case the written prescription must be issued to the pharmacist within seven days and must clearly state its purpose for authorization for emergency dispensing.

The DEA has revised regulations to allow practitioners to write prescriptions for controlled substances electronically. This use of modern technology will allow pharmacies, hospitals, and practitioners to maintain control of dispensing substances reducing prescription errors caused by illegible handwriting and misunderstood oral instructions, as well as integrate prescription records directly into medical records. The overall aim of these new regulations (which are in addition to, not in replace of, previous

regulations) is to reduce forgeries, increase efficiency, and decrease the time patients spend waiting for their prescriptions to be filled. More information can be found on the Key Info Guide: Government Regulations on Prescribing Controlled Substances.

REGULATIONS ON USE OF OPIOIDS TO TREAT ADDICTION

Only OTPs (Opioid treatment programs) may dispense methadone for the treatment of opioid addiction. Buprenorphine sublingual tablets may be prescribed in an office-based setting to treat opioid addiction, only by a properly waivered and certified provider (Substance Abuse and Mental Health Services Administration). Otherwise, opioids may not be prescribed to treat opioid addiction, either for detoxification or maintenance.

FEDERAL AND STATE LAW OVERLAP

Follow the most restrictive regulation. State law regulations may be more restrictive than federal regulations, but can not be less restrictive. State laws may have certain limits and stipulations that federal laws do not. When there is a difference, the most restrictive regulation applies.

SAFEGUARDS IF OPIOIDS ARE DISPENSED IN THE OFFICE

Storage

The level of security measures taken when opioids are dispensed in the office or clinic should match the type and amount of drugs being prescribed. Such measures include but are not limited to the following:

- Keep controlled substances in a locked storage area, such as a cabinet or safe, to which only authorized persons with authority to handle or administer such substances have keys.
- Keep opioids in their original containers-they should only be put into their new containers at the time they are dispensed.
- Bottles with different lot numbers or expiration dates should not be combined.
- If larger amounts of controlled substances are kept at the clinic, a supply of drugs should be kept locked separately and made available only to a very small number of authorized people, with a smaller supply available to other authorized staff.

Inventories

Regular inventories of controlled substances are required by law. Perpetual inventories may be facilitated by using the records of administration and dispensing of each drug.

- If controlled substances are stored in more than one area, a master list should be maintained in order to verify the record keeping for each area and the overall amounts of each drug.
- Supplies accessible to very few authorized people should be inventoried at least once per month, while supplies available to more authorized persons should be inventoried more frequently.
- A log sheet should be kept for each drug so that an inventory can be calculated and recorded on a regular basis.

Dispension

- Dispension records of all controlled substances should be kept separate from the patient's medical record. The date, patient's name and address, drug name, strength, and quantity, and the name of the prescriber and the name of the person who dispensed the controlled substance should be documented.
- Administration records should contain the same information but may be kept in the patient's medical record.
- Controlled substances that are dispensed must be packaged according to the Poison Prevention Packaging Act. They should be labeled with the date, primary practitioner's name and address, prescriber's name, drug name, strength, and quantity, and directions for use.
- The statement "Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed".

Drug Destruction

- Controlled substances which are expired or otherwise not suitable for use due to contamination or other such reason must be destroyed in the presence of authorized persons or returned to the supplier or sent to a reverse distributor. Laws regulating destruction or return of opioids vary by state.
- Records should be kept detailing the date, reason for destruction or return, signatures of those involved, and the drug name, strength, and quantity.

Samples

- Samples should be treated in the same manner as the controlled substances above with regard to storage and record keeping.

Finally, it is advisable to verify your procedures for storage and dispensing with your local DEA office.

PRESCRIPTION DRUG MONITORING PROGRAMS (PDMPS)

PDMPs Vary by State

Prescription Drug Monitoring Programs (PDMPs) provide data on who has received prescriptions for certain controlled substances[39,40]. They are a tool to help reduce misuse and diversion and to get an accurate picture of a patient's past pharmacological treatment with reported medications. The state programs vary, for example, by the schedules of drugs that are encompassed, the number of times per month data is collected, the way the data is submitted and disseminated (Wang and Christo, 2009). Currently, no national system exists[39] but many experts are calling for such a program. In some states, for example, Ohio, you can check the PDMPs in adjacent states. All states have programs, however, a few still need to be funded and activated.

The CDC's guidelines for prescribing opioids[2] recommend that PDMPs be checked at least every 3 months and that checking at every prescription be considered.

Clinical Use of PDMPs

If a PDMP is available in your area, it is helpful to view records or order a report on all new patients. PDMP reports may not be necessary for patients with whom clinicians have a long-standing

relationship or who are perceived to be at lower risk for diversion. PDMP reports can be a good resource when there is little history available or when there is concern based on clinical history, observation, or aberrant use of medication[40]. Other considerations include:

- Only information that pertains to your own patients is generally available[41].
- Providers prescribing opioids are not currently required to use PDMPs except in a few states, for example, Washington; it is an additional risk-assessment tool to help guide treatment decisions[42], however, it is recommended by the current guidelines for prescribing opioids[2]. Their use is recommended by opioid REMSs training for prescribing long-acting opioids, however.
- Some states allow requests for reports on new patients prior to their first appointment.
- PDMPs are helpful when coordinating care with other providers[43].
- Programs in adjacent states should be checked if this is allowed.
- Two states (New York, Oklahoma) are in the process of starting to report prescriptions in real time rather than weekly or less often. This is likely to grow.

Time barrier vs. benefit. The time involved is cited by some doctors as barriers to the use of prescription monitoring programs, however, the added time of querying the database may be more than made up for if it results in helping to identify addiction or diversion. It helps shape decision-making around prescribing appropriately.

PRACTICE TIP

1. If a patient is in pain, having a suspicious finding in the PDMP record does not mean the individual should not have their pain treated. It means they probably need a referral to pain/addiction specialist(s).
2. Put your own name in the program as a way to learn about forged prescriptions and prescriptions you have written that were modified.

PRESCRIPTION DRUG MONITORING PROGRAM REPORTS

What's In a PDMP Report?

Prescription Monitoring Programs produce reports on the following:

1. What medications the patient has obtained from other physicians
2. The number and type of medications the patient is taking

Sample PDMP report:

Request date: 9/5/2009 **Search criteria:** Last Name=Smith, First Name=Alfred; State=NC
Request period: 1/1/2008 to 12/31/2008
Patients matching search criteria:
Alfred Smith, 22 Smith Road, Raleigh, NC 78428
Total prescriptions in request period: 2

Prescribers for prescriptions listed:
John Smith John Smith, MD. 1900 Cavalier St, Raleigh, NC 28759

Pharmacies that dispensed listed prescriptions:
05893769 CVS Store 29 Arkansas St; Landville, NC Phone: 919-743-6790

Fill Date	*Product, Strength, Form*	*Qty*	*Days*	*Pt ID*	*Precriber*	*Written*	*Rx #*	*New/ Refill*	*Pharmacy ID*	*Payment (Insurance, Medicare, Cash, etc)*
9/2/2008	Sublingual Buprenorphine 8mg	30	30	1506	John Smith	8/31/2009	2751411	New	05893769	M2 (Medicaid)
10/3/2008	Sublingual Buprenorphine 8mg	30	30	1506	John Smith	9/30/2008	2751411	Refill	05893769	M2 (Medicaid)

Steps to Follow with a Suspicious PDMP Report

- Ensure that you, in fact, wrote the prescriptions and call the pharmacy if there is a discrepancy.
- Contact the other prescribers on the report[43].
- Discuss the report with your patient to ensure there isn't another explanation (eg: technical error).
- Document the rationale behind your decision to prescribe or to not prescribe[42].

Like an abnormal urine drug test, a PDMP report that indicates doctor-shopping behavior raises the possibility that the patient is abusing the medication or is addicted or diverting medications, but could also mean that the pain is not being managed well enough, which has been called "pseudoaddiction"[44].

MR. BURTON - ABERRANT BEHAVIOR

Question: Given Mr. Burton's possible doctor shopping, which of the safeguards described would address the problem? Please check all that apply.

1. Check prescription drug monitoring program
    - Feedback: Correct. Prescription drug monitoring programs, if they are available, will reveal other prescriptions Mr. Burton has received from other providers using his own name.
2. Check his identification
    - Feedback: Correct. Being sure that Mr. Burton is not using an alias is part of avoiding diversion.
3. Call previous healthcare providers and pharmacists
    - Feedback: Correct. You can request a release form and contact information for past health care providers and pharmacists to check for possible signs of diversion.
4. Urine drug test
    - Feedback: Correct. Use the urine drug test to confirm Mr. Burton's current use/lack of use of opioids and to test for use of illicit drugs.

OPIOID OVERDOSE

Background

- Overdose from prescription drugs is an epidemic, according to the CDC: 33,091 died from opioid overdose in 2015, which is up 16% from 2014[45]. The increase is largely due to an increase in heroin and synthetic opioids other than methadone. A doubling in poisoning deaths from 1999 to 20006 was largely due to an increase in deaths from prescription opioids and corresponded to an increase in opioid prescribing for pain over the same period[46]. And in 2015 drug overdose deaths reached 52,404, higher than any other year prior[45]; 63% involved opioids. ER visits due to prescription drug abuse have doubled in the past five years[47].
- Approximately half of overdose deaths may occur via diversion of prescription opioids[7].
- Risk of overdose is even greater in extended release/long acting opioids because of the high dosage of opioid available in these formulations. Make sure a patient is sufficiently opioid tolerant before prescribing extended release/long acting opioids. A new paradigm for opioid conversion in unmonitored settings calls for treating patients being converted to a new opioid as if they are "naive" to the new drug and to titrate the dose upward carefully, in order to reduce overdose deaths due to conversion[48].
-

Overdose Deaths (Rudd et al., 2016)

Drug	Deaths in 2015 (Rate)	Percent change (2014-2015)
Natural and semisynthetic opioids (morphine, buprenorphine, hydrocodone, hydromorphone, oxycodone, and oxymorphone)	12,727 (3.9%)	+2.6%
Methadone	3,301 (1%)	-9.1%
Heroin	12,989 (4.1)	+20.6%
Synthetic Opioids Other Than Methadone (fentanyl, meperidine)	9,580 (3.1)	+72.2%

*Includes deaths by accidental or intentional overdose, taking the wrong drug, or taking the drug inadvertently

Oxycodone and hydrocodone were the two natural and semisynthetic opioids with the highest rate of overdose in a Washington area study[49].

PRACTICE TIP

Patient education regarding risk in chronic opioid therapy needs to include education on how to ovoid an overdose. This should include the following:

- dosage guidelines
- potentially dangerous drug interactions
- potential for acetaminophen overdose if the opioids are combined with acetaminophen
- safe storage of opioids especially if children are in the household
- not sharing medication with anyone

CAUTION TIP

SAMHSA Opioid Overdose Prevention Toolkit (2014) recommends considering prescribing naloxone along with the patient's initial opioid prescription.

FYI

- *Vivitrol* (extended release, injectable naltrexone), which was recently approved to treat and prevent relapse after opioid detoxification, may make patients more sensitive to opioids as the time for their next scheduled dose nears; patients may accidentally overdose if they restart opioid use at this time[50].
- *Extended-release and long-acting opioids, especially high-potency opioids such as Fentanyl patches (DuragesicTM)* are not intended for patients who have not become physically tolerant of opioids and can result in overdose in an opioid-naive patient.
- *Tramadol (UltramTM) and tramadol hydrochloride/acetaminophen (UltracetTM)* FDA strengthened warnings in 2010 on these medications, emphasizing a risk of suicide in patients who are prone to addictions, taking tranquilizers or antidepressants, have a history of alcohol or drug abuse, or have emotional disturbances or other risks for suicide. The medication may have additive effects with alcohol, other opioids, or illicit drugs[50].

PRACTICE TIPS FOR PREVENTING OVERDOSE

PRACTICE TIPS

- Check Prescription Drug Monitoring Programs at least every 3 months and consider checking at each prescription. These are now available in all states (however, a few states may still be inactive), for prescriptions by other doctors.
- Screen for depression, anxiety, and other mental health problems and substance abuse (current or past) and, if opioids are required to manage pain after alternatives have been tried, use heightened treatment structure as well as more intensive patient education when they are present.
- For patients with multiple risk factors for abuse, avoid use of opioids if there is an alternative treatment; use an appropriately heightened treatment structure if opioids are needed.
- Benzodiazepines should be avoided with opioids. For patients concurrently on benzodiazepines and other psychoactive medications, if opioids are required to manage pain after alternatives have been tried, use heightened treatment structure as well as more intensive patient education.
  Consider whether a patient with anxiety might be better managed with alternative medications. For example, SSRIs can be very effective at reducing anxiety[51]. Another potential alternative is prazocin, which reduces nightmares, improves total and REM sleep, PTSD, and lowers blood pressure[52].
- Monitor patients with new opioid prescriptions and those on relatively higher doses carefully. High doses (100 mg morphine equivalents or higher) of opioids for the treatment of pain strongly increase the risk for overdose.
- Sleep apnea is responsible for a significant number of opioid related deaths. Around 24% of patients on chronic opioid therapy have sleep apnea and it is not limited to those with elevated BMI[53]. Consider sleep apnea studies for patients on high doses of opioids.
- Do not use equianalgesic tables to convert between opioids. Treat the patient as if they are opioid naive[48].

- Consider giving the patient naloxone for use in the event of an overdose, especially when risk for opioid overdose is elevated, for example, with a history of overdose or substance use disorder, with higher opioid dosages (≥50 MME/day), or with benzodiazepine use[2].

CORRELATIONS WITH OVERDOSE

Factors Associated with Risk of Overdose

Higher doses

A study of nearly 10,000 persons receiving chronic opioid therapy found that higher doses, of 100 mg/d or more of morphine equivalent had an 8.9-fold increase for overdose over those receiving 1 to 20 mg/d and moderately high dosages of 50 to 99 mg/d, who had a 3.7 fold increase[54]. The authors note that patient differences accounting for higher doses might also be responsible for the higher rate of overdose with higher doses. In a recent editorial, McLellan and Turner (2010) called use of such high doses "dangerous and questionable" outside of methadone treatment for opioid dependence.

Prescription diversion/illicit use

Approximately half of overdose deaths in a West Virginia study were in persons who were not prescribed an opioid[7].

"Doctor shopping"

Approximately a fifth of overdose deaths in a West Virginia study were in persons who had prescriptions from 5 or more prescribing providers[7].

New prescriptions and refills

A study of unintentional drug overdose death in New Mexico found that the risk of overdose was greatest shortly after an initial prescription or refill of an opioid[54].

Depression

Depression was correlated with overdose in the New Mexico study[54]

Substance misuse

Substance misuse was correlated with overdose in the New Mexico study[54]

Concurrent sedative-hypnotic prescriptions

(e.g., benzodiazepine) was correlated with overdose in the New Mexico study[54]

In a study of overdoses in Washington state, 45% were enrolled in Medicaid[49]. Authors discussed the possibility that the following factors that are higher in this population and that are correlated with greater risk of overdose may be responsible:

- higher rates of mental health problems
- higher rate of prescribing methadone for pain

Factors associated with death among malpractice claims for chronic pain medication management, in claims between 2005 and 2008, were[55]:

- long acting opioids
- additional psychoactive medications

- having 3 or more factors associated with medication misuse

LOPERAMIDE OVERDOSE RISK WHILE SELF TREATING OPIOID WITHDRAWAL

Loperamide (Immodium®), the over-the-counter antidiarrheal medication, which is a μ receptor agonist, is sometimes taken by individuals at doses far beyond therapeutic doses, in order to control withdrawal symptoms from opioids[56]. Self-administered, dangerously high doses of 30 to 200 mg, sometimes augmented by taking a P-glycoprotein inhibitor (e.g., verapamil), have clinical manifestations of opioid toxicity, including miosis, CNS depression and respiratory depression, as well as cardiac dysrhythmias. Overdoses can result in death. Patients presenting with unexplained syncope or unexplained prolongation of the QRS or QTc intervals, should be asked about whether they have taken loperamide. In two reported cases of death associated with taking loperamide, the patients were concurrently on buprenorphine and previously on buprenorphine respectively[56].

NALOXONE KIT FOR PREVENTING OVERDOSE

Naloxone kits are used for the reversal of a narcotic overdose, induced by opioids. The following kits are currently available:

- Single-dose hand-held, auto-injector systems (FDA approved in 2014)
- Muscle syringes. One syringe per 1ml of naloxone (FDA approved)
- Intranasal spray. (Narcan® intranasal spray received FDA approval as of November 2015)

Injectable dosages for intravenous, intramuscular and subcutaneous administration include:

- 1 mg/ml
- 10 ml (multi-dose)

Candidates for naloxone may include patients who are:

- Taking high doses of opioid medication for the prolonged management of chronic pain/illness
- At risk for incomplete cross-tolerance
- Taking extended-release opioid preparations that may pose a risk for overdose
- At risk for overdose due to medically prescribed analgesia, combined with a suspected or confirmed history of substance misuse, or dependence

PRACTICE TIPS

Consider giving the patient naloxone for use in the event of an overdose, especially when risk for opioid overdose is elevated, for example, with a history of overdose or substance use disorder, with higher opioid dosages (≥50 MME/day), or with benzodiazepine use[2].

Naloxone kits can be distributed to family members, friends, peers, employers, non-medical staff/ volunteers, and also to the at-risk patient.

OPIOID ROTATION AND CONVERSION

Reasons for rotation/conversion. Rotation to a new opioid may be considered for the following reasons:

- Adverse effect or allergic response to another opioid
- Lack of or insufficient response with another opioid; however, adding a co-analgesic might be sufficient. Due to genetic variability, there is a variable response to different opioids. Also may be due to tolerance developing or the dose required for a particular opioid exceeding maximum dose.
- Conversion from a short-acting opioid to a long-acting opioid to provide more stable analgesia as well as the convenience of fewer doses
- Conversion from one extended-release/long-acting opioid to another may be necessary due to adverse reactions, insufficient pain relief, or tolerance[57].

Conversion between opioids is complex. A new paradigm for converting between opioids has been proposed based on a review of the literature. They found that opioids and patient response to them are dissimilar enough that the patient needs to be treated as if they are opioid-naive for the new drug and the dose should be titrated up carefully. Oftentimes, the final effective dose is the same for a patient with tolerance as for a patient who is not tolerant of opioids. Careful stepwise dose titration is needed because of the patient variability as well as variable pharmacokinetic and pharmacodynamic properties[58]. Patients should be followed closely during all periods of dose adjustments as if a new patient.

The new paradigm for conversion to another opioid suggests that equianalgesic tables not be used due to safety considerations and variations between the medications and patients[48]. Other considerations include:

- Meticulous monitoring and individual dose titration are indicated with any chronic opioid therapy.
- Take precautions that the patient not self-dose to a dangerously higher dose through limiting prescriptions, patient education, adjunct treatments.
- Consider consultation with a specialist when opioid conversion is needed
- Patients who are not tolerant to opioids should not be prescribed ER/LA opioids.

MR. BURTON - PREVENT OVERDOSE

Question: After resolving all issues related to diversion, which of the following are useful for preventing overdose? (Check all that apply)

1. Check prescription drug monitoring programs, if available
    - Feedback: Correct. Prescription drug monitoring programs can help you avoid prescribing to a patient who is "doctor shopping" a risk factor for overdose.
2. Screen for depression and anxiety
    - Feedback: Correct. Depression and anxiety are associated with a higher risk of overdose and so they should be identified and treated.
3. Avoid concurrent prescriptions for benzodiazepines

- Feedback: Correct. Benzodiazepines in combination with opioids increase the risk of overdose.

4. Monitor him especially carefully during the first few weeks.
    - Feedback: Correct. New narcotic prescriptions are a risk factor for overdose.
5. Switch to methadone to treat his pain.
    - Feedback: Incorrect! Methadone is associated with a higher risk of overdose.
6. Find an alternative treatment to opioids if possible
    - Feedback: Correct. A safe, effective alternative treatment to opioids is always indicated if possible.

METHADONE AND OVERDOSE

Introduction

Methadone, which is prescribed for both treatment of opioid dependence and for pain, has a relatively high rate of overdose compared to other opioids. For this reason and its complex pharmacology, it should only be prescribed for pain by specialists who have a strong understanding of it. Respiratory depression is the main risk.

Increase In Methadone Overdoses

Methadone-related deaths in the U.S. have increased more than any other narcotic-related deaths[59]. The increase from 1999 to 2005 was 468%. In 2005, methadone accounted for around 14% of all poisoning deaths and 24% of all poisoning deaths by narcotics and psychodysleptics.

At least part of the increase may be attributed to an increase in methadone use: Prescription methadone use has increased more than 800% over the past 10 years[60]. Some of the increased numbers is due to improvements in data collection and processing[59].

Factors Contributing to Methadone Overdose

The reasons for methadone-related deaths are complex and not completely clear[17,59]. Some reasons vary by state, for example, in a West Virginia study, over half of methadone deaths were in individuals without prescriptions for the drug[61]. Factors contributing to a high rate of methadone overdose compared to other pain medications include[59]:

- How it is prescribed - Liquid or tablets, not tamper resistant
    - Initial dosing is difficult and equivalence to other opioids is poorly understood by some physicians. Conversion is not linear
    - Methodone is prescribed frequently; it costs less than many other narcotic pain killers.
- How it is taken
- Diversion/substance misuse
- Unique pharmacologic properties[59,61]:
    - prolonged and variable half life (5-150hrs); half life is longer than its effect on pain (only ~6hrs) resulting in an unpredictable accumulation of methadone.
    - delayed onset of analgesia
    - prolonged central nervous system depression; respiratory depression often occurs after analgesia has peaked, as late as day 4 or 5, often during sleep

- multitude of drug interactions that affect dosage in both directions
- increased risk of QT prolongation with risk of torsades de pointes
- variable response in different patients

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SUMMARY

Here is a summary of **recommended** skills, organized by provider core competencies:

Provide patient-centered care

- Thorough patient interviews can serve as the first step in identifying diversion.
- Enhance patient communication via a treatment agreement; it should include the provision that the patient will refrain from sharing medication with others, and should provide information on proper safety and storage of prescription medications.
- Educate the patient on a variety of ways to avoid an overdose.
- Consider prescribing naloxone along with the initial opioid prescription, for patients requiring long term opioid therapy.

Work in interdisciplinary teams

- Work with pharmacists and law enforcement to detect and prevent diversion.
- Involve office members in trying to prevent patient diversion by employing an office protocol.
- Consider a consultation with a specialist due to the complexities of conversion between opioids and when prescribing methadone, due to the many factors to consider in safe prescribing.

Employ evidence-based practice

- Use a heightened treatment structure when opioids are needed.
- Use cautious titration when prescribing opioids to the patient who does not have physiological tolerance to avoid overdose and consider drug interactions.

Apply quality improvement

- Employ a clinical protocol to help prevent diversion, including random callbacks, pill counts, and toxicology screening.
- Employ proper safeguards to prevent diversion if opioids are dispensed in the office; utilize proper storage techniques, keep track of inventories and dispensing, dispose of unused medications according to state laws, and treat samples with the same level of security as other medications.

Utilize informatics

- Utilize available features on prescription pads which help prevent diversion.

- Doctor shopping is a primary source of prescription diversion, and prescription drug monitoring programs should be utilized to catch such maneuvers.
- Keep careful prescribing records for all pain medicine prescribed.
- Federal and state regulations for controlled substances are changed periodically and so it is important to keep up to date; use the Resources section at the end of this module to access the database of federal and state laws, regulations and governmental policies for prescribing a controlled substance.

RESOURCES AVAILABLE THROUGH THIS MODULE:

- A Closer Look at State Prescription Drug Monitoring Programs (DEA FAQ's)
  These FAQs address common questions regarding prescription drug monitoring programs.
- Alliance of States with Prescription Monitoring Programs
  A forum for sharing on Prescription Monitoring Programs
- CDC Guideline for Prescribing Opioids for Chronic Pain
  Clinical guidelines, literature review, and analysis of the evidence on the use of opioids for chronic pain. Recommendations are also made for prescribing opioids for acute pain.
- Database of statutes, regulations, & other policies for pain management
  Database of Statutes, Regulations, and Other Policies for Pain Management
- Disposal of Unused Medicines: What You Should Know
  Describes programs to dispose of unused pain medications and other prescription medications.
- Electronic Prescriptions for Controlled Substances; Final Rule
  The DEA revised regulations to allow electronic prescriptions for controlled substances.
- Official Federal Regulations for Prescribing Opioids
  Official federal regulations concerning the use of controlled substances. The regulations address registration, prescription, and schedules of controlled substances, among other topics pertaining to controlled substances.
- Rx Patrol
  A web based database created by Purdue pharmaceuticals that collects, collates, and analyzes pharmacy crime data. The site looks for patterns, trends, and similarites in the crimes being commited and dissiminates this information to law enforcement groups to aid in apprehending suspects and also sends it to pharmacies.
- SAMHSA Opioid Overdose Prevention Toolkit
  This resource on SAMHSA's website includes several resources: Facts for Community Members; Essentials for First Responders; Safety Advice for Patients; Information for Prescribers; and Resources for Overdose Survivors and Family Members
- State Prescription Monitoring Program Contacts
  This is a list of each state's prescription monitoring program contact information.
- The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System
  The RADARS System is a surveillance system which collects timely product-and geographically-specific data on prescription drug abuse, misuse and diversion.
- VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain

The guideline provides recommendations for practice interventions and evaluations when using opioid therapy to treat chronic non-cancer pain. It is entirely evidence-based and uses clinical algorithms to optimize the use of opioid therapy.

- Zero Unintentional Deaths
  A Campaign to teach individuals and doctors about the risk of death by overdose common in chronic pain patients. Sponsored by Life Source.

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