PA-SUPPORT

Source for Understanding Pain, Prescribing Opioids, and Recovery Treatment

Developed by
Ellen M. Unterwald, PhD
Toby K. Eisenstein, PhD
Joseph L. D'Orazio, MD
David T. O'Gurek, MD
Rany T. Abdallah, MD PhD
Scott M. Rawls, PhD
Martin W. Adler, PhD

Lewis Katz School of Medicine
at Temple University

TEMPLE UNIVERSITY
Lewis Katz School of Medicine

Supported by a contract from the Commonwealth of Pennsylvania

Submitted by Ellen M. Unterwald, PhD
December 13, 2017

Scope of Work:

The purpose of this work is to assist the Pennsylvania Department of State in developing an educational curriculum regarding the safe prescribing of opioid analgesics for health care professions in accordance with Act 126 of 2016. This act directs that "beginning August 1, 2017, licensing boards shall, by joint regulation, implement a safe prescription of a controlled substance containing an opioid curriculum." The professions specifically designated in the act are those with Licensing Boards, including the State Boards of Dentistry, Medicine, Nursing, Optometry, Osteopathic Medicine, and Podiatry.

The following faculty of the Lewis Katz School of Medicine at Temple University (LKSOM) contributed to the development of this curriculum:

Ellen M. Unterwald, PhD
Principal Investigator
Director, Center for Substance Abuse Research
Professor, Department of Pharmacology
Lewis Katz School of Medicine at Temple University
Email: ellen.unterwald@temple.edu
Phone: 215-707-1681

Dr. Unterwald is a Professor of Pharmacology and the Director of the Center for Substance Abuse Research (CSAR) at the Lewis Katz School of Medicine at Temple University. Dr. Unterwald is well-trained in the area of opioid pharmacology as related to pain and addiction. She has authored over 100 peer-reviewed publication related to substance abuse and/or pain, with 50 publications specifically related to opioids. Dr. Unterwald has been responsible for developing and delivering the curriculum for Temple's medical, dental, and podiatry students in the areas of the pharmacology and use of opioid analgesics and the pharmacology of drugs of abuse for over 15 years. She has served on numerous education committees including the Curriculum Committee for the School of Medicine and the Graduate Program Committee in the Department of Pharmacology. Dr. Unterwald is currently involved in developing the new curriculum for Temple medical students on safe opioid prescribing and related substance abuse issues in accordance with the competencies outlined by Drs. Ashburn and Levine, and the Pennsylvania Work Group on "Medical School Education of Opioids and Addiction", and she serves on the Temple Substance Abuse Taskforce. Dr. Unterwald also is the Director of a training program for doctoral students and postdoctoral fellows funded by the National Institute on Drug Abuse/NIH entitled "Drugs of Abuse and Related Neuropeptides" which has been in existence at Temple University for 28 years.

Toby K. Eisenstein, PhD
Co-Investigator
Co-Director, Center for Substance Abuse Research
Professor, Department of Microbiology and Immunology
Lewis Katz School of Medicine at Temple University
Email:tke@temple.edu
Phone: 215-707-8122

Dr. Eisenstein is Co-Director of CSAR and has been since its inception. She is a Professor of Microbiology and Immunology. She has worked at the interface between opioids and the immune system for several decades. Currently, Dr. Eisenstein is the Director of the Cell and Immunology Core of the P30 NIDA Center of Excellence. She has held grants as PI from the National Institute on Drug Abuse (NIDA) to study the effect of opioids on immune function and susceptibility to infection, including effects of development of tolerance and withdrawal. She is also currently a co-investigator on the Department of Defense grant investigating combination therapies to reduce the dose of opioids needed for full analgesia. Previously, she has investigated the effect of opioids on SIV infection in monkeys. She just completed a project sponsored by the Pennsylvania Department of Health to test the analgesic efficacy of combinations of morphine and nontoxic, synthetic cannabinoids in pain models in order to be able to reduce the dose of the opioid while maintaining full analgesic efficacy. As an educator, Dr. Eisenstein is the recipient of a Lindback award for distinguished teaching, and brings extensive experience in communicating information with clarity in the classroom.

Joseph L. D'Orazio, MD
Co-Investigator
Director, Division of Medical Toxicology
Assistant Professor, Department of Emergency Medicine
Lewis Katz School of Medicine at Temple University
Email: Joseph.Dorazio@tuhs.temple.edu

Dr. D'Orazio is an Assistant Professor in the Department of Emergency Medicine at the Lewis Katz School of Medicine (LKSOM) at Temple University. He is trained as both an Emergency Physician and a Medical Toxicologist. He provides emergency care at both Temple University Hospital and Temple University Episcopal Campus. Dr. D'Orazio works in an underserved community with a high rate of drug and alcohol abuse. He runs an inpatient Medical Toxicology service caring for poisoned patients including acute drug overdose and withdrawal. He currently works in a medication-assisted treatment program for patients with opioid dependence in the Department of Family and Community Medicine. He serves on the Substance Abuse Taskforce at the medical school and is actively involved in the education of medical students and residents, including the Temple University Emergency Medicine Residency Rotation in Medical Toxicology. Dr. D'Orazio recently served on the City of Philadelphia Mayor's Office Opioid Abuse Task Force Service Access, Best Practice, & Treatment Composition Subcommittee.

David T. O'Gurek, MD, FAAFP
Co-Investigator
Assistant Professor, Department of Family and Community Medicine
Lewis Katz School of Medicine at Temple University

Email: David.O'Gurek@tuhs.temple.edu

Dr. O'Gurek is an Assistant Professor in the Department of Family and Community Medicine. He provides comprehensive outpatient primary care to patients of all ages as well as runs a medication-assisted treatment program for patients with opioid dependence within his practice. He serves on the Substance Abuse Taskforce at the medical school and is actively involved in the education of medical students and residents, including directing Temple's Family Medicine Clerkship. In addition, he is developing curricula for 3rd year medical students and Internal Medicine residents regarding opioid abuse and pain management. He has previously served on the American Academy of Family Physician's (AAFP) Opioid Abuse and Pain Management Workgroup, and has represented the AAFP nationally on issues related to opioid abuse and pain management, including co-authoring the Academy's position paper (http://www.aafp.org/about/policies/all/pain-management-opioid.html). In addition, he serves as President-Elect of the Pennsylvania Academy of Family Physicians (PAFP) and is the current chair of the AAFP's Commission on Health of the Public and Science. Dr. O'Gurek was named Pennsylvania's Top Physician Teacher by the Pennsylvania Academy of Family Physicians in 2016 and was awarded a Golden Apple Teaching Award by the LKSOM Class of 2017, attesting to his commitment and excellence in education.

Rany T. Abdallah, MD, PhD
Assistant Professor, Clinical Scholar
Department of Anesthesiology
Division of Acute and Chronic Pain
Lewis Katz School of Medicine at Temple University
Co-Investigator
Email: Rany.Abdallah@tuhs.temple.edu

Dr. Abdallah is a Clinical Scholar and Assistant Professor in the Department of Anesthesiology, Divisions of Acute and Chronic Pain, at the Lewis Katz School of Medicine at Temple University. He is board certified in anesthesiology and pain medicine by the American Board of Anesthesiology. Dr. Abdallah completed his Residency training in Anesthesiology at Rush University Medical Center in Chicago and did a Fellowship in Chronic Pain at the University of Pittsburgh Medical Center. Dr. Abdallah runs an active practice that treats patients with many types of chronic pain syndromes including cancer pain, neuropathic pain, complex regional pain syndrome, atypical facial pain and headaches, among others. He is a member of multiple professional societies and serves as a member at large on the newsletter committee of the American Society of Regional Anesthesia, the education and abstract review committees of the North American Neuromodulation Society, and CME and education committee member at large: International Neuromodulation Society. Dr. Abdallah serves on the Substance Abuse Task force at the medical school and is actively involved in the education of medical students and residents as he is the faculty director of the Journal Club. He is involved in multiple research projects, namely in the characterization of visceral abdominal pain and the pathophysiology of complex regional pain syndrome. He is an expert in the use of multi-modal approaches in the

management of pain and is a consultant in the inpatient and outpatient settings for patients with complex chronic pain syndromes.

Scott M. Rawls, PhD
Professor, Department of Pharmacology and Center for Substance Abuse Research
Lewis Katz School of Medicine at Temple University
Co-Investigator
Email: Scott.Rawls@temple.edu

Dr. Rawls is Professor of Pharmacology and a member of CSAR. He has published extensively on opioid pharmacology with an emphasis on analgesic activity, physical dependence and tolerance. He has developed an experimental therapy for cocaine addiction using an FDA-approved β-lactam antibiotic, ceftriaxone, (CTX) and β-lactamase inhibitor, clavulanic acid, which is currently in a phase I clinical trial. In addition to directing a well-regarded, NIH-funded research laboratory investigating several aspects of substance abuse, he is broadly trained in pharmacology and is an outstanding educator. Dr. Rawls developed a curriculum to teach students in K through 12 about abused substances using the flatworm, planaria. [http://www.philly.com/philly/education/The-wormhole-of-addiction-Temple-prof-uses-worms-to-teach-drug-prevention-program.html]. He received an R25 SEADP (Science Education Against Drug Abuse Partnership) award from the National Institute on Drug Abuse (NIDA/NIH) to implement this curriculum in four states. He has twice received a Golden Apple from the medical students at Temple, given by vote of the students to their favorite faculty member.

Martin W. Adler, PhD
Director Emeritus and Senior Advisor, Center for Substance Abuse Research
Professor Emeritus, Department of Pharmacology
Lewis Katz School of Medicine at Temple University
Contributor
Email: Martin.Adler@temple.edu

Dr. Adler is a Professor Emeritus of Pharmacology and Director Emeritus and Senior Advisor of CSAR. Dr. Adler is known worldwide as a premier opioid pharmacologist. He has over 220 peer-reviewed publications and was a recipient of a NIDA Merit Award. His area of expertise is on opioids and pain, as well as opioid effects on body temperature. He has worked extensively on drug interactions. He received the Nathan B. Eddy award from the College on Problems of Drug Dependence, the highest award in the field, for "excellence in drug abuse research". Previously, he was a member of the NIDA delegation to India to evaluate drug abuse research and treatment, and a co-organizer for NIDA of the U.S. State Department and Ministry of Health U.S./China Symposium on Drug Abuse and HIV/AIDS Research in Beijing, China. From 1991 to 2011 he held a major grant from NIDA on "Opioids, Cannabinoids, Chemokines: Functional Implications of Cross-talk". Currently, Dr. Adler is PI on a large Department of Defense grant investigating drug combinations in five preclinical pain models that seeks ways to achieve analgesia with reduced opioid doses. He previously organized an elective course for medical students on drugs of abuse at Temple medical school.

TITLE

PA-SUPPORT

Source for Understanding Pain, Prescribing Opioids, and Recovery Treatment

PA-SUPPORT:
Source for Understanding Pain, Prescribing Opioids, and Recovery Treatment

Curriculum Outline

Introduction to problem and curriculum

Section 1. Assessment of pain

Section 2. Non-opioid treatments for chronic pain

Section 3. Review of the pharmacodynamics and pharmacokinetics of opioid analgesics.

Section 4. Opioids in the management of pain

Section 5. Safe opioid prescribing

Section 6. Information on pain management and opioid prescribing across in special populations

Section 7. Opioids overdose and withdrawal

Section 8. Discontinuing opioids

Section 9. Identification of patients at risk for developing a substance use disorder.

Section 10. Diagnosing opioid use disorder

Section 11. Treating opioid use disorder, managing a chronic disease

Section 12. Treating pain in patients with a history of substance use disorder

Medical Case Studies

Dental Case Studies

Evaluation of knowledge

Commonly used terms:

Adapted from: https://www.cdc.gov/drugoverdose/opioids/terms.html

- **Acute Pain –** Pain that usually starts suddenly and has a known cause, like an injury or surgery. It normally gets better as your body heals and lasts less than three months.
- **Benzodiazepines –** Sometimes called "benzos," are sedatives often used to treat anxiety, insomnia, and other conditions. Combining benzodiazepines with opioids increases a person's risk of overdose and death.
- **Chronic pain –** Pain that lasts 3 months or more and can be caused by a disease or condition, injury, medical treatment, inflammation, or even an unknown reason.
- **Drug misuse –** The use of prescription drugs without a prescription or in a manner other than as directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.
- **Drug abuse or addiction –** Dependence on a legal or illegal drug or medication. See Opioid use disorder.
- **Extended-release/long-acting (ER/LA) opioids –** Slower-acting medication with a longer duration of pain-relieving action.
- **Fentanyl –** Pharmaceutical fentanyl is a synthetic opioid pain medication, approved for treating severe pain, typically advanced cancer pain. It is also used as an anesthetic agent. It is 50 to 100 times more potent than morphine. However, illegally made fentanyl is sold through illegal drug markets for its heroin-like effect, and it is often mixed with heroin and/or cocaine as a combination product. Several fentanyl analogs are available through licit and illicit markets.
- **Heroin –** An illegal, highly addictive opioid drug processed from morphine.
- **Illicit drugs –** The non-medical use of a variety of drugs that are prohibited by law. These drugs can include: amphetamine-type stimulants, marijuana/cannabis, cocaine, heroin and other opioids, synthetic drugs, and MDMA (ecstasy).
- **Immediate-release opioids –** Faster-acting medication with a shorter duration of pain-relieving action.
- **Medication-assisted treatment (MAT) –** Treatment for opioid use disorder combining the use of medications (methadone, buprenorphine, or naltrexone) with counseling and behavioral therapies.
- **Morphine milligram equivalents (MME) –** The amount of milligrams of morphine an opioid dose is equal to when prescribed. This is how to calculate the total amount of opioids, accounting for differences in opioid drug type and strength.
- **Naloxone –** A prescription drug that can reverse the effects of opioid overdose and can be life-saving if administered in time. The drug is sold under the brand name Narcan® or Evzio®.

- **Nonmedical use –** Taking drugs, whether obtained by prescription or otherwise, not in the way, for the reasons,or during the time period prescribed. Or the use of prescription drugs by a person for whom the drug was not prescribed.
- **Non-opioid therapy –** Methods of managing chronic pain that does not involve opioids. These methods can include, but are not limited to, acetaminophen (Tylenol®) or ibuprofen (Advil®), cognitive behavioral therapy, physical therapy and exercise, medications for depression or for seizures, or interventional therapies (injections).
- **Non-pharmacologic therapy –** Treatments that do not involve medications, including physical treatments (e.g., exercise therapy, weight loss) and behavioral treatments (e.g., cognitive behavioral therapy).
- **Opioid –** Natural or synthetic chemicals that interact with opioid receptors on nerve cells in the body and brain, and reduce the intensity of pain signals and feelings of pain. This class of drugs that include the illegal drug heroin, synthetic opioids such as fentanyl, and pain medications available legally by prescription, such as oxycodone, hydrocodone, codeine, morphine, and many others. Opioid pain medications are generally safe when taken for a short time and as prescribed by a doctor, but because they produce euphoria in addition to pain relief, they can be misused.
- **Opioid analgesics –** Commonly referred to as **prescription opioids**, medications that have been used to treat moderate to severe pain in some patients. Categories of opioids for mortality data include:
    - **Natural opioid analgesics,** including morphine and codeine;
    - **Semi-synthetic opioid analgesics,** including drugs such as oxycodone, hydrocodone, hydromorphone, and oxymorphone;
    - **Methadone,** a synthetic opioid;
    - **Synthetic opioid analgesics** other than methadone, including drugs such as tramadol and fentanyl.
- **Opioid use disorder –** A problematic pattern of opioid use that causes significant impairment or distress. A diagnosis is based on specific criteria such as unsuccessful efforts to cut down or control use, or use resulting in social problems and a failure to fulfill obligations at work, school, or home, among other criteria. Opioid use disorder has also been referred to as "**opioid abuse or dependence**" or "**opioid addiction**."
- **Overdose –** Injury to the body (poisoning) that happens when a drug is taken in excessive amounts. An overdose can be fatal or nonfatal.
- **Physical dependence –** Adaptation to a drug that produces symptoms of withdrawal when the drug is stopped.
- **Prescription drug monitoring programs (PDMPs) –** State-run electronic databases that track controlled substance prescriptions. PDMPs help providers identify patients at risk of opioid misuse, abuse and/or overdose due to overlapping prescriptions, high dosages, or co-prescribing of opioids with benzodiazepines.
- **Tolerance –** Reduced response to a drug with repeated use.

Abbreviations

ACOG: American College of Obstetricians and Gynecology

ADH: antidiuretic hormone

ADHD: attention-deficit/hyperactivity disorder

ASSIST: Alcohol, Smoking and Substance Involvement Screening Test

CBT: Cognitive Behavioral Therapy

CNS: Central Nervous System

COWS: Clinical Opioid Withdrawal Scale

CSA: Controlled-Substance Agreement

CSAT: SAMHSA's Center for Substance Abuse Treatment

DATA 2000: Drug Addiction Treatment Act of 2000

ER/LA: extended release/long acting

r-FLACC: Revised Face, Legs, Activity, Cry, Consolability

GRH: gonadotropin releasing hormone

HAART: highly active anti-retroviral therapy

HBV: Hepatitis B Virus

HIV: Human Immunodeficiency Virus

INRS: Individualized Numeric Rating Scale

IPV: intimate partner violence

IR/SA: immediate release/short acting

LSD: Lyseric acid diethylamide

MAOI: monoamine oxidase inhibitors

MAT: medication assisted treatment

MDMA: 3,4-Methylenedioxymethamphetamine, commonly known as "ecstasy"

MME: morphine milligram equivalence

NAS: neonatal abstinence syndrome

NEP: needle exchange program

NET: norepinephrine reuptake transporter

NSAID: Nonsteroidal Anti-Inflammatory Drugs

NMDA: N-methyl-D-aspartic acid

NRS: Numeric Rating Scale

OBOT: office based opioid treatment

OEND: overdose education and naloxone distribution

ORT: Opioid Risk Tool

OTP: outpatient treatment program

OUD: opioid use disorder

PCP: phencyclidine, commonly known as “angel dust”

PDMP: Prescription Drug Monitoring Program

PPA: Patient Prescriber Agreement

PTSD: Post Traumatic Stress Disorder

PWID: persons who inject drugs

REMS: Risk Evaluation and Mitigation Strategies

SBIRT: Screening, Brief Intervention and Referral to Treatment

SEP: Syringe Exchange Programs

SERT: serotonin reuptake transporter

SIS: Supervised Injection Site

SNRI: serotonin and norepinephrine reuptake inhibitor

SSRI: Selective serotonin reuptake inhibitor

TAPS Tool: Tobacco, Alcohol, Prescription medications, and other Substance use

TCA: Tricyclic antidepressant-like

TENS: Transcutaneous Electrical Nerve Stimulation

UDS: urine drug screen

USPSTF: United States Preventive Services Task Force

WHO: World Health Organization

XR-NXT: extended release naltrexone

Introduction

The United States currently is dealing with one of the worst health epidemics in history and the death toll continues to rise (1). On October 26, 2017, The United States Department of Health and Human Services declared the opioid crisis a "public health emergency" (2). The misuse of opioids resulted in 33,091 overdose deaths in 2015 (3), and accounted for 63.1% of the 52,404 total overdose deaths from abused substances in 2015, making drug overdose the leading cause of accidental death in the U.S (4). The epidemic is not abating, as the death rate from synthetic opioids other than methadone (but including fentanyl) increased by 72.2% between 2014 and 2015 (5).

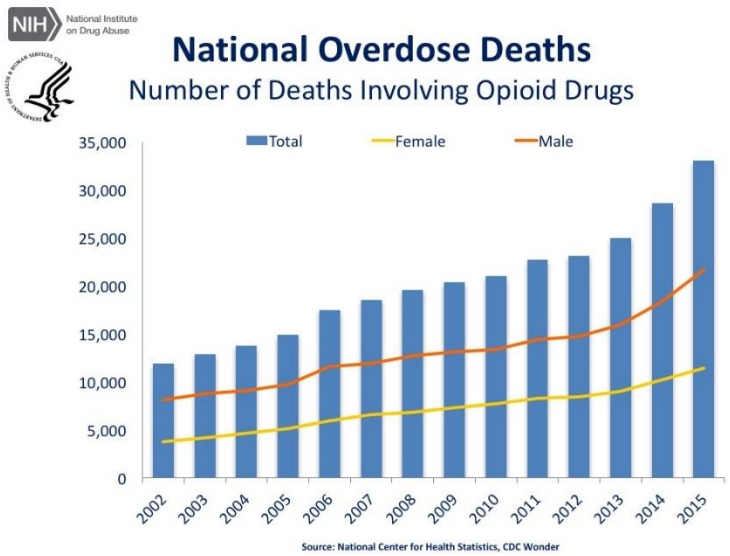


Fig. 1. Number of Overdose Deaths from Opioids, 2002-2015 (3).

In 2016, approximately 11.8 million people age 12 or older misused opioids, which is 4.4% of that population (6). It is estimated that of those that abused opioids,11.5 million used prescription opioids, and 948,000 were heroin users (6). Figure 2 gives a break-down of the prescription opioids that were abused.

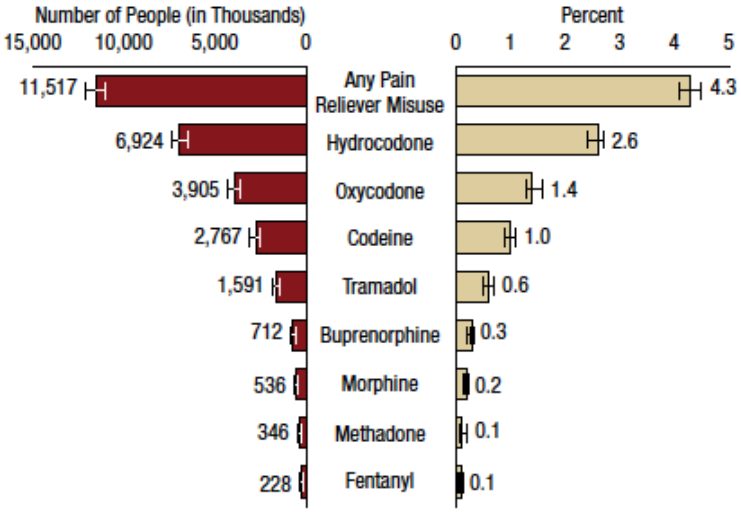


Fig.2. Past year prescription pain reliever misuse among people aged 12 or older, by selected pain reliever subtype: 2016 (6)

When people who misused opioids were asked about the reason they used the drugs, 62.3% gave the major reason as relief of pain (6).

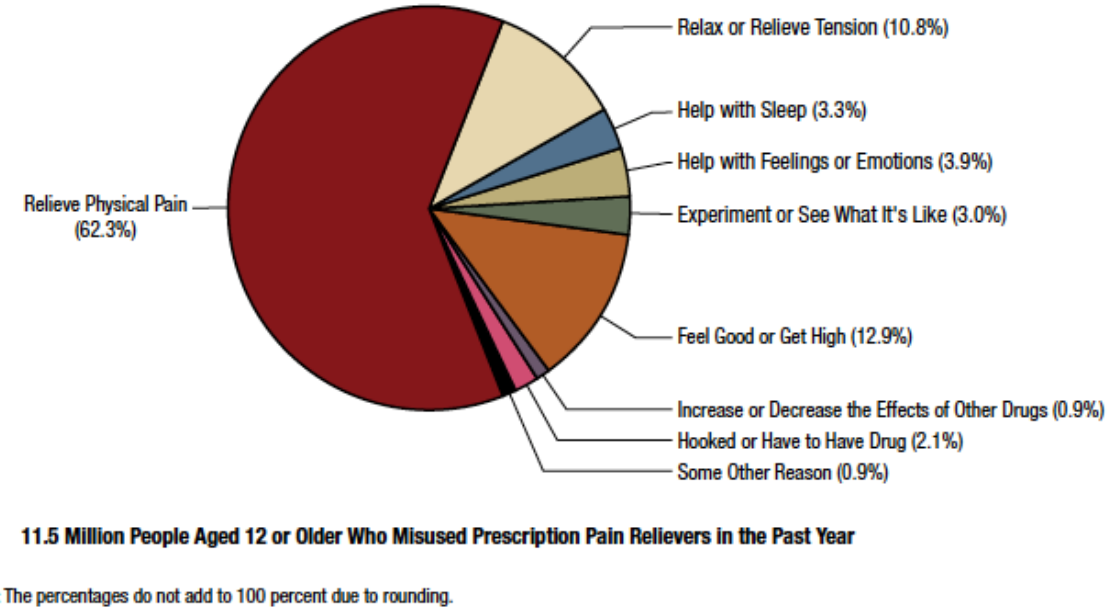


Fig. 3. Self-reported reasons for prescription pain reliever misuse (6).

In Pennsylvania in 2016, there were 4,642 drug-related overdose deaths, an increase of 37% from 2015 (7). According to a report from the national Drug Enforcement Agency (DEA) this represented a jump from 26.7% per 100,000 in 2015 to 36.5 per 100,000 in 2016, while the national average was 16.2 per 100,000 (7). An opioid was identified in 85% of the drug-related overdose deaths in Pennsylvania in 2016.

In 2012, 259 million prescriptions were written for opioids (4), a number that would give each adult in the US their own bottle of opioids (8). The increase in overdose deaths parallels the increases in prescription rates for pain relievers (9). In 1995 the American Pain Society proposed the phrase, "pain as the fifth vital sign." The Veteran's Administration and the Joint Commission on Accreditation of Healthcare Organizations adopted this designation of pain. The Joint Commission set new standards for pain assessment and management that were necessary for accreditation of health care organizations. A 2011 report from the Institute of Medicine of the National Academies estimated that 100 million Americans suffer from chronic pain. Further, this report proposed a set of underlying principles that include acknowledgment that pain can be a disease in itself. The report states that, "Effective pain management is a moral imperative, a professional responsibility, and the duty of people in the healing professions." (10). Yet, the report also acknowledged "the conundrum of opioids", because of the possibility of their diversion and abuse. Thus, the health care professional must find ways to alleviate pain without predisposing the patient to opioid addiction. Unfortunately, this cautionary note did not stem the flow of overprescribing of opioids begun in 1995. Reimbursement policies for medical services that are linked to patient satisfaction with their pain treatment may have had the unintended

consequence of increasing opioid prescribing. Further, pain management not involving opioids was in some cases not reimbursable.

It appears clear that the current national opioid epidemic is partly attributable to the misuse of prescription opioids. Reports substantiate a route to addiction in which people first become dependent on opioids through taking prescription opioids for pain relief or recreational purposes, and then switch to heroin because it costs less and is more readily available than the prescription drugs (11). In Pennsylvania, much of the increase in opioid deaths in 2016 was accounted for by overdoses with drugs containing fentanyl or heroin, rather than from prescription opioids. Out of the 4,642 deaths in Pennsylvania in 2016 caused by drug overdose, toxicology reports indicate 2,395 were positive for fentanyl or a fentanyl derivative (52% compared with 27% in 2015), 2,089 were positive for heroin, and only 1,181 were positive for a prescription opioid analgesic (7).

The unacceptable numbers of deaths caused by opioid overdose, as well as the high prevalence of opioid abuse and dependence that continue on an upward trajectory, has alarmed the country and led to broad reassessments of our current policies. One of the types of recommendations is for mandated training in pain management and in opioid prescribing. At the national level, "The President's Commission on Combating Drug Addiction and Opioid Crisis" has as one of its recommendations that there be "development of a national curriculum and standard of care for opioid prescribers …with an updated set of guidelines for prescription pain medications…" (1).

In 2016, the state of Pennsylvania passed Act 126 on safe opioid prescription education. This act directs that "beginning August 1, 2017, licensing boards shall, by joint regulation, implement a safe prescription of a controlled substance containing an opioid curriculum." (12). The professions specifically designated in the act are those with Licensing Boards, including the State Boards of Dentistry, Medicine, Nursing, Optometry, Osteopathic Medicine, and Podiatry. The objective of this curriculum is to provide an understanding of opioid drugs, and guidelines for their safe prescribing for individuals in these health care professions in accordance with Act 126.

References

1. President's Commission on combating drug addiction and the opioid crisis. 2017. U.S. Department of Health & Human Services. Available at:

https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html

2. https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html

3. National Institute on Drug Abuse. Overdose Death Rates, Revised September 2017. Available at:https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

4. American Society of Addiction Medicine. Opioid Addiction 2016 Facts & Figures. Available at:

https://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf

5. Increases in Drug and Opioid-Involved Overdose Deaths – United States, 2010-2015. Morbidity and Mortality Weekly Report. December 30, 2016. 65: Nos. 50 & 51. 1445-1452.

6. Key Substance Use and Mental Health Indicators in the United States: Results from the 2016 National Survey on Drug Use and Health (NSDUH). Substance Abuse and Mental Health Services Administration (SAMHSA). DHHS. Ahrnsbrak, R., J. Bose, S.L. Hedden, R.N. Lipari, and E. Park-Lee. (2017). Available at:

https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf

7. Analysis of Overdose Deaths in Pennsylvania, 2016. July 2017. DEA-PHL-DIR-034-17. Available at:

https://www.dea.gov/docs/DEA-PHL-DIR-034-17%20Analysis%20of%20Overdose%20Deaths%20in%20Pennsylvania%202016.pdf

8. Opioid Painkiller Prescribing: Where You Live Makes a Difference. CDC, July 2016. Availble at:

https://www.cdc.gov/vitalsigns/opioid-prescribing/

9. Paulozzi et al. Vital Signs: Overdoses of Prescription Opioid Pain Relievers – United States, 1999-2008. Morbidity and Mortality Weekly Report. November 4, 2011. 60(43):1487-1492.

10. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Committee on Advancing Pain Research, Care and Education, Institute of Medicine of the National Academies. National Academies Press,Washington,D.C. (2011).

11. Compton, W.M. C.M. Jones, and G.T. Baldwin. N. Engl. J. Med. 2016. 374:154-63. Relationship between nonmedical prescription-opioid use and heroin use.

12. Available at http://www.legis.state.pa.us/cfdocs/legis/li/uconsCheck.cfm?yr=2016&sessInd=0&act=126

1. Assessment of Pain

"Pain is an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage or described in such terms." [1] This widely accepted definition developed by a taxonomy task force of the International Association for the Study of Pain suggests that pain is a subjective entity. The assessment of pain can be a delicate and intricate process especially during the first patient encounter.

It is important to establish a rapport with the patient and to acknowledge the patient's experience of pain and empathize with it. While a patient-centered approach must be at the core of assessment, it is important to note that patients may exaggerate their pain to achieve a secondary gain. Moreover, patients may deny pain relief after a certain management strategy to prevent the weaning of their opioids. [2] Therefore, it is very important to stress the importance of reporting their pain accurately to formulate a treatment plan and assess the success of the treatments offered.

The evaluation of the patient with acute pain is usually straightforward. A detailed history and physical exam, accompanied by the appropriate studies frequently suffices to formulate a plan of treatment. On the other hand, the evaluation of chronic pain is a much more complex process as patients often have psychological comorbidities. Chronic pain patients may exhibit pain that is out of proportion to any obvious pathology. Their pain generators may be unknown or un-manifested on investigative studies (e.g. fibromyalgia).

Process of assessment

Ideally, a multidisciplinary team would be best to evaluate a patient with complex, chronic pain. However, in our current healthcare environment, the time to evaluate a patient with complex pain is often limited and the assessment lies on a single provider, usually the primary care physician.

Many web-based questionnaires are now available with drop-down menus that enable patients to give greater details about their pain. The use of web-based or paper questionnaires should save the practitioner time and enable more focused questioning. The questionnaire may be completed at home to allow the patient to take their time to answer the questions. This also saves time in the clinical setting as well. See table below for some selected questionnaires that may be of use. These questionnaires are accessible online with simple web search. Regardless of the questionnaire that fits the physician's patient population, the pain assessment encounter should include the following [3]:

Pain History

- Detailed pain history – The acronym OPQRST has been suggested as a mnemonic:
    - O = Onset
    - P = Provocative/Palliative
    - Q = Quality/Character (Neuropathic vs Somatic)
    - R = Region/Radiation
    - S = Severity/Intensity
    - T = Timing of pain (Continuous vs Intermittent)

- Severity/Intensity: There are different rating scales used. The most commonly used is the Numeric Rating Scale (NRS). A patient simply rates pain on a scale between 0 and 10 where "0" represents no pain and "10" represents the "worst pain imaginable."
- Detailed history of previous investigative modalities (e.g., labs, EMGs, imaging)
- Previous treatments tried and their efficacy (e.g., physical therapy, interventional therapy, medications)
- Current medications, including over-the-counter medications, and other treatments

Past Pertinent Medical History

- Comorbidities pertinent to the manifestation of the pain syndrome (dementia, diabetes)
- Comorbidities pertinent to treatment (renal failure, cardiovascular disease, sleep disturbance)

Psychiatric Comorbidity

- Anxiety
- Depression
- Bipolar disorder
- Posttraumatic stress disorder (PTSD)
- Adult attention deficit hyperactivity disorder (ADHD)

Psychosocial Factors

- Make note of personality features that impact pain (e.g., catastrophizing, health-related anxiety, pain-related fear and associated avoidance behaviors) [4]
- Pain coping strategies (e.g., exercise, yoga, meditation)
- Relevant family history, including sexual abuse and adverse childhood events
- Other factors such as cultural issues, employment history, litigation issues, financial situation, family and/or community support

Risk of Addiction (see Section 9 for further details)

- If opioids or cannabinoids are currently being used or will be considered, determine if the addiction risk is low, medium, or high [5]
- Smoking history [6,7]
- History of drug and/or alcohol exposure or abuse
- Family history of drug, alcohol, or psychological/psychiatric problems [8]

Assessment of Function

- Loss of functionality can be assessed using different functionality questionnaires
- Questions should cover relevant areas and usually include impact of pain on domains such as employment, social, recreational, family, or home responsibilities

- Physician should also assess self-care, sleep, and ideally evaluate the overall quality of life

Goals

- Determine patient goals, including social, recreational, and/or occupational tasks, to direct treatment and evaluate effectiveness of therapeutic interventions
- Different patients may have different goals and expectations that may need to be followed up on and managed

Physical examination and testing

- General physical exam and mental status assessment – look for signs of substance abuse/misuse
- Focused examination on areas of pain such as musculoskeletal or neurological examination based on the chief complaint
- Further testing and documentation may be required/considered depending on the patient's history and physical exam:
    - Urine Drug Testing
    - Imaging (x-ray, CT, MRI, etc.)
    - Diaries of pain, sleep, activity and medication intake
    - Opioid agreement

Follow-up visits

Follow-up visits are very important to assess the progress of patients to their goals of pain and functional improvement. In all follow-up visits, it is recommended to review the following:

- Goal achievement
- Diaries of pain and medication
- Analgesic response in terms of function and pain score
- Adverse events to plan of treatment
- Aberrant behavior (e.g., addictive behavior, opioid seeking behavior)
- New plan of action

SELECT RELEVANT PAIN ASSESSMENT TOOLS
Pain and Disability Assessment
Pain Assessment Documentation Tool (PADT)
Brief Pain Inventory
Short Form McGill Pain Questionnaire
The Neuropathic Pain Scale
The Pain Disability Index Score
Psychological Comorbidity Assessment
The Beck Depression Inventory
Personality Assessment Inventory
The Minnesota Multiphasic Personality Inventory (MMPI)
The Pain Catastrophize in Scale
The Tampa Scale for Kinesiophobia
Substance Misuse Assessment
The Current Opioid Misuse Measure (COMM)
Urine Drug Testing

References

1. International Association for the Study of Pain. Pain, IASP Pain Terminology. 1994. http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions&Template=/CM/HTMLDisplay.cfm&ContentID=1728#Pain.

2. Evers GCM. Pseudo-opioid-resistant pain. Support Care Cancer. 1997; 5:457-460.
3. Fishman, Scott M. Bonica's Management of Pain. Chapter 17.

4. Swinkels-Meewisse EJ, Swinkles RA, Verbeek AL, Vlaeyen JW, Oostendorp RA. Psychometric properties of the Tampa Scale for kinesiophobia and the fear-avoidance beliefs questionnaire in acute low back pain. Man Ther 2003; 8:29–36.
5. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med March–April, 2005;6(2):107–112.
6. Jamison RN, Stetson BA, Parris WC. The relationship between cigarette smoking and chronic low back pain. Addict Behav 1991;16(3–4):103.
7. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: prelminary validation of the Opioid Risk Tool. Pain Med 2005;6(6): 432–442.
8. Michna E, Ross EL, Hynes WL, et al. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. J Pain Symptom Manage 2004; 28:250–258.

2. Non-opioid Treatments for Chronic Pain

Single agent pharmacotherapy may be effective when treating acute pain on a short-term basis. However, when managing chronic pain, single measure therapy is typically unsuccessful [1, 2]. Chronic pain management must be multimodal to achieve the best functional outcomes (see figure). A regimen encompassing self-care, pharmacotherapy, psychobehavioral therapy (e.g. cognitive behavioral therapy, mindfulness), physical therapy, and/or interventional therapy (e.g. steroid injections, neurolysis) would offer patients the best chance for success in reaching their functional goals.

Self-Care

The literature suggest that self-management programs may offer benefits for older adults with chronic pain. [3, 4]. These include:

- Home exercise programs
- Aquatic exercise programs
- Yoga
- Massage therapy
- Tai Chi therapy
- Stress reduction
- Pacing activities
- Cold/heat packs
- Stretching
- Listening to favorite music

Pharmacotherapy

It is usually wise to simplify drug regimens. However, the use of a combination of drugs in moderate doses may reduce the risk of adverse events when the drugs are additive or synergistic and the adverse events are commonly dose related. It is important to consider the risk of every medication and only start a new medication when benefits outweigh risks. Common opioid alternatives are:

- *Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):* NSAIDs act by inhibiting prostaglandin synthesis in vivo. They provide excellent analgesic, anti-inflammatory, and antipyretic effects as monotherapy and can be useful in combination with opioids for more severe pain. Although generally safe, special attention should be paid to patients with renal insufficiency and gastrointestinal sensitivity [5,6]. Moreover, NSAIDs may increase the risk of serious thrombotic events [7].
- *Acetaminophen:* A para-aminophenol with analgesic and antipyretic properties. Doses of 600 to 650 mg are more effective than doses of 300 to 325 mg. There does not seem to be additional benefit at doses above 1000 mg [8].
- *Muscle Relaxants:* Multiple medications are classified as muscle relaxants because they reliably produce skeletal muscle relaxation. They have been conventionally prescribed for acute and chronic conditions associated with muscle-related pain. These medications

may cause some sedation; therefore, they should be used cautiously with slow titration. Classes include:
    - Antihistamine (e.g. orphenadrine) – FDA-approved for the relief of discomfort associated with an acute, painful musculoskeletal conditions.
    - Sedatives (e.g. carisoprodol, chlorzoxazone, metaxalone, methocarbamol) – FDA-approved for the relief of discomfort associated with an acute, painful musculoskeletal conditions. [10]
    - Tricyclic antidepressant-like (TCA-like, e.g. cyclobenzaprine)
    - Central alpha-2 agonists (e.g. tizanidine) – FDA-approved for the relief treatment of spasticity due to multiple sclerosis, spinal cord disease, or injury.
    - GABA-agonists (e.g. baclofen) – FDA-approved for the relief treatment of spasticity due to multiple sclerosis, spinal cord disease, or injury.

- *Neuropathic Pain Pharmacotherapy:* It is estimated that 1.5% to 8% of the general population suffer from neuropathic pain [11,12]. Moreover, many painful conditions have a mixed somatic and neuropathic origin that may very well be treated with neuropathic pain pharmacotherapy in combination with other drugs. The major non-opioid classes of medications that have been shown to relieve neuropathic pain are:
    - Antidepressants – Four classes of antidepressants have been studied for treatment of neuropathic pain: tricyclic antidepressants (TCAs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs). Certain TCAs (e.g. amitriptyline, nortriptyline) and SNRIs (e.g. duloxetine, venlafaxine) are considered first line agents for the treatment of neuropathic pain [13].
    - Anticonvulsants – There is extensive evidence that shows that anticonvulsants, namely gabapentin and pregabalin, are effective in the treatment of neuropathic pain [13].
    - Tramadol – Weak opioid with SNRI properties. There is ample evidence that shows its efficacy in treating neuropathic pain [13].
    - Cannabinoids – Although not fully approved in the state of Pennsylvania, extracts of the plant C*annabis sativa* have the potential to aid with the treatment of refractory neuropathic pain [13].

- *Topical Pharmacotherapy* – Several topical analgesics have been tested in a wide range of painful conditions. Many formulations may be used (e.g. creams, foams, gels, lotions, ointments, patches) [14]. In general, you may use topical preparations in the following manner:
    - For strains and sprains – topical NSAIDs (cream, gel, patch)
    - For osteoarthritis – topical NSAIDs and low-concentration topical capsaicin.
    - For neuropathic pain – topical local anesthetic (e.g. lidocaine patch or cream) or high-concentration topical capsaicin.
    - Topical herbal medicines may be used for the treatment of painful conditions.

Psychobehavioral Therapy

The integration of psychological techniques, such as cognitive behavioral therapy (CBT) and mindfulness meditation, to assist patients in coping with chronic pain has been shown to improve pain scores, functional outcomes, and decrease opioid use [15]. These techniques can be implemented in the clinic setting. Otherwise, patients may be referred to a psychobehavioral therapist to take part in private or group therapy.

Physical Therapy

Physical therapy aims at helping patients with functional restoration through therapeutic exercise, activities, and the application of physical agents (e.g. heat, cold, light) [16]. Physical therapists work with patients on balance, endurance, range of motion, strengthening and targeted exercises. They also use modalities such as heat, therapeutic ultrasound and Transcutaneous Electrical Nerve Stimulation (TENS) to provide pain relief. In addition, physical therapists educate patients on how to perform their daily exercises. Patients should be referred to PT when a new musculoskeletal problem arises or when they appear to be physically deconditioned.

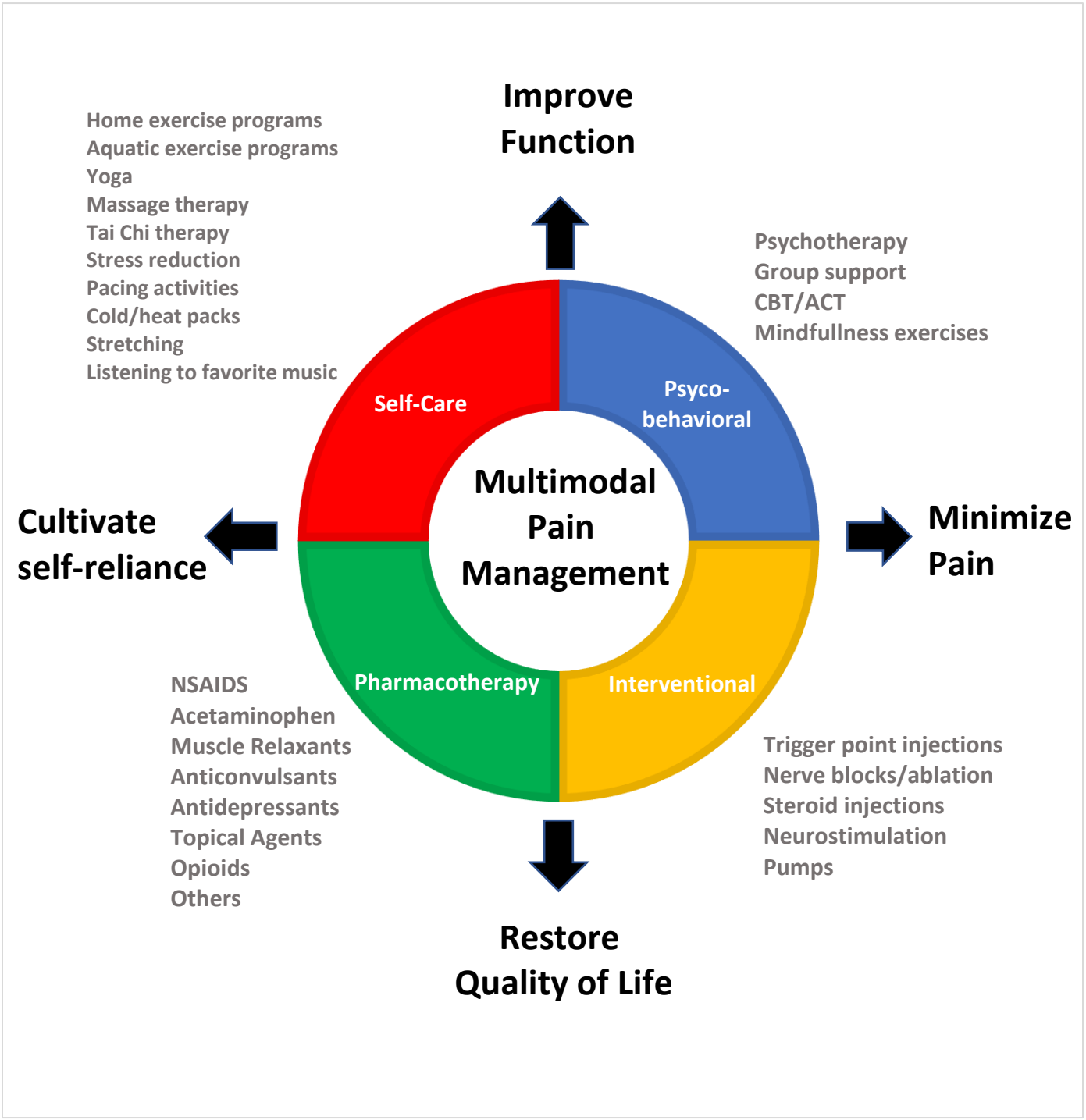
Interventional Therapy

Despite our best efforts, it sometimes difficult to achieve satisfactory pain control with conservative management. It may be necessary to refer patients to specialists (e.g. neurologist, physical medicine, pain management, surgeon) to evaluate for possible procedural or surgical interventions. Interventions may be aimed at symptom management (e.g. steroid injections, neurolysis) or treating the source of the pain (e.g. knee replacement).

Alternative Therapy

Multiple and diverse alternative therapy are widely used for the treatment of chronic pain. The research on these therapies is confusing and contradictory at times. Some patients choose to resort to these therapies when conventional medical treatments have failed. Some of these therapies are [9]:

- Manipulation
- Natural medicine therapies
- Body awareness therapy
- Therapeutic massage
- Breath pattern retraining
- Trigger point manipulation
- Magnetic therapy
- Acupuncture
- Homeopathy
- Touch therapy
- Reiki and energy healing therapies


Improve Function
Home exercise programs
Aquatic exercise programs
Yoga
Massage therapy
Tai Chi therapy
Stress reduction
Pacing activities
Cold/heat packs
Stretching
Listening to favorite music
Psychotherapy
Group support
CBT/ACT
Mindfullness exercises
Self-Care
Psyco-behavioral
Multimodal Pain Management
Cultivate self-reliance
Minimize Pain
NSAIDS
Acetaminophen
Muscle Relaxants
Anticonvulsants
Antidepressants
Topical Agents
Opioids
Others
Pharmacotherapy
Interventional
Trigger point injections
Nerve blocks/ablation
Steroid injections
Neurostimulation
Pumps
Restore Quality of Life

References

1. Gatchel RJ. Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective. American Psychologist. 2004;59(8):795-805.
2. White PF. Multimodal pain management—the future is now! Curr Opin Investig Drugs 2007;8(7):517–518.
3. Reid MC, Papaleontiou M, Ong A, et al. Self-management strategies to reduce pain and improve function among older adults in community settings: a review of the evidence. Pain Medicine (Malden, Mass). 2008;9(4):409-424.
4. Franek, J. Self-management support interventions for persons with chronic disease: an evidence-based analysis. Ontario Health Technology Assessment Series. 2013;13(9):1-60
5. Plantinga L, Grubbs V, Sarkar U, et al. Nonsteroidal Anti-Inflammatory Drug Use Among Persons With Chronic Kidney Disease in the United States. Fam Med 2011;9(5):423-430.
6. Wallace JL. NSAID gastropathy and enteropathy: distinct pathogenesis likely necessitates distinct prevention strategies. Br J Pharmacol. 2012 Jan; 165(1): 67–74.
7. Pirlamarla P, Bond RM. FDA labeling of NSAIDs: Review of nonsteroidal anti-inflammatory drugs in cardiovascular disease. Trends Cardiovasc Med. 2016 Nov;26(8):675-680.
8. Skoglund LA, Skjelbred P, Fyllingen G. Analgesic efficacy of acetaminophen 1000 mg, acetaminophen 2000 mg, and the combination of acetaminophen 1000 mg and codeine phosphate 60 mg versus placebo in acute postoperative pain. Pharmacotherapy 1991;11(5):364–369.
9. Fishman, Scott M. Bonica's Management of Pain.
10. Jackson KC. Evaluation of skeletal muscle relaxant use for acute musculoskeletal pain and injury in ambulatory care. J Pain 2003;4(2 suppl 1):84(934).
11. Torrance N, Smith BH, Bennett MI, et al. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain 2006;7(4):281–289. 2.
12. Hall GC, Carroll D, Parry D, et al. Epidemiology and treatment of neuropathic pain: the UK primary care perspective. Pain 2006;122(1–2):156–162.
13. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015 Feb;14(2):162-73.
14. Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. Cochrane Database Syst Rev. 2017 May 12;5:CD008609.
15. Baker N. Using Cognitive Behavior Therapy and Mindfulness Techniques in the Management of Chronic Pain in Primary Care. Prim Care. 2016 Jun;43(2):203-16.
16. Witttink H, Michel TH. Chronic Pain Management for Physical Therapists. Boston: Butterworth Heinemann; 2002.

3. Opioid Pharmacology: Review of the Pharmacodynamics and Pharmacokinetics of Opioid Analgesics

Classification, chemistry and mechanism of action

Morphine and codeine are naturally occurring opiates derived from opium, a product of the opium poppy. Morphine is the standard against which other opioid analgesics are compared. In addition to the naturally occurring opiate compounds, semi-synthetic and fully synthetic opioids are used to treat pain. Semi-synthetic opioids are derivatives of morphine or codeine with substitutions at key sites which result in altered pharmacodynamic and kinetic properties. Semi-synthetic opioids include heroin (diacetylmorphine), hydrocodone, hydromorphone, oxycodone, and oxymorphone. Synthetic opioids are structurally unrelated to morphine and include compounds such as methadone, meperidine, buprenorphine and fentanyl. Urine drug screens target the morphine structure and thus detect the natural and semi-synthetic opioids due to their metabolites, but not the fully synthetic agents. Specific assays are available to detect synthetic opioids in the urine including fentanyl, buprenorphine and methadone.

All opioids produce their effects by interacting with specific opioid receptors. Opioid analgesics reduce pain by activating opioid receptors at multiple sites in the body including 1) the periphery where they inhibit activation of nociceptors and cells that release pro-nociceptive mediators, 2) the dorsal horn of the spinal cord where they reduce neurotransmission from the terminals of C-fibers, 3) the second order pain transmission pathway where they prevent ascending transmission of pain signals, 4) the midbrain where they activate a descending pain-inhibitory pathway, and 5) in higher brain regions where they dampen the affective/emotional component of pain.

Opioid compounds are classified by their actions at opioid receptors as full agonists, partial agonists, mixed agonist/antagonists or full antagonists. There are three opioid receptors, called mu, kappa, and delta receptors. Each of them can mediate analgesia Most of the commonly used opioid analgesics have highest affinity to the mu receptor, and are therefore classified as mu opioid receptor agonists. Thus, morphine is a full agonist at mu opioid receptors, as is oxycodone and the other high efficacy agents, whereas other opioids such as codeine and buprenorphine function as partial or weak agonists and can only produce moderate pain relief at any dose. The mixed opioid agonist/antagonists are drugs that have agonist properties at one opioid receptor and antagonist or partial agonist actions at another. For example, nalbuphine is an agonist at kappa opioid receptors and an antagonist at mu opioid receptors. The opioid antagonists, including naloxone and naltrexone, bind to opioid receptors without producing a functional response and, in addition, prevent an agonist from binding and activating the receptor. Thus, opioid receptor antagonists can block or reverse the effects of opioid agonists.

Side Effects of Opioid Analgesics

In addition to analgesia, opioid drugs produce a variety of other effects by activation of opioid receptors in the CNS and peripheral tissues. Effects of opioid analgesics that are mediated by activation of opioid receptors in the brain include sedation and mental clouding, nausea and vomiting, miosis, cough suppression, euphoria, and respiratory depression. Respiratory

depression can be of serious consequence as described below (Acute Opioid Toxicity) and is the cause of death in the setting of an overdose. Peripheral side effects of opioid analgesics include constipation, pruritus, urinary retention, and minor effects on cardiovascular function (bradycardia) and smooth muscles of the biliary tract and uterus. Some opioids such as methadone and buprenorphine can prolong the cardiac QTc interval. Chronic use of opioids can lead to decreased hypothalamic function due to decreased secretion of gonadotropin releasing hormone (GRH). The clinical effects from decreased GRH secretion are reduced libido in both men and women, hot flashes, depression, hair loss, and osteopenia. Some other side effects associated with chronic opioid use include sedation and hearing loss. Side effects are dose-dependent and, as discussed below, tolerance can develop to some, but not all opioid effects with repeated opioid administration.

Opioid-induced Hyperalgesia

Chronic use of opioid analgesics is sometimes associated with the development of a state of hyperalgesia. Opioid-induced hyperalgesia is characterized by a paradoxical increase in pain sensitivity in patients receiving opioids for the treatment of pain. Hyperalgesia is thought to result from neuroplasticity in the peripheral and central nervous system that leads to sensitization of pro-nociceptive pathways, although the precise molecular basis is not firmly established. Hyperalgesia has been observed with several opioid analgesics, most commonly morphine, fentanyl, and remifentanil especially when administered by infusion and used in high doses. The potential of developing this syndrome is one reason why the use of opioids for the treatment of chronic pain should proceed with caution. Treatment of opioid-induced hyperalgesia consists most often of reducing the opioid in question and treating with non-opioid medications. If an opioid is needed, switching to methadone or buprenorphine is associated with improved pain relief, due to their ability to act as an NMDA receptor antagonist or kappa opioid receptor antagonist, respectively.

Tolerance and Physical Dependence

Frequent repeated administration of morphine or other opioid analgesics can result in a gradual loss of effectiveness, which is termed tolerance. Tolerance is characterized by a decrease in the effect of the opioid and/or a decrease in the duration of action due to prior exposure to the drug. With tolerance, a larger dose must be administered to achieve the original response. Tolerance is both dose- and time-dependent, with frequent administration of high doses of a full agonist producing tolerance more rapidly than lower doses or with weak agonists. Tolerance develops to some effects of opioids but not to others. For example, tolerance develops to the sedative, analgesic, and respiratory depressant effects of opioids, but not to their effects on the gastrointestinal tract (ie, constipation) or pupil (ie, miosis). Cross-tolerance is an important characteristic of opioids. Thus, if a person shows tolerance to morphine, they will also exhibit tolerance to other mu opioid agonists. Tolerance can be complete or partial and should be considered when switching between different opioids.

Chronic use of opioids for the treatment of pain can result in physical dependence. Physical dependence is characterized by the appearance of a withdrawal syndrome when the drug is

abruptly discontinued or upon administration of an antagonist (e.g., naloxone). Opioid withdrawal is characterized by nausea, vomiting, diarrhea, sweating, muscle aches, abdominal cramping, and anxiety. Its development is both dose- and time-dependent and can occur in as little as 48 hours of opioid exposure. Physical dependence is not equivalent to addiction which is discussed below [Section 10]. Both tolerance and physical dependence are reversible; the signs and symptoms gradually dissipate after the opioid is discontinued (see Section 8 for a description of detoxification from opioids).

Acute Opioid Toxicity: Respiratory Depression

Acute opioid toxicity or overdose can produce profound respiratory depression. Activation of opioid receptors in brain stem respiratory centers results in depressed respiratory rate and tidal volume. Opioids decrease the response of the brainstem respiratory centers to CO_2 tension in the blood, resulting in hypoxia, decreased oxygen saturation, and hypercapnea. Early signs include sedation and bradypnea. Signs of an overdose include depressed respiration, stupor, and miosis. Failure to support respiration leads to pupillary dilation and shock, followed by death. Treatment is to restore ventilation either through artificial respiration or by administration of the opioid receptor antagonist, naloxone. Use of opioid analgesics with other CNS depressants, such as alcohol and benzodiazepines, is dangerous due to enhanced respiratory depression and increased incidence of death.

Contraindications and Cautions in Therapy

Opioid analgesics should be used with particular caution under the following circumstances:

- Impaired pulmonary function. Patients with reduced pulmonary function can experience exaggerated opioid-induced respiratory depression.
- Head trauma. The use of opioids in patients with head injuries requires great care. Cerebral vasodilation can result from carbon dioxide retention caused by opioid-induced depressed respiration. This can be dangerous in patients with elevated intracranial pressure.
- Pregnancy. Use of opioids during pregnancy can produce respiratory depression and physical dependence in the fetus (this is discussed further in Section 6).
- Liver disease. Since opioids are metabolized primarily by the liver, side effects of opioid analgesics may be exaggerated in the presence of severe liver dysfunction due to elevated plasma levels of the active compound. Dose reductions are recommended.
- Renal disease. With impaired renal function, opioid half-lives can be prolonged and active metabolites can accumulate leading to greater side effects. Dose reductions can help to prevent increased side effects in these patients, as can use of agents with inactive metabolites.
- Gastrointestinal conditions. Opioids are contraindicated in patients with paralytic ileus or other GI obstruction. Patients with biliary tract disease should be monitored for worsening symptoms.

Drug Interactions

Adverse interactions can occur between opioid analgesics and other agents (Table 3.1). Prescribers should instruct patients and caregivers that the use of benzodiazepines or other CNS depressants, including alcohol or illicit drugs, with opioid analgesics may result in profound sedation, respiratory depression, coma and death. Concomitant prescribing of opioids and other CNS depressants (eg, tricyclic antidepressants, sedatives, hypnotics, tranquilizers) should be limited to those patients for whom alternative treatment options are inadequate and be of low dose and short duration. Such patients should be followed closely for signs of respiratory depression and sedation. Opioid analgesics, especially meperidine, should not be used with monoamine oxidase inhibitors (MAOI) due to the occurrence of severe reactions including excitation, hyperpyrexic coma and hypertension. Serotonin syndrome and/or opioid toxicity are possible with MAOIs combined with opioids. Some extended release opioids are specifically contraindicated with MAOIs (e.g., tapentadol, morphine). Opioids can reduce the efficacy of diuretics by causing the release of antidiuretic hormone (ADH). Drugs that inhibit or induce cytochrome P450 enzymes can result in elevated or reduced levels of some opioids. For example, the potent 3A4 inhibitors such as ketoconazole, erythromycin, and HIV protease inhibitors, can cause a substantial increase in the plasma concentrations of buprenorphine. Dose modifications may be needed and the patient monitored closely for signs of adverse events.

OPIOID - DRUG INTERACTIONS	ADVERSE EVENT
CNS depressants	Enhanced respiratory depression
Monoamine oxidase inhibitors	CNS excitation, hyperpyrexia, serotonin syndrome
Diuretics	Reduced efficacy of diuretics
Cytochrome P450 inhibitors or inducers	Increased or decreased opioid plasma level.

Table 3.1: Adverse drug interactions with opioid analgesics

Opioid formulations

Opioid analgesics are available as immediate release/short acting (IR/SA) and extended release/long acting (ER/LA) formulations. Usually ER/LA opioids are administered once or twice daily as oral tablets or are available as transdermal patches. IR/SA and ER/LA preparations contain the same active opioid analgesic but the formulation differs to control release rates. ER/LA opioid analgesics are formulated to release the active ingredient gradually thus slowing the onset of action and prolonging the duration of action. Physical tampering with the preparation can bypass the extended release formulation, thus converting it to an IR/SA drug. As such, the ER/LA formulations may be contraindicated in patients at risk for substance misuse. As the amount of opioid in the ER/LA preparations are usually higher than in the IR/SA formulations, tampering with the ER/LA product can result in an opioid overdose. Patients should be counseled against crushing, splitting, chewing or otherwise altering the tablet or patch in any way. It should be noted that some ER/LA formulations may fail in the presence of

alcohol, causing the opioid to be rapidly released. “Alcohol-induced dose dumping” can result in serious opioid toxicity including respiratory depression, leading to hypoxia and death.

Insufficient data are available to indicate if ER/LA opioids are more effective for pain management or are associated with fewer toxicities than IR/SA opioids. In general, if an opioid is deemed necessary for the treatment of pain in an opioid naïve patient, therapy should begin with a low dose of a IR/SA agent. Since they have a shorter half-life, IR/SA opioids are safer and the dose is easier to adjust to desired effect, good analgesia with low side-effects. In patients who are opioid tolerant with chronic pain, conversion to an IR/SA opioid can be more convenient for the patient and can provide a more constant plasma drug levels than ER/LA opioids.

New “abuse-deterrent” formulations of opioid analgesics are under development by pharmaceutical companies. One approach is the formation of ‘tamper resistant’ tablets that cannot be crush or dissolved, and thus cannot be snorted or injected. Another approach is the inclusion of a low dose of opioid antagonist, naloxone or naltrexone, with the opioid analgesic. Taken orally as prescribed, the antagonist has little effect; however, if the dose form is injected intravenously, the antagonist will block the effects of the opioid analgesic. The FDA has supported the development of these new formulations and many are approved for clinical use (see Table 3.2). It should be remembered that abuse-deterrent formulations of opioid analgesics still produce tolerance and dependence, can be taken without medical need (ie, abused), and can result in overdose and death, similar to other dose forms. In order to assess the impact of abuse-deterrent technologies on the opioid crisis, the FDA is requiring all of the companies that have brand name opioids with abuse-deterrent claims to conduct post-market studies to determine the impact those products are having clinically.

Table 3.2. Opioids with FDA-Approved Labeling Describing Abuse-Deterrent Properties FDA has approved these opioids with labeling describing abuse-deterrent properties consistent with the FDA’s Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling:

- OxyContin – oxycodone ER, Purdue Pharma LP
- Targiniq ER – naloxone + oxycodone ER, Purdue Pharma
- Embeda – morphine (20-100 mg) + naltrexone (0.8-4 mg) ER, Alpharma Pharms
- Hysingla ER – hydrocodone ER, Purdue Pharma
- MorphaBond ER – morphine ER, Daiichi Sankyo Inc
- Xtampza ER – oxycodone ER, Collegium Pharm Inc
- Troxyca ER – oxycodone (10-80 mg) + naltrexone (1.2-9.6 mg) ER, Pfizer Inc
- Arymo ER – morphine ER, Egalet
- Vantrela ER – hydrocodone ER, Teva Branded Pharm
- RoxyBond – oxycodone IR, Daiichi Sankyo Inc

There are currently NO generic opioids with FDA-approved abuse-deterrent labeling. [Taken from: FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics]

Transdermal patch preparations of fentanyl and buprenorphine are convenient for the relief of chronic around-the-clock pain. Transdermal patches have a slow onset of action so they cannot be used in the treatment of acute pain. Instead, opioid patch formulations are reserved for patients who were previously maintained on oral opioids and show substantial opioid tolerance. Fentanyl and buprenorphine patches provide pain relief for 72 hours and 7 days, respectively. The absorption of fentanyl or buprenorphine by the transdermal route is influenced by several factors including body temperature, subcutaneous fat, blood flow to the area, and the intactness of the skin. Thus, fever increases the absorption and edema decreases absorption of the medications. Careful patient counseling is needed for safe use of opioid patches because the patches typically contain large doses of opioids. Further, residual drug remaining in the patch after patient use can be harmful to children and pets, so they must be disposed of with care.

Pharmacological Properties of Individual Agents (also see Table 3.3)

- Morphine – Strong agonist at mu opioid receptors used for the treatment of severe pain. Large first-pass metabolism by liver. Active metabolite, morphine-6-glucuronide, which is also a mu receptor agonist with analgesic actions. High abuse liability.
- Codeine – weak or partial mu receptor agonist. Used to treat mild pain most often in combination with acetaminophen. Codeine is metabolized in part to morphine at unpredictable rates. Genetic polymorphisms in the CYP2D6 enzyme lead to variable rates of conversion of codeine to morphine, leading to under treatment in poor metabolizers and overdose in rapid metabolizers. Abuse liability and potential to cause physical dependence lower than morphine.
- Hydromorphone – Semisynthetic strong mu opioid receptor agonist used for the treatment of severe pain. More potent than morphine. High abuse liability.
- Oxymorphone – Semisynthetic strong mu opioid receptor agonist used for the treatment of severe pain. More potent than morphine. No active metabolites. High abuse liability.
- Oxycodone – Semisynthetic mu opioid receptor agonist used for the treatment of moderate to severe pain. Often used in combination with acetaminophen or aspirin. CYP450 activators enhance metabolism. High abuse liability.
- Hydrocodone – Semisynthetic mu opioid receptor agonist used for the treatment of moderate to moderately severe pain. Combination products contain hydrocodone plus acetaminophen or aspirin. High abuse liability.
- Dihydrocodeine - Semisynthetic mu opioid receptor agonist used for the treatment of mild to moderate pain. Combination products contain hydrocodone plus acetaminophen or aspirin.
- Methadone – Synthetic full mu opioid receptor agonist with NMDA receptor antagonist properties. Can be used for the treatment of moderate to severe pain, although not usually a first-line agent. May show better efficacy in the treatment of chronic neuropathic pain and may show lower analgesic tolerance than morphine. With chronic administration, the serum half-life of methadone is significantly prolonged and variable, up to 120 hours. Methadone has been associated with increased risk of QTc prolongation.

- Meperidine – Synthetic full mu opioid receptor agonist with anticholinergic activity. Less effect on gastrointestinal function and pupil, and can produce tachycardia. Used for the treatment of severe pain especially in the emergency department setting. Meperidine has an active metabolite with CNS toxicity and is associated with potential severe drug interactions, limiting its clinical usefulness. High abuse liability.
- Fentanyl – Very potent synthetic full mu receptor agonist. Can be used for the treatment of severe pain, in addition to its use in anesthesia. Less sedating than morphine. Low oral bioavailability and very short duration of action. Available for parenteral administration, as well as transdermal patch and oral lozenge dose forms. High abuse liability.
- Pentazocine – Mixed opioid receptor agonist/antagonist; kappa receptor agonist and mu receptor partial agonist or weak antagonist. Can be used for the treatment of mild to moderate pain. Side effects include tachycardia and dysphoria at high doses.
- Nalbuphene - Mixed opioid receptor agonist/antagonist; kappa receptor agonist and mu receptor antagonist. Used for the treatment of moderate to severe pain. Side effects include dysphoria at high doses due to activation of kappa opioid receptors.
- Buprenorphine – Partial mu receptor agonist and delta/kappa receptor antagonist. Indicated for the treatment of moderate to severe pain, and for the treatment of opioid use disorder. Lower side effects than morphine. Low oral bioavailability; administered parenterally, sublingually, and as a transdermal patch.
- Butorphanol - Mixed opioid receptor agonist/antagonist; strong kappa receptor agonist and mu receptor partial agonist. Used for the treatment of moderate to severe pain, including migraine headaches. Low oral bioavailability; parenteral and intranasal only. Side effects include dysphoria at high doses.
- Tapentadol – Moderate mu receptor agonist and strong inhibitor of NET (norepinephrine reuptake transporter). Indicated for treatment of moderate to severe pain. May show greater efficacy in neuropathic pain and hyperalgesia than others. Adverse effects include seizures at high doses. Lower gastrointestinal side effects than morphine.
- Tramadol – Weak mu receptor agonist with moderate inhibition of SERT (serotonin reuptake transporter) and weak inhibition of NET. Indicated for treatment of moderate pain. Lower effect on respiratory function and gastrointestinal inhibition than morphine and other opioids. Toxicities include seizures at high doses and risk of serotonin syndrome.

Table 3.3: Characteristics of Individual Agents

Drug	Schedule	Trade names IR/SA	Duration of analgesic action IR/SA	Trade names SR/LA	Duration of analgesic action SR/LA	Analgesic efficacy
Morphine	II	generic	4-5 hr IR	MS-Contin Arymo ER	8-12 hr	high
				Avinza Kadian	24 hr	
Morphine + Naltrexone	II			Embeda	12-24 hr	high
Codeine	II	generic	3-4 hr			low
Codeine + Acetaminophen	III	Tylenol with codeine	4-5 hr			low
Hydrocodone + Aspirin or Acetaminophen or Ibuprofen	II	Lortab Lorcet Vicodin Vicoprofen	4-6 hr			moderate
Hydrocodone	II			Hysingla ER, Vantrela ER, Zohydro ER	24 hr	moderate
Hydromorphone	II	Dilaudid	4-5 hr	Exalgo	24 hr	high
Oxycodone	II	generic	3-4 hr	Oxycontin	8-12 hr	moderate
				Xtampza ER	12 hr	
Oxycodone + acetaminophen	II	Percodan Percocet Roxicet	3-4 hr			moderate
Oxycodone + naloxone	II			Targiniq ER	12 hr	moderate
Oxymorphone	II	Opana	3-4 hr	Opana ER	12 hr	high
Dihydrocodeine + aspirin or acetaminophen	III	Synalgos DC, Panlor SS	3-4 hr			moderate
Meperidine	II	Demerol	2-4 hr			high
Tramadol + acetaminophen	IV	Ultracet	4-6 hr			moderate
Methadone	II	Dolophine	6-8 hr*			high

Drug	Schedule	Trade names IR/SA	Duration of analgesic action IR/SA	Trade names SR/LA formulation	Duration of analgesic action SR/LA	Analgesic Efficacy
Fentanyl transdermal patch	II			Duragesic	72 hr	high
Fentanyl lozenge	II	Actiq	2-3 hr			high
Buprenorphine	III	Subutex	6-8 hr			high
Buprenorphine + naloxone	III	Suboxone	6-8 hr			high
Buprenorphine transdermal patch	III			Bustrans	7 days	high
Butorphanol	IV	Stadol	6-8 hr			high
Nalbuphine	0	Nubain	3-6 hr			high
Pentazocine	IV	Talwin	3-4 hr			medium
Pentazocine + acetaminophen	IV	Talacen	3-4 hr			medium
Pentazocine + naloxone	IV	Talwin Nx	3-4 hr			medium

- *Methadone half-life = 24-120 hrs with chronic administration

References

Basic and Clinical Pharmacology, 13th Edition, 2017. Eds, Bertram G. Katzung and Anthony J. Trevor. McGraw Hill, New York, NY

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th Edition. 2017. Eds, Brunton LL, Hilal-Dandan R, Knollmann BC. McGraw Hill, New York, NY

4. The Role of Opioids in the Management of Pain

There is a role for opioids in the management of pain. However, other medications and modalities must be considered and tried first (see Section 2). Before starting opioid therapy, prescribers should establish analgesic and functional goals for the patient. Plans for discontinuation of opioid treatment should be made if benefits do not outweigh risks. Patients can participate by tracking realistic treatment goals with an activity diary. Continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety [1]. Prescribers should be aware of federal and state regulations regarding opioid prescriptions. Moreover, prescribers should be well-versed in converting immediate-release to extended release formulations, and rotating between different long-acting opioids (See Table 3.2).

Before starting a patient on opioids, there are some steps that are recommended:

- Discuss the risks of opioid use including substance abuse, abuse by household contacts, misuse and addiction/physical dependence and tolerance, cross-reactions with other medications, cross-tolerance, life-threatening respiratory depression, and falls.
- Discuss the planned length of treatment and weaning strategy.
- Take a substance abuse history and assess for opioid risk and comorbidities that can be worsened with opioids (see Section 9).
- Obtain a preliminary urine drug test, and review prior primary care physician (PCP) records and medication lists.
- Check the Prescription Drug Monitoring Program (PDMP) for previous or current prescriptions [2]. Please check the PDMP prior to every opioid prescription.
- A Patient Prescriber Agreement (PPA) should be signed by the patient and the prescriber to educate the patient on the conditions of the therapy and the risks associated with it. The PPA also entails that the patient agrees to random drug screening and/or pill counts.
- If planning to initiate methadone therapy, obtain baseline EKG for patients (QTc should be < 450ms).
- Opioids should also be avoided in patients on methadone or buprenorphine maintenance therapy unless prescribed by an addiction specialist (see Section 12)
- Consider non-opioid treatments (see Section 2)
- Prescribers should refer to the Patient Counseling Document (on the FDA REMS program [3]) when discussing with patients and their caregivers the safe usage, risks, and disposal of opioid analgesics. It is important that patients and their caregivers read the medication guide they will receive with every opioid analgesic they obtain.
- Patients and their caregivers should be aware of the Box Warning regarding opioids. Warnings include risk of addiction, abuse, and misuse which can ultimately lead to overdose and death. Instruct patients to swallow opioid analgesic tablets whole to avoid ingestion of a fatal dose. Prolonged use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome, which can be fatal. Co-administration of CYP3A4 inhibitors, such as erythromycin and HIV protease inhibitors, can result in fatal overdose.

Opioids should not be prescribed to patients with active substance abuse and should be cautiously prescribed to patients with mental health comorbidities (see Section 12).

Management of acute pain with opioids

Acute pain is defined as pain with abrupt onset and caused by an injury or other process that is not ongoing [1]. A concrete event is usually the cause of the pain (e.g. sprain, blunt trauma, surgery). A short course of opioid may be effective in treating acute pain and help the patient to mobilize and undergo physical therapy. Opioids should be supplemented with adjuvant therapy such as NSAIDs and acetaminophen to achieve the maximum therapeutic effect with the minimal dose of opioid necessary. The choice of opioid should be individualized based on the severity of the insult and the potency of the opioid (see Table 3.3). Extended release/long-acting opioids should NOT be prescribed for acute pain. Depending on the gravity of the insult and injury, a 3- to 7-day course of opioid should achieve this goal. If the patient was admitted to the hospital for a brief period and administered an effective dose of intravenous opioids for pain relief, a conversion to oral formulation with a reduction in dose of 30% may be prescribed to the patient upon discharge. It is very important that providers prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater than the needed amount for the expected duration of therapy [1]. The expectation is that by the end of the short course of opioid therapy, the remaining aches and pains should be able to be managed with the non-opioid adjuvants.

Management of chronic pain with opioids

Chronic pain is defined as pain that typically lasts more than three months or past the time of normal tissue healing. It can be the result of an underlying medical disease or condition, injury, medical treatment, or generalized inflammation [1]. Unfortunately, pain does not always resolve after the resolution of the initial insult. Patients may develop chronic pain by way of central and/or peripheral sensitization [4]. Moreover, patients may develop chronic conditions that result in chronic pain (e.g. cancer, chronic pancreatitis, diabetic neuropathy).

When managing a patient with chronic pain, treatment should be individualized according to the patient's needs. A multi-modal regimen that incorporates non-opioid medications (e.g. anticonvulsants, antidepressants, NSAIDs) and alternative therapies (e.g. physical therapy, psychotherapy, TENS) is always preferred (see Section 2). This regimen should be tailored based on the patient's condition and contraindications. Opioids may be incorporated into the multimodal regimen once the pain relief and functional goals are agreed upon.

Opioids should be considered on a trial basis when started (30-90 days). For patients with intermittent, waxing and waning pain, the use of low dose immediate release/short acting (IR/SA) opioids is appropriate (see Table 3.1). For patients with opioid tolerance or with constant pain that requires frequent dosing of IR/SA opioid, the daily requirement may be converted to extended-release/long-acting (ER/LA) opioids for a more convenient dosing regimen. When converting from IR/SA to ER/LA, consider reducing the total dosing by 30-50% morphine milligram equivalent (MME) to avoid overdosing the patient, as there may be incomplete cross-tolerance [5-7]. If the trial of 30 to 90 days has not yielded the expected improvement in pain and function, the opioids should be discontinued [1]. The choice of the opioid and dose is based on the potency and efficacy of the opioid (see Table 3.3). If opioids

seem to be helping, but the patient is requiring increasing doses to maintain the same pain relief, consider rotating opioid formulations [5-7]. This is done by converting to a 30-50% lower MME as there may be incomplete cross tolerance. There are numerous online calculators that help with opioid conversion and rotation [8]. There are also numerous phone apps that do the same (e.g. Opioid Converter, OpioidCalc, Opioid Calculator, CDC Opioid Guideline)*. Regardless of the opioid chosen, the lowest effective dose should be prescribed. CDC warns against increasing the daily opioid dosing beyond 90 MME per day, especially if the patient is taking other sedating medications (e.g. benzodiazepine) [1].

**The authors do not have any ties to these apps.*

Monitoring patients prescribed chronic and long-term opioids

It is the providers' responsibility to monitor their patients closely. They should continually perform an opioid benefit-to-harm evaluation approximately every three months. Opioids may lose efficacy over time. If harm of continued opioid therapy outweighs the benefits, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids [1]. Every evaluation should include: detailed physical, pain assessment, functional assessment, mental health assessment, and evaluation of medical co-morbidities that may potentiate opioid adverse effects.
To assess for opioid misuse risk, including the possibility of addiction or diversion:

- Perform urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications, as well as other controlled prescription drugs and illicit drugs [1]. Urine drug screen should be obtained with every change in prescription and if the prescriber suspects any type of abuse or diversion.
- Access the PDMP periodically. We recommend that the PDMP be checked prior to every opioid prescription.
- Providers should frequently monitor for diversion
    - Urine drug testing
    - Pill counts
    - Accounts of medication self-escalation, early refills, and lost or stolen prescriptions
    - Law-enforcement involvement
    - Data from statewide Prescription Drug Monitoring Program
- Discuss potential risks and adverse effects of opioids with patients. If risks of opioids outweigh benefits:
    - Taper opioids (Refer to Section 8)
    - Provide adjuvant therapies to mitigate opioid withdrawal symptoms
    - Provide patient with non-opioid analgesia
    - Consider referral to pain management specialist
- Assess for patterns in behavior that suggest addiction versus therapeutic use. Behaviors suggestive of addiction include declining activity, frequent reports of lost or stolen prescriptions, abusing drugs or alcohol, irritability, rejecting non-opioid analgesics, and unsanctioned dose escalation.

- If a patient is unable to take opioids safely, or is non-adherent with monitoring, then discontinuing of opioids is appropriate even in the setting of clinical benefit.
- Utilize screening tools such as the Opioid Risk Tool (ORT), CAGE-AID, and PHQ-9 to monitor for the possibility of opioid addiction.

References

1. Dowell D, Haegerich TM, Chou R. CDC Guidelines for Prescribing Opioids for Chronic Pain – United States, 2016. MMWR Recomm Rep. 2016 Mar 18;65(1):1-49.
2. http://www.health.pa.gov/Your-Department-of-Health/Offices%20and%20Bureaus/PaPrescriptionDrugMonitoringProgram/Pages/home.aspx#.WgQo82hSyUk
3. https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm
4. Fishman, Scott M. Bonica's Management of Pain.
5. Fine PG, Portenoy RK. Establishing “Best Practices” for Opioid Rotation: Conclusions of an Expert Panel. J Pain Symptom Manage. 2009 Sep; 38(3): 418-425.
6. Knotkova H, Fine PG, Portenoy RK. Opioid Rotation: The Science and the Limitations of the Equianalgesic Dose Table. J Pain Symptom Manage 2009; 38(3):426-439.
7. Kraychete DC, Sakata KR. Use and Rotation of Opioids in Chronic Non-oncologic Pain. Rev Bras Anestesiol. 2012; 62(4): 554-562
8. http://www.globalrph.com/narcoticonv.htm

5. Safe Opioid Prescribing

The use and misuse of opioid analgesics in inherently dangerous. Providers can utilize numerous tools to potentially reduce the risk of misuse, diversion, and overdose. While there is little data to show their efficacy, the risk benefit ratio of these simple tools favors their use for most patients.

Prescription drug monitoring program

Prescription drug monitoring programs (PDMPs) are electronic databases found in almost all states that track patient prescription use behavior and provider prescribing activity in attempt to reduce prescription drug abuse. Providers are able use the database to track patient prescribing history of controlled substances (II-V) and thus obtain information to make an informed prescribing decision. While a subject of ongoing research, PDMPs in conjunction with other regulations have proven to successfully reduce the use of multiple providers (doctor shopping), opioid prescribing, and overdose deaths in numerous states (1-4).

The database is most useful for providers to determine if a patient is being prescribed excessive or dangerous combinations of controlled substances and to support legitimate medical use of these controlled substances. The PDMP is an adjunctive tool to help providers assess for substance abuse disorder and doctor shopping before prescribing a controlled substance. Red flags found on the PDMP include:

- Multiple prescribers
- Numerous dispensing pharmacies
- More than one medication filled contemporaneously within the same controlled substance drug class
- Concurrent opioid and benzodiazepine prescriptions
- Cash payment for controlled substances
- History of medication assisted therapy prescriptions

Data available to providers include type of drug dispensed, quantity of drug dispensed, supply days, date dispensed, prescriber identity, pharmacy identity, and method of payment. As of January 1, 2017 in Pennsylvania, dispensers are required to collect and submit information on controlled substances to the PDMP no later than the close of the subsequent business day (5). Per Pennsylvania Act 191 of 2014, providers are required to query the PDMP and document the information obtained in the patient's medical record for the following encounters:

- "For each patient the first time the patient is prescribed a controlled substance by the prescriber for purposes of establishing a baseline and a thorough medical record; or
- If a prescriber believes or has reason to believe, using sound clinical judgment, that a patient may be abusing or diverting drugs; or
- Each time a patient is prescribed an opioid drug product or benzodiazepine by the prescriber (5).

Providers are not required to query the PDMP during treatment in the emergency department (ED), but PDMP querying is required if a medication is prescribed upon discharge. The Pennsylvania Department of Health recommends that health care providers check the PDMP before prescribing or dispensing a controlled substance in any clinical setting as part of good clinical practice.

Identification of worrisome behavior should trigger a patient conversation and offering of resources for counseling and substance abuse treatment. Conversations with patients regarding questionable prescription use should be done with caution and centered around offering assistance. Documentation of PDMP use is recommended. Common documentation phrases include "Checked PDMP; no red flags identified; safe to proceed with prescription" or "Checked PDMP; opted not to prescribe after determining patient had filled numerous prescriptions for controlled substances from multiple prescribers over the last 3 months. Findings from the PDMP were discussed with the patient and substance abuse treatment resources offered."

While PDMP use is an effective tool in curtailing the prescription opioid epidemic, it should not be the sole mechanism for a provider to determine if a patient has a substance use disorder (6). There are numerous limitations to the PDMP including:

- Data sharing across state lines is sometimes limited
- No data regarding medications administered in health care facility settings
- Accuracy of patient identifiers including name and date of birth upon entering and querying data
- Abuse of prescription or illicit substances not captured by the PDMP
- No agreed upon threshold to define questionable behavior

As of November 2, 2017, the Pennsylvania Prescription Drug Monitoring Program is sharing data with 15 other states and the District of Columbia (5). The sharing of data across states lines helps providers and pharmacists query controlled substance histories regardless of the state in which the prescription was filled.

Controlled-Substance Agreements (CSAs)

Many societies recommend that patients prescribed opioid analgesics should sign an agreement with their provider for treatment, especially for chronic opioid therapy. CSAs (preferred term rather than “pain contract” and “opioid agreement”) are formal sets of rules agreed upon by the prescriber and the patient regarding ongoing opioid therapy. Agreements can be useful for creating a safe environment for prescribing, promoting and monitoring adherence to treatment, screening for substance use disorders, and reducing dangerous misuse by patients. CSAs are utilized more often today as many societies, including the American Academy of Pain Medicine, recommend their use in chronic opioid therapy (see Fig. 5.1 for sample agreement).

There is no widespread accepted format for patient agreements. Some common focal points include informed consent, risks and benefits of treatment including addiction and withdrawal, goals of treatment, prohibited behaviors, and criteria for termination of therapy. CSA behaviors

typically prohibited are use of multiple prescribers and pharmacies, early refills for lost or stolen medication, use of illicit drugs, and concomitant use of benzodiazepines. While regulatory bodies and professional societies have advocated for, and even mandated their use, the evidence that CSAs are effective in improving opioid adherence, reducing adverse events, or mortality is scarce. Creating an appropriate CSA tailored to your patient population is imperative as CSAs are commonly written at reading levels above most patient's capabilities and are sometimes even coercive (7).

Patient name/DOB _____ Physician_____

SAMPLE CONTROLLED SUBSTANCE AGREEMENT

1. I agree that Dr. _____ will be the sole prescriber of opioid pain medications to me and that I will fill my opioid prescriptions at one pharmacy. If an emergency requires an exception to this agreement, I will inform my provider immediately.
2. I will not fill or take other controlled substances including amphetamines, benzodiazepines, or barbiturates unless I get consent from my physician.
3. I will only take my medication at the dose and frequency prescribed by my physician. I agree not to increase my dose without first discussing it with my physician.
4. I will not share, sell or trade my medication with anyone. I agree to store my medication in a safe and secure place at all times.
5. I will safeguard my medication from theft. Lost or stolen medication will not be replaced. I will not request prescription refills earlier than the next regular appointment.
6. I will not use any illegal controlled substances, including marijuana, cocaine, amphetamines, PCP etc... Providing a urine sample may be required of me at any visit for routine drug screening.
7. I understand that my physician will query the state Prescription Drug Monitoring Program for controlled substances filled with each appointment before prescribing.
8. I consent to open communication between my physician and any involved in my care, including pharmacists, other providers, your insurance company, etc...
9. I understand that if I break this agreement, my physician will stop prescribing opioids and may ultimately terminate the physician-patient relationship.

_____	_____	_____
Patient	Signature	Date
_____	_____	_____
Provider	Signature	Date

Figure 5.1: Sample Patient Agreement

Monitoring strategies

With the rise of prescription opioid abuse, providers should have a heightened awareness of substance use disorders in patients on chronic opioid therapy and consider the larger public health risk of prescribing opioids. There are a few techniques that prescribers may utilize to screen for substance use disorders, provide evidence of medication compliance, and decrease the risk for drug diversion. None of these techniques have been validated as strategies proven to improve quality of care or reduce harm, but may be of benefit in specific populations or patient encounters.

The urine drug screen (UDS) is an effective and practical tool to screen patients for both medication compliance and illicit drug use. A UDS can be performed rapidly and easily in an office setting with a point of care urine immunoassay. While there is no widely accepted recommendation on use of UDS in chronic opioid therapy, the UDS can be an adjunctive tool to improve quality and safety of opioid therapy. Unfortunately, the UDS is not a foolproof tool for comprehensive screening, as it will not detect some synthetic opioids. However, the sensitivity for detecting behaviors consistent with substance abuse disorders is increased when used in combination with other tools like querying the PDMP.

Typical point of care UDSs can screen for amphetamines, benzodiazepines, buprenorphine, cocaine, marijuana, methadone, opiates, oxycodone, PCP and other drugs. Repeated positive screens for illicit drugs should trigger serious concern for a substance use disorder, and warrant cessation of chronic opioids and referral to substance abuse treatment. Interpretation of the UDS is a major limitation to performing point of care UDS. For instance, a positive UDS for an illicit drug does not necessarily equal intoxication. For some illicit drugs, the UDS may remain positive days to weeks after last use. Recognizing the common false-positives and false-negatives of the specific UDS used can help providers understand its limitations. A common false-negative is seen with the opiate screen in a setting of fentanyl abuse. Some common false-positives include the marijuana screen for patients prescribed dronabinol for appetite stimulation in the setting of cancer or AIDS, a positive PCP screen with recent dextromethorphan use for cough and cold symptoms, and a positive amphetamine screen in the setting of ADHD treatment. A good history and understanding of the common factors affecting the UDS can help reduce the limitations of the test.

UDS can also be utilized to help assess for compliance as well. A negative oxycodone screen in the setting of chronic therapy with oxycodone would be highly concerning for non-compliance and drug diversion. However, this tool is not foolproof as a single dose of oxycodone prior to performing a UDS would trigger the oxycodone screen positive even in the setting of non-compliance and drug diversion.

Another tool that some providers utilize is an interim “pill count” for stable patients that receive prescriptions for a large number of supply days. Inconsistencies in pill count can be an alarm for drug diversion. Direct observation can be a useful tool in patients prescribed high-dose opioids when there is concern for drug diversion. With this tool, a patient is called to take the medication under supervision of medical staff to observe for signs of intolerance like sedation. Patients who

are prescribed high-dose opioids and divert their medications instead of using them for a medical need will be unlikely to have the necessary tolerance to pass this test.

Guideline-based patient care

The following are a number of international, national, and Pennsylvania-based guidelines for prescribing opioids listed below that can be helpful to guide therapy.

National and International Guidelines

- Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain – United States, 2016: https://www.cdc.gov/media/modules/dpk/2016/dpk-pod/rr6501e1er-ebook.pdf https://www.cdc.gov/drugoverdose/pdf/Guidelines_Factsheet-a.pdf
- World Health Organization (WHO) guidelines on the pharmacological treatment of persisting pain in children with medical illnesses: http://apps.who.int/iris/bitstream/10665/44540/1/9789241548120_Guidelines.pdf

Pennsylvania Prescribing Guidelines

- Emergency Department (ED) Pain Treatment Guidelines: http://www.health.pa.gov/My%20Health/Diseases%20and%20Conditions/M-P/opioids/Documents/PA%20ED%20Guidelines%20Opioids.pdf
- Opioids to Treat Chronic Noncancer Pain: http://www.health.pa.gov/My%20Health/Diseases%20and%20Conditions/A-D/Documents/PA%20Guidelines%20on%20the%20Use%20of%20Opioids%20to%20Treat%20Chronic%20Noncancer%20Pain%20(FINAL%20adopted%20guidelines%20July%202014).pdf
- The Safe Prescribing of Opioids in Orthopedics and Sports Medicine: http://www.health.pa.gov/My%20Health/Diseases%20and%20Conditions/M-P/opioids/Documents/Orthopedics%20and%20Sports%20Medicine%20Guidelines%20FINAL.pdf
- Geriatric Pain Opioid Use and Safe Prescribing: http://www.health.pa.gov/My%20Health/Diseases%20and%20Conditions/A-D/Documents/PA%20Guidelines%20Geriatric%20Pain%20Treatment.pdf
- Obstetrics & Gynecology Opioid Prescribing Guidelines: http://www.overdosefreepa.pitt.edu/wp-content/uploads/2015/12/OB-GYN-FINAL-12-14-15.pdf
- Opioids in Dental Practice: http://www.overdosefreepa.pitt.edu/wp-content/uploads/2015/07/opioid_dental_prescribing_guidelines3_13_15.pdf

References

1. Centers for Disease Control and Prevention. Decline in Drug Overdose Deaths After State Policy Changes — Florida, 2010–2012. MMWR 2014; 63(26);569-574.

2. PDMP Center of Excellence at Brandeis University. Mandating PDMP participation by medical providers: current status and experience in selected states, 2014. Available from: http://www.pdmpexcellence.org/sites/all/pdfs/COE%20briefing%20on%20mandates%20revised_a.pdf

3. Centers for Disease Control and Prevention. State Successes. Available from: https://www.cdc.gov/drugoverdose/policy/successes.html Accessed 11/24/2017

4. Prescription Drug Monitoring Program Center of Excellence at Brandeis. Briefing on PDMP Effectiveness. Available at: http://www.pdmpexcellence.org/sites/all/pdfs/Briefing%20on%20PDMP%20Effectiveness%203rd%20revision.pdf Accessed 11/24/2017

5. Pennsylvania Department of Health. Prescription Drug Monitoring Program. Available from: http://www.health.pa.gov/Your-Department-of-Health/Offices%20and%20Bureaus/PaPrescriptionDrugMonitoringProgram/Pages/home.aspx#.WhhmekqnGUk

6. Griggs CA, Weiner SG, Feldman JA. Prescription drug monitoring programs: examining limitations and future approaches. West J Emerg Med. 2015;16(1):67-70.

7. Tobin DG, Keough Forte K, Johnson McGee S. Breaking the pain contract: A better controlled-substance agreement for patients on chronic opioid therapy. Cleve Clin J Med. 2016;83(11):827-835

6. Pain Management in Special Populations

Geriatrics

The 65 years and older age bracket is the fastest growing sector of the US population. Pain is a common reason for the elderly to seek medical attention. As patients age, medical conditions, especially painful ones, are common (1). The elderly are more likely to have arthritis, cancer, and other chronic medical conditions that cause pain (2). Nearly half of all elderly patients suffer from significant pain, while the incidence is even higher for those living in nursing homes (3,4). There are numerous factors that make treating pain in the elderly population problematic. However, with proper assessment and treatment, providers can effectively manage pain in the elderly and reduce adverse effects (1).

It is common for elderly patients to suffer with cognitive decline as they age. Patients who suffer from declining cognition or even dementia are at higher risk of accidentally taking extra doses of their medication and overdosing. Daily pill box organizers are a helpful tool to prevent medication administration errors in the elderly. Confusion, memory loss, sight and hearing impairment are common problems in the elderly that pose unique hurdles to assessing and treating pain adequately. While the perception of severe pain is commonly preserved in the geriatric population, patients with cognitive difficulties may have difficulty communicating pain. This may lead to adverse events, under-treatment or over-treatment.

As the body ages, there are numerous changes that occur including decreased organ function and diminished arterial blood flow to organs, which can result in alterations in drug distribution and metabolism (5). This is particularly important with medications that are either metabolized by the liver or eliminated by the kidneys, as the function of these organs drastically declines with age. Polypharmacy in the elderly is common, leading to complex drug interactions and higher risk for adverse drug events. In a study of elderly patients that were recently discharged to a skilled nursing facility, on average, each patient was prescribed 14 medications. More than one-third of those medications were identified as ones that could possibly exacerbate underlying geriatric syndromes (6).

The elderly are particularly sensitive to sedating side effects of medications. Confusion, loss of cognition, delirium, sleep disordered breathing, and fall injuries, such as fractures, are common adverse events that occur when sedating medications are prescribed to elderly patients (5). Medications with a known side effect of sedation should be avoided in the elderly.

Elderly patients are also particularly sensitive to gastrointestinal side effects of medications. As people age, the gastrointestinal tract slowly loses function which is manifested by an increased gastric pH, reduced gut motility, prolonged transit times and decreased ability to absorb nutrients. Constipation is a frequent side effect with opioid analgesics, and this phenomenon is heightened in elderly patients (5). It is typically recommended to start a stimulant laxative, such as Senna glycoside, when initiating opioid analgesic therapy in the geriatric population.

To appropriately manage pain and prevent significant adverse events in the elderly, a step-wise, multimodal approach should be utilized. There is significant overlap in concepts of management

for patients with cancer pain and the elderly, leading many providers to rely on the World Health Organization (WHO) analgesic ladder approach (7). The American Geriatric Society published recommendations on Pharmacological Management of Persistent Pain in Older Persons in 2009 (See Figure 6.1) (8).

Figure 6.1 American Geriatric Society Panel Pharmacological Management of Persistent Pain in Older Persons Guideline Recommendations (8)

Non-opioids
(I)Acetaminophen should be considered as initial and ongoing pharmacotherapy in the treatment of persistent pain, particularly musculoskeletal pain, owing to its demonstrated effectiveness and good safety profile (high quality of evidence; strong recommendation).
(A)Absolute contraindications: liver failure (high quality of evidence, strong recommendation).
(B)Relative contraindications and cautions: hepatic insufficiency, chronic alcohol abuse or dependence (moderate quality of evidence, strong recommendation).
(C)Maximum daily recommended dosages of 4 g per 24 hours should not be exceeded and must include "hidden sources" such as from combination pills (moderate quality of evidence, strong recommendation).
(II)Nonselective NSAIDs and COX-2 selective inhibitors may be considered rarely, and with extreme caution, in highly selected individuals (high quality of evidence, strong recommendation).
(A)Patient selection: other (safer) therapies have failed; evidence of continuing therapeutic goals not met; ongoing assessment of risks and complications outweighed by therapeutic benefits (low quality of evidence, strong recommendation).
(B)Absolute contraindications: current active peptic ulcer disease (low quality of evidence, strong recommendation), chronic kidney disease (moderate level of evidence, strong recommendation), heart failure (moderate level of evidence, weak recommendation).
(C)Relative contraindications and cautions: hypertension, *Helicobacter pylori*, history of peptic ulcer disease, concomitant use of corticosteroids or SSRIs (moderate quality of evidence, strong recommendation).
(III)Older persons taking nonselective NSAIDs should use a proton pump inhibitor or misoprostol for gastrointestinal protection (high quality of evidence, strong recommendation).
(IV)Patients taking a COX-2 selective inhibitor with aspirin should use a proton pump inhibitor or misoprostol for gastrointestinal protection (high quality of evidence, strong recommendation).
(V)Patients should not take more than one nonselective NSAID or COX-2 selective inhibitor for pain control (low quality of evidence, strong recommendation).
(VI)Patients taking aspirin for cardioprophylaxis should not use ibuprofen (moderate quality of evidence, weak recommendation).
(VII)All patients taking nonselective NSAIDs and COX-2 selective inhibitors should be routinely assessed for gastrointestinal and renal toxicity, hypertension, heart failure, and other drug–drug and drug–disease interactions (weak quality of evidence, strong recommendation).
Opioids
(VIII)All patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy (low quality of evidence, strong recommendation).
(IX)Patients with frequent or continuous pain on a daily basis may be treated with around-the-clock time-contingent dosing aimed at achieving steady-state opioid therapy (low quality of evidence, weak recommendation).
(X)Clinicians should anticipate, assess for, and identify potential opioid-associated adverse effects (moderate quality of evidence, strong recommendation).
(XI)Maximal safe doses of acetaminophen or NSAIDs should not be exceeded when using fixed-dose opioid combination agents as part of an analgesic regimen (moderate quality of evidence, strong recommendation).
(XII)When long-acting opioid preparations are prescribed, breakthrough pain should be anticipated, assessed, and prevented or treated using short-acting immediate-release opioid medications (moderate quality of evidence, strong recommendation).
(XIII)Only clinicians well versed in the use and risks of methadone should initiate it and titrate it cautiously (moderate quality of evidence, strong recommendation).

(XIV)Patients taking opioid analgesics should be reassessed for ongoing attainment of therapeutic goals, adverse effects, and safe and responsible medication use (moderate quality of evidence, strong recommendation).
Adjuvant Analgesic Drugs
(XV)All patients with neuropathic pain are candidates for adjuvant analgesics (strong quality of evidence, strong recommendation).
(XVI)Patients with fibromyalgia are candidates for a trial of approved adjuvant analgesics (moderate quality of evidence, strong recommendation).
(XVII)Patients with other types of refractory persistent pain may be candidates for certain adjuvant analgesics (e.g., back pain, headache, diffuse bone pain, temporomandibular disorder) (low quality of evidence, weak recommendation).
(XVIII)Tertiary tricyclic antidepressants (amitriptyline, imipramine, doxepin) should be avoided because of higher risk for adverse effects (e.g., anticholinergic effects, cognitive impairment) (moderate quality of evidence, strong recommendation).
(XIX)Agents may be used alone, but often the effects are enhanced when used in combination with other pain analgesics and nondrug strategies (moderate quality of evidence, strong recommendation).
(XX)Therapy should begin with the lowest possible dose and increase slowly based on response and side effects, with the caveat that some agents have a delayed onset of action and therapeutic benefits are slow to develop. For example, gabapentin may require 2 to 3 weeks for onset of efficacy (moderate quality of evidence, strong recommendation).
(XXI)An adequate therapeutic trial should be conducted before discontinuation of a seemingly ineffective treatment (weak quality of evidence, strong recommendation).
Other Drugs
(XXII)Long-term systemic corticosteroids should be reserved for patients with pain-associated inflammatory disorders or metastatic bone pain. Osteoarthritis should not be considered an inflammatory disorder (moderate quality of evidence, strong recommendation).
(XXIII)All patients with localized neuropathic pain are candidates for topical lidocaine (moderate quality of evidence, strong recommendation).
(XXIV)Patients with localized nonneuropathic pain may be candidates for topical lidocaine (low quality of evidence, weak recommendation).
(XXV)All patients with other localized nonneuropathic persistent pain may be candidates for topical NSAIDs (moderate quality of evidence, weak recommendation).
(XXVI)Other topical agents, including capsaicin or menthol, may be considered for regional pain syndromes (moderate quality of evidence, weak recommendation).
(XXVII)Many other agents for specific pain syndromes may require caution in older persons and merit further research (e.g., glucosamine, chondroitin, cannabinoids, botulinum toxin, alpha-2 adrenergic agonists, calcitonin, vitamin D, bisphosphonates, ketamine) (low quality of evidence, weak recommendation).

Providers and patients alike often overlook common non-pharmacologic therapies that have a high benefit to risk ratio in the management of pain. Non-pharmacologic therapies should be first-line interventions in the elderly, especially when the alternatives have a risk of side effects like organ dysfunction and sedation. Treatment such as cold (ice therapy), heat, and physical therapy are worth initiating early in the treatment of pain or in conjunction with pharmacologic therapies (see Section 2 for further details on non-opioid treatments for chronic pain).

Non-opioid analgesic therapies are first line pharmacologic agents in the management of mild to moderate pain. Acetaminophen is usually the first choice and is generally safe in the elderly. Caution should be taken in elderly patients with hepatic disease or on other medications containing acetaminophen (e.g. migraine medications, sleep aids, cough and cold preparations, and combination opioid analgesics). Nonsteroidal anti-inflammatory drugs (NSAIDs) should be prescribed with caution as they often have adverse renal effects. Other non-opioid medications to

consider in the elderly are calcitonin for compression fractures, capsaicin, antidepressants, and anticonvulsants for neuropathic pain (9-12).

Opioids analgesics should be considered for patients with moderate to severe pain, pain causing decreased ability to function, or pain causing diminished quality of life. Providers should take caution when prescribing opioids to the elderly as they may cause adverse effects such as overdose or sedation-associated injuries. Maximizing non-opioid therapies is recommended before initiating opioids. Starting opioid therapy at 25-50% of a typical adult dose and slowly titrating to effect is recommended for elderly patients. Therapeutic goals and effect should be reassessed frequently with elderly patients.

Obstetrics

Opioid use in women has risen as it has in the general population in the US, with one-third of all women of reproductive age filling an opioid analgesic prescription annually. Opioid analgesic prescriptions for pregnant women have also increased in recent years (13-15). In population studies of pregnant women enrolled in Medicaid, 18.5% filled an opioid analgesic prescription in 2000, 22.8% in 2007, and 41.4% in 2009 (13-15). This rise in maternal opioid use correlates with the rise in incidence of neonatal abstinence syndrome (NAS) seen in newborns in the US (14). In 2015, the Commonwealth of Pennsylvania issued guidelines to address the use of opioids for the treatment of pain in pregnant women (16).

Women of reproductive age

Pain management for women of reproductive age should parallel closely with the general population. A multimodal approach with non-pharmacologic and non-opioid therapies should be used as first-line options for pain, especially when mild or moderate. Opioid pain medication should be reserved for severe pain and prescribed judiciously. In addition, clinicians should consider the risk of pregnancy during the period of ongoing opioid analgesic therapy. Patients should be informed of the risk of NAS from maternal opioid use during pregnancy and it should be included in controlled substance/opioid contract agreements. Women of reproductive age receiving chronic opioid analgesic therapy should be offered birth control options or instructed to wean off opioids before they become pregnant.

Pregnant women

While safe prescribing is important in all populations, in pregnancy the provider needs to be mindful of both the patient and of the potential harms to the developing fetus. Teratogenic effects of medications are uncommon and difficult to study, but understanding the risk of pharmacologic therapy in pregnancy is important. NAS is of concern as the incidence is rising in the US. NAS is directly linked to maternal opioid use. It is well known that maternal chronic use of opioid analgesics (licit or illicit) during pregnancy may lead to NAS in the newborn. Non-pharmacologic and non-opioid therapies should be first-line options for treating pain in pregnancy especially considering the current rate of opioid prescribing during pregnancy. Acetaminophen is the analgesic of choice in pregnancy as it has demonstrated safety and efficacy in all stages of pregnancy (17-18). There have been recent concerns that maternal use of acetaminophen is associated with the development of hyperkinetic disorders and attention-deficit/hyperactivity disorder (ADHD)-like behaviors in children (19). However, acetaminophen

is a widely used medication and is the safest pharmacologic option for the treatment of pain and fever in childhood and pregnancy. Acetaminophen should not be withheld, but patients should practice judicious use by taking the lowest effective dosage and for the shortest duration of time (20). NSAIDs are associated with congenital effects. Even short courses of NSAIDs late in pregnancy are associated with premature closure of fetal ductus arteriosus, and therefore are not recommended (21). Salicylates, including aspirin, have also been associated with complications such as bleeding and congenital abnormalities including gastroschisis and premature ductus arteriosus closure late in pregnancy (21-23). However, low-dose aspirin has been shown to improve reproductive outcomes in women with particular risk factors (24).

Reproductive studies looking at the safety of opioid analgesics in pregnancy are limited, but they are generally felt to be safe for the growing fetus. The largest concern for opioid use during pregnancy is chronic use, opioid dependence, and the development of NAS, a life-threatening condition in newborns. The risk of NAS is highest in women who use opioid analgesics in late pregnancy, use chronic long-acting opioids with the history of opioid misuse or another substance use disorder, have exposure to non-opioid psychotropic medications late in pregnancy (tricyclic antidepressants, selective norepinephrine re-uptake inhibitors, selective serotonin reuptake inhibitors, benzodiazepines, non-benzodiazepine hypnotics, anticonvulsants, and antipsychotics), and use tobacco (25). If opioids are required to treat acute pain in pregnancy, providers should utilize the lowest effect dose for the shortest duration. Providers should avoid escalating doses of opioids and continuation of opioids beyond two weeks duration. For chronic pain, the American Pain Society suggests no use of opioids or reducing use of opioids to a minimum during pregnancy (26). Even when opioids are used for pain control, non-pharmacologic therapies and acetaminophen should be maximized as an opioid sparing therapy. Before prescribing opioids, providers should discuss the potential risks to the fetus with patients and options for alternative treatments (27).

Low back pain, carpal tunnel syndrome, and pelvic pain are three common problems women experience during pregnancy (28-30). Reassurance and simple activity changes are often sufficient to reduce pain and help make the condition more tolerable (31). Heat, ice, massage, acupuncture, physical therapy (especially body mechanic training and aquatic therapy), and thermoplastic night splints all have added benefit in the treatment of these painful conditions in pregnancy.

For pregnant women dependent on opioids due to licit or illicit use, it is recommended to avoid withdrawal, as this is associated with worse outcomes for the fetus. Opioid withdrawal in pregnancy is associated with preterm labor and high relapse rates, which put the fetus at risk for complications. Heroin use is associated with low birth weight, preeclampsia, third trimester bleeding, malpresentation, puerperal morbidity, fetal distress meconium aspiration, and communicable diseases such as HIV, hepatitis B, and hepatitis C (32). The use of methadone or buprenorphine (without naloxone) is recommended for the treatment of opioid use disorder during pregnancy to reduce illicit use and improve fetal outcomes such as birth weight, but these medications do not prevent NAS (32,33). Buprenorphine may reduce duration of NAS when compared to methadone-exposed newborns, but both methadone and buprenorphine are associated with improved outcomes (34-35). The maternal dose of methadone or buprenorphine should not be reduced during pregnancy as it may cause relapse and is unlikely to reduce the risk

of NAS. Refer to the PA state guidelines for addiction treatment in pregnancy for further details (36).

Following delivery
Appropriate and adequate pain control is recommended for women experiencing pain following labor and delivery. Uncontrolled pain can prevent a mother's ability to sufficiently care for herself and her newborn. Conversely, over-medication with sedating opioid analgesics can negatively impact care of the newborn including breastfeeding. Opioids are not commonly required for adequate pain relief in this population. Non-pharmacologic therapies, such as ice, heat, and sitz baths, are first-line options and are often sufficient for the relief of pain following most vaginal deliveries. NSAIDs and acetaminophen are second-line agents if non-pharmacologic therapies are ineffective. If opioids are required to control severe pain, it is recommended to use the lowest effective dose for the short duration needed, rather than giving long-acting standing order opioids. For severe perineal trauma or cesarean delivery, postpartum mothers may require oral opioids upon discharge for up to seven days. It is recommended to maximize non-pharmacologic and non-opioid therapies to reduce the dose and duration of therapy with oral opioids.

Non-opioid analgesics such as acetaminophen are first-line therapies for pain control in women who are breastfeeding. Opioids are excreted in breast milk and therefore absorbed by breastfeeding infant. Codeine has been associated with high morphine concentration in the breast milk in certain patients with a "high metabolizer" CYP2D6 polymorphism. NSAIDs are in general safe with breastfeeding when taken short-term. While ibuprofen can be found in low concentration in breast milk at low doses, it is considered safe for breastfed infants.

Pediatrics

Acute pain is a common presenting feature for children seeking medical attention. Pain can be assessed in many ways depending on the child's age and communication capabilities. Because pain is a subjective experience, the ability to effectively provide a report varies with level of development. How a child experiences and reacts to pain reflects numerous variables including his or her emotional state and coping skills. Direct observation should be used to complement self-reported pain. While self-report is a common method, behavioral observation and physiologic measures are sometimes necessary when a child is unable to express their level of pain (37). Caregivers can be a reliable resource when assessing pain in preverbal children, as they understand how the child has reacted to pain in the past (38). This is similarly important in children with developmental disabilities that are unable to communicate their needs (37).

Observational tools exist for patients who are unable to self-report. However, observational assessments may underestimate pain severity especially when compared to patient self-reporting. Some of the commonly used observational tools include Revised Face, Legs, Activity, Cry, Consolability (r-FLACC) tool (see Figure 6.2) and the Individualized Numeric Rating Scale (INRS).

Figure 6.2 The r-FLACC scale is an observational tool to assess pain in children unable to self-report

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

General Approach to pain management in children

Non-pharmacologic measures such as cognitive behavioral and physical therapies should be utilized first for children with acute painful conditions. Pharmacologic strategies should be utilized as a second line therapy. The oral route of administration should be utilized when possible to avoid painful routes of administration such as intramuscular injection. Non-opioid analgesics should be utilized for mild pain. Opioid analgesics should be added to therapy for pain refractory to non-pharmacologic therapy and non-opioid analgesics or children deemed to be in moderate to severe pain (38).

Procedural pain

Strategies to manage procedural pain varies greatly depending on the anticipated intensity and duration of pain. Furthermore, the ability to cope with pain, the child's history of pain, and emotional state should all be considered when managing procedural pain. Fear of the unknown plays a large role in procedural pain for children. Therefore, children and caregivers should be given instructions on what to expect. Caregivers play an important role in comforting their child during a procedure and should be given specific ways of comforting if needed (37).

Therapies can be delivered before, during, and after the procedure to effectively reduce the pain experienced. Multidisciplinary and multimodal approaches should be utilized to best serve the child's needs. Some procedures, depending on the nature the pain and the state of the child's emotions and ability to cope can be performed with little or no pharmacological support via cognitive behavioral strategies (e.g., guided imagery, distraction, play therapy, and tell-show-do) (37). Procedures such as minor laceration repair, may be accomplished with distraction and guided imagery techniques along with the use of noninvasive topical anesthetics (39). Local anesthetics are important adjunctive therapies to effectively minimize pain and should be considered for even the simplest procedures such as venipuncture (37). While cognitive behavior

techniques may not be effective alone for all procedures, their utilization may reduce the dose or depth of sedation needed to perform a procedure (39).

For procedures that predictably cause severe pain, the use of systemic agents is often required. Sedative agents for painful procedures like fracture reduction decreases patient anxiety, but the child still experiences the pain and is not able to communicate. When sedation is necessary, concomitant analgesia should be used to treat painful conditions (37, 39). For non-painful procedures like computed tomography or magnetic resonance imaging, sedatives alone are useful for anxiolysis.

Pain from acute medical illness

While antibiotics may be the key component for treatment of acute medical conditions like otitis media, pharyngitis, meningitis, and pelvic inflammatory disease, pain control should also be addressed in the care plan. Depending on the severity of the pain, pharmacologic intervention may include the use of topical medications, acetaminophen, NSAIDs, or opioid analgesics. As commonly recommended in other populations, acute pain should be first treated with non-pharmacologic local therapies, non-opioid analgesics, and then finally opioids for refractory pain (39). Acetaminophen and ibuprofen should be considered first-line options for the treatment of mild pain in pediatrics.

Opioid analgesics should be considered in children assessed to have moderate to severe pain. Opioid have side effects of sedation and respiratory depression in pediatrics just like adults. The lowest dose effective at reducing pain to a tolerable level should be utilized in pediatrics. This is best achieved by frequent assessment of pain and response to medication while adjusting the dose as necessary. Oral immediate-release medications are recommended when starting opioids for analgesia. Concomitant use of acetaminophen or an NSAID may reduce the dose of opioid needed to control pain (40). Titration of opioids should be based on patient response to the medication. Opioids may be increased 25-50% per day until adequate pain control is achieved, or side effects become intolerable.

Codeine, a common opioid prescribed in pediatrics, is metabolized to morphine to provide analgesia at an unpredictable rate. Genetic polymorphisms in the enzyme CYP2D6 lead to variable rates of conversion of codeine to morphine. This high variability can lead to under treatment in poor metabolizers and overdose in rapid metabolizers. There is no quick, reliable way to predict who are poor or rapid metabolizers, so providers must take caution when prescribing codeine (38, 41).

References

1. Kaye AD, Baluch A, Scott JT. Pain Management in the Elderly Population: A Review. Ochsner J. 2010;10(3): 179–187

2. AGS Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. J Am Geriatr Soc>. 2002;50(6 suppl): S205-S224.

3. Gloth FM III. Pain management in older adults: prevention and treatment. J Am Geriatr Soc. 2001;49:188-199.

4. Ferrell BA, Ferrell BR, Osterweil D. Pain in the nursing home. J Am Geriatr Soc. 1990;38:409-414.

5. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract. 2008;8(4):287-313

6. Saraf AA, Petersen AW, Simmons SF et al. Medications associated with geriatric syndromes and their prevalence in older hospitalized adults discharged to skilled nursing facilities. Hosp Med. 2016;11(10):694.

7. Davies E., Higginson I. J., editors. Better Palliative Care for Older People. Copenhagen, Denmark: World Health Organization; 2004

8. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57((8)):1331–1346

9. Blau LA, Hoehns JD. Analgesic efficacy of calcitonin for vertebral fracture pain. Ann Pharmacother. 2003 Apr;37(4):564-70.

10. Derry S, Rice AS, Cole P, et al. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017 Jan 13;1:CD007393

11. Max MB, Lynch SA & Muir J et al. Effect of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326:1250–1256.

12. McQuay H, Carroll D & Fadad AR et al. Anticonvulsant drugs for management of pain: A systematic review. BMJ 1995;311:1047–1052.DD. Cavalieri TA. Managing Pain in Geriatric Patients. J Am Osteopath Assoc. 2007;107(suppl 4):ES10-ES16 http://jaoa.org/article.aspx?articleid=2093506

13. Desai R J, Hernandez-Diaz S, Bateman B T, Huybrechts K F. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. Obstet Gynecol. 2014;123(5):997–1002

14. Patrick S W, Schumacher R E, Benneyworth B D, Krans E E, McAllister J M, Davis M M. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. JAMA. 2012;307(18):1934–1940

15. Ailes EC, Dawson AL, Lind JN, et al. Opioid prescription claims among women of reproductive age--United States, 2008-2012. MMWR Morb Mortal Wkly Rep. 2015 Jan 23;64(2):37-41. https://www-ncbi-nlm-nih-gov.libproxy.temple.edu/pubmed/25611168

16. Commonwealth of Pennsylvania, PA Medical Society. Obstetrics & Gynecology Pain Treatment. Revised January 14, 2016 http://www.health.pa.gov/My%20Health/Diseases%20and%20Conditions/M-P/opioids/Documents/OpioidGuidelinesOBGYN.pdf

17. Rebordosa C, Kogevinas M, Bech BH, Sørensen HT, Olsen J. Use of acetaminophen during pregnancy and risk of adverse pregnancy outcomes Int J Epidemiol 2009383706–14

18. Black RA, Hill DA. Over-the-counter medications in pregnancy. Am Fam Physician. 2003 Jun 15;67(12):2517-24

19. Liew Z, Ritz B, Rebordosa C, et al. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr. 2014;168(4):313-20

20. Toda K. Is acetaminophen safe in pregnancy? Scand J Pain. 2017 Oct 4 https://www-ncbi-nlm-nih-gov.libproxy.temple.edu/pubmed/28986045

21. Koren G, Florescu A, Costei AM, Boskovic R, Moretti ME. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis Ann Pharmacother 2006405824–9

22. Babb M, Koren G, Einarson A. Treating pain during pregnancy. Can Fam Physician. 2010 Jan; 56(1): 25, 27.

23. Werler MM, Mitchell AA, Moore CA, Honein MA. Is there epidemiologic evidence to support vascular disruption as a pathogenesis of gastroschisis? Am J Med Genet A. 2009;149A(7):1399–406. [PMC free article] [PubMed]

24. James AH, Brancazio LR, Price T. Aspirin and reproductive outcomes. Obstet Gynecol Surv. 2008;63(1):49–57. [PubMed]

25. Desai RJ, Huybrechts KF, Hernandez-Diaz S, et al. Exposure to prescription opioid analgesics in utero and risk of neonatal abstinence syndrome: population based cohort study. BMJ. 2015; 350: h2102.

26. Chou R, Fanciullo G J, Fine P G. et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113–130.

27. Yazdy MM, Desai RJ, Brogly SB. Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature. J Pediatr Genet. 2015 Jun; 4(2): 56–70.

28. Ostgaard HC, Andersson GBJ, Karlsson K. Prevalence of back pain in pregnancy. Spine 1991;16:549-52

29. Mabie W. C. Peripheral neuropathies during pregnancy. Clinical Obstetrics and Gynecology. 2005;48(1):57–66

30. Borg-Stein J., Dugan S. A. Musculoskeletal disorders of pregnancy, delivery and postpartum. Physical Medicine and Rehabilitation Clinics of North America. 2007;18(3):459–476

31. Rathmell JP, Viscomi CM, Ashburn MA. Management of Nonobstetric Pain During Pregnancy and Lactation. Anesth Analg. 1997;85(5):1074-1087

32. Minozzi S, Amato L, Bellisario C, et al. Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database Syst Rev. 2013 Dec 23;(12):CD006318

33. Martin C E, Longinaker N, Terplan M. Recent trends in treatment admissions for prescription opioid abuse during pregnancy. J Subst Abuse Treat. 2015;48(1):37–42.

34. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010;363:2320–2331

35. Meyer MC, Johnston AM, Crocker AM, et al. Methadone and buprenorphine for opioid dependence during pregnancy: A retrospective cohort study. J Addict Med. 2015 Mar-Apr; 9(2): 81–86.

36. Commonwealth of Pennsylvania, PA Medical Society. Use of Addiction Treatment Medications in the Treatment of Pregnant Patients with Opioid Use Disorder. http://www.health.pa.gov/My%20Health/Diseases%20and%20Conditions/M-P/opioids/Documents/Use%20of%20Addiction%20Treatment%20Medications%20in%20the%20Treatment%20of%20Pregnant%20Patients%20with%20Opioid%20Use%20Disorder%20(FINAL).pdf

37. American Academy of Pediatrics. Committee on Psychosocial Aspects of Child and Family Health; Task Force on Pain in Infants, Children, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. Pediatrics. 2001 Sep;108(3):793-7.

38. World Health Organization. WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. World Health Organization; 2012.

39. Coté CJ, Wilson S, American Academy of Pediatrics, et al. Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures: Update 2016. Pediatrics. 2016 Jul;138(1)

40. Sutter KA, Shaw BA, Gerardi JA, et al. Comparison of morphine patient-controlled analgesia with and without ketorolac for postoperative analgesia in pediatric orthopedic surgery. Am J Orthop. 1999;28:351–358.

41. Voronov P, Przbylo HJ, Jagannathan N. Apnea in a child after oral codeine: A genetic variant—An ultrarapid metabolizer. Paediatr Anaesth 2007;17(7):684-7

7. Opioid Overdose and Withdrawal

The United States is currently dealing with one of the worst health epidemics in history which many believe has been fueled by prescription opioids. The non-medical use of opioids is a major public health issue with 10.3 million person reporting non-medical use in 2014 (1). Opioids are commonly diverted from legitimate prescriptions and sold on the street for misuse. Misuse of prescription opioids has strong correlation with heroin use as most heroin users have used prescription opioid prior to initiating heroin (1). Decreasing the quantity of available opioids can lead to a decrease in diversion and abuse (2).

Opioid overdose is typically caused by respiratory depression leading to anoxic injury. It can be due to a therapeutic misadventure or other causes like non-medical misuse seen typically with intravenous heroin use. Chronic use of opioid leads to dependence and abrupt cessation can lead to withdrawal. This section explores opioid misuse, overdose and withdrawal.

Opioids

Opioids are categorized into three separate classes. The first is the opiates, the naturally occurring substances derived from opium from the poppy flower (*Papaver somniferum*). Opiates includes morphine and codeine. The semisynthetic class includes the agents, heroin (diacetylmorphine), hydrocodone and oxycodone. Synthetic opioids are structurally unrelated to morphine and include the compounds methadone, meperidine, and fentanyl. Other synthetic agents such as the fentanyl analogs, acetyl fentanyl and carfentanil along with the designer drug, U-47700 are increasingly found as potent opioid contaminants in heroin.

Opioids can be either be pharmaceutical or illicit products, but all produce their effects by acting on opioid receptors. Both the therapeutic analgesia effect and toxicity from abuse of opioids are mediated by the same receptors (see Section 3 for complete discussion on opioid pharmacology). The most serious adverse effect from opioids is respiratory depression. Activation of opioid receptors in the brain results in a depressed respiratory rate and tidal volume leading to hypoxia.

Route of Administration

Opioids come in numerous formulations for various routes of administration including oral immediate release, oral extended release, sublingual, buccal, intramuscular, intravenous, and transdermal. Heroin, while abused in numerous routes, is commonly administered via intranasal insufflation, intramuscular, or intravenous injection.

Pharmaceutical opioids are most commonly misused via the oral route. Extended release products are intended for once daily, twice daily, or every 72 hrs (transdermal) for a slow, steady release of medication to patients who are tolerant to analgesic effect of opioids. Extended release products typically contain a higher total dose of opioids than their immediate release counterparts. Abuse deterrent formulations exist for some extended release medications to prevent tampering. Otherwise, extended release products can be altered to release the total dose of active medication as a single dose similar to an immediate release formulation. Some examples include: crushing or chewing oxycodone extended release tab, cutting open a fentanyl transdermal patch to ingest contents, or crushing and dissolving a morphine extended release tab

for intravenous injection. Formulations with a high total dose of opioid but without abuse deterrents are at higher risk for misuse and hence diversion.

Figure 7.1 demonstrates the difference in peak plasma concentration, time to peak, and half-life of opioids for various routes of administration. Drugs with early time to peak and higher peak plasma concentrations correlate with higher abuse potential and risk of overdose. For instance, the transdermal route is not a preferred route of exposure for misuse. However, a fentanyl transdermal patch contains a large total dose of opioid. Therefore, it is no surprise that fentanyl transdermal patches are commonly diverted for misuse via other routes of administration (i.e., oral and intravenous).

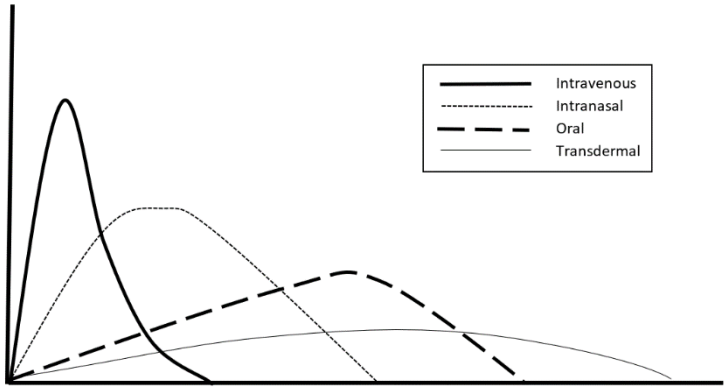


Figure 7.1 Difference in time to peak plasma concentration for various routes of administration

Acute Opioid Overdose and Toxicity

Opioids produce their analgesic and toxic side effects by interacting at opioid receptors in both the CNS and peripheral tissues. When taken in excess, opioids affect the brain stem causing respiratory depression. Opioid overdose is commonly recognized by:

- Sedation
- Respiratory depression
- Pinpoint pupils

Treatment is to restore ventilation either through artificial respiration or by administration of the opioid receptor antagonist, naloxone. The common sequelae of prolonged hypoxia due to opioid overdose include acute myocardial infarction, acute lung injury, acute kidney injury, anoxic brain injury, and multiorgan failure. People that suffer a prolonged sedated state are at high risk for rhabdomyolysis and compartment syndrome.

Benzodiazepines are central nervous system depressants that potentiate the respiratory depression caused by opioids. Prescription opioid overdose deaths frequently involve benzodiazepine exposure (3). It is not recommended to co-prescribe benzodiazepines and opioid analgesics because of their combined increased risk of abuse and overdose.
Some risk factors for opioid overdose include (4):

- High prescribed opioid dose (>100 mg of morphine or equivalent)
- Intravenous injection of opioids
- Relapse in use with recent reduction in tolerance secondary to abstinence whether intentional (detoxification) or involuntary (incarceration)
- Use of opioids in combination with other sedating substances

- Opioid use in the setting of comorbid conditions such as liver disease, obstructive sleep apnea, substance use disorder, and psychiatric disease
- Small children who are unintentionally exposed to opioids (e.g., accidental ingestion of opioid intended for adult member of household)

Chronic use of opioids leads to dependence and tolerance. Dependency to opioids refers to the development of withdrawal symptoms when opioids are discontinued abruptly. People who chronically use opioids develop tolerance to the analgesic, euphoric, sedative, and respiratory depressant effects. In the setting of opioid tolerance, dose escalation is required to achieve the same effects previously experienced at lower doses. Dependence and tolerance to opioids dissipate gradually as opioids are discontinued.

Constipation is a common side effect of both chronic medical and non-medical use of opioids mediated by opioid receptors located in the smooth muscle of the intestinal wall. Chronic use of opioid analgesics is associated with the development of opioid-induced hyperalgesia, a syndrome of paradoxical heightened sensitivity to pain. Decreased hypothalamic function due to chronic opioid use leads to decreased secretion of gonadotropin releasing hormone (GRH). The clinical effects from decreased GRH secretion are reduced libido in both men and women, hot flashes, depression, hair loss, and osteopenia (5). Some other side effects associated with chronic opioid use include sedation and hearing loss.

Opioid Reversal with Naloxone

Naloxone is the opioid receptor antagonist most commonly used by medical and non-medical personnel for the reversal of opioid overdose. When administered, it is readily transported across the blood-brain barrier to block the effects of opioids and quickly reverse the effects of opioid overdose. The goal of therapy is to restore respiratory ventilation and normal oxygenation, not necessarily reverse sedation. Naloxone can be administered via numerous routes including intravenous, intranasal, intramuscular, subcutaneous and inhalational routes. The onset of action with intravenous administration is 1-3 minutes and 3-5 minutes with intranasal administration. The half-life of naloxone is typically quoted as 30-90 minutes but the duration of action is variable and dependent on both the dose of naloxone and opioid used. The recurrence of opioid toxicity is not uncommon, particularly when caused by long-acting opioids like methadone, as the duration of actions of many opioids exceeds that of naloxone.

Administration of naloxone to opioid-dependent patients may precipitate opioid withdrawal. It is recommended to use the lowest dose possible to achieve normal oxygenation in suspected opioid dependent patient to prevent naloxone-induced withdrawal. Treatment can be titrated with small aliquots (as low as 0.04 mg intravenously) of naloxone until the goal is achieved. The use of naloxone in the delivery room for neonates born to mothers who are opioid dependent is contraindicated as naloxone may precipitate life-threatening neonatal abstinence syndrome and convulsions.

When administered naloxone by emergency medical services for opioid overdose, patients have a >90% survival rate. However, about 10% of those non-fatal overdose victims will die in the next year (6). Data from a single-center study in New Haven, CT suggests that emergency

department initiation of buprenorphine significantly reduces illicit opioid use and could potentially decrease mortality rate (7).

Layperson use of intranasal naloxone has been recommended by numerous organizations as it has been shown to reduce overdose deaths, is safe and cost-effective (8). Through the standing order initiative (Act 139 of 2014), all Pennsylvania residents have a prescription for naloxone available to fill in a pharmacy. The standing order is intended to help residents at risk for opioid overdose, including family-members, friends or other persons.

Opioid Withdrawal

Chronic use of opioids leads to a physiologic dependence. Stopping opioids abruptly may cause symptoms of withdrawal. While not life-threatening in adults, acute opioid withdrawal is associated with a constellation of severe dysphoric and painful side effects. Early symptoms of opioid withdrawal include anxiety or irritability, rhinorrhea, diaphoresis, arthralgias, piloerection, and yawning. Later symptoms include gastrointestinal symptoms like cramping, vomiting, and diarrhea along with increased heart rate, restlessness, dilated pupils and tremor. Severity of symptoms can be scored using the Clinical Opioid Withdrawal Scale (COWS), an 11-item scale intended to be administered by a clinician (See Figure 7.2) (9).

The onset, severity, and duration of acute opioid withdrawal is dependent on both patient and opioid factors. High dose dependence on short acting opioids results in early onset, and severe but relatively protracted duration of symptoms. Withdrawal from intravenous heroin use starts approximately 6-12 hours after last use, peaks within 36-72 hours, and may last 7 days (10). Withdrawal from a long-acting agent like methadone is not as severe, but symptoms are prolonged and may last more than 2 weeks.

APPENDIX 1
Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

Figure 7.2 Clinical Opioid Withdrawal Scale (COWS)

The goal for the management of acute opioid withdrawal is to make the natural course of abstinence safe and more comfortable. Several medication strategies have been described including opioid and non-opioid pharmacotherapy. While buprenorphine and methadone are commonly described in the management of acute opioid withdrawal, most opioids including morphine and oxycodone are effective at reducing withdrawal symptoms. Buprenorphine and methadone typically require a special license to prescribe for the treatment of opioid dependency, but Title 21 Code of Federal Regulations Part 1206.07(b), known as the "three-day rule," allows for emergent administration over 72 hours for the purpose of relieving acute opioid withdrawal symptoms. When buprenorphine or methadone are unavailable, administration of other opioids for symptom control is acceptable.

Various non-opioid medications should utilized in conjunction with opioids in a multimodal approach for symptomatic support of anxiety, tremor, arthralgias, vomiting, and diarrhea including clonidine, NSAIDs, and loperamide (see Figure 7.3). The long-term management of opioid use disorder is discussed in Section 11.

Symptoms	Medication(s)
Nausea	ondansetron, metoclopramide
Diarrhea	loperamide
Anxiety, irritability	clonidine
Insomnia	hydroxyzine, trazodone
Pain	NSAIDs

Figure 7.3 Non-Opioid pharmacologic therapies in supportive care of opioid withdrawal

In neonates, opioid withdrawal is different in that it may be life-threatening if unrecognized and not properly treated. Signs include tremors, excessive crying, poor feeding, myoclonic jerks, sleep disturbances, and hyperactive reflexes. Treatment includes non-pharmacologic supportive care, opioid replacement therapy, and non-opioid medication such as phenobarbital and clonidine (11).

References

1. Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. N Engl J Med 2016;374:154-163 http://www.nejm.org/doi/full/10.1056/NEJMra1508490#ref50

2. Surratt HL, O'Grady C, Kurtz SP, et al. Reductions in prescription opioid diversion following recent legislative interventions in Florida. Pharmacoepidemiol Drug Saf 2014;23:314-320

2. Centers for Disease Control and Prevention. Vital Signs: Variation Among States in Prescribing of Opioid Pain Relievers and Benzodiazepines — United States, 2012. MMWR 2014; 63(26);563-568.

4. World Health Organization. Information sheet on opioid overdose. November 2014. Last accessed November 2017 http://www.who.int/substance_abuse/information-sheet/en/

5. Brennan MJ: The eect of opioid therapy on endocrine function. A m J M e d. 2013;126(suppl):S12–S18

6. Weiner SG, Baker, O, Bernson D, et al. One-year mortality of opioid overdose victims who received naloxone by emergency medical services [abstract]. Ann Emerg Med. 2017;70(4):S158

7. D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. JAMA. 2015 Apr 28;313(16):1636-44.

8. Centers for Disease Control and Prevention. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons — United States, 2014. MMWR 2015; 64(23);631-635

9. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003; 35(2):253–9

10. Dole VP. Narcotic addiction, physical dependence and relapse. N Engl J Med 1972;286(18):988–992

11. McQueen K, Murphy-Oikonen J. Neonatal Abstinence Syndrome. N Engl J Med 2016; 375:2468-2479 http://www.nejm.org/doi/full/10.1056/NEJMra1600879#t=article

8. Discontinuing Opioids in Chronic, Non-Cancer Pain

It is always challenging to discontinue opioids for patients with chronic pain. However, the evidence supporting the effectiveness of opioids for chronic, non-cancer related pain is weak. Moreover, chronic opioid use poses major, life-threatening risks, including dependence and overdose (1). The best approach to treatment of chronic pain is multi-modal, using a combination of non-opioid medications (e.g. acetaminophen, NSAIDs, gabapentin, muscle relaxants, topical medications) and non-pharmacologic treatments (e.g. physical therapy, cognitive behavioral therapy, acupuncture, TENS units) (refer to Section 2). Discontinuing opioids in chronic pain patients rarely leads to increased and sustained pain, but health care providers should take steps to avoid unnecessary withdrawal symptoms or exacerbating psychiatric conditions (2, 3).

It is important to start the conversation about weaning or discontinuing opioids with the patient in the context of a comprehensive treatment plan. They may be resistant and may argue their case to continue opioid treatment. However, as you explain the rational of the weaning plan, patients will often follow your recommendations. Depending on the duration and dose of opioids the patient has been receiving, tapering is often necessary to prevent withdrawal symptoms.

Consider the following recommendations for safely tapering and discontinuing opioids that have been used chronically.

1. **Establish the rate of taper**:
    a. Immediate discontinuation if there is evidence of diversion.
    b. Rapid taper (over 2-3 weeks) if the patient has had an adverse outcome (i.e. overdose or substance use disorder)
    c. Slow taper if there are no acute safety concerns. Start with a 10% taper of the original dose per week and assess the patient's pain and functional status (4). For patients who have been on opioids for more than 2 years, tapering every two weeks or even monthly can be considered (5).
2. **Adjust the rate, intensity and duration of taper based on the patient's response and development of withdrawal symptoms**. Patients using short-acting opioids (e.g. oxycodone, hydrocodone) may experience withdrawal symptoms within 6-12 hours of their last dose. The onset of symptoms usually occurs later for patients using long-acting opioids (e.g. OxyContin, MS-Contin) (5). Withdrawal symptoms result from increased sympathetic activity, and commonly include anxiety, palpitations, restlessness, tremor, sweating, nausea, abdominal pain, diarrhea, shivering and rhinorrhea. Reducing the taper to less than 10% per week can minimize withdrawal symptoms. Patients should be informed that on rare occasions, general malaise and other symptoms of mild withdrawal may persist up to 6 months following opioid cessation.
3. **Use medications to treat opioid withdrawal symptoms if needed**. These include clonidine (for restlessness, sweating or tremors), an anti-emetic (nausea), loperamide (diarrhea) and NSAIDS (pain), provided there are no contraindications. Do not use benzodiazepines to treat anxiety or restlessness.
4. **Monitor for psychiatric disorders during the taper and consult with a behavioral health specialist as needed**. If a patient expresses suicidal ideation, refer to a crisis response center, emergency department or facilitate urgent evaluation by a behavioral health specialist.

5. **Do not reverse the taper.** The rate may be slowed or paused while monitoring for and treating withdrawal symptoms, as well as addressing psychiatric disorders.
6. **In patients taking both opioids and benzodiazepines, taper opioids before tapering benzodiazepines**. When tapering benzodiazepines, start a 20% reduction over two weeks and monitor for signs and symptoms of withdrawal.
7. **Consider inpatient withdrawal management** if the taper is poorly tolerated (buprenorphine/naloxone) or if the patient has persistent opioid cravings.
8. **Do not resume opioids or benzodiazepines once they have been stopped**, as they may trigger drug cravings and a return to use.
9. **Seek specialty care for pregnant patients.** Tapering of opioids during pregnancy is contraindicated as it is associated with spontaneous abortion and premature labor (1).
10. **If you suspect or detect illicit drug use, refer the patient to a treatment program** (refer to Section 11).

References

1. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016. MMWR Recomm Rep. 2016 Mar 18;65(1):1-49.
2. Baron MJ, McDonald PW. Significant pain reduction in chronic pain patients after detoxification from high dose opioids. J Opioid Manag. 2006 Sep-Oct;2(5):277-282.
3. Krumova EK, Bennemann P, Kindler D, Schwarzer A, Zenz M, Maier C. Low pain intensity after opioid withdrawal as a first step of a comprehensive pain rehabilitation program predicts long-term nonuse of opioids in chronic noncancer pain. Clin J Pain. 2013 Sep;29(9):760-9.
4. Washington State Agency Medical Directors' Group. Interagency Guideline on Prescribing Opioids for Pain, 3e. June 2015.
5. Berna C, Kulich RJ, Rathmell JP. Tapering Long-Term Opioid Therapy in Chronic Noncancer Pain: Evidence and Recommendations for Everyday Practice. Mayo Clin Proc. 2015 Jun;90(6):828-842

9. Identification of patients who are at risk for developing a substance use disorder (SUD)

Introduction

Opioid use disorder does not discriminate based on age, gender, race, ethnicity, or socioeconomic status. With significant increases in opioid use as well as complications associated with opioid use disorder (OUD) including overdose and death, the identification of patients with OUD as well as those at risk for developing OUD has become increasingly important. Cited risk factors such as socioeconomic factors, psychological comorbidity, family history, and alcohol and other substance use disorders (1), although demonstrated in research, may lead to discriminatory practices for vulnerable individuals within these populations to receive the same type of care that others might receive. Furthermore, risk assessment tools have not been shown to be uniformly predictive across population subgroups. Therefore, there is no distinct best practice for implementing screening for OUD into a practice setting; however, unique protocols can address key issues and features within populations to provide guidance for particular areas of need. In this section, screening and issues critical to identification of individuals at risk and with OUD in special populations will be reviewed.

Screening

Screening and assessment for opioid use disorder should not be considered a passive process that is without risks. Used appropriately, it can certainly lead to effective, evidence-based care; however, used in a careless or unprofessional manner, there is potential for significant harm to the individuals who need help, both immediately and in the near future. Not only must those individuals involved in screening understand the impact of culture, race, and gender on screening and assessment, but they also must understand how their own culture and ethnic background, as well as their life experiences affect the assessment process. Screening should be distinguished from assessment. Screening refers to the process by which people at risk for a disease state or disorder go through a brief intervention that informs the screener of the probability of the presence of a problem, substantiates a concern, or identifies the need for further evaluation. Assessment refers to a thorough evaluation, often performed in the context of a positive screening instrument, to confirm the presence or absence of a disease state.

Currently, the United States Preventive Services Task Force (USPSTF) notes that there is insufficient evidence to assess the efficacy of screening for unhealthy drug use (2). However, given the high prevalence and concurrent significant morbidity and mortality related to OUD, universal screening may be warranted. Additionally, identifying unhealthy drug use can result in improved overall health through avoiding medication interactions, altering prescribing habits, and increasing the quality of care delivered (3-5).

Efficient screening tools are available with simple one or two question options (Figure 9.1).

SCREENER	QUESTION	RESULT INTEPRETATION	SOURCE
SINGLE-ITEM SCREEN	How many times in the past year have you used an illegal drug or a prescription medication for nonmedical reasons?	Positive screen is 1 or more days	6
TWO-ITEM SCREEN FOR CLINICS SERVING US VETERANS	How many days in the past 12 months have you used drugs other than alcohol? How many days in the past 12 months have you used drugs more than you meant to?	Positive screen is 7 or more days Positive screen is 2 or more days	7

Figure 9.1 Validated Screening Tools for Substance Use Disorders (SUDs)

Patients whose screens are negative should be given positive reinforcement for healthy behaviors and encouragement to continue avoiding unhealthy use of drugs and alcohol. Those who screen positive will need further evaluation and a more comprehensive assessment, particularly as these simple screens do not differentiate involvement of a particular substance. A brief screen with a built-in brief assessment specific to OUD is the Tobacco, Alcohol, Prescription medications, and other Substance use (TAPS Tool; Figure 9.2) (8).

TAPS. *Directions:* *Any positive response to a TAPS 1 question moves the patient to answer the TAPS 2 corresponding question. TAPS 2: Yes (1 point) No (0 points). Patients with a TAPS 2 score of 1 or more should have a diagnostic assessment (including those misusing prescription opioids and heroin).*

TAPS-1 In the past 12 months	Screen	TAPS-2 In the past 3 months
RESPONSES: Daily or almost daily, weekly, monthly, less than monthly, never		*RESPONSES: Yes or No*
How often have you used any tobacco?	→	Did you smoke a cigarette containing tobacco? • Did you usually smoke more than 10 cigarettes each day? • Did you usually smoke within 30 minutes after waking?
How often have you had 5 or more (men)/4 or more drinks (women) containing alcohol in once day	→	Did you have a drink containing alcohol? • Did you have 5 or more (men) /4 or more drinks (women) containing alcohol each day? • Have you tried and failed to control, cut down, or stop drinking? • Has anyone expressed concern about your drinking?
How often have you used any drugs including marijuana, cocaine or crack, heroin, methamphetamine (crystal meth), hallucinogens, ecstasy/MDMA?	→	Did you use marijuana (hash, weed)? • Have you had a strong desire or urge to use marijuana at least once a week or more often? • Has anyone expressed concern about your use of marijuana? Did you use cocaine, crack, or methamphetamine (crystal meth)? • Did you use cocaine, crack, or methamphetamine (crystal meth) at least once a week or more often? • Has anyone expressed concern about your use of cocaine, crack, or methamphetamine (crystal meth)? Did you use heroin? • Have you tried and failed to control, cut down, or stop using heroin? • Has anyone expressed concern about your use of heroin?
How often have you used any prescription medications just for the feeling, more than prescribed, or that were not prescribed for you?	→	Did you use prescription opiate pain reliever (for example, Percocet, Vicodin) not as prescribed or that was not prescribed for you? • Have you tried and failed to control, cut down, or stop using an opiate pain reliever? • Has anyone expressed concern about your use of an opiate pain reliever? Did you use medication for anxiety or sleep (for example, Xanax, Ativan, or Klonpin) not as prescribed or that was not prescribed for you? • Have you had a strong desire or urge to use medications for anxiety or sleep at least once a week or more often? • Has anyone expressed concern about your use of medication for anxiety or sleep? Did you use medication for ADHD (for example, Adderall, Ritalin) not as prescribed or that was not prescribed for you? • Did you use a medication for ADHD (for example, Adderall, Ritalin) sleep at least once a week or more often? • Has anyone expressed concern about your use of medication for ADHD (for example, Adderall, Ritalin)?
Any drugs or prescription medications	→	Did you use any other illegal or recreational drugs (for example, ecstasy, molly, GHB, poppers, LSD, mushrooms, special K, bath salts, synthetic marijuana ['spice'], whip-its, etc.)? • What were the other drug(s) your used? (fill in response

Figure 9.2 Tobacco, Alcohol, Prescription medications, and other Substance use (TAPS) Tool

The benefit of the TAPS tool is that there are only a limited number of questions which enable the tool to be more efficiently worked into clinical workflows; however, similar to one-question and two-question screenings, more in-depth assessment may need to be performed. While the TAPS tool was able to identify those with high risk opioid use and moderate-risk use of tobacco, alcohol, and marijuana, it was unable to identify individuals at moderate-risk for other drugs (9), notably the focus of Screening, Brief Intervention and Referral to Treatment (SBIRT). A longer screening test that addresses substance-specific risk and reliably identifies both moderate-risk and high-risk use is available in the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (10) as well as its briefer version (ASSIST-lite) (11).

Special Populations

Pregnancy

While the evidence for routine screening for OUD in pregnancy according to the USPSTF is insufficient, the American College of Obstetricians and Gynecology (ACOG) recommends early universal screening, brief intervention and referral to treatment (12). While no single tool is endorsed, ACOG encourages use of validated, evidence-based tools for screening, such as the 4 Ps (Figure 9.3). Given that OUD affects women of all racial and ethnic groups, as well as all socioeconomic groups, ACOG notes that screening based solely on risk factors or focusing on women with poor adherence to prenatal care can lead to missed cases. Additionally, such a selective strategy further perpetuates stereotypes and the stigma of OUD (13). It should be noted that screening is sensitive and must be done in an appropriate, nonjudgmental manner as many women choose not to disclose substance misuse during pregnancy for fear of the potential repercussions. Some state laws still consider substance misuse during pregnancy to be a form of child abuse, which is punishable by law. Therefore, physicians are encouraged to be aware of state laws regarding reporting and patient confidentiality (14). While urine drug testing has been utilized to detect or confirm substance use, routine testing is largely controversial and should only be done with the patient's full consent, accompanied by a discussion regarding the possible ramifications of a positive test and reporting requirements.

Figure 9.3: 4 Ps

Parents: Did any of your parents have a problem with alcohol or other drug use?

Partner: Does your partner have a problem with alcohol or drug use?

Past: In the past, have you had difficulties in your life because of alcohol of other drugs, including prescription medications?

Present: In the past month, have you drunk any alcohol or used other drugs?

Scoring: Any "yes" should trigger full assessment.

Ewing H. A practical guide to intervention in health and social services with pregnant and postpartum addicts and alcoholics: theoretical framework, brief screening tool, key interview questions, and strategies for referral to recovery resources. Martinez (CA): The Bron Free Project, Contra Costa County Department of Health Services; 1990.

The benefits of screening during pregnancy are not simply related to identification and guiding a pregnant patient to treatment, but also addressing potential risks of neonatal abstinence syndrome (NAS). With both opioid use during pregnancy and NAS on the rise (15), the public health implications of addressing both in the context of appropriate prenatal care can have profound implications on both the pregnant woman and the fetus. The implications of caring for a parent struggling with OUD on the development and health of the infant and child are reviewed below in discussion of adolescent risk factors and screening.

Pediatrics and Adolescents

Substance use in adolescence can disrupt the young person's ability to adequately meet developmental tasks, a central theme of adolescence (16,17). Sustained use interferes with the increasing demands and roles that come with becoming an adult (18). Therefore, an adolescent who has been blunted in his/her development due to substance use will be notably unprepared for the demands of adult life.

The American Academy of Pediatrics (AAP) recommends that all adolescent patients are screened for tobacco, alcohol, and other drug use with a formal, validated screening tool at every health supervision visit and appropriate acute care visits, such as the CRAFFT Screening Interview (Figure 9.4) (19).

The AAP acknowledges that despite the fact that the United States Preventive Services Task Force (USPSTF) felt there was insufficient evidence to assess the efficacy of brief interventions in the adolescent population to reduce substance abuse (20), there is minimum potential for harm and potential for even small population-level benefit.

The CRAFFT Screening Interview

Begin: "I'm going to ask you a few questions that I ask all my patients. Please be honest. I will keep your answers confidential."

Part A

During the PAST 12 MONTHS, did you:	No	Yes
1. Drink any alcohol (more than a few sips)? (Do not count sips of alcohol taken during family or religious events.)	☐	☐
2. Smoke any marijuana or hashish?	☐	☐
3. Use anything else to get high? ("anything else" includes illegal drugs, over the counter and prescription drugs, and things that you sniff or "huff")	☐	☐

For clinic use only: Did the patient answer "yes" to any questions in Part A?

No ☐ → **Ask CAR question only, then stop**

Yes ☐ → **Ask all 6 CRAFFT questions**

Part B	No	Yes
1. Have you ever ridden in a **CAR** driven by someone (including yourself) who was "high" or had been using alcohol or drugs?	☐	☐
2. Do you ever use alcohol or drugs to **RELAX**, feel better about yourself, or fit in?	☐	☐
3. Do you ever use alcohol or drugs while you are by yourself, or **ALONE**?	☐	☐
4. Do you ever **FORGET** things you did while using alcohol or drugs?	☐	☐
5. Do your **FAMILY** or **FRIENDS** ever tell you that you should cut down on your drinking or drug use?	☐	☐
6. Have you ever gotten into **TROUBLE** while you were using alcohol or drugs?	☐	☐

Figure 9.4 CRAFFT Screening Tool for Adolescents

Screenings should be encouraged not simply at well care visits, as studies suggest that adolescents are more likely to report substance use at follow-up or acute visits (21). It is important to note that federal laws guarantee strict confidentiality of information about persons – including adolescents – receiving substance abuse prevention and treatment services. Individuals involved in screening adolescents are encouraged to become aware of federal and state statutes addressing confidentiality.

While adolescence is the period of greatest risk and frequently the first time screening takes place, risk factors for substance use disorders begins much earlier with challenges to an individual's emotional, social, and academic development (Figure 9.5).

Risk Factors for Future SUD

In the Family	Outside of the Family
• **Lack of mutual attachment and nurturing by parents or caregivers** • **Ineffective parenting** • **Chaotic home environment** • **Lack of significant relationship with a caring adult** • **Caregiver who abuses substances, suffers from mental illness, or engages in criminal behavior**	• Inappropriate classroom behavior, such as aggression and impulsivity • Academic failure • Poor social coping skills • Association with peers with problem behaviors, including drug abuse • Misperceptions of the extent and acceptability of drug-abusing behaviors in school, peer, and community environments

Figure 9.5 Risk Factors In and Outside the Family for future SUDs in Pediatric Patients

Many of these risk factors including early aggressive behavior, lack of parental supervision, substance abuse, drug availability, and poverty are not singly predictive of development of SUDs. They do, in fact, coincide with adverse childhood experience (ACE) scores. ACE scores have demonstrated a score-dependent relationship to substance-related behaviors. With regard to OUD, elevated ACE scores are associated with increased rates of prescription drug misuse (22) as well as lifetime illicit drug use, ever having a drug problem, and self-reported SUD (23).

Geriatrics

Despite misconceptions that older adults do not demonstrate high rates of SUDs compared with younger adults, studies suggest that substance use among older adults has been under identified (24). A significant amount of research regarding SUD in geriatric populations, however, is largely focused on alcohol use disorder and therefore risk factors identified are only specific to alcohol and therefore are not necessarily associated with OUD. This is unfortunate because, while male sex is associated with a higher risk of alcohol misuse, female sex is actually more associated with prescription drug abuse (25). Health care providers should consider using the CAGE questionnaire which has been adapted to assess alcohol and other drugs in the form of the CAGE-AID (26). It should be noted, however, that the CAGE-AID has not been fully validated in the geriatric population, nor is it able to distinguish between current and lifetime use (27).

Patients with Chronic Pain

Addressing OUD in the setting of patients with chronic pain requires a multifaceted approach. Prior to initiation of opioid treatment in a patient with chronic pain, risk factor evaluation and assessment should be performed. Moreover, once opioids are initiated, mechanisms for monitoring for signs and symptoms of opioid use disorder must also be part of pain management. Just as our understanding of the pathophysiology and best practices for evidence-based treatment of chronic pain is limited, so too is our knowledge about how to fully assess risk of OUD in a patient who will, or is already receiving, opiate therapy for the treatment of chronic pain. Many traditional risk factors for OUD that exist in other populations, including coexisting

psychological illness like depression, anxiety, or somatoform disorder are present to a large degree in patients with chronic pain. Risk tools and findings have suggested predictive models for identifying those at risk for OUD (Figure 9.6).

Study	Risk Factors	Reference
Webster and Webster (Opioid Risk Tool)	• Family history of substance abuse • Personal history of substance abuse • Age of 45 years or younger • History of preadolescent sexual abuse • Presence of psychological disorders (ADD, OCD, unipolar depression, bipolar disorder, or schizophrenia)	28
Chabal et al.	• Focus on opioids beyond third clinic treatment session • Persistent pattern early refills • Multiple telephone calls or office visits requesting more opioids • Reports of consistent problems with prescription (lost, spilled, stolen) • Obtained from multiple providers, ER, illegal sources	29
Compton et al.	• Belief of addiction • Increasing analgesic dose or frequency • Route of administration preference	30
Atluri and Sudarshan	• Focus on procuring opioids • Opioid overuse • Other substance use • Nonfunctional exaggeration of pain • Unclear and/or improbably pain etiology	31
Manchikanti et al.	• Excessive opiate needs • Deception or lying to obtain controlled substances • Doctor shopping	32

Figure 9.6 Evidence-base Risk Assessment Tools for OUD

While these tools have been validated, each is variable in sensitivity and specificity as well as feasibility of application into clinical practice. While no one tool is recommended, utilizing a validated tool is important, as opposed to selecting randomly from signs and symptoms that might lead to bias or inappropriate care. Documentation of completion of an assessment of risk is important in deciding whether or not to initiate opioid therapy in the treatment of chronic pain. While these tools do not define whether an individual should or should not receive opioid therapy, they must be utilized in the context of the personal and medical details in providing the most appropriate care to patients.

Conclusions

While the USPSTF currently reports insufficient evidence regarding population-based screening for substance use disorder other than alcohol, the current public health climate with OUD has prompted many to consider whether the seriousness of the climate warrants such screening without clear evidence-based guidance. Tools are available to screen generally for SUD as well as tools that are substance-specific. However, no single tool is amenable to being used across all ages and sociodemographic status. Despite variations within special populations and subgroups, risk factors certainly exist as a continuum across the lifespan and should be viewed as such. In fact, with genetics playing a significant role, early life biological as well as psychosocial factors through elevated ACE scores create a potential propensity for increased risk of OUD in adulthood either during pregnancy, during adulthood, or during the older adult years. Given the significance of complications related to OUD, screening can appropriately identify concerning drug use among patients. However, screening should never be considered diagnostic and always requires further assessment and evaluation.

References

1. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. Pain Physician 2012;15(3 Suppl):Es67-92.
2. U. S. Preventive Services Task Force. (2008). Drug use, illicit: Screening. Retrieved October 2, 2017, from http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/drug-use-illicit-screening.)
3. Shapiro B, Coffa D, McCance-Katz. A Primary Care Approach to Substance Misuse. Am Fam Physician. 2013;88(2):113-21.
4. Lindsey WT, Stewart D, Childress D. Drug interactions between common illicit drugs and prescription therapies. Am J Drug Alcohol Abuse. 2012 Jul; 38(4):334-43.
5. Arnsten JH, Demas PA, Grant RW, et al. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. J Gen Intern Med. 2002 May; 17(5):377-81.
6. Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. A single-question screening test for drug use in primary care. Arch Intern Med. 2010;170(13):1155–1160.
7. Tiet QQ, Leyva YE, Moos RH, Frayne SM, Osterberg L, Smith B. Screen of drug use: Diagnostic accuracy of a new brief tool for primary care. JAMA Internal Medicine.2015;175(8):1371–1377.
8. McNeely J, Wu LT, Subramaniam G, et al. Performance of the Tobacco, Alcohol, Prescription Medication and Other Sustance Use (TAPS) Tool for Substance Use Screening in Primary Care Patients. Ann Intern Med. 2016;165(10):690-99.
9. Schwartz RP, McNeely J, Wu LT, et al. Identifying substance misuse in primary care: TAPS Tool compared to the WHO ASSIST. J Subst Abuse Treat. 2017;76:69-76.
10. McNeely J, Strauss SM, Rotrosen, J, Ramautar A, Gourevitch, MN. Validation of an audio computer-assisted self-interview (ACASI) version of the Alcohol, Smoking and

Substance Involvement Screening Test (ASSIST) in primary care patients. Addiction, 2016;111(2), 233–244.
11. Ali R, Meena S, Eastwood B, Richards I, Marsden J. Ultra-rapid screening for substance-use disorders: The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-Lite). Drug and Alcohol Dependence. 2013;132(1–2):352–361.
12. Opioid use and opioid use disorder in pregnancy. Committee Opinion No. 711. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e81-94.
13. Wright TE, Terplan M, Ondersma SJ, et al. The role of screening, brief intervention, and referral to treatment in the perinatal period. Am J Obstet Gynecol 2016;215:539-47.
14. Alcohol abuse and other substance use disorders: ethical issues in obstetric and gynecologic practice. Committee Opinion No 633. American College of Obstetricians and Gyncologists. Obstet Gynecol 2015;125:1529-37.
15. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000–2009. JAMA 2012;307:1934-40.
16. Baumrind D, Moselle KA. A developmental perspective on adolescent drug abuse. Advances in Alcohol and Substance Abuse. 1985;4:41-67.
17. Newcomb MD, Bentler PM. Substance use and abuse among children and teenagers. American Psychologist 1989;44:242-48.
18. Havighurst RJ. Developmental Tasks and Education, 3rd ed. 1972. New York: David McKay.
19. American Academy of Pediatrics. Substance Use Screening, Brief Intervention, and Referral to Treatment for Pediatricians. Pediatrics 2016;138(1):143.
20. Moyer, VA; US Preventive Services Task Force. Primary care behavioral interventions to reduce illicit drug and nonmedical pharmaceutical use in children and adolescents: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160(9):634–639.
21. Knight JR, Harris SK, Sherritt L, et al. Prevalence of positive substance abuse screen results among adolescent primary care pa- tients. Arch Pediatr Adolesc Med. 2007; 161(11):1035–1041.
22. Anda RF, Brown DW, Felitti VJ, Dube SR, Giles WH. Adverse childhood experiences and prescription drug use in a cohort study of adult HMO patients. BMC Public Health 2008;4(8):198.
23. Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF. Childhood abuse, neglect, and household dysfunction and the risk fo illicit drug use: the adverse childhood experiences study. Pediatrics. 2003;111(3):564-72.
24. Atkinson RM, Ganzini L. Substance abuse. In: Coffey CE, Cummings JL, editors. Textbook of geriatric neuropsychiatry.Washington, DC: American Psychiatric Press; 1994. pp. 297–321.
25. Simoni-Wastila L, Yang HK. Psychoactive drug abuse in older adults. Am J Geriatr Pharmacother. 2006 Dec; 4(4):380-94.
26. Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. Wis Med J. 1995; 94(3):135-40.
27. Kuerbis A, Sacco P, Blazer DG, Moore AA. Substance Abuse Among Older Adults. Clin Geriatr Med. 2014;30(#):629-54.

28. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the opioid risk tool. Pain Med 2005;6(6):432-42.
29. Chabal C, Erjavec MK, Jacobson I, et al. Prescription opiate abuse in chronic pain patients: Clinical criteria, incidence, and predictors. Clin J Pain 1997;13(2):150-5.
30. Compton P, Darakjian MA, Miotto K. Screening for addiction in patients with chronic pain and "problematic" substance use: Evaluation of a pilot assessment tool. J Pain Symptom Manage 1998;16(6):355-63.
31. Atluri SL, Sudarshan G. Development of a screening tool to detect the risk of inappropriate prescription opioid use in patients with chronic pain. Pain Physician 2004;7(3):333-8.
32. Manchikanti L, Singh V, Damron KS, et al. Screening for controlled substance abuse in interventional pain management settings: Evaluation of an assessment tool. Pain Physician 2003;6(4):425-33.

10. Diagnosing opioid use disorder (OUD)

Introduction

After screening and evaluation creates suspicion for opioid misuse, a more detailed evaluation is necessary which will aid in either directly providing treatment to a patient with opioid use disorder (OUD) or providing a "warm handoff" to treatment elsewhere. A formal evaluation enables a clinician to make a formal diagnosis of OUD, as well as determine any complications that will be critical to address as part of a comprehensive treatment plan for a patient struggling with OUD. This assessment includes attention, therefore, to both medical as well as psychosocial issues that either preceded or developed directly related to substance misuse. Such an evaluation also clearly distinguishes individuals who formally meet the diagnosis of OUD, as opposed to those with tolerance or dependence. Distinction among these terms is critical to ensuring appropriate treatment and monitoring.

Definitions

Terminology is important in making the diagnosis of opioid use disorder. Many individuals incorrectly use the terms tolerance and dependence to both be consistent with opioid use disorder. There are critical distinctions that must be clarified in order to not only correctly make an assessment of the patient, but also to provide compassionate, patient-centered care.

- Tolerance, a physical effect of repeated drug use, refers to a person's diminished response to a substance that is taken repeatedly (1).
- Dependence, a physical effect often manifested in the absence of a substance in the form of withdrawal, refers to a state in which an individual functions "normally" only under the presence of a substance (2).

It should be noted that both tolerance and dependence can occur without the development of an OUD; however, both are part of the diagnostic criteria for OUD (Figure 10.1).

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period of time than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.

9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. *Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of an opioid.
11. *Withdrawal.

Figure 10.1 DSM-V Criteria for OUD (3)

Severity of OUD is determined based on the number of symptoms with:

- Mild OUD – having 2-3 symptoms
- Moderate OUD – having 4-5 symptoms
- Severe OUD – having 6 or more symptoms

Assessment

In patients with a positive screen, further assessment is needed to differentiate patients with hazardous use, a SUD, or substance dependence. This further assessment should also be performed with patients disclosing opioid misuse or with acute or chronic signs of symptoms of opioid misuse. While the extent of the follow-up assessment is dependent upon the level of treatment engagement, the goals of a comprehensive assessment are much the same as that of collecting a comprehensive history of a patient: establishing a diagnosis of OUD; determining the severity of use; assessing other medical conditions that should be addressed before, during, and after treatment; and assessing social and psychological conditions that may directly or indirectly affect treatment for OUD.

Figure 10.2: **Motivational Interviewing Strategies**

- Open-ended questions
- Listen to the patient
- Don't tell the patient why he/she needs to change. Allow him/her to create his/her own argument for change
- Evaluate what the patient enjoys about using and what he/she does not enjoy about using
- Elicit patient motivations, provide feedback or teach back, and elicit reaction
- Affirm positive qualities in patient decisions and actions

A successful assessment must, however, be patient-centered. A patient-centered environment is nonjudgmental, respectful, and empathetic. Such an environment is more conducive to patients being willing to disclose facts they may be embarrassed or ambivalent about discussing. Motivational interviewing techniques (Figure 10.2) are critical to establishing such an environment, and lead to a patient-centered discussion to understand both opioid misuse as well as approaches to treatment (4).

Complete History

Medical History

A comprehensive medical history will provide both a complete picture of the patient but also should be directed towards any complications that developed as a result of the OUD that may need to be addressed or can alter treatment selections for both the OUD as well as other ongoing medical issues. Medical issues associated with opioid misuse include (5):

- Cardiovascular – endocarditis, septic thrombophlebitis
- Endocrine/Metabolic – osteopenia, hypogonadism, erectile dysfunction, decreased sperm motility, menstrual irregularities, infertility
- Gastrointestinal – constipation, ileus, nausea
- Hepatic – infectious and topic hepatitis
- Infectious – aspiration pneumonia, STIs, cellulitis and abscess, mycotic aneurysm, septic arthritis, hepatitis B, hepatitis C, hepatitis D, HIV
- Neurologic – seizure, sleep disturbances
- Oncologic – hepatocellular carcinoma
- Pulmonary – respiratory failure, exacerbation of sleep apnea
- Renal – rhabdomyolysis, kidney injury, glomerulonephritis, amyloidosis, nephrotic syndrome

Mental Health History

Anxiety disorders, depression, bipolar disorder, posttraumatic stress disorder, and dependent and anti-social personality disorders are more common in individuals with substance use disorders (6-8). SUDs can mimic or induce symptoms of depression or anxiety and therefore a careful history must be taken. The history should focus on symptoms and their relationship to onset of substance use and periods of abstinence to assess whether the diagnosis is more likely to be primary or secondary (substance induced).

Additionally, men and women who misuse illicit drugs have been demonstrated to be at increased risk of being perpetrators or victims of domestic violence, with rates of intimate partner violence (IPV) exceeding 50% in some settings (9-10). Given the significant rates of IPV, patients with identified SUD should be screened for IPV using validated screening tests.

Figure 10.3: **Components of Comprehensive Substance Use History**

- DOC (drug of choice)
- Age of onset
- Method of Use
- Use at height
- Last Use, how much and when
- Frequency of use
- Longest period of sobriety
- Review of other substances
- Negative consequences

Substance Use History (Figure 10.3)

A substance use history provides a comprehensive look at substance use to date. The data will inform the diagnosis, determine disease severity, and inform treatment planning. In addition to opioids, patients should be asked about alcohol, tobacco, marijuana, methadone, methamphetamine, PCP, LSD, benzodiazepines, MDMA, cocaine, and newer designer drugs. The dates of use, frequency, and last use for each

of the substances used will be important to understanding use as well as direct treatment. Assessing the negative consequences of use must be done in order to diagnose OUD and questioning should obtain information regarding effects on physical and mental health, family relationships, employment, and legal issues.

Substance Use Treatment History

It is also useful, particularly when determining level of treatment, to understand what prior attempts at treatment the patient has sought in terms of location, type of treatment, length of time engaged, as well as reasons for relapse after treatment. Discussing this can facilitate an open discussion to assist the patient to reflect on what prior elements of treatment have been successful and what circumstances triggered relapse. Although the purpose is to gather formal treatment, patients may have tried medicines traditionally used for treatment of OUD in a controlled setting under different circumstances. This may provide further insight into whether such treatments would be appropriate for the patient currently.

Family History

While a comprehensive family history is warranted, particularly attention should be paid to history of hazardous substance use as well as SUD in immediate family members. Such discussions put into perspective biological risk factors, with having a parent with SUD being one of the strongest risk factors for developing SUDs (11).

Social History

The social history will provide perspective and provide further dimension to the patient's life and their substance misuse in the context of that life. Key features of the social history that are important to providing context for either initiation or continuation of substance misuse and the treatment of a SUD are the social determinants of health. A comprehensive social history should explore characteristics of social networks (12), family factors (13), housing stability (14), employment status, transportation, and criminal justice involvement, in order to obtain information to get a larger picture of the individual's health (Figure 10.4). While there is currently no evidence for standardized screening for the social determinants of health, there are tools available to complete screening for some or all of the social determinants of health (15-18).

Figure 10.4:
Social Determinants of Substance Use

- Social networks
- Family factors
- Housing stability
- Employment status
- Transportation
- Legal Issues

Physical Examination

The physical examination can be comprehensive or focused based on the historical information obtained. Remembering the medical complications of OUD, historical information may not always elucidate whether medical complications have occurred and therefore a physical examination can identify possible effects of long-term opioid use. Depending upon the route of administration, the sites should be closely inspected. For example, if a patient uses opioids intranasally, examination of the nasal mucosa is important. Additionally, if a patient uses opioids intravenously, the sites of administration should be assessed to monitor for blood vessel sclerosis (often referred to as "track marks"), edema due to blood vessel damage, or signs of

infection. In addition to evaluating for possible complications of OUD, the physical examination can particularly identify signs of opioid intoxication or opioid withdrawal. Opioid intoxication can include findings such as:

- Drowsiness
- Irritability
- "Nodding off"
- Constricted pupils
- Slurred speech
- Memory impairment
- Poor focus or concentration
- Euphoria (19)

The physical examination can also assist in assessing withdrawal (Figure 10.5).

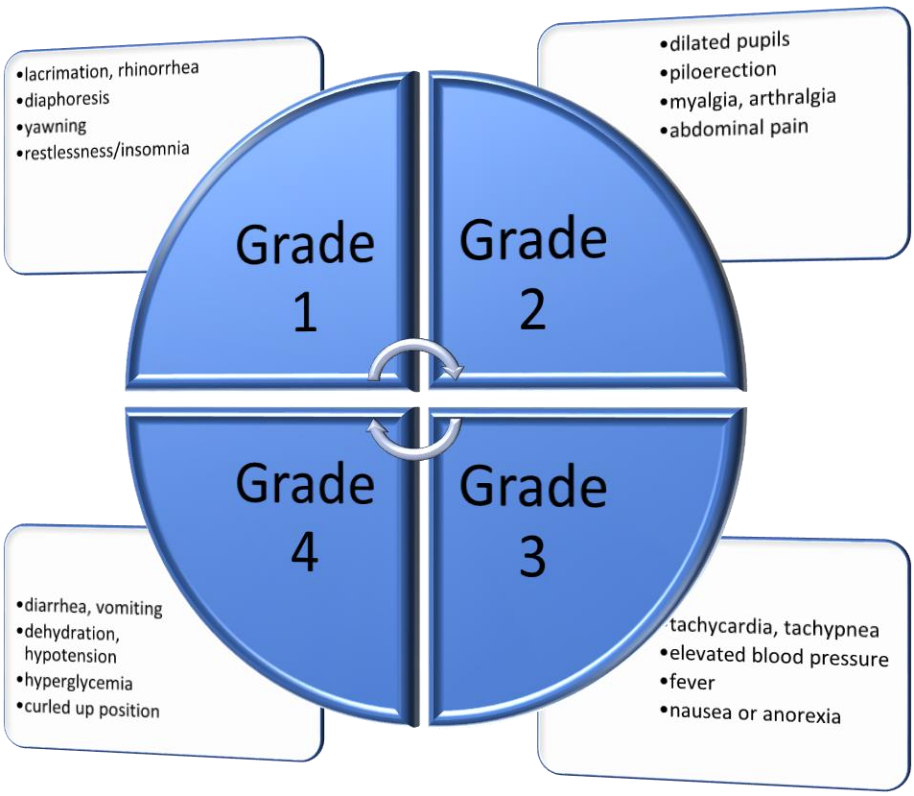


Figure 10.5 Physical Findings Associated with Withdrawal from Opioids

Kosten TR, O'Connor, PG. Management of drug and alcohol withdrawal. N Engl J Med 2003; 348:1786–1795.

Structured assessments of opioid withdrawal can be performed that enable standardized documentation of withdrawal symptoms. (https://www.drugabuse.gov/sites/default/files/files/ClinicalOpiateWithdrawalScale.pdf)

Appropriate testing/tools

There are no required or formal tests that should be included as part of every comprehensive assessment; however, the evaluation can certainly suggest certain testing that may be warranted. For example, for individuals who inject drugs or who may associate sex with drug use, testing for HIV, hepatitis, and sexually transmitted infections would be important. Additionally, pregnancy testing is important for women. Testing should be directed towards potential medical complications based on risk factors as well as in keeping with evidence-based guidelines for screening.

Drug testing (e.g., urine drug screen) is a common test performed as an adjunctive tool for pain management and may also be useful in consideration for a comprehensive drug assessment. Drug testing can either be performed on urine specimens or on oral fluid. Point of care testing is available to have results available immediately for discussion with the patient; however, clinicians must be knowledgeable about drug level cut-off values for a specific point of care testing tool. Additionally, certain prescription or over-the-counter medications may cross-react to provide a positive result for a specific substance on the test. Both false positives as well as false negatives are possible (20). Testing for cocaine, benzodiazepines, and amphetamines should be considered as part of any drug testing tool as these substances can affect treatment if pharmacotherapy is being utilized to treat OUD.

While traditionally reserved for use when prescribing a scheduled substance, the prescription drug monitoring program (PDMP) can be reviewed as part of the comprehensive assessment. PDMPs can be helpful in managing risks of controlled-substance medications being prescribed (21), as well as review prescription drug use over time.

Conclusions

A thorough assessment with particular attention to unique aspects of OUD is critical for patients who screen positive for opioid misuse or for whom there is potential concern for opioid misuse. This assessment enables the clinician to determine the presence of OUD versus tolerance and/or dependence. This evaluation must be performed in a sensitive manner with attention to cultural proficiency, understanding that patients may have different levels of comfort in sharing information related to their substance use. A patient-centered, nonjudgmental approach ensures that information is provided in a safe environment where security and privacy is critical. Once a thorough assessment sheds light onto OUD, clinicians can then bridge the conversation to discuss treatment options for patients.

References

1. National Institute on Drug Abuse. Definition of Tolerance. 2007. Accessed October 20, 2017. Available at: https://www.drugabuse.gov/publications/teaching-packets/neurobiology-drug-addiction/section-iii-action-heroin-morphine/6-definition-tolerance.

2. National Institute on Drug Abuse. Definition of Dependence. 2007. Accessed October 20, 2017. Available at: https://www.drugabuse.gov/publications/teaching-packets/neurobiology-drug-addiction/section-iii-action-heroin-morphine/8-definition-dependence.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). 2013. Arlington, VA: American Psychiatric Publishing.
4. Rollnick S, Miller WR, Butler C. Motivational Interviewing in Health Care: Helping Patients Change Behavior. New York, NY: Guilford Press; 2008:6–7.
5. Saitz R. Medical and surgical complications of addiction. In R. K. Ries, D. A. Fiellin, S. C. Miller, & R. Saitz (Eds.), The ASAM principles of addiction medicine (5th ed.). 2014. Philadelphia, PA: Wolters Kluwer.
6. Compton WM III, Cottler LB, Ben Abdallah A, Phelps DL, Spitznagel EL, Horton JC. Substance dependence and other psychiatric disorders among drug dependent subjects: race and gender correlates. Am J Addict. 2000;9(2):113–125.
7. Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry. 2007;64(5):566–576.
8. Reynolds M, Mezey G, Chapman M, Wheeler M, Drummond C, Baldacchino A. Co-morbid post-traumatic stress disorder in a substance misusing clinical population. Drug Alcohol Depend. 2005;77(3):251–258.
9. Stuart GL, O'Farrell TJ, Temple JR. Review of the association between treatment for substance misuse and reductions in intimate partner violence. Subst Use Misuse. 2009;44(9–10):1298–1317.
10. George S, Boulay S, Galvani S. Domestic abuse among women who misuse psychoactive substances: an overview for the clinician. Addict Disord Their Treat. 2011;10(2):43–49.
11. Stone, A. L., Becker, L. G., Huber, A. M., & Catalano, R. F. (2012). Review of risk and protective factors of substance use and problem use in emerging adulthood. Addictive Behaviors, 37(7), 747–775.
12. Neaigus A, Miller M, Friedman SR, et al. Potential risk factors for the transition to injecting among non-injecting heroin users: a comparison of former injectors and never injectors. Addiction. 2001;96:847–60.
13. Boyd CJ, Mieczkowski T. Drug use, health, family and social support in "crack" users. Addict Behav 1990;15:481-5.
14. Roy E, Haley N, Leclerc P, et al. Drug injection among street youths in Montreal: predictors of initiation. J Urban Health. 2003;80:92–105.
15. National Association of Community Health Centers. PRAPARE. 2016 Accessed Oct 21, 2017. Available at http://www.nachc.org/research-and-data/prapare/.
16. Pratt R, Hibberd C, Cameron IM, Maxwell M. The Patient Centered Assessment Method (PCAM): Integrating the social dimensions of health into primary care. Journal of Comorbidity. 2015;5:110-19.
17. Maxwell M, Hibberd C, Pratt R, Cameron I, Mercer S. Development and Initial Validation of the Minnesota Edinburgh Complexity Assessment Method (MECAM) for use within the Keep Well Health Check. 2011 Accessed October 21, 2017. Available at: http://nebula.wsimg.com/21bdd4a520ae2472bf35d8438a0f0255?AccessKeyId=0E6A7D755E08F1044736&disposition=0&alloworigin=1.

18. Byrne T, Fargo JD, Montgomery AE, Roberts CB, Culhane DP, Kane V. Screening for Homelessness in the Veterans Health Administration: Monitoring Housing Stability through Repeat Screening. Public Health Rep. 2015;130(6):684-692.
19. Fareed A, Stout S, Casarella J, Vayalapalli, Cox J, Drexler K. Illicit Opioid Intoxication: Diagnosis and Treatment. Subst Abuse. 2011;5:17-25.
20. Standridge JB, Adams SM, Zotos AP. Urine drug screening: A valuable office procedure. Am Family Physician.2010;81(5):635–640.
21. Ali, MM, Dowd N, Classen T, Mutter R, Scott P. Prescription drugs monitoring program, nonmedical use of prescription drug and heroin use: Evidence from the National Survey of Drug Use and Health. Addictive Behaviors, 2017;69: 65–77.

11. Treating Opioid Use Disorder, Managing a Chronic Disease

Patient-Centered, Family-Centered, and Trauma-Informed Care

Those struggling with OUD remain stigmatized by society and the medical profession is no exception. Terminology such as "drug seeker" or "frequent flyer" are useless and perpetuate the stigma and challenges that keep clinicians from seeing the person behind the symptoms and the circumstances that have led to their SUD. The treatment of OUD in the United States historically demonstrated a lack of acceptance of a chronic disease model with institutional treatments, exotic and sometime lethal withdrawal procedures, prison-based treatments, and experiments with aversive conditioning (1). Thankfully, treatment options have come a long way. However, the acknowledgement of OUD as a chronic disease has only recently begun to grow.

Figure 11.1**: SAMSHA Guiding Principles of Recovery**

- Recovery emerges from hope.
- Recovery is person driven.
- Recovery occurs via many pathways.
- Recovery is holistic.
- Recovery is supported by peers and allies.
- Recovery is supported through relationships and social networks.
- Recovery is culturally based and influenced.
- Recovery is supported by addressing trauma.
- Recovery involves individual, family, and community strengths and responsibilities.
- Recovery is based on respect.

Center for Substance Abuse Treatment. (2007). National Summit on Recovery: Conference report. DHHS Publication No. (SMA) 07–4276. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Treatment for OUD must include a recovery-oriented model of care (Figure 11.1). While there has been debate over time about what is meant by recovery, recovery is a process that is characterized by sobriety, personal health, and citizenship (2). It must be patient-centered and therefore focus on problems of immediate concern to the patient, thereby increasing recovery potential to maintain sobriety and improve overall physical and mental health. Such treatment requires that professionals meet people where they are at and embrace options of treatment ranging from harm reduction to fully integrated treatment services. Given that recovery does not occur without connection with support services, including family members for social support is important. Involving intimate partners is important to aiding in recovery (3), as the greater the number of individuals in the patient's social network that are still actively using, the less likely an individual is to be successful with recovery (4). It is important to understand that family members, particularly those who does not use drugs, may be reluctant to participate given the history of negative experiences that the family member may have had as a result of the OUD.

As previously noted, individuals with OUD may have also experienced adverse childhood experiences, particularly in the form of neglect and/or trauma and notably during their time using may also have been victims or witness to trauma. Trauma-informed care (5) is critical to recovery-oriented care as untreated trauma-related disorders increase recidivism rates (6) and worsening pain in those with chronic pain (7).

Treatment Planning

With regard to treatment and care, patients with OUD have many decisions to make. Often within a small window of time when seeking help, individuals are confronted with decisions about where and how to access treatment, what treatment forms they are interested in receiving, and what circumstances are best for them at the time. These are difficult decisions and often come with intense angst and difficulty. Information must be offered sensitively and shared decision making is best to ensure that the treatment course is amenable to the patient (Figure 11.2).

Figure 11.2 SAMSHA Shared Decision-Making Tool for Initiation of Medication Assisted Treatment for OUD

http://media.samhsa.gov/MAT-Decisions-in-Recovery/

It is also important to note that individuals will be at different stages of change with regard to their willingness to seek formal treatment for OUD, whatever that might look like. It is therefore important to be aware of the different treatment options that are available for individuals at different stages of change. Recovery is a bridge to be crossed with support regardless of where the individual may fall, and interventions are critical at each access point along the bridge (Figure 11.3).

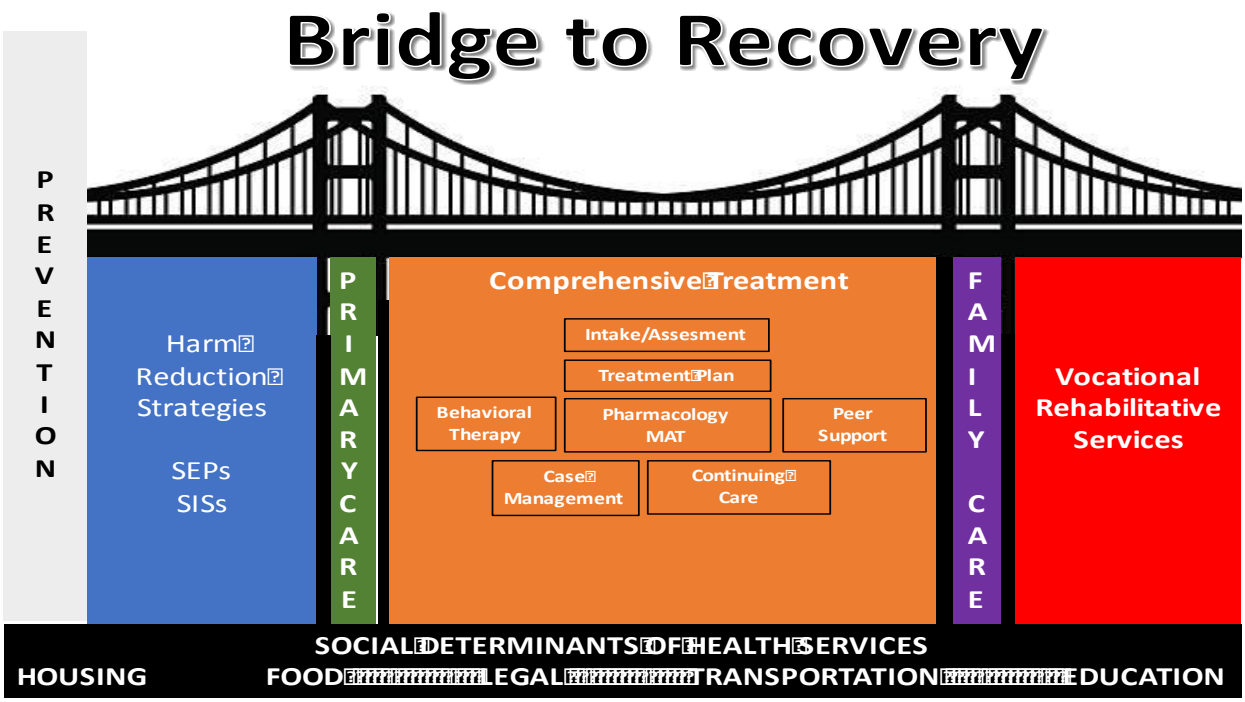


Figure 11.3 Bridge to Recovery with Social Determinants as the Foundation and Treatment Options at Steps along the Path

Harm Reduction Strategies

Overdose Education and Naloxone Distribution (OEND)

Given the public health impact, every patient who misuses opioids or has OUD should receive overdose education and a prescription for naloxone (Figure 11.4) (8). While physicians are able to write a prescription for naloxone, in October of 2015, Dr. Rachel Levine, Physician General of Pennsylvania, wrote a standing order for naloxone to ensure that the residents of Commonwealth are able to obtain the medication for combatting overdose and overdose-related deaths. Naloxone, as a pure opioid antagonist, reverses opioid-related sedation and respiratory depression without psychoactive or abuse potential. It can be administered intravenously, intramuscularly, subcutaneously, and intranasally; however, current formations available for public use in overdose education and naloxone distribution (OEND) programs are administered intramuscular and intranasal.

Figure 11.4 Pennsylvania Department of Health Naloxone Provider's Guide

http://www.ddap.pa.gov/Document Library/Naloxone for Opioid Safety-A Provider%27s Guide to Prescribing Naloxone to Patients Who Use Opioids.pdf

The rationale behind OEND programs is facilitated by the fact that most opioid use does not occur alone and therefore, a bystander can administer naloxone, which takes approximately 2-8 minutes to work. It lasts approximately 30-90 minutes. Sedation and overdose symptoms may return and the individual may need additional administrations; however, the initial use can create time to transport a patient to a health care setting. Introduction of programs into community settings has been demonstrated to be feasible (9-11), as well as to increase knowledge and skills regarding overdose prevention and naloxone administration (12-13). Perhaps most notable, however, is that OEND programs have been demonstrated to reduce overdose in communities (14-15) while not increasing opioid use and actually increasing individuals seeking treatment (16).

Syringe Exchange Programs (SEPs)

Despite proven efficacy, Pennsylvania law prohibits SEPs; however, some local areas have "underground" SEPs that operate with understanding from law enforcement that their services will not be criminalized.

Syringe exchange programs (SEPs), sometimes referred to as needle exchange programs (NEPs) or needle and syringe programs (NSPs), provide access to free sterile syringes and other injection equipment, safe disposal of used syringes, and syringe exchange. Programs were originally developed in Amsterdam in 1983 to address the spread of hepatitis B from contaminated needles, incidentally, just one year before HIV was identified as the virus that caused AIDS (17). The short-term goal of the program is harm reduction to reduce the risk of transmission of blood-borne pathogens including HIV and Hepatitis B and C. The long-term goal of SEPs is to guide individuals through a recovery program with hope of life-long abstinence.

The benefits of SEPs have been demonstrated and include:

- Reduction in transmission of HIV, HBV, and HCV (18, 19)
- Engage persons who inject drugs (PWID) with health care services
- Engage PWID with treatment programs who otherwise might not have sought care
- Cost effectiveness
- Do not increase drug use
- Do not increase crime rates (20)

Supervised Injection Sites (SISs)

A supervised injection site (SIS), also called supervised injection facilities (SIFs), safer injection sites, drug consumption rooms, or supervised injection centers, are controlled health care settings directed at PWID. Under the supervision of trained medical staff, PWID are provided with a safe setting where they can inject pre-obtained drugs in a hygienic environment including provision of sterile needles, learning appropriate technique, and have access to someone who can

immediately administer care if an overdose death should occur. With the primary objectives to reduce drug overdose deaths, soft tissue infections, transmission of blood-borne pathogens, and public injection drug use, SISs also provide additional services including counseling and referrals to health and social services including SUD treatment.

One of the earliest models of a SIS in North America was InSite in Vancouver, Canada, which has produced significant research regarding the benefits as well as avoidance of many of the potential negative consequences of SIS implementation (Figure 11.5).

Benefits	Avoidance of Negative Effects
• Reduction in overdose mortality[21] • Reduction in needle sharing[22] • Improved entry into care[23] • Increased detoxification services[24] • Reduced public disposal of syringes[25] • Reduced new cases of HIV/HCV[26] • No fatal overdoses at InSite[27]	• No increase in community drug use[25] • No increase in crime or public disorder[25] • No increase in drug trafficking or assaults/robbery[28] • Did not promote drug use[29]

Figure 11.5 Research from Vancouver's InSite Model

Determining Treatment Settings

For individuals that are committed to seeking help for their OUD, determining the appropriate setting and where to send individuals is often one of the most frustrating questions for a clinician. Many factors including current intoxication or withdrawal state, medical and behavioral health conditions and complications, readiness to change, relapse history, and current social circumstances are all incredibly important factors that determine an appropriate level of care. Services exist on a continuum including outpatient services, intensive outpatient/partial hospitalization services, residential/inpatient services, and medically managed intensive inpatient services with different variations in between each structure that address patient needs, obstacles, assets, resources, and strengths.

American Society of Addiction Medicine's (ASAM) Criteria is an outcome oriented and results-based criteria to determine the most ideal treatment setting for patients based on comorbidities and risk factors.

https://www.asam.org/resources/the-asam-criteria

Pharmacologic Treatment of OUD

The current pharmacologic agents available for the treatment of OUD are methadone, buprenorphine, and naltrexone. A decision to pursue medication assisted treatment (MAT) for patients struggling with OUD must, as noted above, occur in conjunction with a patient-informed decision to pursue this course. This should include a clear understanding of the expectations

regarding the indications for pharmacologic treatment, the potential side effects, the goals of the patient, the requirements for participating in a MAT program, and their needs based on their comprehensive assessment. However, no current evidence clearly demonstrates which pharmacologic treatment will work for a specific patient with OUD and therefore, there is not often a best practice answer for a particular patient.

One of the decisions, particularly when initiating methadone or buprenorphine, is the length of time that an individual expects to be taking the medication. These medications can be provided for maintenance therapy or for medically supervised withdrawal. Studies have demonstrated that maintenance therapy is more effective than medically supervised withdrawal (30-31), and therefore discussion regarding options of treatment should address potential biases surrounding maintenance therapy (Figure 11.6).

- Maintenance therapy just substitutes one drug for another
- People on maintenance therapy are not truly in recovery
- There are time limits to being on maintenance therapy
- The tolerance and dependence that develops with maintenance medication is the same as having an OUD

Figure 11.6 Myths About Maintenance Therapy

Methadone

With nearly 50 years of experience as a treatment for OUD, methadone has been the longest running pharmacologic treatment (32). As such, evidence strongly demonstrates the efficacy of methadone with increased treatment retention and reductions in illicit opioid use, mortality, criminal behavior, and seroconversion of HIV (32-35). While methadone can be prescribed for the treatment of pain in pill formulation, methadone for the treatment of OUD can only be prescribed in the setting of outpatient treatment programs (OTP). These programs are often freestanding sites, certified by SAMSHA's Division of Pharmacologic Therapies, part of SAMHSA's Center for Substance Abuse Treatment (CSAT) which provides medication-assisted treatment (MAT), as well as counseling and behavioral health services. The formulations of methadone provided at OTPs include liquid concentrate, powder that is dissolved in water, or diskettes that are dissolved in water.

Most clinicians will not be in a position to utilize methadone for the treatment of OUD; however, it is critical for clinicians to understand principles of methadone maintenance therapy to provide care for patients who are taking methadone through an OTP (Figure 11.7). Most patients will present to their OTP daily for medication administration as well as assessment and UDS testing. Some patients, based on circumstances, may be given a take home dose. Both behavioral health and social services are often linked with OTPs to provide patients with needed care. Methadone treatment is always started at a low dose and titrated up to effect; however, methadone has no ceiling effect. Clinicians should be aware of risks of associated QT prolongation, respiratory depression, and significant risks of concurrent benzodiazepine and alcohol use. Therefore, clinicians should be cognizant of drug-drug interactions as well as consider monitoring QT intervals in settings where the patient may be on multiple medications with risks of QT prolongation.

Figure 11.7**: OTP Admission Criteria for Methadone**

Adults

- Meets the diagnosis of OUD
- History of OUD for at least 1 year
    - Unless:
        - Pregnant
        - Former patients up to 2 years since discharge
        - Within 6 months release from incarceration
- Providing voluntary informed consent

Adolescents

- Meets diagnosis of OUD
- 2 documented unsuccessful medically supervised withdrawals or treatments without OUD medications in a 12-month period
- Parental informed consent
- Pediatric assent

Furthermore, clinicians must be aware of potential side effects of methadone including:

- Constipation
- Nausea
- Sweating
- Decreased libido or sexual dysfunction
- Drowsiness
- Amenorrhea
- Weight gain
- Edema

A question that commonly arises regarding patients using methadone for maintenance therapy is how best to address acute pain. There are four common misperceptions regarding acute pain for a patient on maintenance therapy: the maintenance therapy simply provides adequate analgesia; utilizing opioid analgesia results in relapse; using opioid analgesics causes respiratory and CNS depression; and reporting pain is a covert mechanism to simply obtain opioid medications (36). In this setting, non-opioid analgesics should be utilized aggressively. However, for moderate to severe, acute pain, opioids may be used and this should be done in conjunction with the patient's OTP program. Furthermore, selection of medications should be appropriate, as utilizing a mixed agonist/antagonist opioid analgesic can result in significant withdrawal symptoms for a patient. Methadone received through an OTP is not registered through the PDMP and therefore clinicians must be certain to obtain a comprehensive, detailed history, particularly in the setting of pain.

Decisions regarding pain management for a patient engaged with an OTP program should not be made unilaterally, nor should a clinician feel it is simply appropriate to prescribe an opioid or other controlled substance to a patient currently engaged in an OTP program.

Buprenorphine

Prior to 2000, OTP were the only setting where pharmacologic treatment for OUD could be provided; however, the Drug Addiction Treatment Act of 2000 (DATA 2000) enabled qualified physicians who obtained a waiver to prescribe or dispense approved Schedule III, IV, or V medications for the treatment of OUD (Figure 11.7) (37). This transitioned the opportunity for care to be transferred from OTP to office based opioid treatment (OBOT).

- Be licensed to practice in the state in which the prescriber will be working
- Have an active Drug Enforcement Agency (DEA) registration to prescribe Schedule III, IV, or V medications
- Have completed an 8-hour training course in the treatment and management of patients who have opioid use disorder (available in live or online/web formats)
- Supply documentation of successful completion of required training to SAMSHA

Figure 11.7 Criteria for Clinicians to Obtain DATA 2000 Waiver to Provide OBOT

For clinicians interested in obtaining a DATA 2000 Waiver to provide OBOT, online training courses are available at:

https://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-

OBOT is mainly provided through use of buprenorphine. Buprenorphine's efficacy in reducing illicit opioid use, HIV risk behavior, and overdose deaths, along with its efficacy within primary care settings has been clearly demonstrated (32, 38-40), which has led to buprenorphine being listed on the World Health Organization (WHO) list of essential medicines (41). Clinicians who obtain their waiver to provide buprenorphine through an OBOT program initially are able to provide care for up to 30 patients. After a period of a year, each clinician can apply

for an increase in their waiver ultimately to a maximum of 200 patients over a period of time. Available buprenorphine formulations include sublingual tablets, sublingual films, and a subdermal implant. While the length of time for maintenance treatment with buprenorphine is indeterminate, the implant for OUD maintenance therapy is only approved for up to 12 months for patients who have sustained clinical stability, taking a maximum dose of 8 mg of buprenorphine daily. The implant includes 4 rods that are in place for 6 months and can be replaced once for an additional 6 months.

Buprenorphine is a partial opioid receptor agonist and often is prescribed in the combination formulation with naloxone. Dissimilar from methadone, buprenorphine has a ceiling effect and also can be dosed safely such that persons who receive buprenorphine through OTP programs need not attend programs daily. Generally, a maximum dose of 24 mg per day is recommended. Patients presenting to a buprenorphine program typically have the option of office-based induction or home induction, which has been shown to be as effective in retaining individuals in treatment (42). As most formulations of buprenorphine are prescribed as a combination with naloxone, it is important at induction for the individual to have signs and symptoms of withdrawal or else the medication will actually precipitate withdrawal in the patient. Withdrawal symptoms can be treated symptomatically to maintain continued use of the medication and such symptoms must be differentiated from an allergic reaction to buprenorphine (Figure 11.8).

SAMSHA Clinical Guidelines for the Use of Buprenorphine https://store.samhsa.gov/shin/content/SMA05-4003/SMA05-

Symptoms	Medication(s)
Nausea	Ondansetron, metoclopramide
Diarrhea	Loperamide
Anxiety, irritability	Clonidine
Insomnia	Hydroxyzine, trazodone
Pain	NSAIDs

Figure 11.8 Medications to Address Associated Symptoms of Withdrawal

Buprenorphine has been utilized and studied extensively as an alternative option to treatment of OUD in pregnant patients. The formulation used in pregnant patients is buprenorphine alone given lack of proven safety of naloxone in pregnant patients. While methadone has been utilized for a longer period of time with significantly more research to support its use, buprenorphine has not simply been shown to be effective but also infants born to mothers using buprenorphine require lesser doses of morphine in the NICU, have significantly shorter hospital stays, and significantly shorter durations of neonatal abstinence syndrome (NAS) (43).

As with methadone, clinicians must be aware of the potential risks as well as potential side effects of buprenorphine. Particularly for patients on highly active anti-retroviral therapy (HAART) for HIV, there are several medication interactions that must be considered for patients on buprenorphine. Patients taking methadone can be converted from methadone to buprenorphine; however, their methadone dose should be weaned to 30-40 mg daily and they should be stable on this dose for approximately 1 week

before any conversation takes place. As with methadone, issues related to acute and chronic pain will arise with individuals taking buprenorphine. Decisions regarding initiating pain medication for these patients should be coordinated with the patient's OBOT program or OTP.

Naltrexone

Despite the opioid antagonist naltrexone being synthesized in the 1960s, only in 2010 did the Food and Drug Administration (FDA) approve the injectable, extended release naltrexone (XR-NXT) for use after medically supervised opioid withdrawal to prevent relapse to opioid use. While an oral form was approved previously, it is not widely used due to high rates of nonadherence and limited efficacy (44-45). Naltrexone can be prescribed by any clinician and does not require a waiver and need not be prescribed in an OTP; however, the FDA does require Risk Evaluation and Mitigation Strategies (REMS) (http://wwww.vivitrolrems.com), which includes information on appropriate administration techniques. Clinicians, whether prescribing XR-NXT or not, should be knowledgeable about XR-NXT including initiation protocols.

In the assessment, patients should be clearly evaluated for absence of signs and symptoms of opioid withdrawal. If this can be confirmed with a clinical evaluation, the patient will be appropriate for initiation; however, if there is any potential concern, a naloxone challenge can be administered either subcutaneously or intravenously. Naloxone challenges should be performed by experienced clinicians who are able to manage the potential signs and symptoms of withdrawal that may be precipitated as part of the process. Furthermore, clinicians should be aware of potential side effects of XR-NXT which include:

- Headache
- Dizziness
- Nausea
- Diarrhea
- Fatigue
- Back pain

XR-NXT is administered every 4 weeks as a 380 mg IM gluteal injection. As with other pharmacologic agents for the treatment of OUD, there is no criteria by which it can be predicted which individuals will do better with treatment with XR-NXT. However, patients who might be appropriate candidates include those with resistance to opioid receptor agonists, those recently released from controlled environments, those who have not responded well to opioid receptor agonist therapy, and those who are highly motivated.

Counseling & Aftercare Services

Finding a 12-Step Meeting
https://www.addiction.com/meetingfinder/

Patients with OUD benefit from comprehensive treatment services that include both formal counseling and case management. The counseling component aids individuals to address challenges and barriers encountered during the recovery process. The counseling process can assist in addressing coexisting mental health disorders as well as address previous trauma as part of the trauma-informed care approach. Patients on pharmacologic therapy for OUD are also strongly encouraged to participate in formal counseling. Despite research suggesting that there is no difference in outcome between patients who received adjunctive counseling and those who did not (46), the programs in the study were much more formalized than most, including some on-site counseling experience, as well as including patients considered lower risk. Therefore, adjunctive counseling is strongly encouraged for patients using pharmacologic treatment for OUD. In addition, services are available for patients through 12-Step programs through Narcotics Anonymous or Alcoholics Anonymous for patients to find a supportive community. It should be noted that many 12-Step programs are abstinence-based and therefore patients on maintenance therapy may find themselves in an environment not supportive of their current treatment plan.

Conclusions

Treatment for OUD includes a comprehensive approach that must be patient-centered, meeting people where they are at on the stages of change. Clinicians must be aware of the significant social and medical stigma that continues to exist surrounding SUDs. Being aware of the stigma and creating a safe and nonjudgmental environment within the clinical setting is critical to successful treatment of patients struggling with any SUD. The comprehensive assessment for OUD can uproot many previous traumas as well as information that often leads to individuals having elevated ACE scores. Successful treatment must address this previous trauma in the form of trauma-informed care. Counseling and aftercare services will not simply address the OUD but will also address these components that have contributed to continued substance misuse. Additionally, public health strategies at harm reduction have proven to be successful in not simply reducing complications, but also in engaging patients in care who otherwise may never have sought care. Part of the reason for this positive outcome is that these settings provide individuals with the safe and supportive environment needed to make the decision to seek recovery. Pharmacologic options are available for the treatment of OUD being provided in specialty care settings through OTP; however, OBOT integration into primary and behavioral health care settings can create a large impact on treating communities struggling with OUD. While not all clinicians will play as integral a role in this treatment process, all clinicians must have a working knowledge to guide patients on the path to recovery and ensure that the care they are providing does not veer them from this course.

References

1. White WL, Mojer-Torres L. Recovery-Oriented Methadone Maintenance. 2010 Accessed October 20, 2017. Available at: http://www.attcnetwork.org/userfiles/file/GreatLakes/5th%20Monograph_RM_Methadone.pdf.

2. Betty Ford Institute Consensus Panel. What is recovery? A working definition from the Betty Ford Institute. J Subst Abuse Treat 2007;33(3):221-8.
3. Tuten M, Jones HE. A partner's drug-using status impacts women's drug treatment outcome. Drug and Alcohol Dependence. 2003;70(3):327–330.
4. Trocchio S, Chassler D, Storbjörk J, Delucchi K, Witbrodt J, Lundgren L. The association between self-reported mental health status and alcohol and drug abstinence 5 years post-assessment for an addiction disorder in U.S. and Swedish samples. Journal of Addictive Diseases. 2013;32(2):180–193.
5. Substance Abuse and Mental Health Services Administration. Trauma-Informed Care in Behavioral Health Services. Treatment Improvement Protocol (TIP) Series 57. HHS Publication No. (SMA) 13-4801. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2014.
6. Kumar N, Stowe ZN, Han X, Mancino MJ. Impact of early childhood trauma on retention and phase advancement in an outpatient buprenorphine treatment program. American Journal on Addictions. 2016;25(7): 542–548.
7. Barry DT, Beitel M, Cutter CJ, et al. Exploring relations among traumatic, posttraumatic, and physical pain experiences in methadone-maintained patients. Journal of Pain. 2011;12(1):22–28.
8. U.S. Department of Health and Human Services. (2016). The opioid epidemic: By the numbers. Washington, DC: Author.
9. Piper TM, Stancliff S, Rudenstine S, et al. Evaluation of a naloxone distribution and administration program in New York City. Subst Use Misuse. 2008;43(7):858-70.
10. Doe-Simkins M, Walley AY, Epstein A, Moyer P. Saved by the Nose: Bystander-Administered Intranasal Naloxone Hydrochloride for Opioid Overdose. Am J Public Health. 2009;99(5):788-91.
11. Enteen L, Bauer J, McLean R, Wheeler E, Huriaux E, Kral AH, et al. Overdose prevention and naloxone prescription for opioid users in San Francisco. J Urban Health. 2010;87(6):931-41.
12. Tobin KE, Sherman SG, Beilenson P, Welsh C, Latkin CA. Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives. Int J Drug Policy. 2009;20(2):131-6.
13. Wagner KD, Valente TW, Casanova M, et al. Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los Angeles, CA. Int J Drug Policy. 2010;21(3):186-93.
14. Maxwell S, Bigg D, Stanczykiewicz K, Carlber-Racich S. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. J Addict Dis. 2006;25(3):89-96.
15. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ 2013;346:f174.
16. Seal KH, Thawley R, Gee L, et al. Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study. J Urban Health. 2005;82(2):303-11.
17. Vlahov D, Des Jarlais D, Goosby E. Needle exchange programs for the prevention of Human Immunodeficiency Virus Infection: Epidemiology and Policy. Am J of Epidem 2001;154(12):S70-6.
18. Gibson D, Flynn NM, Perales D. Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users. AIDS 2001;15:1329-41.

19. Wodak A, Cooney A. Do Needle Syringe Programs Reduce HIV Infection Among Injecting Drug Users: A Comprehensive Review of the International Evidence. Substance Use & Misuse 2006;41:777-813.
20. Wodak A, Cooney A. Effectiveness of sterile needle and syringe programmes. Int J Drug Policy 2005;16S:S31-44.
21. Marshall BDL, Milloy M-J, Wood E, Montaner JSG, Kerr T. Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: a retrospective population-based study. Lancet 2011; 6736(10):62353-7.
22. Dooling K, Rachlis M. Vancouver's supervised injection facility challenges Canada's drug laws. CMAJ 2010;182(13):1440-4.
23. DeBeck K, Kerr T, Bird L, et al. Injection drug use cessation and use of North America's first medically supervised safer injecting facility. Drug and Alcohol Depend 2011;113(2-3):172-6.
24. Wood E, Tyndall MW, Zhang R, Montaner JSG, Kerr T. Rate of detoxification service use and its impact among a cohort of supervised injecting facility users. Addiction 2007;102:916-19.
25. Kerr T, Stoltz J, Tyndall M, et al. Impact of a medically supervised safer injection facility on community drug use patterns: a before and after study. BMJ 2006;332:220-22.
26. Tyndall MW, Wood E, Zhang R, Lai C, Montaner JSG, Kerr T. HIV seroprevalence among participants at a medically supervised injection facility in Vancouver, Canada: Implications for prevention, care and treatment. Harm Reduction Journal 2006;3:36.
27. Milloy M-J S, Kerr T, Tyndall M, Montaner JSG, Wood E. Estimated Drug Overdose Deaths Averted by North America's First Medically-Supervised Safer Injection Facility. PLoS ONE3(10):e3351. https://doi.org/10.1371/journal.pone.0003351.
28. Wood E, Tyndall MW, Lai C, Montaner JSG, Kerr T. Impact of a medically supervised safer injecting facility on drug dealing and other drug-related crime. Substance Abuse Treatment, Prevention, and Policy 2006;1:13.
29. Kerr T, Tyndall MW, Zhang R, Lai C, Montaner JSG, Wood E. Circumstances of First Injection Among Illicit Drug Users Accessing a Medically Supervised Safer Injection Facility. Am J Public Health 2007;97(7):1228-30.
30. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: A 2-phase randomized controlled trial. Archives of General Psychiatry 2011;68(12):1238–1246.
31. Sees KL, Delucchi KL, Masson C. et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: A randomized controlled trial. JAMA 2000;283(10):1303–1310.
32. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database of Systematic Reviews, 2009; 3:1–19. doi:10.1002/14651858.CD002209.pub2.
33. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: Risk factors and lives saved. Drug and Alcohol Dependence 2009;105(1–2):9–15.
34. Metzger DS, Woody GE, McLellan AT, et al. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: An 18-month prospective follow-up. Journal of Acquired Immune Deficiency Syndromes 1993;6(9):1049–1056.
35. Ball JC, Ross A. The effectiveness of methadone maintenance treatment. 1991. New York, NY. Springer Verlag.

36. Alford DP, Compton P, Samet JH. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. Ann Intern Med 2007;144(2):127-34.
37. Substance Abuse and Mental Health Services Administration. Drug Addiction Treatment Act of 2000. http://burprenorphine.samsha.gov/data.html. Accessed October 28, 2017.
38. Fiellin DA, Moore BA, Sullivan LE, et al. Long-term treatment with buprenorphine/naloxone in primary care: Results at 2–5 years. American Journal on Addictions 2008;17(2):116–120.
39. Edelman EJ, Chantara T, Caffrey S, et al. The impact of buprenorphine/naloxone treatment on HIV risk behaviors among HIV-infected, opioid-dependent patients. Drug and Alcohol Dependence 2014;139:79–85.
40. Degenhardt L, Randall D, Hall W, et al. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: Risk factors and lives saved. Drug and Alcohol Dependence 2009;105(1–2):9–15.
41. Herget G. Methadone and buprenorphine added to the WHO list of essential medicines. HIV/AIDS Policy and Law Review 2005;10(3):23–24.
42. Lee JD, Vocci F, Fiellin DA. Unobserved "home" induction onto buprenorphine. Journal of Addiction Medicine 2014;8(5):299–308.
43. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure. N Eng J Med 2010;363:2320-31.
44. Sullivan MA, Garawi F, Bisaga A, et al. Management of relapse in naltrexone maintenance for heroin dependence. Drug and Alcohol Dependence 2007;91(2–3):289–292.
45. Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction in opioid treatment programs. Treatment Improvement Protocol (TIP) Series 43. 2005. DHHS Publication No. (SMA) 06-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration.
46. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: A 2-phase randomized controlled trial. Archives of General Psychiatry 2011;68(12):1238–1246.

12. Treating Pain in the Setting of Substance Use Disorder

Introduction

In 2010, 1 in 20 persons aged 15 to 64 used an illicit substance at least once per year, 1 in 40 used illicit drugs on a more regular basis (at least once per month), and 1 in 160 used illicit drugs in a manner that put their health at risk (1). As initiatives to increase access to medication assisted therapy (MAT) for patients with substance use disorder (SUD) succeed, providers will more frequently be required to manage acute and chronic medical conditions for patients on MAT (2). Whether acute or chronic, painful conditions are common in patients with SUD and are commonly inadequately managed for various reasons. While one should never assume a patient is feigning a painful condition to obtain opioids, there are numerous red flags that are associated with misuse and abuse (See Figure 12.1). Mindfulness to red flags and utilization of screening tools may assist in the diagnosis of SUD.

Red Flags for Misuse or Abuse of Opioids
Obtaining medications from multiple prescribers (“doctor shopping” or “multisourcing”) especially for controlled medications or medication within the same drug class
Prescription combinations containing multiple sedating medications
Filling medications at numerous pharmacies or paying cash for medications
More concerned about obtaining opioids analgesics than the underlying problem (refusing diagnostic workup)
Unexplained need to escalate dose
Use of street names for drugs (e.g.“oxys,” “percs,” or “xannies”)
Insistence on obtaining more euphorigenic opioids, high abuse combination (opioids plus benzodiazepine or muscle relaxant) or opioids that are easily amenable to abuse
History of drug abuse, SUD, or drug overdose
Reporting multiple medication allergies or sensitivities
Inappropriate administration of medications (e.g. crushing or chewing ER/LA medications, cutting patches)
Calling for refills after hours, late in day, or asking for medications to “get me through the next few days/weekend”
Early refills, lost or stolen medications
Disinterest in non-opioid therapies for pain control including physical therapy and NSAIDs
Functional decline in the face of increasing opioid use

Figure 12.2: Red Flags for Misuse or Abuse of Opioids (3-5)

Acute Pain

Patients with SUD are more likely than the general population to experience an acute painful condition, in particular acute traumatic events (6). However, having a history of a SUD, especially opioid use

disorder, increases the likelihood that the acute painful condition will be sub-optimally treated (7,8). Providers commonly bring their own emotions about opioid use disorder into the care of patients with acute painful conditions preventing adequate pain control. Providers fear being tricked into getting the patient "high," anchoring on "pain seeking behavior," or reference fear of making addiction worse as reasons to withhold adequate doses of opioid for pain control (9).

The treatment of acute pain should be a multimodal approach with both non-pharmacologic and non-opioid medications regardless of SUD status. Acetaminophen and NSAIDs should be first line pharmacological therapy in the treatment of acute pain since they confer low risk for addiction and have been shown to decrease total dose of opioid used in the treatment of severe acute pain (10). Only after failure of first line therapy should providers utilize opioids in the management of acute pain.

Patients dependent on opioids from either misuse or medical use present a unique management problem when attempting to treat acute pain. Effective management necessitates opioids to both maintain the basal requirement of opioid to keep the patient out of withdrawal, while also providing additional medication for analgesia. It may be difficult to estimate the basal opioid dose required to maintain opioid dependent patients out of withdrawal due to various factors including complicated opioid conversion scales and poor predictability of morphine equivalence of recreational opioids. Once the basal dose of opioid is met, additional analgesia is required to treat the painful condition (11, 12). Patients dependent on opioids may also display a tolerance to the analgesic effect of opioids and typically require higher doses for adequate pain control (13).

Chronic Pain

Non-pharmacologic treatments for chronic pain including heat or ice therapy, physical therapy, massage, transcutaneous electrical neurostimulation, osteopathic manipulative therapies, exercise, yoga, acupuncture, and other activities are effective in reducing pain and dysfunction due to musculoskeletal pain, migraine headache, fibromyalgia, and other conditions (See Section 2 for full description of non-opioid treatments for chronic pain). Psychological therapies are beneficial in increasing a patient's ability to cope with chronic painful conditions. Non-opioid medication including NSAIDs, local anesthetics, and steroids are effective therapies to manage chronic pain.

Opioids are not the first-line therapy for chronic pain and should not be routinely prescribed regardless of the presence of a SUD. Opioids should be prescribed for chronic pain in patients with a SUD only if there is a clear indication (e.g., chronic limb ischemia from peripheral arterial disease, cancer associated pain, postoperative period, other non-opioid therapies have failed, and the patient is actively in treatment for SUD and successfully in recovery.

Patients with a complaint of chronic pain deserve adequate and appropriate pain control and the complaint of pain should never be assumed to be a ploy to obtain opioids for misuse. However, a risk-benefit assessment should be made when initiating opioid therapy for chronic pain. Most who suffer from SUD are at higher risk for harm than stand to benefit from opioid therapy for chronic pain, especially with the lack of evidence for benefit of chronic opioids beyond 18 weeks for some conditions.

Patients with an active SUD are at high risk for complications and prescribers should consider not prescribing opioids for various reasons including:

- Inability to ration medications leading to withdrawal or overdose
- Combining opioid analgesics with other sedating substances triggering higher risk for overdose
- Misuse of medication in hazardous unintended routes such as crushing long-acting formulations or injecting triggering higher risk for overdose
- Risk to prescriber for contributing the morbidity or mortality if adverse event occurs
- Lack of evidence showing chronic opioids improve outcomes for chronic pain

Patients initiated on opioid therapy for chronic disease are less likely to abuse prescribed medications if they are actively involved in drug counseling, have a stable social network, and have not recently engaged in substance abuse (14). Patients with a SUD who misuse medications and are initiated on opioids for the treatment of chronic pain, are more likely to start misuse early on in therapy (14).

When opioid pain medications are utilized in patients with a SUD, optimizing therapy to prevent misuse is imperative in order to not exacerbate the disorder. Creating a controlled substance agreement and performing regular screens for drugs of abuse is recommended. Contracts should have clear stated goals, end points, and consequences for non-adherence. Patients receiving long-term opioid therapy should be instructed that frequenting emergency departments for pain control or filling prescriptions for controlled substances from other prescribers is strictly prohibited. Appropriate selection of an opioid is also important when determining most appropriate therapy. Providers should start opioid therapy with immediate release medications instead of high-dose extended-release or long-acting medications (15). Medications at highest risk for abuse, overdose and death should be avoided including ER/LA medications such as methadone, transdermal fentanyl, and oral extended-release formulations of oxycodone, hydrocodone, and morphine. While methadone is commonly prescribed for the treatment of chronic pain especially when due to cancer, it is one of the most common opioids discovered in decedents when cause of death is drug overdose, and ranks just behind heroin, fentanyl, and oxycodone (16-17). The data are inconclusive as to whether patients being treated for chronic pain with a concurrent SUD are at higher or lower risk for overdose when treated with methadone (18-20). The lowest dose necessary to achieve adequate pain control should be prescribed and escalation of dosing should be avoided.

Painful Condition During Medication-Assisted Therapy

Non–opioid medications are preferred for patients receiving medication-assisted therapies such as methadone or buprenorphine. Maximizing non-opioid and non-pharmacologic therapies are imperative when managing pain in the setting of methadone, buprenorphine, or naltrexone therapy.
Methadone, a full agonist long-acting opioid, has grown in popularity for the treatment of chronic pain especially when due to cancer, and particularly when the painful condition is neuropathic (21). Dividing the total daily dose may provide improved analgesic effect. Increasing the total methadone dose may also provide adequate pain control but should be done slowly, with caution, and in conjunction with an expert.

Buprenorphine is typically a once daily medication with a long half-life. With its unique high-affinity, partial opioid agonist effect, the risk of overdose is lowered but so is the efficacy for analgesia. Dividing the total daily dose temporarily (two to four times daily dosing) may provide extra analgesic effect, but additional medication is commonly required for the treatment of acute severe painful conditions.

There are two major options when opioids are required to treat acute pain in the setting of MAT. The first option is to continue buprenorphine maintenance therapy, and to add a short-acting opioid analgesic titrated to achieve therapeutic effect (12,22,23). The dose required to overcome buprenorphine opioid receptor binding is not easily predicted so titrating to effect is recommended. A second option is to discontinue buprenorphine therapy and start a full opioid agonist (e.g., intravenous morphine, fentanyl, or oral oxycodone) therapy to treat acute painful conditions (12,22,23). The duration of action for analgesia is typically shorter than duration of efficacy to suppress opioid withdrawal symptoms (13).

Patients receiving therapy for opioid use disorder or alcoholism are sometimes treated with naltrexone oral tablets or an extended-release depot injectable to prevent relapse. Naltrexone is an opioid antagonist similar to naloxone but with a higher oral efficacy and a longer duration of action. Acute painful conditions requiring opioid analgesics such trauma are difficult to manage in the setting of naltrexone therapy as naltrexone competitively inhibits the action of the opioids. It is recommended to optimize non-opioid strategies such as regional anesthesia, ketamine, and NSAIDs in this setting. Discontinue naltrexone if the patient is prescribed oral daily doses. Larger than usual doses of opioids would likely be required to achieve analgesia, but some have claimed increased sensitivity may also occur as long-term use of naltrexone upregulates the number of opioid receptors and may produces a temporary exaggerated response to opioid analgesics (24). If opioid analgesics are required, short-acting opioids sould be used and titrated to effect in a continuously monitored setting (25,26).

References

1. UNODC, World Drug Report 2012 (United Nations publication, Sales No. E.12.XI.1).

2. U. Sheu R, Lussier D, Rosenblum A, et al. Prevalence and characteristics of chronic pain in patients admitted to an outpatient drug and alcohol treatment program. Pain Med 2008;9(7):911–917.

3. American Academy of Family Physicians; American College of Emergency Physicians; American Medical Association; et al. Stakeholders' challenges and red flag warning signs related to prescribing and dispensing controlled substances [Internet]. Mount Prospect, IL: National Association of Boards of Pharmacy; 2015 Mar [cited 2017 Mar 31]. Available from: https://nabp.pharmacy/wp-content/uploads/2016/07/Red-Flags-Controlled-Substances-03-2015.pdf

4. Covington EC, Kotz MM. Comorbid Pain and Addiction. In: Ries, Richard, et al. *The ASAM Principles of Addiction Medicine.* Fifth edition, Wolters Kluwer Health, 2014.

5. Isaacson JH, Hopper JA, Alford DP et al. Prescription drug use and abuse. Postgraduate Medicine. 2005;118(1):19-26

6. MacLeod JB, Hungerford DW. Alcohol-related injury visits: do we know the true prevalence in U.S. trauma centres? Injury 2011;42(9):922–926.

7. Bourne N. Acute pain management in the opioid-tolerant patient. Nurs Stand 2010;25(12):35–39.

8. Pallasch TJ. Anaesthetic management of the chemically dependent patient. Anesthesia Progress 1992; 39: 157–61.

9. Rapp SE, Ready LB, Nessly ML. Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review. Pain 1995;61(2):195–201.

10. Maund E, McDaid C, Rice S, et al. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphinecrelated side-effects after major surgery: a systematic review. Br J Anaesth 2011; 106:292-297

11. Mehta V, Langford RM. Acute pain management in opioid dependent patients. Anaesthesia 2006; 61: 269-76.

12. Mehta V, Langford R. Acute pain management in opioid dependent patients. Rev Pain. 2009;3(2):10-14

13. Huxtable CA, Roberts LJ, Somogyi AA, et al. Acute pain management in opioid-tolerant patients: a growing challenge. Anaesth Intensive Care. 2011;39(5):804-23.

14. Dunbar SA, Katz NP. Chronic opioid therapy for nonmalignant pain in patients with a history of substance abuse: report of 20 cases.J Pain Symptom Manage 1996;11:163–171

15. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. MMWR Recomm Rep. 2016;65(1):1-49

16. CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016. Available at http://wonder.cdc.gov.

17. DEA Philadelphia Field Division. Anaylsis of Drug-Related Overdose Deaths in Pennsylvania, 2015 https://www.dea.gov/divisions/phi/2016/phi071216_attach.pdf

18. Krebs EE, Becker WC, Zerzan J, et al. Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain. Pain 2011;152:1789–95. http://dx.doi.org/10.1016/j.pain.2011.03.02382.

19. Hartung DM, Middleton L, Haxby DG, et al. Rates of adverse events of long-acting opioids in a state Medicaid program. Ann Pharmacother 2007;41:921–8. http://dx.doi.org/10.1345/aph.1K06683.

20. Ray WA, Chung CP, Murray KT, et al. Out-of-hospital mortality among patients receiving methadone for noncancer pain. JAMA Intern Med 2015;175:420–7. http://dx.doi.org/10.1001/jamainternmed.2014.6294

21. Brown R, Kraus C, Fleming M, Reddy S. Methadone: applied pharmacology and use as adjunctive treatment in chronic pain. Postgrad Med J 2004; 80:654-659.

22. Center for Substance Abuse Treatment. Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS publication no. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.

23. Mehta V, Langford RM. Acute pain management in opioid dependent patients. Anaesthesia 2006; 61: 269-76.

24. Yoburn BC, Luke MC, Pasternak GW, et al. Upregulation of opioid receptor subtypes correlates with potency changes of morphine and DADLE. Life Sci. 1988; 43(16):1319-24.

25. Vickers AP, Jolly A. Naltrexone and problems in pain management. How to manage acute pain in people taking an opioid antagonist. BMJ. 2006;332(7534):132-133

26. Vivitrol (R)[package insert]. Waltham, MA: Alkermes, Inc. 2015

CASE STUDIES

Case 1:

MANAGEMENT OF POST-OPERATIVE PAIN

Philip Templeton is a 32-year-old male who underwent surgical repair of a right fifth metacarpal fracture after punching a wall during an argument with his girlfriend. After the procedure, he was prescribed oxycodone 10 mg every 6 hours as needed for 3 days (a total of 12 tablets) and advised to supplement this with naproxen 500 mg every 8 hours if needed. He was advised to keep the hand elevated and apply ice for 20 minutes every 4 hours. Physical therapy was recommended to begin 7 days post-surgery. Review of the Pennsylvania Department of Health Prescription Drug Monitoring Program database shows no recent opioid prescriptions for Mr. Templeton and he signed a controlled substance agreement with the physician prior to discharge.

Mr. Templeton presents for a follow-up visit 4 days post-surgery where states the pain in his right hand has been constant; he rates his pain as a 10/10 on the Numeric Rating Scale. The pain is sharp and throbbing in nature, worsened by movement, and only relieved by oxycodone. He is asking for more oxycodone, so he can get back to work. He reports not taking naproxen because he did not have any at home and applying ice about once per day.

Mr. Templeton has a past medical history of depression but is on no medications currently. He has smoked marijuana in the past but no recent illicit drug abuse. He smokes cigarettes occasionally and binge drinks with friends about once per month. He has a family history of alcoholism and depression.

On physical exam, Mr. Templeton is calm and appears in no distress. His right hand is moderately tender to palpation and the pain is worse with range of motion. The surgical wound is healing well without redness, swelling, warmth, or discharge. Radiographs of the hand are normal and there is no concern for a surgical complication.

Mr. Templeton states that he has never used opioids for non-medical reasons. He openly admits that the oxycodone makes him feel good but does not think he is misusing them. He is encouraged to maximize NSAID use with acetaminophen and naproxen, use ice therapy and to make an appointment for physical therapy for range of motion exercises, strengthening exercises, and therapeutic ultrasound. A follow-up appointment at the orthopedic office was made for him in two weeks to re-evaluate progress.

Case 2:

ASSESSMENT OF RISK FACTORS FOR SUBSTANCE USE DISORDER (SUD)

(See *Section 9. Identification of patients who are at risk for developing SUD* and *Section 5. Safe opioid prescribing)*

Hakim Miller, a 44-year-old male presents to your office for the first time, and you have previously received and reviewed records from his previous primary care physician. He reports that his previous primary care physician felt uncomfortable continuing to manage his pain medication and he is requesting that you now manage his chronic pain as well as consider an increase in his dose given decreased efficacy over time. He has suffered from chronic knee pain secondary to severe primary osteoarthritis of the R knee with previous images demonstrating subchondral sclerosus. He has previously been trialed on acetaminophen, 3 different NSAIDs, topical pain creams, and injections with limited improvement. He has been evaluated by orthopaedics for knee replacement; however, they are recommending weight loss prior to surgery. He states that he is working with physical therapy, however, he feels that he cannot exercise and is barely even able to walk without his pain medication.

For pain, he is currently prescribed oxycodone 10 mg TID, gabapentin 900 mg TID, and acetaminophen 1000 mg TID which he has been taking for the past 3 months. He was previously taking oxycodone/acetaminophen and his dose was titrated up over time to address pain. With starting physical therapy, he was experiencing increasing pain and reduced functionality. Therefore he was taking oxycodone four times daily on days when he had physical therapy and thus was running out of medicine early. His previous primary care physician felt uncomfortable with his self-adjusting medication and Mr. Miller decided he would seek care elsewhere after their last visit.

His past medical history includes paroxysmal atrial fibrillation, type 2 diabetes mellitus for 11 years (most recent HbA1C 7.2 from 1 month ago), hyperlipidemia, morbid obesity with a BMI of 51, hypertension, depression, and osteoarthritis as noted above. His current medications include rivaroxaban 20 mg daily, metformin 1000 mg BID, glargine 10 units nightly, lisinopril 10 mg daily, hydrochlorothiazide 25 mg daily, atorvastatin 40 mg nightly, duloxetine 60 mg daily, and pain medications as noted above.

His family history is significant for cardiac disease in both parents, and several siblings are in good health. He denies any family history of substance abuse-related issues. His social history reveals that he runs a painting company who has contracts with many different businesses. He needs to travel to sites to observe his employees and meet with clients; however, he has been having increasing difficulty doing so over the past 6-8 months, first requiring a cane and now using a crutch for ambulating. He is married and has no children. He reports using alcohol in his youth but "never very much," and does not currently drink given his pain medications. He used marijuana intermittently in his late teen years but has not used since that time. He has never smoked.

He is asking for a refill on his medications and questions whether his dose can be increased so that he does not run out of his medicine early. He reports that typically he will be out of medicine the last 5-6

days of the month and during this time, his pain is worse, leaving him unable to get around but specifically denies headaches, fevers, chills, nausea, vomiting, diarrhea, or abdominal pain during this time.

The medical practice has a protocol for all patients who are already taking or who are requesting a prescription for opioids, with the Opioid Risk Assessment Tool administered as part of the rooming standard. [

Mark Each box that applies	Female	Male
Family history of substance abuse		
Alcohol	□ 1	□ 3
Illegal drugs	□ 2	□ 3
Rx drugs	□ 4	□ 4
Personal history of substance abuse		
Alcohol	□ 3	□ 3
Illegal drugs	□ 4	□ 4
Rx drugs	□ 5	□ 5
Age between 16-45 yrs.		
	□ 1	□ 1
History of preadolescent sexual abuse		
	□ 3	□ 0
Psychological disease		
ADD, OCD, bipolar, schizophrenia	□ 2	□ 2
Depression	□ 1	□ 1
Scoring Totals		

Score Assessment
0-3 : low risk
4-7 : moderate risk
8+ : high risk

Total score: 2

Based on the Risk Tool, the patient has a risk score of 2, placing him at low risk of opioid abuse. A score of 3 or lower indicates low risk for future opioid abuse, a score of 4 to 7 indicates moderate risk for opioid abuse, and a score of 8 or higher indicates a high risk for opioid abuse. It should be noted that a low score does not indicate that opioids should be utilized in the treatment of pain. The tool does not identify concern for the patient who is self-titrating his medication which is not recommended. While the history provided suggests that the patient has developed tolerance to the current opioid dose, it does not suggest evidence of dependence.

The decision to initiate opioid therapy in this patient will require additional information that are often included in the comprehensive assessment of patient with concern for opioid use including review of the PDMP as well as consideration of drug testing. Clinical decision support tools can assist in making the final determination; however, ultimately, the clinician will need to utilize all the pertinent information available to determine whether he/she will initiate opioid therapy for Mr. Miller.

Case 3:

TREATING ACUTE PAIN WITH MULTIPLE SUBSTANCE USE DISORDER (SUD) RISK FACTORS

(See *Section 9. Identification of patients who are at risk for developing SUD* and *Section 2. Non-opioid treatments for pain*)

Mark Henry is a 58-year-old male who presents for low back pain for 15 days. He reports he was helping his daughter move in to her new apartment the day prior to onset and upon awakening the subsequent day, noted constant bilateral low back pain described as an ache. He also describes having sharp, stabbing pain with bending forwards, backwards, or twisting. He denies any radiation. The pain was initially rated at a 10/10 and currently is rated at an 8/10. He has been unable to get back to work as a postal carrier as his pain limits him from being able to carry the mail. He has never had any similar pain in the past. He denies any fevers, chills, night sweats, weight loss, numbness, tingling, weakness, or issues with incontinence. He tried taking ibuprofen and acetaminophen without improvement but reports a coworker had given him tramadol which did improve his symptoms.

He has a past medical history significant for hypertension and hyperlipidemia. He currently takes amlodipine 10 mg daily and atorvastatin 20 mg daily. His family history is significant for cirrhosis in his father which he reports is related to alcohol and hypertension in his mother. He lives alone and, as noted, works for the post office. He is divorced. He denies any current alcohol use but reports that he "used to drink heavily" and this was, in part, the reason for his marriage ending. He would typically drink after work each day, drinking anywhere from 3-4 beers to one-half pint of brandy. He stopped drinking after a DUI which was 28 years ago. He denies any drug use now or in the past, both prescription and recreational drugs and has never smoked.

His examination demonstrates normal vital signs. He is well appearing however appears slightly uncomfortable sitting on the exam table. He has no tenderness of the cervical, thoracic, lumbar, or sacral spine but has mild bilateral paraspinal tenderness, right greater than left, without palpable spasm. His lumbar flexion is limited to 75 degrees and extension is limited to 10 degrees. He is unable to twist or flex laterally due to pain. His lower extremity strength is intact with 5/5 proximal and distal strength with sensation to light touch intact and 2+ patellar and Achilles reflexes bilaterally. His gait is antalgic.

"Doc, can you get me back to work?"

Mr. Henry is presenting with acute low back pain, a very common acute pain complaint to both primary care offices as well as urgent care centers and emergency rooms. He has tried over-the-counter medication; however, an important clarification on history is to assess the actual dose as well as the actual frequency of medication. Patients may use typical over-the-counter doses of NSAIDs or acetaminophen and therefore may benefit from a higher dose of medicine. Of concern, he did obtain

medication from a friend, obtaining tramadol, although he is not specifically asking for this medication. It is important, if considering continuation of the tramadol, to assess his risk for opioid abuse. The Opioid Risk Assessment Tool can be administered as part of the assessment.

Mark Each box that applies	Female	Male
Family history of substance abuse		
Alcohol	□ 1	□ 3
Illegal drugs	□ 2	□ 3
Rx drugs	□ 4	□ 4
Personal history of substance abuse		
Alcohol	□ 3	□ 3
Illegal drugs	□ 4	□ 4
Rx drugs	□ 5	□ 5
Age between 16-45 yrs.		
	□ 1	□ 1
History of preadolescent sexual abuse		
	□ 3	□ 0
Psychological disease		
ADD, OCD, bipolar, schizophrenia	□ 2	□ 2
Depression	□ 1	□ 1
Scoring Totals		

Total score: 6

Based on the Risk Tool, with a score of 6, Mr. Henry is at moderate risk for opioid abuse. A score of 3 or lower indicates low risk for future opioid abuse, a score of 4 to 7 indicates moderate risk for opioid abuse, and a score of 8 or higher indicates a high risk for opioid abuse. It should be noted that a low score does not indicate that opioids should be utilized in the treatment of pain. Mr. Henry's history is also largely suggestive of a mechanical low back pain that can typically be treated conservatively with non-opioid medications in conjunction with a physical rehabilitative program. Furthermore, a clear goal of return to work is established with the patient's questioning. Working in conjunction with the patient's employer in accommodations also can be useful to facilitate the process for return to work in a safe and appropriate manner for the patient.

While the Mr. Henry may be resistant to utilizing additional ibuprofen or acetaminophen, alternative NSAIDs are certainly an option to address the pain as well as adjunctive therapies. Given that the pain is limiting functionality, an assessment on the effects of this on the patient's psyche is critical to rehabilitation back to his previous baseline.

Case 4:

TREATMENT OF OPIOID USE DISORDER (OUD)

(See *Section 11. Treating OUD as a chronic disease)*

Mary Robinson is a 23-year-old female who presents as an acute appointment for nausea, vomiting, and abdominal pain. She reports her symptoms have been off and on for the past 2 weeks with nausea that persists throughout the day and occasional episodes of early morning non-bloody, non-bilious emesis not associated with meals. She denies any fevers or chills but feels that she must be dehydrated because occasionally when her symptoms happen, she feels like her heart is racing. She denies any diarrhea, urinary symptoms, vaginal discharge, itching, or burning. She reported to the nurse that she "was late" and her last menstrual period (LMP) was 1.5 months ago, typically having a regular cycle. She agreed to provide a urine sample to the nurse and the nurse alerted you prior to going into the room that the test was positive. Ms. Robinson has no significant past medical history; however, on review of her records, she was seen in the emergency room approximately 3 months ago with a chief complaint of "requesting detox." She did not stay for treatment and therefore, there is no further information.

Ms. Robinson reports that she was concerned about pregnancy and states that she was not actively trying to get pregnant and was using condoms for contraception but was concerned several weeks ago when she saw material on the outside of the condom after intercourse. She has only been sexually active with 1 male partner recently and has only 2 lifetime partners. While the pregnancy was not planned and she is feeling anxious, she reports to be excited about the pregnancy and intends to carry the pregnancy to term. She thought that her symptoms could be due to pregnancy. When asked about the ER visit several months ago, she breaks down into tears.

She states that she is "embarrassed.' She had a dental procedure several months prior and was given Tylenol with codeine. After finishing the prescription, she started buying pain medicine off the street and more recently, has been snorting heroin when she has been unable to afford pain medication. When she missed her period, she attempted to stop using because of concern about pregnancy however, has been developing nausea, abdominal pain, chills, palpitations, and vomiting. The only thing that seems to make her symptoms better is using. She is scared about what this means for her pregnancy and wants to know what she can do.

Ms. Robinson requires a more thorough, comprehensive evaluation for opioid use disorder; however, she is exhibiting symptoms of opioid dependence. Given her pregnancy and her desire to carry the pregnancy to term, she requires treatment as her withdrawal symptoms are both a risk to her and the fetus. Pharmacologic treatment approved during pregnancy includes methadone as well as buprenorphine. These therapies should be initiated as soon as possible and in conjunction with psychological treatment for opioid dependence as well as possible OUD. Additionally, her prenatal care process should include discussion about pain management throughout the pregnancy as well as during labor with possible consideration of third trimester consultation with anesthesia. Additional discussions around care of the newborn and neonatal abstinence syndrome (NAS) should also be part of the discussion when initiating pharmacologic therapy.

DENTAL CASES

Contributed by:

Mehran Hossaini, DMD
Professor of Clinical Oral and Maxillofacial Surgery
Chair, Department of Oral & Maxillofacial Pathology, Medicine, Surgery
Temple University Kornberg School of Dentistry

Stanley J. Heleniak, DMD
Dentist Anesthesiologist
Director, Dental Sedation Center
Assistant Professor, Department of Oral and Maxillofacial Pathology, Medicine, and Surgery
Temple University Kornberg School of Dentistry
Assistant Professor, Department of Anesthesiology
Lewis Katz School of Medicine at Temple University

Maria Cordero-Ricardo, DMD, MS, MPH
Clinical Associate Professor and Director of Pediatric Dental Clinic
Department of Pediatric Dentistry and Community Oral Health Sciences
Diplomate of the American Board of Pediatric Dentistry
Temple University Kornberg School of Dentistry

Andrea M. Bell, DMD
Dentist Anesthesiologist
Clinical Assistant Professor
Temple University Kornberg School of Dentistry

Case 1:

PAIN MANAGEMENT FOLLOWING WISDOM TEETH EXTRACTION

History: DJ is a 17-year-old white male who presents for possible removal of his wisdom teeth prior to leaving for college. He has had episodes of "discomfort" with his lower wisdom teeth, but is otherwise asymptomatic. He and his parents are very excited about his college soccer scholarship and are asking to remove his wisdom teeth with the concern that they may become problematic while in college.

Past Medical History: DJ is an otherwise healthy 17-year-old with no reported illnesses, medications, allergies, or surgeries. He is a very active athlete, with no history of alcohol, tobacco, or drug use.

His family history, is generally unremarkable. Mother and father, a nurse and an attorney, are in good health with no family history of chronic illnesses.

Clinical Exam: Generally unremarkable, except partially erupted teeth numbers 1, 16, 17, 32 with evidence of mild pericoronitis. Radiographic examination is similarly unremarkable, except for partially erupted third molars.

Planned Treatment: Everyone agrees that the elective removal of teeth #1, 16, 17, 32 is a reasonable option. DJ and his parents request that the procedure to be performed with nitrous oxide sedation. They are very concerned about post-operative pain management.

DJ's father has experienced "dry socket" after his third molar extractions, and does not want DJ to experience that type of pain. DJ's older sister had "Vicodin" after her wisdom teeth removal with good pain control.

Discussion: As clinicians, we can form our, conscious or unconscious, biases. A patient like DJ can be a perfect example of that bias. Since he is a healthy young athlete, with educated and involved parents, the dentist may think that he poses very little concern for post-treatment pain management and potential opioid mis-use. Therefore, any post-operative pain management may seem appropriate and of low risk.

However, a recent article (1) highlighted some alarming data. This study demonstrated that legitimate opioid use before high school graduation is independently associated with a 33% increase in the risk of future opioid misuse after high school. Therefore, it may be prudent to consider pain management alternatives, even for opioid-naive patients.

Multiple articles, including one published in JADA in 2013 (2), have demonstrated that the combination of ibuprofen and acetaminophen is more effective and will have fewer side effects than combination analgesics containing opioids for acute pain management after molar extractions.

Further, it should be noted that patient and parental education, in cases such as DJ's, is quite important.

In summary, the best approach for DJ would be:

- Patient education and discussion of the appropriate pain relief options, with their pros and cons, based on available evidence
- Prescription of ibuprofen and acetaminophen for post-operative pain management.

References:

1. Miech R, Johnston L, O'Malley PM, Keyes KM, Heard K. Prescription Opioids in Adolescence and Future Opioid Misuse. Pediatrics. 2015 Nov;136(5): e1169-77.

2. Moore PA, Hersh EV. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions: translating clinical research to dental practice. J Am Dent Assoc. 2013 Aug;144(8):898-908.

Case 2:

PAIN MANAGEMENT FOLLOWING A MOUTH INJURY

History: JS a 16-year-old female ice hockey player who presents to the emergency room after a teammate accidentally hits her in the mouth with her hockey stick. She was bleeding from the lip and mouth. JS's mom was at the practice and took her directly to the emergency room for care.

Past Medical History: JS is an otherwise healthy 16-year-old female who reports ADHD which is managed with methylphenidate. She does not take any other medications or have any drug allergies. Two years ago, she had a hospital admission record for appendicitis and appendectomy. She denies regular use of alcohol or drugs, but has consumed alcohol and tobacco with peers.

Family History: Parents are divorced and Dad lives in another state. Mom declines personal history of alcohol, tobacco or drug use, but mentions that Dad was a heavy drinker from time to time.

Clinical Exam: JS has a superficial laceration of the mucosa of the lower lip and has fractured the maxillary central incisor (upper front tooth) so that it shows 2 mm of exposed pulp (nerve) tissue. She does not have signs of a concussion. Her lip is hemostatic and the tooth is tender to direct palpation but otherwise fine. She reports her pain as a 4/10, mostly tender around her lips. Radiographic examination does not show fractures of the mandible and periapical (plain film) of the front teeth, but shows a complicated crown fracture with intact alveolus.

Planned Treatment: Once it is determined that JS is stable, the emergency room care shifts to specialty care and pain management. There is no dentist on staff in the hospital, but JS has a general dentist of record for follow-up care. Upon phone consult with him, she has an appointment for the next morning for definitive treatment. Mom wants something for the pain so JS can be comfortable overnight. She remembers having trouble with post-operative pain control after surgery and wants to stay on top of it.

Discussion: Although JS is female, she does have a few salient risk factors including a diagnosis of ADHD, young age for primary narcotic exposure, and potential family history as a risk factor. She has had some exposure to opioid analgesics through a previous surgery as well as recreational alcohol use, which is not a definitive risk factor but contributes to her overall exposure.

It is most important to actually assess JS's pain versus the impression of her injury. She reports mild pain and is not in apparent distress. The injury may look painful, but crown fractures with pulpal exposures are not typically severely noxious unless stimulated. The mother is the source of concern for pain management and should be counseled on effective pain management protocols including appropriate dosage and scheduling of ibuprofen and acetaminophen in concert.

In summary, the best management for JS is triaging to dentist for definite care and appropriate pain management counseling so that Mom feels empowered to care for her child and JS is comfortable until her condition is resolved.

Case 3:

ACUTE DENTAL PAIN MANAGEMENT DURING MEDICATION-ASSISTED THERAPY

History: WG is a 60-year-old male who presents to the office for consultation regarding extraction of his remaining teeth and pre-prosthetic alveoloplasty. He reports having "no teeth for years" but states he was referred for extraction of "pieces of tooth under the gums" and "bone work" in preparation for fabrication of upper and lower dentures.

Past Medical History: WG reports a past medical history of hypertension, Type II diabetes, osteoarthritis, chronic lower back pain and gout. He provides a current list of medications, which include lisinopril, allopurinol, metformin and buprenorphine/naloxone. With further inquiry, WG reveals active participation in medication assisted treatment for addiction to prescription opioids which he had used long term for the management of his chronic pain. He denies illicit drug use with the exception of marijuana "occasionally". WG additionally smokes "about 4" cigarettes per day (has smoked since the age of "13 or 14"), and drinks "a couple beers every other day".

Physical Examination: A complete dental exam reveals edentulous maxillary and mandibular arches with bulbous bony architecture, precluding fabrication of removable prostheses. Retained roots of maxillary central incisors are asymptomatic but appreciable radiographically. His surgical treatment plan includes exposure and removal of the retained roots along with bony re-contouring in both arches.

WG reports previously successful management of post-op pain relating to tooth extraction with Percocet® but expresses concern that analgesics prescribed following planned procedures "won't work" due to his buprenorphine/naloxone Rx. WG states he plans to discontinue his buprenorphine/naloxone a few days pre-op in order to ensure he can be prescribed something "good… that will work".

"Sound like a plan?"

Discussion: The advent of treatment with the partial opioid receptor agonist buprenorphine has allowed patients to participate in Outpatient Treatment Programs (OTP) without mandatory daily attendance to receive MAT. Often prescribed in conjunction with naloxone, buprenorphine has become a mainstay of office based opioid treatment (OBOT) with management being facilitated by providers qualified under the Drug Addiction Treatment Act of 2000 (DATA 2000).

As in all patients, the approach to treatment of acute pain should utilize acetaminophen and NSAID as first line pharmacological therapy. Placing the patient on a dosing schedule, as outlined below, is a useful way to maximize non-opioid therapy in the management of mild to moderate pain.

Pain Severity	Analgesic Recommendation
Mild	Ibuprofen (200-400 mg) q4-6 hours prn for pain
Mild to Moderate	**Step 1:** Ibuprofen (400-600 mg) q6 hours: fixed intervals for 24 hours **Step 2:** Ibuprofen (400 mg) q4-6 hours prn for pain
Moderate to Severe	**Step 1:** Ibuprofen (400-600 mg) with APAP (500 mg) q6 hours: fixed interval for 24 hours **Step 2:** Ibuprofen (400 mg) with APAP (500 mg) q6 hours prn for pain

APAP = acetaminophen

In the event of failure or anticipated failure of first line drug therapy in the setting of moderate to severe pain, options for management include dividing the total daily dose temporarily (two to four times daily dosing), continuing treatment regimen with addition of a short-acting opioid analgesic titrated to achieve therapeutic effect or discontinuing buprenorphine therapy while initiating treatment with a full opioid agonist (eg,. morphine, oxycodone). When considering the above, however, decisions regarding pain management should be made in concert with the patient's OTP provider.

Case 4:

PAIN MANAGEMENT DURING EXTENSIVE DENTAL PROCEDURES

History: Michelle George is a 24-year-old female who presents to the dental office complaining of multiple cavities, including three areas of her mouth that have been painful for a number of months, and are increasing in intensity. She has recently been seen by another dentist who had prescribed her an antibiotic and Percocet®. She does not wish to return to that dentist as she feels uncomfortable with his personality. There was another dentist she saw about six months ago and didn't like her either. Ms. George states she wants to repair and keep all her teeth and has the means to do so. She says she likes your office persona and feels that this is the dental office for her. "She just wants to be able to eat and enjoy all foods and drinks without pain again". She also states she wishes to be off of pain medications as she has been taking Vicodin® and Percocet® more frequently.

Past Medical History: Her past medical history is significant for fibromyalgia, migraines, TMJ disorder, clinical depression, Lyme disease treatment, and seasonal allergies. Her medications are Vicodin, Percocet, Prozac, Allegra, Zofran, some unknown immune system injection medication, history of low dose ketamine infusions, and birth control pills. She wears an occlusal guard at nighttime. Social history is positive for smoking one pack per day, and she drinks alcohol socially on weekends. She denies illicit drug use history. She was adopted so no family history is available. She complains that after dental appointments her jaw aches for several days. She states she is "not good" with pain and fears pain most. Her diet involves high carbohydrate intake and energy drinks as well as tea with lemon.

Clinical Examination: Ms. George's vital signs are all normal for her age. Head and Neck exam reveal no external swellings or nodes, but there is mild palpation tenderness to right TMJ, masseter and temporalis muscles. There is slight deviation on opening to the right. Intraorally, trismus to 30 mm interincisal opening is noted. Vestibules and floor of mouth are without injection. Oral cancer screening is negative. Multiple carious lesions are noted, many cervical. A parulus is noted on the buccal gingiva opposite tooth number 30 and 14. Both of these teeth are sensitive to percussion and do not react to cold stimulation. Cold stimulation is excessive and prolonged on number 3. Mobility of plus 1 is noted number 30. Radiographic exam reveals multiple carious lesions with penetration to pulp chambers and periodontal ligament space widening apically at numbers 30 and 14. Number 30 also shows furcation area. Otherwise no evidence of periodontal disease is evident.

Plan: After assessing Ms. George's dental conditions, you propose a treatment plan to control and resolve her oral disease and to restore her mouth to normalcy. Consideration must be given to the extensive nature of her treatment requiring multiple appointments, some of longer duration, and expectations for post-operative pain and discomfort, especially with her history of post dental appointment course (ie, TMJ pain, chronic pain syndrome, chronic use of opioids with sensitization, and depression). Post-operative inflammatory reaction and resultant pain is expected, possibly severe in this population of patients. Consideration must be given to minimizing this occurrence and/or controlling it.

Management of this patient should not only involve counseling Ms. George on better dietary habits to reduce dental caries incidence, but treatment should focus on trying to minimize post-operative pain and discomfort so as to reduce the need for dependency on opioid prescriptions and consumption.

Discussion: Strategy should be multi-modal. It starts with preparing the patient for expectations for treatment and assessing what helps her cope. Armed with this information, a plan can be constructed. It can involve shorter appointments where the mouth needs to be open, preemptive analgesia with NSAID and acetaminophen pre-operatively and continued post-operatively on a schedule, pre-operative gabapentin or pregabalin single dose; steroids either as a single intraoral injection intraoperatively or a Medrol dose pack post-operatively for procedures with greater anticipated inflammatory reaction. Long acting local anesthetics, where possible, are suggested as they will give Ms. George time to take additional doses of OTC analgesics and steroids to reach the desired analgesic effect.

Occlusal adjustment in areas of concern and risk for pain should be provided. Home physical therapy for TMJ post-operatively along with occlusal guard use should be taught and encouraged, as well as instructions for a soft diet. If needed, formal physical therapy can be prescribed with a physical therapist. Opioid analgesics can be used if there is “break- through” pain. One will need to choose an opioid or opioid combination with no acetaminophen or with an NSAID to minimize risk of liver toxicity. For example, Vicoprofen, combining a small amount of additional ibuprofen to that which the patient may already be taking along with hydrocodone, or stand-alone morphine for those patients not able to tolerate ibuprofen and already on maximum acetaminophen, should be effective. Duration of therapy should be targeted to no longer than three to five days before reevaluating the patient.

The clinical approach is to give Ms. George every chance to avoid opioid use during the restorative procedures, as she has a history of possible prior opioid abuse and a medical and psychological profile of comorbidities that place her at great risk for developing opioid dependency to cope. A multi modal approach such as this one may help Ms. George greatly and make her happy with your care and ultimately with the state of her new dental health.

Note that it is advisable to consult with the patient’s physician, especially if she has a pain management specialist. Make the physician aware of the extent and expectations of the proposed dental procedures as far as pain and discomfort.

POST-CURRICULUM ASSESSMENT OF KNOWLEDGE

1. Oxycodone is designated as a controlled substance by the Drug Enforcement Agency. Under which schedule is oxycodone classified?
    a. Schedule I
    b. Schedule II
    c. Schedule III
    d. Schedule IV
    e. Schedule V

Answer: b

2. Which of the following opioids is classified by the DEA as Schedule I?
    a. Codeine
    b. Buprenorphine
    c. Heroin
    d. Fentanyl
    e. Morphine

Answer: c

3. Which of the following is an opioid with less than 10% analgesic activity of morphine that is used to treat mild-moderate pain and as an antitussive agent in cough syrup preparations?
    a. Buprenorphine
    b. Codeine
    c. Fentanyl
    d. Hydrocodone
    e. Oxycodone

Answer: b

4. Which one of the following acts as a mu opioid receptor agonist and kappa receptor antagonist and is used as part of Suboxone® to treat heroin dependence?
    a. Buprenorphine
    b. Methadone
    c. Morphine
    d. Naloxone
    e. Naltrexone

Answer: a

5. Which of the following medications may be most beneficial in a patient who is experiencing painful neuropathies?
    a. Acetaminophen
    b. Codeine
    c. Duloxetine
    d. Hydrocodone
    e. Fentanyl

    Answer: c

6. Which of the following medications would be best for pain relief in a 65-year-old patient who has had minor outpatient surgery conducted for correction of cataracts?
    a. Cannabinoids
    b. Duloxetine
    c. Gabapentin
    d. Morphine
    e. Naproxen

    Answer: e

7. Which medication listed below is considered to have the lowest abuse liability?
    a. Duloxetine
    b. Fentanyl
    c. Gabapentin
    d. Ibuprofen
    e. Oxycodone

    Answer: d

8. Most currently available opioid analgesics act at which receptor site?
    a. Delta opioid receptor
    b. Epsilon receptor
    c. Kappa opioid receptor
    d. Mu opioid receptor
    e. Sigma receptor

    Answer: d

9. Which type of pain is most effectively relieved by opioid analgesics?
    a. Severe, constant pain
    b. Intermittent, sharp pain
    c. Neuropathic pain
    d. Pain associated with fibromyalgia
    e. Pancreatic pain

Answer: a

10. Which of the following is ***not*** a predictable result of opioid prescribing?
    a. Addiction
    b. Physical dependence
    c. Withdrawal symptoms
    d. Tolerance
    Answer: a

11. Which of the following endpoints shows the least opioid tolerance?
    a. Analgesia
    b. Constipation
    c. Euphoria
    d. Nausea
    e. Respiratory depression
    Answer: b

12. In the context of chronic pain management, the best approach for the clinical management of hyperalgesia is which of the following?
    a. Abruptly discontinue the opioid administration
    b. Increase the opioid dose
    c. Switch to a more potent opioid agonist
    d. Taper or gradually decrease opioid dose
    Answer: d

13. Which of the following is a principal symptom of opioid use disorder?
    a. Development of tolerance to analgesic effects of opioids
    b. Withdrawal signs such as weight loss and irritability following discontinuation of opioid
    c. Craving for the opioid and compulsive opioid seeking
    d. The presence of physical dependence
    Answer: c

14. Which one of the following agents has the lowest abuse liability?
    a. Codeine
    b. Fentanyl
    c. Heroin
    d. Morphine
    e. Oxycodone
    Answer: a

15. The risk of opioid overdose increases when a person takes a(n)
    a. low dose of an opioid.
    b. long-acting opioid such as methadone or the fentanyl patch
    c. opioid for a short duration of time
    d. shorter acting opioid
    Answer: b

16. Which one of the following agents, when taken in combination with an opioid analgesic, will increase the likelihood of respiratory depression and opioid overdose?
    a. atenolol
    b. caffeine
    c. clonazepam
    d. diltiazem
    e. propranolol
    Answer: c

17. Patient markers for an elevated risk of opioid overdose include
    a. Renal dysfunction
    b. Liver dysfunction
    c. History of suicidal thoughts
    d. Clinical depression
    e. All of the above
    Answer: e

18. Non-opioid alternatives for pharmacological treatment of chronic pain include all of the following except
    a. Acetaminophen
    b. Anticonvulsants
    c. Antidepressants
    d. Antipsychotics
    e. NSAIDs
    Answer: d

19. Mitigation strategies for risk assessment of opioid misuse and diversion include
    a. Screener and opioid assessment for patients with pain (SOAPP)
    b. Use data from prescription drug monitoring program to identify ‘doctor shopping’
    c. Use of urine drug screening
    d. Use of a doctor-patient agreement on adherence
    e. All of the above
    Answer: e

20. Abuse-deterrent formulations for opioid analgesics can include combining the opioid analgesic with which one of the following?
    a. another more potent opioid agonist
    b. a benzodiazepine
    c. an opioid receptor antagonist
    d. a skeletal muscle relaxant
    e. a substance that make it easier for the opioid to be crushed and extracted
    Answer: c

21. Vulnerability to opioid addiction is related to which of the following?
    a. Age
    b. Psychiatric disorders such as schizophrenia or depression
    c. Genetics
    d. Route of administration of the opioid
    e. All of the above
    Answer: e

22. Which of the following are used to assess pain in children?
    a. Self-reported measures of pain
    b. Behavioral measures of pain
    c. Physiologic measures of pain
    d. All of the above
    Answer: d

23. Which of the following is the most likely mechanism underlying opioid-induced flushing of the skin?
    a. Adenosine receptor blockade
    b. Alpha-adrenoceptor activation
    c. Beta-adrenoceptor activation
    d. Histamine release
    e. Serotonin release
    Answer: d

24. Which of the following is the principal opioid alkaloid in opium?
    a. Fentanyl
    b. Meperidine
    c. Methadone
    d. Morphine
    e. Naloxone
    Answer: d

25. Which of the following are useful drug(s) for treatment of opioid use disorder?
    a. methadone
    b. buprenorphine
    c. fentanyl
    d. A & B
    e. A, B & C
    Answer: d

26. Which of the following is an opioid analgesics that can have serious interactions with monoamine oxidase inhibitors and has a toxic metabolite that accumulates with chronic oral dosing?
    a. Hydrocodone
    b. Hydromorphone
    c. Meperidine
    d. Morphine
    e. Pentazocine
    Answer: c

27. Which of the following is an opioid analgesic that activates mu opioid receptors and inhibits the reuptake of serotonin and norepinephrine?
    a. Codeine
    b. Duloxetine
    c. Fentanyl
    d. Oxycodone
    e. Tramadol
    Answer: e

28. A patient presents with hallucinations and delusions. It is determined that the patient is taking a drug that activates kappa opioid receptors and antagonizes mu opioid receptors. Which drug is the patient is most likely taking?
    a. Buprenorphine
    b. Methadone
    c. Naloxone
    d. Pentazocine
    e. Tramadol
    Answer: d

29. Which of the following drugs has an active metabolite that can produce CNS excitation?
    a. Buprenorphine
    b. Codeine
    c. Fentanyl
    d. Meperidine
    e. Methadone
    Answer: d

30. Which of the following drugs is approved by the FDA for medication assisted therapy for the treatment of opioid use disorder?
    a. Flumazenil
    b. Methadone
    c. Morphine
    d. Naloxone
    e. Nalbuphine
    Answer: b

31. Which of the following drugs has the lowest analgesic efficacy?
    a. Codeine
    b. Hydromorphone
    c. Meperidine
    d. Morphine
    e. Oxycodone
    Answer: a

32. A 45-year-old man in a methadone-maintenance program requires knee replacement surgery. Of the drugs listed as part of his anesthetic regimen, which one will most likely require a greater dose than usual?
    a. Atropine
    b. Fentanyl
    c. Halothane
    d. Succinylcholine
    e. Thiopental
    Answer: b

33. A 30-year-old female is admitted to the emergency room with multiple fractured bones following a car accident. She is administered meperidine for her pain. She becomes agitated, develops hypertension, muscle rigidity and has a seizure. Which of the following drugs was the patient most likely taking, to produce this drug-drug interaction?

    a. Clozapine
    b. Diazepam
    c. Ibuprofen
    d. Lithium
    e. Phenelzine
    Answer: e

34. Which one of the following drugs would be the best choice for treatment of pain in a hospitalized patient with COPD?
    a. butorphanol ***
    b. hydromorphone
    c. meperidine
    d. morphine
    e. oxycodone
    Answer: a

35. A comatose 23-year-old male is brought to the emergency room. His respiration is depressed, blood pressure is low, and pupils are constricted. Upon examination, you find needle marks in his arms. Treatment should be started immediately by administration of which one of the following drugs?
    a. Clonidine
    b. Flumazenil
    c. Methadone
    d. Naloxone
    e. Pentazocine
    Answer: d

36. A 54-year-old man, diagnosed with pancreatic cancer, is prescribed morphine for pain control. Adverse reactions to the drug are most likely to include which of the following?
    a. Anxiety
    b. Constipation
    c. Mydriasis
    d. Tachycardia
    e. Urinary incontinence
    Answer: b

37. A 70-year-old female patient with hypertension and renal insufficiency needs a high efficacy analgesic for pain associated with metastatic bone cancer. The most appropriate medication for this patient is
    a. Buprenorphine
    b. Codeine plus aspirin
    c. Hydromorphone
    d. Ibuprofen
    e. Meperidine
    Answer: c

38. An ambulatory 50-year-old male requires treatment for severe pain following knee surgery. He is given a combination of oxycodone and acetaminophen. Which of the following adverse reactions is he most likely to experience?
    a. Diarrhea
    b. Hypertensive crises
    c. Impairment of renal function
    d. Nausea and sedation
    e. Tachyarrhythmias
    Answer: d

39. A 30-year-old man presents to the emergency room, undergoing withdrawal from an unknown drug. His symptoms include mydriasis, diarrhea, gooseflesh and vomiting. The patient is most likely withdrawing from which of the following?
    a. Alprazolam
    b. Cocaine
    c. Heroin
    d. Methamphetamine
    e. Phenobarbital
    Answer: c

40. Which of the following is part of SBIRT?
    a. Asking a patient permission to talk with them about their substance use.
    b. Confronting the patient regarding their lies.
    c. Obtaining a urine drug screen.
    d. Referral for pastoral counseling.
    e. Use of an anti-craving agent (e.g., naltrexone) to aid abstinence.
    Answer: a