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Pharmacological management for opioid-Use Disorders

Ajay Babladikar[1], Abhinaya Koppula[2], Aravinda Swami

[1]*PharmD Intern, Malla Reddy Hospitals, Suraram, Hyderabad– 500055*

[2]*PharmD Intern, Malla Reddy Hospitals, Surararm, Hyderabad – 500055*

[3]*Associate Professor, Malla Reddy Hospitals, Suraram, Hyderabad – 500055.*

***Corresponding author: Ajay Babladikar**

ABSTRACT

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. 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]

GENERAL DIAGNOSTIC CRITERIA FOR OPIOID USE

Diagnostic Criteria for an Opioid-Use Disorder, 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]

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. 13 The risk of adverse outcomes decreases markedly with abstinence from opioids. [9, 16]

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.

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).

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 non-opioid medications that help to control symptoms. [21, 22]

Decreasing Symptoms with α2-Adrenergic Agonists and Other Nonopioid Agents

α2-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 over activity. [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 anti-inflammatory 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.

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 α2-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 over sedate.

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, 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]

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, 28] 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, 26, 27]

Patients who initiate naltrexone treatment must be free of physiological opioid dependence (e.g., >7 days without acute withdrawal symptoms)

Medications for Rehabilitation from an Opioid-Use Disorder

According to the Patient's Treatment Goal, 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 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 (Eg: 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]

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. Higher rates of adherence are seen with opioid maintenance, as described below. 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.

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).

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 effectiveness of methadone maintenance is well established, and this drug is listed among "essential medications" by the World Health Organization. [11] 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]

Buprenorphine Maintenance

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].

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]

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. 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.

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 the 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 non-experts 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.

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