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467 Opioid-Related Disorders

cognitive behavioral techniques have also shown clinically significant improvements in abstinence and reduced cannabis use.

OTHER ADVERSE EFFECTS ■ ■MENTAL ILLNESS The association between marijuana use and increased risk of mental illnesses is an area of major concern. The risk of psychosis increases with the frequent consumption of high-THC-content cannabis (>10% THC). Even upon first exposure, high-potency cannabis can trigger acute psychotic episodes, which constitute one of the main causes for emergency department (ED) visits associated with cannabis use. Most of these psychotic episodes are transient but can become chronic with regular cannabis use. In those vulnerable, cannabis may trigger or exac erbate the presentation of schizophrenia. Many earlier studies (though not all) have linked adolescent cannabis use with higher risk and earlier onset of chronic psychosis, particularly for those using cannabis at higher frequency or with higher D9THC content. A large recent study showed a stronger association between cannabis use during adoles cence and risk of psychotic disorder than that documented in previous studies, consistent with the rise in cannabis potency. Concerns have also been raised regarding cannabis use during adolescence and a higher risk for depression and suicidality, though these associations have been much less studied. PART 13 Neurologic Disorders ■ ■ACCIDENTS Cannabis use increases the risk of injuries when driving under its influence. D9THC impairs judgment, motor coordination, and reac tion time, all necessary for safe driving. Studies have found a direct relationship between blood D9THC levels and impaired driving ability. ■ ■ACUTE AND CHRONIC TOXICITY The increased availability of high-D9THC-content products over the past decade has been paralleled by increased marijuana-related ED vis its and hospital admissions. Such emergencies can be caused by acute toxicity and chronic use syndromes. Cannabis edibles are involved in a significant portion of acute cannabis toxicity events. Patients include children accidentally consuming sweet edibles and infrequent users such as “cannabis tourists” with limited experience of the consumed products or the longer onset time of edible products. Actual D9THC dose is difficult to envisage, for both edible or inhaled products, so naïve or infrequent users are at increased risk of overdosing. Can nabis toxicity is frequently manifested by severe anxiety, tachycardia, and even acute psychoses. Chronic high-dose cannabis use can also induce a cannabis hyperemesis syndrome (presenting as severe cycles of nausea, vomiting, and abdominal pain), a growing cause for ED and hospital admissions. THERAPEUTIC POTENTIAL Currently, no FDA-approved medications contain cannabis-derived THC, although synthetic D9THC (or dronabinol) is approved for treatment of chemotherapy-induced nausea and appetite stimulation. Several countries have approved the cannabis-derived

D9THC:CBD formulation Sativex for treating chronic pain and multiple sclerosis (MS)-induced spasticity. However, evidence of Sativex efficacy in MS is largely based on patient reports. Chronic pain is one of the most frequent indications for which medical marijuana is used. A recent analysis of data from the New York prescription drug monitoring data base, from the years 2017-2019, revealed that chronic pain patients on long-term stable doses of opioid therapy (n >8000) who used medical marijuana for >8 months (compared to those who used medical marijuana for <30 days to 8 months) had a 30–50% reduction in opioid use. ■ ■FURTHER READING Albaugh MD et al: Association of cannabis use during adolescence with neurodevelopment. JAMA Psychiat 78:1, 2021. Evanski JM et al: The first “hit” to the endocannabinoid system? Associations between prenatal cannabis exposure and frontolimbic white matter pathways in children. Biol Psychiatry Glob Open Sci 4:11, 2024.

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Opioid-Related Disorders Opioid analgesics have been used since at least 300 b.c. Nepenthe (Greek for “free from sorrow”) helped the hero of the Odyssey, but widespread opium smoking in China and the Near East has caused harm for centuries. Since the first chemical isolation of opium and codeine 200 years ago, a wide range of synthetic opioids have been developed, and opioid receptors were cloned in the 1990s. Two of the most important adverse effects of all these agents are the development of opioid use disorder and overdose. Prescription opioids are primarily used for pain management, but due to ease of availability individuals procure and misuse these drugs with dire consequences. In 2022, for example, 8.9 million United States residents misused pain relievers and

> “ 76,000 overdose deaths involved opioids, nearly half combined with stimulants. These numbers continue to increase and have accelerated due to mixing of high-potency fentanyl derivatives with other opioids and stimulants. The accelerating death rates are partially because rever sal of fentanyl overdoses can require severalfold larger doses of nalox one than the doses in the

> intranasal devices used for nonmedical street resuscitations. Fentanyl-associated deaths also increased during the COVID-19 pandemic. The World Drug Report attributes the greatest global burden of morbidity and mortality to opioid misuse, including disease transmission, increased health care, crime, law enforcement, family distress, and lost productivity. The terms dependence and addiction have been replaced with opioid use disorder, opioid intoxication, and opioid withdrawal. Opioid use disorder is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; 2022) as the repeated use of the opiate during a 12-month period while producing problems in two or more areas including tolerance, withdrawal, use of greater amounts of opioids than intended, craving, and use despite adverse consequences. This new definition reduces the diagnostic criteria from three problem areas to two, but this reduction has not changed the rates of these disorders because most opioid-using individuals meet more than three criteria.

A striking recent aspect of illicit opioid use has been its marked increase as the gateway to illicit drugs in the United States. Since 2007, prescription opiates have surpassed marijuana as the most common illicit drug that adolescents initially use, although overall rates of opi oid use are far lower than marijuana. The most used opioids had been diverted prescriptions for oxycodone and hydrocodone until about 2015, when fentanyl misuse and lethal overdose rose exponentially. Two opi oid maintenance treatment agents—methadone and buprenorphine— are also misused, but at substantially lower rates, and the partial opioid agonists such as butorphanol, tramadol, and pentazocine are misused even less frequently. Because the chemistry and general pharmacology of these agents are covered in major pharmacology texts, this chapter focuses on neurobiology and pharmacology relevant to opioid use disor der and its treatments. Although the neurobiology of misuse involves all four of the known opioid receptors—mu, kappa, delta, and nociceptin/orphanin—the mu receptor is the most clinically related to opioids. ■ ■NEUROBIOLOGY After binding to mu opioid receptors, opioids downregulate intracel lular messenger systems and activate potassium ion channels, as sum marized in Table 467-1. All opioid receptors are G protein–linked and coupled to the cyclic adenosine monophosphate (cAMP) second mes senger system and to G protein–coupled inwardly rectifying potassium channels (GIRKs). The GIRKs increase permeability to potassium ions, causing hyperpolarization and inhibiting action potential production. Thus, opioids inhibit the activity of all neurons with opioid receptors and induce analgesia, sedation, and drug reinforcement through vari ous brain pathways. Relevant pathways for the reinforcing euphoric effects of opioids include the mesolimbic dopaminergic pathway from the ventral teg mental area (VTA) to the nucleus accumbens (NAc), where opioids indirectly increase synaptic levels of dopamine through inhibition of GABAergic neurons that inhibit both the VTA and the NAc. The positive subjective effects of opioid drugs also include mu receptor desensitization and internalization, potentially related to stimulation of β-arrestin signaling pathways. However, the “high” only occurs when the rate of change in dopamine is fast. Large, rapidly administered doses of opioids block γ-aminobutyric acid (GABA) inhibition and produce a burst of VTA dopamine neuron activity that is associated with a “high” in commonly misused substances. Therefore, routes of administration that slowly increase opioid blood and brain levels, such as oral and transdermal routes, are effective for analgesia and sedation but do not produce an

opioid “high” that follows smoking and intra venous routes. Other acute effects such as analgesia and respiratory β-endorphin enkephalins K+ μ μ Na+ Na+ Gi/o Gi/o AC Nucleus Nucleus PKA PKA BDNF BDNF TH TH cAMP cAMP CREB CREB A B FIGURE 467-1 Normal mu-receptor activation by endogenous opioids inhibits the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-cAMP responseelement binding protein (CREB) cascade in noradrenergic neurons within the locus coeruleus (A) through inhibitory Gi/o protein influence on adenylyl cyclase (AC). Similarly, acute exposure to opioids (e.g., morphine) inhibits this system, whereas chronic exposure to opiates (B) leads to upregulation of the cAMP pathway in an attempt to oppose opioid-induced inhibitory influence. Upregulation of this system is involved in opioid tolerance, and when the opioid is removed, unopposed noradrenergic neurotransmission is involved in opioid withdrawal. Upregulated PKA phosphorylates CREB, initiating the expression of various genes such as tyrosine hydroxylase (TH) and brain-derived neurotrophic factor (BDNF). BDNF is implicated in long-term neuroplastic changes in response to chronic opioids.

TABLE 467-1 Actions of Opioid Receptors RECEPTOR TYPE ACTIONS Mu (μ) (e.g., morphine, buprenorphine) Analgesia, reinforcement euphoria, cough and appetite suppression, decreased respirations, decreased GI motility, sedation, hormone changes, dopamine and acetylcholine release Dysphoria, decreased GI motility, decreased appetite, decreased respiration, psychotic symptoms, sedation, diuresis, analgesia Kappa (κ) (e.g., butorphanol) Analgesia, euphoria, physical dependence, hormone changes, appetite suppression, dopamine release Delta (δ) (e.g., etorphine) Nociceptin/orphanin (e.g., buprenorphine) Analgesia, appetite, anxiety, tolerance to opioids, hypotension, decreased GI motility, 5-HT and NE release Abbreviations: GI, gastrointestinal; 5-HT, serotonin; NE, norepinephrine. CHAPTER 467 depression involve opioid receptors located in other brain areas such as the periaqueductal grey for pain and medulla oblongata for respiration. Opioid tolerance and withdrawal are related to genetic polymor phisms that impact several proteins and that after chronic opioid dos ing affect the functioning of the cAMP–protein kinase A (PKA)–cAMP response-element binding protein (CREB) intracellular cascade within the locus coeruleus (LC) (Fig. 467-1). Up to 50% of the risk for with drawal is related to specific functional polymorphisms including one in the mu opioid receptor gene producing a threefold increase in this receptor’s affinity for opioids and the endogenous ligand β-endorphin. Epigenetic DNA methylation changes in the mu receptor gene also appear to act as compensation by inhibiting gene transcription and reducing the number of mu receptors. Opioid-Related Disorders After chronic opioid dosing and its sustained inhibition of the cAMP molecular cascade as shown in Fig. 467-1, a compensation occurs in this cascade within the LC neurons that mediate opioid toler ance and withdrawal. Noradrenergic (NE) neurons in the LC activate the cerebral cortex. When large opioid doses saturate and activate all of the LC’s mu receptors, action potentials cease. When this direct inhibi tory effect is sustained over weeks and months of opioid use, a second ary set of adaptive changes occur to upregulate cyclic AMP enzyme activity. When the inhibiting opioid is abruptly discontinued, overac tivity occurs in NE neurons of the LC that contribute to withdrawal symptoms (Fig. 467-1). This molecular model of NE neuronal activa tion during withdrawal has had important treatment implications, such as the use of the presynaptic α2-agonists clonidine and lofexidine to treat opioid withdrawal by again suppressing NE neuronal activation Morphine HO H H O N CH3 K+ HO Modified gene expression, neuroplasticity, genetic effects AC

through feedback inhibition of this neuronal activity. Other contribu tors to withdrawal include deficits within the dopamine reward system and overactive neurotransmission within the

glutamatergic system.

■ ■PHARMACOLOGY Tolerance and withdrawal commonly occur with chronic daily use, developing as quickly as 6–8 weeks depending on dose concentration and dosing frequency. Tolerance is primarily pharmacodynamic with relatively limited induction of cytochrome P450 2D6 and 3A4 or other liver enzymes. Metabolism then includes conjugation to glucuronic acid and excretion of small amounts in feces. The plasma half-lives generally range from 2.5 to 3 h for morphine and >22 h for methadone. The shortest half-lives of several minutes are for fentanyl-related opi oids, and the longest are for buprenorphine and its active metabolites, which can block opioid withdrawal for up to 3 days after a single dose. Tolerance to opioids leads to the need for increasing amounts of drugs to sustain the desired euphoric effects—as well as to avoid the discom fort of withdrawal. This combination has the expected consequence of strongly reinforcing misuse once it has started. Methadone taken chronically at maintenance doses is stored in the liver, which may reduce the occurrence of withdrawal between daily doses. The role of endogenous opioid peptides in tolerance and withdrawal is uncertain. PART 13 Neurologic Disorders The clinical features of opioid misuse are tied to the route of admin istration and rapidity of the drug reaching the brain. Intravenous and smoked administration rapidly produces high drug concentrations in the brain. This produces a “rush,” followed by euphoria, a feeling of tranquility, and sleepiness (“the nod”). Heroin produces effects that last 3–5 h, and several doses a day are required to forestall manifestations of withdrawal in chronic users. Symptoms of opioid withdrawal begin 8–10 h after the last dose; lacrimation, rhinorrhea, yawning, and sweat ing appear first. Restless sleep followed by weakness, chills, gooseflesh (“cold turkey”), nausea and vomiting, muscle aches, involuntary move ments (“kicking the habit”), hyperpnea, hyperthermia, and hyperten sion occur in later stages of the withdrawal syndrome. The acute course of withdrawal may last 7–10 days. A secondary phase of protracted abstinence lasts for 26–30 weeks and is characterized by hypotension, bradycardia, hypothermia, mydriasis, and decreased responsiveness of the respiratory center to carbon dioxide. Besides the brain effects of opioids on sedation and euphoria and the combined brain and peripheral nervous system effects on analgesia, a wide range of other organs can be affected. The release of several pitu itary hormones is inhibited, including corticotropin-releasing factor (CRF) and luteinizing hormone, which reduces levels of cortisol and sex hormones and can lead to impaired stress responses and reduced libido. An increase in prolactin also contributes to the reduced sex drive in males. Two other hormones affected are thyrotropin, which is reduced, and growth hormone, which is increased. Respiratory depres sion results from opioid-induced insensitivity of brainstem neurons to increases in carbon dioxide, and in patients with pulmonary disease, this can result in clinically significant complications. In overdoses, aspiration pneumonia is common due to loss of the gag reflex. Opioids reduce gut motility, which is helpful for treating diarrhea but can lead to nausea, constipation, and anorexia with weight loss. Deaths occurred in early methadone maintenance programs due to severe constipa tion and toxic megacolon. Opioids such as methadone may prolong QT intervals and lead to sudden death in some patients. Orthostatic hypotension may occur due to histamine release and peripheral blood vessel dilation, which is an opioid effect usefully applied to managing acute myocardial infarction. During opioid maintenance, interactions with other medications are of concern; these include inducers of the cytochrome P450 system (usually CYP3A4) such as rifampin and carbamazepine. Heroin users, in particular, tend to use opioids intravenously and are likely to be polydrug users, also using alcohol, sedatives, cannabinoids, and stimulants. None of these other drugs are substitutes for opioids, but they have desired additive effects. Therefore, one needs to be

sure that the person undergoing a withdrawal reaction is not also withdraw ing from alcohol or sedatives, which might be more dangerous and more difficult to manage.

Intravenous opioid use carries with it the risk of serious compli cations. The common sharing of hypodermic syringes can lead to infections with hepatitis B and HIV/AIDS, among others. Bacte rial infections can lead to septic complications such as meningitis, osteomyelitis, and abscesses in various organs. Off-target effects or additions of other agents to opioids synthesized in illicit drug labs can lead to serious toxicity. For example, attempts to illicitly manufacture meperidine in the 1980s produced a parkinsonism-inducing neuro toxin, MPTP (Chap. 446). More recently, adding xylazine to illicit fentanyl markedly increased fentanyl's respiratory suppression, leading to overdose deaths. Individuals who inject fentanyl and xylazine also can develop necrosis and have an increased risk of limb amputation. TREATMENT Opioid Overdose The acute treatment of opioid overdose with naloxone or nalmefene is a medical emergency, and after reversal of that life-threatening complication, clinicians have two general treatment options: opioid maintenance or detoxification. Opioid agonist and partial agonist medications are commonly used for both maintenance and detoxi fication purposes. α2-Adrenergic agonists are primarily used for detoxification. Antagonists are used to accelerate detoxification and then continued after detoxification to prevent relapse. The residential medication-free programs have had some success but generally less than the medication-based programs. Success of the various treatment approaches is assessed as retention in treatment and reduced opioid and other drug use; secondary outcomes, such as reduced HIV risk behaviors, crime, psychiatric symptoms, medi cal comorbidity, and overdoses, also indicate successful treatment. Potentially lethal overdoses require rapid recognition and treat ment with naloxone or nalmefene, two highly specific reversal agents that are relatively free of complications. The diagnosis is based on recognition of characteristic signs and symptoms, includ ing shallow and slow respirations, pupillary miosis (mydriasis does not occur until significant brain anoxia supervenes), bradycardia, hypothermia, and stupor or coma. Blood or urine toxicology stud ies can confirm a suspected diagnosis, but immediate management must be based on clinical criteria. If naloxone is not administered, progression to respiratory and cardiovascular collapse leading to death occurs. With fentanyl overdoses, the naloxone dose may be twice that needed for other opioids, and recent rescue preparations contain twice the traditional dosing. Additionally, nalmefene has recently become available for treatment of overdose and has higher potency and lasts longer than naloxone. Opioids generally do not produce seizures except for unusual cases of polydrug use with the opioid meperidine, with high doses of tramadol, or in the newborn. In addition to naloxone, management of overdose requires sup port of vital functions, including intubation if needed (Table 467-2). If the overdose is due to buprenorphine or fentanyl, then naloxone might be required at total doses of 10 mg or greater, but primary buprenorphine overdose is nearly impossible because this agent is a partial opioid agonist, meaning that as the dose of buprenorphine is increased, it has greater opioid antagonist than agonist activity. Thus, a 0.2-mg buprenorphine dose leads to analgesia and seda tion, while a hundred times greater 20-mg dose produces profound TABLE 467-2 Management of Opioid Overdose Establish airway. Intubation and mechanical ventilation may be necessary. Naloxone 0.4–2.0 mg (IV, IM, or endotracheal tube). Onset of action with IV is ~1–2 min. Repeat doses of naloxone if needed to restore adequate respiration or a continuous infusion of naloxone can be used. One-half to two-thirds of the initial naloxone dose that reversed the respiratory depression is administered on an hourly basis (note: naloxone dosing is not necessary if the patient has been intubated).

opioid antagonism, precipitating opioid withdrawal in a person who had opioid use disorder from morphine or methadone. It is important to recognize that the goal is to reverse respiratory depres sion and not to administer so much naloxone that it precipitates opiate withdrawal. Because naloxone only lasts a few hours and most opioids last considerably longer, an IV naloxone drip with close monitoring is frequently employed to provide a continuous level of antagonism for 24–72 h depending on the opioid used in the overdose (e.g., morphine vs methadone). Whenever nalox one has only a limited effect, other sedative drugs that produce significant overdoses must be considered. The most common are benzodiazepines, which have produced overdoses and deaths in combination with buprenorphine. A specific antagonist for benzo diazepines, flumazenil at 0.2 mg/min can rapidly reverse overdoses, but it may precipitate seizures and increase intracranial pressure. Like naloxone, administration for a prolonged period is usually required because most benzodiazepines remain active for consider ably longer than flumazenil. Support of vital functions may include oxygen and positive-pressure breathing, IV fluids, pressor agents for hypotension, and cardiac monitoring to detect QT prolongation, which might require specific treatment. Activated charcoal and gas tric lavage may be helpful for oral ingestions, but intubation will be needed if the patient is stuporous. OPIOID WITHDRAWAL The principles of detoxification are the same for all drugs: to sub stitute a longer-acting, orally active, pharmacologically equivalent medication for the substance being used, stabilize the patient on that medication, and then gradually withdraw the substituted medication. Methadone and buprenorphine are the two principal medications used to treat opioid use disorder. Clonidine, a centrally acting sympatholytic agent, has also been used for detoxification in the United States. By reducing central sympathetic outflow, clonidine mitigates many of the signs of sympathetic overactivity but typically requires augmentation with other agents. Clonidine has no narcotic action and is not addictive. Lofexidine, a clonidine analogue with fewer hypotensive effects, was approved for use in the United States in 2018 for management of opioid withdrawal symptomology. Methadone for Detoxification Dose-tapering regimens for detox ification using methadone range from 2–3 weeks to as long as 180 days, but this approach is controversial given the relative effectiveness of methadone maintenance and the low success rates of detoxification. Unfortunately, most patients tend to relapse to heroin or other opioids during or after the detoxification period, indicative of the chronic and relapsing nature of opioid use disorder. Buprenorphine for Detoxification Buprenorphine does not appear to lead to better outcomes than methadone but is superior to cloni dine in reducing symptoms of withdrawal, in retaining patients in a withdrawal protocol, and in completing treatment, although it can precipitate withdrawal in patients dependent on fentanyl or on maintenance doses of methadone (>80 mg daily). `2-Adrenergic Agonists for Detoxification Several α2-adrenergic agonists have relieved opioid withdrawal by suppressing brain NE hyperactivity. Clonidine relieves some signs and symptoms of opi oid withdrawal such as lacrimation, rhinorrhea, muscle pain, joint pain, restlessness, and gastrointestinal symptoms. Related agents are lofexidine, guanfacine, and guanabenz acetate. Lofexidine can be dosed up to ~2 mg/d and appears to be associated with fewer adverse effects. Clonidine or lofexidine is typically administered orally, in three or four doses per day, with dizziness, sedation, leth argy, and dry mouth as the primary adverse side effects. Outpatientmanaged withdrawal regimens require close follow-up, often with naltrexone maintenance to prevent relapse. Rapid and Ultrarapid Opioid Detoxification The opioid antago nist naltrexone, typically combined with an α2-adrenergic agonist, has been purported to shorten the duration of withdrawal without

significantly increasing patient discomfort. Completion rates using naltrexone and clonidine range from 75 to 81% compared to 40 to 65% for methadone or clonidine alone. Ultrarapid opioid detoxi fication is an extension of this approach using anesthetics but is highly controversial due to the medical risks and mortality associ ated with it.

Medications for Preventing Relapse to Illicit Opioids

Stopping opioid use is much easier than preventing relapse. Long-term relapse prevention for individuals with opioid use disorder requires combined pharmacologic and psychosocial approaches. Chronic users tend to prefer pharmacologic approaches; those with shorter histories of drug use are more amenable to detoxification and psychosocial interventions. Methadone maintenance substitutes a once-daily oral opioid dose for three to four times daily heroin. Methadone saturates the opioid receptors and, by inducing a high level of opioid tolerance, blocks the euphoria from additional opioids. Buprenorphine, a partial opioid agonist, also can be given once daily at sublingual doses of 4–32 mg daily, and in contrast to methadone, it can be given in an office-based primary care setting. CHAPTER 467 Opioid-Related Disorders METHADONE MAINTENANCE Methadone's slow onset of action when taken orally, long elimination half-life (24–36 h), and production of cross-tolerance at doses from 80 to 150 mg are the basis for its efficacy in treatment retention and reductions in IV drug use, criminal activ ity, and HIV risk behaviors and mortality. Methadone can prolong the QT interval at rates as high as 16% above rates in non-methadonemaintained, drug-injecting patients, but it has been used safely in the treatment of opioid use disorder for >40 years. BUPRENORPHINE MAINTENANCE Sublingual buprenorphine main tenance was first approved by the U.S. Food and Drug Administration (FDA) in 2002 as a Schedule III drug for managing opioid use disorder. Unlike the full agonist methadone, buprenorphine is a partial agonist of mu-opioid receptors with a slow onset and long duration of action. Its partial agonism reduces the risk of unintentional overdose but lim its its efficacy to patients who need the equivalent of only 60–70 mg of methadone, and many patients in methadone maintenance require higher doses of up to 150 mg daily. Buprenorphine is combined with naloxone at a 4:1 ratio to reduce its abuse liability. Because of pediatric exposures and diversion of buprenorphine to illicit use, mucosal films are now used rather than sublingual pills that can be crushed and snorted. A long-acting buprenorphine injection that lasts a month is also available to prevent illicit diversion and to enhance compliance. Primary care physicians often prescribe buprenorphine for opioid use disorder, which has reduced opioid-related deaths and druginjection-related medical morbidity with treatment retention as high as 70% over a 6-month follow-up period. Opioid Antagonist Medications Antagonist therapy blocks the action of self-administered opioids and should eventually extinguish the habit, but this therapy is poorly accepted by patients. Naltrexone, a long-acting pure opioid antagonist, can be given orally three times a week, or by monthly injection, which markedly improves adherence, retention, and drug use. Because it is an antagonist, the patient must first be detoxified from opioids before starting naltrexone. It is safe even when taken chronically for years, is associated with few side effects (headache, nausea, abdominal pain), and can be given to patients infected with hepatitis B or C without producing hepatotoxicity. How ever, most providers refrain from prescribing naltrexone if liver func tion tests are three times above normal levels. Naltrexone maintenance combined with psychosocial therapy is effective in reducing heroin use. Medication-Free Treatment Most opioid users enter medicationfree treatments in inpatient, residential, or outpatient settings, but 1- to 5-year outcomes are very poor compared to pharmacotherapy except for residential settings lasting 6–18 months. The residential programs require full immersion in a regimented system with

progressively increasing levels of independence and responsibility within a controlled

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