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Practical Guide to the Management of Acute and Chronic Pain in the Presence of Drug Tolerance for the Healthcare Practitioner

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ABSTRACT

Background: Drug tolerance has been on the rise in recent years worldwide, and consequently, pain management in our population has become challenging.

Methods: Discussed in this review are commonly abused drugs and considerations for treating acute and chronic pain states in patients with substance disorders.

Results: After marijuana, alcohol, and tobacco, the most widely abused substances are oxycodone (Oxycontin), diazepam (Valium), and methylphenidate (Ritalin). Urine testing can detect metabolites of drugs used by patients and is useful for assessing drug abuse, medication diversion, and drug interactions. The comprehensive treatment of pain in a patient with addictive disorder or tolerance must address 3 issues: the patient's addiction, any associated psychiatric conditions, and the patient's pain. Eliciting a detailed history of drug abuse—illicit drugs as well as prescription drugs—and ascertaining if the patient is currently enrolled in a methadone maintenance program for the treatment of drug addiction is vital.

Conclusion: Medical observation, supportive care, multidisciplinary pain management, and timely interventions as necessary are the keys to safe outcomes in these patients.

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INTRODUCTION

Drug tolerance related to the use of illicit and licit drugs is on the rise. An estimated 20 million people in the United States have substance-related disorders, and illicit substances are used by approximately one-third of the population. An estimated one-tenth of the outpatients presenting to general medical practice clinics abuse drugs. Substance abuse is seen in 25%-40% of patients admitted to hospitals and in 40%-60% of major trauma patients. Nonmedical use of pain relievers is a leading form of drug abuse and has resulted in an increase in emergency room visits.[1,2]

Pain management in these patients is a challenge and is negatively influenced by concerns about drug dependence, addiction, and possible life-threatening effects on physiopathological mechanisms. Psychosocial, cultural, environmental, medical, and practical issues are associated with drug abuse, making pain management even more complicated and challenging. Physicians must be cognizant of these issues to provide optimum treatment to patients with substance disorders. This review addresses many of these issues.

Table 1. Common Signs and Symptoms of Acute and Chronic Cocaine Abuse

Acute Exposure	Overdose/Chronic Abuse
Dose-dependent increase in heart rate, blood pressure, hyperthermia	Prolonged QRS, negative chronotropy, and inotropy
Heightened arousal, alertness, vigilance	Asthma, hypersensitivity pneumonitis, pneumopericardium, pulmonary edema, and hemorrhage
Euphoria, anxiety, restlessness	Myocarditis, congestive heart failure, dilated cardiomyopathy
Local anesthesia	Septal perforations/infections
Seizures followed by profound respiratory depression and circulatory collapse → sudden death	Congenital abnormalities: meconium staining, low birth weight, increased rate of sudden infant death syndrome, failure to thrive, and withdrawal in the baby
Vasoconstriction and vasospasm → stroke and/or myocardial infarction	Obstetric complications: uteroplacental insufficiency, preterm labor/delivery, premature rupture of membranes, placental abruption, maternal seizures
Fetal tachycardia, hypertension, intrauterine fetal death	

DRUG TOLERANCE, DEPENDENCE, AND ADDICTION

Tolerance is a physiological response to a medication that necessitates greater quantities of the drug to obtain the same response. People can develop tolerance to several substances, including opioids, benzodiazepines, antidepressants, corticosteroids, alcohol, cardiac medications, antidiabetics, and many other medications used in clinical medicine.

In patients with drug dependence, abrupt cessation or rapid dose reduction resulting in decreasing blood level of the drug and/or administration of an antagonist to the drug can produce a withdrawal syndrome that can include nausea, vomiting, diaphoresis, abdominal cramps, convulsions, and even death. Unlike addiction, which is a pathologic process, physical dependence is an expected physiologic response.

Drug addiction, on the other hand, is a primary, chronic, neurobiological disease characterized by the following behaviors:

- Persistent regular use of a drug
- Compulsive drug-seeking behaviors
- Need for increased dosage
- Loss of control over drug use
- Continual use of a drug despite its consequences
- Craving for the drug

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) is commonly used to define conditions associated with drug abuse and to assess the severity of substance abuse and dependence. However, diagnosing addiction in patients with chronic pain who take prescription pain killers can be difficult because patients often do not satisfy all the criteria in the DSM-IV. They often do not indulge in drug diversion or criminal activities or have evident drug-seeking behavior. Close observation of these patients to detect subtle signs is important. The clinical experience of the healthcare provider can help diagnose the presence of prescription drug abuse in patients with chronic pain.

BIOLOGY OF ILLICIT DRUGS

Cocaine

Cocaine is a derivate of the coca alkaloid that is present in the leafy extract of the shrub *Erythroxylon coca* native to South America. Adding water and ammonia or baking soda and then heating coca converts it to the alkalinized form known as cocaine. The purity of cocaine derived by this method of extraction can be as high as 95% with bioavailability of approximately 80% via the inhalation or intranasal routes and 30% via oral ingestion.[3] The onset of cocaine's euphoric effects occur at 3 minutes with intravenous administration, at 15 minutes with intranasal administration, and at 20 minutes with oral administration. Cocaine is metabolized by the liver and plasma cholinesterases to metabolites that are excreted via the kidneys. Common signs and symptoms seen in acute exposures and chronic abuse/overdose of cocaine are listed in Table 1.

Amphetamines and Designer Drugs

Amphetamines, also known as poor man's cocaine, are not strictly illicit if used correctly. However, this class of drug is often abused and can quickly result in an addiction. Amphetamines stimulate the central nervous system and cause euphoria, personality changes such as aggression, and increased alertness. The routes of use include inhalation, intravenous, and oral. The mechanism of action of amphetamine is by sympathetic stimulation through the release of serotonin, dopamine, and noradrenaline.[4] Only about 70% of the drug is metabolized; the rest is excreted unchanged via the kidneys. Urine

Table 2. Common Signs and Symptoms of Acute and Chronic MDMA Abuse

Acute Exposure	Overdose/Chronic Abuse
Euphoria, increased self-awareness	Detrimental effects on serotonergic neurons in central nervous system → memory and cognitive dysfunction, behavioral problems
Altered mental status, tachycardia, tachypnea, sweating, hyperthermia (similar to acute amphetamine ingestion)	Congenital effects such as cardiac anomalies, cleft lip and palate, biliary atresia, fetal intrauterine growth restriction, intrauterine fetal demise, cerebral hemorrhage
Malignant hyperthermia, rhabdomyolysis, kidney failure, heart failure, disseminated intravascular clotting, fulminant liver failure, stroke, seizure, death	

MDMA, 3,4 methylenedioxymethamphetamine, also known as Ecstasy.

testing can detect an amphetamine several days after its last use because of its variable half-life.

Federally controlled substances altered to produce special effects and bypass legal regulations are termed designer drugs. The most commonly used designer drug is Ecstasy—3,4 methylenedioxymethamphetamine—also called MDMA. Ecstasy is both a stimulant and a hallucinogen, and its effects last from 3 hours to several days. Common signs and symptoms seen in acute exposures and chronic abuse/overdose of MDMA are listed in Table 2.

Hallucinogens

The hallucinogens class includes lysergic acid diethylamide (LSD), mescaline, phencyclidine (PCP), and psilocybin. These drugs cause tolerance and psychological drug dependence but not physical drug dependence or withdrawal.

LSD is an odorless and colorless substance obtained from a rye fungus and the seeds of the morning glory plant. It is semisynthetic and produces psychedelic effects such as distortion of time and perceptions of colored visual patterns and abnormal movements. Psychological effects include dysphoria, euphoria, and changes in emotion and moods.[5] LSD also causes multiple physical effects including dilation of the pupils, salivation, dry mouth, loss of appetite, nausea, blurred vision, perspiration, hyperglycemia, hypertension, tachycardia, and hyperthermia. The mechanism of action of LSD is thought to be predominantly by serotonin neurotransporter interactions. Hallucinogen persisting perception disorder, also known as flashbacks, and psychosis are 2 long-term effects that can be exacerbated by other drugs such as sertraline, fluoxetine, and marijuana.

PCP, also known as angel dust, was initially used as an anesthetic, but that use was discontinued because of the drug's intense psychiatric effects: disorientation, agitation, delirium, and hallucination.[3] PCP and its derivatives also produce the phenomenon of dissociation. The mechanism of action of dissociation is thought to result from antagonist, partial agonist, and agonist effects at various receptors, including the serotonin, adrenergic, and dopaminergic receptors. The dissociation usually lasts for about 10 hours after an onset 1 to 2 hours after oral ingestion of the drug. Ketamine, the most well-known PCP derivative, has analgesic, anesthetic, sedative, and amnesic properties.[6] Ketamine activates the sympathetic system, causing myriad effects such as delirium, depression, amnesia, cognitive dysfunction, and dysfunction in long-term memory. Ketamine has N methyl aspartate (NMDA) blocking effects that are important for the treatment of chronic pain in which the NMDA receptors are often activated. Common signs and symptoms seen in acute exposures and chronic abuse/overdose of hallucinogens are listed in Table 3.

Table 3. Common Signs and Symptoms of Acute and Chronic Hallucinogen Abuse

Acute Exposure	Overdose/Chronic Abuse
Visual, auditory, and tactile hallucinations	Respiratory depression, seizures, coma, or death
Distortions of body image, surroundings, and reality	Premature labor and delivery, fetal intrauterine growth restriction, meconium staining, withdrawal syndrome
Anxiety, panic attacks, fear of going crazy	Deposition in fatty tissue that can eventually result in flashbacks
Hypertension and tachycardia, dilated pupils, increased body temperature (sympathetic discharge not as great as with cocaine and amphetamines)	

Table 4. Common Signs and Symptoms of Acute and Chronic Opioid Abuse

Acute Exposure	Overdose/Chronic Abuse
Coma, circulatory collapse, pinpoint pupils, bradycardia, hypothermia, severe respiratory depression	Acute withdrawal: insomnia, dysphoria, restlessness, tachycardia, tachypnea, hypertension, mydriasis, cravings indicated by rhinorrhea, lacrimation, tremors, piloerection, yawning Rare, but in overdoses, there can be pulmonary edema and myocardial infarction Obstetric complications: impaired fetal growth, neonatal abstinence syndrome characterized by tremulousness, irritability, wakefulness, temperature dysregulation

Marijuana

Marijuana, a hallucinogen extracted from the dried leaves of the *Cannabis sativa* plant, is the most commonly abused illicit substance in the United States.[6,7] The active ingredient in marijuana, tetrahydrocannabinol (THC), has psychoactive properties. The drug is most commonly inhaled although it can also be taken orally. Euphoric effects start within minutes and usually subside within 2-3 hours. THC has a relatively long half-life of up to a week, possibly because of its high lipid solubility. Tachycardia, anxiety, and congestion of the conjunctiva are some of the drug's common side effects, and hallucinations, fear, delusions, violent behavior, and depression are some of its adverse effects. Abrupt cessation after chronic use can lead to withdrawal effects manifested by mood alterations and insomnia. Effects associated with chronic use are confusion, shortened memory span, cognitive impairment, dulling of reflexes, and altered perception of time. Because marijuana has both stimulatory and sedative effects, concomitant use of substances such benzodiazepines and alcohol can augment its sedative effects, while the use of substances such as amphetamines and cocaine can augment its stimulatory effects.[8]

Methadone and Heroin

Commonly abused opioids include heroin and methadone. The cost to the US healthcare system of heroin addiction has been estimated to be $22 billion, and the number of heroin users in the US in 1996 was estimated to be 980,000.[9] An increase in the incidence of heroin abuse among pregnant patients was reported in 2003.[10] Common signs and symptoms seen in acute exposures and chronic abuse/overdoses of opioids are listed in Table 4.

Prescription Drugs

Prescription drug abuse with opioids, nonopioid pain relievers, and sedatives and tranquilizers that are often used as adjuncts to pain medications is on the rise.[7] Commonly abused prescription opioids are oxycodone, morphine, codeine, pentazocine, propoxyphene, and fentanyl. Chronic opioid abuse leads to physical dependence, and its cessation leads to withdrawal. Tolerance and physical dependence may be produced by effects at the locus coeruleus by upregulation of the cyclic monophosphate pathway.

HISTORY AND PHYSICAL EXAMINATION

Patients do not always report their opiate use to treating physicians. About 20% of patients under a physician's care do not self-report or have undetected opiate use.[11] Consequently, self-reporting of illicit drug use can be unreliable in patients with chronic pain who use opioids on a long-term basis.[12–16] Patients on long-term opiate therapy for the treatment of pain in the outpatient setting are susceptible to opioid addiction.[17,18]

Monitoring drug levels to ensure patient safety and optimum treatment is essential for successful long-term pain control. Pain medicine has become a vital component of medical treatments, and every practitioner is faced with the issue of providing adequate pain control for patients. However, the success of pain-reducing strategies depends greatly on the patient's previous drug history and the subsequent interactions between pain medications prescribed. After marijuana, alcohol, and tobacco, the most widely abused substances are oxycodone (Oxycontin), diazepam (Valium), and methylphenidate (Ritalin).[7,19] Physicians must be aware of this problem, treat the signs and symptoms of toxicity, consider options such as urine testing to detect drugs, and monitor drug levels.

URINE TESTING

Urine testing can detect metabolites of drugs used by patients and is useful for assessing drug abuse, medication diversion, and drug interactions. Because drug metabolites are excreted in higher concentrations in urine than in blood plasma, many drugs such as opioids can be detected more easily in urine than in blood plasma. Illicit drugs are present in about

10%-39% of patients being treated for chronic pain.[7,20,21]

Although some pain management centers mandate that patients on opioid treatment submit to urine toxicology screens,[22] 2 studies indicate that physicians infrequently use urine drug testing.[23,24] The integration of patient monitoring and urine testing is more effective in detecting drug compliance than the use of a single modality.[11] In addition, the incidence of illicit drug use in patients decreases with random drug testing.[7]

Urine screening is a basic test for opiates, benzodiazepines, marijuana, cocaine, and amphetamines.[25] A drug analysis urine screening kit is inexpensive; the analysis is done via enzyme immunoassay techniques. The validity of the specimen can be checked by determining the urine temperature, urine creatinine, and urine pH. If the specimen was collected within the last 4 minutes, the temperature should be between 90 and 100°F.[25] A valid urine sample should have a pH of 4.5-8.0.[26] A valid urine sample is not likely to have a creatinine concentration $<$20 mg/dL; a concentration $<$20 mg/dL is most likely the result of dilution.[25]

Although urine screening tests are sensitive, they are not highly specific. Many drugs can be missed in a urine screening, including methadone and oxycodone. Because of the lack of specificity, false positive and false negative results are possible.[18] For example, a false positive result for opiates can result after consumption of poppy seeds. In such cases, results can be disproved or confirmed by gas chromatography and mass spectrometry (GC/MS), one of the most effective confirmatory tests.[8,27] GC/MS can be used to confirm the presence of methadone, benzodiazepines, marijuana (THC), tricyclics, opiates, phenothiazine, anticonvulsants, antihistaminics, and cocaine metabolites. GC/MS disproves 11%-21% of urine screens.[11,12,28]

Interpretation of Urine Drug Tests

Practitioners must be familiar with urine screening and interpret the qualitative tests appropriately. Drug interactions must be considered in any interpretation of screening results.

Use of a single opioid can result in more than 1 metabolite, the metabolic product might itself be another opioid, and multiple opioids could be metabolized to the same opioid, leading to challenges in interpretation. For example, patients using morphine, codeine, and heroin could all test positive for the presence of morphine because morphine, codeine, and heroin all metabolize to morphine. A false positive test for hydromorphone can occur when hydrocodone is taken. False negative results can be seen with rapid metabolizers; heroin has a half-life of 30 minutes and the metabolite acetylmorphine has a half-life of 45 minutes. Urine testing is useful when performed 2-4 days after the use of a drug,[29] unlike hair testing that can detect drug use up to 90 days. Most drugs are detectable within 1-3 days after use.[30] A lipid-soluble drug such as marijuana can be detected in the urine up to 1 week after use.

Factors Affecting the Accuracy of Urine Drug Tests

The accuracy of urine drug testing also depends on the volume, duration, and dosage of the drug. For example, prolonged use of benzodiazepines can be detected in the urine for up to 6 weeks, while most opioids are usually detected up to 3 days after use. Human errors and systemic errors such as contamination and mislabeling are other factors that can lead to inaccurate results.

TREATING PAIN IN PATIENTS WITH ADDICTIVE DISORDERS

The comprehensive treatment of pain in a patient with addictive disorder or tolerance must address 3 issues: the patient's addiction, any associated psychiatric conditions, and the patient's pain. Eliciting a detailed history of drug abuse—illicit drugs as well as prescription drugs—and ascertaining if the patient is currently enrolled in a methadone maintenance program for the treatment of drug addiction are vital.

Acute Pain

Acute pain is commonly experienced after surgery, trauma, or labor or caused by diseases such as cancer. Management of acute pain in the addicted patient often requires higher doses of analgesics than are required in the nonaddicted patient because of the phenomenon of tolerance. In patients with a history of opioid abuse, use of nonopioid therapies as well as nonpharmacological interventions can be helpful. Regional blocks, including peripheral nerve, intrathecal, or epidural blocks, are therapies to be considered in patients with drug addiction.

Opioid-addicted patients may be on methadone maintenance programs. In such cases, the baseline methadone used for drug addiction, as well as therapies for the control of postoperative pain, must be included in the perioperative pain management plan.

Use of opioids in patients with a history of addiction can lead to exacerbation of drug abuse. However, a survey of more than 10,000 patients from 151 burn centers showed no incidence of iatrogenic opioid addiction.[31]

A team-oriented, multimodal approach is necessary for the treatment of patients with drug addictions. The treatment should be consistent, structured, and developed in consultation with relevant medical specialists such as psychiatrists and addiction specialists.

Chronic Pain

Pain that continues beyond the expected time of healing or for more than 3 months is termed chronic pain. Chronic pain can develop when acute pain is prolonged and intense, such as after major surgery, after severe trauma, or as a result of painful disease states. Other factors that can play a role in chronic pain include psychiatric and medical comorbities, tobacco use, head trauma history, body mass index, sleep disorders, medications, social support levels, educational status, and current employment.

Chronic pain can result in psychological disturbances that can lead to disruption of sleep patterns, anorexia, irritability, anger, and depression. Therefore, in contrast to acute pain, the treatment of chronic pain has 2 goals: to increase patient functionality and to control pain. To achieve these goals, a number of treatment and assessment approaches have been developed.[32,33]

Patients with addiction disorders should not be denied medication for pain control. Instead, their treatment plan must include awareness and treatment of the dependence.[34–36]

SPECIFIC THERAPEUTIC MODALITIES

Opioids

Opioids have long been used to treat moderate to severe chronic pain and are the cornerstone of pain control in the postoperative period. Physical dependence and tolerance occur, but the phenomenon of addiction occurs only in some patients. Depending on whether the pain state is acute or chronic, the clinician can choose a short-acting opioid such as hydrocodone, tramadol, morphine, hydromorphone, or oxycodone or a longer-acting opioid in a controlled release delivery system, such as oxycodone controlled-release, various extended-release morphine preparations, fentanyl patch, methadone, buprenorphine preparations, or levorphanol.

Discussing the patient's goals prior to the commencement of opioid therapy for chronic pain is an important step. If the goals are not met within a certain period with reasonable escalation of opioids, then alternate pain therapies and nonopioids should be considered. Weaning and cessation of opioids for a period of time and restarting opioids at a lower dose are options.[37] Short-acting opioids are more likely to induce abuse and tolerance than long-acting opioids such as controlled-release opioids and methadone.[38] Inadequate pain relief could be managed by opioid rotation and an increase in opioid doses.[39]

Methadone can prolong the QT interval, and most clinicians require a baseline electrocardiogram prior to initiation of treatment. Further, methadone has multiple metabolism pathways, and other medicines—even over-the-counter agents—can alter its metabolism and elimination.[29,40]

Oxycodone and extended-release hydromorphone have been reformulated in tamper-resistant preparations that render these agents inactive if they are crushed for snorting or injecting. In December 2012, the US Food and Drug Administration Advisory Committee on Anesthetics and Analgesics rejected the application for an extended-release hydrocodone preparation without acetaminophen (Zohydro), and 1 of the factors in the rejection was the preparation's lack of tamper-resistant safeguards.

Considerations for Patients on Methadone

Increased metabolism of methadone occurs in pregnant patients, so the dose of methadone must be adjusted accordingly. A greater incidence of spontaneous abortion occurs in pregnant patients who are using heroin (10%-20%) than in pregnant patients on methadone maintenance (3%-4%).[40] Pregnant patients on methadone maintenance should be continued on their outpatient dose in the postoperative period. Additional therapies for pain control are to be given above the maintenance dose of methadone in the postoperative period.

Considerations for Patients on Buprenorphine

The FDA approved buprenorphine in 2002 for the treatment of opioid dependence. Buprenophine is an agonist-antagonist, and pain management for patients on buprenorphine can be a challenge. The clinical efficacy of buprenorphine results from its unique molecular structure: it is a kappa agonist providing spinal cord analgesia and a partial mu opioid agonist resulting in withdrawal if patients are taking other opiate agents. Buprenorphine is used to treat addiction in the United States in the form of the sublingual preparation Suboxone, a combination of buprenorphine and naloxone. The primary role of naloxone is to prevent the abuse of Suboxone such as from intravenous injection that would result in rapid opioid antagonist effects.

Several studies in France have validated the use of buprenorphine in pregnancy for maintenance therapy.[41–43] In addition to the French studies, some American studies demonstrated positive findings for the use of buprenorphine as maintenance therapy in pregnant patients with opioid addiction.[42] However, a

Finnish study demonstrated a higher incidence of infant death and neonatal abstinence syndrome in pregnant patients on buprenorphine maintenance therapy compared to the national register.[43]

CONCLUSION

Providing adequate pain management in the presence of drug tolerance is a challenge to practitioners of every medical specialty. Illicit drug use is on the rise in the United States and around the world. Prescription pain relievers such as codeine, meperidine, morphine, fentanyl, hydromorphone, hydrocodone, methadone, and oxycodone; sedatives; and tranquilizers are among the prescription medications that are used and abused nonmedically in the United States.

Benzodiazepines combined with abused sedatives, tranquilizers, and opiates can potentiate the side effects of the drugs taken concurrently and result in intoxication and catastrophic consequences. Urine testing can detect metabolites of commonly abused drugs, and this information can be used to treat patients with pain more effectively and also to improve doctor-patient relationships.

Abrupt cessation of drugs being abused could cause withdrawal symptoms manifesting as convulsions, psychotic episodes, electrolyte imbalances, and hemodynamic changes that could be life threatening. In addition, patients with pain who have histories of drug abuse often present with a multitude of medical and psychosocial issues that hinder pain and symptom management.

The neuropharmacologic phenomena of physical dependence and tolerance and the neuropharmacologic and behavioral phenomenon of addiction should also be taken into consideration when treating pain in drug-abusing patients. Multidisciplinary pain management, supportive care, acute medical observation, and timely interventions as necessary are the keys to safe outcomes in these patients.

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