REVIEW ARTICLE

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Treatment of Opioid-Use Disorders

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N Engl J Med 2016; 375:357-368 | July 28, 2016 | DOI: 10.1056/NEJMra1604339

This article provides an overview of the current treatment of opioid-related conditions, including treatments provided by general practitioners and by specialists in substance-use disorders. The recent dramatic increase in misuse of prescription analgesics, the easy accessibility of opioids such as heroin on the streets, and the epidemic of opioid overdoses underscore how important it is for physicians to understand more about these drugs and to be able to tell patients about available treatments for substance-use disorders.

Opioids include most prescription analgesics as well as products of the poppy plant (e.g., opium, morphine, and codeine).[1] Although opioids usually are prescribed to control pain, diminish cough, or relieve diarrhea, they also produce feelings of euphoria, tranquility, and sedation that may lead the patient to continue to take these drugs despite the development of serious related problems. These problems include the need to escalate doses in order to achieve these desired effects; such levels of opioids can overwhelm respiratory drive and lead to death.[1,2] Opioid-use disorders are seen in persons from all educational and socioeconomic backgrounds. Recognition of such disorders has contributed to efforts to change physicians' prescribing practices and to train first responders regarding the parenteral administration of naloxone (Narcan or Evzio), a mu-opioid receptor antagonist.[2]

In the United States, an estimated 400,000 persons have used heroin in the past month and 4 million have reported nonmedical use of prescription pain relievers.[3-5] By some estimates, almost 17,000 deaths per year are related to opioids; drug poisoning is one of the leading causes of accidental death in the United States. Approximately 3 million persons in the United States and almost 16 million worldwide have a current or past opioid-use disorder.[6] The global burden of disease from opioid-related conditions approaches 11 million life-years lost from health problems, disabilities, and early death.[7]

In the 2013 *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (Table 1), an opioid-use disorder is defined as the repeated occurrence within a 12-month period of 2 or more of 11 problems, including withdrawal, giving up important life events in order to use opioids, and excessive time spent using opioids. A cluster of 6 or more items indicates a severe condition.[4,8]

TABLE 1

Diagnostic Criteria for an Opioid-Use Disorder.

The clinical course of opioid-use disorders involves periods of exacerbation and remission, but the underlying vulnerability never disappears.[1] This pattern is similar to that of other chronic relapsing conditions (e.g., diabetes and hypertension) in which perfect control of symptoms is difficult and patient adherence to treatment is often incomplete. Although persons with opioid problems are likely to have extended periods of abstinence from opioids and often do well,[9] the risk of early death, primarily from an accidental overdose, trauma, suicide, or an infectious disease (e.g., human immunodeficiency virus [HIV] infection), is increased by a factor of 20.[10-15] Legal problems are especially likely in persons with criminal records and high impulsivity.[13] The risk of adverse outcomes decreases markedly with abstinence from opioids.[9,16]

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TREATMENT OF OPIOID-WITHDRAWAL SYNDROMES

Treatment of acute withdrawal syndromes (i.e., medically supervised withdrawal or detoxification)[17] can improve the patient's health and facilitate his or her participation in a rehabilitation program. This treatment also may help patients better consider abstinence from opioids because they can think more clearly once the acute withdrawal phase has passed. However, by itself, medically supervised withdrawal is usually not sufficient to produce long-term recovery, and it may increase the risk of overdose among patients who have lost their tolerance to opioids (i.e., the need for higher doses of the drug to produce effects) and resume the use of these drugs.[10,12] Repeated misuse of opioids produces tolerance as well as long-lasting craving that usually requires additional treatment in order to avoid a relapse of drug use.

The abrupt discontinuation of opioids after long-term, intense use produces symptoms that are opposite to those of the acute effects that result from physiologic changes during drug use. These changes result in what might be called physical dependence, although physical dependence is not part of the official diagnostic nomenclature. Withdrawal syndromes include physical symptoms (e.g., diarrhea and dilated pupils), generalized pain, and psychological symptoms (e.g., restlessness and anxiety) (Table 2).[18] Symptoms of abstinence syndromes after discontinuation of shorter-acting opioids such as heroin begin within hours after receiving the prior dose and decrease greatly by day 4, whereas with misuse of longer-acting opioids, such as methadone (Dolophine), withdrawal begins after several days and decreases at approximately day 10. Opioid antagonist–precipitated withdrawal begins almost immediately and lasts approximately an hour after intramuscular or subcutaneous administration of 0.4 to 2 mg of the short-acting antagonist naloxone every 2 to 3 minutes (up to a total dose of 10 mg). Acute withdrawal symptoms are followed by weeks to months of protracted withdrawal syndromes that include fatigue, anhedonia, a poor appetite, and insomnia.[1,19]

TABLE 2

Clinical Opiate Withdrawal Scale for Measuring Symptoms.

The most effective approach to treating a patient who has withdrawal is to prescribe a long-acting oral opioid (usually methadone or buprenorphine [Buprenex]) to relieve symptoms and then gradually reduce the dose to allow the patient to adjust to the absence of an opioid. However, only licensed addiction-treatment programs (both office-based treatments and inpatient treatments) and physicians who have completed specific training regarding opioid drugs can administer opioids to treat opioid-use disorders.[20] Such medically supervised withdrawal can also involve the use of nonopioid medications that help to control symptoms.[21,22]

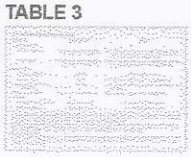
This section thus begins with the more generally available but less effective withdrawal regimen with the use of less closely controlled medications than those that are available in specialty clinics.

This review does not describe ultrarapid protocols that precipitate withdrawal with the use of naltrexone in heavily sedated patients because the close medical monitoring of heavily sedated patients is more expensive and more dangerous and produces no better outcomes than the opioid tapers discussed below. Finally, ultrarapid withdrawal protocols by themselves are not likely to increase long-term abstinence from opioids.

Decreasing Symptoms with α_2-Adrenergic Agonists and Other Nonopioid Agents

As indicated in Table 3, α_2-adrenergic agonists such as clonidine (Catapres) or tizanidine (Zanaflex) can be used on an off-label basis to decrease anxiety, piloerection, and other signs and symptoms of autonomic overactivity.[22] Anxiety and insomnia are treated with benzodiazepines or other sedating drugs. Diarrhea, nausea, and vomiting are addressed with loperamide (Imodium), prochlorperazine (Compazine), or both, along with sports drinks or intravenous fluids. Pain is mitigated with nonsteroidal antiinflammatory agents such as naproxen (Aleve). Such combination therapies are superior to placebo in alleviating symptoms, but they are not as effective in relieving symptoms as a methadone or buprenorphine taper.

TABLE 3



Opioid-free Treatment of Opioid Withdrawal.

Opioids for Treating Withdrawal

Although methadone and buprenorphine for withdrawal are administered only in specialty programs by physicians with special training, it may be useful for nonspecialists to understand these approaches in order to explain the treatment process to patients whom they refer to specialty programs. Because opioid-withdrawal syndromes are caused by rapidly decreasing drug levels after repeated exposure, symptoms can be reduced by administering other opioids to diminish symptoms and then weaning the patient off the new drug.[1,4,23] Although any mu-opioid receptor agonist that is long-acting (to create a smoother withdrawal) and oral (for ease of administration) might work, most studies have focused on methadone or buprenorphine.

Methadone Taper

Methadone, an oral mu-opioid agonist, has a half-life of 15 to 40 hours.[23] Controlled trials show that

the use of methadone tapers in patients who misuse other opioids is superior to placebo and α_2-adrenergic agonist-based regimens for managing withdrawal symptoms and retaining patients in treatment programs.[24]

The condition of patients is first stabilized with a dose that mitigates withdrawal but does not oversedate (Table 4). Then, in outpatients, doses are decreased by 10 to 20% every 1 to 2 days over 2 to 3 weeks or longer.[25] The taper can occur over approximately 1 week in inpatients who are going through withdrawal from short-acting drugs such as heroin and, as discussed below, can be as slow as 3% of the dose per week in patients who are discontinuing methadone maintenance.[26] Flexible administration of the drug on the basis of a patient's response is important.

TABLE 4

Treatment for Symptoms of Opioid Withdrawal with the Use of a Taper with Long-Acting Opioid Agonists or Partial Agonists.

Buprenorphine Taper

Buprenorphine is an analgesic that is available as a sublingual monotherapy or in combination with naloxone as a film strip for sublingual use (e.g., Suboxone or as a generic formulation) or in a buccal dissolving film (Bunavail). This review focuses on buprenorphine itself, which is a mu-opioid receptor partial agonist (binding only partially to the mu-opioid receptor with resulting competitive antagonism of concomitantly administered full agonist drugs), an agonist of delta and opioid-like receptor-1 (or nociceptin) opioid receptors, and a kappa-receptor antagonist.[27-29] Like methadone, it has advantages of oral administration and a long "functional" half-life. (With a half-life of 3 hours, buprenorphine does not easily disassociate from mu-opioid receptors.)

Methadone and buprenorphine produce similar improvements during opioid withdrawal, although buprenorphine is associated with less sedation and respiratory depression. To avoid precipitating more intense withdrawal, buprenorphine should be initiated 12 to 18 hours after the last administration of opioids in patients who misuse shorter-acting opioids (48 hours in patients who are receiving long-acting drugs such as methadone), with initial doses of 4 to 8 mg. Additional doses up to 16 mg may be administered, depending on the patient's response. After the patient's condition is stabilized for 3 to 5 days, the dose is often decreased over 2 or more weeks; more opioid-free urine samples are seen with a 4-week reduction protocol than with a shorter reduction protocol.

APPROACHES TO REHABILITATION AND MAINTENANCE

Background

Once patients express interest in discontinuing or diminishing drug use, the core of care depends on the same kinds of cognitive behavioral approaches that are used for other chronic, relapsing conditions, such as hypertension and diabetes mellitus.[1,30] These approaches include working with patients to encourage motivation to change, enhance adherence to medication through education, reward cooperation with treatment guidelines,[30,31] keep motivation high, and teach ways to minimize relapses to drug use. Most of these elements are part of motivational interviewing.[32]

Unlike some rehabilitation approaches for some other disorders, patients with substance-use disorders are encouraged to participate in self-help programs such as Alcoholics Anonymous and Narcotics Anonymous.[30,33] The combination of education, motivational enhancement, and self-help groups, which are incorporated into individual and group counseling approaches in inpatient and outpatient programs, helps patients change how they think about the ways that opioids affect their lives, recognize that change is possible, and work to decrease behaviors that perpetuate illicit-drug use while developing new behaviors that diminish drug-related problems.[1,30]

Naltrexone for Abstinence-Oriented Opioid Rehabilitation

Naltrexone is a mu-opioid receptor antagonist that blocks opioid effects and helps maintain abstinence from opioids in highly motivated patients.[23,26] It is available in 50-mg daily tablets with effects lasting 24 to 36 hours. To help maintain adherence to treatment when used as part of an outpatient rehabilitation program, it is also available as an extended-release injectable formulation containing 380 mg of naltrexone (Vivitrol) that blocks opioid effects for 1 month.[34-36]

Medication treatment is most effective when it is administered as part of a cognitive behavioral approach (to enhance motivation, work toward behavioral changes, and prevent relapse) with patient participation in a self-help group. Side effects of these medications include gastrointestinal upset, fatigue, and insomnia, as well as elevated levels on liver-function tests at higher doses, although naltrexone is relatively safe in persons who consume large amounts of alcohol and those with hepatitis C or HIV infection.[23,36,37]

Patients who initiate naltrexone treatment must be free of physiological opioid dependence (e.g., >7 days without acute withdrawal symptoms) (Table 5). Opioid-free status can be established by an opioid-free urine sample and a challenge with 0.8 to 1.6 mg of intravenous or intramuscular naloxone with no withdrawal

TABLE 5

symptoms over the next 15 to 30 minutes before receiving naltrexone (at a dose of 50 mg) that same day. An alternative challenge is to administer a small dose of naltrexone (e.g., 12.5 to 25 mg) orally, and if no withdrawal is seen over the next 4 hours, administer 50 mg orally. After the patient's condition is stable and he or she is abstinent from opioids, it may be possible to switch to 100 mg orally on Monday and Wednesday and 150 mg on Friday, or to monthly depot injections. If naltrexone is used following abstinence from opioids after methadone or buprenorphine maintenance, the induction might be slower (e.g., 12.5 mg orally on day 1; 25 mg on days 2 and 3; and then 50 to 100 mg thereafter).[34,38]

Medications for Rehabilitation from an Opioid-Use Disorder, According to the Patient's Treatment Goal.

Efficacy studies have generally used oral rather than intramuscular doses of naltrexone, but both forms are superior to placebo for maintaining abstinence from opioids, with some evidence that monthly injections are superior to oral doses.[35,39] However, in most studies of oral naltrexone, approximately 50% of patients discontinued the drug by 6 weeks, with only 15% remaining in the study at 25 weeks in some evaluations.[40] Higher rates of adherence are seen with opioid maintenance, as described below.[11,41] In addition, because of the loss of tolerance that occurs with abstinence from opioids, the danger of overdoses that may lead to death is enhanced among patients who discontinue naltrexone and return to opioid use.[11]

Opioid Maintenance Approaches

Opioid-dependent persons who are reluctant to or unable to discontinue opioids but want to improve their health and life situation can markedly improve their daily functioning with opioid treatment. Oral opioids to avoid past reinforcement associated with needles, as well as relatively inexpensive, long-lasting opioids to avoid daily withdrawal symptoms and enhance adherence, are available.[10,11,42] Maintenance goals include improving health, avoiding contaminated needles and risks of HIV or hepatitis C infection, improving interpersonal relationships and the ability to work, decreasing craving and the rewarding effects of illicit opioids, and diminishing crimes committed to pay for illicit drugs.

Maintenance programs should include psychological support, require participants to take part in counseling, offer education about how to deal with pain syndromes without misusing prescription opioids, and warn patients to avoid misuse of other drugs such as benzodiazepines and gabapentin (Neurontin) that they might use to create a high while receiving opioid-agonist treatment. It is important to carefully monitor the use of illicit drugs and diversion of the medications for opioid treatment to other users.[43] Although, theoretically, any long-acting oral opioid might be used for maintenance, the only approved drugs for this use in the United States are methadone and buprenorphine.

Methadone Maintenance Approaches

Maintenance treatment with methadone, an oral mu agonist, has been widely used and intensively studied worldwide. In the United States, methadone is offered only through approved and closely monitored clinics that initially require almost daily patient participation in order to receive the drug, although some take-home doses are usually allowed for patients who adhere to program guidelines.

To be eligible for methadone maintenance, patients must have a current opioid-use disorder with physiologic features or have high risks associated with relapse (e.g., during pregnancy). In addition, patients cannot be currently participating in another maintenance program and cannot be especially vulnerable to methadone-related medical complications (e.g., they cannot be dependent on a depressant drug or have severe respiratory or cardiac disease). Dangers associated with methadone include overdose if the dose is increased too quickly during the initial stages of treatment and a potential prolongation of the QT interval on electrocardiography that can contribute to cardiac arrhythmias with doses higher than 100 mg per day.[44-46] Patients must understand their roles and responsibilities as well as the benefits that the program can and cannot offer.

Methadone maintenance treatment occurs in approximately three phases (Table 5).[47] The induction and early stabilization phase (beginning at week 1 and continuing in week 2) begins with initial oral doses of 15 to 30 mg, increasing by 10 to 15 mg every 3 to 5 days to 50 to 80 mg per day. During the late stabilization phase (at approximately weeks 3 to 6), doses are increased as tolerance develops and craving decreases. The most effective dose is 80 to 100 mg per day.[47-50] Patients who receive more than 100 mg per day must be closely monitored for side effects.[44,46,50]

The maintenance phase begins at approximately 6 weeks, with doses adjusted to avoid drug-related euphoria, sedation, or opioid craving. Methadone clinics must be open on weekends in order to meet the needs of most patients,[51] and weekend take-home doses are based on the patient's progress in treatment and determination that he or she is unlikely to divert medications to other persons. The length of the maintenance phase, which depends on the patient's progress in treatment and his or her motivation, can last years to a lifetime.

Tapering off methadone is individualized and may take weeks or months.[26] During and after tapering, close contact with the patient should be maintained because discontinuation of maintenance carries high risks of relapse to the use of illicit drugs and overdoses that may lead to death.[11,52,53]

The effectiveness of methadone maintenance is well established, and this drug is listed among "essential medications" by the World Health Organization.[11,45] Maintenance programs decrease mortality by approximately 50% among persons with opioid-use disorders, decrease acquisition of HIV infection and hepatitis, decrease crime and illicit-substance use, improve social functioning, and increase the rate of retention in rehabilitation programs.[15,50,54,55]

Buprenorphine Maintenance

In the United States, the restriction of methadone to specialized clinics contributed to a search for an alternative oral, long-acting opioid. This search resulted in buprenorphine maintenance therapy.[6,56,57]

Although oral buprenorphine is rapidly destroyed in the liver, it is well absorbed as a sublingual tablet or buccal film.[6,28] Buprenorphine has effects that last for 24 to more than 36 hours. It reduces opioid-withdrawal symptoms and partially blocks intoxication from other opioids.[6,28] Physicians who are approved to prescribe buprenorphine for office-based maintenance were initially limited to 30 such patients at a time, a number that was increased to 275 patients in July 2016. They must prescribe buprenorphine themselves (e.g., not through a nurse practitioner), must offer counseling or be able to refer patients for counseling, and must agree to participate in Drug Enforcement Administration inspections.

The risks associated with buprenorphine include overdoses, especially if it is taken along with depressant drugs, and potential illicit diversion of drugs.[58,59] However, mortality during induction with buprenorphine is lower than that during induction with methadone; this finding contributed to approval for office-based maintenance treatment by physicians with special training and certification.[6]

To discourage the misuse of intravenous buprenorphine, maintenance therapy involves a sublingual or buccal combination of buprenorphine and the short-acting opioid antagonist naloxone, usually in a 4-to-1 ratio across the two drugs.[6,60] Because of the low doses of naloxone administered and the low proportion of this drug that is absorbed orally, this opioid antagonist does not precipitate withdrawal unless it is injected intravenously, in which case the withdrawal symptoms can be sudden and severe.

Patient selection criteria for buprenorphine maintenance resemble the above-mentioned criteria for methadone maintenance.[57] Although treatment protocols vary depending on specific patients' needs, the usual process is briefly discussed here.[56,57,61] The patient must have early signs of withdrawal to avoid precipitating an abstinence syndrome when he or she is taking high doses of the drug of abuse.

The induction phase lasts approximately 7 days in patients who are misusing a short-acting opioid such as heroin. On day 1, typical patients receive 4 to 8 mg of buprenorphine. On day 2, the dose is increased up to 16 mg, with further daily increases by day 7 but rarely a total of more than 30 mg per day. The stabilization phase (at approximately 8 weeks) begins when craving is markedly reduced, opioid misuse is diminished or absent, withdrawal symptoms are absent, and a stable dose has been achieved. If needed, doses can be increased up to 4 mg each week up to a daily dose as high as 32 mg; the condition of most patients stabilizes at 16 to 24 mg. At doses of less than 8 mg per day, the program may not be effective, and higher doses may be required to achieve the maximum effect.[6,10,62]

The maintenance phase begins when the most appropriate dose is established. The usual minimum length of treatment is 12 months, although, as with methadone, risks of relapse and overdose increase when buprenorphine is discontinued.[63] If the patient and physician decide that a buprenorphine taper should be initiated, doses should be decreased slowly while the dose is monitored and adjusted according to the withdrawal symptoms observed.

Strong and consistent data support the effectiveness of buprenorphine maintenance, as compared with placebo and naltrexone, especially at a dose of 16 mg or more per day.[6,61,62] Initiating buprenorphine maintenance as soon as possible (e.g., while the patient is hospitalized or after an emergency department visit) can enhance efficacy.[64] Combining maintenance therapy with a cognitive behavioral approach might improve outcomes.

There are no hard-and-fast rules regarding whether to refer a patient to a clinic for methadone maintenance or for buprenorphine maintenance. Considerations include cost; the availability of methadone clinics and physicians who are trained in administering buprenorphine; the match of demographic factors, educational levels, and socioeconomic backgrounds between the patient and

treatment programs; the patient's coexisting medical and psychiatric conditions; and individual clinician and patient preferences.[65]

Direct comparisons between methadone and buprenorphine show that both approaches improve outcomes, but most studies suggest that methadone maintenance might be associated with higher rates of patient retention.[10,50,65-67] Also, buprenorphine is more expensive than methadone, and the private-office charges for buprenorphine might exceed the usual costs of a methadone clinic. However, buprenorphine is safer than methadone during induction and can be administered in offices of trained clinicians; the availability of treatment in clinicians' offices improves access to opioid maintenance.

Universal agreement on how long a patient should continue to receive maintenance therapies is lacking. Some clinicians prefer to work with patients to attempt to discontinue their medications after approximately 1 year, and others emphasize the high rate of relapse and overdose deaths after leaving these programs and suggest that treatment should be open-ended and potentially lifelong.

Finally, just as this article provides a broad overview of medically supervised withdrawal, this overview of rehabilitation focuses only on the most widely used approaches. Morphine and heroin are used less often than methadone and buprenorphine as maintenance treatments, and fewer data are available regarding their use for this purpose.

CONCLUSIONS

This review describes one person's view of what the usual practicing clinician should know about the current state of treatments for opioid-use disorders. The topics that are likely to be most useful to nonexperts in the field are included. The areas that are not covered (e.g., basic pharmacologic approaches and potential treatments that are still in early stages of development, most of which are not likely to progress to clinical implementation soon) are less likely to have immediate clinical utility.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

No potential conflict of interest was reported.

I thank Walter Ling, George Woody, Sarah Book, Steve Groban, and others in the substance-use field for their advice.

SOURCE INFORMATION

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